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THE INTERNATIONAL NUCLEAR WORKERS STUDY (INWORKS): A COLLABORATIVE EPIDEMIOLOGICAL STUDY TO IMPROVE KNOWLEDGE ABOUT HEALTH EFFECTS OF PROTRACTED LOW-DOSE EXPOSURE

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INWORKS is a multinational cohort study, gathering 308 297 workers in the nuclear industry in France, the United Kingdom and the United States of America, with detailed individual monitoring data for external exposure to ionising radiation. Over a mean duration of follow-up of 27 y, the number of observed deaths was 66 632, including 17 957 deaths due to solid cancers, 1791 deaths due to haematological cancers and 27 848 deaths due to cardiovascular diseases. Mean individual cumulative external dose over the period 1945–2005 was 25 mSv. Analyses demonstrated a significant association between red bone marrow dose and the risk of leukaemia (excluding chronic lymphocytic leukaemia) and between colon dose and the risk of solid cancers. INWORKS assembled some of the strongest evidence to strengthen the scientific basis for the protection of adults from low dose, low-dose rate, exposures to ionising radiation.

INTRODUCTION

The effects of exposure to ionising radiation have been studied for decades, and there is substantial evidence of increased risk for solid cancers and leukaemia due to exposure to ionising radiation, both from epidemiology and from experimental research[(1)]; the health effects of acute, moderate to high radiation doses are well characterised. The primary epidemiological basis for this is the Life Span Cohort of Japanese survivors of the atomic bombings of Hiroshima and Nagasaki[(2)].

The risks associated with protracted or repeated low-dose exposures are more relevant to the public, workers, radiation protection professionals and health practitioners. The current system of radiation protection relies heavily on radiation risk models derived from studies of populations exposed to acute, medium to high doses. Transporting these risk models to low protracted exposures necessitates strong underlying assumptions.

Since the 1980s, studies of nuclear industry workers have been conducted to provide direct information about these effects. These cohorts are well suited for this purpose: they include large number of workers, with individual (person-specific) monitoring of external doses and many years of follow-up. Previous international combined analyses have already been performed, especially the 15-country study[(3)]. As an extension of this previous work, INWORKS was established to provide a stronger basis allowing direct quantification of health risks associated with chronic, low-level exposure to ionising radiation.

MATERIAL AND METHODS

INWORKS is an epidemiological study of mortality among workers in the nuclear industry. The study cohort comprises French, American and British workers in the nuclear industry (fuel preparation, research, power generation, reprocessing of spent fuel) and monitored for external radiation exposure by wearing individual dosimeters. Main characteristics of the study cohort were described previously[(4)].

INWORKS is coordinated by the International Agency for Research on Cancer (IARC, www.iarc.fr). The French, American and British cohorts were established respectively by the Institute for Radiological Protection and Nuclear Safety (IRSN, http://www.irsn.fr),

the National Institute for Occupational Safety and Health >(NIOSH, http://www.cdc.gov/niosh/) and the Public Health England's Centre for Radiation, Chemical and Environmental Hazards (CRCE-PHE, www.gov.uk/government/organisations/public-health-england). The University of North Carolina (UNC, http://www.unc.edu/) and the Center for Research in Environmental Epidemiology (CREAL, www.creal.cat/en_index.html) also participated in the consortium.

The population studied in INWORKS included 308 297 male and female workers. Protocol, inclusion criteria and organ dose calculation have been standardised between the three countries. Follow-up ranged from 1943 to 2005. Underlying causes of death were abstracted from death certificates and coded according to the International Classification of Diseases. Participants entered the study either 1 y after the date of first employment or on the date of first dosimetric monitoring, whichever was later. They remained in the study until the earliest of date of death, date lost to follow-up or end of follow-up.

All workers included in INWORKS had records that provide individual quantitative external radiation dose estimates. Workers in INWORKS were mainly exposed to external radiation, usually gamma rays, and doses were measured regularly with personal dosimeters. For all participating cohorts, records of individual recorded doses have been kept since the very beginning of the industry in the 1940s. Correction factors were derived by dosimeter type to account for bias and associated uncertainties and recorded doses were converted into absorbed organ doses using ICRP conversion coefficients. The method of reconstitution of the individual dosimetric history was published in a specific article[5].

Relative risk (RR) of death was estimated by a model of the form $RR = 1 + \beta d$, as generally used in studies of radiation effects, where d is the dose and β is an estimate of the excess relative risk (ERR) per unit dose. Likelihood-based 90% confidence intervals (CI) were derived. Red bone marrow (RBM) dose was used for the analysis of leukaemia risk excluding chronic lymphocytic leukaemia (CLL) and colon dose for the analysis of combined solid cancers risk. To allow for a latency period between exposure to radiation and death, cumulative doses were lagged by 2 y for analyses of leukaemia mortality and by 10 y for analyses of solid cancer mortality. Data were housed at the IARC. Analyses were performed by all partners.

RESULTS

Characteristics of the INWORKS study are presented in Table 1. Mean length of employment was 15 y. Individual cumulative doses converted to $H_p(10)$ ranged from 0 to 1932 mSv, with a mean of 25 mSv. Corresponding organ doses were 17.4 mGy to colon and 15.9 mGy to RBM. Mean duration of follow-up was 27 y, for a total of 8.2 million person-years. The mean attained age at the end of follow-up was 58 y. The total number of deaths was 66 632, including 17 957 deaths due to solid cancers, 531 deaths due to non-CLL leukaemia and 27 848 deaths due to circulatory diseases.

INWORKS demonstrated a significant association between cumulative RBM dose from external sources and the risk of non-CLL leukaemia (n = 531 deaths), with an ERR of 2.96 per Gy, 90% CI = [1.17; 5.21][6] and between cumulative colon dose and the risk of solid cancers, with an ERR of 0.47 per Gy, 90% CI = [0.18; 0.79][7]. Estimated dose–risk relationships can be compared with those derived from the 15-country study or from the cohort of Japanese A-bomb survivors (Figure 1). It should be noted however that, as detailed by Wakeford[8], the most reliable results from the 15-country study may be for the combined 14 countries excluding Canada. Indeed, the Canadian workers cohort had a large

Table 1. Characteristics of the INWORKS study.

	France	UK	US	INWORKS
Calendar years of follow-up	1968–2004	1946–2001	1944–2005	1944–2005
Workers	59 003	147 866	101 428	308 297
Person-years (millions)	1.5	3.4	3.3	8.2
Deaths (all causes)	6310	25 307	35 015	66 632
All cancers	2552	7558	9638	19 748
Solid cancers	2356	6994	8607	17 957
Non-CLL leukaemia	56	167	311	531
Exposed workers[a]	42 206	130 373	84 587	257 166
Average cumulative colon dose (mGy)[b]	17.6	22.5	20.0	20.9
Average cumulative RBM dose (mGy)[c]	16.2	20.6	18.3	19.1

[a]Workers with cumulative recorded external dose greater than zero.
[b]Average estimated cumulative external dose to the colon, among exposed workers.
[c]Average estimated cumulative external dose to the RBM, among exposed workers.

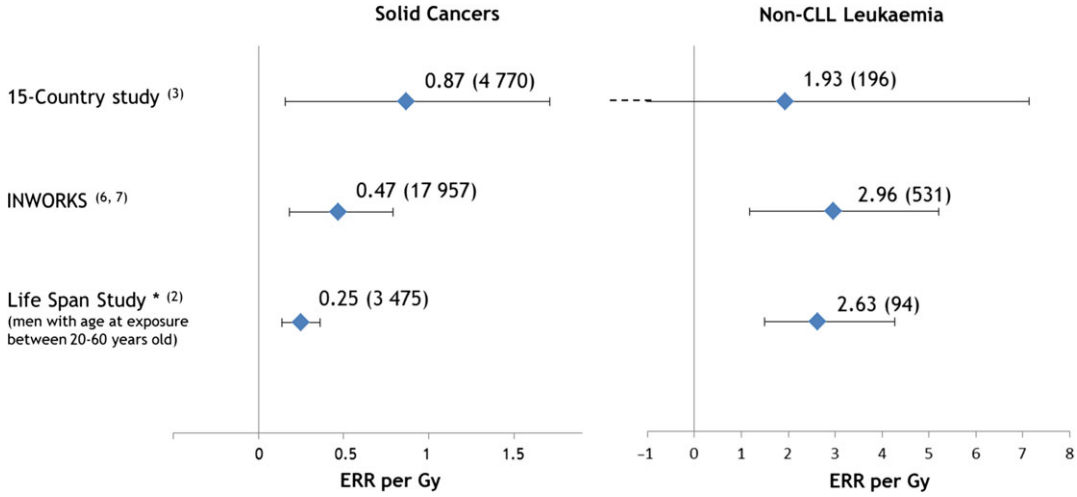

Figure 1. Comparison of the ERR per Gy and associated 90% CIs for solid cancers and leukaemia excluding CLL, estimated from INWORKS, the 15-country study and the Life Span Study of Japanese A-bombs survivors. Numbers in brackets are observed numbers of deaths. *Reported results were calculated at IRSN using the Hiroshima and Nagasaki A-bomb survivors data[2] restricted to men exposed between 20 and 60 y of age using simple linear ERR models.

influence on the high risk estimate observed for all cancers excluding leukaemia, and the exclusion of Canadian workers from the 15-country study led to a reduction of about 40% in the risk estimate. This effect was lately proved to be due to errors in dose assessment[8]. Thus, Figure 1 should be considered in light of a potential similar impact on the ERR for solid cancers estimated from the 15-country study, which makes the risk estimate even more similar to that derived from INWORKS. For non-CLL leukaemia, the ERR per Gy estimated in the Canadian cohort was similar to that of the 15-country study[3], and no such effect was observed.

In INWORKS, sensitivity analyses demonstrated the stability of the estimated associations upon exclusion of each of the 3 countries, adjustment on flags for internal contamination by intakes of radionuclides or neutron exposure, and exclusion of specific cancer types such as lung cancer.

Sensitivity analyses have been performed on restricted dose ranges. Significant associations were observed down to a restricted range of 100 mGy for solid cancer, and of 300 mGy for non-CLL leukaemia. Below those levels, the dose–risk relationships were not significantly different from zero due to large uncertainties but ERR estimates were consistent with those obtained over the whole dose range.

DISCUSSION

INWORKS enabled consolidation of the data from previous country-specific studies of nuclear workers. For the total population of INWORKS, the dose–response relationships for solid cancers and for non-CLL leukaemia were statistically significant, with external radiation exposure protracted over time. At very low doses, i.e. below a few tens of mSv, the statistical uncertainty became important and the dose–response relationships were no longer statistically significant; however, they remained consistent with those estimated over the whole range of doses. The dose–risk associations observed in INWORKS were consistent with those observed in other studies, especially among survivors of the atomic bombings of Hiroshima and Nagasaki. The evidence did not suggest any large 'no risk' threshold for dose, or any possible beneficial effects[9].

While this international study has provided support for an association between long-term exposure to low-dose radiation and an increase in the risk of leukaemia and solid cancers, the radiation-related excess risk associated with these low doses is very small[10]. From the estimated dose–risk relationship, based upon analyses of the death rates from cancer other than leukaemia depending on age and cumulative dose observed in the study cohort, and under the assumption that this relationship was causal, it was estimated that the proportion of death attributable to external exposure to radiation within the population of INWORKS was around 1% of all deaths from solid cancer, and around 6% of all deaths from non-CLL leukaemia[6, 7].

Of course, as with any occupational cohort mortality study, INWORKS has limitations. The main analyses included workers with neutron exposure and internal contamination, but it was not possible to reconstruct the doses due to these exposures[11]. Nevertheless, after the exclusion of workers flagged

for neutron exposure, or internal contamination or monitoring, the estimated associations between dose and mortality due to solid cancers or non-CLL leukaemia persisted, and results showed little evidence of potential bias due to neutron exposure or internal contamination on the estimated radiation dose–risk associations. The absence of data on tobacco consumption was another weakness of the study, but in contrast to the 15-country study[3], additional analysis showed that, after excluding cancers of the lung, the magnitude of the estimated ERR per Gy was similar to that for all solid cancers, suggesting that there was no confounding by smoking[7]. Another weakness was the absence of data on medical radiation exposures. But for confounding to occur, medical radiation exposures would need to be associated with occupational doses, within strata defined by the cross-classification of variables used to model the background mortality rate at zero dose (country, attained age, sex, and calendar period for leukaemia, plus socioeconomic status and duration of employment for solid cancers)[12]. Our primary analyses of solid cancer use a linear model for analysing dose–response associations[13]. But analyses did not simply assume that the data fit a linear model; for both non-CLL leukaemia and solid cancer mortality, the RRs across categories of cumulative dose were examined, showing that the trend in the ERR with dose were well described by a linear function of cumulative dose, and a higher order polynomial function of dose did not substantially improve the models fit. The study team attempted to anticipate and address such weaknesses through design decisions in the study protocol, as well as through analytical decisions and sensitivity analyses; these have been described in the published articles[6, 7]. To date, analyses have used estimates of doses that account for differences in dosimeters over time and between countries; however, analyses have not formally accounted for dose uncertainty in estimation of dose–response associations[9]. Further analyses are scheduled that will allow us to consider this point. A better understanding of the effect of low-dose radiation is warranted, and we consider that large epidemiological studies like INWORKS can contribute by being be integrated into integrative projects, including biologists, toxicologists, dosimetrists and epidemiologists in order to clarify how low-dose radiation affects human beings[14].

INWORKS yielded statistical information to permit relatively precise estimates of cancer mortality risk in a population that tended to accrue low-dose rate exposures over a protracted period of time with a mean duration of employment of 15 y. These findings represent a substantial addition to the scientific basis for understanding the risks of cancer from protracted, low-dose rate, exposure to ionising radiation; and underscore the value of the substantial efforts being made in France, the United Kingdom and the United States of America to continue gathering data for these worker studies. The INWORKS data will also allow analysing the risk of death for specific cancer sites and for non-cancer mortality. In addition, the long follow-up will allow for better estimation of temporal factors affecting the relationship between low-level ionising radiation and mortality.

CONCLUSION

INWORKS assembled some of the strongest evidence to date regarding low-dose radiation effects that may strengthen the scientific basis for the protection of adults from low dose, low-dose rate, exposures to ionising radiation. These results were consistent with one of the assumptions underlying the current radiation protection system that is the extrapolation of the model derived from the study of survivors of the bombings of Hiroshima and Nagasaki to populations repeatedly exposed to low doses. These results support the rationale for radiation protection of populations exposed to low doses of ionising radiation.

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