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ARTICLE

Mortality in the French cohort of nuclear workers

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Abstract – Populations of nuclear workers are particularly relevant to study health effects of protracted exposures to low doses at low dose-rates of ionizing radiation. In France, a cohort of nuclear workers employed by the Commissariat à l'énergie atomique et aux énergies alternatives (CEA), AREVA Nuclear Cycle (AREVA NC), or Électricité de France (EDF), and badge-monitored for external radiation exposure, has been followed-up for several decades. Annual exposure to penetrating photons was reconstructed for each worker. Standardized mortality ratios were calculated using national mortality rates as the reference. Estimates of radiation dose-mortality associations were obtained using linear excess relative risk models. Mortality of 59 004 workers was followed-up between 1968 and 2004, for an average of 25 years. The mean cumulative photon $H_p(10)$ dose was 18.4 mSv in the whole cohort (median value: 2.1 mSv) and 25.7 mSv among exposed workers. At the end of the follow-up, workers were 56 years old on average and 6310 workers had died. A strong healthy worker effect was observed. Estimated dose-risk relationships were consistent with those from other worker studies for all solid cancers and leukaemia excluding chronic lymphocytic leukaemia, but remained associated to a large uncertainty. This cohort is the most informative study ever conducted in France among nuclear workers.

Keywords: epidemiology / health effect / nuclear worker / exposure, occupational

1 Introduction

While health risks induced by high to moderate-dose acute exposure to ionizing radiation (IR) are well characterized (UNSCEAR, 2008; IARC, 2012a), especially by studies on survivors of atomic bombs of Hiroshima and Nagasaki (Douple *et al.*, 2011; Ozasa *et al.*, 2012; Hsu *et al.*, 2013), uncertainty remains regarding the quantification of risks following exposure to protracted low doses of IR, typical of occupational exposures. Populations of nuclear workers are particularly relevant to study potential health effects of low dose and low dose-rate exposures to IR, and cohorts of nuclear workers were implemented worldwide (Vrijheid *et al.*, 2007b). The interest of these studies relies in particular on the availability of individual annual occupational doses monitored in the frame of the radiation protection surveillance.

In France, a large cohort of nuclear workers employed by the Commissariat à l'énergie atomique et aux énergies alternatives (CEA), AREVA Nuclear Cycle (AREVA NC) – formerly COmpagnie GEnérale des MAtières nucléaires (COGEMA) and Électricité de France (EDF) has been followed up by the Institute for Radiological Protection and Nuclear Safety (IRSN). Activities of workers from CEA or AREVA NC encompass research, nuclear fuel production operations (excluding uranium mining and processing) and fuel reprocessing. Workers from EDF were employed in the 19 French nuclear power plants. One strength of this cohort is the availability, for each worker, of the annual doses of external IR he/she cumulated over his/her occupational life.

This cohort allows to compare the mortality of nuclear workers to that of the French general population and to investigate potential radiation-induced risks of death. In the present analysis, the updated mortality of nuclear workers was examined over the 1968–2004 period, and long-term effects of protracted low level IR exposure were examined, with particular focus on cancer and circulatory diseases mortality.

2 Material and methods

This study complies with French ethics recommendations on the use of individual health data and has been approved by the French Data Protection Authority (Comité national de l'informatique et des libertés [CNIL]).

2.1 Study population

The French nuclear worker cohort results from the combination of two nuclear worker cohorts implemented in the 1990s, namely the CEA-AREVA NC cohort

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(Telle-Lamberton *et al.*, 2007; Metz-Flamant *et al.*, 2011b) that included 36 769 workers and the EDF cohort (Rogel *et al.*, 2005; Laurent *et al.*, 2010) that included 22 392 workers. In 2011, these two cohorts were pooled after handling overlapping individuals (Metz-Flamant *et al.*, 2013). The combined cohort includes all workers employed for at least one year by civil CEA or AREVA NC between 1950 and 1994 or by EDF between 1961 and 1994, badge-monitored for radiation exposure and alive on 1 January 1968. Since the previous analysis of this combined cohort (Metz-Flamant *et al.*, 2013), revision of occupational data led to the exclusion of 17 workers. The cohort includes 59 004 individuals.

2.2 Follow-up and mortality data

The mortality follow-up began at the latest of the three following dates: 1 year after the date of hiring, the date of the first dosimetric monitoring, or 01/01/1968 (as individual medical causes of death are available in France from the national death registry only from 1968, see below). The follow-up ended at the date of death or 12/31/2004 for CEA-AREVA NC workers (resp., 12/31/2003 for EDF workers), whichever occurred first. For workers lost to follow-up, it ended at the date of last information (either administrative or dosimetric). Vital statuses were ascertained by linking the cohort with the French National Directory for the Identification of Natural Persons (RNIPP), which is maintained by the National Institute of Statistics and Economic Studies (INSEE) and which gathers information on the vital status of French citizens. Workers who could not be connected to the RNIPP were considered lost to follow-up. Individual causes of death were obtained from the French national registry maintained by the Epidemiology Centre on the medical Causes of Death (CépiDC) of the French National Institute for Medical Research (Inserm). The CépiDC has been registering individual medical causes of death in France since the 01/01/1968. The causes of death were coded according to the International Classification of Disease (ICD) in effect at the time of death: ICD8 (WHO, 1968) from 1968 through 1978, ICD9 (WHO, 1977) from 1979 through 1999, and ICD10 (WHO, 2005) from 2000. Since the previous analysis of this combined cohort (Metz-Flamant *et al.*, 2013), further information on causes of death has been collected and integrated in the study.

2.3 Employment data

Employing companies provided administrative data and job-related information for each worker. Occupational history at the three employing companies was reconstructed for each worker. As workers could change employers during the follow-up period, a time-dependent variable was created to define, each year, the company for which the worker had worked the longest from hiring: CEA, AREVA NC, EDF, or other (mainly for subsidiaries of AREVA NC). Duration of employment was defined as a time-dependent variable that increased from the date of hiring until either the date of termination of employment (and remained at that level thereafter), or the end of follow-up if it occurred during active employment. Socioeconomic status was defined for each worker, based on job title at hiring: managers and engineers, administrative employees, skilled and unskilled workers.

2.4 Radiation exposure data

Period of exposure ranges from 1950 to 2004. Dose reconstruction and dosimetric practices were described elsewhere for the CEA-AREVA NC cohort (Telle-Lamberton *et al.*, 2007; Metz-Flamant *et al.*, 2011b) and the EDF cohort (Laurent *et al.*, 2010). Annual exposure to external IR (primarily gamma rays) was calculated for each worker from individual doses recorded in the frame of radiological protection surveillance and centralized in companies' dosimetric registries. As part of two international collaborative studies (Thierry-Chef *et al.*, 2007, 2015), data was collected on the type of dosimeter used, on exposure conditions, and on dosimeter response. This data was used to convert individual annual recorded doses to personal penetrating photon dose equivalents in soft tissue at a depth of 10 mm ($H_p(10)$) that are expressed in Sievert (Sv) and used in this study.

Some workers may have been exposed to neutrons. However, available information on neutron doses was too sparse and uncertainty associated to dose estimates was too large to include neutron doses in the calculation of external doses (Thierry-Chef *et al.*, 2015). Available information on neutron was used instead to identify workers with substantial exposure to neutrons. A time-dependent flag was thus created. After 1967, this flag labelled the workers as "exposed substantially to neutrons" starting from the first year in which their annual estimated exposure to neutrons exceeded 10% of their annual total external dose. Prior to 1967, this flag was used starting from the first year in which they had any positive neutron dose because of poor performances of film badges used at that period regarding neutron dosimetry.

Some workers may also have been exposed to internal contamination by various radionuclides (isotopes of uranium, plutonium...), depending on their activities. However, individual measurements of doses from radionuclide intakes are not available for the cohort members since this data has only recently been systematically collected and centralized in France. A companion paper investigated the potential confounding induced by internal contamination in the dose-risk analysis in association with external radiation in the cohort, relying on a work-station exposure matrix (Fournier *et al.*, 2015), and potential for internal contamination will not be considered in the present analysis.

2.5 Statistical analysis

Mortality in the cohort was compared to that of the French general population by calculating standardized mortality ratios (SMR) using national mortality rates as the reference. A SMR is the ratio of the number of observed deaths in the cohort to the number of "expected" deaths under the hypothesis that mortality rates are the same in the cohort than in the general population. The SMRs were stratified by calendar period in seven categories (1968/1973/1978/1983/1988/1993/1998+), sex, and attained age in 5-year intervals (<20/25/30/.../75/80/85+). Byar's approximation (Breslow and Day, 1987) was used to estimate 95% confidence intervals (CI) for the SMRs.

Results are presented only for causes of death for which at least 10 deaths were observed. For significant excesses of death, further investigations were performed. We calculated SMRs over categories of following professional characteristics: employing company, socioeconomic status, year of hiring, age at hiring, duration of employment, and cumulative dose. We performed a heterogeneity test for SMRs across categories of company and socioeconomic status and a χ^2(1 degree of freedom) trend test for SMRs across categories of the other variables (Breslow and Day, 1987).

Poisson regression methods were used to estimate the dose-response relationships between cumulative dose of IR and death from cancer, circulatory diseases, or respiratory diseases. We focused analyses on solid cancer, solid cancer excluding lung cancer, lung cancer, non-Hodgkin lymphoma, multiple myeloma, leukaemia excluding chronic lymphocytic leukaemia (CLL), and myeloid leukaemia; CLL were excluded *a priori* from the leukaemia grouping as CLL are generally considered to be non-radiogenic (UNSCEAR, 2008). End-points for which less than 30 deaths occurred (Hodgkin disease, other sub-types of leukaemia) were not investigated to avoid getting strongly uncertain risk estimations. We used linear excess relative risk (ERR) models as classically used in epidemiology of IR (NRC, 2006). The ERR model can be written as $r(x) = 1+\beta x$, where $r(x)$ is the relative rate of death for workers exposed to a cumulative dose x and β is the estimate of the ERR per unit dose (ERR/Sv). Models were stratified by calendar period (defined as above), sex, attained age in 5-year intervals, company (CEA, AREVA NC, EDF, other), duration of employment (<20 y, ≥20 y), and socioeconomic status, except for leukaemia as preliminary analyses showed no association between socioeconomic status and leukaemia mortality. To allow for a latent period in radiation effect, cumulative dose was lagged by 10 years for the study of solid cancer, circulatory diseases, and respiratory diseases and by 2 years for leukaemia analyses, as is usual in epidemiological studies on radiation induced risks (NRC, 2006). Sensitivity analyses were conducted to investigate the influence of adjustment for the neutron flag.

As the objective of radiation epidemiology is to evaluate if there is an increased risk associated to radiation exposure, one sided P values and corresponding 90%CI are often reported (Muirhead *et al.*, 2009). We also report likelihood-based 90% CI for the ERRs. All analyses were performed using the EPICURE software (Preston *et al.*, 1993).

3 Results

3.1 Study population

A total of 59 004 workers were followed-up between 1968 and 2004, for an average of 25 years (Tab. 1). They accrued almost 1.5 million person-years. Most of workers were men (87%). Most of the cohort members (71%) were skilled or unskilled workers, 20% were managers or engineers and 8% were administrative employees; the socioeconomic status was unknown for less than 1% of the cohort members. At the end of follow-up, workers were 56 years old on average. Mean duration of employment was 21 years. The mean cumulative dose was 18.4 mSv in the whole cohort; 72% of the workers had a non-zero cumulative dose, with a mean cumulative dose of 25.7 mSv that reached a maximum of 668.6 mSv. Only 597 (1.0%) workers cumulated a dose larger than 200 mSv, while 35 732 (60.6%) workers cumulated doses less than 50 mSv. As shown in Figure 1, the distribution of cumulative doses is highly right-skewed with a median value of 2.1 mSv (25th percentile: 0.0 mSv, 75th percentile: 17.0 mSv). At the end of the follow-up, only 0.2% of the workers were lost to follow-up and 6310 workers had died. Information on causes of death was available for 97.7% of the deaths.

3.2 Mortality analysis

A strong healthy worker effect was observed in the cohort. Mortality showed a 40% deficit compared to that of the French general population (all-cause SMR = 0.60, 95%CI: 0.59–0.62). Of the 6310 deaths in the cohort, 2552 were due to cancer. The mortality due to solid cancer was 32% lower in the cohort, compared to the French population (Tab. 2). For most of specific cancer sites, the mortality was lower in the cohort than in the general population, albeit not significantly for malignant tumours of the gallbladder, pancreas, peritoneum, bones, *corpus uteri*, and kidney (Tab. 2). For malignant tumours of the breast (women only), ovary, brain, and central nervous system, the SMRs were higher than 1.0 but not significantly. Significantly elevated SMRs were observed for pleural cancer, for which mortality was 69% higher than in the French population, and for skin melanoma which exhibited an excess mortality of 40%. For all tumours of lymphatic and hematopoietic tissues, a slight deficit of mortality was observed (SMR = 0.81, 95%CI: 0.70–0.94), as well as for specific diseases as leukaemia excluding CLL, non-Hodgkin lymphoma, and multiple myeloma – albeit not significantly for the latter. Conversely, a non-significant excess of mortality was noted for Hodgkin disease. For circulatory, respiratory, or digestive diseases, strong healthy worker effects were observed (Tab. 2).

As significant excesses of death were observed for pleural cancer and skin melanoma, further investigations were performed for these cancer sites. Most of deaths due to pleural cancer (76.7%) and skin melanoma (70.5%) occurred among workers whose principal employer (in terms of duration of employment) was CEA, though SMRs showed no statistically significant heterogeneity across companies. For pleural cancer, the SMRs exhibited no heterogeneity across categories of socioeconomic status ($p = 0.43$), even if a significant excess of mortality was observed for skilled workers. No trend appeared in the SMRs across the categories of age at hiring ($p = 0.85$). By contrast, the SMRs decreased significantly as the year of hiring increased, with higher SMRs observed among workers employed in the early years; the SMRs increased as the duration of employment increased ($p = 0.04$). No trend across categories of cumulative dose could be observed ($p = 0.81$). For malignant skin melanoma, no heterogeneity was observed in the SMRs across categories of socioeconomic status ($p = 0.74$) and the SMRs exhibited no trend across categories of year of hiring ($p = 0.65$), age at hiring ($p = 0.32$), nor cumulative dose ($p = 0.25$). But workers with longer periods of employment showed lower excess of mortality than workers with shorter duration of employment ($p = 0.01$) (Tab. 3).

Table 1. Characteristics of the French nuclear worker cohort, 1968–2004.

Characteristics		
Number of workers	59 004	
Number of men (%)	51 568	(87.4)
Socioeconomic status, *n* (%)		
Managers and engineers	12 095	(20.5)
Administrative employees	4591	(7.8)
Skilled workers	33 356	(56.5)
Unskilled workers	8546	(14.5)
Unknown	416	(0.7)
Mean duration of employment, in years (SD)	21.0	(9.8)
Follow-up, in years		
Mean duration (SD)	24.9	(8.9)
Mean age at end of follow-up (SD)	55.9	(12.6)
Vital status on 12/31/2004, *n* (%)		
Deceased	6310	(10.7)
Alive	52 567	(89.1)
Lost to follow-up	127	(0.2)
Number of person-years	1 469 949	
Person-years by principal employing company, *n* (%)		
CEA	816 782	(55.5)
AREVA NC	121 676	(8.3)
EDF	455 039	(31.0)
Other[a]	76 452	(5.2)
Monitoring of external radiation exposure, in years		
Mean duration (SD)	18.4	(9.1)
Mean age at last monitoring (SD)	46.7	(10.6)
Number of exposed[b] workers (%)	42 206	(71.5)
Mean cumulative photon dose, in mSv (SD)		
Whole cohort	18.4	(40.7)
Exposed[b] workers only	25.7	(46.2)
Person-years by categories of 10-y lagged cumulative photon dose in mSv, *n* (%)		
<5	1 128 947	(77.8)
5–20	165 824	(11.3)
20–50	97 484	(6.3)
50–100	48 264	(3.0)
100–200	23 256	(1.3)
≥200	6174	(0.3)
Person-years by status of neutron exposure, *n* (%)		
Not exposed	1 312 876	(89.3%)
Ever exposed	157 073	(10.7%)

SD: standard deviation.
[a] Mainly for subsidiaries of AREVA NC.
[b] With at least one positive recorded dose.

3.3 Analysis of the dose-risk relationship

Results of the dose-response analysis between cumulative dose and mortality are displayed in Table 4. Positive but imprecise estimates of ERR/Sv were observed for solid cancers. When excluding lung cancer from this grouping, an increase in mortality persisted with a large uncertainty. Models for lymphoma and multiple myeloma could not be fitted. For leukaemia excluding CLL, a positive but not significant ERR/Sv was found, while for myeloid leukaemia, we observed a high and significant ERR/Sv based on 36 deaths. The ERR/Sv for all circulatory diseases, ischemic diseases or cerebrovascular diseases were not significant, albeit positive. For respiratory diseases, a positive but not significant ERR/Sv was also observed, while for chronic obstructive pulmonary disease, the estimated ERR/Sv was not positive.

We performed some sensitivity analyses regarding exposure to neutrons. Adjusting the ERR model on the neutron flag only slightly modified the estimated ERRs for solid cancer (adjusted ERR/Sv = 0.37, 90%CI: −0.44–1.30), circulatory diseases (adjusted ERR/Sv = 0.33, 90%CI: −0.72–1.61), respiratory diseases (adjusted ERR/Sv = 1.36, 90%CI: −1.05–5.22), and leukaemia excluding CLL (adjusted ERR/Sv = 2.22, 90%CI: <0–14.13).

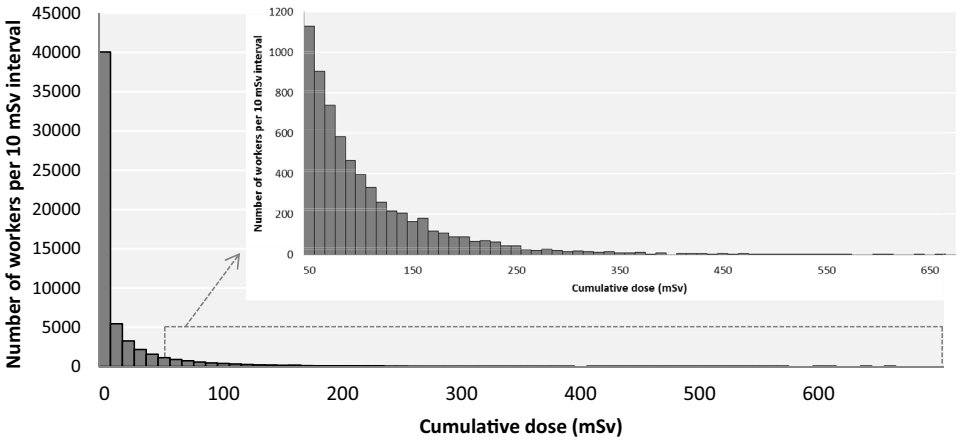


Fig. 1. Distribution of individual cumulative photon doses in the French nuclear worker cohort.

4 Discussion

This cohort study is the most informative ever conducted in France among nuclear workers. The merging of the CEA-AREVA NC and EDF cohorts into a large national cohort resulted in better statistical precision in radiation risk estimates than in previous analyses (Laurent *et al.*, 2010; Metz-Flamant *et al.*, 2011b, 2012). The low percentage of workers lost to follow-up in this cohort reflects the good quality of this study, partly due to the precision of identifying information contained in the companies' personnel files. The overall mortality was lower than that of the French population. Positive but not significant ERR/Sv were observed for solid cancers, leukaemia excluding CLL, ischemic heart diseases, cerebrovascular diseases, and respiratory diseases.

4.1 Cancer mortality

Results confirmed a healthy worker effect in nuclear workers, whose mortality was globally 40% lower than that of the French general population. A healthy worker effect is often observed in occupational cohorts, especially in nuclear workers (Richardson *et al.*, 2007; Vrijheid *et al.*, 2007b; Hammer *et al.*, 2008; Muirhead *et al.*, 2009; Schubauer-Berigan *et al.*, 2015). This well-known effect is generally due to various employment-related components, mainly the healthy hire effect that occurs as healthy people are more likely to enter the workforce than less healthy people and the healthy survivor effect that refers to the process whereby healthy workers remain employed longer than less healthy workers (Howe *et al.*, 1988; Baillargeon, 2001).

We observed a significant excess of death for pleural cancer in the cohort compared to the French population. Similar results have been observed in most studies of nuclear workers (Muirhead *et al.*, 2009; Metz-Flamant *et al.*, 2011a; Merzenich *et al.*, 2014; Schubauer-Berigan *et al.*, 2015). Such an excess was also noted in a cohort of French uranium cycle workers (Samson *et al.*, 2016) that partially overlaps with our cohort (11 deaths by pleural cancer were common to both cohorts); as the authors stated, it was unlikely that the excess could be explained by uranium exposure. The excess of death for pleural cancer in our nuclear worker cohort showed no trend with categories of cumulative dose, but the significant trend in the SMRs associated with duration of employment for pleural cancer suggests that this excess of mortality could be due to some occupational exposure not characterized in this study, albeit this hypothesis cannot be formally confirmed. In France, malignant pleural mesothelioma accounts for about 80% of the pleural cancers among men (42 over 43 deaths occurred among male workers in our study) and asbestos exposure is its main etiological factor (Montanaro *et al.*, 2003). At the time when nuclear industry expanded in France, in the early 1950's, asbestos was widely used in many industries, with a peak in the 1970's, before its use was prohibited in 1990 (Montanaro *et al.*, 2003; Tossavainen, 2004; Goldberg *et al.*, 2006). Asbestos exposure in the early years of nuclear industry may partly explain the elevated SMR for pleural cancer.

As in previous analyses of the CEA-AREVA NC (Metz-Flamant *et al.*, 2011b), an excess of deaths due to malignant skin melanoma was also observed in the cohort. Contrary to cancer of the basal cells of the skin for which exposure to IR is an established risk factor (IARC, 2012a), there is little evidence that IR could induce malignant skin melanoma (UNSCEAR, 2008). Instead, main identified risk factors for skin melanoma are ultraviolet exposure and constitutional factors (including skin reactivity to sunlight and number of moles) (Tucker, 2009). No data on these risks factors are available in the cohort. SMRs for melanoma decreased as duration of employment increased. These results thus do not support the hypothesis of an effect of an unmeasured occupational exposure. Going back in the occupational medical files of the workers who died from malignant skin melanoma could permit retrieving information to explain this excess of mortality.

4.2 Risk of solid cancer

A positive but not significant association between mortality from all solid cancers and cumulative dose was observed in this analysis of the French nuclear workers. Although associated to a large uncertainty, the estimated ERR for solid cancer is consistent with the ERR/Sv estimated in the 15-country study (ERR/Sv = 0.87, 90%CI: 0.16–1.71, $n = 4770$) (Cardis *et al.*, 2007). In the third analysis of the

Table 2. Mortality in the French nuclear worker cohort compared to that of the French population, 1968–2004.

Cause of death	ICD10 codes	*n*	SMR	95%CI
All causes	C00–C97	6310	0.60	0.59–0.62
Solid cancers	C00–C80, C97, except C46.3	2356	0.68	0.65–0.71
Mouth and pharynx	C00–C14, C46.2	109	0.40	0.33–0.49
Oesophagus	C15	92	0.45	0.36–0.55
Stomach	C16	99	0.70	0.57–0.86
Colon	C18	169	0.79	0.67–0.91
Rectum	C19–C21	61	0.69	0.53–0.89
Liver	C22	116	0.59	0.49–0.71
Gallbladder	C23–C24	16	0.70	0.40–1.13
Pancreas	C25	139	0.94	0.79–1.11
Peritoneum	C26, C45.1, C48	47	0.89	0.65–1.18
Nasal cavity	C30–C31	32	0.40	0.27–0.57
Larynx	C32	57	0.41	0.31–0.53
Trachea, bronchus and lung	C33–C34	595	0.66	0.60–0.71
Pleura	C38.4, C45.0	43	1.69	1.22–2.27
Bones and articular cartilage	C40–C41	13	0.61	0.33–1.05
Skin melanoma	C43	44	1.40	1.02–1.88
Breast (women)	C50	70	1.05	0.82–1.33
Corpus uteri (women)	C54–C55, C58	12	0.94	0.49–1.65
Ovary (women)	C56, C57.0–C57.4, C57.8	21	1.11	0.69–1.70
Prostate (men)	C61	149	0.81	0.69–0.95
Bladder	C67, C68	56	0.51	0.39–0.66
Kidney	C64–C66	70	0.89	0.69–1.12
Brain et central nervous system	C70–C72	84	1.03	0.82–1.28
Tumours of lymphatic and hematopoietic tissue				
All	C46.3, C81–C96	196	0.81	0.70–0.94
Hodgkin disease	C81	17	1.13	0.66–1.82
Non Hodgkin lymphoma	C46.3, C82–C85, C88.0, C88.1, C88.3, C91.4, C96	64	0.73	0.56–0.94
Multiple myeloma and IP tumours	C88, C88.2, C88.7, C88.9, C90	36	0.97	0.68–1.35
Leukaemia excluding CLL	C91.0, C91.2, C91.3, C91.5, C91.7, C92–C95	57	0.69	0.53–0.90
Circulatory diseases	G45, I00–I99	1483	0.62	0.59–0.65
Ischemic heart diseases	I20–I25	587	0.64	0.59–0.70
Cerebrovascular diseases	G45, G45.0–G45.2, G45.8–G45.9, I60–I69	338	0.64	0.58–0.71
Respiratory diseases	J00–J99	200	0.41	0.36–0.47
Chronic obstructive pulmonary disease	J40–J44, J47	70	0.41	0.32–0.52
Asthma	J45–J46	12	0.37	0.19–0.64
Digestive diseases	K00–K93	270	0.37	0.32–0.41
Cirrhosis	K70	84	0.28	0.22–0.34

ICD10: tenth revision of the International Classification of Diseases; *n*: observed number of deaths in the cohort; SMR: mortality ratio standardized on calendar period, age, and sex; CI: confidence interval; IP: immuno-proliferative; CLL: chronic lymphocytic leukaemia.

British National Registry of Radiation Workers (NRRW) (Muirhead *et al.*, 2009), the authors reported results for cancer excluding leukaemia, a grouping larger than our solid cancer grouping that excludes lymphoma and multiple myeloma. In the 15-country study, both estimates (for solid cancer and for cancer excluding leukaemia) were comparable (Cardis *et al.*, 2007). The estimated ERR/Sv in the NRRW analysis was 0.28 (90%CI: 0.02, 0.56, $n = 7455$), close to our estimate for solid cancer. Analyses were conducted at the IRSN using the most up-to-date Hiroshima and Nagasaki atomic bomb survivors' mortality data (Life Span Study data, LSS) from 1950–2003 (Ozasa *et al.*, 2012), restricted to men, exposed between the ages of 20 and 60, to derive risk estimates that were comparable to the estimates obtained in the present French nuclear worker combined analyses. Analyses used colon dose in Gray (Gy). The solid cancers ERR/Gy for A-bomb male survivors obtained using an ERR model stratified for attained age, calendar period, and city including modifying effects, was 0.38 (90%CI: 0.08–0.62) for attained age 55 years and age at exposure of 35 years (corresponding respectively to the mean age at end of follow-up and mean age at first exposure in our cohort). Our central estimated ERR/Sv of 0.36 is therefore

Table 3. Variation of the standardized mortality ratios (SMR[a]) for pleural cancer and malignant skin melanoma in the French nuclear worker cohort, 1968–2004.

	Pleural cancer					Skin melanoma				
	n	SMR	95%CI	p_h	p_t	*n*	SMR	95%CI	p_h	p_t
Company										
CEA	33	1.74	1.20–2.44	0.84	–	31	1.55	1.05–2.19	0.17	–
AREVA NC	1	0.78	0.01–4.34			3	1.38	0.28–4.03		
EDF	7	1.87	0.75–3.85			5	0.69	0.22–1.61		
Other	2	1.35	0.15–4.87			5	2.66	0.86–6.20		
Socioeconomic status										
Managers and engineers	6	1.14	0.42–2.48	0.43	–	9	1.38	0.63–2.63	0.74	–
Administrative employees	2	0.91	0.10–3.29			6	2.07	0.75–4.49		
Skilled workers	24	2.07	1.33–3.08			19	1.23	0.74–1.92		
Unskilled workers	11	1.77	0.88–3.17			9	1.43	0.65–2.71		
Unknown	0					1				
Year of hiring										
<1960	18	2.13	1.26–3.36	–	0.05	4	0.54	0.15–1.39	–	0.65
1960–1969	23	1.76	1.12–2.64			29	2.08	1.39–2.99		
1970–1979	1	0.56	0.01–3.10			3	0.69	0.14–2.02		
≥ 1980	1	0.46	0.01–2.57			8	1.39	0.60–2.74		
Age at hiring (years)										
<25	9	1.30	0.59–2.47	–	0.85	16	1.32	0.75–2.14	–	0.32
25–34	22	2.05	1.28–3.10			14	1.10	0.60–1.85		
35–44	9	1.55	0.71–2.94			12	2.39	1.23–4.17		
≥ 45	3	1.49	0.30–4.37			2	1.29	0.15–4.67		
Duration of employment (years)										
<10	3	0.71	0.14–2.07	–	0.04	15	2.15	1.20–3.55	–	0.01
10–19	9	1.37	0.62–2.60			16	1.77	1.01–2.87		
≥ 20	31	2.11	1.44–3.00			13	0.85	0.45–1.45		
Cumulative photon dose (mSv)										
<5	26	1.66	1.09–2.44	–	0.81	29	1.49	1.00–2.14	–	0.25
5-9	3	1.61	0.32–4.70			5	2.09	0.67–4.88		
10–19	2	0.96	0.11–3.48			5	1.89	0.61–4.41		
20–49	8	2.85	1.23–5.62			2	0.59	0.07–2.12		
≥ 50	4	1.29	0.35–3.30			3	0.87	0.18–2.55		

[a] standardized on calendar period, age, and sex. *n* number of observed deaths in the cohort. CI: confidence interval. p_h: bilateral *p*-value of the heterogeneity test, after excluding the unknown category for socioeconomic status. p_t: bilateral *p*-value of the $\chi^2_{(1\ df)}$ Poisson trend test.

consistent with those derived from the LSS, the UK NRWW and the 15-country study. The associated 90%CIs also appear consistent, even if ours were still larger than those estimated in the LSS and UK NRRW studies (Fig. 2).

4.3 Risk of leukaemia

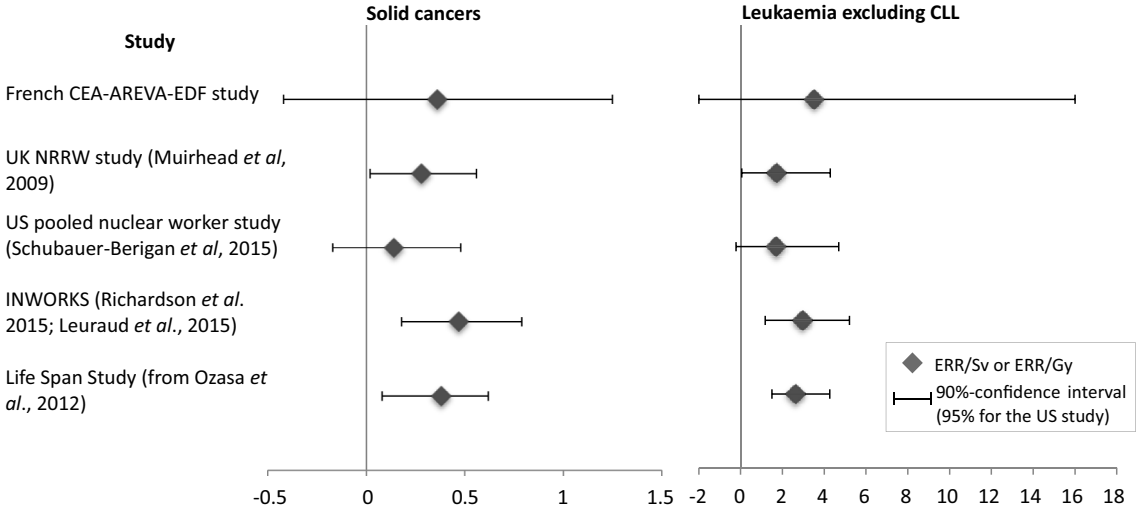
We observed a positive but not significant ERR/Sv for leukaemia excluding CLL. This estimate was higher than the corresponding estimates in the 15-country study (ERR/Sv = 1.93, 90%CI: <0–7.14, *n* = 196) (Cardis *et al.*, 2007), the NRRW study (ERR/Sv = 1.71, 90%CI: 0.06–4.29, *n* = 198) (Muirhead *et al.*, 2009) or the pooled cohort of nuclear workers from the United States of America (U.S.) (ERR % per 10 mSv = 1.70, 95%CI: −0.22–4.70, *n* = 369) (Schubauer-Berigan *et al.*, 2015). Using a simple linear model and dose to bone marrow to derive a risk estimate for leukaemia excluding CLL with the LSS data (Ozasa *et al.*, 2012), as described above, gave an ERR/Gy = 2.63 (90%CI: 1.50–4.27) (Fig. 2). However, these different studies used different sorts of doses (absorbed dose to the red bone marrow due to penetrating photons for the 15-country study and the LSS, equivalent dose due to external radiation for the NRRW study, equivalent dose due gamma, neutron, and tritium in the pooled cohort of U.S. nuclear workers), which hampers a strict comparison of the numerical coefficients. Moreover, the uncertainty associated to our ERR/Sv estimate is large. A significant association with myeloid leukaemia was also found. Other nuclear workers studies showed a higher ERR/Sv for myeloid leukaemia (Richardson and Wing, 2007) or chronic myeloid leukaemia (Muirhead *et al.*, 2009) than for leukaemia excluding CLL. Nevertheless, this result has to be considered with caution as the significant ERR/Sv observed for myeloid leukaemia is our study was mainly due to one death which

Table 4. Excess relative risk[a] of death per Sievert (ERR/Sv) in the French nuclear worker cohort, 1968–2004.

Cause of death	*n*	ERR/Sv	90%CI
Solid cancer	2356	0.36	−0.42–1.25
Solid cancer excluding lung cancer	1761	0.21	−0.66–1.23
Lung cancer	595	0.81	−0.72–2.78
Non Hodgkin lymphoma	64	NC	–
Multiple myeloma and IP tumours	36	NC	–
Leukaemia excluding chronic lymphocytic leukaemia	57	3.52	<0–16.00
Myeloid leukaemia	36	14.95	1.21–43.61
Circulatory diseases	1483	0.31	−0.71–1.52
Ischemic diseases	587	1.06	−0.62–3.23
Cerebrovascular diseases	338	0.65	−1.65–4.01
Respiratory diseases	200	1.20	−1.06–4.68
Chronic obstructive pulmonary disease	70	−0.28	<0–4.99

n: observed number of deaths; CI: likelihood-based confidence interval; IP: immuno-proliferative; NC: convergence not achieved; '<0' is used when the lower bound of the CI could not be estimated.

[a] Estimated from a linear model of cumulative penetrating photon dose lagged by 10 years (except for leukaemia, lagged by 2 years), stratified on calendar period, age, sex, company, duration of employment, and socioeconomic status (except for leukaemia).



*The ERR are expressed per Sievert (Sv) in the French, UK and US studies and per Gray (Gy) (dose to colon or bone marrow) for INWORKS and the LSS. ** cancers excluding leukaemia for the UK and US studies. The ERR/Gy in the LSS were estimated only for men aged between 20 and 60 at time of bombings; the ERR/Gy for solid cancers includes modifying effect of age at exposure and attained age and is given for men at age at exposure 35 years and at attained age 55 years. The French cohort and part of the UK and US cohorts are included in the INWORKS cohort.

Fig. 2. Comparison of the excess relative risks (ERR) per unit dose* estimated for solid cancers** and leukaemia excluding chronic lymphocytic leukaemia (CLL) in the French CEA-AREVA-EDF cohort, the third analysis of the UK National Registry for Radiation Workers (NRRW), the pooled cohort of U.S. nuclear workers, the INWORKS cohort and the Life Span study of Hiroshima and Nagasaki A-bomb survivors.

occurred in the highest dose category. Moreover, some workers may also have been exposed to benzene that is a recognized carcinogenic agent for leukaemia, predominantly acute myelogenous leukaemia (IARC, 2012b); by lack of individual data, the current analyses could not be adjusted on this potential confounder. Implementation of a case-control study nested in the cohort aiming at collecting information on exposures to occupational carcinogens other than IR, as well as on personal habits such as smoking, could be considered. Such study could contribute to improve the assessment of radiation-induced risk of myeloid leukaemia among nuclear workers (Schubauer-Berigan *et al.*, 2007).

4.4 Risk of non-cancer diseases

A positive but not statistically significant association between cumulative dose and mortality from circulatory diseases was observed in this analysis. The central value of the

estimated ERR/Sv was higher than that in the 15-country study (ERR/Sv = 0.09, 90%CI: −0.43–0.70, n = 8412) (Vrijheid *et al.*, 2007a), the NRRW study (ERR/Sv = 0.25, 90%CI: −0.03–0.49, n = 10 509) (Muirhead *et al.*, 2009), the pooled cohort of U.S. nuclear workers (ERR % per 10 mSv = 0.26, 95%CI: −0.25, 0.32) (Schubauer-Berigan *et al.*, 2015) or the LSS (Ozasa *et al.*, 2012), using data restricted to men exposed between the ages of 20 and 60 years (ERR/Gy = 0.11, 90%CI: 0.03–0.19, n = 5852). However, our result appeared unstable as the ERR/Sv was associated with a large CI and adjustment for duration of employment significantly modified the central estimated value of the ERR/Sv (results not shown). In addition, investigating the risk of circulatory diseases associated with IR in nuclear worker studies will require additional efforts as no information on the major known risk factors for these diseases, such as tobacco use, alcohol consumption, hypertension and high body mass index, is currently available in most of these studies (Metz-Flamant *et al.*, 2009; Little *et al.*, 2012).

The estimated ERR/Sv for respiratory diseases in our study is compatible with the risk estimate in the 15-country study (ERR/Sv = 1.16, 90%CI: −0.53–3.84, n = 792) (Vrijheid *et al.*, 2007a) and associated to a large uncertainty. In the LSS, the estimated ERR/Gy among men was lower (ERR/Gy = 0.10, 90%CI: −0.03–0.24, n = 1879) (Ozasa *et al.*, 2012).

4.5 Strengths and potential limitations

A potential limitation may arise from the lack of causes of death before 1968 in France. Among workers who complied with the inclusion criteria of this study, 157 workers from CEA were not included in the cohort as they died before 1968. This problem was discussed by Metz-Flamant *et al.* (2011b) who estimated the SMR for all causes of death including those workers on the 1946–2004 period and showed that it was similar to the SMR for the 1968–2004 period in the CEA–AREVA NC cohort. Moreover, this cohort only includes workers hired by the three employers, CEA, AREVA NC or EDF. In France, there is also a population of workers from contracting companies who operate in the nuclear industry and who are badge-monitored for radiation exposure. This population was not included in the national nuclear worker cohort due to the difficulty of ensuring a high level quality of follow-up (as is the case in the CEA–AREVA NC–EDF cohort). Information in administrative archives of contracting companies is indeed often incomplete, mainly for the years before 1980, making it difficult to reconstitute properly job and dosimetric histories and to link workers' identifiers with national population registries to ascertain vital statuses and causes of death. This difficulty was illustrated by a study of cancer mortality among nuclear contract workers in France (Guérin *et al.*, 2009). Among the 11 577 identified individuals, 4615 (40%) were excluded of the cancer mortality analyses because of uninformative identifiers (name, date of birth...). The results showed a healthy worker effect (all causes SMR = 0.54, 95%CI: 0.47–0.61) of the same order of magnitude than in our study. They also found a statistically significant ERR for all cancers (ERR/100 mSv = 0.56, 95%CI: 0.01–1.6) that appears to be very high but that must be interpreted with caution given the very low number of deaths due to cancer (n = 90) and the probable incompleteness in the dosimetry reconstruction.

The workers included in our study were monitored for external exposure to IR. As data on neutron doses were sparse and subject to uncertainty, we considered only exposure due to penetrating photons in the risk analysis. Workers with a substantial neutron dose were flagged and sensitivity analyses showed that adjusting the ERR model for the neutron flag did not affect the ERR/Sv. A potential bias due to omitting neutron dose in the cumulative dose, if any, may thus be low.

Some workers had also internal contamination from inhaled particles of uranium or plutonium (Canu *et al.*, 2010). Currently, in vivo and bioassay monitoring results for internal deposition of radionuclides are not available for all cohort members. To address that limit, a previous study on the cohort assessed the potential bias in the estimation of the dose-risk relationship due to omitting information on internal contamination (Fournier *et al.*, 2015). Workers at risk of potential internal contamination were identified based on a workstation-exposure matrix. The results suggested that in this cohort, neglecting information on internal dosimetry while studying the association between external dose and cancer mortality did not generate a substantial bias.

Adjustment for socioeconomic status was used to partly take account of the lifestyles of workers, such as smoking habits. Adjustment for determinants of cigarette smoking, such as sex, age, birth cohort, and socioeconomic status, reduces the potential for large systematic differences in smoking prevalence between occupational exposure groups (Axelson, 1989). To further address this concern, we estimated the ERR/Sv for solid cancers excluding lung cancer. Even if the central estimate was lower than the central estimate for all solid cancers, both 90%CI were consistent. Moreover, the lack of association between the cumulative photon dose and the risk of chronic obstructive pulmonary disease, which is known to be strongly associated to smoking, is in favour of a weak confounding by smoking (Richardson *et al.*, 2014).

This is the largest study of French nuclear workers conducted so far in France. Despite a long follow-up (1968–2004), this combined cohort, which is characterised by a particularly low mean cumulative exposure to IR (18 mSv), presents a lack of statistical power to precisely estimate risks associated to low doses of IR. This is mainly due to the young age of workers at last observation (56 years), while most of deaths due to cancer occur later in life. Extending the follow-up of this cohort in the future is thus crucial.

Another way to reach better power in epidemiological studies is to conduct combined analyses of several studies to increase the size of the population. The French cohort contributed to a large international combined analysis of nuclear workers coordinated by the International Agency for Cancer Research (the INWORKS project) (Hamra *et al.*, 2016; Laurier *et al.*, 2017). A pooled cohort of 308 297 workers from France, the United Kingdom, and the U.S., was assembled and an extensive work on the dosimetry was performed to ensure homogeneity in the calculation of doses due to penetrating photons among the three countries (Thierry-Chef *et al.*, 2015). Radiation induced risks of leukaemia and solid cancers could be estimated with a good level of precision. A significant dose-risk relationship was observed between mortality by leukaemia excluding CLL and red bone marrow dose (ERR/Gy = 2.96, 90%CI: 1.17–5.21) (Leuraud *et al.*, 2015) and also between mortality by solid cancer and colon dose (ERR/Gy=0.47, 90%

CI: 0.18–0.79) (Richardson *et al.*, 2015). The results showed no heterogeneity in the country specific risk estimates. Figure 2 summarizes the results of the dose-risk analyses for solid cancer and for leukaemia in INWORKS (Richardson *et al.*, 2015; Leuraud *et al.*, 2015), the French nuclear worker cohort, the NRRW study (Muirhead *et al.*, 2009), the pooled cohort of U.S. nuclear workers (Schubauer-Berigan *et al.*, 2015), and in the LSS (analyses restricted to men, exposed between the ages of 20 and 60). It displays the estimated ERR per unit dose as published in the different studies: the ERR are thus expressed per Sv in the French, UK and U.S. studies and per Gy for INWORKS and the LSS. Figure 2 reflects how, despite large uncertainties in the French study, central estimates of the ERR are in good agreement across the different studies.

5 Conclusion

Cohorts of nuclear workers are particularly relevant to study potential health risks induced by exposure to low doses of IR delivered at low dose rates, as they permit direct assessment of dose-risk relationships and thus prevent making hypotheses when extrapolating coefficients derived in a frame of acute high dose exposure, as is the case in the LSS. The study of the French nuclear worker cohort shows that workers are globally in better health than the general population. The estimated risks following occupational exposure to IR remain associated to large uncertainties. Further analyses based on a longer follow-up will allow improving the precision of risk estimates. Other ways to improve the assessment of radiation related-risks include a better characterization of other sources of occupational exposures and personal risk factors for the diseases of interest and the continuation of international collaborations.

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