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Prostate cancer mortality risk in relation to working underground in the Wismut cohort study of German uranium miners, 1970-2003

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) The study's cohort design is indicated in the title, page 1
		(*b*) An informative and balanced summary of what was done and what was found has been provide in the abstract
Introduction		
Background/rationale	2	The scientific background and rationale for the investigation being reported has been explained, page 4
Objectives	3	Specific objectives, including any prespecified hypotheses, have been stated, page 4
Methods		
Study design	4	Key elements of study design have been presented early in the paper, page 5-7
Setting	5	The setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection have been described, pages 4 & 8
Participants	6	(*a*) *Cohort study*—The eligibility criteria, and the sources and methods of selection of participants have been cited and described on page 4. Methods of follow-up have been cited and described on page 4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed – No matching was performed *Case-control study*—NOT APPLICABLE
Variables	7	All outcomes, exposures, predictors, potential confounders, and effect modifiers have been defined, page 6. Diagnostic criteria, in terms of ICD codes are given on page 5
Data sources/ measurement	8*	For each variable of interest, sources of data and details of methods of assessment (measurement) are give on page 4 & 6
Bias	9	Efforts to address potential sources of bias are given in the discussion section, page 12
Study size	10	Explanations on how the study size was arrived at are cited on page 4
Quantitative variables	11	Explanations of how quantitative variables were handled in the analyses are given on pages 6 & 7.
Statistical methods	12	(*a*) All statistical methods, including those used to control for confounding are described, pages 6 & 7
		(*b*) Any methods used to examine subgroups and interactions are described on pages 6 & 7
		(*c*) Missing data were addressed on page 5
		(*d*) *Cohort study*—Loss to follow-up was addressed in the citations on page 4
		(*e*) Sensitivity analyses were not relevant.

Continued on next page

Results		
Participants	13*	(a) Numbers of individuals at each stage of study (i.e. person-years at risk) are reported on in table 1
		(b) Give reasons for non-participation at each stage – NOT RELEVANT
		(c) Consider use of a flow diagram – NOT RELEVANT
Descriptive data	14*	(a) Characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders are given, in tables 1&2
		(b) Number of participants with missing data for each variable of interest is indicated by the overall "Percentage of Missing Causes of Death" on page 5
		(c) *Cohort study*—Follow-up time (eg, average and total amount) has been given on page 8
Outcome data	15*	*Cohort study*—Numbers of outcome events or summary measures over time are reported in figure 1
		Case-control study—NOT APLICABLE
		Cross-sectional study— NOT APLICABLE
Main results	16	(*a*) Unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval) are given in table 2. table 2 makes clear which confounders were adjusted for and why they were included.
		(*b*) category boundaries when continuous variables were categorized were already reported in the methods section, page 6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period – this was not possible due to limitations in the methodology (i.e. Poisson Regression with a stratified baseline model)
Other analyses	17	Other analyses done—eg analyses of subgroups and interactions, are reported in table 3
Discussion		
Key results	18	Key results with reference to study objectives are summarised on page 10
Limitations	19	Limitations of the study, taking into account sources of potential bias or imprecision are discussed on pages 10, 11 & 12. Direction and magnitude of any potential bias are discussed on page 12.
Interpretation	20	A cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence is given in the conclusions section.
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	The source of funding and the role of the funders for the present study on which the present article is based are given in the "Acknowledgement" at the end of the paper.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Original paper

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Prostate cancer mortality risk in relation to working underground in the Wismut cohort study of German uranium miners, 1970-2003

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Abstract

Objective: A recent study and comprehensive literature review has indicated that mining could be protective against prostate cancer. This indication has been explored further here, by analysing prostate cancer mortality in the German "Wismut" uranium miner cohort which has detailed information on the number of days worked underground.

Design: An historical cohort study of 58,987 male mine workers with retrospective follow-up before 1999 and prospective follow-up since 1999.

Setting and participants: Uranium mine workers employed during the period 1970-1990 in the regions of Saxony and Thuringia, Germany, contributing 1.42 million person years of follow-up ending in 2003.

Outcome measure: Simple Standardised Mortality Ratio (*SMR)* analyses were applied, to assess differences between the national and cohort prostate cancer mortality rates, and complemented by refined analyses done entirely within the cohort. The internal comparisons applied Poisson regression excess relative prostate cancer mortality risk model with baseline stratification by age and calendar year and a whole range of possible explanatory covariables that included days worked underground, years worked at high physical activity and radiation.

Results: The analysis is based on miner data for 263 prostate cancer deaths. The overall *SMR* was 0.85 (95% CI 0.75; 0.95). A linear excess relative risk model with the number of years worked at high physical activity and the number of days worked underground as explanatory covariables provided a statistically significant fit when compared to the baseline model (p=0.039). Results (with 95 % confidence intervals) for the *ERR* per day worked underground indicated a statistically significant (p=0.0096) small protective effect of $-5.59(-9.81;-1.36).10^{-5}$.

Conclusions: Evidence is provided from the German Wismut cohort in support of a protective effect from working underground on prostate cancer mortality risk.

Introduction

Prostate cancer is the second most common cancer diagnosed among men (after lung cancer), and is the sixth most common cause of cancer death among men world-wide [1]. In the European Union in 2006, prostate cancer was the most common form of incident cancer and the third most common form of cancer death in men (Table 3 of [2]). Prostate cancer incidence in Germany has also become the most common form of incident cancer disease in men. It is notable that the prostate cancer mortality rates were approximately constant in the former eastern German Democratic Republic (GDR) between 1960 and 1980, but rose during the same time by 50% in West Germany [3].

Prostate cancer is, in general, a slow-growing tumour with a long latency and an uncertain aetiology. The prevalence of latent microscopic prostate tumours has been shown to be quite high in the elderly in most populations i.e. at least 50 percent in men over the age of 70 years [4]. Although there are only a few established risk factors for prostate cancer such as age, race and a family history of prostate cancer [5] there are also several mooted detrimental and protective associations.

The possible detrimental associations include early baldness [6], shift-work [7], arsenic exposures [8] and oestrogen exposures [9]. Some evidence exists for radiation related prostatic detrimental effects from studies on patients after diagnostic radiation procedures [10], occupationally exposed British nuclear workers [11], military and civil pilots and flight attendants [12], and persons exposed by the Chernobyl accident [13]. There was little evidence of a prostate cancer risk radiation dose response in the Japanese A-bomb survivors [14].

The possible protective associations include high sexual and/or androgenic activity [15], UV and/or vitamin D [16], high Physical Activity (PA) [17] and melatonin [18-21]. For a cohort of U.S. male health professionals, [22] reported that for fatal prostate cancer, a recent smoking history, taller height, higher BMI, family history, and high intakes of total energy, calcium and α-linolenic acid were associated with a statistically significant increased risk but higher vigorous PA level was associated with lower risk.

A recent Australian population-based case-control study and literature review [23] has indicated that mining could be protective against prostate cancer. [23] concluded that the relationship between mining and prostate cancer could possibly be connected to levels of either PA or changes in melatonin production caused by periods working underground and that these relationships deserve further investigation. Differential risk could not be reported in [23] because all but one of the studies reviewed did not report on working periods underground and over ground. The main purpose of the present paper is to explore these indications further by analysing prostate cancer mortality risk in a cohort of male mine workers involved in uranium extraction at the former Wismut company in East Germany applying both external (national male rates for the former GDR) and internal baselines. New covariables for occupational PA and time spent underground have been specially created for this investigation. Simple *SMR* analyses are complemented by refined analyses done entirely within the cohort.

The German "Wismut" uranium mine workers cohort has currently been followed-up from 1.1.1946 to 31.12.2003, with almost 2 million person-years of observation and has already been described in detail [24]. It is currently the largest miners cohort study and several analyses of the detrimental health effects data pertaining to the 58,987 male former employees, have recently been published [25-31].

There are several occupational risk factors for detrimental health effects, relevant to the cohort members, particularly with respect to lung cancer, including exposure to radon, gamma radiation, long-lived radionuclides, [32], fine dust, arsenic dust and quartz dust [33], diesel and asbestos [34]. Previous analyses have shown that the mortality from prostate cancer in this cohort (1960-2006) is notably lower than in the comparison population of the former GDR (*SMR* = 0.88, 95%CI = 0.78; 1.00 [25]). The total absorbed dose to the prostate has not yet been calculated. However since the absorbed dose to non-respiratory track organs is dominated by external gamma radiation and the contributions of radon progeny, radon gas and particularly long-lived radionuclides are expected to be small [35], only the gamma radiation is explicitly considered here. The effective gamma doses have been converted into prostate organ dose via Voxel model dose conversion factors [36].

Material and Methods

Cohort definition, time periods and mortality follow-up.

Full details of the cohort have already been given [26, 28]. Every cohort member contributes to the number of person years starting 180 days after the date of first employment and ending at the earliest of date of loss to follow-up, date of death, or end of follow-up (31.12.2003). Due to the relatively high Percentage of Missing Causes of Death (PMCD) of 37.25% and the systematic variation of PMCD with calendar time from 1946 to 1969, the main analyses here are based on the subset of Wismut miner cohort data covering the period 1970-2003 for which the PMCD is 3.56%. Consequently, no corrections for missing causes of death have been made. This difference in PMCD is due to the late start of data collection for this cohort on 1.1.1999, linked with the fact that death certificates were rarely kept by the authorities for more than 30 years.

National rates for the former GDR covering the same calendar-year range are applied for the external comparisons. Former disease codes of the comparison external baseline rates for the GDR were re-coded via earlier ICD revisions to the 10^{th} ICD-code [37], which was applied throughout. This recoding process was complicated by several revisions to ICD codes during the period of data coverage, and German reunification. Population prostate cancer rates are not available just for the relevant mining region of Thuringia and Saxony. Consequently, the external rates applied here cover the total area of the former GDR (including East-Berlin) during the time period 1970–1997; in contrast, from 1998 the rates pertain to the former GDR states and the whole of Berlin. The codes used here in the various time periods are as follows: 1970–1978 ICD 8, code number 185; 1979 ICD 8, code number 179-189 for the urogenital system; 1980–1997 ICD 9, code number 185; 1998–2003 ICD 10, code number C61 all for Prostate cancer.

Analysis.

The methods applied here require the tabulation of the individual data as described below and in previous analyses [28-30]. Quantitative risk evaluation methods were based on the simple *SMR* model, considered both with and without an exposure response to various possible explanatory covariables, for external comparisons and comparisons just within the cohort. The more refined analysis entirely within the cohort (internal comparisons) applied Poisson regression excess relative prostate cancer mortality risk model with baseline stratification by

age and calendar year and a whole range of possible explanatory covariables: age (*a*), year (*y*), gamma organ dose (*g*), years at medium Physical Activity (PA) (*mpa*), years at high PA (*hpa*), days worked underground (*u*) and time since last underground shift (*t*).

Data Tabulations.

Tabulations of person-years at risk and cancer deaths were created with the DATAB module of the EPICURE software [38]. Cross-classifications were made by attained age, *a*, in 16 categories (<15, 15–<20, 20–<25, … , 85+ years), individual calendar year, *y*, in 58 categories, and cumulative gamma prostate doses (8 categories: 0, >0–<50, 50–<100, 100–<150, 150–<200, 200–<300, 300–<400, 400+ mGy). For the current analysis new covariables for occupational PA and time spent underground have been specially created. Exact shift information relating to daily underground and overground activities in each calendar year was used. The number of days worked underground in any one calendar year was then accumulated over calendar year in 8 categories (0, >0–<1000, 1000–<2000, 2000–<3000, 3000–<4000, 4000–<5000, 5000–<6000, 6000+ days). For the PA categories, information on the job type in each calendar year was extracted from the Wismut records. Each of the several hundred job types had already been classified into three levels of PA corresponding to different breathing rates for the purpose of organ dose calculations e.g. job types hewer, metal worker and lorry driver were classified as high, medium and low PA respectively. The number of years worked in each of the high and medium PA classes were then accumulated over calendar year each in 8 categories (0, >0–<5, 5–<10, 10–<15, 15-<20, 20–<25, 25–<30, 30+ years). Choice of units (years or days) reflects the quality of the information available in the mining records.

Standardized Mortality Ratios.

Mortality rates observed in the cohort were compared with the GDR external rates. The first stage of the *SMR* analysis for prostate cancer has been done as described previously for extra–pulmonary cancers [26] with some extensions that allow a comparison of internal (miner cohort) and external (former GDR) baseline (spontaneous) rates. The simplest *SMR* model relates the rates in the population of interest (the miner cohort) to a multiple of the rates from the external population (the former GDR).

If $\lambda^*(a, y)$ denotes the external rates as a function of age and calendar year and $\lambda(a, y)$ denotes the observed rates in the miners cohort, then the *SMR* model can be written as

$$\lambda(a, y) = \beta \cdot \lambda^*(a, y) \quad (1)$$

where the β is a fit parameter and represents the *SMR*.

However it is also possible to fit a relative risk (*RR*) model

$$RR(a, y, w) = \beta_1 \cdot \lambda^*(a, y) \cdot (1 + \beta_2 (g)) \quad (2)$$

to estimate the effects of various possible explanatory covariables, such as gamma organ dose (g), based on the GDR external rates, assuming that the *SMR* for the background rates is identically equal to 1, i.e. β_1 is fixed to unity during the optimisation. In this case, β_2 is a fit parameter that then gives the simple Excess Relative Risk (*ERR*) per unit of exposure relative to the external GDR rates. It is also possible to test if the external GDR rates are different from the internal baseline rates in the miner cohort by simply freeing the parameter β_1 and repeating the optimisation. All of the parameters β, β_1 and β_2 can be multiplied by a two level categorical variable for either levels of PA or time spent underground.

Refined *ERR* models with baseline stratification by age and calendar year were employed – if $r(a, y, g, mpa, hpa, u, t)$ is the prostate cancer mortality rate and $r_0(a,y) = r(a,y,0,0,0,0,0)$ is the baseline disease rate for non-exposed individuals, $g = 0$, $mpa = 0$ …etc. then

$$R(a, y, g, mpa, hpa, u, t) = r_0(a, y) \cdot \{1+ERR(g, mpa, hpa, u, a, t)\}, \quad (3)$$

where *ERR* is the excess relative risk factorised into a function of exposure, f(g, mpa, hpa, u) and a modifying function, h(a, t):

$$ERR(g, mpa, hpa, u, a, t) = f(g, mpa, hpa, u) \cdot h(a, t) \quad (4)$$

The gamma organ dose, years at medium PA, years at high PA and days worked underground were each included:

singularly, $f(g) = \alpha\, g$, etc, and pair-wise $f(g, mpa) = \alpha_1\, g + \alpha_2\, mpa$, etc. (5)

in the linear *ERR* model, both with and without the modifying function, and assessed with model selection techniques to arrive at the model with the lowest deviance with respect to the baseline model, by forward selection. Backwards selection was also tested. Finally the

preferred linear model was tested for non-linearity and time or age effect modification (i.e. adding g*(a, t)* functions to the model).

Maximum likelihood with the AMFIT module of the EPICURE software [38] was used for estimation of the *SMR* and *ERR* fit parameters associated with equations 1 to 5 above.

Results

There were 263 prostate cancer deaths during 1.42 million person years of observation between 1970 and 2003. The absolute and cumulative numbers of prostate cancer deaths in the full Wismut cohort (1946–2003) are shown in Figures. 1a and 1b as a function of calendar year from 1960 and age attained from 20 years. It can be seen from these figures that a) the absolute number of prostate cancers occurring reaches a maximum in the category 75 to 80 years of age, due to the age distribution in the cohort, and increases steadily from 1970 to 2003, with no prostate cancer deaths occurring between 1960 and 1969 b) the cumulative number of prostate cancers increases as a function of age attained and calendar year.

The mean values (and ranges) of age-attained, mean number of days worked underground and mean number of years worked at high PA are 47 (14-103) years, 1649 (0-10704) days and 3.5 (0-44) years respectively. Table 1 gives the category specific values for the number of prostate cancer deaths and person-years, for the number of years worked at high PA and days spent underground categories of mine workers.

SMR results (comparison with external rates).

The number of deaths (1970–2003) observed (O), was significantly lower ($p < 0.001$) than expected (E) from national rates. The *SMR* value with 95% confidence intervals (CI) is 0.85 (0.75; 0.95). Quantitative differences between GDR external rates and internal cohort rates can be assessed directly from a categorical *SMR* analysis in categories of attained-age and calendar year. Some statistically significantly low categorical *SMR* values were found mainly in the age group 65 to 75 years, and in the calendar period from 1991 to 1995 (results not shown). The overall *SMR* with 95% confidence intervals when recomputed by two categories of below and above mean time spent underground (1649 days) becomes 0.92 (0.76; 1.07) and 0.79 (0.65; 0.92) respectively. The *SMR* recomputed by two categories of below and above mean time worked at high PA (3.52 years) becomes 0.82 (0.69; 0.94) and 0.91 (0.73; 1.10) respectively.

Simple *ERR* parametric cohort risk models (comparisons with external and internal rates).

Cumulative exposure effects for various covariables in terms of *ERR* per unit exposure and 95% CIs are given in the first results column of Table 2. The *ERR*/day worked underground, relative to the external GDR rates, is -4.44 (-7.11; -1.76).10^{-5} and was found to be the statistically strongest exposure effect (p = 0.001) i.e. protective for the number of days worked underground relative to the external rates. A similar value of -3.3 (-7.2; 0.06) .10^{-5} relative to the internal controls was found (Table 2, second results column), although of reduced statistical significance (p = 0.097). This latter result is connected with a baseline SMR of 0.93 (0.78; 1.08) (Table 2, second results column). The *SMR* model did not converge (NC) for the gamma organ dose relative to the external baseline rates. A statistically significant (p-value = 0.03) protective *ERR*/Gy for prostate gamma doses, relative to the internal baseline of -1.27 (-2.4; -0.14) was also found (Table 2, second results column).

Refined *ERR* parametric cohort risk models.

The statistical significance of *ERR*/Gy for prostate gamma doses reported with the simple analysis was not confirmed by the refined analysis (*ERR*/Gy=-1.18 (-2.4; 0.02), see table 2, third results column). A preferred model by forward selection of the covariables gamma organ dose, *g*, years at medium PA, *mpa*, years at high PA, *hpa* and days worked underground, *u* taken linearly one or two at a time was found to be the model that included both *hpa* and *u* (Table 3). This model had a reduction in deviance with respect to the stratified baseline model of 6.5, (p = 0.04) by the Likelihood Ratio test. This model provided the results in the last column of table 2, (with 95 % confidence intervals) for: the *ERR* per day worked underground, which indicates a statistically significant (p=0.0096) small protective effect of -5.59(-9.81;-1.36).10^{-5} and; for the *ERR* per year worked at high physical activity, which indicates a statistically significant (p = 0.0443) small detrimental effect of 0.021 (0.001; 0.040). Models that included just *hpa* or just *u* did not result in statistically significant risks (Table 2, third results column) or lead to statistically significant model improvement (Table 3). Testing of the quadratic or parabolic forms for *hpa* and *u* or testing risk effect modification by attained age (Table 3) or time since last underground shift (results not shown) did not lead to statistically significant model improvement. The dose response forms for the preferred model and the adjusted non-parametric risks with 95% confidence intervals are shown in Figure 2. It was not possible to confirm this result by backwards selection since the models with all 6 main covariables failed to converge.

Discussion

The Wismut cohort is one of the largest single occupational cohorts and one of only a few cohorts with detailed information on the number of shifts worked underground. Although the number of shifts was documented, it is not known if these were early morning, day-time or night shifts. A substantial proportion (25%) of person-years are contributed by mine workers who did not work underground which generally ensures the stability of analyses based on internal rates. The *ERR* per unit of various exposures have been modelled relative to the internal rates and relative to the external rates for the general population of the former GDR.
A statistically significant (p = 0.001) negative response for the *ERR* per day worked underground, when modelled in relation to the general population of the former GDR, is reported here. There are some indications of unit exposure responses of the *ERR* which are negative (protective) for gamma prostate dose, (p= 0.03 and 0.055 for the simple and refined models respectively) with respect to the internal rates. Rather than being protective, the gamma dose is a possible proxy variables for the number of days worked underground since there are moderate degrees of correlations between these covariables (ρ = 0.68 for the correlation between time dependent cumulative gamma prostate doses and the number of days worked underground, see also table 1). Indications that the gamma dose may be acting as a proxy could be tested here directly by the creation of new categories of mine workers, with numbers of years worked at high or medium PA and the number of days worked underground and the application of model selection techniques.

The assumption is made in this paper that radon and long-lived radionuclides make only minor contributions to the total prostate dose. Previous analyses have shown that the *ERR* per 100 WLM of radon exposure, based on internal Poisson models, was not elevated for prostate cancer (*ERR*/100 WLM= 0.000, 95%CI, -0.024; 0.024, [29]). None of the radiation covariables (i.e. gamma organ dose, but also including long-lived radionuclides and radon), when tested by inclusion singularly as linear risks in refined internal Poisson regression models, resulted in a deviance drop of more than 3 with respect to the baseline model which was stratified on age-attained and calendar year.

A linear excess relative risk model with the number of years worked at high physical activity and the number of days worked underground as explanatory covariables provided a

statistically significant fit when compared to the baseline model (p = 0.039). Results (with 95% CI) for the *ERR* per day worked underground indicated a statistically significant (p = 0.0096) small protective effect at $-5.59(-9.81;-1.36).10^{-5}$ and, for the *ERR* per year worked at high physical activity, a statistically significant (p = 0.0443) small detrimental effect at 0.021 (0.001; 0.040). This main result provides new evidence in support of the protective effect of working underground which is manifested with respect to the internal and the external rates.

The number of days worked underground is connected with a particular hypothesis for reduced prostate cancer rates e.g. melatonin production rates (as described in detail in [23] and references therein). In summary, melatonin has been shown to have anti-cancer properties acting through several mechanisms [18-21]. The production of melatonin in the pineal gland is regulated by the natural diurnal light-level cycle, with suppressed production during the day which is restored at night. Underground miners on day shifts would have a reduced exposure to visible light leading to an extended melatonin production period.

The relation between physical activity and prostate cancer risk was classified as "probable" with respect to an increased risk, by the IARC in 2002 [39] but no definite mechanisms have been identified for a relation between PA and prostate cancer. Several plausible mechanisms have been postulated which include modulation of testosterone and vitamin D levels by PA, a link between physical inactivity and over-weight/obesity and a beneficial modulation of immune function through exercise (see [40] for a review). A recent systematic review and meta-analysis [41] considered 13 studies with occupational physical activity, considered to be "higher-quality" studies and reported that 9 studies gave a decreased risk, one study an increased risk and 3 studies reported no association. Two other studies have reported increased risks: [42] found that intensity of occupational PA was associated with increased prostate cancer risk and [43] reported an increased risk for obese men (BMI over 30) who were physically active for more than 1 hour per day and in men with high baseline energy intake.

A statistically significant increase in risk with increasing high PA is observed here, in contrast to the IARC classification and the majority of other studies. It is important to note that the variable physical activity here measures only part of the total PA and could be prone to misclassification. The PA variable is limited to the work period at the Wismut company (the mean duration of work at the company 14 years) and no leisure time activities could be

considered. The classification is simply based on job type without consideration of possible changes in physical activity in a specific job over time e.g. due to improved technical "labour-saving" equipment. Physical activity could also be an indicator of socioeconomic status, because the jobs with low PA are more likely to be associated with higher education.

Another possible source of bias in the results based on external comparisons that should be considered is the selection bias known as the healthy worker effect. However this effect, which can generally lead to occupational cohorts presenting mortality risks less than the general population, is not indicated since the risks are similar with respect to internal and external baselines. The occurrence of this form of bias could also be tested here by considering all solid cancer minus the sites that have already been linked to the main mine radiation exposure (lung, larynx, tongue, mouth and pharynx). For this group of cancers the *SMR* with 95%CI is 1.01 (0.97; 1.04) also indicating that the healthy worker effect is not having a significant influence on the prostate cancer results in this cohort.

A further source of bias, possibly affecting the decrease in risk with increasing duration of working underground based on internal comparisons, could be the healthy worker survivor effect. Unhealthy workers may move from working underground to working at the surface. Consequently, the duration of working underground may be higher in the healthy group compared to the unhealthy group, leading to artificially protective effects in relation to duration of working underground. However this effect has been tested for by fitting the preferred model, that included both the number of days worked underground and number of years worked at high physical activity, to the sub-group of all solid cancers minus the sites that have already been linked to the main mine radiation exposure (lung, larynx, tongue, mouth and pharynx) and minus prostate. No significant trends were found ($p>0.5$ for the linear trend of ERR with respect to the number of days worked underground and $p=0.11$ for the linear trend of ERR with number of years worked at high physical activity) indicating that the healthy worker survivor effect is not directly biasing the results for prostate cancer.

Although there is no general consensus as to whether radiation exposure is associated with prostate cancer risk [44], an X-ray procedure risk doubling dose of about 20 mGy for prostate cancer incidence has been reported [10]. The magnitudes and ranges of the gamma prostate organ doses in the Wismut study (with the prostate cancer mortality cases having a range up

to 444 mGy) should be large enough to find such an increased risk at the 20 mSv level given the similar relative biological effect of X-rays and gamma rays. However, a gamma risk, at this 20 mSv level, has not been found in the Wismut cohort data for prostate cancer mortality.

Yang et al [8] reported that *SMR*s for prostate cancer declined gradually in a SW costal district of Taiwan after the arsenic contaminated artesian well drinking-water supply was improved to a tap-water system. Since arsenic dust exposures are also available for the Wismut miners [33], an arsenic covariable could be added to the preferred model for physical activity and time worked underground described above, but this only resulted in a deviance drop of 1.2 and a p-value of 0.33 for the associated arsenic risk coefficient and did not confound the main risks from the preferred model.

Although there were 264 prostate cancer deaths in the whole cohort, only one occurred before 1970. This is consistent with prostate cancer generally being a type of cancer that occurs predominantly in old-age coupled with the observation that – due to miners entering and leaving the cohort at various points in time during the follow-up period – the cohort aged, on average, at half the rate of any individual, i.e. in 1960 and 2003 the mean ages of cohort members were 35 and 57 years respectively. Consequently it is very important to continue work on extending the current follow-up period.

Conclusions

This work has provided evidence in support of a protective effect for prostate cancer mortality from working underground and could be interpreted as support for "The Melatonin Hypothesis". A linear internal excess relative risk model with the number of years worked at high physical activity and the number of days worked underground as explanatory covariables provided a statistically significant fit when compared to the baseline model ($p = 0.039$). Results (with 95% CI) for the *ERR* per day worked underground indicated a statistically significant ($p = 0.0096$) small protective effect at $-5.59(-9.81;-1.36).10^{-5}$. It is this main result that provides the new evidence in support of the protective effect of working underground which is also manifested with respect to the external rates. Additional computations made to examine the influence of biases due to either the healthy worker selection effect or the healthy worker survivor effect indicate that the results are unbiased in these two respects, but the effects of such biases cannot be entirely excluded.

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Figure Captions

Fig 1a The number of prostate cancer deaths in the Wismut cohort as a function of calendar year. The left-hand ordinate and crosses show the simple numbers and the right-hand ordinate and line show the cumulative numbers.

Fig. 1b The number of prostate cancer deaths in the Wismut cohort as a function of age-attained. The left-hand ordinate and crosses show the simple numbers and the right-hand ordinate and line show the cumulative numbers.

Fig 2 The upper panel shows the *ERR* and 95%CI as a function of mean number of years with high PA and corresponds to the risk given in the last column of Table 2. The non-parametric points with 95%CI are adjusted for mean number of days worked underground. The lower panel shows the *ERR* and 95%CI as a function of mean number of days worked underground and corresponds to the risk given in the last column of Table 2. The non-parametric points with 95%CI are adjusted for mean number of years with high PA.

Figures

Figure 1a.

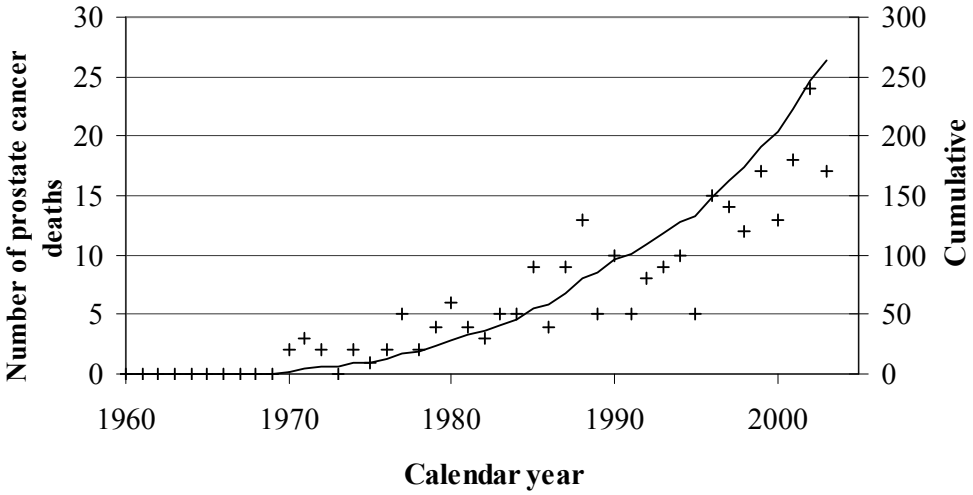


Figure 1b.

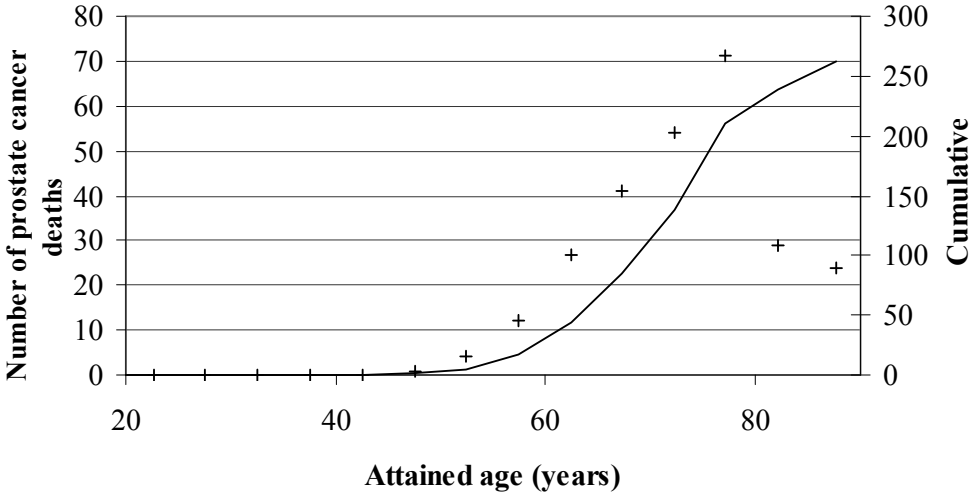
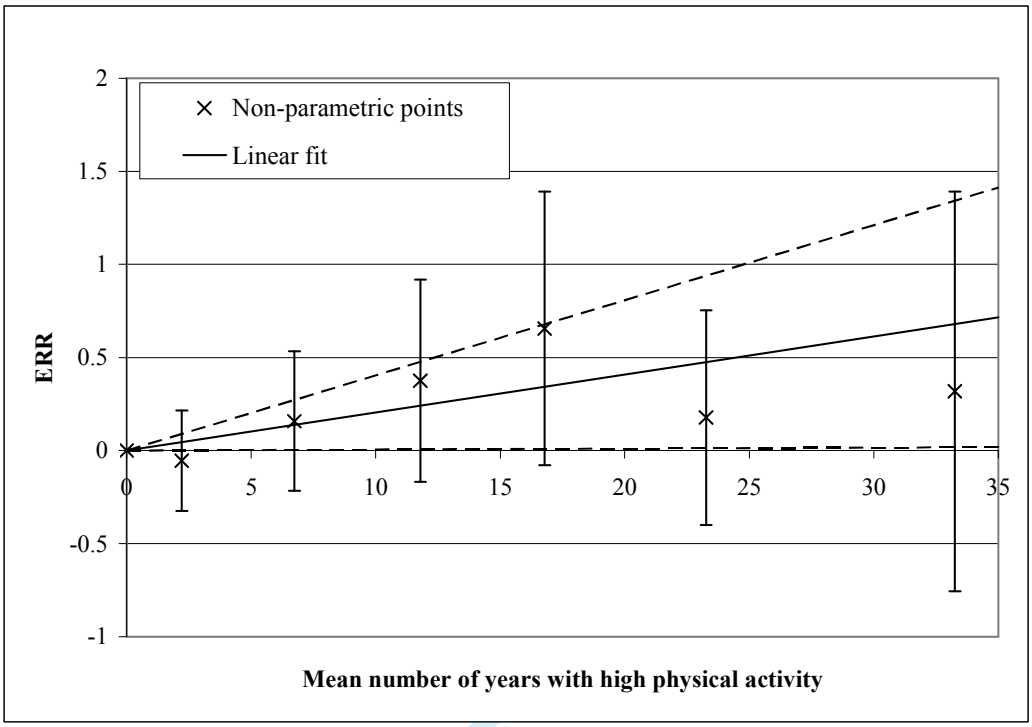


Figure 2.



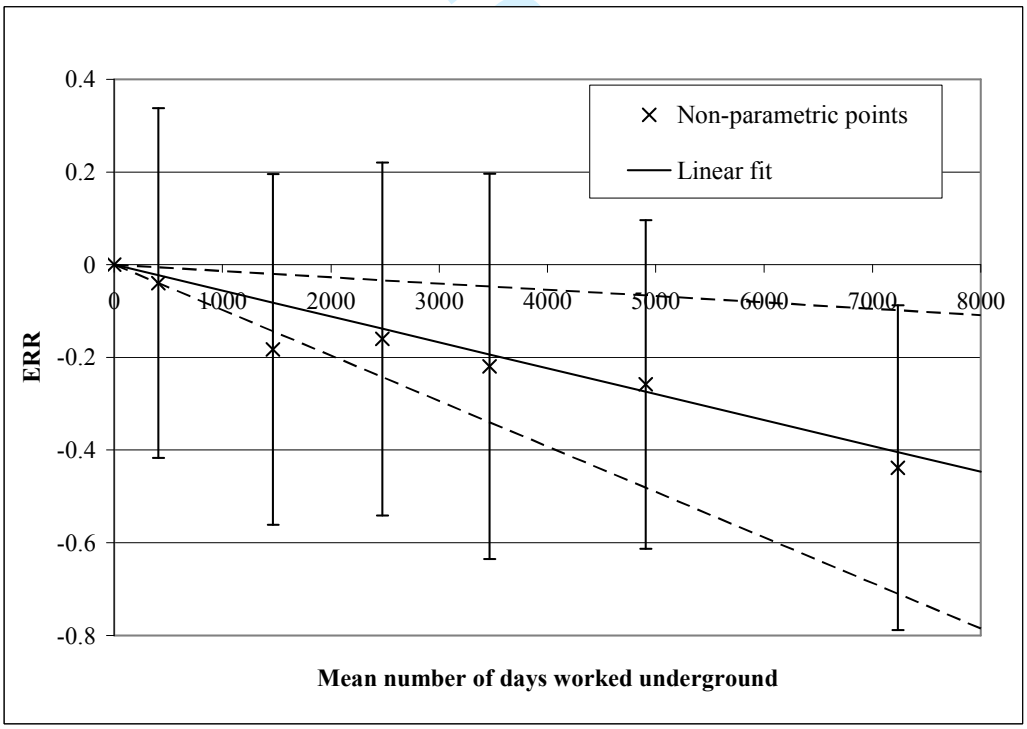


Table 1 Category means and ranges for the number of days worked underground and the number of years worked at high physical activity (PA). In each category the number of deaths from prostate cancer mortality, the number of person-years at risk and the mean prostate gamma dose (with standard deviation) are given.

Category means (and ranges) mean number of days worked underground	**number of prostate cancer deaths**	**number of person-years**	**mean gamma prostate dose** (mGy, with standard deviation)
0	67	360536	1.1 (4.4)
408 (2 – 999.9)	46	429624	7.5 (9.9)
1466 (1000 – 1999.8)	30	184782	24.5 (26.7)
2475 (2000 – 2999.8)	34	139204	42.0 (44.2)
3465 (3000 – 3999.9)	24	97808	68.3 (65.5)
4908 (4000 – 5999.9)	37	138138	111.4 (93.9)
7236 (6000 – 10704)	25	74836	156.9 (127.4)
mean number of years worked at high PA			
0	122	726358	9.8 (28.1)
2.2 (1 – 4)	52	342896	19.2 (33.1)
6.7 (5 – 9)	37	165377	47.0 (46.9)
11.8 (10 – 14)	22	87297	94.5 (73.5)
16.8 (15 – 19)	16	54598	148.3 (94.2)
23.3 (20 – 29)	11	40425	199.4 (123.1)
33.3 (30 – 42)	3	7978	238.3 (163.0)

Table 2 Results of fitting the models. The first and second numerical partitions are for the Standardized Mortality Ratios (*SMR*) (from Eqs. 1 and 2). The third and fourth numerical partitions are for the Excess Relative Risk (*ERR*) internal regression models with baseline stratification on age and calendar year (from Eqs. 3, 4 and 5). Values given in parentheses represent 95% Wald type Confidence Intervals (CI) and the *p*-values represent the statistical significance of the parameter values (and not the statistical significance of model improvement by their inclusion in the model). The p-values are only given if they are less than 0.05. Models that did Not Converge are identified with NC

Covariable name (unit)	**β_2, *ERR*/unit exposure relative to external baseline (i.e. with β_1, fixed at unity)**	**β_1, free, internal to external baseline ratio**	**β_2, *ERR*/unit relative to internal baseline (i.e. with β_1, free)**	**α, *ERR*/unit exposure**	**α_1 α_2 *ERR*/unit exposure**
Gamma (Gy)	NC	0.90 (0.78; 1.02)	-1.27 (-2.4; -0.14) (p = 0.03)	-1.18 (-2.4; 0.02)	
Medium PA (years)	-0.010 (-0.019; -0.001), (p = 0.04)	0.87 (0.74; 0.99)	-0.003 (-0.17; 0.01)	-0.003 (-0.016; 0.011)	
High PA (years)	-0.003 (-0.016; 0.010)	0.81 (0.69; 0.93)	0.01 (-0.01; 0.03)	0.013 (-0.008; 0.033)	α_1 = 0.021 (0.001; 0.040) (p = 0.04)
Underground work (10^5days)	-4.44 (-7.11; -1.76) (p = 0.001)	0.93 (0.78; 1.08)	-3.30 (-7.20; 0.06)	-3.07 (-7.12; 0.99)	α_2 = -5.59(-9.81;-1.36) (p = 0.01)

Table 3 Results of applying Model selection techniques with the likelihood ratio test for variable selection. The changes in degrees of freedom (*d.f.*) and deviance are all with respect to the stratified baseline model which had a deviance of 3178.9 for a *d.f.* of 555433. *g, mpa, hpa, u* and *a* represent gamma organ dose, years at medium PA, years at high PA, days worked underground and age attained respectively. The top section represents a sub-set of seven models (preferred model in bold) from a complete sorted list of all models tested, for which the probability of model improvement with respect to the stratified baseline model had a *p*-value under 0.10. The lower section represents the model selection results for all 4 models with single exposure covariables – none of which resulted in a statistically significant model improvement when compared to the baseline model.

Covariables in model, form			**Δ *d.f.***	**Δ deviance**	***p*-value**
u, linear	***hpa, linear***		***2***	***6.47***	***0.039***
u, linear	*mpa*, linear	*hpa*, linear	3	7.25	0.064
u, linear	*hpa*, linear	*a*, exponential	3	7.23	0.065
u, linear	*hpa*, linear	*a*, power	3	7.15	0.067
u, linear	*hpa*, linear	*hpa,* squared	3	7.06	0.070
u, linear	*u*, squared	*hpa*, linear	3	6.75	0.080
u, squared	*hpa*, linear		2	5.04	0.080
	ERR/unit exposure (SE)				
g, linear	$-1.2\ (0.6).10^{-3}$		1	2.61	0.107
u, linear	$-3.1\ (2.1).10^{-5}$		1	1.88	0.171
hpa, linear	$1.3\ (1.1).10^{-2}$		1	1.61	0.204
mpa, linear	$-2.8\ (7.0).10^{-3}$		1	0.15	0.697

Prostate cancer mortality risk in relation to working underground in the Wismut cohort study of German uranium miners, 1970-2003

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Keywords:	EPIDEMIOLOGY, Epidemiology < ONCOLOGY, Prostate disease < UROLOGY

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) The study's cohort design is indicated in the title, page 1
		(*b*) An informative and balanced summary of what was done and what was found has been provide in the abstract
Introduction		
Background/rationale	2	The scientific background and rationale for the investigation being reported has been explained, page 4
Objectives	3	Specific objectives, including any prespecified hypotheses, have been stated, page 4
Methods		
Study design	4	Key elements of study design have been presented early in the paper, page 5-7
Setting	5	The setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection have been described, pages 4 & 8
Participants	6	(*a*) *Cohort study*—The eligibility criteria, and the sources and methods of selection of participants have been cited and described on page 4. Methods of follow-up have been cited and described on page 4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed – No matching was performed *Case-control study*—NOT APPLICABLE
Variables	7	All outcomes, exposures, predictors, potential confounders, and effect modifiers have been defined, page 6. Diagnostic criteria, in terms of ICD codes are given on page 5
Data sources/ measurement	8*	For each variable of interest, sources of data and details of methods of assessment (measurement) are give on page 4 & 6
Bias	9	Efforts to address potential sources of bias are given in the discussion section, page 12
Study size	10	Explanations on how the study size was arrived at are cited on page 4
Quantitative variables	11	Explanations of how quantitative variables were handled in the analyses are given on pages 6 & 7.
Statistical methods	12	(*a*) All statistical methods, including those used to control for confounding are described, pages 6 & 7
		(*b*) Any methods used to examine subgroups and interactions are described on pages 6 & 7
		(*c*) Missing data were addressed on page 5
		(*d*) *Cohort study*—Loss to follow-up was addressed in the citations on page 4
		(*e*) Sensitivity analyses were not relevant.

Continued on next page

Results		
Participants	13*	(a) Numbers of individuals at each stage of study (i.e. person-years at risk) are reported on in table 1
		(b) Give reasons for non-participation at each stage – NOT RELEVANT
		(c) Consider use of a flow diagram – NOT RELEVANT
Descriptive data	14*	(a) Characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders are given, in tables 1&2
		(b) Number of participants with missing data for each variable of interest is indicated by the overall "Percentage of Missing Causes of Death" on page 5
		(c) *Cohort study*—Follow-up time (eg, average and total amount) has been given on page 8
Outcome data	15*	*Cohort study*—Numbers of outcome events or summary measures over time are reported in figure 1
		Case-control study—NOT APLICABLE
		Cross-sectional study— NOT APLICABLE
Main results	16	(*a*) Unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval) are given in table 2. table 2 makes clear which confounders were adjusted for and why they were included.
		(*b*) category boundaries when continuous variables were categorized were already reported in the methods section, page 6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period – this was not possible due to limitations in the methodology (i.e. Poisson Regression with a stratified baseline model)
Other analyses	17	Other analyses done—eg analyses of subgroups and interactions, are reported in table 3
Discussion		
Key results	18	Key results with reference to study objectives are summarised on page 10
Limitations	19	Limitations of the study, taking into account sources of potential bias or imprecision are discussed on pages 10, 11 & 12. Direction and magnitude of any potential bias are discussed on page 12.
Interpretation	20	A cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence is given in the conclusions section.
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	The source of funding and the role of the funders for the present study on which the present article is based are given in the "Acknowledgement" at the end of the paper.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Original paper

Linda Walsh, Florian Dufey, Annemarie Tschense, Maria Schnelzer, Marion Sogl & Michaela Kreuzer.

Prostate cancer mortality risk in relation to working underground in the Wismut cohort study of German uranium miners, 1970-2003

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Abstract

Objective: A recent study and comprehensive literature review has indicated that mining could be protective against prostate cancer. This indication has been explored further here, by analysing prostate cancer mortality in the German "Wismut" uranium miner cohort which has detailed information on the number of days worked underground.

Design: An historical cohort study of 58,987 male mine workers with retrospective follow-up before 1999 and prospective follow-up since 1999.

Setting and participants: Uranium mine workers employed during the period 1970-1990 in the regions of Saxony and Thuringia, Germany, contributing 1.42 million person years of follow-up ending in 2003.

Outcome measure: Simple Standardised Mortality Ratio (*SMR)* analyses were applied, to assess differences between the national and cohort prostate cancer mortality rates, and complemented by refined analyses done entirely within the cohort. The internal comparisons applied Poisson regression excess relative prostate cancer mortality risk model with baseline stratification by age and calendar year and a whole range of possible explanatory covariables that included days worked underground, years worked at high physical activity with gamma radiation treated as a confounder.

Results: The analysis is based on miner data for 263 prostate cancer deaths. The overall *SMR* was 0.85 (95% CI 0.75; 0.95). A linear excess relative risk model with the number of years worked at high physical activity and the number of days worked underground as explanatory covariables provided a statistically significant fit when compared to the baseline model (p=0.039). Results (with 95 % confidence intervals) for the *ERR* per day worked underground indicated a statistically significant (p=0.0096) small protective effect of $-5.59(-9.81;-1.36).10^{-5}$.

Conclusions: Evidence is provided from the German Wismut cohort in support of a protective effect from working underground on prostate cancer mortality risk.

Introduction

Prostate cancer is the second most common cancer diagnosed among men (after lung cancer), and is the sixth most common cause of cancer death among men world-wide [1]. In the European Union in 2006, prostate cancer was the most common form of incident cancer and the third most common form of cancer death in men (Table 3 of [2]). Prostate cancer incidence in Germany has also become the most common form of incident cancer disease in men. It is notable that the prostate cancer mortality rates were approximately constant in the former eastern German Democratic Republic (GDR) between 1960 and 1980, but rose during the same time by 50% in West Germany [3].

Prostate cancer is, in general, a slow-growing tumour with a long latency and an uncertain aetiology. The prevalence of latent microscopic prostate tumours has been shown to be quite high in the elderly in most populations i.e. at least 50 percent in men over the age of 70 years [4]. Although there are only a few established risk factors for prostate cancer such as age, race and a family history of prostate cancer [5] there are also several mooted detrimental and protective associations.

The possible detrimental associations include early baldness [6], shift-work [7], arsenic exposures [8], diesel fume exposure [9] and oestrogen exposures [10]. Some evidence exists for radiation related prostatic detrimental effects from studies on patients after diagnostic radiation procedures [11], occupationally exposed British nuclear workers [12], military and civil pilots and flight attendants [13], and persons exposed by the Chernobyl accident [14]. There was little evidence of a prostate cancer risk radiation dose response in the Japanese A-bomb survivors [15]. A recent meta-analysis of 24 cohort studies has concluded that an association of smoking with prostate cancer incidence and mortality exists [16].

The possible protective associations include high sexual and/or androgenic activity [17], UV and/or vitamin D [18], high Physical Activity (PA) [19] - although some inconsistent results are observed for PA - and melatonin [20-23]. For a cohort of U.S.A. male health professionals, [24] reported that for fatal prostate cancer, a recent smoking history, taller

height, higher BMI, family history, and high intakes of total energy, calcium and α-linolenic acid were associated with a statistically significant increased risk but higher vigorous PA level was associated with lower risk.

A recent Australian population-based case-control study and literature review [25] has indicated that mining could be protective against prostate cancer. [25] concluded that the relationship between mining and prostate cancer could possibly be connected to levels of either PA or changes in melatonin production caused by periods working underground and that these relationships deserve further investigation. Differential risk could not be reported in [25] because all but one of the studies reviewed did not report on working periods underground and over ground. The main purpose of the present paper is to explore these indications further by analysing prostate cancer mortality risk in a cohort of male mine workers involved in uranium extraction at the former Wismut company in East Germany applying both external (national male rates for the former GDR) and internal baselines. New covariables for occupational PA and time spent underground have been specially created for this investigation. Simple *SMR* analyses are complemented by refined analyses done entirely within the cohort.

The German "Wismut" uranium mine workers cohort has currently been followed-up from 1.1.1946 to 31.12.2003, with almost 2 million person-years of observation and has already been described in detail [26]. It is currently the largest miners cohort study and several analyses of the detrimental health effects data pertaining to the 58,987 male former employees, have recently been published [27-33].

There are several occupational risk factors for detrimental health effects, relevant to the cohort members, particularly with respect to lung cancer, including exposure to radon, gamma radiation, long-lived radionuclides, [34], fine dust, arsenic dust and quartz dust [35], asbestos [36] and diesel exposure. However exposure covariables for the latter two quantities are not available in the cohort data. Previous analyses have shown that the mortality from prostate cancer in this cohort (1960-2006) is notably lower than in the comparison population of the former GDR (*SMR* = 0.88, 95%CI = 0.78; 1.00 [27]). The total absorbed dose to the prostate has not yet been calculated. However since the absorbed dose to non-respiratory track organs is dominated by external gamma radiation and the contributions of radon progeny, radon gas and particularly long-lived radionuclides are expected to be only a few percent [37], only the

gamma radiation is explicitly considered here, as a potential confounder. The effective gamma doses have been converted into prostate organ dose via Voxel model dose conversion factors [38].

Material and Methods

Cohort definition, time periods and mortality follow-up.

Full details of the cohort have already been given [28, 30]. Every cohort member contributes to the number of person years starting 180 days after the date of first employment and ending at the earliest of date of loss to follow-up, date of death, or end of follow-up (31.12.2003). Due to the relatively high Percentage of Missing Causes of Death (PMCD) of 37.25% and the systematic variation of PMCD with calendar time from 1946 to 1969, the analyses here are based on the subset of Wismut miner cohort data covering the period 1970-2003 for which the PMCD is 3.56%. Consequently, no corrections for missing causes of death have been made. This difference in PMCD is due to the late start of data collection for this cohort on 1.1.1999, linked with the fact that death certificates were rarely kept by the authorities for more than 30 years.

National rates for the former GDR covering the same calendar-year range are applied for the external comparisons. Former disease codes of the comparison external baseline rates for the GDR were re-coded via earlier ICD revisions to the 10th ICD-code [39], which was applied throughout. This recoding process was complicated by several revisions to ICD codes during the period of data coverage, and German reunification. Population prostate cancer rates are not available just for the relevant mining region of Thuringia and Saxony. Consequently, the external rates applied here cover the total area of the former GDR (including East-Berlin) during the time period 1970–1997; in contrast, from 1998 the rates pertain to the former GDR states and the whole of Berlin. The codes used here in the various time periods are as follows: 1970–1978 ICD 8, code number 185; 1979 ICD 8, code number 179-189 for the urogenital system; 1980–1997 ICD 9, code number 185; 1998–2003 ICD 10, code number C61 all for Prostate cancer.

Analysis.

The Poisson regression methods applied here require the tabulation of the individual data as described below and in previous analyses [30-32]. Poisson regression is a likelihood based method for the quantitative analysis of event-time tables [40]. Quantitative risk evaluation methods were based on the simple *SMR* model, considered both with and without an exposure response to various possible explanatory covariables, for external comparisons and comparisons just within the cohort. The more refined analysis entirely within the cohort (internal comparisons) applied Poisson regression excess relative prostate cancer mortality risk model with baseline stratification by age and calendar year and a whole range of possible explanatory covariables: age (*a*), year (*y*), gamma prostate dose (*g*), years at medium Physical Activity (PA) (*mpa*), years at high PA (*hpa*), days worked underground (*u*) and time since either first or last underground shift (*t*).

Data Tabulations.

Tabulations of person-years at risk and cancer deaths were created with the DATAB module of the EPICURE software [41] for the whole cohort data (1946-2003), so that the covariables of interest could be accumulated from the beginning of the cohort. The period of interest here was then selected to be 1970-2003 during the data-analysis and model fitting procedures. Cross-classifications were made by attained age, *a*, in 16 categories (<15, 15–<20, 20–<25, … , 85+ years), individual calendar year, *y*, in 58 categories, and cumulative gamma prostate doses, with a five-year lag-time (8 categories: 0, >0–<50, 50–<100, 100–<150, 150–<200, 200–<300, 300–<400, 400+ mGy). For the current analysis new covariables for occupational PA and time spent underground have been specially created. Exact shift information relating to daily underground and overground activities in each calendar year was used. The number of days worked underground in any one calendar year was then accumulated over calendar year in 8 categories (0, >0–<1000, 1000–<2000, 2000–<3000, 3000–<4000, 4000–<5000, 5000–<6000, 6000+ days). For the PA categories, information on the job type in each calendar year was extracted from the Wismut records. Each of the several hundred job types had already been classified into three levels of PA corresponding to different breathing rates for the purpose of organ dose calculations e.g. job types hewer, metal worker and lorry driver were classified as high, medium and low PA respectively. The number of years worked in each of the high and medium PA classes were then accumulated over calendar years of employment, each in 8 categories (0, >0–<5, 5–<10, 10–<15, 15-<20, 20–<25, 25–<30, 30+ years). Choice of units (years or days) reflects the quality of the information available in the mining records.

Standardized Mortality Ratios.

Mortality rates observed in the cohort were compared with the GDR external rates. The first stage of the *SMR* analysis for prostate cancer has been done as described previously for extra–pulmonary cancers [28] with some extensions that allow a comparison of internal (miner cohort) and external (former GDR) baseline (spontaneous) rates. Justifications for the generally preferable internal comparison (done entirely within the cohort), connected with differences in the maturity of the smoking epidemic between the cohort and the GDR, have recently been given [32]. The simplest *SMR* model relates the rates in the population of interest (the miner cohort) to a multiple of the rates from the external population (the former GDR).

If $\lambda^*(a, y)$ denotes the external rates as a function of age and calendar year and $\lambda(a, y)$ denotes the observed rates in the miners cohort, then the *SMR* model can be written as

$$\lambda(a, y) = \beta \cdot \lambda^*(a, y) \quad (1)$$

where the β is a fit parameter and represents the *SMR*.

However it is also possible to fit a relative risk (*RR*) model

$$RR(a, y, g) = \beta_1 \cdot \lambda^*(a, y) \cdot (1 + \beta_2 (g)) \quad (2)$$

to estimate the effects of various possible explanatory covariables, such as gamma prostate dose (g), based on the GDR external rates, assuming that the *SMR* for the background rates is identically equal to 1, i.e. β_1 is fixed to unity during the optimisation. In this case, β_2 is a fit parameter that then gives the simple Excess Relative Risk (*ERR*) per unit of exposure relative to the external GDR rates. It is also possible to test if the external GDR rates are different from the internal baseline rates in the miner cohort by simply freeing the parameter β_1 and repeating the optimisation. All of the parameters β, β_1 and β_2 can be multiplied by a two level categorical variable for either levels of PA or time spent underground.

Refined *ERR* models with baseline stratification by age and calendar year were employed – if $r(a, y, g, mpa, hpa, u, t)$ is the prostate cancer mortality rate and $r_0(a,y) = r(a,y,0,0,0,0,0)$ is the baseline disease rate for non-exposed individuals, $g = 0$, $mpa = 0$ …etc. then

$$R(a, y, g, mpa, hpa, u, t) = r_0(a, y) \cdot \{1+ERR(g, mpa, hpa, u, a, t)\}, \quad (3)$$

where *ERR* is the excess relative risk factorised into a function of exposure, f(*g, mpa, hpa, u*) and a modifying function, h(*a, t*):

$$ERR(g, mpa, hpa, u, a, t) = f(g, mpa, hpa, u) \cdot h(a, t) \quad (4)$$

The gamma prostate dose, years at medium PA, years at high PA and days worked underground were each included:

singularly, $f(g) = \alpha\, g$, etc, and pair-wise $f(g, mpa) = \alpha_1\, g + \alpha_2\, mpa$, etc. (5)

in the linear *ERR* model, both with and without the modifying function, and assessed with model selection techniques to arrive at the model with the lowest deviance with respect to the baseline model, by forward selection. Backwards selection was also tested. Finally the preferred linear model was tested for non-linearity, by adding quadratic terms for exposure covariables, and time or age effect modification (i.e. adding g(*a, t*) functions to the model).

Maximum likelihood with the AMFIT module of the EPICURE software [41] was used for estimation of the *SMR* and *ERR* fit parameters associated with equations 1 to 5 above. Confidence Intervals (CI) were computed at the 95% level and the Wald type CI are given since, although very similar intervals were found with the profile likelihood based CIs, some of the lower limits could not be numerically calculated with the latter method.

Results

Out of the total 58,987 cohort members in the complete follow-up period between 1946 and 2003, 55,435 members were included in the follow-up from 1970 specifically considered in the risk analysis presented here. In total, 20,920 persons were deceased (of which 1,560 died before 1970), 35,294 were alive and 2,773 were lost to follow-up (of which 1,992 were lost before 1970). There were 263 prostate cancer deaths observed during 1.42 million person years of observation between 1970 and 2003. The cumulative numbers of observed and expected prostate cancer deaths in this period are shown in Figures. 1a and 1b as a function of calendar year from 1970 and age attained from 40 years. The absolute number of prostate cancers occurring reaches a maximum in the category 75 to 80 years of age, due to the age distribution in the cohort, and increases steadily from 1970 to 2003 and the cumulative number of prostate cancers increases as a function of age attained and calendar year.

The mean values (and ranges) of age-attained, mean number of days worked underground and mean number of years worked at high PA are 47 (14-103) years, 1649 (0-10704) days and 3.5 (0-44) years respectively. Table 1 gives the category specific values for the number of prostate cancer deaths and person-years, for the number of years worked at high PA and days spent underground categories of mine workers.

***SMR* results (comparison of cohort rates with external rates, Eq 1).**

The number of deaths (1970–2003) observed (O), was significantly lower ($p < 0.001$) than expected (E) from national rates. The *SMR* value with 95% confidence intervals (CI) is 0.85 (0.75; 0.95). Quantitative differences between GDR external rates and internal cohort rates can be assessed directly from a categorical *SMR* analysis in categories of attained-age and calendar year. Some statistically significantly low categorical *SMR* values were found mainly in the age group 65 to 75 years, and in the calendar period from 1991 to 1995 (results not shown). The overall *SMR* with 95% confidence intervals when recomputed by two categories of below and above mean time spent underground (1649 days) becomes 0.92 (0.76; 1.07) and 0.79 (0.65; 0.92) respectively. The *SMR* recomputed by two categories of below and above mean time worked at high PA (3.52 years) becomes 0.82 (0.69; 0.94) and 0.91 (0.73; 1.10) respectively.

Simple *ERR* parametric cohort risk models (comparison of cohort rates with external rates, Eq 2).

Cumulative exposure effects for various covariables in terms of *ERR* per unit exposure and 95% CIs are given in the first results column of Table 2. The *ERR*/day worked underground, relative to the external GDR rates, is -4.44 (-7.11; -1.76).10^{-5} and was found to be the statistically strongest exposure effect (p = 0.001) i.e. decreased for the number of days worked underground relative to the external rates. A similar value of -3.3 (-7.2; 0.06) .10^{-5} relative to the internal controls was found (Table 2, second results column), although of reduced statistical significance (p = 0.097). This latter result is connected with a baseline SMR of 0.93 (0.78; 1.08) (Table 2, second results column). The *SMR* model did not converge (NC) for the gamma prostate dose relative to the external baseline rates. A statistically significant (p-value = 0.03) decreased *ERR*/Gy for prostate gamma doses, relative to the internal baseline of -1.27 (-2.4; -0.14) was also found (Table 2, second results column).

Refined *ERR* parametric cohort risk models (Eqs 3-5).

The statistical significance of *ERR*/Gy for prostate gamma doses reported with the simple analysis was not confirmed by the refined analysis (*ERR*/Gy=-1.18 (-2.4; 0.02), see table 2, third results column). Although the coefficient for gamma dose was of borderline statistical significance in the univariate model, the forward selection did not keep the gamma prostate dose in the multivariate model. A preferred model by forward selection of the covariables gamma prostate dose, *g*, years at medium PA, *mpa*, years at high PA, *hpa* and days worked underground, *u* taken linearly one or two at a time was found to be the model that included both *hpa* and *u* (Table 3). This model had a reduction in deviance with respect to the stratified baseline model of 6.5, ($p = 0.04$) by the Likelihood Ratio test. This model provided the results in the last column of table 2, (with 95 % confidence intervals) for: the *ERR* per day worked underground, which indicates a statistically significant (p=0.01) small decreased effect of $-5.59(-9.81;-1.36).10^{-5}$ and; for the *ERR* per year worked at high physical activity, which indicates a statistically significant (p = 0.04) small detrimental effect of 0.021 (0.001; 0.040). The clinical significance of the results can be assessed by obtaining the number of deaths from prostate cancer prevented in this cohort from working underground, obtained from the fitted background and fitted excess number of cases in the preferred model. Depending on whether the slightly increased risk from high physical activity is accounted for or not, this number is either 14 or 22 prostate cancer deaths respectively.

Models that included just *hpa* or just *u* did not result in statistically significant risks (Table 2, third results column) or lead to statistically significant model improvement (Table 3). No evidence for an interaction between *hpa* and *u* was indicated by including a cross term in the preferred model (p>0.5). Testing of the quadratic or parabolic forms for *hpa* and *u* or testing risk effect modification by attained age (Table 3) or time since first or last underground shift (results not shown) did not lead to statistically significant model improvement. The dose response forms for the preferred model and the adjusted non-parametric risks with 95% confidence intervals are shown in Figure 2. It was not possible to confirm this result by backwards selection since the models with all 6 main covariables failed to converge.

Discussion

The Wismut cohort is one of the largest single occupational cohorts and one of only a few cohorts with detailed information on the number of shifts worked underground. Although the number of shifts was documented, it is not known if these were early morning, day-time or

night shifts. A substantial proportion (25%) of person-years are contributed by mine workers who did not work underground which generally ensures the stability of analyses based on internal rates. The *ERR* per unit of various exposures have been modelled relative to the internal rates and relative to the external rates for the general population of the former GDR.

A statistically significant (p = 0.001) negative response for the *ERR* per day worked underground, when modelled in relation to the general population of the former GDR, is reported here. There are some indications of unit exposure responses of the *ERR* which are decreased for gamma prostate dose, (p= 0.03 and 0.055 for the simple and refined models respectively) with respect to the internal rates. Rather than being decreased, the gamma dose is a possible proxy variables for the number of days worked underground since there are moderate degrees of correlations between these covariables (ρ = 0.68 for the correlation between time dependent cumulative gamma prostate doses and the number of days worked underground, see also table 1). Indication that the gamma dose may be acting as a proxy was tested here directly by the creation of new categories of mine workers, with numbers of years worked at high or medium PA and the number of days worked underground and the application of model selection techniques.

The assumption is made in this paper that radon and long-lived radionuclides make only minor contributions to the total prostate dose. Previous analyses have shown that the *ERR* per 100 WLM of radon exposure, based on internal Poisson models, was not elevated for prostate cancer (*ERR*/100 WLM= 0.000, 95%CI, -0.024; 0.024, [31]). None of the radiation covariables (i.e. gamma prostate dose, but also including long-lived radionuclides and radon), when tested by inclusion singularly as linear risks in refined internal Poisson regression models, resulted in a deviance drop of more than 3 with respect to the baseline model which was stratified on age-attained and calendar year.

A linear excess relative risk model with the number of years worked at high physical activity and the number of days worked underground as explanatory covariables provided a statistically significant fit when compared to the baseline model (p = 0.039). Results (with 95% CI) for the *ERR* per day worked underground indicated a statistically significant (p = 0.01) small decreased effect at $-5.59(-9.81;-1.36).10^{-5}$ and, for the *ERR* per year worked at high physical activity, a statistically significant (p = 0.04) small detrimental effect at 0.021 (0.001; 0.040). This main result provides new evidence in support of the decreased effect of working underground which is manifested with respect to the internal and the external rates.

The number of days worked underground is connected with a particular hypothesis for reduced prostate cancer rates e.g. melatonin production rates (as described in detail in [25] and references therein). In summary, melatonin has been shown to have anti-cancer properties acting through several mechanisms [20-23]. The production of melatonin in the pineal gland is regulated by the natural diurnal light-level cycle, with suppressed production during the day which is restored at night. Underground miners on day shifts would have a reduced exposure to visible light leading to an extended melatonin production period.

The relation between physical activity and prostate cancer risk was classified as "probable" with respect to an increased risk, by the IARC in 2002 [42] but no definite mechanisms have been identified for a relation between PA and prostate cancer. Several plausible mechanisms have been postulated which include modulation of testosterone and vitamin D levels by PA, a link between physical inactivity and over-weight/obesity and a beneficial modulation of immune function through exercise (see [43] for a review). A recent systematic review and meta-analysis [44] considered 13 studies with occupational physical activity, considered to be "higher-quality" studies and reported that 9 studies gave a decreased risk, one study an increased risk and 3 studies reported no association. Two other studies have reported increased risks: [45] found that intensity of occupational PA was associated with increased prostate cancer risk and [46] reported an increased risk for obese men (BMI over 30) who were physically active for more than 1 hour per day and in men with high baseline energy intake.

A statistically significant increase in risk with increasing high PA is observed here, in contrast to the IARC classification and the majority of other studies. It is important to note that the variable physical activity here measures only part of the total PA and could be prone to misclassification. The PA variable is limited to the work period at the Wismut company (the mean duration of work at the company 14 years) and no leisure time activities could be considered. The classification is simply based on job type without consideration of possible changes in physical activity in a specific job over time e.g. due to improved technical "labour-saving" equipment. Physical activity could also be an indicator of socioeconomic status, because the jobs with low PA are more likely to be associated with higher education.

Another possible source of bias in the results based on external comparisons that should be considered is the selection bias known as the healthy worker effect. However this effect, which can generally lead to occupational cohorts presenting mortality risks less than the general population, is not indicated since the risks are similar with respect to internal and external baselines. The occurrence of this form of bias could also be tested here by considering all solid cancer minus the sites that have already been linked to the main mine radiation exposure, i.e. radon (lung, larynx, tongue, mouth and pharynx). For this group of cancers the *SMR* with 95%CI is 1.01 (0.97; 1.04) also indicating that the healthy worker effect is not having a significant influence on the prostate cancer results in this cohort.

A further source of bias, possibly affecting the decrease in risk with increasing duration of working underground based on internal comparisons, could be the healthy worker survivor effect. Unhealthy workers may move from working underground to working at the surface. Consequently, the duration of working underground may be higher in the healthy group compared to the unhealthy group, leading to artificially decreased effects in relation to duration of working underground. However this effect has been tested for by fitting the preferred model, that included both the number of days worked underground and number of years worked at high physical activity, to the sub-group of all solid cancers minus the sites that have already been linked to the main mine radiation exposure (lung, larynx, tongue, mouth and pharynx) and minus prostate. No significant trends were found ($p>0.5$ for the linear trend of ERR with respect to the number of days worked underground and $p=0.11$ for the linear trend of ERR with number of years worked at high physical activity) indicating that the healthy worker survivor effect is not directly biasing the results for prostate cancer.

Although there is no general consensus as to whether radiation exposure is associated with prostate cancer risk [47], an X-ray procedure risk doubling dose of about 20 mGy for prostate cancer incidence has been reported [11]. The magnitudes and ranges of the gamma prostate organ doses in the Wismut study (with the prostate cancer mortality cases having a range up to 444 mGy) should be large enough to find such an increased risk at the 20 mSv level given the similar relative biological effect of X-rays and gamma rays. However, a gamma risk, at this 20 mSv level, has not been found in the Wismut cohort data for prostate cancer mortality.

Yang et al [8] reported that *SMR*s for prostate cancer declined gradually in a SW costal district of Taiwan after the arsenic contaminated artesian well drinking-water supply was

improved to a tap-water system. Since arsenic dust exposures are also available for the Wismut miners [35], an arsenic covariable could be added to the preferred model for physical activity and time worked underground described above in a subsidiary analysis, but this only resulted in a deviance drop of 1.2 and a p-value of 0.33 for the associated arsenic risk coefficient and did not confound the main risks from the preferred model.

An examination of the effects of smoking on the risk of prostate cancer mortality, as indicated in [16] could not be carried out for the Wismut cohort due to only a very limited amount of information on smoking being available [29].

Although there were 264 prostate cancer deaths in the whole cohort, only one occurred before 1970 i.e. during the period with a higher percentage of missing causes of death. This is consistent with prostate cancer generally being a type of cancer that occurs predominantly in old-age coupled with the observation that – due to miners entering and leaving the cohort at various points in time during the follow-up period – the cohort aged, on average, at half the rate of any individual, i.e. in 1960 and 2003 the mean ages of cohort members were 35 and 57 years respectively. Consequently it is very important to continue work on extending the current follow-up period.

Conclusions

This work has extended the evidence in support of a decreased, possibly protective, effect for prostate cancer mortality from working underground provided in [25] and could be interpreted as support for "The Melatonin Hypothesis". A linear internal excess relative risk model with the number of years worked at high physical activity and the number of days worked underground as explanatory covariables provided a statistically significant fit when compared to the baseline model ($p = 0.039$). Results (with 95% CI) for the *ERR* per day worked underground indicated a statistically significant ($p = 0.0096$) small decreased, possibly protective, effect at $-5.59(-9.81;-1.36).10^{-5}$. It is this main result that provides the new evidence in support of the protective effect of working underground which is also manifested with respect to the external rates. Additional computations made to examine the influence of biases due to the gamma doses, the healthy worker selection effect and the healthy worker survivor effect indicate that the results are unbiased in these respects, but the effects of such biases cannot be entirely excluded.

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Figure Captions

Fig 1a The cumulative number of prostate cancer deaths observed in the Wismut cohort and expected from GDR rates as a function of calendar year.

Fig. 1b The cumulative number of prostate cancer deaths observed in the Wismut cohort and expected from GDR rates as a function of age-attained..

Fig 2 The upper panel shows the *ERR* and 95%CI as a function of mean number of years with high PA and corresponds to the risk given in the last column of Table 2. The non-parametric points with 95%CI are adjusted for mean number of days worked underground. The lower panel shows the *ERR* and 95%CI as a function of mean number of days worked underground and corresponds to the risk given in the last column of Table 2. The non-parametric points with 95%CI are adjusted for mean number of years with high PA.

Figures

Figure 1a.

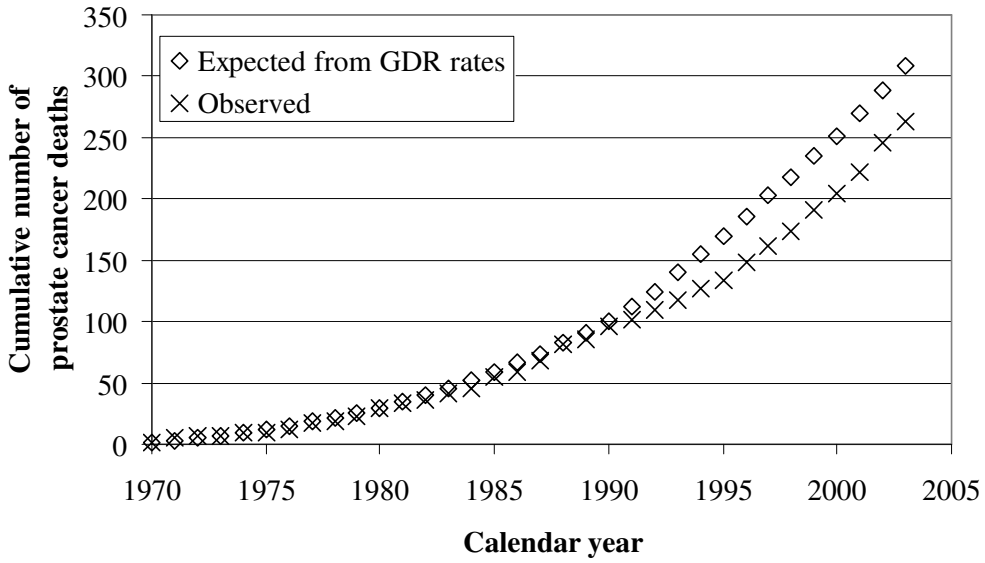


Figure 1b.

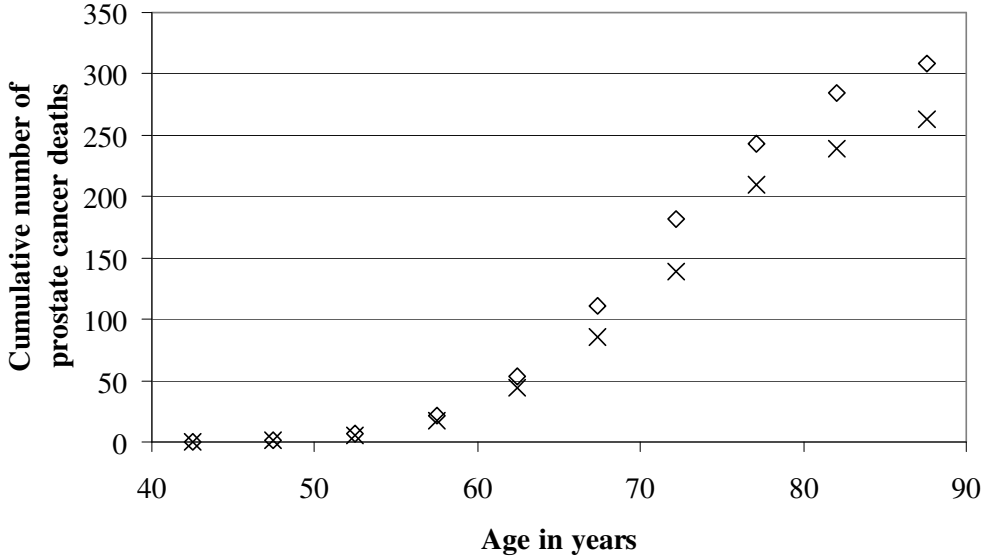
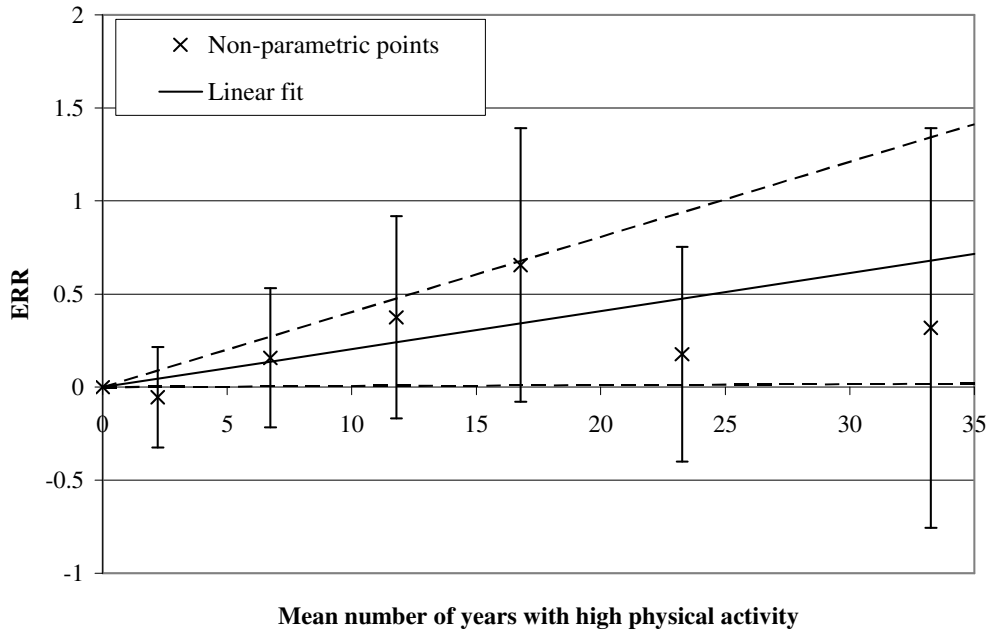


Figure 2.



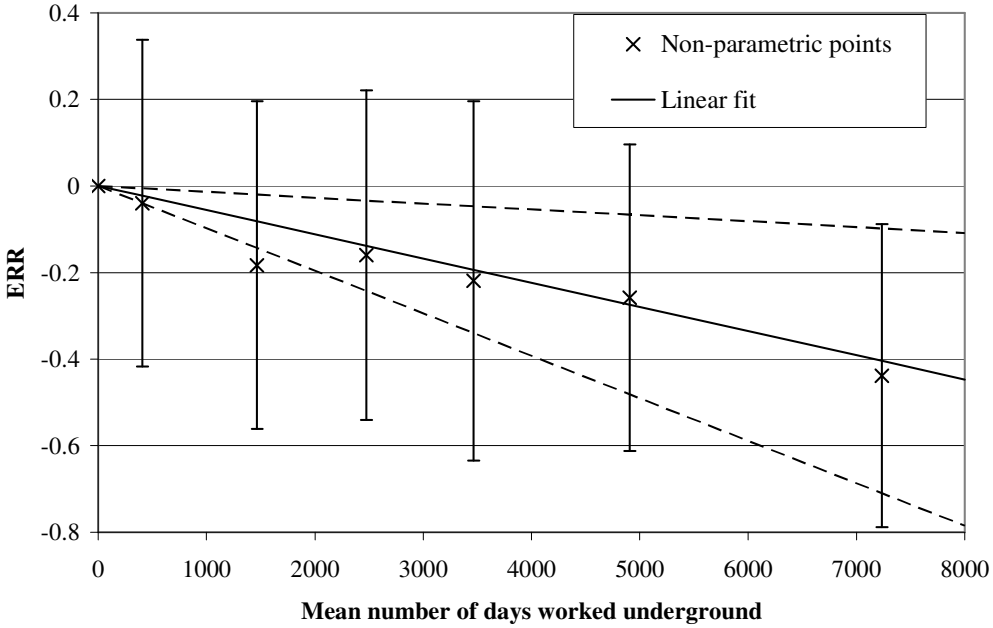


Table 1 Category means and ranges for the number of days worked underground and the number of years worked at high physical activity (PA). In each category the number of deaths from prostate cancer mortality, the number of person-years at risk (rounded) and the mean cumulative person-year weighted gamma prostate dose (with standard deviation) are given.

Category means (and ranges) mean number of days worked underground	**number of prostate cancer deaths**	**number of person-years**	**mean gamma prostate dose** (mGy, with standard deviation)
0	67	360536	1.1 (4.4)
408 (2 – 999.9)	46	429624	7.5 (9.9)
1466 (1000 – 1999.8)	30	184782	24.5 (26.7)
2475 (2000 – 2999.8)	34	139204	42.0 (44.2)
3465 (3000 – 3999.9)	24	97808	68.3 (65.5)
4908 (4000 – 5999.9)	37	138138	111.4 (93.9)
7236 (6000 – 10704)	25	74836	156.9 (127.4)
mean number of years worked at high PA			
0	122	726358	9.8 (28.1)
2.2 (1 – 4)	52	342896	19.2 (33.1)
6.7 (5 – 9)	37	165377	47.0 (46.9)
11.8 (10 – 14)	22	87297	94.5 (73.5)
16.8 (15 – 19)	16	54598	148.3 (94.2)
23.3 (20 – 29)	11	40425	199.4 (123.1)
33.3 (30 – 42)	3	7978	238.3 (163.0)

Table 2 Results of fitting the models. The first and second numerical partitions are for the Standardized Mortality Ratios (*SMR*) (from Eq 2). The third and fourth numerical partitions are for the Excess Relative Risk (*ERR*) internal regression models with baseline stratification on age and calendar year (from Eqs. 3, 4 and 5) for the univariate and multivariate models respectively. Values given in parentheses represent 95% Wald type Confidence Intervals (CI) and the *p*-values represent the statistical significance of the parameter values (and not the statistical significance of model improvement by their inclusion in the model). Models that did Not Converge are identified with NC.

Covariable name (unit)	**β_2, *ERR*/unit exposure relative to external baseline (i.e. with β_1, fixed at unity)**	**β_1, free, internal to external baseline ratio**	**β_2, *ERR*/unit relative to internal baseline (i.e. with β_1, free)**	**α, *ERR*/unit exposure**	**α_1 α_2 *ERR*/unit exposure**
Gamma (Gy)	NC	0.90 (0.78; 1.02) ($p < 0.001$)	-1.27 (-2.4; -0.14) ($p = 0.03$)	-1.18 (-2.4; 0.02) ($p = 0.055$)	
Medium PA (years)	-0.010 (-0.019; -0.001), ($p = 0.04$)	0.87 (0.74; 0.99) ($p < 0.001$)	-0.003 (-0.17; 0.01) ($p > 0.5$)	-0.003 (-0.016; 0.011) ($p > 0.5$)	
High PA (years)	-0.003 (-0.016; 0.010) ($p > 0.5$)	0.81 (0.69; 0.93) ($p < 0.001$)	0.01 (-0.01; 0.03) ($p = 0.26$)	0.013 (-0.008; 0.033) ($p = 0.24$)	α_1 = 0.021 (0.001; 0.040) ($p = 0.04$)
Underground work (10^5days)	-4.44 (-7.11; -1.76) ($p = 0.001$)	0.93 (0.78; 1.08) ($p < 0.001$)	-3.30 (-7.20; 0.06) (p=0.097)	-3.07 (-7.12; 0.99) (p =0.14)	α_2 = -5.59(-9.81;-1.36) ($p = 0.01$)

Table 3 Results of applying Model selection techniques with the likelihood ratio test for variable selection. The changes in degrees of freedom (*d.f.*) and deviance are all with respect to the stratified baseline model which had a deviance of 3178.9 for a *d.f.* of 555433. *g, mpa, hpa, u* and *a* represent gamma prostate dose, years at medium PA, years at high PA, days worked underground and age attained respectively. The top section represents a sub-set of seven models (preferred model in bold) from a complete sorted list of all models tested, for which the probability of model improvement with respect to the stratified baseline model had a *p*-value under 0.10. The lower section represents the model selection results for all 4 models with single exposure covariables – none of which resulted in a statistically significant model improvement when compared to the baseline model.

Covariables in model, form			**Δ *d.f.***	**Δ deviance**	***p*-value**
u, linear	***hpa, linear***		***2***	***6.47***	***0.039***
u, linear	*mpa*, linear	*hpa*, linear	3	7.25	0.064
u, linear	*hpa*, linear	*a*, exponential	3	7.23	0.065
u, linear	*hpa*, linear	*a*, power	3	7.15	0.067
u, linear	*hpa*, linear	*hpa,* squared	3	7.06	0.070
u, linear	*u*, squared	*hpa*, linear	3	6.75	0.080
u, squared	*hpa*, linear		2	5.04	0.080
	ERR/unit exposure (SE)				
g, linear	$-1.2\ (0.6).10^{-3}$		1	2.61	0.107
u, linear	$-3.1\ (2.1).10^{-5}$		1	1.88	0.171
hpa, linear	$1.3\ (1.1).10^{-2}$		1	1.61	0.204
mpa, linear	$-2.8\ (7.0).10^{-3}$		1	0.15	0.697

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Prostate cancer mortality risk in relation to working underground in the Wismut cohort study of German uranium miners, 1970-2003

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) The study's cohort design is indicated in the title, page 1
		(*b*) An informative and balanced summary of what was done and what was found has been provide in the abstract
Introduction		
Background/rationale	2	The scientific background and rationale for the investigation being reported has been explained, page 4
Objectives	3	Specific objectives, including any prespecified hypotheses, have been stated, page 4
Methods		
Study design	4	Key elements of study design have been presented early in the paper, page 5-7
Setting	5	The setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection have been described, pages 4 & 8
Participants	6	(*a*) *Cohort study*—The eligibility criteria, and the sources and methods of selection of participants have been cited and described on page 4. Methods of follow-up have been cited and described on page 4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed – No matching was performed *Case-control study*—NOT APPLICABLE
Variables	7	All outcomes, exposures, predictors, potential confounders, and effect modifiers have been defined, page 6. Diagnostic criteria, in terms of ICD codes are given on page 5
Data sources/ measurement	8*	For each variable of interest, sources of data and details of methods of assessment (measurement) are give on page 4 & 6
Bias	9	Efforts to address potential sources of bias are given in the discussion section, page 12
Study size	10	Explanations on how the study size was arrived at are cited on page 4
Quantitative variables	11	Explanations of how quantitative variables were handled in the analyses are given on pages 6 & 7.
Statistical methods	12	(*a*) All statistical methods, including those used to control for confounding are described, pages 6 & 7
		(*b*) Any methods used to examine subgroups and interactions are described on pages 6 & 7
		(*c*) Missing data were addressed on page 5
		(*d*) *Cohort study*—Loss to follow-up was addressed in the citations on page 4
		(*e*) Sensitivity analyses were not relevant.

Continued on next page

Results		
Participants	13*	(a) Numbers of individuals at each stage of study (i.e. person-years at risk) are reported on in table 1
		(b) Give reasons for non-participation at each stage – NOT RELEVANT
		(c) Consider use of a flow diagram – NOT RELEVANT
Descriptive data	14*	(a) Characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders are given, in tables 1&2
		(b) Number of participants with missing data for each variable of interest is indicated by the overall "Percentage of Missing Causes of Death" on page 5
		(c) *Cohort study*—Follow-up time (eg, average and total amount) has been given on page 8
Outcome data	15*	*Cohort study*—Numbers of outcome events or summary measures over time are reported in figure 1
		Case-control study—NOT APLICABLE
		Cross-sectional study— NOT APLICABLE
Main results	16	(*a*) Unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval) are given in table 2. table 2 makes clear which confounders were adjusted for and why they were included.
		(*b*) category boundaries when continuous variables were categorized were already reported in the methods section, page 6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period – this was not possible due to limitations in the methodology (i.e. Poisson Regression with a stratified baseline model)
Other analyses	17	Other analyses done—eg analyses of subgroups and interactions, are reported in table 3
Discussion		
Key results	18	Key results with reference to study objectives are summarised on page 10
Limitations	19	Limitations of the study, taking into account sources of potential bias or imprecision are discussed on pages 10, 11 & 12. Direction and magnitude of any potential bias are discussed on page 12.
Interpretation	20	A cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence is given in the conclusions section.
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	The source of funding and the role of the funders for the present study on which the present article is based are given in the "Acknowledgement" at the end of the paper.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Original paper

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Prostate cancer mortality risk in relation to working underground in the Wismut cohort study of German uranium miners, 1970-2003

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Abstract

Objective: A recent study and comprehensive literature review has indicated that mining could be protective against prostate cancer. This indication has been explored further here, by analysing prostate cancer mortality in the German "Wismut" uranium miner cohort which has detailed information on the number of days worked underground.

Design: An historical cohort study of 58,987 male mine workers with retrospective follow-up before 1999 and prospective follow-up since 1999.

Setting and participants: Uranium mine workers employed during the period 1970-1990 in the regions of Saxony and Thuringia, Germany, contributing 1.42 million person years of follow-up ending in 2003.

Outcome measure: Simple Standardised Mortality Ratio (*SMR)* analyses were applied, to assess differences between the national and cohort prostate cancer mortality rates, and complemented by refined analyses done entirely within the cohort. The internal comparisons applied Poisson regression excess relative prostate cancer mortality risk model with background stratification by age and calendar year and a whole range of possible explanatory covariables that included days worked underground, years worked at high physical activity with gamma radiation treated as a confounder.

Results: The analysis is based on miner data for 263 prostate cancer deaths. The overall *SMR* was 0.85 (95% CI 0.75; 0.95). A linear excess relative risk model with the number of years worked at high physical activity and the number of days worked underground as explanatory covariables provided a statistically significant fit when compared to the background model (p=0.039). Results (with 95 % confidence intervals) for the *ERR* per day worked underground indicated a statistically significant (p=0.0096) small protective effect of $-5.59(-9.81;-1.36).10^{-5}$.

Conclusions: Evidence is provided from the German Wismut cohort in support of a protective effect from working underground on prostate cancer mortality risk.

Introduction

Prostate cancer is the second most common cancer diagnosed among men (after lung cancer), and is the sixth most common cause of cancer death among men world-wide [1]. In the European Union in 2006, prostate cancer was the most common form of incident cancer and the third most common form of cancer death in men (Table 3 of [2]). Prostate cancer incidence in Germany has also become the most common form of incident cancer disease in men. It is notable that the prostate cancer mortality rates were approximately constant in the former eastern German Democratic Republic (GDR) between 1960 and 1980, but rose during the same time by 50% in West Germany [3].

Prostate cancer is, in general, a slow-growing tumour with a long latency and an uncertain aetiology. The prevalence of latent microscopic prostate tumours has been shown to be quite high in the elderly in most populations i.e. at least 50 percent in men over the age of 70 years [4]. Although there are only a few established risk factors for prostate cancer such as age, race and a family history of prostate cancer [5] there are also several mooted detrimental and protective associations.

The possible detrimental associations include early baldness [6], shift-work [7], arsenic exposures [8], diesel fume exposure [9] and oestrogen exposures [10]. Some evidence exists for radiation related prostatic detrimental effects from studies on patients after diagnostic radiation procedures [11], occupationally exposed British nuclear workers [12], military and civil pilots and flight attendants [13], and persons exposed by the Chernobyl accident [14]. There was little evidence of a prostate cancer risk radiation dose response in the Japanese A-bomb survivors [15]. A recent meta-analysis of 24 cohort studies has concluded that an association of smoking with prostate cancer incidence and mortality exists [16].

The possible protective associations include high sexual and/or androgenic activity [17], UV and/or vitamin D [18], high Physical Activity (PA) [19] - although some inconsistent results are observed for PA - and melatonin [20-23]. For a cohort of U.S.A. male health professionals, [24] reported that for fatal prostate cancer, a recent smoking history, taller

height, higher BMI, family history, and high intakes of total energy, calcium and α-linolenic acid were associated with a statistically significant increased risk but higher vigorous PA level was associated with lower risk.

A recent Australian population-based case-control study and literature review [25] has indicated that mining could be protective against prostate cancer. [25] concluded that the relationship between mining and prostate cancer could possibly be connected to levels of either PA or changes in melatonin production caused by periods working underground and that these relationships deserve further investigation. Differential risk could not be reported in [25] because all but one of the studies reviewed did not report on working periods underground and overground. The main purpose of the present paper is to explore these indications further by analysing prostate cancer mortality risk in a cohort of male mine workers involved in uranium extraction at the former Wismut company in East Germany applying both external (national male rates for the former GDR) and internal backgrounds. New covariables for occupational PA and time spent underground have been specially created for this investigation. Simple Standardised Mortality Ratio (*SMR*) analyses are complemented by refined analyses done entirely within the cohort.

The German "Wismut" uranium mine workers cohort has currently been followed-up from 1.1.1946 to 31.12.2003, with almost 2 million person-years of observation and has already been described in detail [26]. It is currently the largest miners cohort study and several analyses of the detrimental health effects data pertaining to the 58,987 male former employees, have recently been published [27-33].

There are several occupational risk factors for detrimental health effects, relevant to the cohort members, particularly with respect to lung cancer, including exposure to radon, gamma radiation, long-lived radionuclides, [34], fine dust, arsenic dust and quartz dust [35], asbestos [36] and diesel exposure. However exposure covariables for the latter two quantities are not available in the cohort data. Previous analyses have shown that the mortality from prostate cancer in this cohort (1960-2006) is notably lower than in the comparison population of the former GDR (*SMR* = 0.88, 95%CI = 0.78; 1.00 [27]). The total absorbed dose to the prostate has not yet been calculated. However since the absorbed dose to non-respiratory track organs is dominated by external gamma radiation and the contributions of radon progeny, radon gas and particularly long-lived radionuclides are expected to be only a few percent [37], only the

gamma radiation is explicitly considered here, as a potential confounder. The effective gamma doses have been converted into prostate organ dose via Voxel model dose conversion factors [38].

Material and Methods

Cohort definition, time periods and mortality follow-up.

Full details of the cohort have already been given [28, 30]. Every cohort member contributes to the number of person years starting 180 days after the date of first employment and ending at the earliest of date of loss to follow-up, date of death, or end of follow-up (31.12.2003). Due to the relatively high Percentage of Missing Causes of Death (PMCD) of 37.25% and the systematic variation of PMCD with calendar time from 1946 to 1969, the analyses here are based on the subset of Wismut miner cohort data covering the period 1970-2003 for which the PMCD is 3.56%. Consequently, no corrections for missing causes of death have been made. This difference in PMCD is due to the late start of data collection for this cohort on 1.1.1999, linked with the fact that death certificates were rarely kept by the authorities for more than 30 years.

National rates for the former GDR covering the same calendar-year range are applied for the external comparisons. Former disease codes of the comparison external background rates for the GDR were re-coded via earlier ICD revisions to the 10th ICD-code [39], which was applied throughout. This recoding process was complicated by several revisions to ICD codes during the period of data coverage, and German reunification. Population prostate cancer rates are not available just for the relevant mining region of Thuringia and Saxony. Consequently, the external rates applied here cover the total area of the former GDR (including East-Berlin) during the time period 1970–1997; in contrast, from 1998 the rates pertain to the former GDR states and the whole of Berlin. The codes used here in the various time periods are as follows: 1970–1978 ICD 8, code number 185; 1979 ICD 8, code number 179-189 for the urogenital system; 1980–1997 ICD 9, code number 185; 1998–2003 ICD 10, code number C61 all for Prostate cancer.

Analysis.

The Poisson regression methods applied here require the tabulation of the individual data, into grouped data records, as described below and in previous analyses [30-32]. This is because the input data for Poisson regression needs to consist of records containing the number of prostate cancer cases, the number of person-years and the mean values of the possible explanatory covariables. Poisson regression is a likelihood based method for the quantitative analysis of such records or "event-time tables" [40], whereby the rates to be modelled are computed as the ratios of prostate cancer cases to person-years for each record in the input data set. Descriptions of the background rates (i.e. the spontaneous rates) were necessary to assess the excess risks, whereby such descriptions can either be based on models derived directly from the cohort data (internal comparisons) or from data on the GDR population rates (external comparisons).

Quantitative risk evaluation methods were based on the simple *SMR* model, where the SMR is the ratio of the observed number of prostate cancer deaths in the cohort to the number of prostate cancer deaths expected in the comparison population, (see [40], pages 65-68). It is possible that an increased or decreased overall SMR could be a result of either an occupational or life-style exposure effect in the data. This can be tested directly by considering the simple SMR model with an exposure response to various possible explanatory covariables, for external and internal comparisons. In the case of the SMR model for external comparisons with an exposure response, a background SMR is computed (i.e. the overall ratio of the observed background number of prostate cancer deaths in the cohort to the number of prostate cancer deaths expected in the comparison population) with an additional SMR that is linearly dependent on the covariable of interest.

The more refined analysis entirely within the cohort (internal comparisons) applied Poisson regression excess relative prostate cancer mortality risk model with background rate stratification by age and calendar year and a whole range of possible explanatory covariables: age (*a*), year (*y*), gamma prostate dose (*g*), years at medium Physical Activity (PA) (*mpa*), years at high PA (*hpa*), days worked underground (*u*) and time since either first or last underground shift (*t*).

Data Tabulations.

Tabulations of person-years at risk and cancer deaths were created with the DATAB module of the EPICURE software [41] for the whole cohort data (1946-2003), so that the covariables of interest could be accumulated from the beginning of the cohort. The period of interest here

was then selected to be 1970-2003 during the data-analysis and model fitting procedures. Cross-classifications were made by attained age, *a*, in 16 categories (<15, 15–<20, 20–<25, … , 85+ years), individual calendar year, *y*, in 58 categories, and cumulative gamma prostate doses, with a five-year lag-time (8 categories: 0, >0–<50, 50–<100, 100–<150, 150–<200, 200–<300, 300–<400, 400+ mGy). For the current analysis new covariables for occupational PA and time spent underground have been specially created. Exact shift information relating to daily underground and overground activities in each calendar year was used. The number of days worked underground in any one calendar year was then accumulated over calendar years of employment in 8 categories (0, >0–<1000, 1000–<2000, 2000–<3000, 3000–<4000, 4000–<5000, 5000–<6000, 6000+ days). For the PA categories, information on the job type in each calendar year was extracted from the Wismut records. Each of the several hundred job types had already been classified into three levels of PA corresponding to different breathing rates for the purpose of organ dose calculations e.g. job types hewer, metal worker and lorry driver were classified as high, medium and low PA respectively. The number of years worked in each of the high and medium PA classes were then accumulated over calendar years of employment, each in 8 categories (0, >0–<5, 5–<10, 10–<15, 15-<20, 20–<25, 25–<30, 30+ years). Choice of units (years or days) reflects the quality of the information available in the mining records.

Standardized Mortality Ratios.

Mortality rates observed in the cohort were compared with the GDR external rates. The first stage of the *SMR* analysis for prostate cancer has been done as described previously for extra–pulmonary cancers [28] with some extensions that allow a comparison of internal (miner cohort) and external (former GDR) background (spontaneous) rates. Justifications for the generally preferable internal comparison (done entirely within the cohort), connected with differences in the maturity of the smoking epidemic between the cohort and the GDR, have recently been given [32]. The simplest *SMR* model relates the rates in the population of interest (the miner cohort) to a multiple of the rates from the external population (the former GDR).

If $\lambda^*(a, y)$ denotes the external rates as a function of age and calendar year and $\lambda(a, y)$ denotes the observed rates in the miners cohort, then the *SMR* model can be written as

$$\lambda(a, y) = \beta \cdot \lambda^*(a, y) \qquad (1)$$

where the β is a fit parameter and represents the *SMR*.

However it is also possible to fit a relative risk (*RR*) model

$$RR(a, y, g) = \beta_1 \cdot \lambda^*(a, y) \cdot (1 + \beta_2 (g)) \quad (2)$$

to estimate the effects of various possible explanatory covariables, such as gamma prostate dose (g), based on the GDR external rates, assuming that the *SMR* for the background rates is identically equal to 1, i.e. β_1 is fixed to unity during the optimisation. In this case, β_2 is a fit parameter that then gives the simple Excess Relative Risk (*ERR*) per unit of exposure relative to the external GDR rates. It is also possible to test if the external GDR rates are different from the internal background rates in the miner cohort by simply freeing the parameter β_1 and repeating the optimisation. All of the parameters β, β_1 and β_2 can be multiplied by a two level categorical variable for either levels of PA or time spent underground.

Refined *ERR* models with background stratification by age and calendar year were employed – if $r(a, y, g, mpa, hpa, u, t)$ is the prostate cancer mortality rate and $r_0(a,y) = r(a,y,0,0,0,0,0)$ is the background disease rate for non-exposed individuals, $g = 0$, $mpa = 0$ …etc. then

$$R(a, y, g, mpa, hpa, u, t) = r_0(a, y) \cdot \{1+ERR(g, mpa, hpa, u, a, t)\}, \quad (3)$$

where *ERR* is the excess relative risk factorised into a function of exposure, f(g, mpa, hpa, u) and a modifying function, h(a, t):

$$ERR(g, mpa, hpa, u, a, t) = f(g, mpa, hpa, u) \cdot h(a, t) \quad (4)$$

The gamma prostate dose, years at medium PA, years at high PA and days worked underground were each included:

singularly, $f(g) = \alpha\, g$, etc, and pair-wise $f(g, mpa) = \alpha_1\, g + \alpha_2\, mpa$, etc. (5)

in the linear *ERR* model, both with and without the modifying function, and assessed with model selection techniques to arrive at the model with the lowest deviance with respect to the background model, by forward selection. Backwards selection was also tested. Finally the preferred linear model was tested for non-linearity, by adding quadratic terms for exposure covariables, and time or age effect modification (i.e. adding g(a, t) functions to the model).

Maximum likelihood with the AMFIT module of the EPICURE software [41] was used for estimation of the *SMR* and *ERR* fit parameters associated with equations 1 to 5 above.

Confidence Intervals (CI) were computed at the 95% level and the Wald type CI are given since, although very similar intervals were found with the profile likelihood based CIs, some of the lower limits could not be numerically calculated with the latter method.

Results

Out of the total 58,987 cohort members in the complete follow-up period between 1946 and 2003, 55,435 members were included in the follow-up from 1970 specifically considered in the risk analysis presented here. In total, 20,920 persons were deceased (of which 1,560 died before 1970), 35,294 were alive and 2,773 were lost to follow-up (of which 1,992 were lost before 1970). There were 263 prostate cancer deaths observed during 1.42 million person years of observation between 1970 and 2003. The cumulative numbers of observed and expected prostate cancer deaths in this period are shown in Figures. 1a and 1b as a function of calendar year from 1970 and age attained from 40 years. The absolute number of prostate cancers occurring reaches a maximum in the category 75 to 80 years of age, due to the age distribution in the cohort, and increases steadily from 1970 to 2003 and the cumulative number of prostate cancers increases as a function of age attained and calendar year.

The mean values (and ranges) of age-attained, mean number of days worked underground and mean number of years worked at high PA are 47 (14-103) years, 1649 (0-10704) days and 3.5 (0-44) years respectively. Table 1 gives the category specific values for the number of prostate cancer deaths and person-years, for the number of years worked at high PA and days spent underground categories of mine workers.

SMR results (comparison of cohort rates with external rates, Eq 1).

The total number of deaths from prostate cancer (1970–2003) observed (O), was significantly lower ($p < 0.001$) than expected (E) from national rates. The *SMR* value with 95% confidence intervals (CI) is 0.85 (0.75; 0.95). Quantitative differences between GDR external rates and internal cohort rates can be assessed directly from a categorical *SMR* analysis in categories of attained-age and calendar year. Some statistically significantly low categorical *SMR* values were found mainly in the age group 65 to 75 years, and in the calendar period from 1991 to 1995 (results not shown). The overall *SMR* with 95% confidence intervals when recomputed by two categories of below and above mean time spent underground (1649 days) becomes 0.92 (0.76; 1.07) and 0.79 (0.65; 0.92) respectively. The *SMR* recomputed by two categories

of below and above mean time worked at high PA (3.52 years) becomes 0.82 (0.69; 0.94) and 0.91 (0.73; 1.10) respectively.

Simple *ERR* parametric cohort risk models (comparison of cohort rates with external rates, Eq 2).

Cumulative exposure effects for various covariables in terms of *ERR* per unit exposure and 95% CIs are given in the first results column of Table 2. The *ERR*/day worked underground, relative to the external GDR rates, is -4.44 (-7.11; -1.76).10^{-5} and was found to be the statistically strongest exposure effect (p = 0.001) i.e. decreased for the number of days worked underground relative to the external rates. A similar value of -3.3 (-7.2; 0.06) .10^{-5} relative to the internal controls was found (Table 2, second results column), although of reduced statistical significance (p = 0.097). This latter result is connected with a background SMR of 0.93 (0.78; 1.08) (Table 2, second results column). The *SMR* model did not converge (NC) for the gamma prostate dose relative to the external background rates. A statistically significant (p-value = 0.03) decreased *ERR*/Gy for prostate gamma doses, relative to the internal background of -1.27 (-2.4; -0.14) was also found (Table 2, second results column).

Refined *ERR* parametric cohort risk models (Eqs 3-5).

The statistical significance of *ERR*/Gy for prostate gamma doses reported with the simple analysis was not confirmed by the refined analysis (*ERR*/Gy=-1.18 (-2.4; 0.02), see table 2, third results column). Although the coefficient for gamma dose was of borderline statistical significance in the univariate model, the forward selection did not keep the gamma prostate dose in the multivariate model. A preferred model by forward selection of the covariables gamma prostate dose, *g*, years at medium PA, *mpa*, years at high PA, *hpa* and days worked underground, *u* taken linearly one or two at a time was found to be the model that included both *hpa* and *u* (Table 3). This model had a reduction in deviance with respect to the stratified background model of 6.5, (p = 0.04) by the Likelihood Ratio test. This model provided the results in the last column of table 2, (with 95 % confidence intervals) for: the *ERR* per day worked underground, which indicates a statistically significant (p=0.01) small decreased effect of -5.59(-9.81;-1.36).10^{-5} and; for the *ERR* per year worked at high physical activity, which indicates a statistically significant (p = 0.04) small detrimental effect of 0.021 (0.001; 0.040). The clinical significance of the results can be assessed by obtaining the number of deaths from prostate cancer prevented in this cohort from working underground, obtained from the fitted background and fitted excess number of cases in the preferred model.

Depending on whether the slightly increased risk from high physical activity is accounted for or not, this number is either 14 or 22 prostate cancer deaths respectively.

Models that included just *hpa* or just *u* did not result in statistically significant risks (Table 2, third results column) or lead to statistically significant model improvement (Table 3). No evidence for an interaction between *hpa* and *u* was indicated by including a cross term in the preferred model (p>0.5). Testing of the quadratic or parabolic forms for *hpa* and *u* or testing risk effect modification by attained age (Table 3) or time since first or last underground shift (results not shown) did not lead to statistically significant model improvement. The dose response forms for the preferred model and the adjusted non-parametric risks with 95% confidence intervals are shown in Figure 2. It was not possible to confirm this result by backwards selection since the models with all 6 main covariables failed to converge.

Discussion

The Wismut cohort is one of the largest single occupational cohorts and one of only a few cohorts with detailed information on the number of shifts worked underground. Although the number of shifts was documented, it is not known if these were early morning, day-time or night shifts. A substantial proportion (25%) of person-years are contributed by mine workers who did not work underground which generally ensures the stability of analyses based on internal rates. The *ERR* per unit of various exposures have been modelled relative to the internal rates and relative to the external rates for the general population of the former GDR.
A statistically significant (p = 0.001) negative response for the *ERR* per day worked underground, when modelled in relation to the general population of the former GDR, is reported here. There are some indications of unit exposure responses of the *ERR* which are decreased for gamma prostate dose, (p= 0.03 and 0.055 for the simple and refined models respectively) with respect to the internal rates. Rather than being decreased, the gamma dose is a possible proxy variables for the number of days worked underground since there are moderate degrees of correlations between these covariables (ρ = 0.68 for the correlation between time dependent cumulative gamma prostate doses and the number of days worked underground, see also table 1). Indication that the gamma dose may be acting as a proxy was tested here directly by the creation of new categories of mine workers, with numbers of years worked at high or medium PA and the number of days worked underground and the application of model selection techniques.

The assumption is made in this paper that radon and long-lived radionuclides make only minor contributions to the total prostate dose. Previous analyses have shown that the *ERR* per 100 WLM of radon exposure, based on internal Poisson models, was not elevated for prostate cancer (*ERR*/100 WLM= 0.000, 95%CI, -0.024; 0.024, [31]). None of the radiation covariables (i.e. gamma prostate dose, but also including long-lived radionuclides and radon), when tested by inclusion singularly as linear risks in refined internal Poisson regression models, resulted in a deviance drop of more than 3 with respect to the background model which was stratified on age-attained and calendar year.

A linear excess relative risk model with the number of years worked at high physical activity and the number of days worked underground as explanatory covariables provided a statistically significant fit when compared to the background model ($p = 0.039$). Results (with 95% CI) for the *ERR* per day worked underground indicated a statistically significant ($p = 0.01$) small decreased effect at $-5.59(-9.81;-1.36).10^{-5}$ and, for the *ERR* per year worked at high physical activity, a statistically significant ($p = 0.04$) small detrimental effect at 0.021 (0.001; 0.040). This main result provides new evidence in support of the decreased effect of working underground which is manifested with respect to the internal and the external rates.

The number of days worked underground is connected with a particular hypothesis for reduced prostate cancer rates e.g. melatonin production rates (as described in detail in [25] and references therein). In summary, melatonin has been shown to have anti-cancer properties acting through several mechanisms [20-23]. The production of melatonin in the pineal gland is regulated by the natural diurnal light-level cycle, with suppressed production during the day which is restored at night. Underground miners on day shifts would have a reduced exposure to visible light leading to an extended melatonin production period.

The relation between physical activity and prostate cancer risk was classified as “probable” with respect to an increased risk, by the IARC in 2002 [42] but no definite mechanisms have been identified for a relation between PA and prostate cancer. Several plausible mechanisms have been postulated which include modulation of testosterone and vitamin D levels by PA, a link between physical inactivity and over-weight/obesity and a beneficial modulation of immune function through exercise (see [43] for a review). A recent systematic review and meta-analysis [44] considered 13 studies with occupational physical activity, considered to be

"higher-quality" studies and reported that 9 studies gave a decreased risk, one study an increased risk and 3 studies reported no association. Two other studies have reported increased risks: [45] found that intensity of occupational PA was associated with increased prostate cancer risk and [46] reported an increased risk for obese men (BMI over 30) who were physically active for more than 1 hour per day and in men with high background energy intake.

A statistically significant increase in risk with increasing high PA is observed here, in contrast to the IARC classification and the majority of other studies. It is important to note that the variable physical activity here measures only part of the total PA and could be prone to misclassification. The PA variable is limited to the work period at the Wismut company (the mean duration of work at the company 14 years) and no leisure time activities could be considered. The classification is simply based on job type without consideration of possible changes in physical activity in a specific job over time e.g. due to improved technical "labour-saving" equipment. Physical activity could also be an indicator of socioeconomic status, because the jobs with low PA are more likely to be associated with higher education.

Another possible source of bias in the results based on external comparisons that should be considered is the selection bias known as the healthy worker effect. However this effect, which can generally lead to occupational cohorts presenting mortality risks less than the general population, is not indicated since the risks are similar with respect to internal and external backgrounds. The occurrence of this form of bias could also be tested here by considering all solid cancer minus the sites that have already been linked to the main mine radiation exposure, i.e. radon (lung, larynx, tongue, mouth and pharynx). For this group of cancers the *SMR* with 95%CI is 1.01 (0.97; 1.04) also indicating that the healthy worker effect is not having a significant influence on the prostate cancer results in this cohort.

A further source of bias, possibly affecting the decrease in risk with increasing duration of working underground based on internal comparisons, could be the healthy worker survivor effect. Unhealthy workers may move from working underground to working at the surface. Consequently, the duration of working underground may be higher in the healthy group compared to the unhealthy group, leading to artificially decreased effects in relation to duration of working underground. However this effect has been tested for by fitting the

preferred model, that included both the number of days worked underground and number of years worked at high physical activity, to the sub-group of all solid cancers minus the sites that have already been linked to the main mine radiation exposure (lung, larynx, tongue, mouth and pharynx) and minus prostate. No significant trends were found ($p>0.5$ for the linear trend of ERR with respect to the number of days worked underground and $p=0.11$ for the linear trend of ERR with number of years worked at high physical activity) indicating that the healthy worker survivor effect is not directly biasing the results for prostate cancer.

Although there is no general consensus as to whether radiation exposure is associated with prostate cancer risk [47], an X-ray procedure risk doubling dose of about 20 mGy for prostate cancer incidence has been reported [11]. The magnitudes and ranges of the gamma prostate doses in the Wismut study (with the prostate cancer mortality cases having a range up to 444 mGy and the cohort person-year weighted mean gamma prostate dose of 34mGy) should be large enough to find such an increased risk at the 20 mSv level given the similar relative biological effect of X-rays and gamma rays. However, a gamma risk, at this 20 mSv level, has not been found in the Wismut cohort data for prostate cancer mortality.

Yang et al [8] reported that *SMR*s for prostate cancer declined gradually in a SW coastal district of Taiwan after the arsenic contaminated artesian well drinking-water supply was improved to a tap-water system. Since arsenic dust exposures are also available for the Wismut miners [35], an arsenic covariable could be added to the preferred model for physical activity and time worked underground described above in a subsidiary analysis, but this only resulted in a deviance drop of 1.2 and a p-value of 0.33 for the associated arsenic risk coefficient and did not confound the main risks from the preferred model.

An examination of the effects of smoking on the risk of prostate cancer mortality, as indicated in [16] could not be carried out for the Wismut cohort due to only a very limited amount of information on smoking being available [29].

Although there were 264 prostate cancer deaths in the whole cohort, only one occurred before 1970 i.e. during the period with a higher percentage of missing causes of death. This is consistent with prostate cancer generally being a type of cancer that occurs predominantly in old-age coupled with the observation that – due to miners entering and leaving the cohort at various points in time during the follow-up period – the cohort aged, on average, at half the

rate of any individual, i.e. in 1960 and 2003 the mean ages of cohort members were 35 and 57 years respectively. Consequently it is very important to continue work on extending the current follow-up period.

Conclusions

This work has extended the evidence in support of a decreased, possibly protective, effect for prostate cancer mortality from working underground provided in [25] and could be interpreted as support for "The Melatonin Hypothesis". A linear internal excess relative risk model with the number of years worked at high physical activity and the number of days worked underground as explanatory covariables provided a statistically significant fit when compared to the background model ($p = 0.039$). Results (with 95% CI) for the *ERR* per day worked underground indicated a statistically significant ($p = 0.0096$) small decreased, possibly protective, effect at $-5.59(-9.81;-1.36).10^{-5}$. It is this main result that provides the new evidence in support of the protective effect of working underground which is also manifested with respect to the external rates. Additional computations made to examine the influence of biases due to the gamma doses, the healthy worker selection effect and the healthy worker survivor effect indicate that the results are unbiased in these respects, but the effects of such biases cannot be entirely excluded.

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Figure Captions

Fig 1a The cumulative number of prostate cancer deaths observed in the Wismut cohort and expected from GDR rates as a function of calendar year.

Fig. 1b The cumulative number of prostate cancer deaths observed in the Wismut cohort and expected from GDR rates as a function of age-attained..

Fig 2 The upper panel shows the *ERR* and 95%CI as a function of mean number of years with high PA and corresponds to the risk given in the last column of Table 2. The non-parametric points with 95%CI are adjusted for mean number of days worked underground. The lower panel shows the *ERR* and 95%CI as a function of mean number of days worked underground and corresponds to the risk given in the last column of Table 2. The non-parametric points with 95%CI are adjusted for mean number of years with high PA.

Figures

Figure 1a.

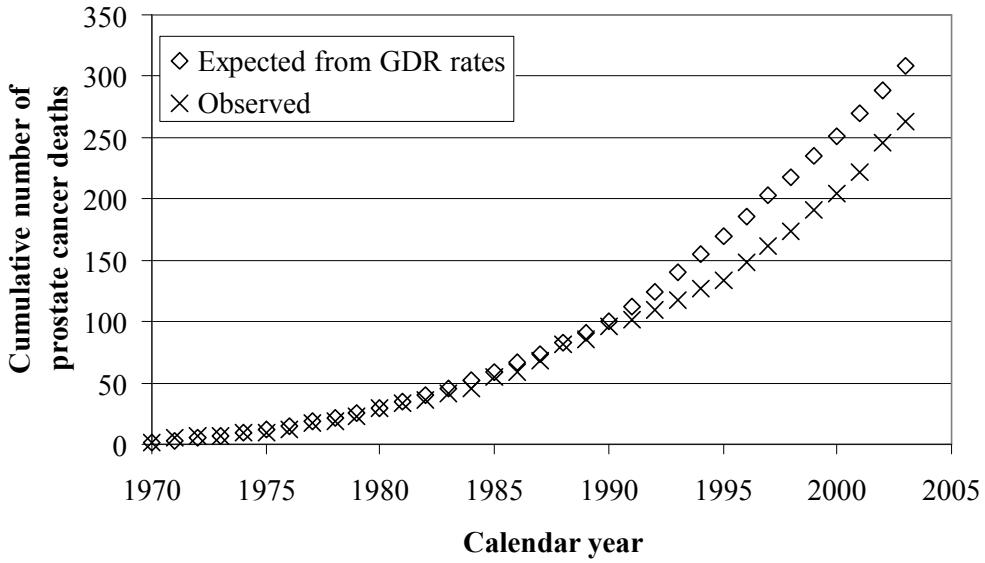


Figure 1b.

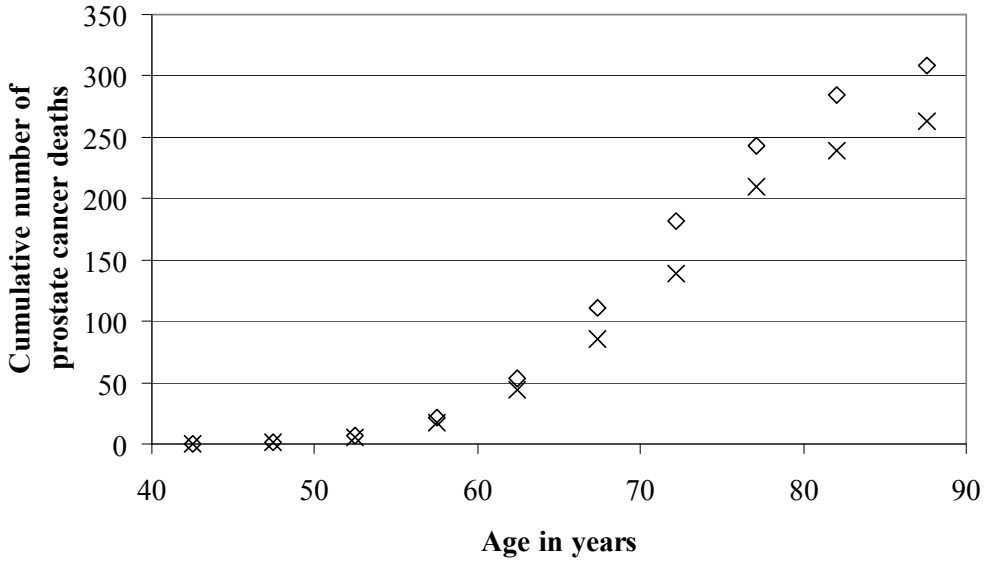
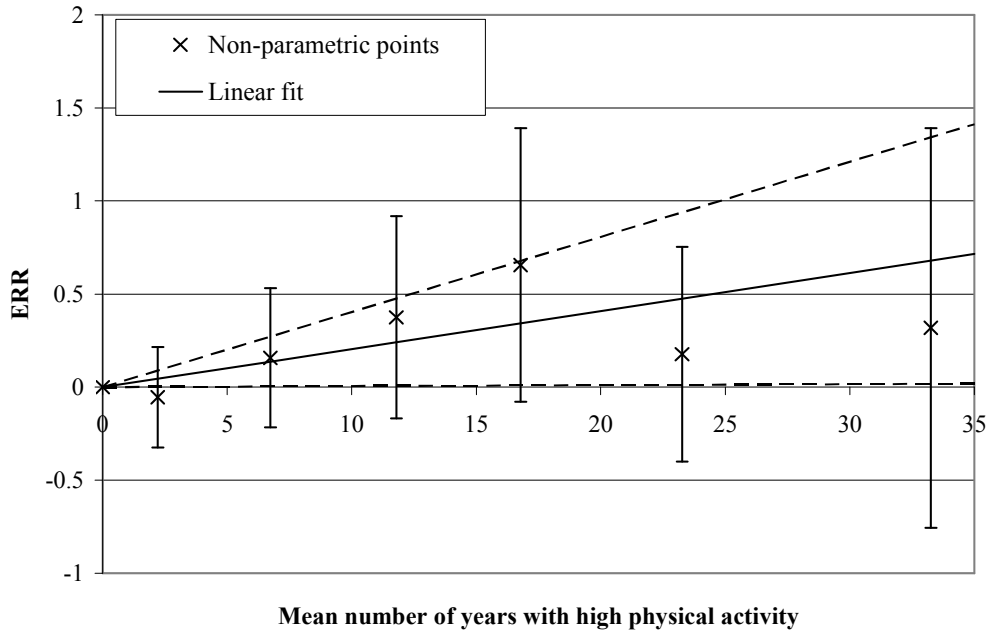


Figure 2.



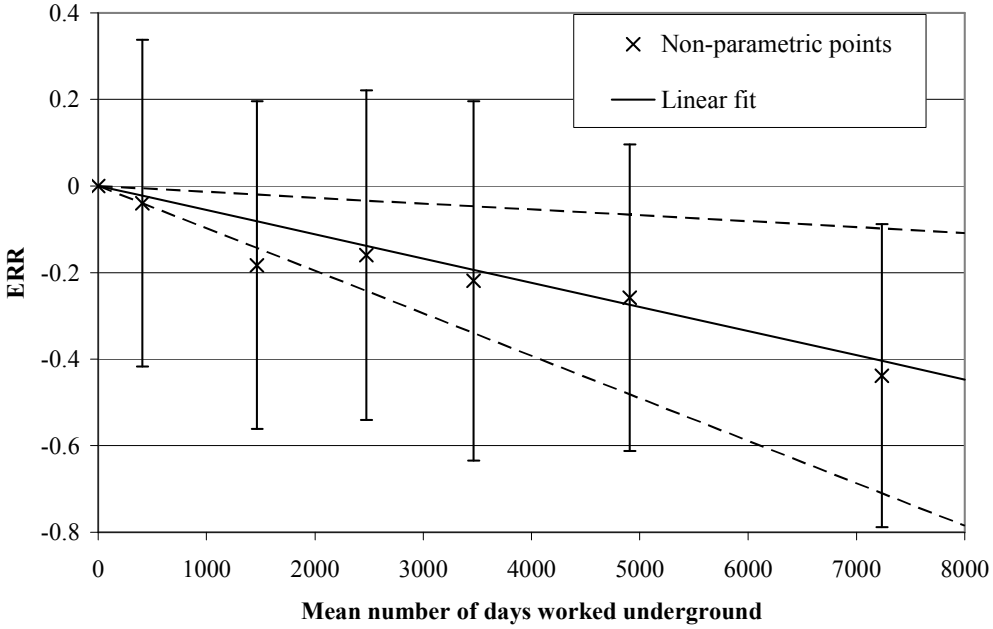


Table 1 Category means and ranges for the number of days worked underground and the number of years worked at high physical activity (PA). In each category the number of deaths from prostate cancer mortality, the number of person-years at risk (rounded) and the mean cumulative person-year weighted gamma prostate dose (with standard deviation) are given.

Category means (and ranges)	**number of prostate cancer deaths**	**number of person-years**	**mean gamma prostate dose** (mGy, with standard deviation)
mean number of days worked underground			
0	67	360536	1.1 (4.4)
408 (2 – 999.9)	46	429624	7.5 (9.9)
1466 (1000 – 1999.8)	30	184782	24.5 (26.7)
2475 (2000 – 2999.8)	34	139204	42.0 (44.2)
3465 (3000 – 3999.9)	24	97808	68.3 (65.5)
4908 (4000 – 5999.9)	37	138138	111.4 (93.9)
7236 (6000 – 10704)	25	74836	156.9 (127.4)
mean number of years worked at high PA			
0	122	726358	9.8 (28.1)
2.2 (1 – 4)	52	342896	19.2 (33.1)
6.7 (5 – 9)	37	165377	47.0 (46.9)
11.8 (10 – 14)	22	87297	94.5 (73.5)
16.8 (15 – 19)	16	54598	148.3 (94.2)
23.3 (20 – 29)	11	40425	199.4 (123.1)
33.3 (30 – 42)	3	7978	238.3 (163.0)

Table 2 Results of fitting the models. The first and second numerical partitions are for the Standardized Mortality Ratios (*SMR*) (from Eq 2). The interpretation of β_1 is that it represents the overall ratio of the observed background number of prostate cancers deaths in the cohort to the number of prostate cancer deaths expected in the comparison GDR population – and β_2 is the additional incremental SMR that is linearly dependent on the covariable of interest listed in the first column of the table i.e. an ERR/unit exposure of the covariable of interest. The third and fourth numerical partitions are for the Excess Relative Risk (*ERR*) internal regression models with background rates stratification on age and calendar year (from Eqs. 3, 4 and 5) for the univariate option in Eq 5 (parameter α) and the multivariate option in Eq 5 (parameter α_1 and α_2) models respectively. Values given in parentheses represent 95% Wald type Confidence Intervals (CI) and the *p*-values represent the statistical significance of the parameter values (and not the statistical significance of model improvement by their inclusion in the model). Models that did Not Converge are identified with NC.

Covariable name (unit)	β_2, *ERR*/unit exposure relative to external background (i.e. with β_1, fixed at unity)	β_1, free, internal to external background ratio	β_2, *ERR*/unit exposure relative to internal background (i.e. with β_1, free)	α, *ERR*/unit exposure	α_1 α_2 *ERR*/unit exposure
Gamma (Gy)	NC	0.90 (0.78; 1.02) ($p < 0.001$)	-1.27 (-2.4; -0.14) ($p = 0.03$)	-1.18 (-2.4; 0.02) ($p = 0.055$)	
Medium PA (years)	-0.010 (-0.019; -0.001), ($p = 0.04$)	0.87 (0.74; 0.99) ($p < 0.001$)	-0.003 (-0.17; 0.01) ($p > 0.5$)	-0.003 (-0.016; 0.011) ($p > 0.5$)	
High PA (years)	-0.003 (-0.016; 0.010) ($p > 0.5$)	0.81 (0.69; 0.93) ($p < 0.001$)	0.01 (-0.01; 0.03) ($p = 0.26$)	0.013 (-0.008; 0.033) ($p = 0.24$)	α_1 = 0.021 (0.001; 0.040) ($p = 0.04$)
Underground work (10^5days)	-4.44 (-7.11; -1.76) ($p = 0.001$)	0.93 (0.78; 1.08) ($p < 0.001$)	-3.30 (-7.20; 0.06) (p=0.097)	-3.07 (-7.12; 0.99) (p =0.14)	α_2 = -5.59(-9.81;-1.36) ($p = 0.01$)

Table 3 Results of applying Model selection techniques with the likelihood ratio test for variable selection. The changes in degrees of freedom (*d.f.*) and deviance are all with respect to the stratified background model which had a deviance of 3178.9 for a *d.f.* of 555433. *g, mpa, hpa, u* and *a* represent gamma prostate dose, years at medium PA, years at high PA, days worked underground and age attained respectively. The top section represents a sub-set of seven models (preferred model in bold) from a complete sorted list of all models tested, for which the probability of model improvement with respect to the stratified background model had a *p*-value under 0.10. The lower section represents the model selection results for all 4 models with single exposure covariables – none of which resulted in a statistically significant model improvement when compared to the background model.

Covariables in model, form			**Δ *d.f.***	**Δ deviance**	***p*-value**
u, linear	***hpa, linear***		***2***	***6.47***	***0.039***
u, linear	*mpa*, linear	*hpa*, linear	3	7.25	0.064
u, linear	*hpa*, linear	*a*, exponential	3	7.23	0.065
u, linear	*hpa*, linear	*a*, power	3	7.15	0.067
u, linear	*hpa*, linear	*hpa,* squared	3	7.06	0.070
u, linear	*u*, squared	*hpa*, linear	3	6.75	0.080
u, squared	*hpa*, linear		2	5.04	0.080
	ERR/unit exposure (SE)				
g, linear	$-1.2\ (0.6).10^{-3}$		1	2.61	0.107
u, linear	$-3.1\ (2.1).10^{-5}$		1	1.88	0.171
hpa, linear	$1.3\ (1.1).10^{-2}$		1	1.61	0.204
mpa, linear	$-2.8\ (7.0).10^{-3}$		1	0.15	0.697

Original paper

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Prostate cancer mortality risk in relation to working underground in the Wismut cohort study of German uranium miners, 1970-2003

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Abstract

Objective: A recent study and comprehensive literature review has indicated that mining could be protective against prostate cancer. This indication has been explored further here, by analysing prostate cancer mortality in the German "Wismut" uranium miner cohort which has detailed information on the number of days worked underground.

Design: An historical cohort study of 58,987 male mine workers with retrospective follow-up before 1999 and prospective follow-up since 1999.

Setting and participants: Uranium mine workers employed during the period 1970-1990 in the regions of Saxony and Thuringia, Germany, contributing 1.42 million person years of follow-up ending in 2003.

Outcome measure: Simple Standardised Mortality Ratio (*SMR)* analyses were applied, to assess differences between the national and cohort prostate cancer mortality rates, and complemented by refined analyses done entirely within the cohort. The internal comparisons applied Poisson regression excess relative prostate cancer mortality risk model with background stratification by age and calendar year and a whole range of possible explanatory covariables that included days worked underground, years worked at high physical activity with gamma radiation treated as a confounder.

Results: The analysis is based on miner data for 263 prostate cancer deaths. The overall *SMR* was 0.85 (95% CI 0.75; 0.95). A linear excess relative risk model with the number of years worked at high physical activity and the number of days worked underground as explanatory covariables provided a statistically significant fit when compared to the background model (p=0.039). Results (with 95 % confidence intervals) for the *ERR* per day worked underground indicated a statistically significant (p=0.0096) small protective effect of $-5.59(-9.81;-1.36).10^{-5}$.

Conclusions: Evidence is provided from the German Wismut cohort in support of a protective effect from working underground on prostate cancer mortality risk.

Introduction

Prostate cancer is the second most common cancer diagnosed among men (after lung cancer), and is the sixth most common cause of cancer death among men world-wide [1]. In the European Union in 2006, prostate cancer was the most common form of incident cancer and the third most common form of cancer death in men (Table 3 of [2]). Prostate cancer incidence in Germany has also become the most common form of incident cancer disease in men. It is notable that the prostate cancer mortality rates were approximately constant in the former eastern German Democratic Republic (GDR) between 1960 and 1980, but rose during the same time by 50% in West Germany [3].

Prostate cancer is, in general, a slow-growing tumour with a long latency and an uncertain aetiology. The prevalence of latent microscopic prostate tumours has been shown to be quite high in the elderly in most populations i.e. at least 50 percent in men over the age of 70 years [4]. Although there are only a few established risk factors for prostate cancer such as age, race and a family history of prostate cancer [5] there are also several mooted detrimental and protective associations.

The possible detrimental associations include early baldness [6], shift-work [7], arsenic exposures [8], diesel fume exposure [9] and oestrogen exposures [10]. Some evidence exists for radiation related prostatic detrimental effects from studies on patients after diagnostic radiation procedures [11], occupationally exposed British nuclear workers [12], military and civil pilots and flight attendants [13], and persons exposed by the Chernobyl accident [14]. There was little evidence of a prostate cancer risk radiation dose response in the Japanese A-bomb survivors [15]. A recent meta-analysis of 24 cohort studies has concluded that an association of smoking with prostate cancer incidence and mortality exists [16].

The possible protective associations include high sexual and/or androgenic activity [17], UV and/or vitamin D [18], high Physical Activity (PA) [19] - although some inconsistent results are observed for PA - and melatonin [20-23]. For a cohort of U.S.A. male health professionals, [24] reported that for fatal prostate cancer, a recent smoking history, taller

height, higher BMI, family history, and high intakes of total energy, calcium and α-linolenic acid were associated with a statistically significant increased risk but higher vigorous PA level was associated with lower risk.

A recent Australian population-based case-control study and literature review [25] has indicated that mining could be protective against prostate cancer. [25] concluded that the relationship between mining and prostate cancer could possibly be connected to levels of either PA or changes in melatonin production caused by periods working underground and that these relationships deserve further investigation. Differential risk could not be reported in [25] because all but one of the studies reviewed did not report on working periods underground and overground. The main purpose of the present paper is to explore these indications further by analysing prostate cancer mortality risk in a cohort of male mine workers involved in uranium extraction at the former Wismut company in East Germany applying both external (national male rates for the former GDR) and internal backgrounds. New covariables for occupational PA and time spent underground have been specially created for this investigation. Simple Standardised Mortality Ratio (*SMR*) analyses are complemented by refined analyses done entirely within the cohort.

The German "Wismut" uranium mine workers cohort has currently been followed-up from 1.1.1946 to 31.12.2003, with almost 2 million person-years of observation and has already been described in detail [26]. It is currently the largest miners cohort study and several analyses of the detrimental health effects data pertaining to the 58,987 male former employees, have recently been published [27-33].

There are several occupational risk factors for detrimental health effects, relevant to the cohort members, particularly with respect to lung cancer, including exposure to radon, gamma radiation, long-lived radionuclides, [34], fine dust, arsenic dust and quartz dust [35], asbestos [36] and diesel exposure. However exposure covariables for the latter two quantities are not available in the cohort data. Previous analyses have shown that the mortality from prostate cancer in this cohort (1960-2006) is notably lower than in the comparison population of the former GDR (*SMR* = 0.88, 95%CI = 0.78; 1.00 [27]). The total absorbed dose to the prostate has not yet been calculated. However since the absorbed dose to non-respiratory track organs is dominated by external gamma radiation and the contributions of radon progeny, radon gas and particularly long-lived radionuclides are expected to be only a few percent [37], only the

gamma radiation is explicitly considered here, as a potential confounder. The effective gamma doses have been converted into prostate organ dose via Voxel model dose conversion factors [38].

Material and Methods

Cohort definition, time periods and mortality follow-up.

Full details of the cohort have already been given [28, 30]. Every cohort member contributes to the number of person years starting 180 days after the date of first employment and ending at the earliest of date of loss to follow-up, date of death, or end of follow-up (31.12.2003). Due to the relatively high Percentage of Missing Causes of Death (PMCD) of 37.25% and the systematic variation of PMCD with calendar time from 1946 to 1969, the analyses here are based on the subset of Wismut miner cohort data covering the period 1970-2003 for which the PMCD is 3.56%. Consequently, no corrections for missing causes of death have been made. This difference in PMCD is due to the late start of data collection for this cohort on 1.1.1999, linked with the fact that death certificates were rarely kept by the authorities for more than 30 years.

National rates for the former GDR covering the same calendar-year range are applied for the external comparisons. Former disease codes of the comparison external background rates for the GDR were re-coded via earlier ICD revisions to the 10th ICD-code [39], which was applied throughout. This recoding process was complicated by several revisions to ICD codes during the period of data coverage, and German reunification. Population prostate cancer rates are not available just for the relevant mining region of Thuringia and Saxony. Consequently, the external rates applied here cover the total area of the former GDR (including East-Berlin) during the time period 1970–1997; in contrast, from 1998 the rates pertain to the former GDR states and the whole of Berlin. The codes used here in the various time periods are as follows: 1970–1978 ICD 8, code number 185; 1979 ICD 8, code number 179-189 for the urogenital system; 1980–1997 ICD 9, code number 185; 1998–2003 ICD 10, code number C61 all for Prostate cancer.

Analysis.

The Poisson regression methods applied here require the tabulation of the individual data, into grouped data records, as described below and in previous analyses [30-32]. This is because the input data for Poisson regression needs to consist of records containing the number of prostate cancer cases, the number of person-years and the mean values of the possible explanatory covariables. Poisson regression is a likelihood based method for the quantitative analysis of such records or "event-time tables" [40], whereby the rates to be modelled are computed as the ratios of prostate cancer cases to person-years for each record in the input data set. Descriptions of the background rates (i.e. the spontaneous rates) were necessary to assess the excess risks, whereby such descriptions can either be based on models derived directly from the cohort data (internal comparisons) or from data on the GDR population rates (external comparisons).

Quantitative risk evaluation methods were based on the simple *SMR* model, where the SMR is the ratio of the observed number of prostate cancer deaths in the cohort to the number of prostate cancer deaths expected in the comparison population, (see [40], pages 65-68). It is possible that an increased or decreased overall SMR could be a result of either an occupational or life-style exposure effect in the data. This can be tested directly by considering the simple SMR model with an exposure response to various possible explanatory covariables, for external and internal comparisons. In the case of the SMR model for external comparisons with an exposure response, a background SMR is computed (i.e. the overall ratio of the observed background number of prostate cancer deaths in the cohort to the number of prostate cancer deaths expected in the comparison population) with an additional SMR that is linearly dependent on the covariable of interest.

The more refined analysis entirely within the cohort (internal comparisons) applied Poisson regression excess relative prostate cancer mortality risk model with background rate stratification by age and calendar year and a whole range of possible explanatory covariables: age (*a*), year (*y*), gamma prostate dose (*g*), years at medium Physical Activity (PA) (*mpa*), years at high PA (*hpa*), days worked underground (*u*) and time since either first or last underground shift (*t*).

Data Tabulations.

Tabulations of person-years at risk and cancer deaths were created with the DATAB module of the EPICURE software [41] for the whole cohort data (1946-2003), so that the covariables of interest could be accumulated from the beginning of the cohort. The period of interest here

was then selected to be 1970-2003 during the data-analysis and model fitting procedures. Cross-classifications were made by attained age, *a*, in 16 categories (<15, 15–<20, 20–<25, … , 85+ years), individual calendar year, *y*, in 58 categories, and cumulative gamma prostate doses, with a five-year lag-time (8 categories: 0, >0–<50, 50–<100, 100–<150, 150–<200, 200–<300, 300–<400, 400+ mGy). For the current analysis new covariables for occupational PA and time spent underground have been specially created. Exact shift information relating to daily underground and overground activities in each calendar year was used. The number of days worked underground in any one calendar year was then accumulated over calendar years of employment in 8 categories (0, >0–<1000, 1000–<2000, 2000–<3000, 3000–<4000, 4000–<5000, 5000–<6000, 6000+ days). For the PA categories, information on the job type in each calendar year was extracted from the Wismut records. Each of the several hundred job types had already been classified into three levels of PA corresponding to different breathing rates for the purpose of organ dose calculations e.g. job types hewer, metal worker and lorry driver were classified as high, medium and low PA respectively. The number of years worked in each of the high and medium PA classes were then accumulated over calendar years of employment, each in 8 categories (0, >0–<5, 5–<10, 10–<15, 15-<20, 20–<25, 25–<30, 30+ years). Choice of units (years or days) reflects the quality of the information available in the mining records.

Standardized Mortality Ratios.

Mortality rates observed in the cohort were compared with the GDR external rates. The first stage of the *SMR* analysis for prostate cancer has been done as described previously for extra–pulmonary cancers [28] with some extensions that allow a comparison of internal (miner cohort) and external (former GDR) background (spontaneous) rates. Justifications for the generally preferable internal comparison (done entirely within the cohort), connected with differences in the maturity of the smoking epidemic between the cohort and the GDR, have recently been given [32]. The simplest *SMR* model relates the rates in the population of interest (the miner cohort) to a multiple of the rates from the external population (the former GDR).

If $\lambda^*(a, y)$ denotes the external rates as a function of age and calendar year and $\lambda(a, y)$ denotes the observed rates in the miners cohort, then the *SMR* model can be written as

$$\lambda(a, y) = \beta \cdot \lambda^*(a, y) \qquad (1)$$

where the β is a fit parameter and represents the *SMR*.

However it is also possible to fit a relative risk (*RR*) model

$$RR(a, y, g) = \beta_1 \cdot \lambda^*(a, y) \cdot (1 + \beta_2 (g)) \quad (2)$$

to estimate the effects of various possible explanatory covariables, such as gamma prostate dose (g), based on the GDR external rates, assuming that the *SMR* for the background rates is identically equal to 1, i.e. β_1 is fixed to unity during the optimisation. In this case, β_2 is a fit parameter that then gives the simple Excess Relative Risk (*ERR*) per unit of exposure relative to the external GDR rates. It is also possible to test if the external GDR rates are different from the internal background rates in the miner cohort by simply freeing the parameter β_1 and repeating the optimisation. All of the parameters β, β_1 and β_2 can be multiplied by a two level categorical variable for either levels of PA or time spent underground.

Refined *ERR* models with background stratification by age and calendar year were employed – if $r(a, y, g, mpa, hpa, u, t)$ is the prostate cancer mortality rate and $r_0(a,y) = r(a,y,0,0,0,0,0)$ is the background disease rate for non-exposed individuals, $g = 0$, $mpa = 0$ …etc. then

$$R(a, y, g, mpa, hpa, u, t) = r_0(a, y) \cdot \{1+ERR(g, mpa, hpa, u, a, t)\}, \quad (3)$$

where *ERR* is the excess relative risk factorised into a function of exposure, f(g, mpa, hpa, u) and a modifying function, h(a, t):

$$ERR(g, mpa, hpa, u, a, t) = f(g, mpa, hpa, u) \cdot h(a, t) \quad (4)$$

The gamma prostate dose, years at medium PA, years at high PA and days worked underground were each included:

singularly, $f(g) = \alpha\, g$, etc, and pair-wise $f(g, mpa) = \alpha_1\, g + \alpha_2\, mpa$, etc. (5)

in the linear *ERR* model, both with and without the modifying function, and assessed with model selection techniques to arrive at the model with the lowest deviance with respect to the background model, by forward selection. Backwards selection was also tested. Finally the preferred linear model was tested for non-linearity, by adding quadratic terms for exposure covariables, and time or age effect modification (i.e. adding g(a, t) functions to the model).

Maximum likelihood with the AMFIT module of the EPICURE software [41] was used for estimation of the *SMR* and *ERR* fit parameters associated with equations 1 to 5 above.

Confidence Intervals (CI) were computed at the 95% level and the Wald type CI are given since, although very similar intervals were found with the profile likelihood based CIs, some of the lower limits could not be numerically calculated with the latter method.

Results

Out of the total 58,987 cohort members in the complete follow-up period between 1946 and 2003, 55,435 members were included in the follow-up from 1970 specifically considered in the risk analysis presented here. In total, 20,920 persons were deceased (of which 1,560 died before 1970), 35,294 were alive and 2,773 were lost to follow-up (of which 1,992 were lost before 1970). There were 263 prostate cancer deaths observed during 1.42 million person years of observation between 1970 and 2003. The cumulative numbers of observed and expected prostate cancer deaths in this period are shown in Figures. 1a and 1b as a function of calendar year from 1970 and age attained from 40 years. The absolute number of prostate cancers occurring reaches a maximum in the category 75 to 80 years of age, due to the age distribution in the cohort, and increases steadily from 1970 to 2003 and the cumulative number of prostate cancers increases as a function of age attained and calendar year.

The mean values (and ranges) of age-attained, mean number of days worked underground and mean number of years worked at high PA are 47 (14-103) years, 1649 (0-10704) days and 3.5 (0-44) years respectively. Table 1 gives the category specific values for the number of prostate cancer deaths and person-years, for the number of years worked at high PA and days spent underground categories of mine workers.

***SMR* results (comparison of cohort rates with external rates, Eq 1).**

The total number of deaths from prostate cancer (1970–2003) observed (O), was significantly lower ($p < 0.001$) than expected (E) from national rates. The *SMR* value with 95% confidence intervals (CI) is 0.85 (0.75; 0.95). Quantitative differences between GDR external rates and internal cohort rates can be assessed directly from a categorical *SMR* analysis in categories of attained-age and calendar year. Some statistically significantly low categorical *SMR* values were found mainly in the age group 65 to 75 years, and in the calendar period from 1991 to 1995 (results not shown). The overall *SMR* with 95% confidence intervals when recomputed by two categories of below and above mean time spent underground (1649 days) becomes 0.92 (0.76; 1.07) and 0.79 (0.65; 0.92) respectively. The *SMR* recomputed by two categories

of below and above mean time worked at high PA (3.52 years) becomes 0.82 (0.69; 0.94) and 0.91 (0.73; 1.10) respectively.

Simple *ERR* parametric cohort risk models (comparison of cohort rates with external rates, Eq 2).

Cumulative exposure effects for various covariables in terms of *ERR* per unit exposure and 95% CIs are given in the first results column of Table 2. The *ERR*/day worked underground, relative to the external GDR rates, is -4.44 (-7.11; -1.76).10^{-5} and was found to be the statistically strongest exposure effect (p = 0.001) i.e. decreased for the number of days worked underground relative to the external rates. A similar value of -3.3 (-7.2; 0.06) .10^{-5} relative to the internal controls was found (Table 2, second results column), although of reduced statistical significance (p = 0.097). This latter result is connected with a background SMR of 0.93 (0.78; 1.08) (Table 2, second results column). The *SMR* model did not converge (NC) for the gamma prostate dose relative to the external background rates. A statistically significant (p-value = 0.03) decreased *ERR*/Gy for prostate gamma doses, relative to the internal background of -1.27 (-2.4; -0.14) was also found (Table 2, second results column).

Refined *ERR* parametric cohort risk models (Eqs 3-5).

The statistical significance of *ERR*/Gy for prostate gamma doses reported with the simple analysis was not confirmed by the refined analysis (*ERR*/Gy=-1.18 (-2.4; 0.02), see table 2, third results column). Although the coefficient for gamma dose was of borderline statistical significance in the univariate model, the forward selection did not keep the gamma prostate dose in the multivariate model. A preferred model by forward selection of the covariables gamma prostate dose, *g*, years at medium PA, *mpa*, years at high PA, *hpa* and days worked underground, *u* taken linearly one or two at a time was found to be the model that included both *hpa* and *u* (Table 3). This model had a reduction in deviance with respect to the stratified background model of 6.5, (p = 0.04) by the Likelihood Ratio test. This model provided the results in the last column of table 2, (with 95 % confidence intervals) for: the *ERR* per day worked underground, which indicates a statistically significant (p=0.01) small decreased effect of -5.59(-9.81;-1.36).10^{-5} and; for the *ERR* per year worked at high physical activity, which indicates a statistically significant (p = 0.04) small detrimental effect of 0.021 (0.001; 0.040). The clinical significance of the results can be assessed by obtaining the number of deaths from prostate cancer prevented in this cohort from working underground, obtained from the fitted background and fitted excess number of cases in the preferred model.

Depending on whether the slightly increased risk from high physical activity is accounted for or not, this number is either 14 or 22 prostate cancer deaths respectively.

Models that included just *hpa* or just *u* did not result in statistically significant risks (Table 2, third results column) or lead to statistically significant model improvement (Table 3). No evidence for an interaction between *hpa* and *u* was indicated by including a cross term in the preferred model (p>0.5). Testing of the quadratic or parabolic forms for *hpa* and *u* or testing risk effect modification by attained age (Table 3) or time since first or last underground shift (results not shown) did not lead to statistically significant model improvement. The dose response forms for the preferred model and the adjusted non-parametric risks with 95% confidence intervals are shown in Figure 2. It was not possible to confirm this result by backwards selection since the models with all 6 main covariables failed to converge.

Discussion

The Wismut cohort is one of the largest single occupational cohorts and one of only a few cohorts with detailed information on the number of shifts worked underground. Although the number of shifts was documented, it is not known if these were early morning, day-time or night shifts. A substantial proportion (25%) of person-years are contributed by mine workers who did not work underground which generally ensures the stability of analyses based on internal rates. The *ERR* per unit of various exposures have been modelled relative to the internal rates and relative to the external rates for the general population of the former GDR.
A statistically significant (p = 0.001) negative response for the *ERR* per day worked underground, when modelled in relation to the general population of the former GDR, is reported here. There are some indications of unit exposure responses of the *ERR* which are decreased for gamma prostate dose, (p= 0.03 and 0.055 for the simple and refined models respectively) with respect to the internal rates. Rather than being decreased, the gamma dose is a possible proxy variables for the number of days worked underground since there are moderate degrees of correlations between these covariables (ρ = 0.68 for the correlation between time dependent cumulative gamma prostate doses and the number of days worked underground, see also table 1). Indication that the gamma dose may be acting as a proxy was tested here directly by the creation of new categories of mine workers, with numbers of years worked at high or medium PA and the number of days worked underground and the application of model selection techniques.

The assumption is made in this paper that radon and long-lived radionuclides make only minor contributions to the total prostate dose. Previous analyses have shown that the *ERR* per 100 WLM of radon exposure, based on internal Poisson models, was not elevated for prostate cancer (*ERR*/100 WLM= 0.000, 95%CI, -0.024; 0.024, [31]). None of the radiation covariables (i.e. gamma prostate dose, but also including long-lived radionuclides and radon), when tested by inclusion singularly as linear risks in refined internal Poisson regression models, resulted in a deviance drop of more than 3 with respect to the background model which was stratified on age-attained and calendar year.

A linear excess relative risk model with the number of years worked at high physical activity and the number of days worked underground as explanatory covariables provided a statistically significant fit when compared to the background model ($p = 0.039$). Results (with 95% CI) for the *ERR* per day worked underground indicated a statistically significant ($p = 0.01$) small decreased effect at $-5.59(-9.81;-1.36).10^{-5}$ and, for the *ERR* per year worked at high physical activity, a statistically significant ($p = 0.04$) small detrimental effect at 0.021 (0.001; 0.040). This main result provides new evidence in support of the decreased effect of working underground which is manifested with respect to the internal and the external rates.

The number of days worked underground is connected with a particular hypothesis for reduced prostate cancer rates e.g. melatonin production rates (as described in detail in [25] and references therein). In summary, melatonin has been shown to have anti-cancer properties acting through several mechanisms [20-23]. The production of melatonin in the pineal gland is regulated by the natural diurnal light-level cycle, with suppressed production during the day which is restored at night. Underground miners on day shifts would have a reduced exposure to visible light leading to an extended melatonin production period.

The relation between physical activity and prostate cancer risk was classified as “probable” with respect to an increased risk, by the IARC in 2002 [42] but no definite mechanisms have been identified for a relation between PA and prostate cancer. Several plausible mechanisms have been postulated which include modulation of testosterone and vitamin D levels by PA, a link between physical inactivity and over-weight/obesity and a beneficial modulation of immune function through exercise (see [43] for a review). A recent systematic review and meta-analysis [44] considered 13 studies with occupational physical activity, considered to be

"higher-quality" studies and reported that 9 studies gave a decreased risk, one study an increased risk and 3 studies reported no association. Two other studies have reported increased risks: [45] found that intensity of occupational PA was associated with increased prostate cancer risk and [46] reported an increased risk for obese men (BMI over 30) who were physically active for more than 1 hour per day and in men with high background energy intake.

A statistically significant increase in risk with increasing high PA is observed here, in contrast to the IARC classification and the majority of other studies. It is important to note that the variable physical activity here measures only part of the total PA and could be prone to misclassification. The PA variable is limited to the work period at the Wismut company (the mean duration of work at the company 14 years) and no leisure time activities could be considered. The classification is simply based on job type without consideration of possible changes in physical activity in a specific job over time e.g. due to improved technical "labour-saving" equipment. Physical activity could also be an indicator of socioeconomic status, because the jobs with low PA are more likely to be associated with higher education.

Another possible source of bias in the results based on external comparisons that should be considered is the selection bias known as the healthy worker effect. However this effect, which can generally lead to occupational cohorts presenting mortality risks less than the general population, is not indicated since the risks are similar with respect to internal and external backgrounds. The occurrence of this form of bias could also be tested here by considering all solid cancer minus the sites that have already been linked to the main mine radiation exposure, i.e. radon (lung, larynx, tongue, mouth and pharynx). For this group of cancers the *SMR* with 95%CI is 1.01 (0.97; 1.04) also indicating that the healthy worker effect is not having a significant influence on the prostate cancer results in this cohort.

A further source of bias, possibly affecting the decrease in risk with increasing duration of working underground based on internal comparisons, could be the healthy worker survivor effect. Unhealthy workers may move from working underground to working at the surface. Consequently, the duration of working underground may be higher in the healthy group compared to the unhealthy group, leading to artificially decreased effects in relation to duration of working underground. However this effect has been tested for by fitting the

preferred model, that included both the number of days worked underground and number of years worked at high physical activity, to the sub-group of all solid cancers minus the sites that have already been linked to the main mine radiation exposure (lung, larynx, tongue, mouth and pharynx) and minus prostate. No significant trends were found ($p>0.5$ for the linear trend of ERR with respect to the number of days worked underground and $p=0.11$ for the linear trend of ERR with number of years worked at high physical activity) indicating that the healthy worker survivor effect is not directly biasing the results for prostate cancer.

Although there is no general consensus as to whether radiation exposure is associated with prostate cancer risk [47], an X-ray procedure risk doubling dose of about 20 mGy for prostate cancer incidence has been reported [11]. The magnitudes and ranges of the gamma prostate doses in the Wismut study (with the prostate cancer mortality cases having a range up to 444 mGy and the cohort person-year weighted mean gamma prostate dose of 34mGy) should be large enough to find such an increased risk at the 20 mSv level given the similar relative biological effect of X-rays and gamma rays. However, a gamma risk, at this 20 mSv level, has not been found in the Wismut cohort data for prostate cancer mortality.

Yang et al [8] reported that *SMR*s for prostate cancer declined gradually in a SW coastal district of Taiwan after the arsenic contaminated artesian well drinking-water supply was improved to a tap-water system. Since arsenic dust exposures are also available for the Wismut miners [35], an arsenic covariable could be added to the preferred model for physical activity and time worked underground described above in a subsidiary analysis, but this only resulted in a deviance drop of 1.2 and a p-value of 0.33 for the associated arsenic risk coefficient and did not confound the main risks from the preferred model.

An examination of the effects of smoking on the risk of prostate cancer mortality, as indicated in [16] could not be carried out for the Wismut cohort due to only a very limited amount of information on smoking being available [29].

Although there were 264 prostate cancer deaths in the whole cohort, only one occurred before 1970 i.e. during the period with a higher percentage of missing causes of death. This is consistent with prostate cancer generally being a type of cancer that occurs predominantly in old-age coupled with the observation that – due to miners entering and leaving the cohort at various points in time during the follow-up period – the cohort aged, on average, at half the

rate of any individual, i.e. in 1960 and 2003 the mean ages of cohort members were 35 and 57 years respectively. Consequently it is very important to continue work on extending the current follow-up period.

Conclusions

This work has extended the evidence in support of a decreased, possibly protective, effect for prostate cancer mortality from working underground provided in [25] and could be interpreted as support for "The Melatonin Hypothesis". A linear internal excess relative risk model with the number of years worked at high physical activity and the number of days worked underground as explanatory covariables provided a statistically significant fit when compared to the background model ($p = 0.039$). Results (with 95% CI) for the *ERR* per day worked underground indicated a statistically significant ($p = 0.0096$) small decreased, possibly protective, effect at $-5.59(-9.81;-1.36).10^{-5}$. It is this main result that provides the new evidence in support of the protective effect of working underground which is also manifested with respect to the external rates. Additional computations made to examine the influence of biases due to the gamma doses, the healthy worker selection effect and the healthy worker survivor effect indicate that the results are unbiased in these respects, but the effects of such biases cannot be entirely excluded.

Acknowledgement The German Federal Commissioner for Data Protection and Freedom of Information has issued a special approval for this research which constitutes an exemption from the necessity to obtain human subjects approvals. This work was partially funded by the EU Alpha-Risk project and by the Federal Ministry of Education and Research (BMBF), Germany (Competence Network Radiation Research). The authors thank the German Federation of Institutions for Statutory Accident Insurance and Prevention (DGUV) and the Miners' Occupational Compensation Board (Bergbau Berufsgenossenschaft) for their continuous support over many years. The field work for the follow-up was conducted by I+G Gesundheitsforschung and Mediveritas GmbH. Their commitment helped to achieve the low percentage of lost to follow-up. We also thank the members of the Wismut Working Group of the German Radiation Protection Commission for their continued advice. Thanks are also due to Dr. Nina Petoussi-Henss for providing the gamma dose factor for converting effective dose to organ dose. We would also like to thank Prof. Donald A. Pierce for useful discussions and three reviewers for comments and suggestions that lead to an improved paper.

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Figure Captions

Fig 1a The cumulative number of prostate cancer deaths observed in the Wismut cohort and expected from GDR rates as a function of calendar year.

Fig. 1b The cumulative number of prostate cancer deaths observed in the Wismut cohort and expected from GDR rates as a function of age-attained..

Fig 2 The upper panel shows the *ERR* and 95%CI as a function of mean number of years with high PA and corresponds to the risk given in the last column of Table 2. The non-parametric points with 95%CI are adjusted for mean number of days worked underground. The lower panel shows the *ERR* and 95%CI as a function of mean number of days worked underground and corresponds to the risk given in the last column of Table 2. The non-parametric points with 95%CI are adjusted for mean number of years with high PA.

Figures

Figure 1a.

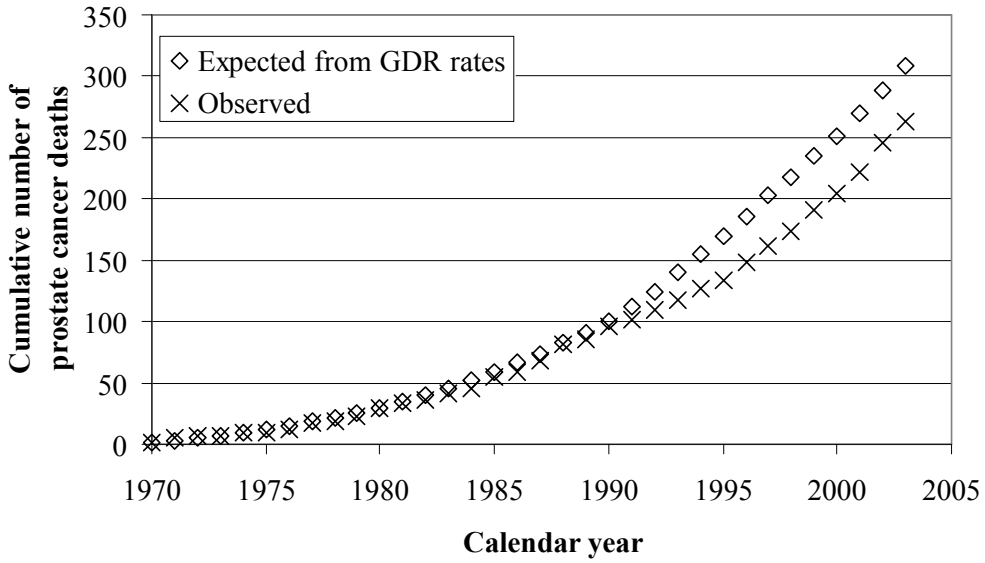


Figure 1b.

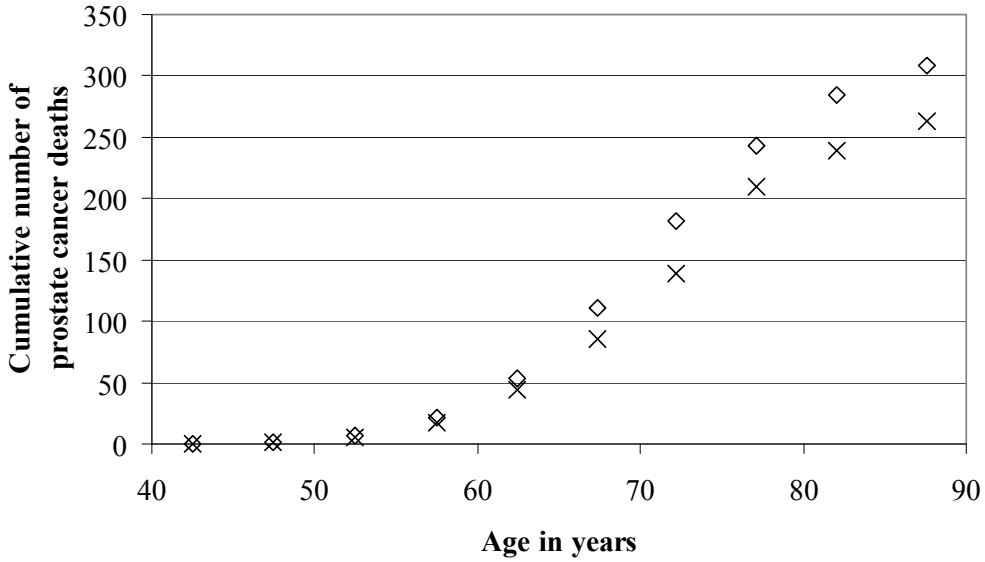
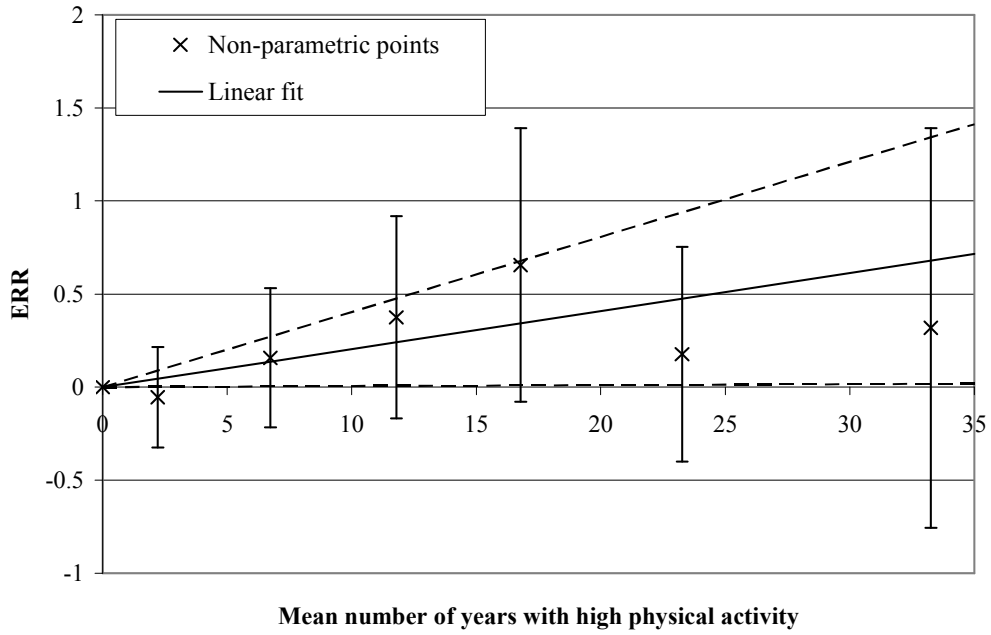


Figure 2.



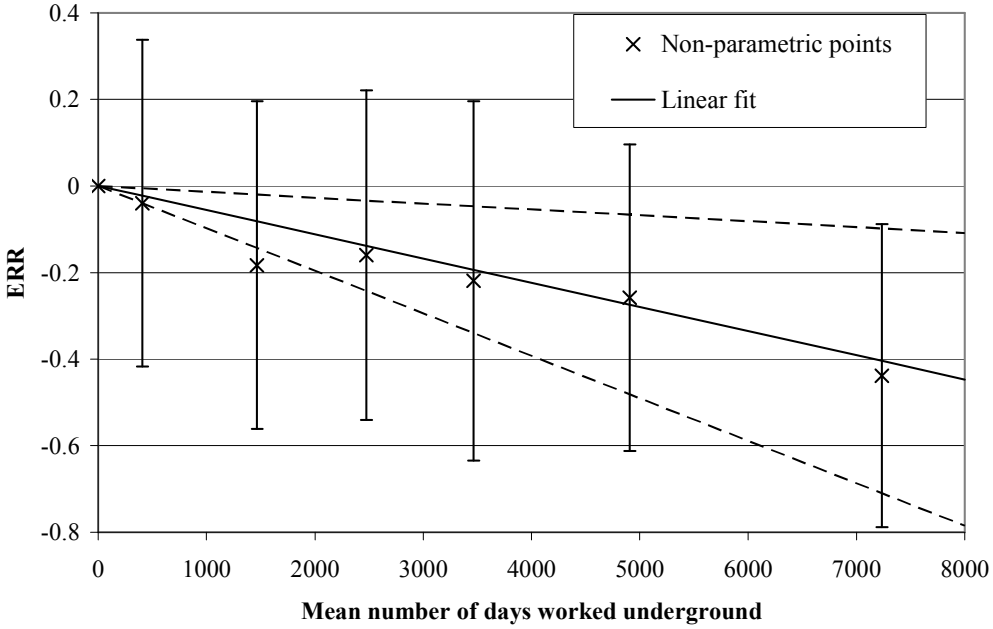


Table 1 Category means and ranges for the number of days worked underground and the number of years worked at high physical activity (PA). In each category the number of deaths from prostate cancer mortality, the number of person-years at risk (rounded) and the mean cumulative person-year weighted gamma prostate dose (with standard deviation) are given.

Category means (and ranges)	**number of prostate cancer deaths**	**number of person-years**	**mean gamma prostate dose** (mGy, with standard deviation)
mean number of days worked underground			
0	67	360536	1.1 (4.4)
408 (2 – 999.9)	46	429624	7.5 (9.9)
1466 (1000 – 1999.8)	30	184782	24.5 (26.7)
2475 (2000 – 2999.8)	34	139204	42.0 (44.2)
3465 (3000 – 3999.9)	24	97808	68.3 (65.5)
4908 (4000 – 5999.9)	37	138138	111.4 (93.9)
7236 (6000 – 10704)	25	74836	156.9 (127.4)
mean number of years worked at high PA			
0	122	726358	9.8 (28.1)
2.2 (1 – 4)	52	342896	19.2 (33.1)
6.7 (5 – 9)	37	165377	47.0 (46.9)
11.8 (10 – 14)	22	87297	94.5 (73.5)
16.8 (15 – 19)	16	54598	148.3 (94.2)
23.3 (20 – 29)	11	40425	199.4 (123.1)
33.3 (30 – 42)	3	7978	238.3 (163.0)

Table 2 Results of fitting the models. The first and second numerical partitions are for the Standardized Mortality Ratios (*SMR*) (from Eq 2). The interpretation of β_1 is that it represents the overall ratio of the observed background number of prostate cancers deaths in the cohort to the number of prostate cancer deaths expected in the comparison GDR population – and β_2 is the additional incremental SMR that is linearly dependent on the covariable of interest listed in the first column of the table i.e. an ERR/unit exposure of the covariable of interest. The third and fourth numerical partitions are for the Excess Relative Risk (*ERR*) internal regression models with background rates stratification on age and calendar year (from Eqs. 3, 4 and 5) for the univariate option in Eq 5 (parameter α) and the multivariate option in Eq 5 (parameter α_1 and α_2) models respectively. Values given in parentheses represent 95% Wald type Confidence Intervals (CI) and the *p*-values represent the statistical significance of the parameter values (and not the statistical significance of model improvement by their inclusion in the model). Models that did Not Converge are identified with NC.

Covariable name (unit)	β_2, *ERR*/unit exposure relative to external background (i.e. with β_1, fixed at unity)	β_1, free, internal to external background ratio	β_2, *ERR*/unit exposure relative to internal background (i.e. with β_1, free)	α, *ERR*/unit exposure	α_1 α_2 *ERR*/unit exposure
Gamma (Gy)	NC	0.90 (0.78; 1.02) ($p < 0.001$)	-1.27 (-2.4; -0.14) ($p = 0.03$)	-1.18 (-2.4; 0.02) ($p = 0.055$)	
Medium PA (years)	-0.010 (-0.019; -0.001), ($p = 0.04$)	0.87 (0.74; 0.99) ($p < 0.001$)	-0.003 (-0.17; 0.01) ($p > 0.5$)	-0.003 (-0.016; 0.011) ($p > 0.5$)	
High PA (years)	-0.003 (-0.016; 0.010) ($p > 0.5$)	0.81 (0.69; 0.93) ($p < 0.001$)	0.01 (-0.01; 0.03) ($p = 0.26$)	0.013 (-0.008; 0.033) ($p = 0.24$)	α_1 = 0.021 (0.001; 0.040) ($p = 0.04$)
Underground work (10^5days)	-4.44 (-7.11; -1.76) ($p = 0.001$)	0.93 (0.78; 1.08) ($p < 0.001$)	-3.30 (-7.20; 0.06) (p=0.097)	-3.07 (-7.12; 0.99) (p =0.14)	α_2 = -5.59(-9.81;-1.36) ($p = 0.01$)

Table 3 Results of applying Model selection techniques with the likelihood ratio test for variable selection. The changes in degrees of freedom (*d.f.*) and deviance are all with respect to the stratified background model which had a deviance of 3178.9 for a *d.f.* of 555433. *g, mpa, hpa, u* and *a* represent gamma prostate dose, years at medium PA, years at high PA, days worked underground and age attained respectively. The top section represents a sub-set of seven models (preferred model in bold) from a complete sorted list of all models tested, for which the probability of model improvement with respect to the stratified background model had a *p*-value under 0.10. The lower section represents the model selection results for all 4 models with single exposure covariables – none of which resulted in a statistically significant model improvement when compared to the background model.

Covariables in model, form			**Δ *d.f.***	**Δ deviance**	***p*-value**
u, linear	***hpa, linear***		***2***	***6.47***	***0.039***
u, linear	*mpa*, linear	*hpa*, linear	3	7.25	0.064
u, linear	*hpa*, linear	*a*, exponential	3	7.23	0.065
u, linear	*hpa*, linear	*a*, power	3	7.15	0.067
u, linear	*hpa*, linear	*hpa,* squared	3	7.06	0.070
u, linear	*u*, squared	*hpa*, linear	3	6.75	0.080
u, squared	*hpa*, linear		2	5.04	0.080
	ERR/unit exposure (SE)				
g, linear	$-1.2\ (0.6).10^{-3}$		1	2.61	0.107
u, linear	$-3.1\ (2.1).10^{-5}$		1	1.88	0.171
hpa, linear	$1.3\ (1.1).10^{-2}$		1	1.61	0.204
mpa, linear	$-2.8\ (7.0).10^{-3}$		1	0.15	0.697

Reviewer(s)' Comments to Author:

Reviewer: Jennifer Girschik
PhD Candidate
Western Australian Institute for Medical Research
AUSTRALIA

No conflict of interest to declare

The authors have in general addressed my comments on the methods. However, I still find that the methods, as currently described, are difficult to follow. While these methods have been similarly described in more radiation focused journals, I believe they would be poorly understood by a more general epidemiological or biomedical audience.

REPLY: We have added some extra detailed text at the beginning of the analysis section to illucidate more qualitatively on the methods applied. There may have been some confusion caused by the inconsistent use of background and baseline rates (i.e. the spontaneous prostate cancer death rates) – this has now been changed to background rates throughout the paper.

Minor comments: In the data tabulations section the categorisation of number of days worked underground is still described as being accumulated over calendar year, which is confusing when the cateogories contain more than 365 days. This would be better described as being accumulated over years of employment.

REPLY: We have made the suggested change

Line 21 page 4 'over ground'; Line 40 page 6 'overground'. This can also be termed above ground mining.

REPLY: We have made the text consistent and used 'overground' in both places.

The authors have in general addressed my comments on the results. However, I still find the results, and in particular Table 2, difficult to interpret. Again, while results have been similarly described in more topic-specific radiation journals, I believe a more general epidemiological audience, including clinicians, would also have difficulty with interpreting the results as currently presented.

REPLY: We have added some extra text in the table caption to illucidate on the qualitative interpretation of the results – this interpretation of results should now also be aided by the extra text in the analysis section.

Minor comments:
LIne 56, page 13 should the word 'costal' be 'coastal'?

REPLY: We have made the suggested correction.

Reviewer: Estelle RAGE
Pharm D - Epidemiologist, PhD
Institute for Radiological Protection and Nuclear Safety (IRSN)
FRANCE

Competing interests: None

The authors have been responsive to the suggestions; Modifications and complementary information have been added or justified, and I thank them for that.

Nevertheless, I still have two very minor comments to note about the answers.

First point:

Question: “The total of person-years could be indicated in the table as well as total mean gamma dose.
REPLY The total number of person-years and overall mean gamma dose is given in the main text.”

--> Unless I am wrong, I have not found the overall mean gamma dose in the main text. In this case, please could you add it?
REPLY: Sorry this was our mistake, thanks very much for spotting this. We have made the suggested addition in the middle of page 14.

Second point:
Question: “Page 12, last paragraph, 3rd and 4th line: please write “gamma prostate dose” instead of “gamma prostate organ dose.
REPLY We have done as the reviewer suggested”

--> “gamma prostate organ dose” has not been modified in “gamma prostate dose” (p.13) - Please could you modify it?
REPLY: We have made the suggested addition.