The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: Design, Epidemiological Methods and Descriptive Results

Authors: M. Vrijheid, E. Cardis, M. Blettner, E. Gilbert, M. Hakama, et. al.

Source: Radiation Research, 167(4) : 361-379

Published By: Radiation Research Society

URL: https://doi.org/10.1667/RR0554.1

RADIATION RESEARCH **167**, 361–379 (2007)
0033-7587/07 $15.00

The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: Design, Epidemiological Methods and Descriptive Results

M. Vrijheid,[a,1] E. Cardis,[a] M. Blettner,[b] E. Gilbert,[c] M. Hakama,[d,e] C. Hill,[f] G. Howe,[g] J. Kaldor,[h] C. R. Muirhead,[i] M. Schubauer-Berigan,[j] T. Yoshimura,[k] Y-O. Ahn,[l] P. Ashmore,[m] A. Auvinen,[d,n] J-M. Bae,[o] H. Engels,[p] G. Gulis,[q] R. R. Habib,[r] Y. Hosoda,[s] J. Kurtinaitis,[t] H. Malker,[u] M. Moser,[v] F. Rodriguez-Artalejo,[w] A. Rogel,[x] H. Tardy,[a] M. Telle-Lamberton,[y] I. Turai,[z] M. Usel[aa] and K. Veress[bb]

[a] International Agency for Research on Cancer, Lyon, France; [b] Institut für Medizinische Biometrie, University of Mainz, Germany; [c] Radiation Epidemiology Branch, Division of Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland; [d] University of Tampere, Tampere, Finland; [e] Finnish Cancer Registry, Helsinki, Finland; [f] Institut Gustave-Roussy, Villejuif, France; [g] Department of Epidemiology, Mailman School of Public Health, Columbia University, New York; [h] National Centre in HIV Epidemiology and Clinical Research, Sydney, Australia; [i] Radiation Protection Division, Health Protection Agency, Chilton, Didcot, United Kingdom; [j] National Institute for Occupational Safety and Health, Cincinnati, Ohio; [k] Department of Clinical Epidemiology, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Kitakyushu, Japan; [l] Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea; [m] Radiation Protection Bureau, Health Canada, Ottawa, Canada (currently at McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Canada); [n] STUK—Radiation and Nuclear Safety Authority, Helsinki, Finland; [o] Department of Preventive Medicine, Cheju National University College of Medicine, Chejudo, Korea; [p] The Nuclear Research Centre (SCK.CEN), Radiation Protection Division, Mol, Belgium and the Federal Agency for Nuclear Control (FANC), Brussels, Belgium; [q] Department of Hygiene and Epidemiology, Faculty of Health Care and Social Work, Trnava University, Department of Hygiene and Epidemiology, Trnava, Slovak Republic; [r] Faculty of Health Sciences, American University of Beirut, Lebanon; [s] Retired, 1-41-4 Higashi-nakano, Nakano-ku, Tokyo 164-0003, Japan; [t] Lithuanian Cancer Registry, Vilnius University Oncology Institute, Vilnius, Lithuania; [u] Midsweden Research and Development Center, Sundsvall Hospital, Sundsvall, Sweden; [v] Federal Office of Public Health, Bern, Switzerland; [w] Department of Preventive Medicine and Public Health, School of Medicine, Universidad Autonoma de Madrid, Spain; [x] Service Central d'Appui en Santé au travail, Electricité de France, Paris, France; [y] Institut de Radioprotection et de Sûreté Nucléaire, Fontenay-aux-Roses, France; [z] National "Frederic Joliot-Curie" Research Institute for Radiobiology and Radiohygiene of the National "Fodor József" Public Health Centre, Budapest, Hungary; [aa] Medical Inspectorate of Factories, Geneva, Switzerland; and [bb] Department of Dermatology, Venereology and Dermatooncology, Semmelweis University, Budapest, Hungary

Vrijheid, M., Cardis, E., Blettner, M., Gilbert, E., Hakama, M., Hill, C., Howe, G., Kaldor, J., Muirhead, C. R., Schubauer-Berigan, M., Yoshimura, T., Ahn, Y-O., Ashmore, P., Auvinen, A., Bae, J-M., Engels, H., Gulis, G., Habib, R., Hosoda, Y., Kurtinaitis, J., Malker H., Moser, M., Rodriguez-Artalejo, F., Rogel, A., Tardy, H., Telle-Lamberton, M., Turai, I., Usel, M. and Veress, K. The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: Design, Epidemiological Methods and Descriptive Results. *Radiat. Res.* 167, 361–379 (2007).

Radiation protection standards are based mainly on risk estimates from studies of atomic bomb survivors in Japan. The validity of extrapolations from the relatively high-dose acute exposures in this population to the low-dose, protracted or fractionated environmental and occupational exposures of primary public health concern has long been the subject of controversy. A collaborative retrospective cohort study was conducted to provide direct estimates of cancer risk after low-dose protracted exposures. The study included nearly 600,000 workers employed in 154 facilities in 15 countries. This paper describes the design, methods and results of descriptive analyses of the study. The main analyses included 407,391 nuclear industry workers employed for at least 1 year in a participating facility who were monitored individually for external radiation exposure and whose doses resulted predominantly from exposure to higher-energy photon radiation. The total duration of follow-up was 5,192,710 person-years. There were 24,158 deaths from all causes, including 6,734 deaths from cancer. The total collective dose was 7,892 Sv. The overall average cumulative recorded dose was 19.4 mSv. A strong healthy worker effect was observed in most countries. This study provides the largest body of direct evidence to date on the effects of low-dose protracted exposures to external photon radiation.

INTRODUCTION

Current protection standards for environmental and occupational exposures to ionizing radiation are based mainly on cancer risk estimates derived from studies of atomic bomb survivors (*1*). However, the validity of extrapolations from this comparatively high-dose acute exposure situation to the low-dose, protracted or fractionated exposures of pri-

[1] Address for correspondence: International Agency for Research on Cancer, 150, Cours Albert Thomas, 69372 Lyon Cedex 08, France; e-mail: vrijheid@iarc.fr.

mary public health concern has long been the subject of controversy.

Studies of cancer risk among workers in the nuclear industry are particularly well suited for the direct estimation of the effects of protracted, low-level ionizing radiation exposure for several reasons (*2*). First, very large numbers of workers have been employed by this industry (over 1 million workers in the world). Second, these working populations are relatively stable, providing an opportunity to investigate long-term low-level radiation exposures through appropriate follow-up. Third, individual real-time monitoring of potentially exposed personnel has been carried out with the use of personal dosimeters (at least for external photon exposures) and the measurements have been kept, thereby providing reliable information on which to base epidemiological estimates of radiation-induced cancer risk.

A number of previous studies of nuclear workers have provided radiation-related risk estimates (*3*), but their precision has been limited by the sample size of individual studies. To improve the precision of risk estimates, it is therefore necessary to combine data across multiple cohorts. This approach has been used previously at both the national (*4–7*) and international (*8, 9*) level.

The International Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry was carried out in 15 countries to improve the precision of direct estimates of radiation-induced cancer risk after protracted low doses of ionizing radiation and to strengthen the scientific basis for setting radiation protection standards. The study is referred to as the 15-Country Study throughout this paper.

This paper presents the epidemiological design, methods and results of descriptive analyses of the 15-Country Study. Details of the radiation risk estimation methods and findings concerning the relationship between external radiation dose and risk of cancer mortality in the cohorts are described elsewhere (*10, 11*), as are the details of the study of errors in dose estimates (*12*).

METHODS

Study Design

The 15-Country Study was designed as a multinational retrospective cohort study of radiation workers in the nuclear industry.[2] The study included cohorts from Australia, Belgium, Canada, Finland, France, Hungary, Japan, Korea, Lithuania, the Slovak Republic, Spain, Sweden, Switzerland, the UK and the U.S. (Table 1). Cohorts of nuclear workers in Germany and the Russian Federation were considered for inclusion but did not meet the study inclusion criteria.

The mortality of the workers in the cohorts was ascertained, and information on radiation exposure, employment history and other demographic characteristics was collected. The study used a common core protocol and a detailed procedures document to facilitate comparability of study design in all cohorts (*13–15*). This paper describes the principles underlying the procedures and summarizes procedures adopted by the participating cohorts. Detailed procedures adopted by each cohort can be found elsewhere (*15*).

The 15-Country Study includes all cohorts of nuclear industry workers from the UK National Registry for Radiation Workers (NRRW) study (*5*) and the previous 3-Country combined study (*8, 9*), except the Rocky Flats cohort (*16*) because of the large number of workers in that cohort with potential for internal contamination. The 3-Country study combined the existing cohorts of Oak Ridge National Laboratory (ORNL) (*17*), Hanford (*18*) and Rocky Flats (*16*) in the U.S., Sellafield, the UK Atomic Energy Authority (UKAEA) and the Atomic Weapons Establishment (AWE) in the UK (*4*), and Atomic Energy of Canada Limited (AECL) in Canada (*19*). However, as will be described later, the inclusion criteria in the 15-Country study differed somewhat from those used in previous studies, and hence not all of the workers from these previous studies are included in the 15-Country study. Results from some of the national components of the 15-Country Study have recently been published (*6, 7, 20–27*) as well as the first results from the 15-Country Study itself (*10*).

Inclusion and Definition of Cohorts

To be eligible for inclusion in the 15-Country Study, a cohort had to satisfy the following quality criteria, which were established *a priori* (*14*):

1. All members of the cohort had the potential for whole-body external exposure to ionizing radiation through working in the nuclear industry.
2. Non-selective, 95% or better, identification of all potential study subjects (i.e. coverage) was possible.
3. Monitoring of external radiation exposure was conducted routinely by use of personal dosimeters assigned to workers likely to be exposed to ionizing radiation, and historic records for individuals included in the study were kept.
4. Information was available on historical monitoring policies and practices.
5. Estimates of the whole-body dose from individual external exposure measurements were available for all workers on at least a yearly basis from the time of first exposure.
6. Information on a minimum set of variables was available for individuals in the cohort (see below).
7. The mechanisms of follow-up were not selective (for example restricted to current workers).
8. A high level of completeness of ascertainment of vital status and cause of death was possible.

Study cohorts were defined either from the employment or dosimetric records of a participating facility or organization, from a centralized national dose registry, or from a registry of radiation workers (Table 1). Not all eligible facilities in each participating country were included in the study; in most cases, this is because the facility concerned did not agree to participate. The participation of facilities was independent of known or suspected excess cancer risk.

Workers employed at more than one facility in the same country or employed more than once at the same facility were identified where feasible and their occupational and exposure histories reconstructed. Doses received before employment in a participating facility, and in non-participating facilities, were obtained where available. Overlaps between different cohorts within one country were identified as well as, where possible, overlaps between different countries (Table 1).

Inclusion of Study Subjects

All routinely monitored individuals in a particular facility during the study period were eligible for inclusion in the study cohorts, irrespective of their age, sex, nationality, ethnic group, type of employment, job title or activity. The following exclusion criteria were used:

1. *Workers employed less than 1 year,* if there were logistic reasons that

[2] In this paper, the term nuclear industry is used to refer to facilities engaged in the production of nuclear power, the manufacture of nuclear weapons, the enrichment and processing of nuclear fuel, the production of radioisotopes, or reactor or weapons radiation research. Uranium mining is not included.

would make their follow-up difficult. France CEA-COGEMA, France EDF, Korea, Spain and Switzerland excluded workers employed for less than 1 year from their initial cohorts; the UK excluded workers employed less than 6 months; the U.S. nuclear power plant (NPP) cohort excluded workers who had been monitored for less than 1 year.
2. *Workers who were not monitored for external radiation dose.* The majority of countries (Australia, Canada, France, Hungary, Japan, Korea, Slovakia, Spain and Switzerland) included only monitored workers in their cohorts.
3. *Contract workers,* if there were no means to reconstruct their exposure and employment history and follow them up for cancer risk in a non-selective manner. Such workers were excluded from the cohorts in Belgium, France, Hungary, Slovakia, Switzerland and the UK as well as from the U.S. Hanford, NPP and ORNL cohorts.

Follow-up Procedures

For logistic and legal reasons, mechanisms for follow-up differed in different countries but were chosen to ensure non-selective and uniform follow-up for the entire cohort under study. Vital status and causes of death were ascertained through linkage with national or regional death registries where possible. In countries where this was not possible, appropriate records of local authorities, such as commune of birth or of last known residence (France-CEA-COGEMA, Japan, Switzerland), or of the participating facilities (Spain) were used. In the French-EDF cohort, vital status was ascertained from company records but crosslinked with the national population registry; causes of death were then obtained from the national cause of death registry (*26*). In Japan, municipalities keep resident records, but, by law, records for persons who move away or die are kept for 5 years only. Because of this, it was not possible to ensure complete follow-up of the cohort from the beginning of nuclear operations in 1957. The follow-up period was therefore restricted to the period 1986–1992 (*6*).

Table 2 summarizes the sources of vital status and cause of death information used for each cohort. Date of last known vital status for individual workers was determined as whichever was earliest: date of end of study, date of death, date of emigration (in countries where this latter information was available systematically), or date of loss to follow-up. Cohorts with passive follow-up (Table 3) considered subjects to be alive if they had not been identified as deceased or as having emigrated in the sources of vital status shown in Table 2.

Cause of Death Coding

The minimum information requested for each death was the underlying cause, coded according to ICD rules and the ICD revision used at the time. Where possible, the associated (contributing) causes of death, coded according to the same procedures as the underlying cause, were also obtained. For external comparisons with country-specific rates, it was judged important that the coding rules should correspond to those used within each country. Causes of death were therefore provided in ICD 6, 7, 8, 9 and 10 depending on year and country. The list of ICD codes used in these revisions for the causes of death studied is given in the Appendix.

Definition of the Study Period

For a participating facility, the start of the study period was the earliest date possible once the minimum criteria for study were satisfied; i.e., subjects were monitored for radiation dose and under observation for the event of interest (mortality) (Table 2). In some cases, however, study periods started later, for example, if complete dosimetric data were not available before this date. In such a case, only workers employed after that date, or for whom complete reconstruction of doses prior to that date was possible in a non-selective fashion, were included. This was the case, for example, at AECL (Canada), where a fire destroyed dosimetric archives in 1956. Only workers who started employment after that date were included in the study.

The end of the study period was as late as possible and was the latest date for which mortality follow-up was thought to be complete.

Collection of Individual Information

A minimum set of variables to be collected for each cohort member was identified at the start of the study. It included general information on demographic variables (date of birth, sex, socio-economic status, vital status, and date and cause of death for workers who had died) and employment history, including start and end of employment (or monitoring if employment dates were not available), category of worker (employee or contractor), organization where employment took place, and, where possible, start and end dates and job title for each employment period. Identifying information was collected at the national level but was not sent to IARC.

Dosimetric information was collected from records of individual facilities and/or national dose registries. Information on external radiation exposure history included, for *each study subject,* for *each year* of monitoring and for *each facility* where a dose was received, the year and organization/facility where the dose was received, the total equivalent dose from external exposures only, and the high-energy (>100 keV) X- and γ-ray equivalent dose (in mSv).

Information on offsite or transfer doses (i.e. radiation doses received before, during or after employment in other facilities) was obtained with as much detail on period and facility of exposure as available. Flags identifying workers who had potentially received substantial doses from neutrons or internal contamination were constructed (*12*). Where available, the neutron and internal equivalent doses were also collected.

Information collected on socio-economic status (SES) was, by necessity, country-specific and depended on the information available in records of individual facilities. Countries derived an SES classification based on job title and/or on education. Recommendations were that SES based on job title should correspond to the code of job of longest duration, if possible; alternatively, the code of the first (preferably) or last job could be used. SES was coded using a minimum of four categories, corresponding broadly to the British Registrar General's classification (*28*) or to the categories: white collar professional, white collar others, blue collar skilled, blue collar others. The SES classification based on education used the workers' most recent educational level if possible (otherwise at entry to the facility). The SES classifications used in the main analyses (*10, 11*) are summarized in Table 6; exact definitions can be found in the full study report (*29*).

Because of the importance of SES as a potential confounder of solid cancer and all-cause mortality risk, the following facilities were excluded from these analyses: Japan and U.S.-INL because they did not provide any SES measures and Ontario Hydro in Canada because SES was missing for a large part of the workers. In the solid cancer and all-cause mortality analyses, SES was missing for only 6% of workers.

Detailed information on smoking was available only in a few facilities, where it was of uncertain quality and was difficult to obtain for all workers because it had to be extracted from medical records. Some centers therefore conducted surveys of smoking habits in samples of the current workforce to assess the degree of correlation between smoking and radiation dose (see the Results).

Data validation was conducted at both the national and international levels; it included both the review of descriptive information concerning follow-up procedures and their success and the conduct of consistency and random sample checks.

A study of errors in recorded doses was carried out within the framework of the 15-Country Study to (1) evaluate the comparability of recorded dose estimates across facilities and time and (2) identify and quantify sources of bias and uncertainties in dose estimates so that they could be taken into account in the radiation risk analyses. Details and results are presented in ref. (*12*).

TABLE 1
Summary of Cohorts Included in the 15-Country Study

Study cohort	Definition	Nuclear power plants	Other and mixed activity facilities	Year of start of operations	Basis for cohort definition	Overlap between facilities/cohorts: Identified	Overlap between facilities/cohorts: Employees assigned to:	Reference
Australia	Employees of ANSTO at Lucas Heights Research Laboratories	0	1	1959	Personnel records	N/A	—	(*25*)
Belgium	Employees of Electrabel in Doel and Tihange, SCK.CEN, Belgonucleaire, and Belgoprocess	2	3	1953	Personnel records	yes, within country and with EDF	facility of first employment	(*24*)
Canada	Employees of AECL-Nuclear Research, and the power generating facilities operated by Ontario Hydro, Hydro Québec and New Brunswick Electric[a]	3	1	1944	National dose registry	yes, within country	facility where highest dose was received	(*7*)
Finland	Employees of two nuclear power plants Loviisa and Olkiluto-and one nuclear research facility-Fir 1	2	1	1960	National dose registry	yes, within country and with Sweden	facility of longest employment	(*20*)
France CEA-COGEMA	Employees of the fuel cycle facility COGEMA and the nuclear research facilities of CEA, monitored for radiation exposure in only one company[b]	1	8	1946	CEA and COGEMA personnel records	yes, with EDF	facility of first employment	(*23*)
France EDF	Status employees of EDF monitored for radiation exposure	22	0	1956	Dosimetric records	yes, with CEA-COGEMA and Belgium	facility of first employment	(*26*)
Hungary	Employees of the nuclear power plant Paks	1	0	1982	Personnel records	N/A	—	
Japan	Employees of 16 nuclear power plants and 17 mixed activity facilities registered on RADREC	16	17	1957	RADREC dose registry	Not assigned	—	(*6*)
Korea (South)	Employees of KHNP (formerly KEPCO) in 4 facilities: Kori, Ulchin, Wolsong, and Yonggwang	4	0	1977	Personnel records	yes, within country	facility of last employment	
Lithuania	Employees of the Ignalina Nuclear Power Production Facility	1	0	1984	National dose registry	N/A	—	
Slovak Republic	Employees of the Nuclear Power Plant Jaslovské Bohunice	1	0	1973	Personnel records	N/A	—	(*21*)
Spain	Employees of two nuclear fuel cycle facilities: Juzabado and Enresa, and 8 power plants.	8	2	1968	Personnel records	yes, within country	facility of first employment	

TABLE 1
Continued

Study cohort	Definition	Nuclear power plants	Other and mixed activity facilities	Year of start of operations	Basis for cohort definition	Overlap between facilities/cohorts: Identified	Overlap between facilities/cohorts: Employees assigned to:	Reference
Sweden	Employees of fuel cycle facility ABB atom, nuclear research facility Atomenergi AB (Studsvick), and 4 power plants	4	2	1954	National dose registry	yes, within country and with Finland	facility of last employment	
Switzerland	Employees of four power plants: Beznau, Mühleberg, Gösgen, and Leibstadt	4	0	1957	National dose registry, dosimetric records	yes, within country	facility of last employment	
UK	Employees of BNFL plc, the UKAEA and its legacy companies, the AWE, the Central Electricity Generating Board and the South of Scotland Electricity Board and their legacy companies, Amersham plc, Rolls-Royce and Associates, and the Ministry of Defence	12	20	1946	National Registry for Radiation Workers (NRRW)	yes, between companies	facility of first employment	(*5*)
U.S. Hanford	Employees of the Hanford site	0	1	1944	Personnel records	yes, with ORNL	Hanford	(*18*)
U.S. INL	Employees of the INL, including contractors, subcontractors, and civilian U.S. Navy workers	0	1	1949	Personnel records	no, but checked later[c]	—	(*27*)
U.S. NPP	Employees of 15 Commercial nuclear power plant utilities	15	0	1960	Personnel records	yes, within cohort	facility of last employment	(*22*)
U.S. ORNL	Employees of the ORNL	0	1	1943	Personnel records	only workers not previously employed in DOE facilities included		(*17*)

Note. N/A, not applicable.

[a] These companies represented 2 mixed facility sites (AECL), and 21 nuclear power reactors at 6 sites.

[b] For logistic reasons, the present study did not include workers who had been monitored both at CEA and at COGEMA.

[c] Overlap between INL and the Hanford and ORNL cohorts could not be identified in the framework of the current study; linkage was conducted at a later stage, however, and showed that only 2% of the cohort of 64,000 INL workers had been employed in one of these facilities.

Definition of the Main Study Population

The main study population was defined as all workers who had been employed in at least one of the study facilities for at least 1 year, who had been monitored for external radiation exposure, and whose doses resulted predominantly from exposure to higher-energy photon radiation. Workers with potential for substantial doses (of the order of 10% of the whole-body dose) from other radiation types (neutrons, very high- and very low-energy photons, internal intake of various radionuclides) were excluded from this population since their doses may not have been estimated systematically in a suitable way for epidemiological analyses (*12*). Because the aim of the study was to estimate the effect of low-dose-rate exposures, workers were also excluded from analyses if they were known to have been involved in a radiation incident or accident or if they had exceptionally high annual doses, since it is possible that these doses were received at a high dose rate. Workers with exceptionally high annual doses were defined as those who had received at least one annual on-site dose of 250 mSv or more (the dose

TABLE 2
Periods and Sources of Data used for Follow-up

Cohort	Study period	Source of vital status and cause of death data
Australia	1972–1998	National Death Index (1980–) and New South Wales Cancer Registry (1972–)
Belgium	1969–1994	National Population Registry (vital status, 1953–) and National Institute for Statistics (cause, 1969–)
Canada	1956–1994	Canadian Mortality Database
Finland	1971–1997	National Mortality and Cancer Registry database
France CEA-COGEMA	1968–1994	Municipality of birth of worker (vital status), National cause of death registration
France EDF	1968–1994	Company personnel and pension files cross-linked with the national population registry (vital status) and national cause of death registration
Hungary	1985–1998	National Office for Population Registration (vital status) and Central Office for Statistics (cause of death)
Japan	1986–1992	Vital status records of municipality of residence (vital status information kept for 5 year), National Vital Statistics database (cause of death)
Korea (South)	1992–1997	National Death Certificate Database, Central Cancer Registry, National Federacy of Medical Insurance Databases, and population-based cancer registries
Lithuania	1984–2000	Lithuanian address bureau (vital status), Population Registry (vital status and cause of death)
Slovak Republic	1973–1993	Population Registry (vital status), local authority (cause of death)
Spain	1970–1996	Records of medical services of participating facilities
Sweden	1954–1996	National Mortality and Cancer Registry databases
Switzerland	1969–1995	Local authority records (vital status) and Federal Office of Statistics (cause of death)
UK	1955–1992	National Health Service Central Registers, plus cross-checks at other offices
U.S. Hanford	1944–1986	Social Security Administration (SSA) database, U. S. National Death Index (NDI, 1979–), Washington State (1968–1989) and California State (1960–1986) vital statistics files, National Center for Health Statistics (cause of death)
U.S. INL	1960–1996	SSA (pre 1979), NDI (1979–), U.S. Health Care Financing Administration
U.S. NPP	1979–1997	U.S. National Death Index
U.S. ORNL	1943–1984	SSA, Health Care Financing Administration, ORNL personnel records, Tennessee Division of Motor Vehicles, National Center for Health Statistics (cause of death)

criterion in use in many countries for identifying a radiation accident of medical significance).

Statistical Methods

Expected numbers of deaths in each cohort were calculated, using the GETRATES module in EPICURE (*30*), by applying age- (in 5-year groups), sex-, and calendar year- (in 5-year bands) specific mortality rates from the standard national population to the corresponding person-years at risk in the cohort. In each country, the WHO national mortality rates (WHOSIS: http://www3.who.int/whosis/menu.cfm) were used as reference rates because rates for the regions of interest were not systematically available. In some countries, rates were not available for very early years; in this case, rates of the nearest 5-year period afterward were used as reference rates. Standardized mortality ratios (SMRs) were calculated as the ratio of the observed to the expected number of deaths. Confidence intervals were 95% likelihood-based intervals and were calculated under the assumption of a Poisson distribution of the number of observed deaths.

SMRs were calculated for two groups of causes of death: mortality from all causes and mortality from all cancers. SMRs were calculated separately for different age groups (<40, 40–59 and 60+), calendar periods (10-year categories, not shown in this paper) as well as by duration of employment (<5 years, 5–10 years, 10+ years) to assess whether any differences occurred between these groups. Tests for differences and trends in SMRs according to factors such as age and duration of employment were based on χ^2 statistics (*31*).

Relative risks (RRs) for all-cause mortality were estimated by category of SES using Poisson regression, stratifying on age, sex, calendar period and facility. These analyses as well as analyses by level of radiation dose presented elsewhere (*10, 11*) always relied on internal comparisons of radiation doses within the cohort.

Ethics

The study was approved by the IARC Ethical Review Committee and by the relevant ethics committees of the participating countries. The procedures followed were in accordance with the ethical standards of the responsible committees on human experimentation (institutional or regional) and with the Helsinki Declaration [(*32*), revision depending on the country]. The study did not involve contact with study subjects.

RESULTS

Participating Facilities

A total of 154 facilities (Table 1) participated in the study, including 96 nuclear power plants and 58 ''other and mixed activity facilities'', i.e., facilities that were involved in enrichment and processing of nuclear fuel, nuclear weapons manufacture, radioisotope production, or reactor or weapons research.

Completeness of Vital Status and Cause of Death Ascertainment

Most cohorts were able to ascertain the vital status of over 95% of workers (Table 3). Probabilistic linkage (whereby the probability of a true match is calculated on the basis of the combination of matching identifiers and a link is considered positive if it has the highest probability of being a true match and the probability exceeds a specific

TABLE 3
Completeness of Follow-up

Cohort	Type of follow-up	Method of linkage	Vital status ascertainment: Percentage complete[a]	Vital status ascertainment: How evaluated	Cause of death ascertainment: Percentage complete[b]
Australia	passive	probabilistic	84.7	15.3% not traceable, mainly in early time period[c]	99.6
Belgium	active	deterministic for vital status; probabilistic for cause of death	98.0	2% not traceable	90.8
Canada	passive	probabilistic	97.6	definite and probable linkage	99.9
Finland	passive	deterministic	99.1	0.9% emigrated workers	99.3
France CEA-COGEMA	partly passive[d]	deterministic	97.4	2.6% not traceable	95.7
France EDF	active	deterministic	99.9	0.1% incomplete indentifiers	94.3
Hungary	active	deterministic	99.1	0.9% not traceable	99.1
Japan	active	deterministic	100	Workers who were lost to follow-up were not included in the cohort (see also Table 1)	99.4
Korea (South)	active	deterministic	99.9	0.1% with incomplete personal identifiers	98.3
Lithuania	active	probabilistic	86.9	11% lost to follow-up 2% emigration	100.0
Slovak Republic	active	deterministic	99.0	1% emigrated workers	91.1
Spain	active	deterministic	99.3	0.7% emigrated workers	100.0
Sweden	passive	deterministic	96.8	~0.5% failure of linkage, 2.7% emigration	99.7
Switzerland	active	deterministic	97.6	0.5% lost to follow-up, 1.9% emigration	97.0
UK	passive	deterministic	97.7	0.5% not traceable, 2.3% emigration	100.0
U.S. Hanford	passive	combination of deterministic and probabilistic[e]	97.3	proportion of deaths in Washington State (1968–81) that were also identified through the SSA or the NDI	98.5
U.S. INL	active	deterministic	84.8	15.2% lost to follow-up	95.2
U.S. NPP	passive	combination of deterministic and probabilistic[f]	~100	Completeness of NDI estimated in other studies (*35–37*)	99.6
U.S. ORNL	active	deterministic	93.2	6.8% not traceable based on information provided by the SSA	98.9

[a] Percentage of all workers for whom vital status was known.
[b] Percentage of deaths for which cause of death was known.
[c] National Death Index was not available until 1980; before this date, cancer deaths were ascertained from the New South Wales cancer registry, but deaths from causes other than cancer remained largely untraced. Vital status follow-up was virtually complete in the period 1980–1998 (*25*).
[d] Depending on the municipality of birth, persons were either positively declared as alive, or they were presumed alive (*23*).
[e] Probability linkages with the Washington State (1968–1989) and the California State (1960–1986) vital statistics files; deterministic linkages with other sources.
[f] Deterministic linkage was used first; then probabilistic linkage to resolve individuals with multiple links; then manual linkage for remaining problems.

threshold) was used for only five cohorts (Australia, Canada, Lithuania and partly in U.S.-Hanford and U.S.-NPP); elsewhere linkage was deterministic (i.e., a link is defined as positive when all predefined identifiers match).

Follow-up for some of the cohorts (Australia, Canada, Finland, Sweden, UK, U.S.-NPP, U.S.-Hanford, and partly in France CEA-COGEMA) was passive, and hence completeness of follow-up could not be assessed directly. In these cohorts, the percentage of completeness of follow-up either was based on external estimates of the completeness of the mortality database used for linkage or was calculated counting emigrated and, if possible, untraceable workers as lost to follow-up (Table 3). Reported completeness may therefore be artificially high in some instances, and comparisons of completeness of follow-up across countries may be misleading. Emigration was identified in some but not all countries with passive follow-up through population registries, for example in Finland and the UK. It should be noted that national mortality databases used for passive linkage in Australia, Canada, Finland, Sweden, UK and the U.S.-NPP cohort provided essentially complete coverage of deaths occurring within the country (*25, 33–38*). Follow-

TABLE 4
Numbers of Excluded Workers and Main Study Population

Cohort	All workers	Reasons for exclusion[a] Employment <12 months	Not monitored	Internal contamination	Neutrons	Dose >250 mSv/year or incident	Other reasons[b]	Main study population
Australia	2,327	303	0	3	1,179	0	87	877
Belgium	7,201	645	1,389	87	297	0	130	5,037
Canada	54,492	13,990	0	88	136	1	1,789	38,736
Finland	11,966	4,720	1,247	0	80	0	214	6,782
France CEA-COGEMA	29,857	0	4	14,204	3,094	0	649	14,796
France EDF	22,397	10	0	22	760	2	99	21,510
Hungary	3,444	114	0	8	0	0	0	3,322
Japan	114,900	31,133	0	0	0	0	27	83,740
Korea (south)	9,189	1144	0	20	0	0	133	7,892
Lithuania	4,986	461	34	0	0	96	0	4,429
Slovak Republic	2,776	140	76	945	0	119	14	1,590
Spain	3,727	89	0	0	0	1	4	3,633
Sweden	30,233	12,921	290	28	76	0	766	16,347
Switzerland	1,822	37	0	0	0	0	0	1,785
UK	121,686	7,189	345	23,253	7,485	70	206	87,322
U.S. Hanford	44,106	11,171	7,149	513	574	2	31	29,332
U.S. INL	63,988	21,343	27,255	301	957	7	902	25,570
U.S. NPP	60,657	5,923	732	0	4,333	1	3,850	49,346
U.S. ORNL	8,314	2,378	0	258	70	1	390	5,345
Total	598,068	113,711	38,521	39,730	19,041	300	9,291	407,391

[a] A single worker may appear in more than one category of exclusion.
[b] No annual dose, no dose in participating facility, overlap with other cohort, errors or problems in dosimetry, errors in employment or vital status dates, other errors.

up of the U.S.-Hanford and ORNL cohorts involved cross-checking various sources of information as indicated in Table 2 to ensure reasonably complete follow-up (*17*).

The percentage of cause of death ascertainment ranged from 91% in Belgium to 100% in Lithuania, Spain and the UK (Table 3). In Belgium, the French EDF cohort, and Slovakia, the percentage completeness of ascertainment of cause of death was less than 95%. In Belgium and Slovakia, centralized death registries could not be accessed to retrieve cause of death (*21, 24*). In Belgium, consent from the next of kin was needed to obtain cause of death, and in 9% of the deaths probabilistic linkage could not find the person (e.g. due to death abroad) or consent could not be obtained. In Slovakia, cause of death was missing only for subjects who had died outside the country. In France-EDF, one-third of the missing causes of deaths corresponded to deaths abroad and one-fourth to individuals born abroad and not found by the population registry. Assessment of SMRs by age, sex and time period showed no evidence that ascertainment may have been different for different groups of workers (for example less recent workers) in these cohorts, however.

Study Population

A total of 407,391 out of 598,068 workers (68%) met the inclusion criteria for the study (Table 4). The major reason for exclusion was employment less than 1 year (113,711 workers, 19.2%). The collective dose was 1,088 Sv among all workers before exclusions were made; 27% of this collective dose was excluded.

Overall, 38,521 workers (6.5%) were excluded because they had not been monitored, 39,730 (6.7%) because of possible substantial internal contamination, and 19,041 (3.2%) because of possible substantial neutron doses. The largest number of exclusions for neutrons and internal contamination involved CEA-COGEMA workers in France (nearly 50% of all workers) and workers from the UK (mainly Sellafield, UKAEA and AWE). In these cohorts, the excluded workers represented respectively 77% and 53% of the external collective dose. It is noted that in these cohorts, detailed individual information was not available on actual intakes. Hence it is possible that a number of workers were excluded who in fact might not have received substantial doses but who had the potential for such doses. As anticipated, few workers were excluded for neutrons or internal contamination in most commercial nuclear power plants (NPPs), where the potential for such doses is generally low for the majority of workers. In the Slovakian NPP, 945 workers were excluded for internal contamination; this included workers exposed to tritium in one plant and workers exposed to a mixture of nuclides during maintenance and general repairs.

Further exclusions involved 300 workers (0.05%) who were involved in a radiation incident/accident or had received an annual dose of 250 mSv or more. In Slovakia, 119 workers were excluded for having been in one of the two accidents, which took place in 1976 and 1977.

A total of 9,291 workers were excluded for other reasons (Table 4). A total of 3,845 workers were excluded from the U.S.-NPP cohort because only career doses were available or because a default dose had been attributed at one commercial plant (ConEd). In Canada, 1,784 workers were excluded because they were employed before or at the time when a fire destroyed dosimetry records at AECL in 1956.

Characteristics of the Main Study Population

The 407,391 workers included in the main study population were followed up for a total of over 5 million person-years (Table 5). Only 5.9% of the workers in the main study population had died by the end of the follow-up. There were 24,158 deaths, of which 6,794 were cancer deaths. The largest numbers of deaths were recorded in the UK, U.S.-INL and U.S.-Hanford cohorts. Despite the size of the Japanese and U.S.-NPP cohorts, they contributed relatively few deaths due to the shorter follow-up periods.

The worker populations studied were young, with an average age at end of follow-up of 46.2 years, ranging from 36.3 in Korea to 56.7 in ORNL in the U.S. (Table 5). The average age at first exposure was 30.7 years overall; this did not differ greatly between cohorts. The average length of follow-up was relatively short overall (12.7 years); this range was quite large, however, from 4.6 years in Japan and Korea to 25.6 years at ORNL in the U.S. The average duration of employment was 10.5 years and ranged from 6.7 years in Finland to 15.8 years at EDF in France.

The overall average cumulative dose was 19.4 mSv, ranging from 3.8 mSv in CEA-COGEMA (France) to 62.3 mSv in Switzerland. The large range of average doses between cohorts can partly be explained by differences in monitoring practices (*12*). In the CEA-COGEMA cohort, for example, many unexposed workers were monitored in earlier years and therefore were included in the study.

The maximum cumulative dose received by any worker in the cohort was of the order of 1,500 mSv. The total collective dose (unlagged) in the combined cohort was 7,892 person-Sv. With a lag time of 10 years, i.e. the lag time used in analyses of mortality from all cancers (*15, 16*), the total collective dose was 4,842 person-Sv.

Of the 407,391 workers, 90% were men (367,602). Ninety-eight percent of the collective dose was received by men, and 88% of the collective dose was received before the age of 50. Twenty-eight percent of the dose was received before 1975, 58% between 1975 and 1989, and the remaining 14% after 1989.

Socio-economic Status

In most countries the relative risk for all-cause mortality was higher among workers from lower socio-economic classes compared to workers from higher socio-economic classes (Table 6). Only in the cohorts from Canada New Brunswick, Slovakia and Spain were somewhat reversed patterns found, with lower relative risks in lower socio-economic classes. However, numbers of deaths were small in these cohorts and confidence intervals were wide and mostly included one. Person-year distributions by SES and cumulative dose categories showed that the potential for receiving higher dose also varied with SES, with administrative personnel in Australia, for example, unlikely to receive high exposures, and skilled manual personnel receiving the highest doses at AECL in Canada and in U.S.-Hanford.

Standardized Mortality Ratios

SMRs showed a strong healthy worker effect (HWE) everywhere (Table 7): The SMRs for all-cause mortality were statistically significantly lower than 100 in all countries and varied from less than 50 in France-EDF, Hungary, Lithuania, Spain and U.S. NPPs to 80 or more in Finland and Sweden. SMRs for cancer mortality were higher than for all-cause mortality in most cohorts and ranged from less than 60 in Finland and Spain to above 90 in Sweden and Switzerland and above 100 in Korea.

Increasing SMRs for all-cause mortality with increasing age were found in nearly all countries with more than 100 deaths (Table 8). There was evidence for a significant increasing trend in SMRs for all-cause mortality with increasing duration of employment in Australia; elsewhere there was either no trend or actually decreasing trends (significant in six cohorts: Finland, Japan, Korea, Sweden, Switzerland and the UK) (Table 8).

Low SMRs for all-cause mortality (not shown) were seen in early periods (before 1970) in several cohorts (Canada, Hungary, Sweden, U.S.-Hanford, U.S.-INL, U.S.-NPP). These SMRs were generally based on small numbers of deaths and thus are quite variable. In most countries SMRs did not differ significantly between men and women (*29*). In Belgium and U.S.-NPP, significantly higher SMRs were seen in women than in men, whereas in the UK and U.S.-Hanford, significantly higher SMRs were seen in men.

Results of Smoking Surveys

Surveys of smoking habits among workers were conducted in Belgium, Finland, Japan and Spain. Previous studies had been conducted at Hanford in the U.S., at AECL in Canada, and at UKAEA. Out of the seven study cohorts where this was considered, three (AECL, Belgium, Japan) (*19, 24, 39*) showed a positive association and four (Finland, UKAEA, Spain[3] and Hanford) (*20, 40, 41*) showed no association between radiation dose and smoking.

DISCUSSION

We designed the 15-Country Study to improve the precision of direct estimates of radiation-induced cancer risk

[3] J. Laynez and J. S. Bernar, Study on the consumption of tobacco and alcohol in relation to ionizing radiation dose in workers of the Spanish CC.NN facility Spanish Nuclear Industry Association (UNESA), 2005.

TABLE 5
Characteristics of the Main Study Population

Cohort	Main study population	Person-years	Number of deaths: All causes	Number of deaths: All cancer	Average age at first exposure (years)
Australia	877	12,110	56	20	31.2
Belgium	5,037	77,246	322	90	28.8
Canada	38,736	473,880	1,204	417	30.8
Finland	6,782	90,517	317	34	31.3
France CEA-COGEMA	14,796	224,370	645	229	28.8
France EDF	21,510	241,391	371	119	28.9
Hungary	3,322	40,557	104	40	30.3
Japan	83,740	385,521	1,091	432	31.7
Korea (South)	7,892	36,227	58	21	28.0
Lithuania	4,429	38,458	102	25	32.7
Slovak Republic	1,590	15,997	35	10	27.6
Spain	3,633	46,358	68	25	31.2
Sweden	16,347	220,501	669	194	30.6
Switzerland	1,785	22,051	66	24	32.5
UK	87,322	1,370,101	7,983	2,273	30.2
U.S. Hanford	29,332	678,833	5,564	1,331	31.3
U.S. INL	25,570	505,236	3,491	924	32.3
U.S. NPP	49,346	576,682	983	340	30.4
U.S. ORNL	5,345	136,673	1,029	246	30.1
Total	407,391	5,192,710	24,158	6,794	30.7

[a] The average length of follow-up is less than the average length of employment in several facilities due to fact that follow-up started later than operations in these countries.

after protracted low doses of ionizing radiation and to strengthen the scientific basis for setting radiation protection standards.

Studies of cancer risk among workers in the nuclear industry are particularly well suited for the direct estimation of the effects of low doses and dose rates of ionizing radiation. These studies also have some limitations, however, that may affect their informativeness. Although the nuclear industry started in the 1940s (before the explosion of the atomic bombs in Hiroshima and Nagasaki), many nuclear workers did not start employment and receive exposures until later. Indeed, until the 1960s, the nuclear industry was mainly restricted to research, weapons manufacturing and the fuel cycle (including the enrichment and refining of nuclear fuel and its reprocessing). Commercial power production started in the 1960s in a number of countries, with many more reactors starting in the 1970s and 1980s. Thus the number of nuclear workers for whom many decades of follow-up is available is relatively small; the average follow-up in studies of the earliest nuclear facilities is generally not much greater than 20 or 25 years, with the majority of workers being still relatively young at the time of end of follow-up.

Studies of individual cohorts of nuclear industry workers have limited power; the size of the studied cohorts in the epidemiological literature (from a few hundred to tens of thousands of workers) is generally too small to allow the detection of the small increases in risk expected in relation to the typically low cumulative external radiation doses received. To maximize the information about the effects of low-dose protracted exposures from these studies, it is therefore necessary to combine data across cohorts and countries. This, however, needs to be done with extreme care to ensure the comparability of the information being pooled. In the 15-Country Study, much effort has therefore gone into assessing and ensuring comparability, including a common core protocol, agreed procedures, a detailed study of errors in dose estimates, and assessment of heterogeneity of risk across cohorts.

Confounding

Potential confounding factors in this study, which could not be evaluated directly due to lack of adequate information, include other carcinogenic exposures in the work environment (including asbestos, solvents and, in some types of facilities, exposure to various radionuclides), unrecorded exposures received in previous or subsequent jobs, and other nonoccupational factors such as smoking. In the absence of direct information, indirect information on the presence or absence of confounding by a factor can be obtained by examining associations between radiation dose and diseases known to be related to this factor. Within the 15-Country Study, therefore, confounding by tobacco smoking was assessed indirectly by analyses of mortality from lung cancer, smoking-related cancers and non-malignant respiratory diseases, in particular chronic obstructive bronchitis and emphysema (*10, 11*). Analyses of cancers excluding lung and pleural cancers were also conducted because of the potential for confounding by smoking, internally incorporated

TABLE 5
Extended

Average age at end of follow-up (years)	Average length of follow-up (years)	Average length of employment (years)[a]	Individual cumulative dose (mSv)		Collective cumulative dose (Sv)	
			Average	Median	Lag 0 years	Lag 10 years
50.5	13.8	11.0	6.1	0.9	5.4	4.0
47.6	15.3	14.3	26.6	3.0	134.2	95.9
44.4	12.2	8.6	19.5	1.5	754.3	515.7
45.5	13.3	6.7	7.9	2.5	53.2	29.7
45.6	15.2	13.4	3.8	0.0	55.6	37.4
40.7	11.2	15.8	15.8	5.0	340.2	125.1
44.0	12.2	12.7	5.1	0.0	17.0	5.0
44.0	4.6	7.8	18.2	4.2	1526.7	630.6
36.3	4.6	7.0	15.5	2.7	122.3	34.0
42.4	8.7	8.3	40.7	18.0	180.2	41.9
38.5	10.1	10.7	18.8	3.1	29.9	12.4
44.9	12.8	11.7	25.5	2.3	92.7	62.6
45.0	13.5	7.2	17.9	5.8	291.8	145.4
46.1	12.4	11.8	62.3	19.5	111.2	69.1
46.6	15.7	12.2	20.7	3.7	1810.1	1314.7
55.3	23.2	11.3	23.7	4.3	695.4	564.0
53.9	19.8	10.5	10.0	0.5	254.6	221.5
45.1	11.7	11.4	27.1	4.3	1336.0	858.3
56.7	25.6	12.7	15.2	4.2	81.1	74.8
46.2	12.7	10.5	19.4	3.1	7891.9	4842.1

radionuclides, and other occupational carcinogens such as asbestos.

Socio-economic status (SES) was also considered to be an important potential confounder in this study: SES characteristics are known to be associated with a number of health outcomes, including cancer incidence and mortality (*42*). SES is thought to be a surrogate for factors such as tobacco smoking and diet. Further, certain job titles within the nuclear industry may be more frequent among some socio-economic strata of the workers, and if such jobs should entail a different level of received dose, a confounding effect could result. SES has been shown to be associated with both exposure and disease in a number of the cohorts included in the current study, as described above. Direct adjustment of analyses for SES was therefore conducted in all the main analyses in the 15-Country Study. Radiation risk analyses conducted with and without adjustment for SES (*11*) indeed showed that SES had a substantial effect on the risk estimates for all cancers excluding leukemia and for lung cancer, confirming that it is an important confounder in these analyses.

Errors in Doses

Measured doses of radiation received by workers of the nuclear industry are subject to errors. It was therefore necessary, within the 15-Country Study, to assess the importance of such errors and to take them into account where necessary. This was the purpose of the study of errors in dosimetry (*12*), and dose estimates in the main analyses have been adjusted to take into account the main sources of systematic errors identified in that study. It is further noted that workers with potentially unmeasured or inadequately measured doses (i.e. workers with substantial doses from neutrons, very high- and very-low energy photons, and internal intake of various radionuclides) were excluded from the main analysis population (*12*).

Follow-up and Cause of Death Ascertainment

Loss to follow-up in cohort studies can result in biased risk estimates if the loss is related to dose and/or to the outcome of interest. In the 15-Country Study, as discussed above, the completeness of follow-up was generally above 90%, although in countries with passive follow-up this percentage was difficult to estimate. Three cohorts did not reach 90% completeness of follow-up: Australia, Lithuania, and U.S.-INL. In Australia, problems of follow-up were related to the fact that the National Death Index was not available until 1980; before this date, cancer deaths were ascertained from the New South Wales cancer registry, but deaths from causes other than cancer remained largely untraced. Vital status follow-up was virtually complete in the period 1980–1998 (*25*). The follow-up of INL workers was active, and about 15% of the subjects could not be traced in the framework of the 15-Country Study. Further follow-up, however, improved the vital status ascertainment with little change in dose–response results (*27*). The Lithuanian cohort was small and added little information to the overall risk estimates. There is little reason to think, therefore, that the loss to follow-up in these countries would be an important source of bias.

The comparability of mortality data is a fundamental requirement when evaluating risk estimates related to radia-

TABLE 6
Person-years (PY) by Socio-economic Status (SES) and Dose Categories; Numbers of Deaths and Relative Risks by SES Categories

	SES classification used[a]	PY (by cumulative dose mSv) total	<5	5–50	50–200	200+	No. of deaths from all causes	RR (95% CI)[b]
Australia								
Job title	Management, professional	3,828	3,151	620	49	0	7	1
	Technical	3,955	3,307	564	71	0	13	1.92 (0.78–5.17)
	Administrative	835	716	108	0	0	11	3.55 (1.35–9.98)
	Craftsperson/trader	3,505	3,189	266	24	0	25	2.49 (1.09–6.46)
	Unknown	44	44	0	0	0	0	—
Belgium								
Education	University	23,092	18,455	3,157	1,165	269	46	1
	Higher education	22,288	17,345	3,356	1,270	276	40	0.90 (0.58–1.41)
	Secondary education (6 years)	17,736	14,351	2,631	616	60	78	1.25 (0.86–1.83)
	Secondary education (3 years), primary education	10,767	9,228	1,175	178	41	144	1.22 (0.88–1.73)
	Unknown	3,687	2,662	598	294	119	14	0.80 (0.42–1.42)
Canada - AECL								
Job title	Professional, intermediate	59,545	43,298	11,023	4,175	934	115	1
	Skilled non-manual	44,983	40,865	3,475	496	84	63	1.50 (1.05–2.12)
	Skilled manual	24,439	15,325	4,570	3,184	1,258	102	1.54 (1.17–2.01)
	Partly skilled, unskilled	10,832	7,747	2,354	588	71	72	2.17 (1.60–2.92)
	Unknown	56,172	44,772	8,453	2,430	337	181	1.24 (0.98–1.57)
Canada - Hydro Quebec								
Job title	Professional, intermediate	10,910	10,093	738	46	18	14	1
	Skilled non-manual	3,271	3,251	16	0	0	3	1.08 (0.21–3.95)
	Skilled manual, partly skilled, unskilled	7,854	7,177	574	95	0	8	1.67 (0.83–3.43)
	Unknown	3,675	3,428	212	18	0	16	2.18 (0.83–3.43)
Canada - New Brunswick								
Job title	Professional	939	716	164	57	0	2	1
	White collar skilled	5,060	4,784	171	94	0	11	1.11 (0.29–7.24)
	Blue collar skilled	6,401	6,061	228	98	6	8	0.60 (0.15–4.00)
	Blue collar unskilled	2,023	2,019	1	0	0	3	0.67 (0.11–5.19)
	Unknown	4,304	4,222	48	18	0	16	1.36 (0.37–8.79)
Finland								
Education	University, academic	6,409	5,880	518	0	0	10	1
	Higher education, secondary education	61,559	56,194	5,114	83	0	167	1.54 (0.85–3.14)
	Unknown	22,867	20,278	2,403	46	0	140	2.01 (1.10–nd)
France - EDF								
Job title	Professional, intermediate	41,677	37,111	3,744	771	12	39	1
	Skilled non-manual	15,810	15,018	653	104	9	27	2.65 (1.59–4.34)
	Skilled manual, partly skilled, unskilled	182,962	162,998	16,354	3,201	133	277	2.36 (1.70–3.37)
	Unknown	1,291	1,107	126	30	0	28	12.42 (6.54–23.2)
France - CEA-COGEMA								
Job title	Professional, intermediate	115,078	110,086	4,194	520	23	255	1
	Skilled non-manual	48,284	47,798	317	18	0	152	1.15 (0.92–1.42)
	Skilled manual, partly skilled, unskilled	59,870	55,689	3,513	431	0	237	1.64 (1.36–1.99)
	Unknown	1,775	1,761	13	0	0	1	0.25 (0.01–1.10)
Hungary								
Education	University, college, higher technical school	9,633	9,546	74	0	0	13	1
	Secondary school, lower secondary school	19,651	19,355	254	7	0	35	1.52 (0.83–2.99)
	Primary school	10,769	10,483	225	15	0	47	2.20 (1.21–4.28)
	Unknown	608	599				9	13.25 (5.43–30.9)

TABLE 6
Continued

	SES classification used[a]	PY (by cumulative dose mSv) total	<5	5–50	50–200	200+	No. of deaths from all causes	RR (95% CI)[b]
Korea (South)								
Education	University, college	8,549	7,792	689	63	0	5	1
	High school, high school + college	20,243	18,874	1,134	196	0	40	2.69 (1.14–7.91)
	Middle school, primary school	7,493	6,401	781	288	10	13	2.37 (0.88–7.47)
Lithuania								
Job title	Managers, engineers	10,980	8,744	2,049	147	23	17	1
	Clerical staff	1,552	1,234	298	20	0	0	—
	Operators, technicians, specialists	6,987	5,465	1,376	109	22	16	1.92 (0.95–3.85)
	Skilled, unskilled	15,905	13,979	1,715	149	14	48	2.16 (1.27–3.88)
	Unknown	3,136	2,644	461	5	6	21	5.78 (3.00–11.24)
Slovak Republic								
Job title	University	1,610	1,420	162	21	0	7	1
	High school	2,574	2,231	304	29	0	10	0.91 (0.35–2.54)
	Vocational training, basic education	11,343	9,831	1,294	195	10	13	0.30 (0.11–0.83)
	Unknown	506	479	16	5	0	5	1.03 (0.23–4.09)
Spain								
Education	Higher technical	4,596	4,050	370	152	13	11	1
	Medium technical	12,787	11,354	827	518	69	19	0.84 (0.39–1.93)
	Vocational training	26,085	22,323	2,129	1,305	298	31	0.69 (0.35–1.50)
	Primary school	2,957	2,369	233	288	59	7	0.64 (0.22–1.77)
Sweden								
Job title	Professional, intermediate	27,098	20,670	5,791	562	26	49	1
	Skilled non-manual	59,381	49,053	8,959	1,074	128	168	1.31 (0.96–1.83)
	Skilled manual	103,633	86,439	14,724	2,017	101	351	1.69 (1.26–2.33)
	Partly skilled, unskilled	17,967	15,675	2,089	137	10	56	2.24 (1.51–3.33)
	Unknown	13,092	12,232	786	29	0	45	5.09 (3.30–7.83)
Switzerland								
Job title	Professional, intermediate	4,681	3,335	746	487	104	10	1
	Skilled non-manual	1,456	767	225	420	42	2	0.99 (0.15–3.78)
	Skilled manual, partly skilled, unskilled	15,553	11,254	2,168	1,778	301	53	1.52 (0.78–3.23)
	Unknown	426	295	104	26	0	1	0.79 (0.04–4.20)
UK - AEA, AWE								
Job title	Professional, intermediate	178,957	124,700	47,840	5,311	206	899	1
	Skilled non-manual	49,310	37,804	10,376	644	44	442	1.38 (1.23–1.55)
	Skilled manual	73,935	52,610	18,771	1,796	92	665	1.58 (1.42–1.75)
	Partly skilled, unskilled	81,494	55,658	22,274	1,678	222	1,661	1.68 (1.53–1.84)
	Unknown	16,700	15,882	673	112	0	34	0.88 (0.59–1.26)
UK - others								
Job title	Non-industrial	348,041	261,826	67,423	15,205	2,570	1,017	1
	Industrial	592,650	447,990	99,866	35,921	5,912	2,962	1.43 (1.33–1.54)
	Unknown	36,958	27,283	7,822	1,494	58	300	1.45 (1.24–1.70)
U.S. Hanford								
Job title	Professional, intermediate	275,927	199,247	67,300	7,380	727	1,274	1
	Skilled non-manual	135,692	123,443	11,455	153	1	639	1.43 (1.28–1.60)
	Skilled manual, partly skilled	247,121	158,253	64,603	15,909	5,138	3,218	1.39 (1.29–1.49)
	Unskilled	25,630	21,734	3,440	23	0	433	1.48 (1.32–1.66)
U.S.NPP								
Education	University	169,896	145,456	18,514	5,072	665	189	1
	College	183,436	140,577	28,696	11,553	2,291	319	1.49 (1.24–1.80)
	High school, secondary school	184,593	146,077	27,070	9,819	1,215	412	1.79 (1.50–2.14)
	Unknown	39,728	36,424	2,572	588	81	63	1.52 (1.12–2.03)
U.S. ORNL								
Pay code	Monthly	63,271	46,389	15,120	1,409	34	320	1
	Weekly	21,735	13,854	6,123	1,414	149	194	1.56 (1.30–1.86)
	Hourly	52,697	36,982	13,277	1,814	109	515	1.54 (1.33–1.78)

[a] SES classification as used in the main radiation risk analyses (*10*, *11*).
[b] RR: relative risk; 95% CI: 95% confidence interval.

TABLE 7
Standardized Mortality Ratio (SMR) by Cohort

Cohort	Mortality from all causes			Mortality from all cancers		
	Obs	SMR	95% CI	Obs	SMR	95% CI
Australia	56	55	42–71	20	65	41–98
Belgium	322	69	62–77	90	62	50–76
Canada	1,204	62	59–66	417	76	69–84
Finland	317	86	77–96	34	54	38–75
France CEA-COGEMA	645	59	55–64	229	65	57–73
France EDF	371	49	44–54	119	62	52–74
Hungary	104	40	33–48	40	68	49–91
Japan	1,091	78	73–82	432	87	79–95
Korea (South)	58	52	40–67	21	103	65–153
Lithuania	102	40	33–49	25	67	44–97
Slovak Republic	35	53	37–73	10	69	35–122
Spain	68	45	35–57	25	57	38–83
Sweden	669	80	74–86	194	95	82–109
Switzerland	66	77	60–97	24	91	59–133
UK	7,983	78	76–80	2,273	81	78–84
U.S. Hanford	5,564	74	73–76	1,331	80	76–85
U.S. INL	3,491	70	67–72	924	72	68–77
U.S. NPP	983	41	39–44	340	65	59–73
U.S. ORNL	1,029	72	68–77	246	82	72–93

Note. SMR = ratio of observed number of deaths (Obs) to number expected from national statistics.

tion dose and is determined by the accuracy of certification of cause of death and the comparability of cause-of-death coding across countries and periods. It was not possible in this study to collect and assess the accuracy of death certificates in all countries. Several studies of the comparability of mortality data and coding have been reported over the past few decades (*43, 44*). Results showed overall discrepancies at the three-digit and particularly at the four-digit level of the ICD-8 and 9 classifications. Problems arose particularly in the selection of the underlying cause of death when multiple cancer sites were mentioned. In the 15-Country Study, associated causes of death (i.e., other causes mentioned on the death certificate) were available in eight countries (France, Hungary, Korea, Slovakia, Swe-

TABLE 8
Standardized Mortality Ratio (SMR) for All-Cause Mortality by Age and Duration of Employment

	Obs	SMR (95% CI) by age				SMR (95% CI) by duration of employment			
		<40 years	40–59 years	>60 years	χ^2 trend *P* value[a]	<5 years	5–10 years	>10 years	χ^2 trend *P* value
Australia	56	31 (5–95)	34 (14–65)	63 (47–83)	0.09	25 (8–57)	43 (20–81)	66 (48–87)	0.03
Belgium	322	71 (50–97)	61 (51–72)	78 (67–91)	0.15	68 (51–90)	94 (74–118)	64 (56–73)	0.23
Canada	1,204	48 (41–55)	61 (56–67)	70 (65–77)	<0.001	63 (58–69)	59 (52–66)	63 (57–69)	0.93
Finland	317	72 (56–92)	83 (71–95)	119 (93–149)	0.004	104 (91–119)	70 (53–90)	54 (39–72)	<0.001
France CEA-COGEMA	645	56 (46–67)	55 (49–61)	68 (60–76)	0.04	63 (51–75)	57 (47–69)	59 (54–65)	0.77
France EDF	371	41 (34–48)	53 (46–61)	62 (47–80)	0.004	61 (46–80)	47 (36–59)	48 (42–54)	0.17
Hungary	104	18 (10–30)	43 (34–54)	80 (49–121)	<0.001	22 (11–39)	48 (35–64)	40 (30–52)	0.26
Japan	1,091	90 (76–104)	74 (68–80)	79 (71–86)	0.47	92 (85–100)	76 (68–85)	56 (49–63)	<0.001
Korea (south)	58	48 (32–68)	51 (34–74)	145 (52–313)	0.18	78 (53–109)	50 (32–75)	25 (12–47)	0.003
Lithuania	102	35 (24–49)	41 (32–52)	61 (28–113)	0.22	39 (28–53)	37 (26–51)	46 (31–64)	0.57
Slovak Republic	35	69 (40–111)	36 (19–61)	71 (32–132)	0.71	85 (44–145)	36 (16–70)	50 (30–78)	0.27
Spain	68	35 (20–55)	48 (35–66)	52 (30–85)	0.24	50 (30–75)	37 (23–57)	48 (33–67)	0.97
Sweden	669	71 (58–87)	75 (67–85)	89 (79–99)	0.03	90 (81–100)	78 (67–91)	67 (57–77)	0.001
Switzerland	66	65 (33–114)	78 (55–108)	80 (52–118)	0.61	101 (65–150)	96 (62–139)	51 (32–76)	0.02
UK	7,983	67 (62–74)	72 (69–75)	82 (80–85)	<0.001	82 (78–86)	81 (77–85)	75 (73–78)	0.001
U.S. Hanford	5,564	48 (43–55)	63 (60–66)	84 (82–87)	<0.001	73 (70–77)	74 (70–79)	75 (73–79)	0.33
U.S. INL	3,491	44 (37–51)	55 (52–59)	81 (78–85)	<0.001	68 (64–72)	73 (68–78)	70 (66–73)	0.56
U.S. NPP	983	27 (24–32)	41 (37–45)	61 (54–68)	<0.001	41 (37–47)	42 (38–47)	41 (37–45)	0.78
U.S. ORNL	1,029	58 (45–72)	58 (53–65)	87 (80–94)	<0.001	69 (63–76)	74 (63–87)	74 (68–81)	0.31

Note. SMR = ratio of observed number of deaths (Obs) to number expected from national statistics.
[a] 2-sided *P* value.

den, Switzerland, the UK and the U.S.). Including associated causes of death added nine deaths from leukemia excluding CLL deaths and 322 deaths from cancers other than leukemia. Risk estimates changed very little when cancers coded as associated causes of deaths were included (*11*). Only five of the deaths with leukemia as underlying cause of death had another cancer as associated with death, so the potential for misclassification of leukemia deaths seems minimal. Further, since misclassification of specific cancer causes does not affect the group of all cancers combined, the potential for misclassification in the group of all cancers combined, one of the main groupings of cases of death used for the setting of radiation protection standards, also appears to be small.

Exclusion of Workers from the Main Analyses

A total of 190,677 workers were excluded from the main analyses in the International Study. Overall, 113,711 workers employed less than 1 year in any of the participating facilities were excluded from the study cohorts. The practice of excluding workers with short durations of employment is common in occupational cancer epidemiology. This is justified by the fact that such workers may not be comparable to longer-term workers with respect to their risk of cancer: They may have worked only for a short period because they were unwell, and they are more likely to have spent a substantial part of their working life in other occupational settings where they may have received other exposures for which no information is available.

Overall 39,730 workers were excluded from the main study population because they were identified as having ‘‘potential for substantial doses’’ from internal contamination, and 19,041 were excluded because of potential for substantial doses from neutrons. These two groups overlap, because a high proportion of workers had potential for both. Excluding these workers reduced the statistical power of the study since they had higher photon doses (46.6 mSv on average) than the workers in the main study population (19.4 mSv). The accuracy of the risk estimates was, however, improved since these workers may also have had substantial unmeasured doses.

Healthy Worker and Healthy Worker Survivor Effects

In many occupational cohorts such as these, initial selection of workers that are healthy enough for employment commonly leads to observations of deficits in common causes of mortality compared to the general population. This leads to a healthy worker effect (HWE) (*45, 46*). To avoid bias due to the HWE, therefore, estimates of radiation-induced risk in nuclear workers studies generally rely on internal comparisons of risk by level of radiation dose rather than on comparisons with the general population. Analyses of SMRs in this study show a strong HWE for all-cause mortality and in most countries a slightly smaller HWE for all cancer mortality. SMRs in some countries were quite low, of the order of 60 or less. This could indicate incomplete ascertainment in deaths in these countries, but it may also arise because of regional differences in mortality rates, since the SMRs presented are based on national rates. Indeed, analyses of the INL data using appropriate regional mortality rates show SMRs that are much closer to 100 (*27*).

The observation of lower all-cause SMRs in early periods in some countries suggests incomplete mortality ascertainment in these years. These results are based on very small numbers of deaths, however, since most of the deaths in the study have occurred since 1970. Any bias related to ascertainment in early years is therefore likely to have little impact on the risk estimates.

The observation of increasing SMRs for all-cause mortality with increasing age found in nearly all countries with large numbers of deaths is consistent with reports of HWE in other occupational cohorts where the initial healthy worker selection effect wears off as the study subjects age (*47*). The observation of stationary or even decreasing SMRs with increasing duration of employment seen in most cohorts, however, indicates that a health-related selection bias may be of concern even for internal comparisons. Such a selection bias, termed the healthy worker survivor effect (HWSE), operates when workers in good health stay in employment longer and may accumulate higher doses, while those in ill health (and at high mortality risk) terminate employment earlier or move to work in non-radiation areas. Adjustment of analyses for duration of employment (which, as discussed above, appears to be related both to cancer mortality and to radiation dose) is an important way of reducing the impact of the HWSE, and this was conducted in all main analyses of the 15-Country Study (*10, 11*).

CONCLUSIONS

The International Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry was carried out using a common core protocol in 15 countries and provides the largest body of direct evidence to date on the effects of low-dose protracted exposures to external photon radiation. The follow-up periods in most countries were relatively short and the majority of workers were comparatively young at the end of the follow-up. Ninety-four percent of workers were still alive at the end of the follow-up. Additional follow-up of these populations would therefore be extremely informative to further improve the precision of risk estimates.

APPENDIX
List of ICD Codes for Causes of Death Studied

Cause of death	ICD revision (range of codes) 6	7	8	9	10
All cancers	140.0–205.9 237.0–237.9	140.0–207.9 237.0–237.9	140.0–207.9 238.0–238.9	140.0–207.9 208.0–208.9 237.5–237.9 239.6	C–
Buccal and pharynx[a]	140.0–149.9	140.0–149.9	140.0–149.9	140.0–149.9	C0–C14
Esophagus[a]	150.0–150.9	150.0–150.9	150.0–150.9	150.0–150.9	C15
Stomach[a]	151.0–151.9	151.0–151.9	151.0–151.9	151.0–151.9	C16
Small intestine	152.0–152.9	152.0–152.9	152.0–152.9	152.0–152.9	C17
Colon	153.0–153.9	153.0–153.9	153.0–153.9	153.0–153.9	C18
Rectum	154.0–154.9	154.0–154.9	154.0–154.9	154.0–154.9	C20
Liver[a]	155[b]	155.0	155.0–155.1	155.0–155.1	C22
Biliary tract		155.1	156.0–156.9	156.0–156.9	C23–C24
Pancreas[a]	157.0–157.9	157.0–157.9	157.0–157.9	157.0–157.9	C25
Nasal cavity[a]	160.0–160.9	160.0–160.9	160.0–160.9	160.0–160.9	C30–C31
Larynx[a]	161.0–161.9	161.0–161.9	161.0–161.9	161.0–161.9	C32
Lung[a]	162[c]	162.0–162.1	162.0–162.9	162.0–162.9	C33–C34
Pleura		162.2	163.0	163.0–163.9	C38.4
Bone	196.0–196.9	196.0–196.9	170.0–170.9	170.0–170.9	C40–C41
Connective tissue	197.0–197.9	197.0–197.9	171.0–171.9	171.0–171.9	C49
Melanoma	190.0–190.9	190.0–190.9	172.0–172.9	172.0–172.9	C43–C44
Breast (women)	170.0–170.9	170.0–170.9	174.0–174.9	174.0–174.9	C50
Cervix uteri[a]	171.0–171.9	171.0–171.9	180.0–180.9	180.0–180.9	C53
Uterus	172.0–172.9	172.0–172.9	181.0–182.9	179.0–179.9 181.0–182.9	C54–C55
Ovary	175.0–175.9	175.0	183.0	183.0	C56
Prostate	177.0–177.9	177.0–177.9	185.0–185.9	185.0–185.9	C61
Testis	178.0–178.9	178.0–178.9	186.0–186.9	186.0–186.9	C62
Bladder[a]	181.0–181.9	181.0–181.9	188.0–188.9	188.0–188.9	C67
Kidney[a]	180.0–180.9	180.0–180.9	189.0–189.1	189.0–189.1	C64
Ureter[a]			189.2	189.2	C66
Brain	193.0–193.9 237.0–237.9	193.0–193.9 237.0–237.9	191.0–192.9 238.0–238.9	191.0–192.9 237.5–237.9 239.6	C70–C72
Thyroid	194.0–194.9	194.0–194.9	193.0–193.9	193.0–193.9	C73
Ill-defined and secondary	198.0–199.9 156 163 165	198.0–199.9 156 163 165	195.0–199.9	195.0–199.9	C80
Non-Hodgkin lymphoma (NHL)	200.0–200.9 202.0–202.9	200.0–200.9 202.0–202.9	200.0–200.9 202.0–202.9	200.0–200.9 202.0–202.9	C82–C83
Hodgkin's disease	201.0–201.9	201.0–201.9	201.0–201.9	201.0–201.9	C81
Multiple myeloma	203.0–203.9	203.0–203.9	203.0–203.9	203.0–203.9	C90
Leukemia	204.0–204.9	204.0–204.9	204.0–207.9	204.0–208.9	C91–C95
Leukemia excluding CLL	204.1–204.3	204.1–204.3	204.0 205.0–207.0 207.2	204.0 204.2 204.8 205.0–208.0 208.2	C91.0 C91.2–C91.7 C92–C94 C95.0 C95.2
Chronic lymphocytic		204.0	204.1	204.1	C91.1
Acute lymphocytic (ALL)			204.0	204.0	C91.0
Other lymphocytic				204.2 204.8	C91.2–C91.7
Lymphocytic-unspecified			204.9	204.9	C91.9
All lymphocytic	204.0	204.0	204	204	C91
Acute leukemia		204.3	204.0 205.0 206.0 207.0	204.0 205.0 206.0 207.0 208.0	C91.0 C92.0 C93.0 C94.0 C95.0

APPENDIX
Continued

Cause of death	ICD revision (range of codes) 6	7	8	9	10
Acute myeloid (AML)	204.1[d]	204.1[d]	205.0	205.0	C92.0
Chronic myeloid (CML)			205.1	205.1	C92.1
All myeloid	204.1	204.1	205	205	C92
Benign tumors	210.0–229.9	210.0–229.9	210.0–239.9	210.0–239.9	D10–D36
Non-cancer causes					
Circulatory diseases		330–334 400.0–468.9 684 782	390.0–458.9 673 782	390.0–459.9 673 785	I00–I99 J60–J69 O88.2 R00–R02 R57
Ischemic heart disease		420 422.1	410–414	410–414	I20–I25
Heart failure		434.1–434.2	427.0–427.1	428	I50
Deep vein thrombosis and pulmonary embolism		463–466 684	450 451 453 673	415 451 453 673	126 I60–I69 I80 I82
Cerebrovascular disease		330–334	430–438	430–438	O88.2
Other circulatory disease		400.0–468.9 (excluding 420,422.1, 434.1,434.2,463–466) 782	390.0–458.9 (excluding 410–414, 427.0,427.1,430–438,450,451,453) 782	390.0–459.9 (excluding 410–415,428, 430–438,451,453) 785	I00–I99 (excluding I20–26,150, I60–69,I80,I82) R00–R02 R57
Respiratory diseases	470.0–475.9 500.0–527.9	470.0–475.9 500.0–527.9	460.0–479.9 490.0–519.9	460.0–479.9 487.1–519.9	J00–J06 J20–J99
Emphysema	527.1	527.1	492	492	J43
Bronchitis	501–502	501–502	490–491	490–491	J40–J42 J44.1 J44.8
Chronic obstructive pulmonary disease NOS				496	J44.0 J44.9
Digestive disease	530.0–587.9	530.0–587.9	520.0–577.9	520.0–579.9	K00–K93
Liver cirrhosis	581.0–581.9	581.0–581.9	571.0–571.9	571.2 571.5–571.6	K74 K70.3
External causes of death	800.0–999.9 E–	800.0–999.9 E–	800.0–999.9 E–	800.0–999.9 E–	V00–V99 W00–W99 X00–X99 Y00–Y99
Unknown cause		795	795–796	798–799	R96 R98–R99

[a] Included in category ''smoking-related solid cancers'' (IARC monograph Vol. 83, 2004).
[b] In ICD rev. 6, biliary and liver cancers cannot be separated.
[c] In ICD rev. 6, lung and pleura cannot be separated; subjects with ICD-6 equal to 162 were assigned to lung.
[d] In ICR rev. 6 and ICD rev. 7, acute and chronic myeloid leukemia cannot be separated.

ACKNOWLEDGMENTS

The authors are grateful to the late Sir Richard Doll and to Professors Jacques Estève and Bruce Armstrong, who helped start this study; to the late Mr. Len Salmon, who inspired the study of errors in dosimetry; to all persons in the participating countries who worked on the data collection and validation; and to the representatives and staff of the nuclear facilities included in the study for their open collaboration.

Financial support for coordination of the International Study was provided by the European Union (contracts F13P-CT930066, F14P-CT96-0062, FIGH-CT1999-20001), the U.S. Centers for Disease Control and Prevention (Co-operative agreement U50/CCU011778), and the Canadian Nuclear Safety Commission. These sponsors had no role in study design, data collection, analysis or interpretation. Funding was also obtained from one of the collaborating institutes: the Japanese Institute for Radiation Epidemiology. Funding sources for the national studies included Australian Nuclear Science and Technology Organisation; Nuclear Research Center (SCK.CEN), Belgium; Health Canada and Statistics Canada; La Ligue Nationale contre le Cancer, France; La Compagnie Générale des Matière Nucléaire, France; Electricité de France; Ministry of Education, Culture, Sports, Science and Technology in Japan; Ministry of Science & Technology (MOST) in Korea; Spanish Nuclear Safety Council; the

U.K. Health and Safety Executive; and the U.S. Department of Energy. A. Rogel was an employee of the nuclear industry at the time the study was carried out. No other authors have conflicts of interest to declare.

Received: January 20, 2006; accepted: September 29, 2006

REFERENCES

1. ICRP, *1990 Recommendations of the International Commission on Radiological Protection.* Publication 60, International Commission on Radiological Protection, Pergamon Press, Oxford, 1991.
2. E. Cardis, D. Richardson and A. Kesminiene, Radiation risk estimates in the beginning of the 21st century. *Health Phys.* **80**, 349–361 (2001).
3. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), *Sources and Effects of Ionizing Radiation.* United Nations, New York, 2000.
4. L. Carpenter, C. Higgins, A. Douglas, P. Fraser, V. Beral and P. Smith, Combined analysis of mortality in three United Kingdom nuclear industry workforces, 1946–1988. *Radiat. Res.* **138**, 224–238 (1994).
5. C. R. Muirhead, A. A. Goodill, R. G. Haylock, J. Vokes, M. P. Little, D. A. Jackson, J. A. O'Hagan, J. M. Thomas, G. M. Kendall and G. L. Berridge, Occupational radiation exposure and mortality: Second analysis of the National Registry for Radiation Workers. *J. Radiol. Prot.* **19**, 3–26 (1999).
6. Epidemiology Study Group of Nuclear Workers (Japan), First analysis of mortality of nuclear industry workers in Japan, 1986–1992. *J. Health Phys.* **32**, 173–184 (1997).
7. L. B. Zablotska, J. P. Ashmore and G. R. Howe, Analysis of mortality among Canadian nuclear power industry workers after chronic low-dose exposure to ionizing radiation. *Radiat. Res.* **161**, 633–641 (2004).
8. IARC Study Group on Cancer Risk among Nuclear Industry Workers, Direct estimates of cancer mortality due to low doses of ionizing radiation: an international study. *Lancet* **344**, 1039–1043 (1994).
9. E. Cardis, E. S. Gilbert, L. Carpenter, G. Howe, I. Kato, B. K. Armstrong, V. Beral, G. Cowper, A. Douglas and L. D. Wiggs, Effects of low doses and low dose rates of external ionizing radiation: Cancer mortality among nuclear industry workers in three countries. *Radiat. Res.* **142**, 117–132 (1995).
10. E. Cardis, M. Vrijheid, M. Blettner, E. Gilbert, M. Hakama, C. Hill, G. Howe, J. Kaldor, C. R. Muirhead and K. Veress, Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. *Br. Med. J.* **331**, 77 (2005).
11. E. Cardis, M. Vrijheid, M. Blettner, E. Gilbert, M. Hakama, C. Hill, G. Howe, J. Kaldor, C. R. Muirhead and K. Veress, The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: Estimates of radiation-related cancer risks. *Radiat. Res.* **167**, 396–416 (2007).
12. I. Thierry-Chef, M. Marshall, J. Fix, F. Bermann, E. S. Gilbert, C. Hacker, B. Heinmiller, W. Murray, S. Ohshima and E. Cardis, The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: Study of errors in dosimetry. *Radiat. Res.* **167**, 380–395 (2007).
13. E. Cardis and J. Esteve, *International Collaborative Study of Cancer Risk Among Nuclear Industry Workers, I—Report of the Feasibility Study.* Report 92/001, IARC, Lyon, 1992.
14. E. Cardis and J. Esteve, *International Collaborative Study of Cancer Risk Among Nuclear Industry Workers, II—Protocol.* Report 92/001, International Association for Research on Cancer, Lyon, 1992.
15. E. Cardis, M. Martuzzi and E. Amoros, *International Collaborative Study of Cancer Risk Among Nuclear Industry Workers, III—Procedures Document, rev. 1.* Report 97/002, International Association for Research on Cancer, Lyon, 1997.
16. G. S. Wilkinson, G. L. Tietjen, L. D. Wiggs, W. A. Galke, J. F. Acquavella, M. Reyes, G. L. Voelz and R. J. Waxweiler, Mortality among plutonium and other radiation workers at a plutonium weapons facility. *Am. J. Epidemiol.* **125**, 231–250 (1987).
17. S. Wing, C. M. Shy, J. L. Wood, S. Wolf, D. L. Cragle and E. L. Frome, Mortality among workers at Oak Ridge National Laboratories—evidence of radiation effects in follow-up through 1984. *J. Am. Med. Assoc.* **265**, 1397–1402 (1991).
18. E. S. Gilbert, E. Omohundro, J. A. Buchanan and N. A. Holter, Mortality of workers at the Hanford site: 1945–1986. *Health Phys.* **64**, 577–590 (1993).
19. M. A. Gribbin, J. L. Weeks and G. R. Howe, Cancer mortality (1956–1985) among male employees of Atomic Energy of Canada Limited with respect to occupational exposure to external low-linear energy transfer ionizing radiation. *Radiat. Res.* **133**, 375–380 (1993).
20. A. Auvinen, E. Pukkala, H. Hyvonen, M. Hakama and T. Rytomaa, Cancer incidence among Finnish nuclear reactor workers. *J. Occup. Environ. Med.* **44**, 634–638 (2002).
21. G. Gulis, Cancer occurrence among radiation workers at Jaslovske Bohunice nuclear power plant. *Cent. Eur. J. Public Health* **11**, 91–97 (2003).
22. G. R. Howe, L. B. Zablotska, J. J. Fix, J. Egel and J. Buchanan, Analysis of the mortality experience amongst U.S. nuclear power industry workers after chronic low-dose exposure to ionizing radiation. *Radiat. Res.* **162**, 517–526 (2004).
23. M. Telle-Lamberton, D. Bergot, M. Gagneau, E. Samson, J. M. Giraud, M. O. Neron and P. Hubert, Cancer mortality among French Atomic Energy Commission workers. *Am. J. Ind. Med.* **45**, 34–44 (2004).
24. H. Engels, G. M. Swaen, J. Slangen, L. van Amersvoort, L. Holmstock, E. Van Mieghem, I. Van Regenmortel and A. Wambersie, Radiation exposure and cause specific mortality among nuclear workers in Belgium (1969–1994). *Radiat. Prot. Dosim.* **117**, 373–381 (2005).
25. R. R. Habib, S. M. Abdallah, M. Law and J. Kaldor, Mortality rates among nuclear industry workers at Lucas Heights Science and Technology Centre. *Aust. N. Z. J. Public Health* **29**, 229–237 (2005).
26. A. Rogel, N. Carre, E. Amoros, M. Bonnet-Belfais, M. Goldberg, E. Imbernon, T. Calvez and C. Hill, Mortality of workers exposed to ionizing radiation at the French National Electricity Company. *Am. J. Ind. Med.* **47**, 72–82 (2005).
27. M. K. Schubauer-Berigan, G. V. Macievic, D. F. Utterback, C. Y. Tseng and J. T. Flora, *An Epidemiologic Study of Mortality and Radiation-Related Risk of Cancer Among Workers at the Idaho National Engineering and Environmental Laboratory, a U.S. Department of Energy Facility. Health-Related Energy Research Branch.* HHS (NIOSH) Publication No. 2005-131, National Institute for Occupational Safety and Health, Bethesda, MD, 2005.
28. Office of Population Censuses and Surveys (OPCS), *Classification of Occupations and Coding Index.* HM Stationery Office, London, 1980.
29. E. Cardis, M. Vrijheid, M. Blettner, E. Gilbert, M. Hakama, C. Hill, G. Howe, J. Kaldor, C. R. Muirhead and K. Veress, *Report on the 15-Country Collaborative Study of Cancer Risk Among Radiation Workers in the Nuclear Industry: Radiation Related Cancer Risks.* International Association for Research on Cancer, Lyon, in press.
30. EPICURE. HiroSoft International Corporation, Seattle, WA, 1990.
31. N. E. Breslow and N. E. Day, *Statistical Methods in Cancer Research, Volume II, The Design and Analysis of Cohort Studies.* Publication No. 82, IARC, Lyon, 1987.
32. World Medical Association Declaration of Helsinki, Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects, Amended by the 35th World Medical Assembly, Venice, Italy, 1983.
33. G. R. Howe, Use of computerized record linkage in cohort studies. *Epidemiol. Rev.* **20**, 112–121 (1998).
34. H. S. Shannon, E. Jamieson, C. Walsh, J. A. Julian, M. E. Fair and A. Buffet, Comparison of individual follow-up and computerized record linkage using the Canadian Mortality Data Base. *Can. J. Public Health* **80**, 54–57 (1989).
35. M. K. James, M. E. Miller, R. T. Anderson, A. S. Worley and C. F. Longino, Jr., Benefits of linkage to the National Death Index in the Longitudinal Study of Aging. *J. Aging Health* **9**, 298–315 (1997).

36. M. M. Doody, J. S. Mandel, J. H. Lubin and J. D. Boice, Jr., Mortality among United States radiologic technologists, 1926–90. *Cancer Causes Control* **9**, 67–75 (1998).

37. M. M. Doody, H. M. Hayes and R. Bilgrad, Comparability of national death index plus and standard procedures for determining causes of death in epidemiologic studies. *Ann. Epidemiol.* **11**, 46–50 (2001).

38. C. R. Muirhead, A. A. Goodill, R. G. E. Haylock, J. Vokes, M. P. Little, D. A. Jackson, J. A. O'Hagan, J. M. Thomas, G. M. Kendall and G. L. C. Berridge, *Second Analyses of the National Registry for Radiation Workers: Occupational Exposure to Ionising Radiation and Mortality.* Report NRPB-R307, National Radiological Protection Board, Chilton, 2000.

39. M. Murata, T. Miyake, Y. Inoue, S. Ohshima, S. Kudo, T. Yoshimura, S. Akiba, T. Tango, Y. Yoshimoto and H. Matsudaira, Life-style and other characteristics of radiation workers at nuclear facilities in Japan: Base-line data of a questionnaire survey. *J. Epidemiol.* **12**, 310–319 (2002).

40. L. Carpenter, P. Fraser, M. Booth, C. Higgins and V. Beral, Smoking habits and radiation exposure. *J. Radiol. Prot.* **9**, 286–287 (1989).

41. G. Peterson, E. S. Gilbert, J. A. Buchanan and R. G. Stevens, A case-control study of lung cancer ionizing radiation, and tobacco smoking among males at the Hanford sites. *Health Phys.* **58**, 3–11 (1990).

42. B. W. Stewart and P. Kleihues, *World Cancer Report.* International Association for Research on Cancer, Lyon, 2003.

43. C. Percy, E. Stanek and L. Gloeckler, Accuracy of cancer death certificates and its effect on cancer mortality statistics. *Am. J. Public Health* **71**, 242–250 (1981).

44. C. Percy and C. Muir, The international comparability of cancer mortality data—Results of an international death certificate study. *Am. J. Epidemiol.* **129**, 934–946 (1989).

45. L. Carpenter, V. Beral, P. Fraser and M. Booth, Health related selection and death rates in the United Kingdom Atomic Energy Authority workforce. *Br. J. Ind. Med.* **47**, 248–258 (1990).

46. G. R. Howe, A. M. Chiarelli and J. P. Lindsay, Components and modifiers of the healthy worker effect: Evidence from three occupational cohorts and implications for industrial compensation. *Am. J. Epidemiol.* **128**, 1364–1375 (1988).

47. J. Baillargeon, Characteristics of the healthy worker effect. *Occup. Med.* **16**, 359–366 (2001).