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The thesis is based on the following publications, which are referred to in the text by their Roman numerals (I–V):

I Rahu M, Rahu K, Auvinen A, Tekkel M, Stengrevics A, Hakulinen T, Boice JD Jr, Inskip PD. Cancer risk among Chernobyl cleanup workers in Estonia and Latvia, 1986–1998. *Int J Cancer* 2006;119:162–168.

II Rahu K, Hakulinen T, Smailyte G, Stengrevics A, Auvinen A, Inskip PD, Boice JD Jr, Rahu M. Site-specific cancer risk in the Baltic cohort of Chernobyl cleanup workers, 1986–2007. *Eur J Cancer* 2013;49:2926–2933.

III Rahu K, Rahu M, Tekkel M, Bromet E. Suicide risk among Chernobyl cleanup workers in Estonia still increased: an updated cohort study. *Ann Epidemiol* 2006;16:917–919.

IV Rahu K, Auvinen A, Hakulinen T, Tekkel M, Inskip PD, Bromet EJ, Boice JD Jr, Rahu M. Chernobyl cleanup workers from Estonia: follow-up for cancer incidence and mortality. *J Radiol Prot* 2013;33:395–411.

V Rahu K, Bromet EJ, Hakulinen T, Auvinen A, Uusküla A, Rahu M. Non-cancer morbidity among Estonian Chernobyl cleanup workers: a register-based cohort study. *BMJ Open* 2014;4:e004516.

Contribution of Kaja Rahu to the original publications:

Paper I: KR participated in the study design, linked the Estonian data, performed the data analyses, participated in the interpretation of the data, and critically revised the manuscript.

Paper II: KR participated in the study design, linked the Estonian data, performed the data analyses, participated in the interpretation of the data, and wrote the first draft of the manuscript.

Papers III, IV: KR participated in the study design, linked and analyzed the data, participated in the interpretation of the data, and wrote the first draft of the manuscript.

Paper V: KR participated in the study design, analyzed the data, participated in the interpretation of the data, and wrote the first draft of the manuscript.

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ABBREVIATIONS

AHS	Adult Health Study
ARS	acute radiation sickness
BEIR	Committee on the Biological Effects of Ionizing Radiation
Bq	becquerel (unit of radioactivity)
CI	confidence interval
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CT	computed tomography
ECDR	Estonian Causes of Death Registry
ECR	Estonian Cancer Registry
EHIF	Estonian Health Insurance Fund
EOR	excess odds ratio
EPR	Estonian Population Registry
ERR	excess relative risk
FISH	fluorescence in situ hybridization
GPA	glycophorin A
Gy	gray (unit of absorbed radiation dose)
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
LSS	Life Span Study of atomic bomb survivors
NA	not available
NPP	nuclear power plant
OR	odds ratio
PIN	personal identification number
PIR	proportional incidence ratio
RR	rate ratio
SIR	standardized incidence ratio
SMR	standardized mortality ratio
STUK	Radiation and Nuclear Safety Authority
Sv	sievert (unit of equivalent radiation dose)
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
WISMUT	study of German uranium miners

1. INTRODUCTION

The accident at the Chernobyl nuclear power plant (NPP) in Ukraine on April 26, 1986 is considered the most severe incident in the nuclear power industry in terms of radioactivity released into the environment [1, 2]. The most affected areas were large parts of Ukraine, Belarus and the Russian Federation (hereafter, Russia), but wind carried the radioactive cloud across the entire northern hemisphere. During the first few days, the local population within a 30-km zone around the Chernobyl NPP was evacuated.

In the aftermath of the accident, approximately 530,000 people from throughout the former Soviet Union were sent to the radioactively contaminated area for environmental cleanup and related activities [1]. Among those people were over 17,000 men from the Baltic countries. The cleanup workers stayed in the Chernobyl region for months, and their average recorded radiation dose was 0.1 Gy [3].

The effects of ionizing radiation have been extensively investigated, and radiation has been verified as the carcinogen with sufficient evidence in humans [4]. However, less is still known about the non-cancer effects of radiation and the risks at low-dose level (<0.1 Gy), because detection of low risks requires large cohorts with high-quality data on individual doses and confounding factors.

To monitor the possible radiation-related adverse health consequences for cleanup workers and the populations of the most contaminated areas, and to contribute to new knowledge in the radiation epidemiology, the All-Union Distributed Clinico-Dosimetric Registry was created in 1986. After the dissolution of the Soviet Union in 1991, health registries continued their work independently in the former Soviet republics [1]. At that point, the usage of these so-called Chernobyl registries for epidemiological purposes largely depended on each country's general approach to epidemiology, including the availability of educated epidemiologists, and on the level of the research infrastructure, particularly the presence and overall quality of health/ population databases [5]. The most productive epidemiological research uses the information resources of the Russian National Medical Dosimetric Registry [6–12].

Investigation of health effects of the Estonian, Latvian and Lithuanian cleanup workers became possible in collaboration with researchers from Finland and U.S., taking advantage of more or less similar population-based health registry systems and linkage facilities in the three Baltic countries [13]. The current thesis focuses on the morbidity and mortality of the cleanup workers from the Baltic countries. More attention is paid to measuring the health effects among cleanup workers from Estonia because of the proximity of and easy access to different registries. It is hoped that the results of this kind of epidemiological study will help to relieve the anxiety that has sometimes emerged among members of society who exaggerate the adverse health outcomes caused by ionizing radiation from the Chernobyl accident.

2. REVIEW OF THE LITERATURE

The focus on radiation epidemiology in recent decades has aimed to determine the late health effects after low dose and low dose-rate protracted exposure. Conventionally, the upper limit for an acute low dose is considered to be 0.1 Gy and for a low dose-rate 0.005 Gy per hour [14, 15]. There is ongoing debate about the risk magnitude and the shape of the dose-response curve at the low dose level for different cancer sites and diseases other than cancer [16].

2.1. Health effects of ionizing radiation

Epidemiological evidence of the dose-dependent disease risks of ionizing radiation has been periodically reviewed and evaluated in the comprehensive reports of the International Agency for Research on Cancer (IARC) [4], the U.S. National Research Council Committee on the Biological Effects of Ionizing Radiation (BEIR) [15], and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) [1, 17, 18] with special annexes on the consequences of the Chernobyl accident [1, 19], which include data on the Chernobyl cleanup workers from the Baltic countries. These reports rely on analyses of cohorts exposed to ionizing radiation of various types and dose levels, and information about potential confounding factors [20]. Risk estimates derived from numerous studies can be used to establish radiation protection guidelines for occupationally exposed cohorts and the general population [21–23].

2.1.1. Cohorts exposed to ionizing radiation

This section provides a brief description of the major cohorts that serve as a source of information for risk estimation in radiation epidemiology. First, the units must be clarified. The units for the radiation doses quantified below could be Gy or Sv, as it has been presented in the referenced publications. In principle, Gy is the unit for absorbed dose, and Sv is the unit for the weighted quantity of the absorbed dose (equivalent dose) in the case of high linear energy transfer radiation (neutrons, α-particles). For low linear energy transfer radiation (X-rays, γ-rays), the absorbed dose equals the equivalent dose [15, 24]. In the literature, Sv is frequently used because of its familiarity and previous usage, although Gy should be used instead [23]. If Gy and Sv are used interchangeably in the same study, some confusion in comparisons can result [7, 9, 25, 26].

Atomic bomb survivors

Invaluable knowledge about the health effects of ionizing radiation has been derived from the Life Span Study (LSS), which investigates the cohort of atomic bomb survivors from Hiroshima and Nagasaki. The cohort was created on the basis of Japan’s 1950 census and consisted of 93,741 men and women of all ages who resided within 10 km of the bombs' hypocenter, and 26,580 residents of Hiroshima or Nagasaki who were not in the cities at the time of the bombings [27]. Received radiation doses (predominantly external acute γ-radiation and neutron radiation) were assessed retrospectively depending on the survivor's location and shielding; the doses cover a wide range of 0–2 Gy (mainly below 0.1 Gy; for 0.5% of survivors, the doses were above 2 Gy) [27, 28]. The cohort has been continuously followed for cause-specific mortality through the family registry system [29], and for site-specific cancer incidence through the cancer registries of Hiroshima and Nagasaki [26, 30]. The Adult Health Study (AHS) fixed the sub-cohort of survivors (19,961 subjects) and started follow up in 1958 with biennial clinical examinations and laboratory tests to determine incident cases of diseases [25]. Additional cohorts of 3289 subjects exposed *in utero* and 76,814 subjects born to exposed parents have been followed up for mortality and disease incidence [27].

Occupationally exposed workers

The main occupationally exposed cohorts include medical radiation workers, nuclear industry workers (workers at power stations, nuclear weapons and fuel enrichment facilities), underground miners and aircrew. This category also includes Chernobyl cleanup workers. Generally, radiation workers are exposed to low-level protracted radiation, and their received doses are measured and recorded, or reconstructed from their work history records [31]. The risk of cancer among British radiologists has been studied for more than a century [32]. Eight major cohorts with a total of 278,300 radiologists and radiologic technologists from six countries were followed for cancer incidence and mortality during different time periods between 1897 and 1997 [33, 34]. Mortality among nuclear industry workers from 15 countries was analyzed in the pooled cohort of 407,391 individuals with a mean cumulative dose of 19.4 mSv and a total follow-up time of 5.2 million person-years [35]. The incidence of cancer (a 22,366 person cohort) [36] and circulatory diseases (a 18,856 person cohort) [37] has been investigated among employees at the Mayak nuclear weapons facility in Russia since 1948. The mean cumulative external doses were 0.66 Gy for men and 0.52 Gy for women [38]. A large cohort of 58,982 uranium miners from Eastern Germany (the WISMUT cohort) who were exposed to radon was followed for mortality in 1946–2008 with a mean duration of 37 years (2.2 million person-years) [39]. Combined Nordic cohorts of 10,211 airline pilots and 10,066 cabin attendants, exposed to cosmic radiation were monitored for cancer incidence during 177,243 and 237,627 person-years, respectively [40, 41]. Another analysis investigated cancer and non-cancer mortality in a joint cohort of 93,771 airline crew members from 10 countries with a total follow-up of two million person-years [42].

Patients exposed to radiation

Patients diagnosed or treated with radiation provide valuable data for dose-dependent estimates across a broad dose range of few mGy in diagnostic procedures reaching tens of Gy to the targeted organ in the course of treatment [15, 43]. A large cohort of 680,211 Australians exposed to computed tomography (CT) scans in childhood or adolescence was followed up for cancer incidence in 1985–2007 for an average of 9.5 years [44]. Causes of mortality during 37,542 person-years were analyzed in an international cohort of 1736 patients who were injected with the radiographic contrast agent Thorotrast during cerebral angiography between 1932 and 1956 [45]. A cohort of 36,792 Swedes who underwent diagnostic procedures with radioiodine was investigated for thyroid cancer incidence in 1958–1998 [46]. The association between repeated chest X-ray fluoroscopy and breast cancer incidence was explored in a cohort of 4940 U.S. women treated for tuberculosis in 1925–1954 and followed up for an average of 30 years [47].

Radiotherapy with recorded doses to the organs is widely used in cancer treatment; therefore, cohorts of patients can be monitored for late adverse effects, such as a second cancer or cardiovascular disease [43, 48]. A cohort of 182,057 U.S. women with breast cancer was followed in 1973–2005 for the second solid cancer after radiotherapy [49]. In a case-control study of 2168 breast cancer patients from Sweden and Denmark, the risk of ischemic heart disease was studied in 1958–2007 [50].

Environmentally exposed populations

Although everyone is exposed to natural or man-made background radiation, people living near nuclear facilities, exposed to fallout from atmospheric nuclear testing or accidents in NPP (e.g., Chernobyl and Fukushima), or exposed to radon in their residences, constitute the population at risk from environmental radiation. In general, these populations (except the victims of accidents) are exposed to low dose-rate radiation, but their cumulative lifetime doses can reach a considerable level [51]. Received doses are not directly measured; rather, they are estimated based on the distance from the source of radiation or deposition density of radionuclides in soil [15]. Cancer incidence in 1982–2004 and mortality in 1950–2004 was investigated in a population living near uranium mining and milling facilities in Grants, New Mexico that included a total of 1549 incident cancer cases and 3694 cancer deaths [52]. A cohort of nearly 30,000 individuals who were living in the Techa riverside villages (Russia) and therefore exposed to uranium fission products released into the river from the Mayak nuclear facility was followed for leukemia incidence in 1953–2007 [53], solid cancer mortality in 1950–2007 [54] and mortality from circulatory diseases in 1950–2003 [55]. Finnish children aged <15 years living within 15 km of the NPPs were studied for childhood leukemia [56]. Individual data from the 13 European studies of lung cancer risk after radon exposure at home were pooled together (7148 cases, 14,208 controls) and reanalyzed [57].

2.1.2. Cancer risk

The first evidence of elevated radiation-related cancer mortality was found among British radiologists [32] and Japanese atomic bomb survivors [29]. Since then (the middle of the 20th century), dose-dependent cancer risk has been the subject of investigation. (All following numerical risk estimates are statistically significant unless otherwise stated.)

Leukemia

Excess risk of leukemia can emerge as soon as two years after radiation exposure and therefore is the first indication of radiation risk in a certain cohort [58, 59]. According to the present knowledge, the dose-response relationship for leukemia incidence is best described by the non-linear model with no threshold, i.e., the excess relative risk (ERR) per unit dose decreases at low dose levels [30, 60]. Despite of that, the linear model is widely used. In the LSS sub-cohort of adult males with an average acute exposure of 0.5 Gy, for whom the linear dose-response model for leukemia incidence was applied for the comparison purposes, an ERR=2.04 per Gy was observed [30]. In comparison, a meta-analysis of 10 cohorts (including Techa riverside residents, Chernobyl cleanup workers, 15-country study) of adults (mostly men) environmentally or occupationally exposed to low-level protracted radiation, revealed an ERR=0.19 per 0.1 Gy for leukemia incidence and mortality [61]. In the pooled cohort of nuclear industry workers from 15 countries with low dose-rate exposure, a non-significant ERR=1.93 per Sv for leukemia mortality was found [62]. An elevated leukemia incidence was seen in the cohort of U.S. radiologic technologists who worked before 1950; however, due to lack of individual dosimetry data, the ERRs were not available [63]. In the cohort of patients who had undergone the diagnostic CT with radiation dose per scan of 4.5 mSv, an excess risk of leukemia ERR=0.035 per 0.01 Gy was observed with lag time of five years [44]. The highest risk for leukemia has been observed among those who were exposed at young ages [30]. Chronic lymphocytic leukemia (CLL) is not considered to be radiation-induced [64] and was therefore excluded in the aforementioned studies (except [44]).

Other cancer sites

In a comprehensive report on site-specific solid cancer incidence in the LSS cohort in 1958–1998, dose-response was best described by a linear no-threshold model over a dose range of 0–2 Gy. For all solid cancers, an ERR=0.35 per Gy for males and an ERR=0.58 per Gy for females was observed at age 70 after exposure at age 30. An increased dose-dependent incidence was found for cancers of the thyroid, central nervous system (CNS), oral cavity, esophagus, stomach, colon, liver, lung, non-melanoma skin, female breast, ovary, and urinary bladder. Although the relative cancer risk declined with attained age, the analysis provided evidence of persistent risk throughout the lifetime, regardless of age at exposure [26]. Follow-up of the LSS cohort for cancer mortality during 1950–2003 demonstrated a similar cancer risk pattern, with ERR=0.31 per Gy for males and ERR=0.66 per Gy for females for all solid cancers in the same age interval [29].

In the 15-country nuclear industry worker mortality study, a non-significant ERR=0.58 per Sv for all cancers other than leukemia was found when Canada with incomplete data was excluded (ERR=6.65 per Sv). In the site-specific analysis, increased risk was apparent solely for lung cancer [65]. The Mayak nuclear worker cohort (not included in the 15-country study) was followed for cancer incidence in 1948–2004. An ERR=0.07 per Gy of external exposure for all solid cancers (cancers of the lung, liver and bone have been excluded) was observed [36]. In another study, association between internal plutonium exposure and risk for cancers of the lung and liver was evident [66]. A radon-related lung cancer mortality risk was found in the WISMUT cohort [67]. The cancer risk in the Canadian medical worker cohort between 1969 and 1987 was significantly lower than was expected from the rates of the general Canadian population. An elevated risk was observed only for thyroid cancer [68]. In the Nordic cohort of airline cabin crew members, an increased incidence was apparent for cancers of the breast and skin melanoma among women, and for cancers of the skin (melanoma and non-melanoma) and the combined category of alcohol-related sites among men. Male airline pilots experienced higher risk for skin (melanoma and non-melanoma) cancer. However, these findings were considered not to be related to cosmic radiation [40, 41]. In the large mortality study of airline crews from 10 countries, a deficit of deaths due to radiation-related cancers as a group was found in male cockpit crew; elevated mortality was apparent for skin melanoma, not directly related to occupational exposure. Mortality from radiation-related cancers among the cabin crew did not exceed that in the population of respective countries; albeit excess mortality from non-melanoma skin cancer and non-Hodgkin lymphoma was observed among men [42].

In the cohort of people exposed to CT scans in childhood or adolescence, higher risks for brain cancer (ERR=0.015 per 0.01 Gy) and for all other solid cancers (ERR=0.027 per 0.01 Gy) were apparent after brain CT with lag time of 10 years [44]. Thorotrast-patients exposed to low-level α-particles experienced almost three-fold increased cancer mortality in relation to the comparison group that received a non-radioactive contrast agent [45]. No evidence of an elevated risk of thyroid cancer was found among adult Swedish patients without previous exposure to radiation therapy to the neck or suspicion of the thyroid tumor, and who were exposed to ^{131}I in diagnostics with a mean thyroid dose of 0.94 Gy [46]. An excess risk for breast cancer of ERR=1.61 per Gy occurred among

U.S. tuberculosis patients who were examined with frequent X-ray fluoroscopy (88 times on average) and therefore received a mean external dose to the chest of 0.79 Gy [47]. Among the U.S. breast cancer patients receiving radiotherapy, an excess risk of cancers of the lung, esophagus, pleura, bone and soft tissues was seen among the high-dose group (≥1 Gy) [49].

The population living in counties near uranium mining and milling facilities in New Mexico did not experience a higher cancer incidence compared with the general New Mexico population in 1982–2004, with the exception of a 40% increase in lung cancer among men [52]. No indication of a higher risk of childhood cancer in 1975–2004 was found among the Finnish population living near the NPPs [56]. In the Techa river cohort, an ERR=0.61 per Gy for solid cancer mortality was observed in 1950–2007 [54]. A pooled analysis of the 13 European case-control studies with detailed smoking history and radon measurements in homes revealed an increase in lung cancer risk by 8.4% per 100 Bq/ m^3 of radon [57].

2.1.3. Non-cancer disease risk

Although cancer is the major acknowledged effect of radiation in the exposed populations, various non-cancer adverse health effects associated with tissue damage caused by high acute exposures have been recognized [1, 23]. A dose-dependent excess mortality from circulatory and digestive diseases (above a dose level of 2 Gy) was first reported in the LSS cohort in 1992 [69]. Accumulated time and knowledge have shifted the non-cancer disease risk to the lower dose levels. To date, evidence of non-cancer disease risk in radiation epidemiology is mainly based on mortality data, since administratively registered death records are available and easy to use for linkages. Morbidity outcomes are reported for a few cohorts, e.g., atomic bomb survivors, Mayak nuclear facility employees and Chernobyl cleanup workers.

Circulatory diseases

The circulatory disease risk in cohorts that were environmentally or occupationally exposed to moderate or low-level radiation was recently reviewed and summarized by Little et al. [70, 71]. A meta-analysis of 10 studies (including LSS, Mayak employees, Chernobyl cleanup workers, 15-country study) demonstrated elevated mortality for ischemic heart disease (ERR=0.10 per Sv), cerebrovascular diseases (ERR=0.20 per Sv), and all other circulatory diseases as a group (ERR=0.10 per Sv). The atomic bomb survivors participating in AHS during 1958–1998, showed an increased incidence of hypertension (ERR=0.03 per Sv) and myocardial infarction among individuals under 40 years of age (ERR=0.25 per Sv) when the quadratic dose-response model was used [25]. The entire LSS cohort, followed for mortality in 1950–2003, revealed excess risks of ERR=0.11, 0.09, and 0.14 per Gy for all circulatory diseases, stroke and heart disease, respectively. The linear no-threshold dose-response model was suggested; however, the association below 0.5 Gy was weak. The best estimate of a threshold dose for stroke was 0.5 Gy; for heart disease it was 0 Gy [72].

The 15-country nuclear industry worker mortality study did not provide significant dose-dependent excess mortality estimates for circulatory diseases, reflecting no or undetectable risk of circulatory diseases given the low radiation doses the nuclear workers received [73]. An elevated incidence of ischemic heart disease (ERR=0.145 per Gy) and cerebrovascular diseases (ERR=0.511 per Gy) under a linear dose-response relationship was observed in the Mayak nuclear worker cohort in 1948–2005. The risk was significantly higher at doses above 1.0 Gy for ischemic heart disease and 0.2 Gy for cerebrovascular diseases. Increased mortality from circulatory diseases was not evident, possibly because of losses to follow-up [37]. No indication of a dose-dependent rise in mortality from circulatory diseases was apparent in the WISMUT cohort in 1946–2008 [39]. Mortality from circulatory diseases in the Canadian medical worker cohort in 1951–1987 was significantly lower than that of the general population. No estimates per unit dose were provided [68]. However, increased mortality from all circulatory diseases and cerebrovascular diseases was found among U.S. radiological technologists (90,284 individuals followed in 1983–1997) who started their work before 1950 and therefore had higher exposures than those who started in 1960 and afterwards [74]. Markedly reduced mortality from cerebrovascular and cardiovascular diseases was found in the aircrew members of 10 countries; albeit the decrease in mortality from cerebrovascular diseases in the male cabin crew sub-cohort did not reach statistical significance [42].

In the Thorotrast-exposed cohort, a 60% higher mortality from cerebrovascular diseases was found in relation to the comparison group that received a non-radioactive contrast agent [45]. The case-control study of breast cancer patients from Sweden and Denmark, who received radiotherapy between 1958 and 2001 with a mean dose of 4.9 Gy to the heart revealed an ERR=0.074 per Gy for ischemic heart disease under a linear no-threshold model [50].

There was no evidence of increased mortality from cardiovascular and cerebrovascular diseases in the population living in counties near uranium mining and milling facilities in New Mexico compared with the general population of New Mexico [52]. Preliminary data for mortality from circulatory diseases in the Techa river cohort in 1950–2003 demonstrated ERRs=0.036 and 0.056 per 0.1 Gy with a 15-year lag-time and a linear model for all circulatory diseases and for ischemic heart disease, respectively [55].

Cataract

Cataract has been classified as a deterministic effect of radiation with a conventional threshold dose of 0.5 Gy for radiation protection purposes [23]. However, recent studies have suggested a need to lower this dose limit and reconsider the threshold model [75]. An elevated dose-dependent cataract surgery incidence of ERR=0.32 per Gy was observed in the AHS cohort of

6066 subjects in 1986–2005. A linear model with threshold dose of 0.5 Gy provided the best fit [76]. A borderline increase in cataract development of 18% was found in the cohort of U.S. radiological technologists when the workers with the highest dose category (mean, 60 mGy) were compared with those with the lowest dose category (mean, 5 mGy) [77].

Other diseases

Risk estimates for other non-cancer diseases related to ionizing radiation come mainly from the LSS data, as the cohort of atomic bomb survivors includes both genders, all ages at exposure, a wide dose range, long follow-up, high-quality incidence and mortality data, and information about confounding factors. Thus, the following are the results from different LSS analyses. A thyroid examination of 4091 cohort members in 2000–2003 revealed a linear dose-dependent increase in the prevalence of benign thyroid nodules (excess odds ratio EOR=1.53 per Sv) and cysts (EOR=0.89 per Sv) [78]. In the AHS cohort of 10,339 persons, an elevated linear dose-dependent incidence for thyroid disease (ERR=0.33 per Sv), chronic liver disease and cirrhosis (ERR=0.15 per Sv), and uterine myoma (ERR=0.46 per Sv) was found in 1958–1998 [25]. A follow-up of 86,611 subjects for respiratory disease mortality in 1950–2005 resulted with linear dose-dependent excess deaths from all respiratory diseases (ERR=0.17 per Gy) and pneumonia/ influenza (ERR=0.20 per Gy) [79]; a follow-up in 1950–2003 demonstrated increased mortality for all respiratory diseases (ERR=0.23 per Gy) and all digestive diseases (ERR=0.20 per Gy) [29]. Two decades after the bombings, the prevalence of anxiety and somatization symptoms was higher among AHS subjects who were in the city compared with those who were not [80]. In the cohort of 11,951 first-generation offspring of atomic bomb survivors born between May 1946 and December 1984, no association between parental radiation dose and an increased risk of disease was observed [81].

2.1.4. Summary

Cancer and circulatory diseases are the major late health effects attributable to low doses of ionizing radiation. In interpreting certain risk estimates it must be born in mind that development of the disease after radiation exposure is highly dependent on gender, age at exposure, attained age and time since exposure; the least sensitive are adult men [15, 23]. Although it is impossible to distinguish radiation-induced disease cases from those caused by other risk factors, epidemiological studies can demonstrate the causal relationship between radiation and the disease in sufficiently large exposed cohorts with detailed data on doses and confounding variables, and follow-up over decades [82–84]. The precision of risk estimates is influenced by dose uncertainties, the magnitude of the risk, the accuracy of the diagnosis, co-morbidity biases, personal reporting errors, a lack of data about potential confounders and the choice of models [16]. Thus, in epidemiological studies, it is difficult to evaluate radiation-related cancer risk at doses below 0.1 Gy and circulatory disease risk at doses below 0.5 Gy [16, 23]. Considerable effort has been directed toward quantifying the direct risk estimates in the low-dose range and extrapolating the risks where direct estimates were unavailable [15].

Summarizing available data for low-dose range, the U.S. National Research Council adopted the linear no-threshold model for solid cancers, the linear-quadratic model for leukemia, and left undecided the model for non-cancer diseases because of insufficient data [15]. Based on recent epidemiological and biological research, the question of disease risk at low doses, and even possible beneficial doses remains unanswered [82, 85–87].

2.2. The Chernobyl nuclear accident

As a consequence of an experimental low-power engineering test with switched-off safety systems in the Chernobyl NPP, the two powerful explosions damaged the reactor building and destroyed the reactor. The estimated total release of radioactivity was ~14×10^{18} Bq, mostly due to short-lived radionuclides. The noble gases contributed half of the total release [1, 88]. In comparison, the overall release from the accident in Fukushima NPP in 2011 was 10% of that in Chernobyl [2], and the bombings of Hiroshima and Nagasaki released less than 1% of that in Chernobyl [89]. However, the number of premature deaths caused by the Chernobyl accident was estimated to be approximately two orders of magnitude less than that from the bombings in Japan [88].

2.2.1. Affected populations

As the Chernobyl NPP in Ukraine is located 20 km from the border with Belarus and 140 km from the border with Russia, these three countries were the most contaminated [1, 19]. Inhabitants from the vicinity of the Chernobyl NPP (115,000 people, including the town of Pripyat with nearly 50,000 residents in the distance of 3 km from NPP) were evacuated shortly after the accident. After 1986, an additional 216,000 people were relocated from the strict radiation control areas (>555×10^3 Bq/ m^2). Approximately 6.4 million people in the former Soviet Union stayed in the contaminated regions, which had radioactivity levels of 37×10^3–555×10^3 Bq. The average effective doses (from external and internal irradiation, excluding the thyroid dose) for these population groups were estimated to be 31 mSv, 61 mSv and 9 mSv, respectively [1, 90]. The average effective dose for the residents of Pripyat was assessed at 10 mSv as they were the first to be evacuated [91].

The highest radiation doses were received by the staff of the NPP and emergency workers (~1000 people) immediately after the accident. Film badges worn by the staff, were overexposed, and the firemen did not have dosimeters. However, measured exposure rates near the reactor reached 10–100 Gy per hour [19].

Cleanup workers (530,000 people; the number has been re-evaluated) were brought into the contaminated area from throughout the former Soviet Union. The largest cohorts were registered in Ukraine (229,000 people), Russia (188,000 people) and Belarus (91,000 people) [1]. The cleanup workers performed different activities for longer or shorter periods between 1986 and 1991; therefore, the doses they received varied substantially. The average of the external doses recorded in the national registries was 117 mGy, and the distribution of doses was skewed toward the lower values [1, 90]. Compulsory registration and long-term health monitoring was set up for cleanup workers and for the population groups from the most contaminated territories and for their children born after 1986. The Chernobyl accident triggered the improvement of cancer surveillance systems in Ukraine, Belarus and Russia with specialized thyroid and hematological cancer registries, and childhood cancer registries [19].

Increased radioactivity levels were also registered outside the former Soviet Union. For other European countries with population of about 500 million people, the average effective dose is estimated to be 0.3 mSv [1].

2.2.2. Cancer risk

Leukemia

Several studies have investigated the post-Chernobyl leukemia risk in Ukraine, Belarus and Russia and in distant countries. No convincing evidence of an increase in leukemia attributable to childhood, *in utero* or adult exposure to radiation has been found [1, 58, 90, 92–94].

In a nested case-control study of the Ukrainian cleanup worker cohort in 1986–2000 with reconstructed individual doses, an ERR=2.73 per Gy for non-CLL was found using the linear model [95]. An updated analysis for the extended time period of 1986–2006 revealed an ERR=1.87 per Gy for non-CLL [96]. In both analyses, the ERR reached statistical significance after CLL was included. Another pooled case-control study (cases diagnosed in 1990–2000) was nested in the Russian, Belarusian and Baltic cohorts of cleanup workers and used the same method for dose reconstruction that was used in the Ukrainian study. A non-significant ERR=0.50 per 0.1 Gy was observed for non-CLL with the linear model at doses above 0.2 Gy. The ERR for CLL was similar to that for non-CLL. In the same study, an ERR=2.81 per 0.1 Gy for non-Hodgkin's lymphoma was found [97]. A Russian cohort study of cleanup workers revealed an ERR=4.98 per Gy for non-CLL in the earlier period 1986–1997 and an ERR= −1.64 per Gy in the later period of 1998–2007. Leukemia risk in the cohort in comparison to the male population, quantified by standardized incidence ratio (SIR), was 1.71 over the entire follow-up period [12].

Thyroid cancer

The striking increase in thyroid cancer incidence emerged 3–4 years after the accident among residents of Ukraine, Belarus and Russia who were exposed to radioactive iodine as children or adolescents and was the most pronounced among the youngest members of that population [58, 93]. A Ukrainian cohort of 12,514 individuals who were exposed before 18 years of age was followed for thyroid cancer incidence in 1998–2007. A dose-dependent ERR=1.91 per Gy of thyroid dose was observed [98]. In the prevalence study in Belarus, 11,611 persons aged 18 years or younger at exposure were screened for thyroid cancer between 1996 and 2004. For thyroid doses below 5 Gy, an ERR=2.15 per Gy was apparent [99]. The Russian cohort of 97,191 children and adolescents with follow-up for thyroid cancer in 1991–2008, revealed an ERR=3.22 per Gy of thyroid dose [100].

There has been particular interest in thyroid cancer incidence in the cleanup worker cohorts, as early responders were at greater risk for thyroid exposure due to short-lived radioiodines. A cohort study of 103,427 Russian cleanup workers living in the European part of Russia demonstrated a higher thyroid cancer incidence in relation to the entire male population of Russia in 1986–2003 (SIR=3.47). Although the highest increase appeared among those who began their mission within a month after the accident (SIR=6.62), no association with recorded radiation doses was found [11]. Another cohort study of 150,813 Ukrainian cleanup workers from six oblasts revealed similar increased thyroid cancer incidence compared with the entire male population of Ukraine in 1986–2010 (SIR=3.50). The highest risk estimate (SIR=3.86) was observed among those who were sent to the Chernobyl area in 1986. Documented radiation doses were not taken into account [101]. In a nested case-control study within cleanup worker cohorts from Belarus, Russia and the Baltic countries, reconstructed individual doses were used, and an ERR=0.29 per 0.1 Gy for thyroid cancer in the male subjects was found [102].

Other cancer sites

Although ecological studies among the adult local population of Ukraine, Belarus and Russia provided an upward trend in cancer incidence, this increase has likely occurred because of better reporting and was not related to higher contamination [19, 93, 103, 104]. A detailed ecological epidemiological study conducted to describe breast cancer incidence trends in Belarus and Ukraine demonstrated increases throughout both countries, likely reflecting improvements in diagnosis and registration. However, a two-fold increase was found in the most contaminated regions, particularly among younger women [105].

There are few studies reporting the solid cancer incidence among the cleanup workers. An analysis of the cohort of 55,718 men from Russia with a mean dose of 0.13 Gy who worked in the 30-km zone in 1986–1987 and underwent at least one clinical examination in 1991–2001 revealed a non-significant ERR=0.33 per Gy for all solid cancers. None of the site-specific estimates was significantly elevated [8]. An increasing “oncological morbidity” trend and higher age-specific rates among Latvian cleanup workers registered in the Latvian State Register (5399 men) compared with the population controls was mentioned by Eglite et al., but no risk estimates were given [106].

In a large study of 40 European countries, average whole-body doses to adults were estimated for the period of 1986–2005 based on measurements in each country and then projected up to 2065. Cancer incidence and mortality data were obtained from various sources, e.g., cancer registries and WHO databases. Fractions of all cancer cases (except leukemia, thyroid and non-melanoma skin cancer) attributable to fallout from the Chernobyl accident up to 2065 were predicted to be 0.01% for all countries, ranging from none in the least contaminated countries (e.g., Estonia) to 0.23% in the most contaminated regions in Ukraine, Belarus and Russia. The percentages of cancer deaths for the same regions were 0.01%, none and 0.18%, respectively [107]. As Finland was one of the most contaminated countries outside the former Soviet Union [107], a comprehensive study was carried out to evaluate the cancer risk by four exposure categories in Finland after the Chernobyl accident (1988–2007). No excess cancer incidence related to the radiation was found, with the possible exception of colon cancer among women [108].

2.2.3. Non-cancer outcomes

Acute radiation sickness

Whole-body exposure to a single ionizing radiation dose of more than 1 Gy can induce acute radiation sickness (ARS) [109]. Doses above 10 Gy over a short time period are estimated to be lethal, and survival at doses at 5–10 Gy is likely only with intensive medical care [110]. ARS was verified in 134 emergency workers with an external whole-body dose range of 0.8–16 Gy measured with biological dosimetry. Of the ARS patients 28 died in 1986, and 20 deaths were among those with doses above 6.5 Gy. No cases of ARS were diagnosed in the local population [19].

Mental health

The psychological aftermath of the Chernobyl accident has been acknowledged by the Chernobyl Forum as the major long-term public health problem among exposed populations, as millions of people were affected [111]. Radiation accidents remind people of the nuclear bombings in Hiroshima and Nagasaki and implicate long-lasting mental health effects such as post-traumatic stress disorder, depression, anxiety, and medically unexplained physical symptoms [112, 113]. Forced relocation caused additional distress for hundreds of thousands of people [90, 114]. Studies on the mental health consequences of the accident over a 25-year period have been reviewed by Bromet et al. [113, 115].

In a prevalence study in 1992, self-report scores indicated a higher prevalence of anxiety and depression among residents of Gomel, Belarus (1617 exposed persons) compared with residents of Tver, Russia (1427 unexposed persons) [116]. A case-control study of 797 mothers of young children in 2005–2006 in Ukraine revealed higher rates of depression, post-traumatic stress disorder and poor self-rated health among evacuee mothers [117]. A case-control study in Kiev was undertaken to compare the cognitive functioning of evacuated children born in 1985–1986 (265 persons) with that of their classmates (261 persons) in 2005–2006 at 19 years of age. No differences in measures (stratified by parental education) of cognitive functioning, university attendance and self-reported memory problems were found. However, the mothers of the evacuated children were three times more concerned about their children's memory problems than were the mothers of their classmates [118].

The mental health of 295 Ukrainian cleanup workers was evaluated via an interview conducted in 2003–2004. The results were compared with those of 397 population controls from the national survey in 2002 using the same questionnaire. The cleanup workers reported higher rates of severe headache, depression, post-traumatic stress disorder and suicidal ideation, but not of alcoholism compared with controls [119]. In a cohort study among 59,207 Russian cleanup workers, a dose-dependent ERR=0.40 per Gy for mental disorders diagnosed during clinical examinations was found [6]. A study of a sub-cohort of Latvian cleanup workers from the Latvian State Register (1412 men) demonstrated a higher risk of depression and psychosomatic disorders among those working within the 10-km zone or on the roof of the reactor [120]. Deaths due to chronic alcoholism were mentioned in the Latvian cohort [106]. Given the mutuality of mental and physical health, it has been suggested to investigate and treat these diseases in parallel in the exposed populations [113].

Other outcomes

Evidence regarding the non-cancer disease risk associated with the Chernobyl accident is limited. A dose-related excess of subclinical hypothyroidism (EOR=0.10 per Gy) and benign thyroid tumors (ERR=2.07 per Gy) was found among the population of the most contaminated regions in Ukraine, exposed in childhood and screened for thyroid diseases in 1998–2000 [121, 122].

The cohort of 61,017 Russian cleanup workers with a mean dose of 0.11 Gy was followed for circulatory diseases in 1986–2000. Cases of circulatory diseases were identified during clinical examinations. ERRs=0.36, 0.41 and 0.45 per Gy were observed for hypertension, ischemic heart disease and cerebrovascular diseases, respectively [10]. In an earlier study, 59,207 cleanup workers were examined for several diseases between 1986 and 1996. Dose-dependent excess was found for hypertension, cerebrovascular diseases, endocrine and metabolic diseases, diseases of the nervous system and diseases of the digestive system [6]. Confounding lifestyle factors were not considered in either study.

In an extensive study in Ukraine, 8607 cleanup workers were assessed for cataract 12 and 14 years after exposure. The analysis demonstrated EOR=1.70 per Gy for all cataract (stages 1–5) and suggested a threshold dose of 0.5 Gy [123].

Notable excess risk of adverse pregnancy outcome (congenital malformations, stillbirths, premature births) associated with radiation exposure after the Chernobyl accident is unlikely to emerge given the low dose level that the local population received. The high rate of congenital malformations observed in Belarus and Ukraine needs further investigation, as it is not clear, whether it was linked to *in utero* exposure, better registration or changed definitions [19, 88, 124, 125].

2.2.4. Summary

The only inarguable long-term radiation-related health effect of the Chernobyl accident demonstrated so far has been the dose-response increase in thyroid cancer incidence among the residents of Ukraine, Belarus and Russia, who were exposed to radioactive iodine at young ages. Evidence of dose-dependent excess of other cancers or non-cancer diseases remains inconclusive and needs further investigation [1, 90, 93, 125].

Mental health disorders in the affected populations, although not directly radiation-related, but well-known consequences of the disasters, definitely require more attention [115]. Although research has shown that the low-level radiation exposure that the local population and most cleanup workers received is not associated with a substantially increased incidence of cancer and circulatory diseases [1, 15], it has been extremely difficult to gain the public's trust and deliver scientific information to the exposed populations [126–128]. These populations continue to live in fear of future adverse health outcomes and to view themselves as "Chernobyl victims", which hinders their efforts to rebuild their lives [88, 127]. A gap exists between the experts' and the public's perceptions about radiation [127, 129].

When interpreting the obvious increase in disease incidence and mortality trends in the Soviet Union after the Chernobyl accident, it is important to consider both the influence of Gorbachev's anti-alcohol campaign, which was launched in 1985 and linked to a short-term decline in mortality [130], and the socio-economic crisis and subsequent collapse of the country in 1991, which was accompanied by a sharp increase in mortality [125]. Fixed cohorts of cleanup workers serve as an invaluable source when investigating cancer and non-cancer disease risks after low-level protracted radiation exposure, but it should be born in mind that comparisons with population rates may be misleading because of the closer health surveillance of the cleanup workers [125, 131].

2.3. Results of the early stage of the Estonian study of Chernobyl cleanup workers

The Chernobyl accident had an impact on Estonia primarily due to sending nearly 5000 men for cleanups in the radioactively contaminated area. Studies targeting the health of these men contribute to worldwide research focused on the health effects of protracted low-dose radiation exposure. The Estonian study of Chernobyl cleanup workers was set up to analyze cancer risk in the cohort. With financing from the National Cancer Institute (U.S.) and Radiation and Nuclear Safety Authority (STUK, Finland) and with intellectual and in-kind support from U.S. and Finnish colleagues, new components were added to the research: a questionnaire study, thyroid screening, follow-up for cause-specific mortality, biodosimetry and hereditary minisatellite mutations among the offspring [132].

2.3.1. Questionnaire study

The postal questionnaire study of cleanup workers was conducted in 1992–1995. A total of 3704 questionnaires were completed by May 15, 1995 with a response rate of 81.4% and representing 76.6% of the total cohort. Additional information was received about respondent characteristics describing socio-demographic background, Chernobyl mission, previous exposure to radiation, health behavior, a family history of diseases, and gender and date of birth of the children [133, 134].

The vast majority of the respondents (85.8%) were 20–39 years old at the beginning of their mission. They were mostly Estonians or Russians by ethnicity (54.3% and 34.8%, respectively); other ethnicities (Ukrainians, Belarusians, Latvians, Lithuanians) represented 10.2%. Nearly two-thirds of the men (65.5%) had secondary or secondary-special education, and 8.5% had a university degree.

Most of the cleanup workers entered the Chernobyl area in 1986 (62.6%); fewer entered in 1987 (22.8%) or in subsequent years (14.3%). They were sent to the contaminated area as military reservists (84.7%), were in regular army service (5.6%) or were contract workers (3.8%). The cleanup workers were mainly involved in topsoil removal; the transport of people, building materials and topsoil; building demolition; building construction (including the new town Slavutich); and washing buildings, roads and trees. Clearing the radioactive debris from roofs near the destroyed reactor or constructing the sarcophagus was reported by 11.5% and 1.1% of respondents, respectively. Among the respondents, 80.0% wore breathing masks, 30.6% reported having worn protective clothing, and 12.8% did not use any protective clothing.

Smoking was quite common among the cleanup workers: 69.0% reported current smoking, and 13.1% reported previous smoking. One-third of men reported drinking alcohol once a week or more frequently. Nearly half of the men did not change their drinking habits; 30.5% of the respondents reported drinking more since returning from their mission.

During 1995–1996, an additional 184 complete questionnaires were received and the final number of questionnaires reached 3888, which could slightly modify the frequencies published by Tekkel et al [133, 134].

2.3.2. Site-specific cancer incidence

The cleanup workers were followed from their return to Estonia until December 31, 1993. The database of the Address Bureau of Estonia was used to determine the vital status with the corresponding date. The cancer cases diagnosed in the cohort and the site-specific cancer incidence rates in the male population 1986–1993 were obtained from the Estonian Cancer Registry (ECR) [135, 136].

The 4742 identified cohort members contributed 30,643 person-years at risk, with an average of 6.5 years. The SIR with 95% confidence interval (CI) was used to estimate the cancer risk in the cohort in relation to the male population. The follow-up resulted in 25 cancer cases vs. 26.46 expected (SIR=0.94; 95% CI 0.61–1.39). No increased overall or site-specific cancer risk was apparent. The highest (but not statistically significant) relative risk (SIR=4.52; 95% CI 0.93–13.20) was observed for non-Hodgkin's lymphoma. The risk estimates for tobacco-related and alcohol-related cancers were somewhat elevated, but they did not reach statistical significance. No leukemia or thyroid cancer cases were diagnosed in the cohort.

2.3.3. Cause-specific mortality

Deaths in the cleanup worker cohort in 1986–1993 were determined from the death certificates kept at the Statistical Office of Estonia. The cause-specific mortality rates in the male population were calculated using death files. Follow-up of the cleanup workers for cause-specific mortality was performed in the same manner used for cancer incidence. The standardized mortality ratio (SMR) with 95% CI was used to measure the mortality risk in the cohort in comparison with the male population [135, 136].

Overall, 144 deaths occurred in the cohort vs. 147.59 expected (SMR= 0.98; 95% CI 0.82–1.14). No elevated death risk was apparent for the broad categories of neoplasms or diseases of the circulatory system, respiratory system or digestive system. An obvious increase in suicide emerged (SMR=1.52; 95% CI 1.01–2.19).

2.3.4. Thyroid diseases occurrence

A total of 1984 cleanup workers participated in the thyroid screening conducted in 1995 with the collaboration of thyroid specialists and radiologists from U.S. The thyroid examination included palpation and high-resolution ultrasonography [137, 138]. The size and location of the detected nodules were recorded. Needle biopsy was recommended for all nodules with a diameter of 1 cm or larger. Blood samples were drawn from men with biopsied nodules and from 2% of men without nodules. Chernobyl service history and lifestyle variables were taken from military records and questionnaires.

Thyroid nodules were detected by ultrasound in 201 cleanup workers; 77 of these were biopsied. Two thyroid cancers and three benign follicular neoplasms were confirmed. Possible neoplasms were identified in 10 men, and benign nodular disease was identified in 44 men. No association was found between the prevalence of thyroid nodules and documented radiation dose, time of arrival in the Chernobyl area, duration of the mission, or working close to the damaged reactor. Biodosimetry results did not reveal a higher prevalence of thyroid nodules among men with possibly higher radiation doses. However, both men with thyroid cancer entered the area shortly after the accident, in May 1986.

2.3.5. Biodosimetry

Although the majority of the cleanup workers had their official records with documented radiation doses, lot of uncertainties surrounded those dose estimates [139]. Thus, two biological methods were used to get information about past exposure to whole-body ionizing radiation: biological dosimetry based on the glycophorin A (GPA) mutational assay of red blood cells [140, 141] and chromosome translocation analyses of lymphocytes by fluorescence in situ hybridization (FISH) [142].

Peripheral blood of 33 ml was drawn from 3197 cleanup workers and 78 population controls in 1993–1996. The blood samples were transported to STUK in Helsinki [143].

For the GPA analysis, 3 ml blood samples were forwarded to the University of California and the University of Pittsburgh, U.S. The GPA analyses of 453 Estonian cleanup workers and 281 Latvian cleanup workers were compared with those of 27 Estonian population controls, 24 Latvian controls and 94 U.S. controls; no consistent differences in GPA locus mutations were found between the exposed and unexposed men. Given the sensitivity of GPA analysis, it was unlikely to detect a biological effect of radiation doses below 10 cGy. GPA assay indicated that the mean dose of the cleanup workers did not greatly exceed 10 cGy [141, 143].

The FISH method was used to estimate radiation doses for 118 Estonian cleanup workers, 29 Estonian population controls and 21 U.S. population controls. Blood samples of 20 ml were analyzed at the Oak Ridge Institute for Science and Education, Lawrence Livermore National Laboratory and STUK [142, 143]. No differences in translocation frequency were observed between the exposed and unexposed men, although most of the cleanup workers belonged to the high-dose group based on their work history. FISH analysis confirmed the mean radiation dose of 10–11 cGy received by the cleanup workers.

2.3.6. Hereditary minisatellite mutations among the offspring

To evaluate the genetic risk of ionizing radiation among the offspring of the cleanup workers, DNA minisatellite mutation frequencies were assessed [144]. The study included 192 families of cleanup workers who had a child born before Chernobyl mission and a child conceived after return from the Chernobyl area. Blood samples of 20 ml were collected from the father, the mother and at least two children and delivered to STUK for DNA analysis. The final study cohort included 147 fathers, 147 mothers, 148 pre-Chernobyl children and 155 post-Chernobyl children. The minisatellite mutation frequency of the post-Chernobyl children was compared with that of their pre-Chernobyl siblings. Results of the conditional logistic regression revealed a slight but non-significant increase in the minisatellite mutation frequency in the post-Chernobyl children compared with their pre-Chernobyl siblings (odds ratio (OR) =1.33; 95% CI 0.80–2.20). Some evidence of elevated minisatellite mutation frequency was found among the post-Chernobyl children of fathers with a documented radiation dose above 20 cGy (OR=3.00; 95% CI 0.97–9.30).

3. AIMS OF THE RESEARCH

The general objective of this research was to estimate the long-term health effects due to the Chernobyl nuclear accident among Baltic cleanup workers.

The specific objectives were as follows:

1. To measure site-specific cancer risk in the combined Baltic cohort of Chernobyl cleanup workers (Estonia, Latvia and Lithuania) and among the Estonian cleanup workers (Papers I, II, IV).
2. To analyze the cause-specific mortality risk in the cohort of Estonian cleanup workers, with special attention to the elevated suicide risk found in the early years of follow-up (Papers III, IV).
3. To determine whether non-cancer morbidity in the cohort of Estonian cleanup workers is higher than expected (Paper V).

4. MATERIALS AND METHODS

This thesis is based mainly on the data of the Estonian Chernobyl cleanup workers. In the cancer risk analysis, data of the Latvian and Lithuanian cohorts were also used.

4.1. Assembly and follow-up of the cohorts

The Estonian, Latvian and Lithuanian cohorts of cleanup workers included men who worked in the Chernobyl area after the accident and were therefore exposed to ionizing radiation. Cohort studies with a similar design were initiated in the Baltic countries after their independence was regained in 1991; such studies aimed to investigate the adverse health effects of the Chernobyl accident.

4.1.1. Estonian cohort of cleanup workers (Papers I–IV)

The Estonian cohort of Chernobyl cleanup workers was assembled using official lists (mainly in Russian) from the following institutions: the General Staff of Estonian Defence Forces (lists of the former Soviet Army), the former Chernobyl Radiation Registry, the former Ministry of Social Welfare and the Chernobyl Committee (with the former Green Movement) (Figure 1).

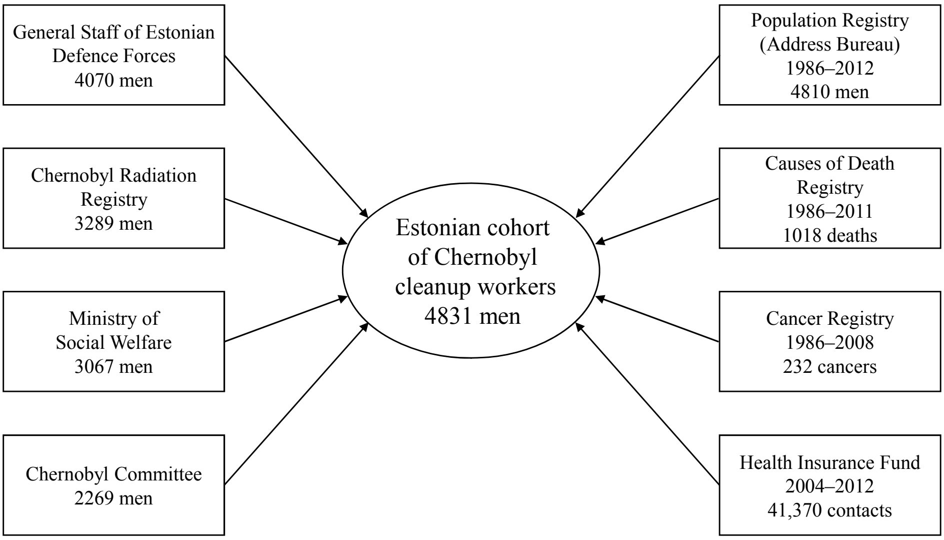

Figure 1. Assembling the cohort of Estonian Chernobyl cleanup workers in 1992, and follow-up through the registries 1986–2012.

These lists included each worker's surname, given name(s), father's name, date of birth, place of residence, mission start and end dates, and documented whole-body radiation dose. As each person could be on several lists, the records were linked, and duplicates were removed. A more detailed description of the process is provided elsewhere [133]. Finally, the cohort consisted of 4831 men (mainly military reservists) who were sent to the Chernobyl area in 1986–1991.

The cohort of cleanup workers was followed through the Estonian Population Registry (EPR) in 1992–2012 in order to get missing unique personal identification numbers (PIN) and to update vital status (living in Estonia/ dead/ emigrated) with the corresponding date, ethnicity and education. Emigrations before the EPR was established in 1992 were taken from the paper database of the former Address Bureau. Twenty one untraced cohort members (0.4%) were excluded from the analysis.

Cancer cases diagnosed in the cohort in 1986–2008 were determined by linkage with the ECR [145] and were coded according to the International Classification of Diseases 9th Revision (ICD-9) (Paper I) or 10th Revision (ICD-10) (Papers II, IV).

Deaths with an underlying cause and the date of death in 1986–2011 in the cohort were obtained via linkage with the so-called Estonian scientific mortality database (individual records of the Estonian Causes of Death Registry (ECDR) with personal identifiers and harmonized codes over the different time periods) [146, 147]. During the study period, three classifications were used to code causes of death: the Soviet classification (abridged ICD-9) [148], the ICD-9 and the ICD-10. The Death causes studied (Papers III, IV) with a corresponding classification are presented in Table 1.

The PIN, name, date of birth and place of residence were used to link records. Identifying the cohort members and linkage in the early stage of the study was complicated and time-consuming because unique PINs have been in use in Estonia only since 1992. In the registers, names may have been spelled using different or no rules of transliteration from the Russian alphabet into Estonian: e.g., *Гямяляйнен*: Hämäläinen/ Gjamjaljainen/ Gyamyalyainen; *Юрий*: Juri/ Jüri/ Youri; *Paxy*: Rahu/ Rakhou; *Кая*: Kaja/ Khaya. Incomplete dates of birth or missing addresses made some determinations difficult. During the follow-up period, linkage facilities have improved considerably, which helped to reduce the number of untraced persons. Two duplicate records were removed, which explains the decrease in the cohort size from 4833 to 4831 men during the follow-up [135, Papers I–V].

Person-years at risk for each cohort member were counted from a worker's return from the Chernobyl area until his death, emigration or the end of the study period, whichever date came first. If the dates of arrival in and return from the Chernobyl area were both missing (128 subjects), January 1, 1987 was imputed for return; if only the date of return was missing (16 subjects), 92 days (the median duration of the mission) was added to the date of arrival.

Table 1. Coding of causes of death of interest in the Estonian Causes of Death Registry: Soviet Classification in 1986–1993, ICD-9 in 1994–1996, and ICD-10 in 1997–2011

Cause of death	Soviet 1986–1987	Soviet 1988–1993	ICD-9 1994–1996	ICD-10 1997–2011
All causes	1–185	1–205	001–E999	A00–Y98
Infectious diseases	1–44	1–44	001–139	A00–B99
Respiratory tuberculosis	9	9	010–012	A15, A16
Neoplasms	45–67	45–67	140–239	C00–D48
Malignant neoplasms	45–66	45–66	140–208	C00–C97
Mouth, pharynx	45	45	140–149	C00–C14
Digestive organs	46–51	46–51	150–159	C15–C26
Trachea, bronchus, lung	53	53	162	C33, C34
CNS	NA	NA	191, 192	C70–C72
Thyroid gland	NA	NA	193	C73
Leukemia	65	65	204–208	C91–C95
Radiation-related sites	NA	NA	142, 150, 151, 153, 162, 170, 173, 188, 189, 191, 192, 193, 204–208	C07, C08, C15, C16, C18, C33, C34, C40, C41, C44, C64–C68, C70–C72, C73, C91–C95
Alcohol-related sites	NA	NA	141–149, 150, 153, 154, 155, 161	C01–C14, C15, C18–C21, C22, C32
Circulatory diseases	84–102	84–102, 196–205	390–459	I00–I99
Ischemic heart disease	90–95	90–95	410–414	I20–I25
Cerebrovascular diseases	98, 99	98, 99, 196–205	430–438	I60–I69
Respiratory diseases	103–114	103–114	460–519	J00–J99
Digestive diseases	115–127	115–127	520–579	K00–K93
External causes	160–185	160–175	E800–E999	V01–Y98
Transport accidents	160–164	160–162	E800–E848	V01–V99
Suicide	183	173	E950–E959	X60–X84
Homicide	184	174	E960–E978, E990–E999	X85–Y09, Y35, Y36
Undetermined injury	185	175	E980–E989	Y10–Y34
Selected alcohol-related causes	73, 75, 122, 165	73, 75, 122, 163	291, 303, 571.0–571.3, E860	F10, G31.2, K70, X45
Unknown causes	159	159	799	R99

NA not available

4.1.2. The sub-cohort of Estonian cleanup workers and the unexposed comparison cohort (Paper V)

In the non-cancer morbidity analysis (Paper V), a sub-cohort of cleanup workers living in Estonia in January 1, 2004 and with attained age of 35–69 years was studied (3680 men). An unexposed population-based comparison cohort was selected from the EPR as a stratified random sample of men living in Estonia in January 1, 2004 and with an age distribution (5-year age groups) corresponding to the sub-cohort of Estonian cleanup workers. The exposed to unexposed ratio was 1:2, with the 5% extra men in each age group. After excluding 87 men who had worked in the Chernobyl area, 7631 men remained in the unexposed comparison cohort. Each person contributed to the total person-years at risk the time period from January 1, 2004 until the date of death, emigration or until December 31, 2012 (whichever was the earliest). Morbidity cases diagnosed alive in 2004–2012 were obtained from the Estonian Health Insurance Fund (EHIF) database [149] by record linkage, using the PIN as a key variable. The first occurrence of three-digit ICD-10 codes (with the exception of four-digit codes for some alcohol-induced diseases) for diseases other than cancer, external causes of morbidity, and examinations or counseling were considered.

4.1.3. Latvian cohort of cleanup workers (Papers I, II)

Assembling the Latvian cohort of Chernobyl cleanup workers and record linkages were the responsibility of the Latvian Cancer Registry staff; the procedures used were described previously [13, 141]. Briefly, the cohort of 5860 men was identified from the records of Chernobyl Registry, the Chernobyl Association (lists of the former Soviet Army) and the Health Ministry. The follow-up of the cohort was provided in a manner similar to that used for the Estonian cohort. Unique PINs were attached to the cohort members by linkage with the Latvian Population Registry. Records were matched by surname, given name(s), father's name, date of birth and place of residence. Each cleanup worker was followed through the population registry from his return until December 31, 1998 to update vital status (living in Latvia/ dead/ emigrated) with the corresponding date (Paper I). Further follow-up appeared to be questionable (Paper II). Because of insufficient data, 314 (5.4%) men could not be traced, and they were excluded from the analysis.

Cancer cases in the cohort in 1986–2007 were extracted via linkage with the Latvian Cancer Registry [145] and were coded according to the ICD-9 (Paper I) or ICD-10 (Paper II). The person-years at risk for each person were calculated from his return from the mission until death, emigration or December 31, 1998 (the earliest date) (Paper I). The date of return from the Chernobyl area was known for all of the cohort members.

4.1.4. Lithuanian cohort of cleanup workers (Paper II)

Data collection and recording of the Lithuanian cohort of Chernobyl cleanup workers was performed in the Lithuanian Cancer Registry and has been published [13, 150]. Briefly, personal records from the Lithuanian Medical Centre (lists of the former Soviet Army), lists of the Chernobyl Movement and rosters compiled by the Lithuanian Parliament for compensation purposes were used. The final cohort consisted of 6923 men. At the early stage of the study, the cohort was linked to the Lithuanian Population Registry in order to get unique PINs. Record matches were found by surname, given name(s), father's name, date of birth and place of residence.

Cancer cases in the cohort in 1986–2007 were determined via linkage with the Lithuanian Cancer Registry [145] and were coded according to the ICD-10 (Paper II). Because of inadequate data for follow-up, 239 (3.5%) men were excluded from the analysis.

4.2. Exposure

Chernobyl cleanup workers were predominantly exposed to γ-radiation emitted by the spontaneous decay of various radionuclides released by the accident, mainly ^{131}I (a half-life of 8 days, therefore a concern for early responders), ^{134}Cs (a half-life of 2 years) and ^{137}Cs (a half-life of 30 years) [1]. The cumulative whole-body external radiation doses received were measured using the individual or group dosimeters or were estimated by work area measurements [1, 151]. The readings were documented in the cleanup workers' personal military passports and military records; depending on the method used, there could be uncertainties of 50–500% [1, 139]. The cumulative external radiation dose limit permitted by the Minister of Defense of the Soviet Union for cleanup workers was 25 cGy in 1986 and decreased afterwards to 10 cGy in 1987 and 5 cGy in 1988–1991 [3, 151]. Although documented radiation doses could exceed the limits, these boundaries are clearly seen in Figure 2, where doses are presented by the year of arrival and duration of the mission (9 persons with radiation doses over 40 cGy and 458 persons with a mission duration longer than 300 days – not overlapping – were excluded). Internal organ doses were not assessed.

Biological dosimetry for small sub-cohorts of the Baltic cleanup workers (453+118, 281 and 48 men from Estonia, Latvia and Lithuania, respectively) resulted in a mean radiation dose of 10–11 cGy [140–142]. This estimate supports the assumption that the average of the received true doses did not exceed the average of the recorded doses, and uncertainties were likely not only in the lower readings (Paper II).

While the individual radiation doses documented in the lists and military passports were not completely reliable [133, 151] and were missing for a large percentage of the cleanup workers (15.9, 20.7 and 26.1% in the Estonian, Latvian and Lithuanian cohort, respectively), the time of arrival in the

Chernobyl area and the duration of the mission were used as proxy variables for radiation exposure (Papers I–V).

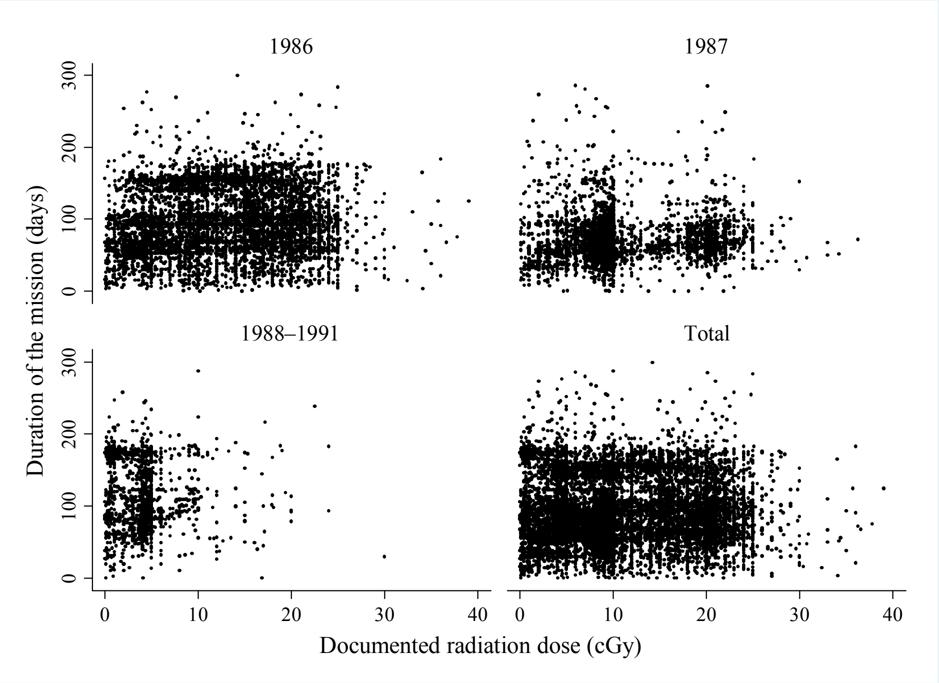

Figure 2. Documented radiation doses in the Baltic cohort of cleanup workers by the year of arrival and duration of the mission in the Chernobyl area.

Based on the results of the previous cancer incidence and mortality analyses of the Estonian Chernobyl cleanup workers [135], the observed low mean cumulative external whole-body radiation dose in the Baltic cohort [141, 142, Papers I, II, IV] and the conclusions of the Chernobyl Forum about the aftermath of the accident [111], "being a Chernobyl cleanup worker" was regarded as the most realistic expression of a general exposure estimate in the current study.

4.3. Relative risk assessment

Depending on the study's outcome and available data, different relative risk measures were used: SIR (Papers I, II, IV), proportional incidence ratio (PIR) (Paper II), SMR (Papers III, IV), ratio of SIRs (Paper IV), ratio of SMRs (Paper IV), mortality rate ratio (RR) (Paper III), and morbidity RR (Paper V). All relative risk measures were accompanied by the 95% CI, assuming a Poisson distribution of the observed number of cases. Linkages and data analyses were performed using Visual FoxPro (Microsoft Corporation, Redmond, Washington) and Stata (StataCorp LP, College Station, Texas).

4.3.1. Cancer risk measures (Papers I, II, IV)

Paper I

Overall and site-specific cancer risk in the combined cohort of Estonian and Latvian cleanup workers for the period of 1986–1998 in relation to the respective country's male population was assessed by the SIR, expressed as the ratio of observed to expected number of cancer cases [152]. The expected number of cases for each country was calculated by multiplying the total number of person-years at risk in the country-specific cohort stratified by 5-year age groups and 5-year calendar periods by the corresponding cancer incidence rates in the male population of Estonia or Latvia; the results were summed up afterwards. SIRs were also calculated separately for the Estonian and Latvian cohorts.

For selected cancer sites, SIRs were computed in the combined cohort stratified by the time of arrival in the Chernobyl area (April–May 1986; June–December 1986; 1987–1991), duration of the mission (<85; ≥85 days), time since return from the Chernobyl area (<5; 5–9; ≥10 years), age at start of follow-up (<20; 20–29; ≥30 years), and documented radiation dose (<9.6; ≥9.6 cGy).

The selection of tobacco-related cancer sites (oral cavity, oropharynx, hypopharynx, esophagus, pancreas, larynx, lung, and urinary organs) and alcohol-related cancer sites (oral cavity, oropharynx, hypopharynx, esophagus, liver, and larynx) was based on monographs published by the IARC [153, 154].

Paper II

For the subsequent cancer risk analysis in 1986–2007, the Baltic cohort of cleanup workers (Estonia, Latvia and Lithuania) was compiled. It was impossible to count person-years at risk for the Latvian and Lithuanian cohorts due to incomplete follow-up for deaths and emigrations; therefore, the alternative site-specific cancer risk estimate PIR was used [155]. The PIR was calculated as the ratio of observed to expected cancer cases for the combined Baltic cohort and separately for each country. The expected number of site-specific cancers in each cohort was calculated by multiplying the total number of cancer cases in the country-specific cohort by the respective site-specific proportion in the male population of Estonia, Latvia or Lithuania by 5-year age groups and 5-year calendar periods. To obtain the total number of observed and expected site-specific cancers in the Baltic cohort, the respective numbers in each cohort were summed.

Prostate cancer was excluded from the analysis because of an obvious detection bias in the Latvian cohort (13, 53 and 29 incident cases from the Estonian, Latvian and Lithuanian cohort, respectively). As the site-specific PIRs are, by definition, mutually dependent [156], excess prostate cancer cases would have skewed the PIRs not only in the Latvian cohort but also in the combined Baltic cohort.

In addition, stratified analysis was carried out for the selected cancer sites according to the time of arrival in the Chernobyl area (April–May 1986; June–December 1986; 1987–1991), duration of the mission (<90; ≥90 days), age at arrival (<30; 30–39; ≥40 years), and documented radiation dose (<5.0; 5.0–9.9; ≥10.0 cGy).

For comparison, the site-specific SIRs (described above) were calculated for the Estonian cohort for the same follow-up period (1986–2007). As the site-specific SIR is approximately equal to the corresponding PIR multiplied by the overall SIR [157] – the SIR for all cancers (except prostate) in the Estonian cohort (1.08) was used as a conversion coefficient to estimate the site-specific SIRs in the Baltic cohort. This conversion would work under the assumption that the SIR for all cancers (except prostate) in the Baltic cohort would be comparable to that of the Estonian cohort.

Three broad categories of cancer sites were formed, as listed by Cogliano et al. [64] based on updated information from IARC monographs [4, 158]: (1) radiation-related sites (salivary glands, esophagus, stomach, colon, lung, bone, non-melanoma skin, urinary organs, CNS, thyroid gland, and leukemia (excluding CLL)); (2) alcohol-related sites (oral cavity, pharynx, esophagus, colon, rectum, liver, and larynx); (3) tobacco-related sites (oral cavity, pharynx, esophagus, stomach, colon, rectum, liver, pancreas, nose and sinuses, larynx, lung, urinary organs, and myeloid leukemia).

Paper IV

Similarly to the analysis concerning the combined cohort of Estonian and Latvian cleanup workers (Paper I), overall and site-specific cancer risk solely in the Estonian cohort for the extended time period of 1986–2008 was measured by the SIR (described above).

To estimate the effect of different characteristics on cancer risk, the ratio of SIRs for selected cancer sites was modeled with Poisson regression, with the logarithm of the expected number of cases as the offset variable [159]. Year of arrival in the Chernobyl area (1986; 1987–1991), duration of the mission (<92; ≥92 days), time since return from the Chernobyl area (<7; 7–13; ≥14 years), age at start of follow-up (<30; 30–39; ≥40 years), ethnicity (Estonian; non-Estonian), education (higher or secondary; basic or less), and documented radiation dose (<5.0; 5.0–9.9; ≥10.0 cGy) were included in the models.

Combined categories of radiation-related and alcohol-related cancer sites were defined, as presented in Paper II.

4.3.2. Death risk measures (Papers III, IV)

Paper III

The death risk in the Estonian cleanup worker cohort compared with the male population in 1986–2002 was assessed by the SMR, calculated like SIR (see above), except that the number of cancer cases was replaced with the number of deaths. The expected number of deaths was calculated by applying mortality rates in the male population to the corresponding person-years at risk in the cohort by 5-year age groups and 5-year time periods. Death causes were grouped into broad categories. Special attention was paid to suicide.

To evaluate the effect of time since return (<5; 5–9; ≥10 years) from the Chernobyl area on the suicide risk, the mortality RR between the subgroups in the cohort was modeled with Poisson regression [159]. The models were adjusted for attained age (5-year age groups), year of arrival in the Chernobyl area (1986; 1987–1991), and duration of the mission (<93; ≥93 days).

Paper IV

In the updated death risk analysis among the Estonian cleanup workers, the follow-up was prolonged to 26 years, i.e., 1986–2011. The SMR (described above) was used to estimate the all-cause and cause-specific death risk in the cohort in relation to the male population.

In a separate analysis, the ratios of the SMRs for selected causes of death were modeled with Poisson regression, with the logarithm of the expected number of cases as the offset variable [159] to evaluate the effect of different characteristics on death risk. The models were compiled similarly to those used in the cancer risk analysis (see above).

Radiation-related and alcohol-related cancer sites were selected as listed by Cogliano et al. [64]. Follow-up for deaths from these cancers began in 1994 because of the less-detailed Soviet classification used in the earlier years. A combined category of alcohol-related causes included mental disorders due to alcohol, degeneration of the nervous system due to alcohol, alcoholic liver disease, and accidental alcohol poisoning. Due to over-coding of alcoholism instead of alcohol poisoning in the ECDR, it was reasonable to combine alcohol-related causes [147].

4.3.3. Non-cancer disease risk measures (Paper V)

Non-cancer disease risk in the Estonian cleanup worker cohort in 2004–2012 was estimated by the morbidity RR. Poisson regression models were used, in which person-years at risk were summed by 5-year age groups [159]. In the external analysis, morbidity in the cleanup worker cohort was compared to that in the unexposed population cohort. Diagnoses were grouped into the broad categories with selected specific diagnoses. The RRs were adjusted for age at diagnosis by 5-year age groups. A combined category of alcohol-induced diagnoses included mental disorders due to alcohol, degeneration of the nervous system due to alcohol, alcoholic cardiomyopathy, alcoholic liver disease, alcohol-induced pancreatitis, accidental alcohol poisoning, intentional self-poisoning by alcohol, and poisoning by alcohol, undetermined intent.

An internal analysis between subgroups in the cleanup worker cohort focused on the possible effects of year of arrival in the Chernobyl area (1986; 1987–1991), duration of the mission (<92; ≥92 days), documented radiation dose (<5.0; 5.0–9.9; ≥10.0 cGy), ethnicity (Estonian; non-Estonian), and education (higher or secondary; basic or less) on the non-cancer morbidity risk. The RRs were mutually adjusted for the listed characteristics and age at diagnosis by 5-year age groups. The selection of the diagnoses and external causes of morbidity was based on the findings from previous reports of non-cancer disease risks in the radiation-exposed cohorts [6, 9, 25, 29, 37, 119, 135].

4.3.4. Potential confounding

It is obvious that a cohort of cleanup workers could differ from the general male population (or an unexposed comparison cohort) in some characteristics that have an effect on health outcomes. Smoking and heavy alcohol consumption are strong risk factors for many diseases [158, 160, 161]. Although the prevalence of smoking and alcohol consumption among the cleanup workers was studied in a questionnaire survey distributed by mail, these data could not be used in the analyses due to a large proportion of unknown values and a lack of longitudinal data on these characteristics. Instead, education and ethnicity were used as surrogates for health behavior, but this information was available only for the Estonian cleanup workers. In Estonia, smoking and heavy alcohol consumption are more prevalent among less-educated men [162–164]. Although population-based health (behavior) prevalence studies have not reported differences in smoking and drinking habits by ethnicity [162–164], non-Estonian and/ or less-educated men experience higher mortality [165, 166], particularly alcohol-related mortality [167]. According to the 1989 census, Estonians made up 60.3% of the male population of Estonia aged over 20 years; Russians accounted for 29.4% and other ethnicities 10.3%. In the same age group, 13.2% of persons were with higher education [168]. Given the somewhat different distribution of the cleanup worker cohort and the general male population by education and ethnicity, these characteristics were taken into account in the analyses as potential confounders.

4.4. Ethics

The Chernobyl cleanup worker studies were carried out according to the ethical regulations applied in each of the Baltic countries. Data from Latvia and Lithuania were transmitted for analyses to Estonia without personal identifiers. The Estonian study protocol was approved by the Tallinn Medical Ethics Committee (no. 28, March 18, 1998 and no. 1939, February 11, 2010), and by the Estonian Data Protection Inspectorate (no. 2.2-3/10/120r, April 9, 2010).

5. RESULTS

The findings are presented in detail in Papers I–V. The following provides a description of the analyzed cohorts, a brief summary of overall and site-specific cancer risk in the Estonian and combined Baltic cohort, all-cause and cause-specific death risk in the Estonian cohort, and non-cancer morbidity risk in the Estonian cohort. As it is important to represent updated scientific results in the controversial area of Chernobyl health-related consequences [127], different time periods have been used for the data analyses.

5.1. Cohort characteristics

In this section, distribution of the main characteristics is given for country-specific cohorts and for the combined Baltic cohort. General information is presented to describe the Estonian sub-cohort and the unexposed comparison cohort.

5.1.1. The Baltic cohort of cleanup workers (Papers I–IV)

The Baltic cohort of cleanup workers included 17,040 men identified for follow-up – 4810 from Estonia, 5546 from Latvia and 6684 from Lithuania (Table 2). The mean and median age at arrival in the Chernobyl area was 31 years and was equal in the three cohorts. Approximately half of the men were sent to the Chernobyl area in 1986. Shortly after the accident (in April-May), 29.0% from the Estonian, 15.5% from the Latvian and 7.5% from the Lithuanian cleanup workers started their work. They stayed in the contaminated area for 106 days on average, with a median duration of 82 days. A few persons worked in the Chernobyl area longer than six months (Figure 2).

The radiation dose was documented for 78.5% of cleanup workers, with a mean dose of 10.9 cGy (9.9, 11.8 and 10.9 cGy in the Estonian, Latvian and Lithuanian cohorts, respectively). The mean and median duration and documented radiation dose with interquartile range by country and time of arrival are provided in Table 3.

Ethnicity and education were available only for the Estonian cleanup workers. Estonians and non-Estonians were almost equally represented, and most of the men had a secondary or higher education (74.4% of the men with a known educational level).

Table 2. Characteristics of the Baltic cohort of Chernobyl cleanup workers

Characteristic	Estonia	Latvia	Lithuania	Baltic cohort
	No. (%)	No. (%)	No. (%)	No. (%)
Total	4810 (100)	5546 (100)	6684 (100)	17,040 (100)
Age at arrival in the Chernobyl area (full years)				
<20	103 (2.1)	118 (2.1)	146 (2.2)	367 (2.2)
20–29	1811 (37.7)	2180 (39.3)	2416 (36.1)	6407 (37.6)
30–39	2260 (47.0)	2593 (46.8)	3058 (45.8)	7911 (46.4)
40–49	480 (10.0)	596 (10.7)	900 (13.5)	1976 (11.6)
≥50	28 (0.6)	59 (1.1)	67 (1.0)	154 (0.9)
Unknown	128 (2.7)	0 (–)	97 (1.5)	225 (1.3)
Time of arrival in the Chernobyl area (year, month)				
1986, 4–5	1393 (29.0)	857 (15.5)	500 (7.5)	2750 (16.1)
1986, 6–12	1508 (31.4)	2167 (39.1)	1845 (27.6)	5520 (32.4)
1986, unknown	22 (0.5)	0 (–)	1 (0.0)	23 (0.1)
1987–1991	1759 (36.6)	2522 (45.5)	4241 (63.5)	8522 (50.0)
Unknown	128 (2.7)	0 (–)	97 (1.5)	225 (1.3)
Duration of stay in the Chernobyl area (days)				
<30	270 (5.6)	389 (7.0)	439 (6.6)	1098 (6.4)
30–89	1915 (39.8)	2867 (51.7)	3439 (51.5)	8221 (48.2)
90–149	1531 (31.8)	1407 (25.4)	1520 (22.7)	4458 (26.2)
150–209	852 (17.7)	700 (12.6)	825 (12.3)	2377 (14.0)
≥210	75 (1.6)	183 (3.3)	363 (5.4)	621 (3.6)
Unknown	167 (3.5)	0 (–)	98 (1.5)	265 (1.6)
Documented dose (cGy)				
<5.0	1101 (22.9)	845 (15.2)	908 (13.6)	2854 (16.7)
5.0–9.9	1272 (26.4)	1312 (23.7)	1657 (24.8)	4241 (24.9)
≥10.0	1673 (34.8)	2240 (40.4)	2376 (35.5)	6289 (36.9)
Unknown	764 (15.9)	1149 (20.7)	1743 (26.1)	3656 (21.5)
Ethnicity				
Estonian	2353 (48.9)			
Non-Estonian	2451 (51.0)			
Unknown	6 (0.1)			
Education				
Higher	370 (7.7)			
Secondary	2883 (59.9)			
Basic or less	1121 (23.3)			
Unknown	436 (9.1)			

Table 3. Measured exposures in the Baltic cohort of Chernobyl cleanup workers

Exposure	Estonia	Latvia	Lithuania	Baltic cohort
1986, April–May				
Documented radiation dose (cGy)				
Mean	9.2	14.0	11.9	10.9
Median	8.0	15.0	10.0	9.9
Interquartile range	5.3–11.4	8.8–19.0	5.1–15.9	5.7–15.3
Duration of stay in the Chernobyl area (days)				
Mean	106	92	109	102
Median	101	75	68	84
Interquartile range	61–149	57–98	31–153	56–142
1986, June–December				
Documented radiation dose (cGy)				
Mean	12.5	15.0	15.0	14.2
Median	12.7	16.0	15.8	15.0
Interquartile range	8.1–17.6	11.0–19.8	9.9–21.0	9.4–19.6
Duration of stay in the Chernobyl area (days)				
Mean	106	90	106	100
Median	101	84	91	93
Interquartile range	75–141	55–109	57–122	60–123
1987–1991				
Documented radiation dose (cGy)				
Mean	8.2	8.2	9.2	8.7
Median	7.6	8.6	9.0	8.5
Interquartile range	4.0–9.3	4.4–9.7	5.0–10.0	4.5–10.0
Duration of stay in the Chernobyl area (days)				
Mean	96	120	114	112
Median	79	80	76	77
Interquartile range	57–109	57–123	57–111	57–115
1986–1991				
Documented radiation dose (cGy)				
Mean	9.9	11.8	10.9	10.9
Median	8.8	10.0	9.7	9.6
Interquartile range	4.6–14.6	6.7–18.0	5.0–16.0	5.2–16.3
Duration of stay in the Chernobyl area (days)				
Mean	102	104	111	106
Median	92	80	78	82
Interquartile range	62–142	56–113	56–119	57–124

5.1.2. The sub-cohort of Estonian cleanup workers and the unexposed comparison cohort (Paper V)

The sub-cohort of Estonian cleanup workers and the unexposed comparison cohort analyzed in the non-cancer morbidity study included 3680 and 7631 men, respectively. The mean age at the start of follow-up was 48 years for both cohorts. The sub-cohort of cleanup workers did not differ from the whole Estonian cleanup worker cohort in terms of the time of arrival in the Chernobyl area, the mean duration of the mission or the mean received radiation dose. The percentage of non-Estonians and less-educated persons was higher in the exposed cohort, although the educational level was unknown for 16.4% of the subjects in the unexposed cohort. Almost all of the men had at least one record in the EHIF database (93.6% of the exposed cohort and 95.3% of the unexposed cohort).

5.2. Cancer risk in the Baltic cohort of cleanup workers (Papers I, II)

Paper I

The combined Estonian and Latvian cohort included 10,332 men who contributed 113,194 person-years at risk during the follow-up period of 1986–1998. Overall, 155 cancer cases were observed vs. 133.85 expected (SIR=1.15; 95% CI 0.98–1.34) (Figure 3). A significantly elevated risk was observed for thyroid cancer (SIR=7.06; 95% CI 2.84–14.55; 7 cases) and brain cancer (SIR=2.14; 95% CI 1.07–3.83; 11 cases). No significant excess of leukemia was found (7 observed vs. 4.55 expected cases).

A stratified analysis revealed the highest SIR for thyroid cancer among those men who started their mission in April–May 1986 (SIR=18.10; 95% CI 4.93–46.37; 4 cases). A higher risk for all cancers and brain cancer was apparent in subjects with a longer duration of the mission (≥85 days). The men with higher radiation doses did not experience an increased cancer incidence.

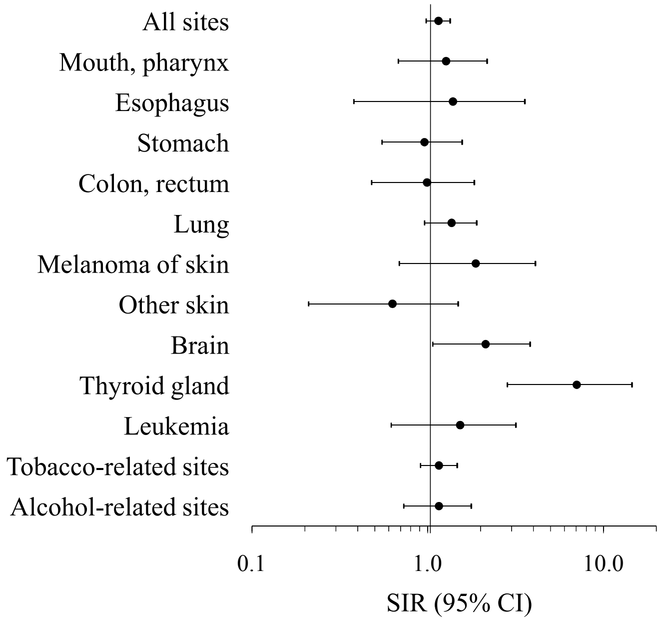

Figure 3. Standardized incidence ratios (SIR) with 95% confidence intervals (CI) by cancer site in the combined cohort of Estonian and Latvian Chernobyl cleanup workers, 1986–1998.

Paper II

The updated cancer risk analysis for 1986–2007 included 17,040 cleanup workers from Estonia, Latvia and Lithuania. During the study period, 756 cancer cases were diagnosed. There was an excess of cancers of the thyroid (PIR=2.76; 95% CI 1.63–4.36; 18 cases) and esophagus (PIR=1.52; 95% CI 1.06–2.11; 35 cases) (Figure 4). No increase was observed for leukemia or the combined category of radiation-related cancer sites.

In the stratified analysis, a higher proportion of thyroid cancers was found among the men who arrived in the Chernobyl area in April–May 1986 (PIR=6.38; 95% CI 2.34–13.89; 6 cases) and those with higher radiation doses (≥10 cGy) (PIR=4.12; 95% CI 1.97–7.57; 10 cases). Brain cancers were overrepresented among early responders (arrival in 1986) with longer mission (≥90 days) (PIR=2.08; 95% CI 1.07–3.63; 12 cases).

Approximate SIRs (converted from PIRs) demonstrated the same site-specific cancer risk pattern with slightly higher point estimates. The excess risk for overall cancer and for combined alcohol-related cancer sites reached borderline statistical significance (SIR=1.08; 95% CI 1.00–1.16 and SIR=1.16; 95% CI 1.00–1.31, respectively).

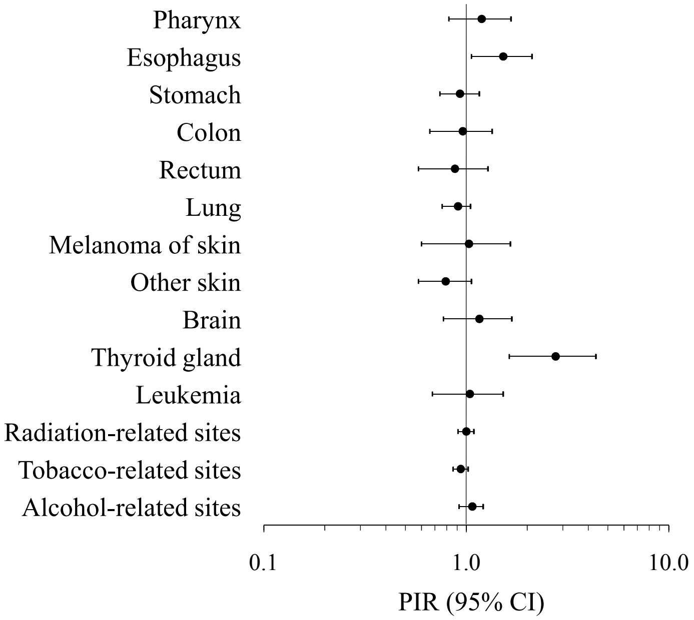

Figure 4. Proportional incidence ratios (PIR) with 95% confidence intervals (CI) by cancer site in the Baltic cohort of Chernobyl cleanup workers, 1986–2007.

5.3. Cancer risk in the Estonian cohort of cleanup workers (Papers I, II, IV)

Paper I

During the follow-up period of 1986–1998, 4786 Estonian cleanup workers contributed 51,739 person-years at risk. A total of 75 cancer cases were observed vs. 64.34 expected (SIR=1.17; 95% CI 0.92–1.46). No elevated risk was found for any cancer sites. The highest SIR was seen for thyroid cancer (SIR=3.88; 0.47–14.02), based on two cases diagnosed in men who entered the Chernobyl area in May 1986. An indication of increased incidence was observed for brain cancer (SIR=2.39; 95% CI 0.88–5.20; 6 cases). No leukemia cases were detected.

Paper II

In the updated analysis, the follow-up of 4810 cleanup workers was extended to 2007 and produced 85,600 person-years at risk. Overall, 195 cancer cases were observed (13 prostate cancers were excluded) vs. 180.10 expected (SIR=1.08; 95% CI 0.93–1.23). Cancer risk quantified by SIR revealed a higher incidence for cancers of the pharynx (SIR=2.16; 95% CI 1.15–3.70; 13 cases), esophagus (SIR=2.26; 95% CI 1.09–4.16; 10 cases), CNS (SIR=2.06; 95% CI 1.06–3.59;

12 cases), and combined alcohol-related cancer sites (SIR=1.34; 95% CI 1.01–1.74; 56 cases). Although the PIRs were quite close to the corresponding SIRs, for CNS and alcohol-related cancers, the PIRs did not reach statistical significance. No risk for thyroid cancer, leukemia or radiation-related cancer sites as a group was found.

Paper IV

So far, the maximum available follow-up for cancer incidence covered the period of 1986–2008, with 89,023 person-years at risk. Overall, 232 cancer cases were observed vs. 218.00 expected (SIR=1.06; 95% CI 0.93–1.20) (Figure 5). One additional year (compared with Paper II) did not change the risk pattern markedly; however, the risk for pharyngeal (SIR=2.41; 95% CI 1.38–3.91; 16 cases), esophageal (SIR=2.38; 95% CI 1.23–4.15; 12 cases) and alcohol-related cancer sites as a group (SIR=1.42; 95% CI 1.09–1.80; 66 cases) became somewhat stronger. There were almost twice as many CNS cancers observed than expected, but the finding was not statistically significant. No evidence of an increase in the incidence of radiation-related cancer sites as a group was found. Two thyroid cancers (vs. 1.42 expected) and seven leukemias (vs. 5.75 expected) were diagnosed.

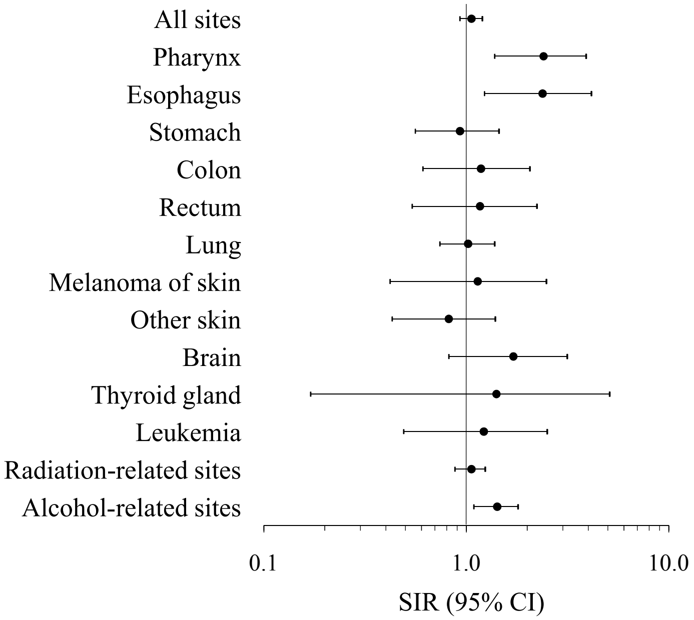

Figure 5. Standardized incidence ratios (SIR) with 95% confidence intervals (CI) by cancer site in the Estonian cohort of Chernobyl cleanup workers, 1986–2008.

The ratios of SIRs did not show statistically significant differences for overall cancer risk or the risk of radiation-related or alcohol-related cancers by the year of arrival in the Chernobyl area, duration of the mission or time since return. After additional adjustment for potential confounders (ethnicity and education), the RRs for the year of arrival in the Chernobyl area, duration of the mission or time since return did not change markedly. However, significantly higher risk for overall and alcohol-related cancer incidence was observed among less-educated cleanup workers.

5.4. Death risk in the Estonian cohort of cleanup workers (Papers III, IV)

Paper III

A total of 4786 men contributing 67,322 person-years at risk were included in the analysis. During the follow-up in 1986–2002, 550 deaths were registered vs. 545.97 expected (SMR=1.01; 95% CI 0.92–1.09). There was no evidence of increased risk for mortality due to neoplasms. One leukemia death occurred, and no thyroid cancer deaths were registered. However, elevated mortality was found for brain cancer (SMR=2.78; 95% CI 1.02–6.05; 6 cases). No increased mortality risk was observed for diseases of the circulatory system, respiratory system or digestive system, or for external causes of mortality as a group.

An excess number of suicides was apparent – 69 observed vs. 52.37 expected cases (SMR=1.32; 95% CI 1.03–1.67). The adjusted RRs for suicide remained close to unity throughout the time since the workers' return from the Chernobyl area: 1.09 (95% CI 0.56–2.10) for 5–9 years and 1.00 (95% CI 0.48–2.05) for 10 or more years compared with less than five years.

Paper IV

During the extended follow-up period of 1986–2011, 4810 men contributed 98,979 person-years at risk. Overall, 1018 deaths were observed vs. 999.32 expected (SMR=1.02; 95% CI 0.96–1.08) (Figure 6). Excess mortality from all malignant neoplasms was not found. The number of leukemia deaths was close to the expected (4 vs. 4.33); no thyroid cancer deaths were reported. Elevated mortality from combined radiation-related cancers was not evident. A statistically significant excess mortality was observed for cancers of the mouth and pharynx (SMR=1.82; 95% CI 1.11–2.81; 20 deaths) and for the combined category of alcohol-related cancers in 1994–2011 (SMR=1.64; 95% CI 1.23–2.15; 53 deaths). No indication of increased mortality risk for diseases of the circulatory system, respiratory system or digestive system, or for all external causes or for selected alcohol-related causes as a group was apparent. However, statistically significant suicide risk was seen in the cohort (SMR=1.30; 95% CI 1.05–1.60; 90 cases).

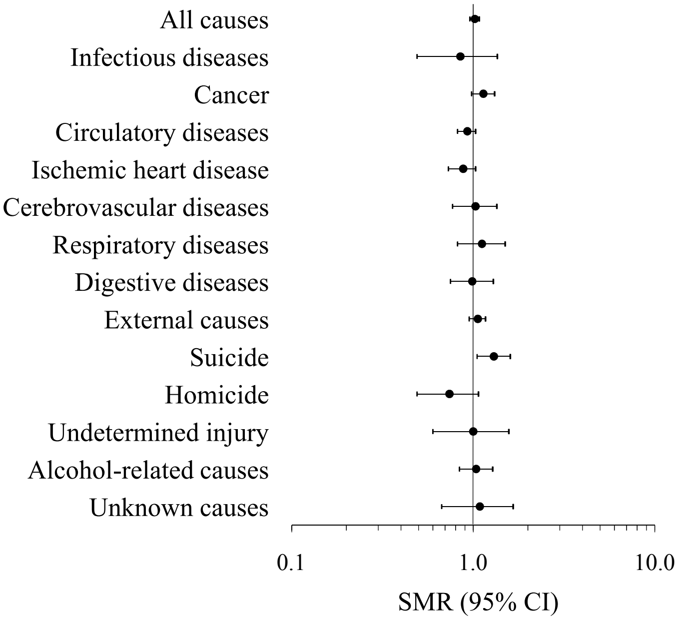

Figure 6. Standardized mortality ratios (SMR) with 95% confidence intervals (CI) by cause of death in the Estonian cohort of Chernobyl cleanup workers, 1986–2011.

The ratios of SMRs revealed lower all-cause mortality among those cohort members who entered the Chernobyl area in 1986 (adjusted RR=0.87; 95% CI 0.76–0.99), and higher all-cause mortality for those with a longer mission (adjusted RR=1.23; 95% CI 1.09–1.40). The risk of death rose significantly after seven years since return from the Chernobyl area. Mortality from cancer or circulatory diseases was not influenced by the year of arrival in the Chernobyl area, duration of the mission or time since return. Elevated mortality from external causes or selected alcohol-related causes was found for cleanup workers with Chernobyl service exceeding three months. The suicide risk did not decrease with increasing time since return. Additional adjustment for ethnicity and education did not change the RRs for the variables concerning the Chernobyl mission, but both characteristics had a strong effect on mortality; non-Estonians and the less-educated cleanup workers experienced a higher risk for all-cause mortality, cancer mortality, and mortality due to selected alcohol-related causes. The risk of suicide and death from circulatory diseases were higher among the less-educated persons. No radiation dose effect on all-cause mortality or cancer mortality was observed.

5.5. Non-cancer disease risk in the Estonian cohort of cleanup workers (Paper V)

An exposed cohort of 3680 men and an unexposed cohort of 7631 men were followed in 2004–2012, during which the cohorts contributed 30,674 and 65,112 person-years at risk, respectively. The exposed cohort had 41,370 contacts with health services, compared with 86,441 contacts in the unexposed cohort. Members of both cohorts had an average of 12 different diagnoses based on three-digit ICD-10 codes.

A very small increase of borderline significance in all-disease risk emerged among the cleanup workers in relation to the unexposed cohort (RR=1.01; 95% CI 1.00–1.03) (Figure 7). From the non-cancer effects of interest, elevated morbidity was observed for diseases of the thyroid gland (RR=1.69; 95% CI 1.38–2.07) and ischemic heart disease (RR=1.09; 95% CI 1.00–1.18), but not for cataract. Stress reactions, depression, severe headaches and sleep disorders were not more frequently diagnosed among the cleanup workers.

Increased morbidity in the exposed cohort was apparent for the broad categories of diseases of the nervous system, digestive system, musculoskeletal system, selected alcohol-induced diagnoses, and for external causes of morbidity.

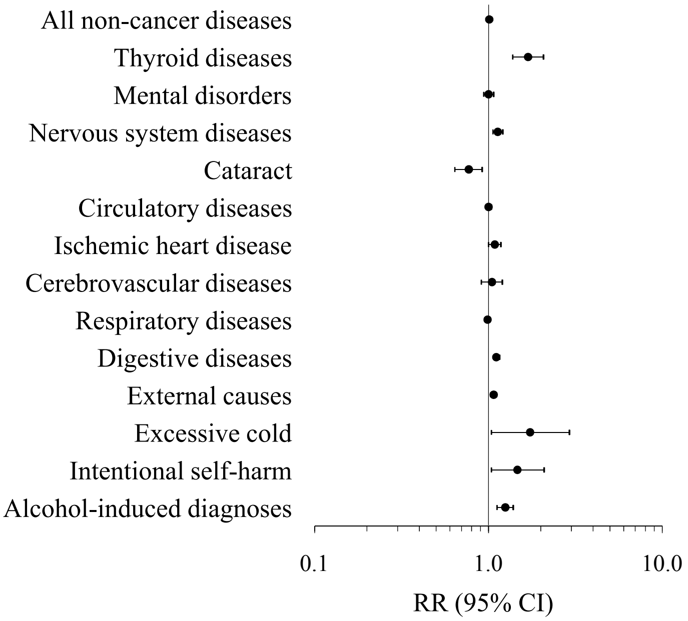

Figure 7. Morbidity rate ratios (RR) with 95% confidence intervals (CI) by selected diseases and causes of morbidity in the Estonian cohort of Chernobyl cleanup workers, 2004–2012.

Mutually adjusted morbidity RRs between sub-groups in the exposed cohort revealed more depressive disorders and stress reactions (RR=1.27; 95% CI 1.00–1.62), and severe headaches (RR=1.69; 95% CI 1.10–2.60) among early responders. Thyroid disease morbidity was not related to the year of arrival in the Chernobyl area. Longer mission did not increase the morbidity of any disease. Including the documented radiation dose in the models did not markedly alter the point estimates of the morbidity RRs for the year of arrival or duration of the mission; no association was detected between radiation dose and morbidity from any of the selected diseases. Ethnicity and education had stronger effect on morbidity than characteristics related to the Chernobyl mission; acute myocardial infarction (RR=1.53; 95% CI 1.03–2.26), cerebrovascular diseases (RR=1.65; 95% CI 1.30–2.11), diseases of liver (RR=1.42; 95% CI 1.07–1.90), calculus of the kidney and ureter (RR=1.99; 95% CI 1.39–2.85), severe headaches (RR=1.48; 95% CI 1.03–2.12), and alcohol-induced morbidity (RR=1.37; 95% CI 1.15–1.63) were more common while mental disorders (RR=0.82; 95% CI 0.74–0.92) were less common among non-Estonians. Less-educated cleanup workers had higher risk for diseases of the nervous system (RR=1.20; 95% CI 1.05–1.37), cerebrovascular diseases (RR=1.61; 95% CI 1.25–2.08), intentional self-harm (RR=2.73; 95% 1.48–5.05) and alcohol-related morbidity (RR=1.76; 95% CI 1.44–2.15), but lower morbidity from in situ and benign neoplasms (RR=0.76; 95% CI 0.61–0.96).

6. DISCUSSION

The Baltic cohort study of Chernobyl cleanup workers was undertaken primarily to investigate the effect of protracted exposure to low-dose radiation on cancer incidence, with particular interest in leukemia. However, as the findings show, more than twenty years of follow-up has not yielded evidence of an appreciable burden of radiation-related cancers. Instead, greater evidence has emerged of excess occurrence of outcomes not directly attributable to radiation exposure, namely higher incidence of alcohol-related cancers, and a persistently elevated suicide risk in the Estonian cohort.

6.1. Cancer risk

The current study revealed that Baltic cleanup workers were at small to no increased cancer risk after 22 years of follow-up. For most solid cancers, the minimum latency period may be 10–20 years [82], and, as it became apparent from the atomic bomb survivors, the risk can last throughout the lifetime [26]. Thus, it may be too early to see an elevated cancer risk in the cohort. However, there are no convincing radiation-related cancer risk estimates in epidemiological studies with a mean radiation dose level of about 0.1 Gy or below [16, 23], which was the case for the cohorts of the Chernobyl cleanup workers.

6.1.1. Leukemia

Although increased leukemia risk is frequently reported in populations exposed to radiation [30, 61], the 26 leukemia cases detected in the Baltic cohort in 1986–2007 did not represent a higher proportion of incident cases. The indication of excess leukemias in the Latvian cohort (based on 7 cases during follow-up until 1998) was not supported by Estonian or Lithuanian data. As the risk of radiation-induced leukemia peaks 5–15 years after exposure and declines afterwards, new cases of leukemia among cleanup workers will unlikely be related to radiation [1]. This finding is in accord with the outcome of a nested case-control study of Russian, Belarusian and Baltic cleanup workers [97], and it is inconsistent with the increased leukemia risk observed in Russian and Ukrainian cleanup workers studies, both of which were based on substantially larger cohorts [12, 95, 96] but did not have the advantage of population-based cancer registries. Any increase in the risk of leukemia in the Baltic cohort relative to the general male population of the three countries was too small to be detectable in a cohort of this size. Hence, the finding is consistent with no effect, as well as an effect of the size expected given the dose level.

6.1.2. Thyroid cancer

A causal link between radiation exposure and thyroid cancer has been well documented, but excess risk has emerged primarily following exposure in childhood, among women, and at thyroid doses above 1 Gy [46, 60, 169]. The thyroid cancer incidence among the cleanup workers has been under close surveillance because of the potential exposure to radioiodine ^{131}I among early entrants; any inhalation would result in internal radiation doses [1]. Follow-up of the Estonian-Latvian cohort in 1986–1998 and the Baltic cohort in 1986–2007 revealed an elevated thyroid cancer risk, which was concentrated among those who began their mission shortly after the accident. This outcome is in line with a Russian and Ukrainian cohort studies in which a higher thyroid cancer incidence was reported among cleanup workers in relation to the general population [11, 101], but these findings should be interpreted with caution. Thyroid screening among the Estonian cleanup workers in 1995 [137] and regular medical examinations in the Latvian [106], Lithuanian [170], Russian [11] and Ukrainian [101] cohorts likely contributed to the excess number of thyroid cancers. However, even if SIR or PIR is divided by a coefficient of 1.5–3 to take into account the screening effect [171], an excess of thyroid cancer still remains among early entrants. The case-control study nested in the Russian, Belarusian and Baltic cohorts, and therefore not influenced by rates in the general population, demonstrated a somewhat higher risk of thyroid cancer among male cleanup workers per unit thyroid dose than was reported for male atomic bomb survivors aged 30 years at exposure [26, 102].

Although the proportion of thyroid cancers among cohort members with higher radiation doses was four times that of the general population during the follow-up in 1986–2007, it could not inferred with confidence that a higher recorded dose has contributed to the excess risk, nor can this possibility be excluded. However, when interpreting thyroid cancer risk in the Baltic cohort, one should keep in mind the small number of cases, as thyroid cancer is a rare disease.

6.1.3. CNS cancer

The association between adult radiation exposure and tumors of the CNS (dominantly benign) has been reported in the UNSCEAR 2006 Report [60], based mainly on atomic bomb survivor data [172]. A causal relationship between ionizing radiation and CNS cancers was evaluated recently by the working group at IARC [4, 64]. This conclusion was derived primarily from studies of childhood radiotherapy patients, and from the LSS, the only epidemiological study so far that has reported an association between adult exposure and incidence of CNS tumors [26, 173]. However, excess risk of CNS cancer per unit dose was not detected in 1991–2001 among Russian cleanup workers [8]. The first evidence of increased brain cancer incidence among Baltic cleanup workers (based on 11 cases) was observed in the Estonian-Latvian cohort in

1986–1998. In the extended follow-up, the excess risk persisted in the Estonian but not in the Latvian cohort, and was not apparent in the Lithuanian cohort. An elevated proportion of brain cancer cases in the Baltic cohort was observed in the men whose mission started in 1986 and lasted longer; however, this outcome was based on just 12 cases and could easily be a chance finding. No association was detected between increased brain cancer risk and the documented radiation dose in the Baltic cohort.

6.1.4. Other cancer sites

Although a dose-dependent site-specific cancer risk has been apparent in large exposed cohorts, e.g., atomic bomb survivors [26], no indication of increased risk of radiation-related cancer sites as a group was apparent in the Estonian or in the joint Baltic cohort. Furthermore, no excess risk for site-specific cancers was reported among the Russian cleanup workers when individuals with potentially higher doses were selected for the analysis [8]. In the current study, higher risk for radiation-related cancers was expected to see among those cleanup workers who were sent to the Chernobyl area shortly after the accident or who remained there for longer time period and most likely received higher cumulative radiation doses. However, efforts to evaluate cancer risk according to exposure characteristics have not yielded convincing results – no significant differences between exposure levels were demonstrated in the Estonian or in the Baltic cohort, albeit these findings were based on a small number of cases. The radiation-related cancer risk in the cohort has been undetectable given the relatively low radiation dose level, with the possible exception of excess thyroid cancer risk among early entrants.

There was no evidence of an elevated proportion of cases of the broad categories of cancer sites or selected single sites in the Baltic cohort. However, the significantly higher proportion of esophageal cancers gave some hints about alcohol abuse in the cohort, as alcohol is a strong risk factor for esophageal cancer [158].

The impact of alcohol seemed to be pronounced in the Estonian cohort, which had an excess risk of pharyngeal, esophageal and therefore of combined alcohol-related cancer sites quantified by SIR in 1986–2008. Extended follow-up of the Estonian cohort revealed a higher overall and especially alcohol-related cancer incidence among cohort members with a basic education compared with their counterparts with higher or secondary education. This finding is not surprising given the more prevalent alcohol consumption among less-educated men [164] and the educational inequalities reported for cancer mortality in Estonia [174].

6.2. Death risk in the Estonian cohort

Although mortality data are widely used in radiation epidemiology [e.g., 29, 73], no studies yet have reported register-based cause-specific mortality among Chernobyl cleanup workers, with the sole exception of the Estonian cohort study. A preliminary analysis of the Russian cleanup workers demonstrated significantly lower all-cause mortality, with a deficit of deaths due to malignant neoplasms, and injuries and poisoning, but an excess of deaths due to circulatory diseases in relation to the male population of Russia [7]. However, the authors admitted that the 15% lower overall mortality measured by SMR could have been because of incomplete data on deaths, as it has been difficult to obtain relevant information through annual clinical follow-ups.

Because of a lack of follow-up for mortality among Latvian and Lithuanian cleanup workers, the death risk analysis was based solely on Estonian data. The all-cause mortality in the cohort of cleanup workers was at the level expected from the mortality rates of the male population during the earlier period of 1986–2002 and through the extended follow-up until 2011. This outcome could be biased by the healthy-worker effect, since the majority of the cleanup workers were military reservists or in regular army service [133], and were most likely healthier than the male population. However, this risk-reducing effect was counterbalanced by the effect of education and ethnicity: a small proportion of men with higher education and an overrepresentation of non-Estonians in the cleanup worker cohort should have led to a higher mortality compared with the male population [165–167]. The mortality pattern by the broad categories of death causes did not change markedly during the two studied time periods; no elevated mortality was found for cancer, diseases of the circulatory system, respiratory system, digestive system, or for external causes as a group.

6.2.1. Cancer

Mortality data are used in radiation-related cancer risk analyses in parallel with the incidence data (e.g., in the LSS) [26, 29], or they can be the only source when incident cases are unavailable (e.g., in the 15-country study of nuclear industry workers) [65]. The cancer mortality analysis for the Estonian cleanup worker cohort, although based on a follow-up period that was three years longer than that used for incidence, did not provide additional information about the cancer risk among the cleanup workers. No significantly elevated mortality from radiation-related cancers was observed; however, mortality due to alcohol-related cancers was 61% higher in the cohort of cleanup workers than in the male population. No differences by exposure characteristics (year of arrival, duration of the mission and documented radiation dose) were detected in the cancer mortality; however, educational and ethnical inequalities were apparent: less-educated and/ or non-Estonians had poorer outcomes. Although the increased alcohol-related cancer risk in the cohort suggested a rise in mortality due to alcohol-induced causes other than cancer, no such increase was observed.

6.2.2. Circulatory diseases

Dose-dependent mortality from circulatory diseases as the major cause of death in developed countries has been reported in many cohorts exposed to radiation [70]. Excess mortality from all circulatory diseases, stroke and heart disease was observed in atomic bomb survivors, but no clear association was seen at exposures below 0.5 Gy [72]; however, a follow-up of nuclear industry workers from 15 countries resulted in no significant findings regarding a dose-dependent rise in mortality from circulatory diseases [73]. No elevated risk for circulatory disease mortality was found in the Estonian cohort of cleanup workers. The SMRs for all circulatory diseases, ischemic heart disease and cerebrovascular diseases remained near unity, which demonstrated the small to non-existent circulatory disease risk in the cohort. Early arrival in the Chernobyl area, longer mission or higher documented radiation dose did not increase the circulatory disease mortality; however, higher educational level appeared to be a protective factor. As estimation of radiation-related circulatory disease risk below doses of 0.5 Gy requires large cohorts, the Estonian cohort of cleanup workers with low dose level is far too small to quantify the radiation-related circulatory disease risk, if one exists.

6.2.3. Suicide

A significantly higher suicide rate in the Estonian cohort of cleanup workers compared with that of the male population emerged shortly after the workers returned from the Chernobyl area [135]. Updated analyses revealed no decline in the SMRs, which were 1.32 in 1986–2002 and 1.30 in 1986–2011. Epidemiological studies confirm that psychiatric symptoms related to catastrophic environmental exposures are intractable; they are frequently associated with suicide attempts, depression and post-traumatic stress disorder, which in turn relate strongly to the risk of suicide [175–177]. The Chernobyl cleanup workers were sent into a stressful and dangerous environment with no or misleading information about the exposure and possible long-term health effects. The deliberate withholding of information by Soviet authorities has led to suspicion and mistrust of any attempts to put the potential health risk in perspective and relieve their anxiety. This uncertainty generated rumors and misapprehensions, and radiation fears were exaggerated [178, 179]. Tarlap described in his memoirs that most cleanup workers had consumed more alcohol during their Chernobyl service than at any other time in their civil lives, and alcohol use was even recommended [133, 180]. There is evidence that suicides are strongly related to alcohol dependence among middle-aged men in Estonia [181].

Estonia is known for its relatively high male suicide rates [182, 183]. Gorbachev's anti-alcohol campaign in the mid-1980s contributed to keeping suicide rates lower in 1986–1991 [184], but rapid socioeconomic changes from 1991 onwards were followed by a sharp increase in suicide rates among men, with a peak in 1994 [182]. Despite the high and fluctuating background rates, the suicide risk among the cleanup workers did not reverse with the time since their return from the Chernobyl area.

When interpreting the suicide risk in the Estonian cohort, it should be born in mind that the rate of death due to undetermined injuries increased rapidly after 1991, and some suicides could have been hidden in this nonspecific category [183, 185]. The point estimate for the SMR for the joint category of suicide and undetermined injury was lower than that for suicide alone, but it still demonstrated a statistically significant excess risk in the cohort.

The increased suicide risk is in accord with results from the Ukrainian cleanup worker study that found a twofold elevated risk of suicide ideation [119], and although a dose-dependent excess risk for mental disorders as a group has been found in the Russian study [6], the suicide risk among cleanup workers other than Estonian cohort has not been investigated.

6.3. Non-cancer morbidity risk in the Estonian cohort

The first and only analysis of non-cancer morbidity among the Estonian cohort of Chernobyl cleanup workers revealed elevated morbidity for diseases of the nervous system, digestive system, musculoskeletal system, ischemic heart disease, and for external causes. The most salient excess risk was observed for thyroid diseases, for intentional self-harm, exposure to excessive cold, and selected alcohol-induced diagnoses.

6.3.1. Thyroid diseases

As the early cleanup workers could receive internal irradiation from short-lived radioiodine accumulating in the thyroid gland, their risk of thyroid diseases should have been under special attention. However, the only study of non-cancer disease incidence among cleanup workers from Russia demonstrated an excess risk of endocrine and metabolic diseases as a group, but it did not provide risk estimates for thyroid diseases [6]. Evidence of benign thyroid diseases after radiation exposure has been summarized by Ron and Brenner [186], who concluded that the reported associations were weak and the elevated risk occurred mainly in subjects who received high doses, were exposed at young ages, or were women. Bearing in mind that the cohort of cleanup workers includes only adult men who were exposed to low doses, the elevated morbidity of thyroid diseases cannot be completely (if at all) attributed to radiation. This interpretation is supported by the lack of excess among the early entrants or subjects with the highest documented radiation doses. At the same time, the possibility of closer medical examination sought by the cleanup workers, and therefore higher rate ratio cannot be excluded. During thyroid screening among the Estonian cleanup workers in 1995, no clear correlation was found between the prevalence of thyroid nodules and the year of arrival or the documented radiation dose [137].

6.3.2. Mental health

Natural or manmade disasters inflict psychological consequences on the affected populations, which can be greater than the physical impact if nuclear contamination is of concern [187, 188]. As a silent and invisible exposure and well-known carcinogen [4], ionizing radiation easily feeds dreadful perceptions. The Chernobyl cleanup workers were exposed not only to radiation, but also to a lack of protective gear and to poor living conditions, sometimes doing meaningless jobs and drinking large amounts of alcohol [133, 180]. Thus, the mental health of the cleanup workers was of concern.

The current morbidity analyses showed a mixed pattern of mental and neurological disorders. Based on the results from a study of Ukrainian cleanup workers [119], the higher rates of depression, anxiety, post-traumatic stress disorder, and headaches were expected. So far, there was no overall increase in mental disorders as a group, or in physician-diagnosed depression or anxiety. During the follow-up period, the cleanup workers used health care services significantly less frequently for stress reactions than the unexposed cohort did. No excess of severe headaches or sleep disorders was found among the cleanup workers. However, depression and stress reactions, and severe headaches were more frequent in the early entrants. Elevated morbidity due to intentional self-harm is also an indicator of psychological distress and is consistent with the increased suicide rate in the cohort.

Excess morbidity emerged for alcohol-induced diseases – mental disorders due to alcohol and degeneration of the nervous system due to alcohol. Morbidity from alcohol-induced diagnoses as a group was 25% higher among cleanup workers than in the unexposed cohort. Considering how common alcohol abuse is among (less-educated) men in Estonia [164], it is not surprising that the cleanup workers used alcohol to cope with a stressful situation (and presumably still do).

Although Ukrainian cleanup workers reported more mental disorders than controls, no excess of alcoholism was observed [119]. This illustrates how the analysis of similar cohorts with different design and risk measures can produce entirely opposite results. Very likely, mental disorders other than alcoholism were under-diagnosed in the Estonian cohort, and the prevalence of alcoholism was underestimated in the Ukrainian cohort. It is common for people not to seek professional help for mental health problems [112]. Untreated mental disorders can manifest as unexplained physical complaints, such as headache or back pain, and they are risk factors for somatic diseases (e.g., thyroid diseases or diseases of the digestive system) [189, 190]. Thus, it is important to pay attention to both mental and somatic diseases among the Chernobyl cleanup workers simultaneously.

6.3.3. Other outcomes

Evidence that low-dose radiation can increase the incidence of circulatory diseases has been found in the LSS [25]. Although the Russian cleanup worker cohort, with a mean dose of 0.11 Gy, demonstrated significant dose-dependent excess for hypertension, ischemic heart disease and cerebrovascular diseases [10], the borderline increase in ischemic heart disease morbidity observed in the Estonian cleanup worker cohort cannot be attributed to the biological effects of radiation exposure, since the Estonian cohort was with low average radiation dose. This conclusion is also supported by the mortality analyses in 1986–2011 with no excess deaths from circulatory diseases.

An increased risk of cataract, observed in atomic bomb survivors [25] and Ukrainian cleanup workers [123] did not emerge in the Estonian cohort. An observed statistically significant deficit of cataract cases may be an occasional finding without any epidemiological relevance. Although recent studies have indicated that the conventional threshold for radiation-induced cataract at 0.5 Gy should be lowered [71, 75], it is unlikely that radiation-related cataract will be detectable among the Estonian cleanup workers in the future, given the low dose level.

The elevated morbidity found for digestive diseases as a group is consistent with the outcome from the Russian cleanup worker study, which showed a significant dose-dependent excess for this category of diseases [6]. Nevertheless, this finding in the Estonian cohort could hardly be related to radiation, as alcohol abuse is a strong risk factor for digestive diseases, and alcohol-related outcomes were apparent among the cleanup workers.

For the external causes, the highest risk estimate was seen for exposure to excessive cold, which is most likely attributable to homelessness and suggests that periods of homelessness were more common among the cleanup workers than among the men in the comparison cohort.

6.4. Strengths and limitations of the study

6.4.1. Strengths

1. In the Baltic countries, the cohort studies of Chernobyl cleanup workers are well-designed studies with cohort members ascertained from multiple overlapping sources and with good potential for use in long-term follow-up.
2. In Estonia, the register-based follow-up of the cohort through record linkage for vital status, cancer incidence and mortality is almost complete.

3. The current study is the only one to date that has quantified the register-based cause-specific mortality, particularly the suicide risk among Chernobyl cleanup workers in relation to the male population.

6.4.2. Limitations

Exposure level and cohort size

Recent studies of Chernobyl cleanup workers have focused on dose-response analyses of leukemia and thyroid cancer [11, 12, 95–97, 102]. Because of the small size and the uncertainties in the dose estimates, the Baltic study cannot substantially contribute to the evaluation of the shape of the dose-response curve. Documented doses were based on whole-body external irradiation and were recorded in military passports, but the reliability of these doses remained unclear, i.e., despite the implemented dose limits, errors of higher or lower recordings of doses were possible [151]. Nevertheless, biodosimetry and dose reconstruction for the Baltic cleanup workers have confirmed that the average of the true doses is unlikely to have exceeded the average of the documented doses (10–11 cGy) [140–142]. Thus, the Baltic cleanup workers can be treated as a cohort with low-dose radiation exposure in general, but individual doses cannot be completely trusted. The small size and relatively low dose level of the cohort reduce the statistical power. However, the power was sufficient to detect a persistently elevated risk of suicide among the Estonian cleanup workers.

Follow-up

Theoretically, conducting register-based cohort study in each of the Baltic countries seems trouble-free; unique PINs assigned to each resident make linkages easy and fast. However, PINs were introduced only in 1992, when countrywide population registers were established, and it took some years to utilize PINs in the all other registers, including the cancer and causes of death registers. The identification of Chernobyl cleanup workers through the population register and initial linkages with cancer and mortality data were performed without the advantage of PINs. This kind of procedures could have caused linkage errors in both directions and left some cohort members unidentified. Persons, who were not matched with the record in the population register, could have emigrated before 1992 or could have had a misspelled name.

Turmoil, surrounding the data protection laws and practices in the Baltic countries in the 2000s prohibited record linkages and disallowed the use of death certificate information to update cancer data [191]. Cancer registries were under threat of closure because of plans to create integrated health information systems for all diseases and for all purposes. These activities restricted the complete follow-up of Latvian and Lithuanian cleanup workers and prevented the use of more traditional methods of analysis for the Baltic cohort. The future of epidemiological research in the Baltic countries as elsewhere depends heavily on the influence of data protection regulations, for which a balance between privacy and the public's interest must be found [192–194].

Morbidity analysis

The morbidity analysis was limited to the period between 2004 and 2012, and no prior information was available. Thus, it was impossible to specify incident cases or assess the early effects of exposure. The given diseases may have included preliminary diagnoses that were not confirmed afterwards. The possibility of diagnostic errors is associated with the use of a reimbursement-administrative database that was not originally created for research purposes, but proved to be an important data source for medical studies in Estonia [195–197]. However, because of universal health insurance, covering 95% of the population of Estonia [149], this kind of non-differential misclassification of diagnoses would be expected to affect the exposed and unexposed cohorts in a similar fashion [156].

7. CONCLUSIONS

1. The risk of cancer development among Chernobyl cleanup workers from the Baltic countries was at the same level as in the male population of these countries; however, an elevated thyroid cancer risk among the early entrants cannot be excluded.
2. Mortality among the Estonian Chernobyl cleanup workers did not differ from that of the male population of Estonia, with the exception of a persistent excess of suicides, likely associated with no or misleading information about the exposure and possible long-term health effects.
3. No obvious increase of non-cancer morbidity consistent with the effects of radiation was found among Estonian Chernobyl cleanup workers; an observed excess of benign thyroid diseases may be the result of closer medical attention.
4. A quarter of a century after the Chernobyl accident, no evidence of harmful health effects of protracted low-dose radiation exposure was observed; albeit small risks may have remained undetectable. Some deleterious health effects found among the cleanup workers can be explained as a consequence of disease screening, more intensive medical surveillance and unhealthy behaviors.
5. Given the disease and mortality risk pattern among Chernobyl cleanup workers, it is important to consider mental and somatic diseases simultaneously.

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SUMMARY IN ESTONIAN

Baltimaade Tšernobõli veteranide haigestumus ja suremus: registripõhine kohortuuring

Ioniseeriva kiirguse efekti tervisele on palju uuritud ning sellekohaste tööde tulemusi üldistavaid ajakohastatud raporteid üllitavad Rahvusvaheline Vähiuuringute Keskus (IARC), USA Riikliku Teaduste Akadeemia Ioniseeriva Radiatsiooni Bioloogiliste Efektide Komitee (BEIR) ja ÜRO Aatomikiirguse Efektide Teaduskomitee (UNSCEAR) [1, 4, 15]. Selle kiirguse kõik liigid kuuluvad IARCi klassifikatsiooni alusel kantserogeenide rühma 1 – leidub küllaldaselt tõendeid nende vähki tekitavast efektist inimestel.

Andmeid ioniseeriva kiirguse terviseefektide kohta on saadud epidemioloogiliste uuringutega, sealhulgas kohortuuringutega. Valdav osa tänapäeva teadmistest kiirguse hilistagajärgedest pärineb uuringust nimetusega *Life Span Study*, milles on jälgitud Hiroshima ja Nagasaki 1945. aasta tuumaplahvatuse üleelanute ja võrdlusisikute kohorti (algselt kokku ~120 000 isikut) tänapäevani. Muud kohordid, kelle terviseseisundi jälgimine on andnud uusi teadmisi, võib rühmitada järgmiselt: a) kutsetöötajad (nt radioloogid, tuumajaamade töötajad, radioaktiivse maagi kaevanduste töötajad ning lennumeeskonnad ja salongipersonal); b) patsiendid (eksponeeritud radiodiagnostika ja -teraapia käigus); c) eksponeeritud elukohajärgne rahvastik (nt tuumapolügoonide ümbruskonna, kõrge loodusliku kiirgustasemega alade ja tööstuskatastroofi tõttu saastatud piirkondade asukad).

Kui suurte kiirgusannuste korral tuntakse suhteliselt hästi sellest tingitud tervisekahjustusi, siis väikeste annuste (<0,1 Gy) efektide kohta puudub selgus, sest uurimine eeldab täpseid andmeid individuaalse ekspositsiooni ja segavate tegurite kohta suurtes kohortides, kelle liikmete tervist tuleb jälgida pika aja vältel. Ometigi vajatakse teadmisi väikeste kiirgusannuste efektist esmajoones kiirguskaitse eemärgil [21–23].

Pärast 26. aprillil 1986 asetleidnud avariid Tšernobõli tuumajaamas asuti Obninskis kohe looma üleliidulist registrit radioaktiivsele kiirgusele eksponeeritute (kohapealne, evakueeritud ja ümberasustatud rahvastik, puhastustöödel osalenud inimesed, kõrge riski aladel sündinud lapsed) kohta. See register tugines Nõukogude Liidus rajatud piirkondlike registrite andmetele, riigi lagunemise järel jätkus osa registrite sõltumatu tegevus ja nende andmestikku kasutav epidemioloogiline uurimistöö.

Hinnanguliselt saadeti Tšernobõli piirkonda avariijärgsetele puhastustöödele ligikaudu 530 000 isikut (Tšernobõli veterani), nende hulgas 229 000 Ukrainast, 188 000 Venemaalt, 91 000 Valgevenest ja veidi üle 17 000 Baltimaadest [1]. Eksponeeritute registri andmevara on epidemioloogiliste uuringute tegemiseks kõige tulemuslikumalt kasutanud Vene Riiklik Meditsiiniline Dosimeetriaregister [6–12]. Et radioaktiivne saastatus kandus Tšernobõlist kaugele ja kattis kogu põhjapoolkera, on selle võimalikke tagajärgi analüüsitud paljudes riikides mitut tüüpi uuringute (ökoloogiline, kohort-, juhtkontroll-, pesastatud juhtkontrolluuring) abil [93]. Paraku on teaduskirjandusse ja meediasse jõudnud (ranget) eelretsenseerimist mitte läbinud uurimistulemused, mis on saadud ebatäielike algandmete või oskamatu analüüsi alusel. Seetõttu on tekkinud kaks vastandlikku leeri [179]: üks võimendab avarii tagajärgi kohalike asukate, sh veteranide tervisele ja süüdistab kõigis tekkinud tervisehädades Tšernobõli, teine kasutab olukorra hindamisel korrektselt tehtud uurimusi ja väldib ennatlike liialdatud üldistuste tegemist. UNSCEARi raport kui tänapäeva autoriteetseim allikas ioniseeriva kiirguse pikaajaliste terviseefektide kohta annab järgmise kokkuvõtte [1]: praeguseks on radiatsioonist tingituna ilmnenud kilpnäärmevähi-haigestumuse tõus lapseeas eksponeeritute hulgas; täiendavat kinnitust vajab leukeemia, vereringehaiguste ja kae suurenenud risk veteranidel; üldrahvastiku haigestumuse ja suremuse avariijärgne järsk tõus viitab pigem registreerimise paranemisele ja sotsiaal-majandusliku kriisi mõjule Nõukogude Liidu lagunemisel.

Seni viimasesse, aastal 2011 ilmunud UNSCEARi raportisse on võetud nii käesoleva töö tulemusi sisaldava artikli [artikkel I] kui ka kahe artikli [133, 135] andmed varasema perioodi epidemioloogilistest uuringutest Eesti Tšernobõli veteranide kohta. Eelnenud uuringutega, mille tegemiseks saadi oluline oskusteave ning rahaline toetus Soomest (Vähiregister, Kiirguskaitse Keskus) ja USAst (Riiklik Vähiinstituut), alustati alul Eestis, hiljem Lätis ja Leedus. Need uuringud kavandati esialgselt vähihaigestumuse (eelkõige leukeemiariski) analüüsimiseks Tšernobõli veteranide hulgas.

Postiküsitlus 1992–1995 (vastamismäär 81,4%) andis teavet veteranide rahvuse, hariduse, ameti, tervisekäitumise, Tšernobõli piirkonnas viibimise asjaolude, seal tehtud töö iseloomu, nn ametlike kiirgusannuste, perekonnas esinenud haiguste ja veteranide laste kohta [133, 134]. Linkimisuuringuga saadi esimesed teadmised veteranide vähihaigestumusest ja suremusest ajavahemikul 1986–1993 [135, 136]; ainsa statistiliselt olulise leiuna oli veteranide kohordis enesetapusuremus 1,5 korda kõrgem kui meesrahvastikus. 1995. aastal korraldatud kilpnäärme-skriiningul osales 1984 veterani; diagnoositi kaks kilpnäärmevähki, ei leitud seost kilpnäärmesõlmede levimuse ja eksponeeritust iseloomustavate tunnuste vahel [137, 138].

Et ametlike kiirgusannuste usaldusväärsus tekitas kahtlust, tehti uuringud eesmärgil määrata nüüdisaegsete biodosimeetria meetoditega – GPA- [141, 143] ja FISH-meetod [142, 143] – veteranide kohordis saadud tegelikud kiirgusannused; mõlemad meetodid näitasid, et veteranide kohordi keskmine neeldunud kiirgusannus jäi vahemikku 10–11 cGy, mis ei erinenud ametlikust keskmisest annusest. Uuringus, milles mõõdeti Tšernobõli veteranide lastel mutatsioonide sagedust DNA minisatelliitides, ei tuvastatud selle seost isa eksponeeritusega radiatsioonile; mõningane kõrgem sagedus suurima annusega (20 cGy või rohkem) veteranide rühmas võis olla tõlgendatav juhuleiuna [144].

Tšernobõli avarii kui ajaloo rängim tuumatööstuskatastroof [1, 2] puudutas Eestit peamiselt ligi 5000 mehe saatmisega puhastustöödele radioaktiivselt saastunud piirkonnas. Nende meeste tervist käsitlevad uuringud moodustavad ühe osa maailmas tehtavast uurimistööst väikeste kiirgusannuste terviseefektide hindamiseks.

Eesmärgid

Töö üldeesmärk oli hinnata Tšernobõli tuumaavarii pikaajalist efekti puhastustööde veteranide tervisele.

Töö alaeesmärgid olid:

1. Mõõta vähiriski paikmeti Tšernobõli veteranide Balti ühendkohordis (Eesti, Läti ja Leedu) ja eraldi Eestist pärit veteranide kohordis (artiklid I, II, IV).
2. Analüüsida Eestist pärit Tšernobõli veteranide kohordi surmariski surmapõhjuseti rõhuasetusega varasemal jälgimisel täheldatud kõrgenenud enesetapuriskile (artiklid III, IV).
3. Teha kindlaks, kas Eestist pärit Tšernobõli veteranide kohordi haigestumus teiste haiguste (v.a vähk) korral on eeldatust kõrgem (artikkel V).

Andmed ja metoodika

Eesti Tšernobõli veteranide kohort moodustati 1992. aastal tollase Eesti Kaitsejõudude Peastaabi, Tšernobõli radiatsiooniregistri, Sotsiaalhoolduse Ministeeriumi ja Eesti Tšernobõli Komitee (k.a Eesti Rohelise Liikumise) nimistute põhjal. Kohorti kuulub 4831 meest, kes aastatel 1986–1991 töötasid Tšernobõli piirkonnas. Iga Tšernobõli veterani andmeid täpsustati ja eluseisundit (elab Eestis/ surnud/ emigreerunud) jälgiti alul kunagise aadressbüroo, hiljem rahvastikuregistri vahendusel kuni 31.12.2012. Jälgida ei õnnestunud 21 meest (0,4% kohordist), kes jäeti analüüsist välja. Kohordis 1986–2008 diagnoositud vähijuhud ja diagnoosi kuupäev tehti kindlaks Eesti Vähiregistriga linkimisel (artiklid I, II, IV). Kohordi liikmete surmad 1986–2011 (surmapõhjus ja surma kuupäev) sedastati linkimisel nn teadusliku surmaandmekoguga, mis sisaldab Surma põhjuste registri ühtlustatud koodidega üksikkirjeid ja on loodud hõlbustamaks esmajoones epidemioloogiliste uuringute tegemist [146, 147]. Surmade kodeerimisel kasutati vaadeldaval ajavahemikul kolme klassifikaatorit: nõukogude mugandatud ICD-9 [148], ICD-9 ja ICD-10. Linkimiseks kasutati isikukoodi, nime, sünnikuupäeva ja elukohta. Kohordi iga liikme jälgimise inimaastate arvestus algas Tšernobõli piirkonnast Eestisse tagasijõudmise kuupäevast ja lõppes surma, emigreerumise või analüüsiperioodi lõppemise kuupäevaga olenevalt sellest, milline neist sündmustest varem esines.

Inimaastate arvestuses liideti kõigi isikute inimaastad viie aasta vanuserühmade ja üldjuhul viie aasta kalendriperioodide järgi, sealjuures arvestades, et jälgimisaja vältel liigub kohordi liige ühest vanuserühmast ja ühest jälgimisperioodist teise. Nendel veteranidel (16 meest), kellel puudus Eestisse tagasijõudmise aeg (kuupäev) – millest alustatakse inimaastate arvestust, liideti kokkuleppeliselt Tšernobõli jõudmise kuupäevale 92 päeva (Tšernobõlis viibimise kestuse mediaan). Kui veteranidel (128 meest) puudusid Tšernobõli jõudmise ja Eestisse naasmise aeg, pandi viimaseks tinglikult 01.01.1987.

Mittevähihaigestumuse analüüsi (artikkel V) võeti: a) veteranide alakohort, kes seisuga 01.01.2004 elas Eestis ja kuulus vanusevahemikku 35–69 aastat (3680 meest), ning b) võrdluskohort – kihitatud juhuvalim rahvastikuregistrist, et tagada viie aasta vanuserühmades veteranide ja võrdlusisikute arvuline suhe 1:2 koos 5% ülekaetusega (7631 meest). Andmed nendes kohortides esinenud haigusjuhtude kohta 2004–2012 koguti isikukoodi abil tehtud linkimisel Eesti Haigekassa ravikindlustuse andmekoguga. Inimaastate arvestusse läks aeg alates 01.01.2004 kuni kuupäevani, mil esines üks järgnevatest sündmustest – surm, emigreerumine või vaatlusperioodi lõpp 31.12.2012.

Lätis ja Leedus võeti Tšernobõli veteranide kohordi moodustamisel eeskuju Eesti kohortuuringust. Kummaski riigis tegelesid algandmete kogumisega eri registritest ja nimekirjadest ning edasiste linkimistega vähiregistri töötajad [13]. Läti kohort hõlmab 5860 veterani, kellest puuduvate andmete tõttu jäi analüüsist välja 314 (5,4%); vastavad arvud Leedu kohta on 6923 ja 239 (3,5%). Nii Lätis kui Leedus jälgiti kohordi vähihaigestumust ajavahemikul 1986–2007. Eesti, Läti ja Leedu kohort moodustavad koos analüüsituna Balti ühendkohordi suurusega 17 040 meest, kes töötasid Tšernobõli piirkonnas 1986–1991 ja kelle vähiriski mõõdeti perioodil 1986–2007.

Tšernobõli piirkonnas saadud kumulatiivne kiirgusannus mõõdeti individuaalsete või rühmadosimeetritega, või hinnati annused tööpiirkonnas tehtud mõõtmiste alusel. Kiirgusannused kanti sõjaväepiletitesse. Ametlikult kehtestatud piirannus oli 25 cGy aastal 1986, 10 cGy 1987 ja 5 cGy 1988–1991 [151]. Nii ametlike dooside kui ka hiljem biodosimeetria meetoditega määratud annuste aritmeetiline keskmine oli ~10 cGy [140–142]. Et individuaalsed dokumenteeritud kiirgusannused ei olnud usaldusväärsed ja puudusid suurel osal veteranidest, kasutati ekspositsiooni eri tasemete hindamiseks Tšernobõli mineku aega ja seal viibimise kestust. Pidades silmas varasemaid uurimusi Eesti Tšernobõli veteranide vähihaigestumuse ja suremuse kohta [135], suhteliselt madalaid kumulatiivseid kiirgusannuseid [141, 142] ja Tšernobõli Foorumi järeldusi avarii hilistagajärgede kohta [111], iseloomustab käesolevas töös peamist ekspositsiooni kuulumine Tšernobõli veteranide kohorti.

Tulenevalt konkreetse alauuringu eesmärkidest ja andmete olemasolust on töös kasutatud mitmeid suhtelise riski näitajaid: standarditud haigestumusmäär (SIR) (artiklid I, II, IV), võrdelise haigestumuse suhe (PIR) (artikkel II), standarditud suremusmäär (SMR) (artiklid III, IV), SIRide suhe (artikkel IV), SMRide suhe (artikkel IV), suremuskordajate suhe (RR) (artikkel III) ja haigestumuskordajate suhe (RR) (artikkel V). Nende näitajate hajuvust on iseloomustatud 95% usaldusvahemikuga eeldusel, et tegelik juhtude arv vastab Poissoni jaotusele.

Suhtelist vähiriski Eesti ja Läti ühendkohordis 1986–1998 (artikkel I) mõõdeti SIRiga, mis arvutatakse tegeliku ja eeldatava vähijuhtude arvu suhtena

[152]. Sisuliselt näitab eeldatav juhtude arv, kui palju vähijuhte oleks veteranide hulgas registreeritud siis, kui kohordi vähihaigestumus oleks olnud samal tasemel kui meesrahvastikus. Eeldatav vähijuhtude arv kummaski kohordis arvutati inimaastate korrutamisel riigi meesrahvastiku vähihaigestumuskordajatega viie aasta vanuserühmade ja viie aasta kalendriperioodide kaupa; saadud arvud summeeriti. Sarnast arvutuskäiku SIRi leidmiseks kasutati vähiriski mõõtmisel Eesti kohordis 1986–2008 (artikkel IV).

Radiatsiooni-, suitsetamis- ja alkoholisõltuvad vähipaikmed eristati IARCi monograafiate [4, 153, 154, 158] andmete põhjal.

Balti kohordi suhtelise vähiriski arvutustes 1986–2007 (artikkel II) ei olnud võimalik leida inimaastate arvu Läti ega Leedu kohordis, sest puudusid täielikud jälgimisandmed asetleidnud surmade ja emigreerumiste kohta. Seetõttu kasutati SIRi asemel alternatiivnäitajat PIR [155], samuti tegeliku ja eeldatava vähijuhtude arvu suhet, kuid eeldatav vähijuhtude arv iga vähipaikme jaoks riigiti leiti sõltuvalt selle paikme juhtude arvu proportsioonist riigi meesrahvastikus viie aasta vanuserühmade ja viie aasta kalendriperioodide kaupa. PIR esitati ka radiatsiooni-, suitsetamis- ja alkoholisõltuvate vähipaikmete rühmade kohta.

Surmariski Eesti kohordis 1986–2002 (artikkel III) ja 1986–2011(artikkel IV) hinnati SMRi abil, mille arvutuskäik on sarnane SIRi leidmisega: üksnes nüüd tugines arvutus surma-, mitte haigusjuhtudele [152].

Valitud vähipaikmete ja surmapõhjuste analüüsil Eesti kohordi siseseks võrdluseks (artikkel IV) kasutati Poissoni regressioonmudeleid, milles suhtelist riski näitas SIRide või SMRide suhe [159]. Hinnati Tšernobõli mineku aja, seal viibimise kestuse ja dokumenteeritud kiirgusannuse efekti vähihaigestumusele ja suremusele. Mudelid kohandati vanusele, haridusele ja rahvusele. Varasema perioodi enesetapuriski kohordisisesel analüüsil oli riskinäitajaks enesetapukordajate suhe (artikkel III).

Eesti veteranide mittevähihaigestumuse analüüsil (artikkel V) kasutati eksponeeritud ja eksponeerimata kohordi võrdlemisel ning Tšernobõli veteranide kohordi siseses võrdluses Poissoni regressioonmudeleid haigestumuskordajate suhte leidmiseks [159]. Diagnooside ja välispõhjuste rühmitamisel tugineti uurimustele mittevähihaiguste riski kohta radiatsioonile eksponeeritud kohortides [6, 9, 25, 29, 37, 119, 135].

Andmeohje, linkimine ja andmeanalüüs tehti programmidega Visual FoxPro (Microsoft Corporation, Redmond, Washington) ja Stata (StataCorp LP, College Station, Texas).

Tulemused

Vähirisk

Eesti ja Läti andmete koosanalüüs 1986–1998 näitas (artikkel I), et 113 194 inimaasta jooksul diagnoositi 155 vähijuhtu *vs.* 133,85 eeldatavat (SIR=1,15; 95% CI 0,98–1,34). Kõrgenenud risk esines kilpnäärmevähi (SIR=7,06; 95% CI

2,84–14,55; 7 juhtu) ja peaajuvähi (SIR=2,14; 95% CI 1,07–3,83; 11 juhtu) korral. Kihitatud analüüs näitas suurimat kilpnäärmevähi- haigestumuse tõusu meestel, kes alustasid Tšernobõli piirkonnas tööd 1986. aasta aprillis-mais (SIR=18,10; 95% CI 4,93–46,37; 4 juhtu). Leukeemiariski ei ilmnenud.

Kolme Balti riigi ühendkohordis (artikkel II) diagnoositi 1986–2007 756 vähijuhtu. Kõrgeim risk oli kilpnäärmevähi (PIR=2,76; 95% CI 1,63–4,36; 18 juhtu) ja söögitoruvähi (PIR=1,52; 95% CI 1,06–2,11; 35 juhtu) korral. Kilpnäärmevähi-risk oli märgatavaim 1986. aasta aprillis-mais Tšernobõli piirkonda lähetatutel (PIR=6,38; 95% CI 2,34–13,89; 6 juhtu). Peaajuvähki diagnoositi rohkem 1986. aastal Tšernobõli saabunute ja seal kauem viibinute hulgas (PIR=2,08; 95% CI 1,07–3,63; 12 juhtu). Kõrgenenud riski ei esinenud leukeemia ega radiatsioonisõltuvate vähipaikmete rühma puhul.

Eesti kohordi pikim jälgimisaeg 1986–2008 andis 89 023 inimaastat (artikkel IV), mille jooksul diagnoositi 232 vähijuhtu *vs.* 218,00 eeldatavat (SIR=1,06; 95% CI 0,93–1,20). Risk haigestuda oli kõrgem neeluvähi (SIR=2,41; 95% CI 1,38–3,91; 16 juhtu), söögitoruvähi (SIR=2,38; 95% CI 1,23–4,15; 12 juhtu) ja alkoholisõltuvate vähipaikmete rühma (SIR=1,42; 95% CI 1,09–1,80; 66 juhtu) korral. Ei täheldatud kõrgenenud riski kilpnäärmevähi ega leukeemia korral; samuti ei ilmnenud üldist, radiatsiooni- ega alkoholisõltuvat vähi liigriski olenevalt Tšernobõli saabumise aastast, seal viibimise kestusest ega Eestisse tagasipöördumisest möödunud ajast. Üldine ja alkoholisõltuv vähirisk oli kõrgem madalama haridustasemega veteranide seas.

Surmarisk

Mitte kummalgi jälgimisperioodil – aastatel 1986–2002 koos 67 322 inimaastaga ja 1986–2011 koos 98 979 inimaastaga (artiklid III ja IV) – ei erinenud Eesti Tšernobõli veteranide kohordi üldsuremus meesrahvastiku omast: perioodide SMRid olid vastavalt 1,01 (95% CI 0,92–1,09; 550 surmajuhtu) ja 1,02 (95% CI 0,96–1,08; 1018 surmajuhtu). Surmariski hindamisel surmapõhjuseti ilmnes kõrgenenud risk suu- ja neeluvähi (SMR=1,82; 95% CI 1,11–2,81; 20 surmajuhtu 1986–2011) ja alkoholisõltuvate vähipaikmete rühma (SMR=1,64; 95% CI 1,23–2,15; 53 surmajuhtu 1994–2011) puhul. Enesetapurisk oli kõrge 1986–2002 (SMR=1,32; 95% CI 1,03–1,67; 69 enesetapujuhtu) ega vähenenud analüüsiperioodi pikenedes kuni aastani 2011 (SMR=1,30; 95% CI 1,05–1,60; 90 enesetapujuhtu).

SMRide suhted osutasid madalamale üldsuremusele 1986. aasta aprillis-mais Tšernobõli piirkonda saabunud veteranide hulgas (SMR=0,87; 95% CI 0,76–0,99). Kõrgem üldsuremus esines Tšernobõlis kauem viibinute hulgas (SMR=1,23; 95% CI 1,09–1,40); neil veteranidel täheldati kõrgemat riski välispõhjustest tingitud surmade ja alkoholisõltuvate surmade korral. Kõrgem üldsuremus, vähisuremus ja suremus alkoholisõltuvate põhjuste tõttu ilmnes vähem haritud ja mitte eesti rahvusest veteranide hulgas. Enesetapu- ja vereringehaiguste risk oli samuti kõrgem vähemharitute seas.

Teiste haiguste risk

Perioodil 2004–2012 veteranide kohordi jälgimine 30 674 ja võrdluskohordi jälgimine 65 112 inimaasta vältel tuvastas vastavalt 41 370 ja 86 441 kontakti terviseteenustega. Kummagi kohordi liikmetel esines keskmiselt 12 eri diagnoosi (ICD-10 kolmekohaliste koodide järgi).

Veteranide kohordi ja võrdluskohordi haigestumuskordajate suhe RR oli 1,01 (95% CI 1,00–1,03) kõigi haiguste (v.a vähk), 1,69 (95% CI 1,38–2,07) kilpnäärmehaiguste ja 1,09 (95% CI 1,00–1,18) südame isheemiatõve korral. Veteranidel ei diagnoositud sagedamini kaed, depressiooni, stressreaktsioone, peavalusündroome ega unehäireid, kuid nad haigestusid sagedamini närvisüsteemi, seedeelundite ning lihasluukonna- ja sidekoehaigustesse. Ka ilmnes neil võrdluskohordist rohkem alkoholi tarvitamisega seotud diagnoose ja haiguste välispõhjuseid.

1986. aastal Tšernobõli piirkonda lähetatud meestel esines hilisematest saabujatest sagedamini depressiooni, stressreaktsioone ja peavalusündroome. Samas rahvuse ja hariduse efekt haigestumusele oli suurem Tšernobõlis viibimist iseloomustavate tunnuste (mineku aasta, viibimise kestus) efektist. Mitte-eestlastel diagnoositi sagedamini neerukivitõbe, peaajuveresoonte haigusi, ägedat südameinfarkti, peavalusündroome ning alkoholi tarvitamisega seotud haigusi ja haiguste välispõhjuseid. Eestlastel esines sagedamini psüühika- ja käitumishäireid.

Järeldused

1. Baltimaade Tšernobõli veteranide vähirisk oli samal tasemel nende riikide meesrahvastiku vähiriskiga. Siiski ei saa jätta tähelepanuta kilpnäärmevähihaigestumuse tõusu esimeste Tšernobõli lähetatute hulgas nende potentsiaalse eksponeerituse tõttu lühikese poolestusajaga radioaktiivse joodi isotoobile ^{131}I.
2. Eesti Tšernobõli veteranide suremus ei erinenud riigi meesrahvastiku suremusest; ainsa erandina esines veteranide seas suhteliselt enam enesetappe, mis on ilmselt seotud teadmatusega saadud kiirgusannuste kohta ja hirmuga tulevikus avalduda võivate radiatsiooniriskide ees.
3. Eesti Tšernobõli veteranide haigestumus teistesse haigustesse (v.a vähki) ei näidanud seost radiatsiooniga; ilmnenud kilpnäärmehaiguste liigrisk võib seletuda veteranide sagedama arstliku kontrolliga.
4. Veerand sajandit pärast Tšernobõli avariid puudub tõendus pikaajaliste väikeste kiirgusannuste põhjustatud tervisekahjustuste kohta Baltimaade veteranide kohordis, kuigi madalad riskid võisid jääda avastamata kohordi väiksuse tõttu. Mõnede tervisehäirete suurenenud sagedust veteranidel võib selgitada haiguste skriininguga, ulatuslikuma meditsiinilise järelvalvega ja ebatervislike eluviisidega.
5. Tšernobõli veteranide haigestumus- ja suremusnäitajaid teades osutub oluliseks pöörata samaaegselt tähelepanu nii somaatilistele kui psüühilistele haigustele.

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