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An Epidemiological Study of Lung Cancer and Selected Other Cancers among Namibian Uranium Workers

Raymond Agius,[a] Evridiki Batistatou,[a] Matthew Gittins,[b] Steve Jones,[c,d] Roseanne McNamee,[b] Hanhua Liu,[a] Amir Rashid,[a] Martie van Tongeren,[a,1] Gunhild von Oertzen,[e] Richard Wakeford[a]

[a] Centre for Occupational and Environmental Health, Division of Population Health, Health Services Research & Primary Care, School of Health Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester M13 9PL United Kingdom; [b] Centre for Biostatistics, Division of Population Health, Health Services Research & Primary Care, School of Health Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester M13 9PL United Kingdom; [c] Dalton Nuclear Institute, Pariser Building, Manchester, M13 9PL United Kingdom; [d] SJ Scientific Ltd. Summerhill, Cheddleton, Leek, Staffordshire, ST13 7DW, United Kingdom; [e] VO Consulting, Swakopmund, Namibia

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The Rössing Uranium Limited (RUL) open-cast uranium mine in Namibia has operated since 1976. Studies of underground uranium miners from Europe and North America have shown increased cancer risks (principally lung cancer). We explored the association between radiation doses and selected cancers in RUL mineworkers. Employees with at least one-year of continuous employment between 1976 and 2010 were included. Incident cancer cases [lung, extra-thoracic airways (ETA), leukemia, brain and kidney] occurring before the end of 2015 were identified from the Namibian and South African National Cancer Registries, and RUL's occupational health provider. Using a case-cohort design, data on exposure and confounding factors were collected for all cancer cases among the study cohort and a stratified random sample (sub-cohort) of the cohort, including cases. Radiation doses were estimated based on annual dose records held by RUL. In total, 76 cancer cases (32 lung, 18 ETA, 8 leukemia, 9 brain, 9 kidney) and a sub-cohort of 1,121 sampled from 7,901 RUL employees were included. A weighted Cox model, adjusted for available known confounders, produced a rate ratio (95% CI) for lung cancer of 1.42 (0.42, 4.77) and 1.22 (0.26, 5.68), respectively, for medium and higher cumulative lung dose categories compared to the lower category, and 1.04 (0.95, 1.13) for a dose increase of 10 mSv. This study faced considerable challenges with respect to case ascertainment, exposure estimates, and ensuring accuracy of key variables. Persuasive consistent evidence for elevated cancer risk was not found for radiation or other exposures studied at the Rössing uranium mine.

INTRODUCTION

Epidemiological studies of underground uranium miners have examined the risk of lung cancer from exposure to naturally occurring radon gas and its short-lived radioactive decay products (*1–6*). Radon-222 is a link in the radioactive decay chain of uranium-238, and in some underground uranium mines, particularly in the early years of mining when ventilation was absent or poor, concentrations of radon were high, leading to increased rates of lung cancer mortality (*1–3*). The risk of lung cancer from exposure to radon-222 is mainly due to its short-lived progeny, in particular, polonium-218 and polonium-214, which if deposited in the airways, emits densely ionizing alpha-particles that are particularly damaging to adjacent tissues (*2, 3*). Uranium miners are also exposed to penetrating gamma radiation emitted by uranium and its decay products and other sources in the surrounding rocks, and to dust containing uranium and thorium, and their long-lived radioactive decay products (such as radium-226). Similarly, workers in surface uranium mines and mills are exposed to radiation from radon decay products (RDP), external gamma radiation and long-lived radioactive dust (LLRD), although generally at much lower levels (*7–9*).

The Rössing Uranium Ltd (RUL) mine has been in operation since 1976 and is an open-cast uranium mine in the Erongo Region of Namibia (*10*). It consists of a large open pit where low grade, uranium-bearing granite alaskite rock is mined. The rock is blasted, loaded onto trucks, hauled to crushers, and then fed to a chemical processing plant where uranium is extracted from the ore and purified to produce uranium oxide for export.

This study investigated the risks of cancers of the lung and extra-thoracic airways (ETA), leukemia, kidney cancer and brain tumors in the RUL workforce in relation to total radiation exposure (RDP, gamma and LLRD). These cancers were selected because of previous evidence linking them with radiation exposure (*11–15*); brain tumors were included, as previous work (unpublished) at RUL was

[1] Corresponding author: Martie van Tongeren, The University of Manchester, Manchester, United Kingdom, email: martie.j.van-tongeren@manchester.ac.uk.

TABLE 1
Definition of the Case Groups Included in the Case-Cohort Study [ICD-10 code *(17)*]

Upper respiratory tract cancer (extra-thoracic airways, ETA, cancer) (C31-C33);
Bronchial / lung cancer (C34);
Leukemia, but including some other relevant cancers of the lympho-hematopoietic system (lymphoblastic lymphomas, but excluding chronic lymphocytic leukemia and other lymphomas, since these are not considered to be radiation-related[14,15]) (C83.5-C91.0, C92-C95);
Brain tumors (C70-C71) and
Kidney cancer (C64).

suggestive of an excess of such cases in the workforce (*16*). Other occupational exposures at the Rössing mine, such as diesel exhaust fumes and sulfuric acid mist, were also considered.

METHODS

Study Design

The study cohort was defined as RUL employees with at least one year of continuous employment between the beginning of 1976 and the end of 2010. A case-cohort design was adopted to provide internal risk comparisons between exposure groups. Six groups of employees were defined for inclusion: five case groups corresponding to the five cancer groups of interest (Table 1) (*17*) and the "sub-cohort" of workers.

Assembly of the Study Cohorts

The study cohort was identified from the Medixx Occupational Health Services' database (the occupational health provider at RUL) and RUL Human Resources and Pension Fund files. Demographic and employment data (national ID and/or passport number, full name, date of birth, sex, nationality, ethnicity, dates of starting and finishing employment and workplace tasks, job title(s) and date and cause of death) for the study cohort were extracted from the Medixx and Human Resources and Pension Fund databases. An audit of a sample of the initial data supplied was carried out and disagreements reconciled before agreeing on the final cohort dataset.

The sub-cohort was a stratified (by sex and decade of birth) random sample of the study cohort. Where possible, a minimum of 24 workers was selected from each stratum, with additional workers randomly selected to be proportional in size to the full stratum, with a maximum of 200 in any stratum. Overall, the sub-cohort was 14.5% of the study cohort; a higher proportion was chosen for the earlier birth strata as these were thought to be most informative with regards to cancer occurrence and level of exposures.

Ascertainment of Cancer Cases of Interest

The registration of cancer was followed up from the first date of employment at RUL to the end of 2015. All cancers among the study cohort were sought from mapping a combination of key data (i.e., national ID and/or passport number, full name, date of birth, sex, nationality, ethnicity) to two cancer registries: Namibia National Cancer Registry (NNCR) (*18–20*) and South African National Cancer Registry (SANCR) (*18, 19, 21*). Successive data requests were made to NNCR. Cross validation procedures comparing results of repeated iterations of identical data requests from the cancer registries and comparing cancer cases identified in the cancer registries to cases recording cancer citing evidence (e.g., histopathology, radiotherapy or oncology reports) in the Medixx database showed non-trivial discrepancies and suggested under-ascertainment from the cancer registries. Hence, the study team decided to include all cases with an unequivocal diagnosis of a cancer of interest in any one of the three sources, NNCR, SAACR and Medixx. However, where outputs reported a cancer of interest for a case from one but not all data sources, that case was deemed "less certain" and so sensitivity analyses limited to the "certain" cases were additionally conducted. Further details on case assessment can be found in the Supplementary Material S1[2] (https://doi.org/10.1667/RADE-23-00051.1.S1).

Exposure Assessment

Work histories, medical X-ray exposures and selected potential confounders were requested for members of all cancer case groups and the sub-cohort from RUL, who were ignorant of case status.

Individual radiation doses were estimated from average exposures received within representative similar exposure groups (SEGs) of workers, as routinely defined by RUL based on occupation and work area. RUL provided data on radiation doses, gathered for the purposes of radiological protection, in the form of committed effective doses (CEDs) by calendar year and SEG, broken down by exposure pathway (RDP, gamma and LLRD). The effective dose is the sum of the absorbed doses of radiation received by each of the organs/tissues of the body, where each absorbed dose is weighted by a factor representing the type of radiation and by a factor representing the sensitivity of each organ/tissue to radiation-induced damage. The CED is the effective dose committed to be received over a period of 50 years after the initial exposure. Doses from gamma radiation and RPD can be assumed to be received entirely at the time when exposure occurred. However, inhaled uranium, thorium and their long-lived progeny in LLRD are retained for differing periods in the various organs/tissues of interest and continue to deliver dose over periods from weeks to years after intake has occurred.

For this study, knowledge of the doses received by the organ/tissue of interest by each study subject between first exposure and diagnosis of cancer (or equivalent for non-cases) was required, and recorded CEDs were converted accordingly. Methods of sampling and of calculating CED from measurements have changed over time, and details of these methods, together with the dosimetric factors employed (particularly dose per unit intake factors for inhalation of radionuclides), were used to calculate organ/tissue doses.

Cumulative doses from gamma and RDP were calculated as the sum of recorded annual CEDs up to a given time of interest. Gamma doses were assumed to be delivered uniformly across all organs/tissues, while those from RDP were assumed to be delivered to the airways and lung only. For LLRD, CED values were first adjusted to allow for changes in the dose per unit intake recommendations, adopting the International Atomic Energy Agency (IAEA) values currently used by RUL (22). CEDs included assumptions about the relative proportions of radionuclides present together with physical and chemical properties of the LLRD, which vary between areas of the mine.

Back-calculations to the organ/tissue doses due to inhalation of LLRD were estimated by data provided in a computer application

[2] Editor's note. The online version of this article (DOI: https://doi.org/10.1667/RADE-23-00051.1) contains supplementary information that is available to all authorized users.

(*23*), which includes dose conversion factors published by the IAEA (*22*) as used by RUL. This database provides values for the committed dose per unit intake of each radionuclide in terms of both CED and committed doses to individual organs/tissues for seven periods: from the first committed doses received during the initial year after intake up to those received during the conventional 50-year period after intake. Simple curves fitted to these data converted CED attributable to a particular organ/tissue in a particular year to a dose received by the organ/tissue at a specified time after intake and summed over each year of exposure. The organ/tissue radiation doses used in the analyses were equivalent doses, which are the absorbed doses received by an organ/tissue weighted by standard radiation weighting factors: 1 for sparsely ionizing gamma radiation and 20 for densely ionizing alpha particle radiation. Equivalent doses are measured in sievert (Sv).

Doses were "lagged" to account for latency period for a particular cancer: 5 years for lung, ETA, brain and kidney cancer, and 2 years for leukemia. Cumulative total radiation dose, and doses from gamma, RDP and LLRD components, were each categorized in three tertiles of the case dose distribution for the organs/tissues relevant to each cancer of interest. In addition, continuous radiation dose metrics and average annual total radiation dose were estimated. Further details on exposure assessment can be found in Supplementary Material S2 (https://doi.org/10.1667/RADE-23-00051.1.S1).

Other Exposures

All SEGs were assigned to one of three exposure categories (higher, middle, lower) for respirable crystalline silica, diesel engine exhaust and acid mist. Exposure groups were assigned at the beginning of this study. Medical radiation doses, mainly received through chest radiographs, were estimated for specific organ/tissues based on a review of the employees' medical records and classified in three exposure categories.

Other Potential Confounders

Sex, decade of birth, socio-economic status, nationality/ethnicity and smoking were considered as potential confounders and details of these for study participants were requested. Smoking data were incomplete. Socio-economic status (SES) was assessed indirectly via income category classification of jobs into unskilled/semiskilled and skilled/management. The terms used to classify by ethnicity were those used in the company records: "white", "coloured", "black", while nationality was defined as Namibian, South African or Rest of the World.

Vital Status

The follow-up of workers who died before the end of 2015 should be "censored" at date of death. However, information on vital status was not routinely available. At the time of data collection (2017–2018), 7% of the study participants were still in employment, 2% had left employment and were known to be alive, and 6% were known to have died. The vital status of the remainder (85%) was unknown, and in the absence of access to Namibian mortality records (*20*), for these we estimated age at death based on age at leaving RUL and average remaining life expectancy at that age. Average remaining life expectancies at a given age were taken from the WHO Global Health Observatory data repository (*24*) for the year 2000, and also took into account of country of origin, sex, and income category (i.e., SES). Workers known to have emigrated from Namibia or South Africa were censored at the date of leaving RUL; otherwise, workers were assumed to have remained in Namibia or South Africa.

Statistical Analysis

A "weighted" Cox Proportional Hazards (PH) model with robust standard errors (*25, 26*) was implemented with weights allowing for different probabilities of being included in the case-cohort analyses: 1 for a case and the inverse of the stratum-specific sampling fraction for members of the sub-cohort. In addition, a stratified Proportional Hazards model, where study participants are stratified into groups based on nationality/ethnicity and birth cohort, was used. This approach avoided any assumptions about direction or magnitude of the effect of the stratifying variables. In this analysis, the exposure relative risk was a weighted average of the within-stratum relationships between risk and exposure. To avoid a stratum containing a case but no other study subjects, stratification was by nationality/ethnicity and birth cohort only, with SES included as a model covariate.

The cancer risk period was between the date of first employment at RUL and the earliest of the participant's date of cancer diagnosis, date of death (if unavailable, estimated as described above, see Vital Status), date of leaving RUL if a worker emigrated outside Namibia and South Africa, or the censor date of end-2015. The timescale for the analyses was defined by participant age, which provides automatic adjustment for age in exposure group comparisons.

Cumulative exposure estimates were calculated for all individuals at relevant ages: ages at cancer diagnosis and equivalent for non-cases. Rate ratios (RR) (with 95% CI) reported the estimated change in risk of developing cancer at any time during the risk period compared to the lower exposure group (for categorical variables) or per unit increase of exposure (for continuous variables). Statistical models also included sex, birth cohort, income category, a combined nationality and ethnicity classification and medical radiation exposure (lower/middle/higher). In addition, all models included three variables related to smoking information: two binary "missing-indicator" variables and a continuous smoking variable, pack-years, where one pack-year represents smoking 20 cigarettes per day for one year. The first binary variable has the value 1 if smoking status is completely unknown, or zero for everyone else; the second has the value 1 if the person is known to be a smoker but with pack per day unknown, and is zero for everyone else. The pack-years variable was set to zero for never smokers and for the two groups with any kind of missing smoking information. If all three variables are included in the same model, the three estimated rate ratios have the same reference group, namely: never smokers. Some models also included silica, diesel or acid mist exposures, represented as 2-category (middle/higher vs. lower) variables.

All analyses were carried out using STATA v15 (*27*).

Statistical Power

Power calculations were based on a case-control study with 10 controls per case and the assumption that approximately half the study participants were exposed and half unexposed. For each cancer outcome, the number of cases needed to achieve 80% power using a two-sided test with Type 1 error P value of 0.05, is 76 if the true or is 2 or more and 33 if it is 3 or more. For 50% power the figures are 38 and 17, respectively.

Ethical Approval

Ethical approval and permissions were obtained from The University of Manchester Research Ethics Committee (ref: ethics/060416), the Ministry of Health and Social Services of the Republic of Namibia (ref: 17/3/3) and the Medical Ethics Committee of the University of the Witwatersrand, South Africa (M160945).

RESULTS

The study cohort contained 7,901 workers, most of whom were men (89%). Almost 40% were born in the decade 1951–1960. Workers in the cohort were described by RUL records as "black" (53%), "coloured" (19%) or

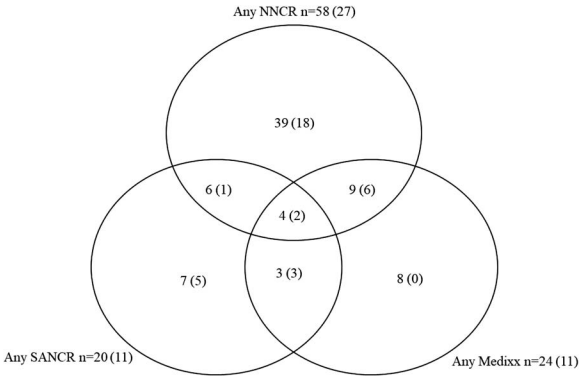

FIG. 1. Cancer Ascertainment: Cases of Interest (and "Certain" Cases) by Sources. NNCR, Namibian National Cancer Registry; SANCR, South African National Cancer Registry; Medixx, occupational health provider at Rössing Uranium Limited.

"white" (27%). Median duration of employment was 5.3 years. Further details can be found in Supplementary Material S4 (https://doi.org/10.1667/RADE-23-00051.1.S1). In total, 1,148 workers (14.5% of the cohort) were included in the sub-cohort, of whom 81.7% were males; 18 (2%) had less than one year employment and 9 (1%) others provided incomplete significant information, and were therefore excluded, leaving 1121 in the sub-cohort.

In total, 285 potential cases of cancers of any type in the RUL workforce were identified from NNCR (Supplementary Figs. S1 and S2; https://doi.org/10.1667/RADE-23-00051.1.S1); additional potential cases were also identified from the SANCR (548) and Medixx (166). After review, 76 cancer cases of interest were identified: 32 of lung cancer, 18 ETA cancers, 9 brain tumors, 8 leukemia (or closely related to leukemia), and 9 kidney cancer. Figure 1 shows the final number of all cases of interest by source and "certainty," after application of the review criteria.

The majority of cases were born between 1941 and 1960, with the mean age at diagnosis ranging from 47 (kidney cancer) to nearly 60 years (lung cancer). Only 3 cancers were identified in females. Approximately equal numbers were found in black, colored and white ethnic groups, despite black workers being 53% of the study cohort. There were 35 cancer cases of interest with "high certainty" (Fig. 1). Of these, 20 were lung cancer, 7 ETA cancer, 2 were leukemia, 3 brain cancer and 3 kidney cancer.

Estimated cumulative total radiation dose to the lung ranged from 0 mSv (for 2 cases) to 272 mSv, with a median dose of 40 mSv. The estimated mean cumulative total dose and the gamma, RDP, and LLRD components are reported in Table 2 for cases in each cancer group. The rate ratios for middle and higher cumulative total dose categories for lung cancer were 1.42 (95% CI: 0.42, 4.77) and 1.22 (95% CI: 0.26, 5.68) compared to the lower dose category, respectively (Table 3). However, the CIs were wide (and include 1.0), and there does not appear to be a dose response. For continuous cumulative total dose, the rate ratios was 1.04 (95% CI: 0.95,1.13) for lung cancer per 10 mSv (Table 4). No statistically significant results were observed for the other cancer sites (Tables 3 and 4). Further detailed results for the different cancer sites are presented in Supplementary Material S5–S9; https://doi.org/10.1667/RADE-23-00051.1.S1).

A clear association between smoking and risk of cancer was observed, particularly for lung cancer where for every 10 pack-years smoked, the risk multiplied by 1.30 (95% CI: 1.09,1.53) (Supplementary Material S5 and Supplementary Table S6; https://doi.org/10.1667/RADE-23-00051.1.S1). Compared to never smokers, the rate ratios for those with no smoking information and those who were known smokers without information on pack-years smoked, were 3.33 (95% CI 1.12,9.87) and 3.49 (95% CI: 0.37,33.10), respectively. The rate ratios for lung cancer for those born after 1961 compared to those born before was 3.77 (95% CI: 0.82,17.29). Compared to white Namibians, the rate ratios for colored Namibians was 13.86 (95% CI: 2.74,70.04), but only 0.6 (95% CI 0.10,3.75) for black Namibians. The rate ratios for the middle/higher category of diesel engine exhaust compared to the lower category was 2.63 (95% CI: 0.40,17.08).

Further analyses included each of the individual components of total radiation dose, gamma, RDP and

TABLE 2
Descriptive Statistics of Estimated Exposure in the Cancer Cases of Interest

	Factor	Stat/Category	Lung	ETA	Leukemia	Brain	Kidney
	No. cases		32	18	8	9	9
Cumulative equivalent dose to organ/tissue of interest	Total (mSv)	Mean (s.d)	49.5 (29.3)	57.7 (33.5)	5.4 (3.0)	4.6 (2.4)	5.2 (2.7)
	Gamma (mSv)	Mean (s.d)	4.5 (2.4)	4.7 (2.4)	4.9 (2.6)	4.6 (2.3)	4.6 (2.3)
	RDP (mSv)	Mean (s.d)	33.9 (20.4)	34.8 (34.1)	-	-	-
	LLRD (mSv)	Mean (s.d)	11.0 (5.4)	18.1 (9.1)	0.54 (0.29)	0.02 (0.01)	0.56 (0.29)
	Age at diagnosis	Mean (min; max)	59.0 (37.0, 75.9)	58.7 (36.6, 74.1)	52.2 (38.7, 69.9)	51.8 (32.6, 72.7)	47.1 (35.9, 66.8)
	Year of diagnosis	Mean (min; max)	2006 (1985, 2015)	2003 (1986, 2015)	2003 (1985, 2015)	2004 (1989, 2013)	1999 (1982, 2014)

Abbreviations: ETA = extra-thoracic airways, RPD = radon decay products, LLRD = long-lived radioactive dust.

TABLE 3
Adjusted* Rate Ratios for Middle and Higher Categories of Cumulative Total Radiation Dose with 5-Year (2-year for Leukemia) Latency

Cancer of interest	No. cases	No. in sub-cohort	Unadjusted rate ratios (95% CI)	Adjusted* rate ratios (95% CI)
Lung				
Lower (<22.1 mSv)	11	456	1 (ref cat)	1 (ref cat)
Middle (≥22.1 to <80 mSv)	11	437	1.58 (0.68,3.70)	1.42 (0.42, 4.77)
Higher (≥80 mSv)	10	228	1.63 (0.69,3.87)	1.22 (0.26, 5.68)
Extra-thoracic Airways				
Lower (<30 mSv)	6	514	1 (ref cat)	1 (ref cat)
Middle (≥30 to <120 mSv)	6	446	1.50 (0.50, 4.50)	0.94 (0.20, 4.44)
Higher (≥120 mSv)	6	161	2.95 (0.92, 9.44)	1.41 (0.19, 10.49)
Brain Cancer				
Lower (<1.5 mSv)	3	417	1 (ref cat)	1 (ref cat)
Middle (≥1.5 to <5.8 mSv)	3	440	1.39 (0.28,6.85)	0.60 (0.11, 3.36)
Higher (≥5.8 mSv)	3	264	2.35 (0.51,10.78)	0.60 (0.10, 3.39)
Leukemia				
Lower (<0.01 mSv)	2	108	1 (ref cat)	1 (ref cat)
Middle (≥0.01 to <2.0 mSv)	3	333	0.49 (0.08, 2.85)	0.61 (0.13, 2.86)
Higher (≥2.0 mSv)	3	680	0.29 (0.05, 1.81)	0.29 (0.04, 2.29)
Kidney Cancer				
Lower (<2.4 mSv)	3	525	1 (ref cat)	1 (ref cat)
Middle (≥2.4 to <6.1 mSv)	3	300	2.49 (0.47, 13.07)	1.94 (0.30, 12.64)
Higher (≥6.1 mSv)	3	296	2.43 (0.40, 14.77)	1.82 (0.14, 24.40)

* Adjusted for sex, birth cohort, income category, smoking, medical X-ray exposure category and nationality/ethnicity category.

LLRD, as continuous variables (Table 4). A statistically significant association was seen between continuous gamma dose and risk of lung cancer (RR = 1.63; 95% CI: 1.13, 2.34). However, when gamma dose was represented as a categorical variable [middle, RR = 1.32 (95% CI: 0.44, 4.01); higher, RR = 0.92 (95% CI: 0.23, 3.64)], no statistically significant rate ratios were observed and there was no evidence of a dose-response. No significant associations were observed for RDP dose (Table 4). A statistically significant association was seen for continuous LLRD lung dose and lung cancer risk [RR = 1.07 (95% CI: 1.00,1.14)] (Table 4). In the corresponding categorical analysis, non-statistically significant rate ratios of 2.13 (95% CI: 0.63, 7.16) for the Middle and 2.65 (95% CI: 0.57, 12.38) for higher LLRD dose (Supplementary Material S5 and Supplementary Table S9; https://doi.org/10.1667/RADE-23-00051.1.S1) were found.

Between-person correlations of the three exposure components were high (0.75–0.82). There was no evidence of excess risk associated with either RDP or LLRD cumulative lung doses when all three components of cumulative total dose were included in the same model (Supplementary Material S5.2 and Supplementary Table S11; https://doi.org/10.1667/RADE-23-00051.1.S1). However, the relationship with gamma dose remained at RR = 1.91 (95% CI: 1.09, 3.35) per 10 mSv.

The stratified analysis for lung cancer (Table 5) resulted in only very minor differences compared to the main, "unstratified" analysis. Additional pre-specified sensitivity analyses were also carried out, the results for which can be found in the Supplementary Material (Supplementary Material S5.2 and S5.3; https://doi.org/10.1667/RADE-23-00051.1.S1).

DISCUSSION

In this study, we investigated whether occupational exposure to radiation and other exposures at the Rössing Uranium Limited mine in Namibia were associated with an

TABLE 4
Adjusted* Rate Ratios per 10 mSv of Cumulative Total Radiation Dose with 5-Year (2-year for Leukemia) Latency

Continuous cumulative Dose	Lung RR (95% CI)*	ETA RR (95% CI)*	Brain RR (95% CI)*	Leukemia RR (95% CI)*	Kidney RR (95% CI)*
Total	1.04 (0.95, 1.13)	1.01 (0.97, 1.05)	0.88 (0.38, 2.03)	1.33 (0.45, 3.96)	1.01 (0.58, 1.75)
Gamma	1.63 (1.13, 2.34)	1.37 (0.89, 2.11)	0.88 (0.38, 2.03)	1.36 (0.45, 4.15)	1.02 (0.57, 1.80)
RDP+	1.02 (0.88, 1.19)	1.02 (0.91, 1.14)	-	-	-
LLRD+	1.07 (1.003, 1.14)	1.01 (0.96, 1.06)	-	-	-

* Adjusted for sex, birth cohort, income category, smoking, medical X-ray exposure category and nationality/ethnicity category.
+Lung and ETA only; doses received by other tissues are negligible (Table 2).

TABLE 5
Adjusted* Lung Cancer Rate Ratios from the Stratified Analysis for Middle and Higher Categories, and Per 10 mSv of Cumulative Total Radiation Dose with 5-Year Latency

Categorical dose	RR (95% CI)
Lower (<22.1 mSv)	1 (ref cat)
Middle (≥22.1 to <80 mSv)	1.44 (0.43, 4.87)
Higher (≥80 mSv)	1.19 (0.24, 5.93)
Continuous dose	**RR (95% CI)***
Total	1.04 (0.96, 1.13)
Gamma	1.60 (1.15, 2.23)
RDP	1.04 (0.87, 1.24)
LLRD	1.07 (0.99, 1.16)

* Adjusted for sex, income category, smoking, medical X-ray exposure category.

increased risk of developing specific types of cancer (lung and ETA cancers, leukemia, kidney and brain cancers) among its employees. However, the ability of the study to find statistically significant relationships with exposure was very low for leukemia, kidney and brain cancer, due to the small numbers of cases (8, 9 and 9, respectively). Only lung and kidney cancers yielded increased rate ratios, though not statistically significant, when considering categorical cumulative total radiation doses after adjustment for confounders. No statistically significant associations were found with any of the cancers of interest when using continuous cumulative total radiation dose estimates in the analyses. When considering the individual components of the total radiation dose, a statistically significant elevated risk for lung cancer was observed for continuous gamma dose; this appears to be at odds with the results when using Gamma dose categories.

Lung cancer has been causally linked to exposure to radon decay products in underground hard-rock mining of uranium and other metals (*1–6, 28–33*). Exposure to RDP in underground mines has been high, with typical cumulative lung doses between 1,500 and 68,000 mSv (*2, 3*). In comparison, the mean cumulative lung dose from RDP in the workers from the open-cast RUL mine was much lower at 43 mSv.

Gamma radiation exposure increases the risk of most types of cancer, including lung cancer, but the evidence derives largely from groups exposed to moderate and high doses of >100 mSv (*14, 15*). In comparison, the mean cumulative gamma dose to the lung for the RUL sub-cohort was <5 mSv. The correlation between elevated gamma dose and lung cancer is interesting because it suggests that the higher gamma dose could be indicative of a higher LLRD dose, which has remained undetected. This is plausible, as the LLRD dose at RUL is assessed by work area and not by individual, leaving room for large variability within an SEG. Studies of uranium miners and millers in Germany (*7, 9*) have examined exposures to LLRD. In the study of uranium millers (*9*) average cumulative lung doses from LLRD were estimated to be 60 mSv, and no association with lung cancer risk was found. In the RUL sub-cohort, the mean cumulative lung dose from LLRD was 11 mSv.

The case-cohort design (which relies on internal cancer risk comparisons between groups within the workforce with different degrees of exposure) avoided the bias linked to the healthy worker effect that could occur in comparisons with an external population. The design also avoided another potential bias in such comparisons when there is differential detection and/or recording of cancer in a workforce compared to an external group. With respect to this latter issue, the Namibia National Cancer Registry (NNCR) was established in 1995 when RUL, in cooperation with the Namibian Ministry of Health and the Cancer Association of Namibia, collected information on all cancer cases reported to the Windhoek state pathology laboratory and the then-single existing private pathology laboratory (*20*). Initially, cancer registrations in the NNCR were gathered from historical records held in the central region of Namibia. The interest in cancer in the RUL workforce, together with the existence of the Medixx services and its database for Rössing workers, meant that it was highly likely that ascertainment of cancer cases among members of the RUL workforce was better than that for the general population of Namibia. Consequently, comparison of incidence rates in the RUL workforce with those for Namibia would have been biased and would not have produced credible results.

We did not have access to mortality records, with the exception of incomplete data held by RUL. This precluded comparisons of mortality rates. In any event, use of Namibian mortality data has only been possible since 2016 and the quality of cause of death information is not known (*20*).

Ascertainment of Cancer Cases

There were substantial limitations to the cancer data available for this study. As noted above, the NNCR started in 1995, and although identification of cancer cases among the RUL workforce was one of the motivating factors in the establishment of the NNCR, cancers from this period of study (1976–2015) could have been missed. Repeated iterations of identical data requests from NNCR did not yield consistent search results, either in the number of cancers or their classification. Neither the NNCR nor the SANCR have been included in the latest volume (Volume XI) of Cancer Incidence in Five Continents (*34*), raising questions over the accuracy and completeness of the data included in the two registries. Cancer data from occupational health records (Medixx) would not be expected to be complete, as they cover only the period of employment of an individual. Thus, overall, under-ascertainment of cancer cases in this cohort is very likely.

To better understand what factors might be linked to under-ascertainment, we investigated the risk of any cancer except non-melanoma skin cancer (NMSC). This indicated large differences in risk in opposite directions to expectation for ethnicity, nationality, SES and birth cohort (see Supplementary Material S3; https://doi.org/10.1667/RADE-23-00051.1.S1). For example, the apparent risk of any cancer other than NMSC for black Namibians was much lower than for other ethnicities and nationalities. Our interpretation was that such differences reflected differential case ascertainment rather than ethnicity/nationality truly affecting risk to this extent. Since ethnicity/nationality breakdown varies between exposure groups, such under-ascertainment, if left unaddressed, would bias exposure comparisons.

To address this issue, first, we included the factors thought to be linked to under-ascertainment as covariates in the main (unstratified) exposure analyses. Second, ethnicity/nationality and birth cohort were treated as stratifying variables with SES included as a covariate. Arguably, the latter approach, which estimates exposure rate ratios within strata, is superior, but in practice the two methods gave nearly identical results. While reassuring, we cannot rule out the possibility that under-ascertainment due to other unmeasured factors has led to some bias.

Limited Exposure/Dose Data

Gamma radiation doses received from sources external to the body are, in effect, delivered instantaneously, and it may be assumed to be a reasonable approximation that the recorded annual gamma CED is the gamma dose received by each tissue/organ in that year. RPD are inhaled and deliver their dose almost entirely to the respiratory tract over a matter of days, so the annual CED received from RPD will be essentially delivered in the year of intake.

The doses received from LLRD are derived from radioactivity measurements and International Commission on Radiological Protection (ICRP) models of the behavior of dust in the respiratory tract, based on parameters such as retention time in lung tissue and particle size. The parameters recommended by IAEA for ore dust are conservative, particularly for retention in the respiratory tract (*22*). Consequently, the back-calculations of lung and ETA doses from annual CED records are likely to overestimate the actual doses received by the workers in this study.

The doses used in this study are equivalent doses; that is, they are absorbed doses to organs/tissues weighted by the radiation weighting factors defined by ICRP for specific types of radiation in the context of radiological protection. Therefore, these radiation weighting factors are conservative and may not be the most accurate weighting factors for the purposes of an epidemiological study. However, for alpha-particles and lung cancer, as in this study, the radiation weighting factor of 20 may not be too far removed from the actual weighting factor that should be applied to absorbed doses (*3*).

Despite the limitations dictated by having to use annual CEDs recorded for radiological protection purposes, the equivalent doses used in the study are considered to be reasonable approximations to the organ/tissue doses actually received by workers, albeit that the accuracy of the dose estimates will vary with the type of exposure experienced at the Rössing mine.

An audit was performed to explore the origin of dose measurements entered in the radiation dose matrices provided by RUL for the study. However, the data available were deemed not of sufficient quantity or quality to determine temporal trends in radiation dose levels. This raised further questions regarding the quality of data available for this epidemiological study. The full report of this limited audit is provided in Supplementary Material S10 (https://doi.org/10.1667/RADE-23-00051.1.S1).

The Three Components of Dose in the Analyses

A factor that is not causally related to a disease, but measured with relatively high precision, can appear to be more important than a true causal risk factor that is measured with lower precision, if these factors are strongly correlated (*35*). Strong correlations were present between the three components of the cumulative total radiation dose. Any analysis purporting to estimate the relationship between risk and any one component would likely be biased by its correlation with another component. The analysis including all three components of cumulative dose in principle has the ability to estimate the independent effect of each component. The association between gamma and lung cancer remained when LLRD and RDP were included. Given the high correlation between gamma and LLRD and the inability of correcting for errors in dose estimation, we cannot be confident that we have disentangled the independent contributions of gamma and LLRD.

Background Radiation Exposure

Radiation exposure in the environment is ubiquitous and unavoidable, so RUL workers will have received radiation doses outside the mine. In areas of uranium (and thorium) deposits, as in the vicinity of the Rössing mine, these exposures can be significant, but in this study, it has not been possible to account for environmental sources of radiation exposure.

Non-Radiation Occupational Exposure Data

The available measurement data on silica, diesel engine exhaust and (sulphuric) acid mist were insufficient to develop quantitative estimates of exposure for workers in different SEGs. Our group subjectively assessed the exposure semi-quantitatively.

Statistical Methods, Confounding and Missing Data

To allow for potential confounding data and differential case capture, we included sex, birth cohort, income

category, nationality/ethnicity, medical radiation exposure and smoking in Proportional Hazards regression models with age as the time scale. Simple measures of other occupational exposures were included in some models. We are not aware of any omitted confounder that could have biased the results. However, despite efforts to fill gaps, information on income band was missing for 12%, on medical exposures for 50% and on smoking for 27% of workers; there was no smoking data for 33% of lung cancer cases.

For smoking, as described in the Methods section, three variables related to smoking information were included in the models: two binary "missing-indicator" variables and a continuous smoking variable, the former to address the lack of detailed smoking history for a proportion of the participants. Thus, we maintained the sample size and consequently the study power, while maximizing smoking history without introducing further residual confounders. Lack of smoking information was strongly related to short duration of employment and thus also to low-cumulative radiation dose, providing potential for bias. We retained those lacking "missing" smoking data in the analyses by creating an "unknown" category and comparing their risk with that of non-smokers: the corresponding lung cancer analysis suggested this group contained many smokers since the rate ratios was high at 3.33 (95% CI: 1.12, 9.87). For those subjects with some smoking information, the highest recorded number of cigarettes was used to create a pack-years measure, since annual smoking data were inconsistent. The estimated rate ratios associated with 10 pack-years was low [RR = 1.30 (95% CI: 1.09, 1.53)], which probably reflects measurement error in smoking. If so, then a degree of residual confounding by smoking may still be present.

In our (non-stratified) model we assumed that the effects of covariates did not change with age, maintaining the proportional hazards assumption of the Cox model. This assumption seems less defensible for variables that may be indicators of differential case capture (e.g., ethnicity/nationality and birth cohort) as differential case-capture could change over time. This assumption is not included in the stratified models, the results of which did not appear to differ from the main results, indicating that any violations of the proportional hazards assumption did not substantially affect the results. The models also assumed that the effect of radiation exposure was the same across all groups (e.g., men, women, Namibian, South African, smokers and non-smokers). In principle, "interaction terms", could have specified models which allow radiation effects to differ between groups, but the power of the study to find significant differences between groups would have been extremely low.

CONCLUSION

This study presented considerable challenges, particularly with respect to case ascertainment, exposure estimates, and ensuring accuracy of available information about key variables. These are important uncertainties that should be acknowledged when interpreting the study findings. Some analyses suggest the possibility that for some cancer patients, the mine environment may have contributed to the development of their disease. However, we conclude that this study does not provide strong and consistent evidence that radiation or other exposures at the Rössing uranium mine caused an increased risk of cancers in the workforce.

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