Original Research Article

ENVIRONMENTAL EPIDEMIOLOGY

OPEN

Dose–response analysis of protracted absorbed organ dose and site-specific cancer incidence in Sweden after the Chernobyl nuclear power plant accident

Martin Tondel[a,b*], Tobias Nordquist[b], Mats Isaksson[c], Christopher Rääf[d], Robert Wålinder[a,b]

Background: Adult males in Sweden exhibit an increased risk of cancer associated with an increased absorbed dose to the colon from the Chernobyl accident.

Methods: A closed cohort, with information on hunter status, included all individuals living in northern Sweden in 1986. Complete annual information on exposure to ^{137}Cs at the dwelling coordinate was available for a total of 2,104,101 individuals. A nested case-control method with four controls matched for year of cancer diagnosis and year of birth, was used. Individual absorbed organ doses were calculated between 1986 and 2020 including external and internal exposure. Hazard ratios (HR) per mGy with 95% confidence intervals (95% CI) were calculated using conditional logistic regression adjusted for rural/nonrural habitat, education level and pre-Chernobyl cancer incidence 1980 to 1985. A total of 161,325 cancer cases in males and 144,439 in females were included.

Results: The adjusted HR per mGy for all cancer sites combined was 1.027 (95% CI = 1.022, 1.031) in males and 1.011 (95% CI = 1.006, 1.017) in females. In a post hoc analysis accounting for both remaining confounding from hunter lifestyle and the pre-Chernobyl cancer incidence by county, the adjusted HR per mGy for all cancer sites combined was 1.014 (95% CI = 1.009, 1.019) in males and 1.000 (95% CI = 0.994, 1.006) in females. The post hoc analysis suggested an increased risk of cancer in the colon, pancreas, and stomach, respectively, in males, and lymphoma in females.

Conclusions: Increased cancer risk estimates were found for some specific cancer sites but remaining uncontrolled confounding due to hunter lifestyle could not be ruled out.

Key Words: ^{137}Cs, dosimetry, radiation, cancer incidence, NCI, hazard ratio, Chernobyl

INTRODUCTION

A steam explosion occurred on April 26, 1986, at 1.23 AM (local time) at reactor 4 of the Chernobyl nuclear power plant (NPP) in Ukraine resulting in a large release of radioactive material. The radioactive emissions continued until May 6 when workers succeeded in cooling the core and the emissions almost ceased. The first indication of a nuclear accident came from the Swedish NPP at Forsmark, 150 km north-east of Stockholm, at 07.00 on April 28 when workers were prevented from entering the plant for the morning shift due to high radioactive contamination registered on their shoes. Outdoor measurements of radioactivity showed 3 to 5 times higher values than the natural background. Eight hours later, at 15.30, it was concluded that the radiation did not emanate from the Forsmark nuclear power station.[1]

Two measurement stations, with low-volume samplers collecting ambient aerosols, were in operation in Sweden in 1986: at Utlängan outside Karlskrona in the southern part of Sweden and at Landsort in the archipelago outside of Stockholm. Increased levels of airborne radioactivity were noted at the station in Utlängan on April 27, about 25 hours after the accident. The radioactive cloud reached Landsort, 360 km north of Utlängan, on April 28, about 52 hours after the accident, at 04.23 Swedish time.[2] The fallout of radionuclides was initially by dry deposition, including ^{131}I, ^{134}Cs, ^{137}Cs and so-called "hot particles" on April 27 to 28 on the island of Gotland, as well as in the Stockholm area. However, most of the deposition of cesium was by wet deposition during heavy rainfall along the eastern coast of Sweden from Stockholm in the south to Umeå in the north, from afternoon of April 28 until April 30. It has been estimated that as much as about 10% of the total

[a]Occupational and Environmental Medicine, Department of Medical Sciences, Uppsala University, Uppsala, Sweden; [b]Occupational and Environmental Medicine, Uppsala University Hospital, Uppsala, Sweden; [c]Department of Medical Radiation Sciences, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; and [d]Medical Radiation Physics, Department of Translational Medicine, Lund University, Malmö, Sweden.

Supported by Uppsala County Council (1040418) through the Regional Agreement on Medical Training and Clinical Research (ALF) with Uppsala University.

The datasets generated and/or analyzed in our study are not publicly available due to privacy reasons and a nondisclosure agreement with the National Board of Health and Welfare providing us with the cancer diagnoses. We also have a binding statement with the Regional Ethics Committee in Uppsala to make the data on individual cancer diagnosis available exclusively to the research group at the Department of Medical Sciences, Uppsala University. These medical data are stored for 10 years according to the policy of Uppsala University for Medical Research Data. Data can only be made available to researchers who meet the criteria for access to confidential data following a decision by the Uppsala University Institutional Data Access Committee.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.environepidem.com).

*Corresponding Author. Address: Occupational and Environmental Medicine, Department of Medical Sciences, Uppsala University, SE-751 85 Uppsala, Sweden. E-mail: martin.tondel@medsci.uu.se (M. Tondel).

Environmental Epidemiology (2023) 7:e277

Received 10 July, 2023; Accepted 29 September, 2023

Published online 2 November 2023

DOI: 10.1097/EE9.0000000000000277

quantity of radioactive cesium released may have been deposited in Sweden.[3]

Overall, the deposition of ^{137}Cs was unequally distributed over Sweden up to more than 100 kBq/m^2 compared to the remaining deposition of ^{137}Cs from the atmospheric nuclear weapons tests of 2 to 3 kBq/m^2.[4,5] The Swedish Food Agency introduced an intervention level of ^{137}Cs at 300 Bq/kg to all foodstuff produced in Sweden or imported from May 16, 1986.[6] An additional intervention level of a maximum of 1,500 Bq/kg was introduced in 1987 for game and reindeer meat, wild berries, mushrooms, freshwater fish, and nuts sold to the public. Although these food items have relatively high levels of contamination, they constitute only a small part of the total food intake, and therefore lead to a small contribution to the yearly effective dose. The Swedish Food Agency concluded that the target for the effective dose to the population of 1 mSv/year could still be fulfilled even after introducing these new intervention levels for products from the forest ecosystem.[7,8] However, hunters and reindeer herders were identified as vulnerable groups as their lifestyle involves higher consumption of food products not purchased from shops. As a consequence, the Swedish Radiation Safety Authority, together with the Swedish Defence Research Agency (FOI), launched a program in 1996 to regularly monitor reindeer herders and hunters with whole-body counting to continue the time series of measurements conducted since 1960.[9,10]

Epidemiological studies on the incidence of cancer in Sweden after the Chernobyl NPP accident have been hampered by a lack of comprehensive methods to estimate the absorbed dose to different body organs, and the relation to cancer incidence. A positive association has been found in northern Sweden between the ground deposition of ^{137}Cs (kBq/m^2), and total cancer incidence, indicating that this could be used as a proxy for the absorbed dose, however, no relation with specific cancer sites was found.[11–13]

Following the Chernobyl NPP accident, a trend of increased thyroid cancer incidence was seen in children in Belarus and Ukraine, from 1990.[14,15] Later epidemiological studies confirmed that this increase in childhood thyroid cancer was related to the absorbed dose to the thyroid from the radioactive release after the accident, with an increased risk still 30 years after the Chernobyl accident.[16–22]

To explore the dose–response relationship between time-integrated external and internal dose to the population in Sweden after the Chernobyl NPP accident and site-specific cancer incidence, our research group has developed a method for dosimetry based on the nationwide measurement system within the municipalities introduced in 1990 and whole-body measurements in Sweden.[23–25] This dosimetric model has been applied in a recent study to investigate cancer incidence in a nested case-control study in a closed cohort restricted to adult males in northern Sweden where the exposure resulting from the Chernobyl NPP accident was highest. The average dose to the colon in this study was found to be 1.77 mGy for cancer cases, compared to 1.73 mGy in controls. Cancers previously associated with radiation exposure were lumped together in a category named organ-specific cancer (stomach, colon, liver, lung, prostate, urinary bladder, thyroid, and leukemia) showing an adjusted hazard ratio (HR) of 1.019 (95% CI = 1.014, 1.024) per mGy during the follow-up period of 1991 to 2015.[26]

We have now expanded this study to include females and children and have extended the follow-up period by 5 years to December 31, 2020. Moreover, we have refined our radiation dose model so that it is now possible to estimate the absorbed dose to each body organ.[27] Of special interest are birth cohort analyses of thyroid cancer, which have not been done previously in Sweden. We have thus included the contribution of ^{131}I by inhalation and the ingestion of milk when assessing the absorbed dose to the thyroid. Hence, the main aim of our study was to examine the dose–response relationship in greater detail, than in previous studies, in deciles, as well as the adjusted HR per mGy, and to include sex-specific birth cohort analyses.

MATERIAL AND METHODS

Population

The study base was all individuals living in the 9 most northern counties of Sweden (Norrbotten, Dalarna, Södermanland, Jämtland, Västmanland, Gävleborg, Västerbotten, Uppsala, and Västernorrland) in 1986 (n = 2,230,549) provided by Statistics Sweden (SCB). As all individuals in Sweden have a unique personal identity number, this information can be linked to other registers maintained by SCB to obtain annual individual information on dwelling coordinates, rural/nonrural habitat, county, family identity, date of emigration, and date of death. The Swedish National Land Survey has assigned each inhabitant in Sweden annually updated dwelling coordinates that can linked to the digital deposition map of ^{137}Cs to obtain an individual value of the deposition of ^{137}Cs at each dwelling location. SCB has defined rural and nonrural (including urban) areas since 1960, and this definition is updated every fifth year by SCB. A rural area is defined as a population center with fewer than 200 inhabitants, where a population center is defined as a congregation of buildings where the greatest distance between buildings is 200 meters.[28] As a consequence, rural areas are very sparsely populated areas and nonrural areas include both urban and semiurban areas.

All hunters in Sweden require a license for their hunting weapon, which is issued and registered by the Swedish National Police Agency. Using the individual's personal identity number, SCB could link this hunter register from 1986 for all adults ≥18 years of age to the population register each year, until December 31, 2020. The population register also contains information on others in the same household (family identity). On April 28, 1986, 41,288 hunter households (120,033 individuals) and 899,915 nonhunter households (1,984,068 individuals) were identified. Any person living in a household including at least one hunter, was defined as belonging to the hunter household category, until not living together, that is, did not hold the same family identity any longer.

On April 28, 1986, the final closed cohort available for analysis included 2,104,101 individuals (1,055,017 males and 1,049,084 females) after excluding duplicates of reused personal identity numbers (n = 1,440), those missing information on dwelling coordinates (n = 10,598), children born from April 29 to December 31, 1986 (n = 17,044), those with a cancer diagnosis between 1958 and April 27, 1986 (n = 45,862) and those with missing information on family identity (n = 52,007), with or without a combination of these excluding factors (Figure 1).

Exposure Assessment

The time-integrated total absorbed organ dose (mGy) from 1986 and onward was calculated for each individual up to the year of first cancer diagnosis, death, or emigration, whichever was first, or up to December 31, 2020, being alive without cancer. The dose was calculated in the same way for cancer cases and controls. A manual explaining the method of dose assessment has been published separately, to the benefit of other users, and the method is therefore only schematically presented in Figure 2.[29] The program code in R is also available (https://github.com/absorbedDose/absorbedDose).

The absorbed organ doses were calculated based on published absorbed dose rate coefficients and were validated by published observations from the literature. Examples of the validation of model estimates for ^{131}I-intakes via dairy milk and the inhalation of ^{131}I from the Chernobyl cloud in Sweden can be found in Rääf et al, where the model estimates and reported

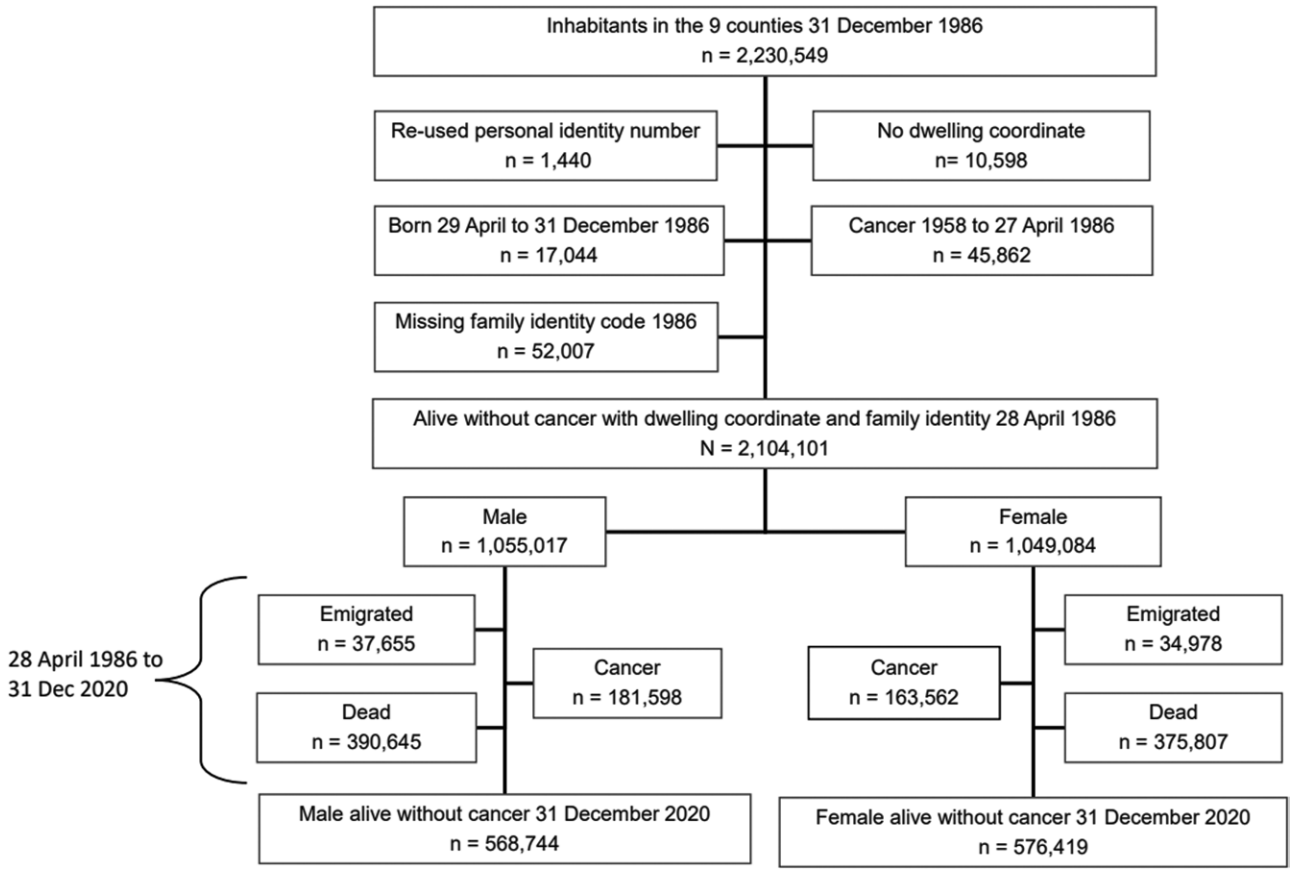

Figure 1. Flow-chart of the population included in the study.

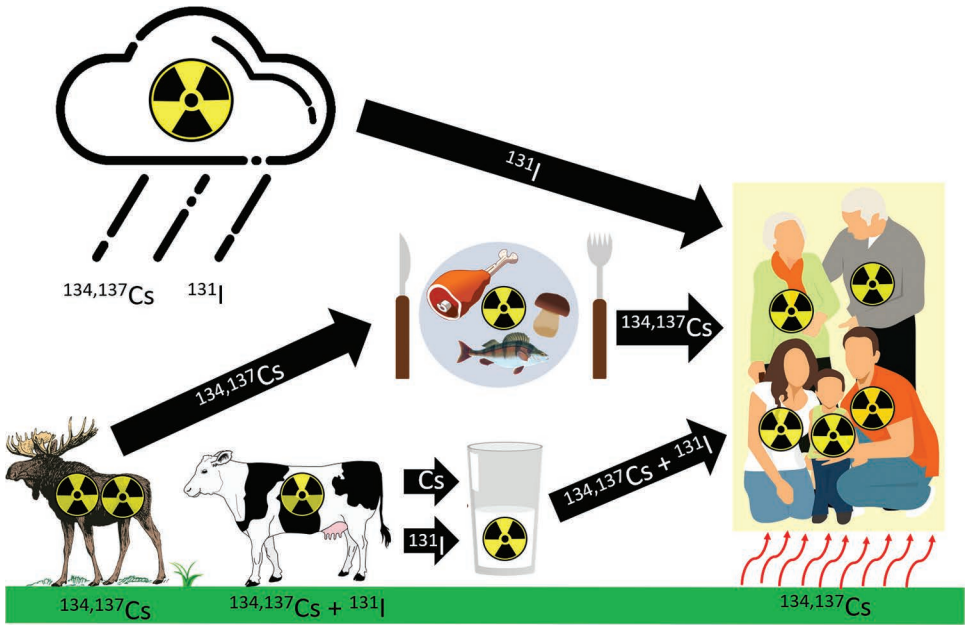

Figure 2. The absorbed organ dose consists of two contributions: external exposure and internal exposure. The external exposure is due to radiation from radioactive elements in the air and on the ground. The internal exposure is due to the inhalation of radioactive elements in the air, and the ingestion of contaminated foodstuffs.[29]

measurements agreed within a factor of two.[24] For radioactive cesium isotopes, the transfer model relating the county average of the deposited cesium activity was originally derived from whole-body measurements.[30] We have found that whole-body

contents of ^{137}Cs reported for rural inhabitants in Russia correspond with our model predictions for Swedish populations, again within a factor of two. Furthermore, the values for rural inhabitants of Russia fall between the values predicted for Swedish hunters and Swedish urban residents.[31] Later comparisons with data from Finland and Norway show that the model is also applicable to these geographical regions.[32] Finally, regarding the radiation dose due to external gamma radiation from the ground deposition of radioactive cesium isotopes and other more short-lived fission products from the Chernobyl fallout, our model was discussed and compared with experimentally determined retrospective dose assessments in construction materials in buildings in rural settlements in the areas affected by the Chernobyl fallout in Russia.[23]

Cancer Statistics

The National Board of Health and Welfare has collected details of all incident cases of cancer in Sweden in the National Cancer Registry since 1958, consistently coded according to the International Classification of Diseases, version 7. The National Cancer Institute (NCI) in the United States has identified 16 cancer sites associated with ionizing radiation in males and 18 cancer sites in females.[33] Since our latest publication, the NCI has added the central nervous system, gall bladder, kidneys, esophagus, oral cavity and pharynx, pancreas, and rectum to the list of radiation-associated cancers.[26] Therefore, we developed absorbed dose rate coefficients for all these radiation-associated cancer sites, together with a radiation-associated remainder category.[27] The unique Swedish personal identity number in the population register at Statistics Sweden made it possible, by register linkage, to obtain annual updated information on incident cancer diagnosis in each person from the National Cancer Registry at the National Board of Welfare up to 2020. As the National Cancer Registry was started in 1958, it was possible to exclude cancer diagnoses before start of follow-up on April 28, 1986, to avoid cancer-prone individuals or cancer treatment (cytostatic drugs and radiation treatment) from obfuscating a potential relationship to the absorbed organ dose.

Statistical Methods

As we analyzed the absorbed organ dose for each cancer site, we applied three latency periods: 2 years for leukemia with a follow-up period from January 1, 1988, to December 31, 2020, 3 years for thyroid cancer (January 1, 1989, to December 31, 2020), and 5 years for all solid cancers (January 1, 1991, to December 31, 2020) as suggested by the World Health Organization.[34] As in our previous study, a nested case-control methodology was chosen due to the protracted dose during the follow-up period.[26] However, due to the use of three different latency periods applied, we had to use three study bases to randomly retrieve controls; January 1, 1988 (for leukemia cases), January 1, 1989 (for thyroid cancer), and January 1, 1991 (for solid cancers). For each incident cancer case, four living controls were matched for sex, year of diagnosis, and year of birth ± 2 years. At the start of each of the follow-up period, we removed individuals with a previous cancer diagnosis. To treat the controls in the same way, a new control was randomly chosen if a control had a diagnosis of cancer prior to that of the cancer case. Hence, for males 161,325 cases and 645,299 controls (we failed to find four controls for one male case) and for females 144,439 cases and 577,756 controls were included

Table 1.

Number of incident cancer cases (n) in the 9 counties considered in the analysis, and the relevant follow-up time after the Chernobyl nuclear NPP accident in 1986

		Follow-up period	Males		Females	
Cancer site	**ICD-7**		**n**	**%**	**n**	**%**
Breast	170, 1701, 1702, 1707, 1708, 1709	1991–2020	214	0.13	40665	28.15
Central nervous system	1921, 1930, 1931, 1938, 1939	1991–2020	3658	2.27	4184	2.90
Colon	1530, 1531, 1532, 1533, 1534, 1536, 1538, 1539	1991–2020	10954	6.79	11558	8.00
Gall bladder	1551	1991–2020	432	0.27	1169	0.81
Kidney	1800, 1809	1991–2020	3793	2.35	2567	1.78
Leukemia	2040, 2044, 2047, 2049, 2050, 2051, 2059, 2060, 2061, 2069, 2070, 2071, 2072, 2073, 2079	1988–2020	2540	1.57	2049	1.42
Liver	1550	1991–2020	2040	1.26	1173	0.81
Lung	1620, 1621	1991–2020	10612	6.58	9478	6.56
Lymphoma	2001, 2002, 2003, 201, 2021, 2022	1988–2020	6667	4.13	5245	3.63
Esophagus	1500, 1508, 1509	1991–2020	1844	1.14	689	0.48
Oral cavity and pharynx	1400, 1401, 1408, 1409, 1410, 1417, 1418, 1419, 1420, 1425, 1426, 1428, 1429, 143, 144, 146, 147, 148, 1450, 1457, 1458, 1459	1991–2020	3111	1.93	1994	1.38
Other leukemias*	2024, 203, 2041, 208, 209	1988–2020	5388	3.34	4107	2.84
Ovaries	175, 1750, 1751, 1758, 1759	1991–2020	0	0.00	5018	3.47
Pancreas	157	1991–2020	3248	2.01	3458	2.39
Prostate	177	1991–2020	58216	36.09	0	0.00
Rectum	1540, 1541, 1548	1991–2020	7278	4.51	5397	3.74
Remainder	all other ICD-7 codes	1991–2020	26688	16.54	25514	17.66
Stomach	151, 1510, 1511, 1518, 1519	1991–2020	4065	2.52	2553	1.77
Thyroid	194	1989–2020	642	0.40	1575	1.09
Urinary bladder	1810, 1816	1991–2020	9935	6.16	3279	2.27
Uterus	171, 172, 174	1991–2020	0	0.00	12767	8.84
All sites combined	140–209		161325	100.00	144439	100.00

Cancer sites are coded using the International Classification of Diseases, version 7 (ICD-7). Latency periods of 2–5 years were used, as suggested by the World Health Organization.

*Hairy cell leukemia, chronic lymphatic leukemia, multiple myeloma, myelofibrosis, polycytemia vera.

in the statistical analysis, Table 1. Thus, cancer cases and controls could be treated identically when calculating the duration of exposure.

We calculated HRs with 95% confidence intervals (95% CI) through conditional logistic regression using the Cox proportional hazard survival model with strata for date of diagnosis in the statistical package SAS, version 9.4. HRs were calculated in deciles based on the number of cancer cases at each cancer site using the absorbed dose in that organ for cases and controls, using the first decile as the reference category. The results are presented in graphs as the average absorbed dose to that organ in each decile. For all cancer sites considered together, an absorbed total-body dose was calculated using the external absorbed organ dose rate coefficient for the colon to represent the whole body, and for the internal absorbed body dose, an averaged value over all organ dose rate coefficients was used.[29] The intention of creating deciles at each cancer site for each sex was to obtain equally large CIs in all deciles. However, as a consequence of the dose distribution, the dose intervals were narrower in the lower deciles and the broadest dose interval was found in the uppermost decile due to more sparse data. HRs were also calculated using a linear model with total absorbed organ dose per mGy as a continuous variable, expressed as HR per mGy. The material was also divided into birth cohorts: 0 to 19, 20 to 39, 40 to 59 and ≥60 years of age in 1986.

As each cancer case was matched to four controls for year of birth, age was not considered to assert confounding (crude HR). Urban lifestyle, socioeconomic status, and pre-Chernobyl cancer incidence by cancer site were considered as potential confounding factors (adjusted HR). Urban lifestyle defined as rural/nonrural habitat is a crude way of including ambient air pollution, occupational exposure, and food habits, whereas socioeconomic status is classified by level of education. Likewise, educational level is an indirect measure of an aggregate of risk factors for cancer, including tobacco smoking, occupational exposure, and nonspecific lifestyle factors. Habitat in 1986 (rural/nonrural) and socioeconomic status, defined as the highest educational level attained during follow-up, were included in the model, Table 2. The average pre-Chernobyl cancer incidence by county and sex from 1980 to 1985 was included in the model to adjust for potential regional confounding, using data retrieved from the National Board of Health and Welfare database (https://sdb.socialstyrelsen.se/if_can/val.aspx). The pre-Chernobyl cancer incidence by county is presented in Tables 3 and 4.

Our study was approved by the Regional Ethics Committee in Uppsala (Reg. No. 2014/184 with the extension Reg. No. 2014/184/1).

RESULTS

The incident cancer cases included in our study (n = 305,764) are presented with the relevant follow-up period in Table 1. The variables used in the regression models are presented in Tables 2, 3 and 4. Habitat and educational levels were slightly skewed between the sexes. The mean absorbed dose to the whole body was higher for males than for females. For all cancer sites combined, the mean absorbed dose for all male cases (1.53 mGy) was higher than for their controls (1.48 mGy), and the findings were similar for females: 1.21 mGy versus 1.19 mGy, respectively, Tables 5 and 6.

The mean absorbed dose to male organs was higher in cases than in their controls, except for lymphoma and the thyroid gland, Table 5. This can be explained by a higher contribution from internal dose for males compared to females. In females, the mean absorbed dose to the central nervous system, liver, lungs, lymphoma, remainder, and stomach was slightly higher in the controls than in the cancer cases, Table 6.

The adjusted HR per mGy was slightly lower than the crude HR per mGy for most cancer sites, indicating a weak positive confounding effect. The adjusted HR per mGy for all sites combined was higher for males, 1.027 (95% CI = 1.022, 1.031), than for females, 1.011 (95% CI = 1.006, 1.017). The adjusted HR per mGy was significantly increased for cancer in the gall bladder, lungs, pancreas, and prostate in males, respectively, and in females for cancer in the breast, pancreas, and other leukemias, respectively. Cancer sites not known to be associated with radiation (male breast, lymphoma, other leukemias) showed nonsignificant adjusted HR per mGy, except for other leukemias in females, where a higher adjusted HR per mGy of 1.034 (95% CI = 1.002, 1.067) was found. Considering the upper CI, no cancer site showed an adjusted HR significant less than 1.000, Tables 7 and 8.

The dose–response curves for the cancer sites with deciles, support the use of a linear function, as more rare cancers show a higher uncertainty in each risk estimate by deciles (male breast, male gall bladder, female esophagus, and male thyroid cancer), Figure S1; http://links.lww.com/EE/A246.

The results of the birth cohort analyses showed a higher mean total-body dose for all cancer sites combined in all age groups, except for females 0 to 19 years of age in 1986 (Table 9; Figure 3) The adjusted HR per mGy, in all cancer sites combined, was not increased in the age cohort 0–19 years, but a tendency toward a higher adjusted HR per mGy was seen with aging cohorts in both sexes (Figure 3).

Age cohort analyses were also performed for thyroid cancer. In the cohort aged 0 to 19 years (in 1986) an adjusted HR per mGy of 0.950 (95% CI = 0.772, 1.171) for males was shown and 0.948 (95% CI = 0.868, 1.035) for females. No significant adjusted HRs per mGy were seen for thyroid cancer in the other birth cohorts in either of the sexes (data not shown). Across all ages, the adjusted HRs for thyroid cancer per mGy were 0.976 (95% CI = 0.897, 1.061) in males and 1.015 (95% CI = 0.966, 1.066) in females, Table 7 and 8.

Table 2.

Variables used in the regression model to adjust for confounding

		Males				Females			
		Cases		Controls		Cases		Controls	
		n	%	n	%		%		%
Habitat 1986	Rural	39670	24.59	165391	25.63	31322	21.69	128334	22.21
	Nonrural	121655	75.41	479908	74.37	113117	78.31	449422	77.79
	Total	161325	100.00	645299		144439	100.00	577756	100.00
Highest level of education 1986–2020	Low (≤9 y)	67519	41.85	273183	42.33	56146	38.87	219666	38.02
	Intermediate (10–12 y)	58338	36.16	234273	36.30	52034	36.02	211427	36.59
	High (>12 y)	28660	17.77	113337	17.56	29502	20.43	121854	21.09
	Missing	6808	4.22	24506	3.80	6757	4.68	24809	4.29
	Total	161325	100.00	645299	100.00	144439	100.00	577756	100.00

Table 3.

The 6-year average male cancer incidence expressed as 100,000/year in each of the 9 counties pre-Chernobyl (1980–1985) used in the regression model to adjust for confounding

	County								
Male cancer site	**Uppsala**	**Södermanland**	**Västmanland**	**Dalarna**	**Gävleborg**	**Västernorrland**	**Jämtland**	**Västerbotten**	**Norrbotten**
Breast	0.39	0.80	0.68	1.05	0.46	0.51	0.73	0.54	0.62
Central nervous system	11.77	15.70	14.41	14.01	13.63	11.70	11.73	15.49	10.52
Colon	28.08	29.57	27.17	25.57	29.43	34.06	30.81	31.24	17.21
Gall bladder	2.46	4.13	1.63	3.51	4.01	4.29	2.44	2.59	2.23
Kidney	13.19	18.12	19.85	19.14	19.12	21.64	21.03	15.63	13.48
Leukemia	7.00	7.86	7.21	7.12	8.02	8.18	7.59	8.83	7.78
Liver	4.79	3.73	6.39	6.89	8.81	7.79	7.83	6.39	7.04
Lung	37.30	54.33	49.89	45.19	48.55	42.34	31.04	30.31	35.23
Lymphoma	14.99	15.85	15.62	12.96	15.92	15.85	17.36	16.58	16.34
Esophagus	4.27	2.93	3.40	5.25	7.43	4.52	2.69	3.12	2.85
Oral cavity and pharynx	7.90	9.32	9.65	7.12	10.99	11.43	12.23	7.88	9.89
Other leukemias*	15.62	13.72	13.32	12.95	14.43	14.22	16.87	20.38	14.73
Pancreas	17.97	16.78	15.09	16.22	19.00	19.34	17.11	16.58	12.49
Prostate	103.78	158.42	91.94	99.21	97.04	109.07	113.46	95.38	74.10
Rectum	17.45	20.12	19.83	21.94	21.64	21.74	17.37	22.14	13.35
Remainder	57.66	67.62	64.31	59.44	70.88	64.92	64.05	54.21	46.05
Stomach	28.98	27.43	26.62	28.13	30.41	36.60	30.32	33.42	31.30
Thyroid	1.95	3.20	2.45	1.75	2.30	1.63	1.71	2.72	3.46
Urinary bladder	29.88	29.18	26.50	24.40	26.09	27.94	29.35	25.41	23.50
All sites combined	403.65	496.79	414.45	409.87	447.24	454.98	432.05	407.75	341.04

*Hairy cell leukemia, chronic lymphatic leukemia, multiple myeloma, myelofibrosis, polycytemia vera.

Table 4.

The 6-year average female cancer incidence expressed as 100,000/year in each of the 9 counties pre-Chernobyl (1980–1985) used in the regression model to adjust for confounding

	County								
Female cancer site	**Uppsala**	**Södermanland**	**Västmanland**	**Dalarna**	**Gävleborg**	**Västernorrland**	**Jämtland**	**Västerbotten**	**Norrbotten**
Breast	88.51	101.25	89.44	125.80	87.61	98.78	111.55	91.32	68.83
Central nervous system	14.59	14.14	15.48	12.70	11.94	13.67	11.50	13.26	11.50
Colon	31.99	36.44	31.21	30.05	32.38	37.80	29.76	31.97	20.68
Gall bladder	10.69	9.51	6.29	11.53	10.00	8.38	8.51	7.93	6.00
Kidney	12.21	13.73	14.38	15.49	15.91	13.52	12.51	13.13	10.34
Leukemia	5.33	5.41	6.03	7.81	6.93	5.76	8.50	6.69	5.11
Liver	6.09	5.68	5.20	5.71	5.91	4.89	5.00	4.52	4.47
Lung	15.48	17.83	17.80	15.14	12.39	15.16	11.26	11.88	10.99
Lymphoma	12.07	11.62	13.42	14.33	13.53	13.15	8.75	9.84	10.08
Esophagus	2.68	2.38	1.51	2.21	2.62	1.88	3.25	1.91	1.92
Oral cavity and pharynx	3.69	4.49	6.58	5.47	5.45	7.27	3.00	6.01	3.96
Other leukemias*	8.90	8.45	8.49	12.11	8.64	11.78	11.75	17.34	12.14
Ovaries	17.05	22.44	25.62	23.76	21.47	23.28	19.76	24.07	19.79
Pancreas	16.90	16.24	16.83	15.84	16.36	17.03	13.51	15.71	14.81
Rectum	18.02	16.77	14.24	17.82	17.74	19.67	13.01	17.50	10.09
Remainder	59.41	61.92	59.85	54.27	72.62	57.72	66.78	54.50	52.36
Stomach	17.14	16.37	18.21	18.52	16.25	22.03	17.01	20.35	16.35
Thyroid	6.37	5.15	6.97	4.66	4.55	5.25	5.25	7.52	5.11
Urinary bladder	9.16	8.59	9.32	8.39	7.84	8.39	8.76	8.19	6.26
Uterus	33.64	40.52	43.83	36.45	39.66	37.31	36.27	32.93	24.02
All sites combined	389.01	417.96	409.74	437.13	409.43	422.07	404.20	395.88	314.26

*Hairy cell leukemia, chronic lymphatic leukemia, multiple myeloma, myelofibrosis, polycytemia vera.

Post hoc Analysis

A post hoc analysis of all cancer sites combined in males showed that the relatively high adjusted HR per mGy of 1.027 (95% CI = 1.022, 1.031) could be explained by the contribution from the internal dose, with a HR per mGy of 1.058 (95% CI = 1.050, 1.065). For females, the contribution from internal dose to all cancer sites combined seemed to be of minor importance, as the internal adjusted HR per mGy of 1.029 (95% CI = 1.014, 1.044) did not influence the overall risk estimate of 1.011 (95% CI = 1.006, 1.017). The same pattern remained in the analysis after removing all households ever being classified as a hunter household during the entire period from 1986 to 2020. Therefore, a post hoc analysis was performed in which all individuals living in the two counties with the lowest radioactive fallout after the Chernobyl NPP accident in 1986 at baseline (Norrbotten and Dalarna counties) were removed. The mean total-body dose for all cancer sites combined increased, but the difference between cases and controls was smaller: in males 1.89 versus 1.86 mGy, respectively and in females 1.49 versus 1.50 mGy, respectively. The results of the post hoc analysis are given in Post hoc analysis, Tables 1–5; http://links.lww.com/EE/A247.

Table 5.

Total absorbed organ dose in males, including external exposure (^{134}Cs, ^{137}Cs, short-lived nuclides), internal exposure (^{134}Cs, ^{137}Cs) and for the absorbed dose to the thyroid, also ^{131}I through inhalation and ingestion of milk

		Total organ dose (mGy)						
Male cancer site		**Mean**	**SD**	**Median**	**p5**	**p95**	**Min**	**Max**
Breast	Case	1.678	1.561	1.158	0.266	4.561	0.159	9.849
	Control	1.623	1.494	1.143	0.258	4.578	0.154	11.694
Central nervous system	Case	1.179	1.126	0.746	0.172	3.438	0.103	8.739
	Control	1.165	1.127	0.737	0.173	3.479	0.043	8.099
Colon	Case	1.358	1.249	0.936	0.203	3.841	0.083	10.460
	Control	1.299	1.214	0.877	0.194	3.683	0.068	9.653
Gall bladder	Case	1.228	1.157	0.803	0.165	3.453	0.114	7.198
	Control	1.075	1.023	0.698	0.175	3.155	0.106	8.139
Kidney	Case	1.453	1.329	1.022	0.222	4.012	0.124	9.504
	Control	1.417	1.298	0.987	0.213	4.008	0.080	9.662
Leukemia	Case	1.587	1.526	1.109	0.230	4.620	0.086	11.993
	Control	1.517	1.441	1.048	0.220	4.268	0.074	13.075
Liver	Case	1.380	1.305	0.967	0.198	3.881	0.121	10.155
	Control	1.362	1.262	0.927	0.206	3.868	0.063	9.505
Lung	Case	1.569	1.459	1.081	0.233	4.390	0.096	10.746
	Control	1.525	1.428	1.044	0.227	4.351	0.081	11.820
Lymphoma	Case	1.412	1.345	0.995	0.206	4.088	0.080	10.379
	Control	1.433	1.352	0.992	0.207	4.092	0.077	11.410
Esophagus	Case	1.149	1.085	0.750	0.173	3.307	0.081	6.352
	Control	1.140	1.078	0.755	0.171	3.256	0.050	7.811
Oral cavity and pharynx	Case	1.223	1.149	0.809	0.185	3.543	0.081	8.878
	Control	1.220	1.179	0.776	0.180	3.597	0.072	7.960
Other leukemias*	Case	1.494	1.367	1.075	0.213	4.161	0.075	11.291
	Control	1.457	1.354	1.020	0.215	4.072	0.070	11.595
Pancreas	Case	1.501	1.354	1.095	0.213	4.065	0.083	10.158
	Control	1.371	1.280	0.951	0.205	3.927	0.096	10.415
Prostate	Case	1.507	1.377	1.029	0.223	4.243	0.065	10.875
	Control	1.438	1.346	0.957	0.217	4.128	0.060	10.785
Rectum	Case	1.441	1.336	0.997	0.219	4.080	0.114	9.975
	Control	1.401	1.315	0.963	0.211	3.941	0.069	11.428
Remainder	Case	1.754	1.581	1.316	0.275	4.748	0.114	14.332
	Control	1.717	1.585	1.254	0.260	4.750	0.120	15.204
Stomach	Case	1.278	1.224	0.839	0.176	3.652	0.072	9.455
	Control	1.237	1.172	0.819	0.185	3.584	0.065	8.796
Thyroid	Case	1.405	1.100	1.046	0.257	3.485	0.152	7.095
	Control	1.476	1.179	1.102	0.260	3.736	0.160	8.091
Urinary bladder	Case	1.275	1.183	0.859	0.192	3.630	0.071	7.988
	Control	1.239	1.163	0.824	0.185	3.551	0.057	8.519
All sites combined	Case	1.534	1.401	1.105	0.230	4.245	0.073	12.587
	Control	1.480	1.371	1.045	0.223	4.143	0.066	12.471

*Hairy cell leukemia, chronic lymphatic leukemia, multiple myeloma, myelofibrosis, polycytemia vera.

The dose–response curves for the different cancer sites were flattened, in the deciles, in both sexes, but also a weaker slope was noticed, expressed as HR per mGy, Post hoc analysis, eFigure 1; http://links.lww.com/EE/A248. However, a significant adjusted HR per mGy remained, after removing Norrbotten and Dalarna counties, for cancer in the pancreas 1.058 (95% CI = 1.018, 1.099), prostate 1.013 (95% CI = 1.005, 1.021), and lungs 1.017 (95% CI = 1.000, 1.035) in males. Two new sites emerged in males with statistically significant adjusted HR per mGy: colon cancer, 1.035 (1.012, 1.058) and stomach cancer, 1.077 (1.034, 1.123), respectively. In females, no significant increased adjusted HR per mGy remained, but lymphoma 1.039 (1.005, 1.074) and esophagus cancer 1.126 (1.018, 1.245) emerged in the 7 counties studied, compared with the results of the analysis for all 9 counties. For all cancer sites combined, the adjusted HR per mGy was 1.014 (1.009, 1.019) in males and 1.000 (0.994, 1.006) in females, respectively; Post hoc analysis, Table 6–8 and Post hoc analysis, Figure 2; http://links.lww.com/EE/A247.

DISCUSSION

To the best of our knowledge, this is the first study to present cancer-site-specific risk estimates, expressed as HRs per mGy, based on absorbed doses to individual body organs for a population exposed to the Chernobyl fallout. Despite our attempt to adjust for pre-Chernobyl cancer incidence, remaining unadjusted confounding that was revealed in our post hoc analysis. We therefore consider our risk estimates from our post hoc analysis to be more reliable. Comparing the analysis of 9 versus 7 counties, significant adjusted HR for all cancer sites combined remained in males, but not in females. Taking into account both the adjusted HR per mGy and the results of the analysis in deciles, our results in the post hoc analysis, suggest an association between the low-dose radiation from the Chernobyl NPP accident and colon cancer, pancreas cancer, and stomach cancer in males, respectively, but only lymphoma in females. However, there could still be remaining uncontrolled confounding resulting from hunter lifestyle, inherent in our dose assessment model, that we could not quantify in relation to the increasing absorbed doses to hunters living in the counties with the highest fallout from the Chernobyl NPP accident.

Epidemiological cancer research following the Chernobyl NPP accident aimed at estimating the effects of protracted radiation exposure has often relied only on the external absorbed dose, ignoring the contribution from the internal dose.[11–13,26,35]

Table 6.

Total absorbed organ dose in females, including external exposure (^{134}Cs, ^{137}Cs, short-lived nuclides), internal exposure (^{134}Cs, ^{137}Cs) and for the absorbed dose to the thyroid, also ^{131}I through inhalation and ingestion of milk

		Total organ dose (mGy)						
Female cancer site		**Mean**	**SD**	**Median**	**p5**	**p95**	**Min**	**Max**
Breast	Case	1.109	1.096	0.676	0.160	3.302	0.022	8.973
	Control	1.090	1.094	0.642	0.158	3.284	0.019	9.758
Central nervous system	Case	1.085	1.086	0.655	0.160	3.303	0.089	7.811
	Control	1.087	1.080	0.644	0.160	3.300	0.044	7.348
Colon	Case	1.144	1.053	0.757	0.175	3.200	0.077	7.707
	Control	1.111	1.058	0.710	0.171	3.233	0.050	9.009
Gall bladder	Case	1.092	1.049	0.667	0.157	3.254	0.104	6.638
	Control	1.030	1.013	0.613	0.150	3.041	0.063	6.561
Kidney	Case	1.207	1.135	0.797	0.178	3.446	0.056	7.249
	Control	1.163	1.095	0.763	0.176	3.338	0.060	8.529
Leukemia	Case	1.262	1.151	0.887	0.191	3.570	0.085	8.631
	Control	1.234	1.182	0.815	0.184	3.640	0.049	8.886
Liver	Case	1.127	1.070	0.728	0.173	3.295	0.100	6.500
	Control	1.129	1.074	0.723	0.171	3.311	0.089	7.422
Lung	Case	1.281	1.189	0.864	0.200	3.680	0.080	8.585
	Control	1.295	1.219	0.844	0.195	3.718	0.049	8.944
Lymphoma	Case	1.178	1.102	0.794	0.169	3.465	0.058	7.413
	Control	1.183	1.119	0.789	0.171	3.430	0.024	9.280
Esophagus	Case	1.034	1.015	0.627	0.152	3.206	0.099	6.118
	Control	1.009	0.980	0.626	0.152	2.935	0.044	6.474
Oral cavity and pharynx	Case	1.113	1.090	0.678	0.167	3.284	0.096	7.307
	Control	1.112	1.111	0.669	0.166	3.337	0.041	8.511
Other leukemias*	Case	1.206	1.129	0.828	0.178	3.492	0.058	8.417
	Control	1.160	1.098	0.773	0.172	3.370	0.064	8.756
Ovaries	Case	1.088	1.042	0.702	0.161	3.165	0.039	9.237
	Control	1.061	1.026	0.669	0.159	3.152	0.042	8.029
Pancreas	Case	1.261	1.131	0.860	0.185	3.449	0.106	6.945
	Control	1.169	1.104	0.769	0.178	3.389	0.048	8.767
Rectum	Case	1.163	1.064	0.788	0.179	3.294	0.082	8.333
	Control	1.134	1.074	0.740	0.172	3.304	0.042	8.855
Remainder	Case	1.480	1.302	1.091	0.234	4.033	0.094	11.793
	Control	1.484	1.341	1.069	0.227	4.118	0.081	14.228
Stomach	Case	1.075	1.032	0.686	0.156	3.074	0.101	6.483
	Control	1.082	1.048	0.682	0.158	3.169	0.087	7.617
Thyroid	Case	1.507	1.147	1.188	0.247	3.703	0.155	8.378
	Control	1.472	1.159	1.125	0.249	3.727	0.156	9.241
Urinary bladder	Case	1.087	1.043	0.691	0.164	3.195	0.079	9.495
	Control	1.067	1.022	0.658	0.159	3.077	0.044	8.093
Uterus	Case	1.042	0.980	0.688	0.156	3.006	0.043	7.692
	Control	1.030	0.991	0.655	0.153	3.036	0.034	8.970
All sites combined	Case	1.210	1.109	0.829	0.184	3.410	0.050	10.565
	Control	1.194	1.115	0.796	0.180	3.418	0.023	10.052

*Hairy cell leukemia, chronic lymphatic leukemia, multiple myeloma, myelofibrosis, polycytemia vera.

In only a few epidemiological studies have attempts been made to estimate the absorbed dose resulting from internal contamination, for example, populations near the Semipalatinsk nuclear weapons testing site in Kazakhstan and in the Techa River Cohort in Russia. A study on the population living near Semipalatinsk (n = 19,545), with an average dose of 634 mSv, showed a significant dose–response relationship for solid cancers in 1960 to 1999, based on individual dose estimates, including exposure from the internal dose. Age at main exposure was analyzed in three age groups (0–19, 20–39, and ≥40 years) showing age-category specific relative risks of all solid tumors of 1.22 (95% CI = 0.98, 1.48), 2.22 (95% CI = 1.95, 2.52), and 2.46 (95% CI = 2.11, 2.84), respectively.[36] In our study, we also found an increase in cancer risk with increasing age at exposure: that is, an elevated HR per mGy for all cancer combined in males ≥40 years of age, and in females ≥60 years of age (post hoc analysis; Figure 2). These results contradict the general understanding that the excess relative cancer risk is higher following exposure to the same radiation dose at a younger age than later in life.[37] However, this belief has been challenged in a later study on the Japanese atomic bomb survivors (Life Span Study), showing that the most radiation-induced cancer risks do not, as often assumed, decrease with increasing age at exposure. This observation suggests a promotional processes in radiation carcinogenesis in the middle age compared to a more important cancer initiation process at younger age.[38] In the latest evaluation of biological mechanisms, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) suggests that at very low doses of ionizing radiation, the cancer promotive effect through the production of reactive oxygen species might predominate in the carcinogenesis.[39] We have also hypothesized that a late-stage cancer promotor effect might have explained the relatively short latency period observed in our first follow-up studies in Sweden after the Chernobyl NPP accident.[11,12]

An increase in the incidence in colon cancer was seen in females in Finland after the Chernobyl NPP accident, showing an excess rate ratio of 0.06 (95% CI = 0.02, 0.11) per mSv, but not for other cancer sites.[35] In our post hoc analysis the adjusted HR per mGy for colon cancer was 1.015 (95% CI = 0.992, 1.038) in females and 1.035 (95% CI = 1.012, 1.058) in males. The follow-up time in the Finnish study was

Table 7.

Hazard ratio per milliGray absorbed dose (HR per mGy) with 95% confidence intervals (95% CI) in males

Male cancer site	Radiation associated	Crude HR per mGy (95% CI)	Adj HR per mGy (95% CI)
Breast	No	1.024 (0.928–1.131)	1.060 (0.941–1.196)
Central nervous system	Yes	1.011 (0.979–1.044)	1.017 (0.985–1.051)
Colon	Yes	1.041 (1.023–1.059)	1.017 (0.996–1.038)
Gall bladder	Yes	1.142 (1.038–1.256)	1.155 (1.045–1.277)
Kidney	Yes	1.022 (0.994–1.050)	1.015 (0.987–1.044)
Leukemia	Yes	1.034 (1.004–1.066)	1.031 (0.998–1.064)
Liver	Yes	1.012 (0.974–1.051)	1.010 (0.970–1.051)
Lung	Yes	1.022 (1.007–1.037)	1.029 (1.014–1.045)
Lymphoma	No	0.988 (0.968–1.009)	0.986 (0.965–1.007)
Esophagus	Yes	1.007 (0.961–1.056)	0.988 (0.939–1.039)
Oral cavity and pharynx	Yes	1.002 (0.969–1.036)	1.014 (0.978–1.051)
Other leukemias*	No	1.021 (0.998–1.044)	1.003 (0.981–1.027)
Pancreas	Yes	1.079 (1.049–1.111)	1.072 (1.034–1.112)
Prostate	Yes	1.038 (1.032–1.045)	1.040 (1.033–1.046)
Rectum	Yes	1.023 (1.004–1.043)	1.004 (0.984–1.025)
Remainder	Yes	1.015 (1.006–1.023)	1.002 (0.993–1.011)
Stomach	Yes	1.030 (1.000–1.060)	1.001 (0.967–1.037)
Thyroid	Yes	0.946 (0.875–1.022)	0.976 (0.897–1.061)
Urinary bladder	Yes	1.027 (1.008–1.046)	1.016 (0.997–1.036)
All sites combined		1.029 (1.025–1.033)	1.027 (1.022–1.031)

Follow-up times according to Table 1. HR is adjusted for urban lifestyle, socioeconomic status and average pre-Chernobyl cancer incidence 1980–1985 by cancer site (adj HR per mGy). Radiation-associated cancer classified according to BEIR VII and NCI.

*Hairy cell leukemia, chronic lymphatic leukemia, multiple myeloma, myelofibrosis, polycytemia vera.

Table 8.

Hazard ratio per milliGray absorbed organ dose (HR per mGy) with 95% confidence intervals (95% CI) in females

Female cancer site	Radiation associated	Crude HR per mGy (95% CI)	Adj HR per mGy (95% CI)
Breast	Yes	1.017 (1.007–1.027)	1.020 (1.010–1.030)
Central nervous system	Yes	0.998 (0.967–1.030)	0.995 (0.964–1.027)
Colon	Yes	1.030 (1.010–1.050)	1.014 (0.992–1.037)
Gall bladder	Yes	1.062 (0.998–1.129)	1.057 (0.993–1.125)
Kidney	Yes	1.037 (0.997–1.078)	1.033 (0.993–1.075)
Leukemia	Yes	1.021 (0.979–1.064)	1.021 (0.980–1.065)
Liver	Yes	0.998 (0.939–1.061)	0.997 (0.938–1.060)
Lung	Yes	0.990 (0.972–1.009)	0.995 (0.976–1.014)
Lymphoma	No	0.995 (0.968–1.023)	1.006 (0.978–1.035)
Esophagus	Yes	1.026 (0.943–1.117)	1.027 (0.944–1.118)
Oral cavity and pharynx	Yes	1.001 (0.957–1.046)	1.005 (0.957–1.055)
Other leukemias*	No	1.039 (1.008–1.072)	1.034 (1.002–1.067)
Ovaries	Yes	1.026 (0.996–1.057)	1.026 (0.996–1.057)
Pancreas	Yes	1.076 (1.041–1.112)	1.069 (1.030–1.109)
Rectum	Yes	1.026 (0.998–1.055)	1.002 (0.970–1.035)
Remainder	Yes	0.998 (0.987–1.008)	0.990 (0.979–1.001)
Stomach	Yes	0.993 (0.953–1.036)	0.996 (0.950–1.044)
Thyroid	Yes	1.027 (0.979–1.078)	1.015 (0.966–1.066)
Urinary bladder	Yes	1.019 (0.982–1.058)	1.016 (0.979–1.055)
Uterus	Yes	1.013 (0.993–1.033)	1.010 (0.990–1.030)
All sites combined		1.014 (1.008–1.019)	1.011 (1.006–1.017)

Follow-up times according to Table 1. HR is adjusted for urban lifestyle, socioeconomic status and average pre-Chernobyl cancer incidence 1980–1985 by cancer site (adj HR per mGy). Radiation-associated cancer classified according to BEIR VII and NCI.

*Hairy cell leukemia, chronic lymphatic leukemia, multiple myeloma, myelofibrosis, polycytemia vera.

20 years (1988–2007) and the dose assessment relied only on the external dose for the first year after the accident, whereas we used a time-integrated absorbed colon dose considering both internal and external contributions. Although cancer in the pancreas and stomach are regarded as being associated with exposure to radiation, we only found this relationship in males.[33] Our finding of an increased risk of lymphoma in females in Sweden after the Chernobyl NPP accident is difficult to explain, only relying on literature. First, the classification of lymphoma has changed over time, which makes it difficult to compare epidemiological studies with inconsistent classification across studies, that is, if chronic lymphatic leukemia (CLL) should be included as a kind of lymphoma. Second, there has been a tradition in epidemiology to exclude CLL when analyzing leukemia because CLL previously has been regarded as not associated with ionizing radiation.[37] Moreover, the NCI does not regard lymphoma as being associated with exposure to ionizing radiation.[33] However, according to a recent review article, exposure to ionizing radiation may be a (weak) risk factor for lymphoma.[40] To reduce the possibility of obfuscating our results by using a broad definition of lymphoma, we restricted our definition of lymphoma to include only those sharing the same precursor cell, immature lymphoblasts, and more mature lymphoid tissues with malignant transformation to lymphoma.

We found no increased risk of thyroid cancer in our study, in the original analysis or in the birth cohort analysis. No previous studies carried out in the Nordic countries have revealed an increased risk of thyroid cancer following the Chernobyl NPP accident. No increase in thyroid cancer was identified after the Chernobyl NPP accident in relation to the ^{137}Cs fallout at parish level or at the dwelling coordinate in two previous Swedish studies.[11,12] Neither was an increased risk found in a Finnish study on thyroid cancer following the Chernobyl NPP accident, with presumably similar doses to the public as in our study.[41] However, our dose calculations are more thorough than all these previous ecological studies, as we estimate the time-integrated internal and external absorbed dose to the thyroid from ^{131}I and ^{134,137}Cs for each person. In spite of the detailed dose calculations, the thyroid doses were too low to identify any increased risk of thyroid cancer. A likely explanation to the low thyroid doses in our study, are the exhaustive protective measures regarding cattle grazing and the dairy milk control during the first weeks after the fallout in Sweden, together with a good iodine status in the Swedish population.[42]

Beside epidemiological studies showing increased incidence of childhood thyroid cancer in Belarus and Ukraine after the Chernobyl NPP accident, there have also been reports of an increased thyroid cancer incidence among children and adolescents after the Fukushima Dai-ichi accident in 2011. This was explained as being the result of the extra screening program involving 300,000 prefecture residents aged 0 to 18 years.[43] However, there is still debate as to whether screening was the only reason for the observed increase, or whether radiation from the Fukushima Dai-ichi accident could have contributed to the increased incidence in thyroid cancer.[44]

People in villages along the Techa River in the Southern Urals were exposed to external as well of internal contributions, through the consumption of water, milk, and food contaminated with ^{137}Cs, ^{90}Sr, ^{89}Sr, and other fission products, from the Mayak nuclear weapons production facility during the period 1949 to 1956.[45] The mean stomach dose in the Techa River study follow-up period was 52 mGy (n=17,435) showing a statistically significant linear dose–response relationship for all solid cancers, but the statistical power was inadequate to analyze the effect of age at the initial exposure.[45]

Our calculated adjusted HR per mGy for males of 1.027 (95% CI = 1.022, 1.031) for all cancers combined was considerably higher than that found for adult males in our previous study, of 1.013 (95% CI = 1.009, 1.017).[26] The post hoc analysis in the present study showed that this higher risk estimate could be explained by the contribution from the internal dose in

Table 9.

Absorbed total-body dose in milliGray (mGy)

			All cancer sites combined (total-body dose in mGy)						
Sex	**Age (April 28, 1986)**		**mean**	**SD**	**median**	**p5**	**p95**	**Min**	**Max**
Males	0–19 y	case	1.534	1.345	1.095	0.250	4.172	0.088	10.934
		control	1.517	1.330	1.101	0.247	4.160	0.082	10.040
	20–39 y	case	1.637	1.452	1.201	0.252	4.463	0.084	12.454
		control	1.597	1.448	1.164	0.248	4.387	0.073	12.454
	40–59 y	case	1.610	1.470	1.154	0.238	4.433	0.081	12.587
		control	1.537	1.417	1.087	0.230	4.286	0.066	12.471
	≥60 y	case	1.292	1.180	0.899	0.195	3.621	0.073	10.457
		control	1.258	1.172	0.859	0.192	3.559	0.069	11.238
Females	0–19 y	case	1.398	1.202	1.013	0.228	3.831	0.089	10.565
		control	1.399	1.227	0.987	0.226	3.831	0.092	10.052
	20–39 y	case	1.262	1.143	0.873	0.193	3.567	0.050	8.653
		control	1.256	1.153	0.857	0.193	3.568	0.044	9.234
	40–59 y	case	1.238	1.142	0.837	0.185	3.501	0.050	10.265
		control	1.220	1.144	0.806	0.182	3.497	0.045	9.353
	≥60 y	case	1.051	0.955	0.712	0.163	2.978	0.053	8.281
		control	1.020	0.955	0.661	0.160	2.950	0.023	8.145

All cancer sites combined are presented and divided by sex in birth cohorts.

The adjusted HR per mGy, in all cancer sites combined, was not increased in the age cohort 0–19 years, but a tendency toward a higher adjusted HR per mGy was seen with aging cohorts in both sexes, Figure 3.

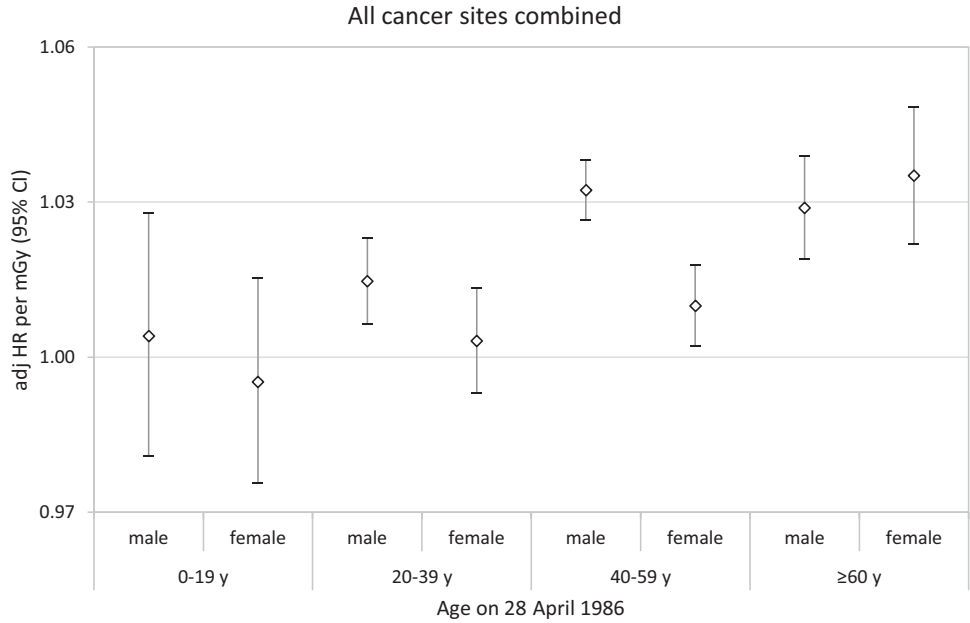

Figure 3. Adjusted hazard ratios per milliGray total-body dose (adj HR per mGy) with 95% confidence intervals. All cancer sites combined are presented and divided by sex in birth cohorts. Follow-up time according to Table 1. HR is adjusted for urban lifestyle, socioeconomic status and average pre-Chernobyl cancer incidence 1980–1985.

males. This seemed to be of minor importance in females, and therefore did not influence the overall risk estimate.

A nonradiation-related risk factor, that is, the hunter lifestyle was also found to increase the risk and was a strong confounding factor in the time period 2001 to 2015, as we have reported previously.[46] As hunter household is closely associated with hunter status and the dose algorithm for internal dose, it was not possible to disentangle hunter lifestyle as risk factor for cancer from the absorbed dose to hunter households. Hence, we could not rule out remaining confounding from hunter lifestyle in males aged 40 to 59 years at the time of the Chernobyl NPP accident, as this age group reached the general age-dependent increase in cancer incidence of all causes after the year 2000. The oldest birth cohort, ≥60 years of age, might not be so sensitive to this confounding since they can be assumed to have passed their peak in cancer incidence by year 2000. It is unfortunate from an epidemiological point of view, which the counties with the lowest Chernobyl fallout coincided with those with the lowest pre-Chernobyl cancer incidences, but also with the highest prevalence of male hunters, and this could not be completely adjusted for in the statistical model. In an attempt to estimate the confounding contribution from hunter lifestyle, we removed all hunter households in the post hoc analysis, but the same pattern remained. We could confirm remaining uncontrolled confounding from hunter lifestyle together with county difference in cancer incidence, after removing individuals living in the two counties with the lowest radioactive fallout after the Chernobyl accident at baseline in 1986 (Norrbotten and Dalarna counties), leaving 7 counties in the post hoc analysis. In spite of the somewhat lower statistical power when analyzing data from only 7 counties, a significant HR per mGy remained for cancer

in the pancreas, prostate and lungs, respectively and also in all cancer sites combined for males. Two new sites in males emerged (colon and stomach) as significant in the post hoc analysis. No significant increase in HR per mGy remained in females, but esophagus cancer and lymphoma emerged as new significant cancer sites, compared with the analysis of all 9 counties. No increased risk of thyroid cancer was found in terms of adjusted HR per mGy, adjusted HR per deciles, or in the birth cohort analyses.

The results of the post hoc analysis of all cancer sites combined can be expressed as the adjusted excess HR per mGy (adjusted EHR), with values of 0.01402 (95% CI = 0.00939, 0.01866) for males and 0.00032 (95% CI = –0.00568, 0.00637) for females. These values can be compared with the results from the latest follow-up of the solid cancer incidence in the Life Span Study, at doses <100 mGy, showing a linear excess relative risk per mGy of 0.00032 (95% CI = –0.00012, 0.00085) for males and 0.00040 (–0.00025, 0.00115) for females.[47]

Strengths and Limitations

Two important strengths of our study are the size of the cohort and the detailed time-integrated dose assessment on individual level for each sex, including both internal and external absorbed doses, taking into account the assumption that those in a hunter household have a higher internal dose due to the consumption of unregulated game. This is important, as all members of the household (adults and children) probably share the same food habits. Compared with our previous exposure assessment model, we have reduced misclassification by adding municipality-specific shielding factors for dwellings. Another strength is that we have taken into account the dose contribution both from ^{131}I and ^{134,137}Cs when calculating the time-integrated absorbed dose to the thyroid. Moreover, the high resolution obtained from the aerial measurements of ^{137}Cs made it possible to reduce misclassification of the external absorbed dose compared to ecological studies. Expressing the cancer risk in terms of the HR per mGy, justified by the linear no-threshold model, has the advantage of being able to use the full range of exposure data, and not relying only on a reference population of individuals not exposed to the Chernobyl fallout, which is difficult to define in the low-dose range.[39,48] A similar statistical method has also been used when analyzing childhood cancer in Switzerland in relation to background radiation, including the contribution from ^{137}Cs fallout from the Chernobyl NPP accident.[49] In this Swiss study, the HR per mSv of cumulative external dose was 1.04 (95% CI = 1.01, 1.06) for all cancers combined, which is higher than our all cancer-site HR per mGy. In our study design, we tried to maximize exposure contrast, but at the same time could exclude larger cities in the south of Sweden that could have contributed to unknown lifestyle factors acting as confounding factors. Therefore, studying the population in northern Sweden, could to some extent, take geographical differences in lifestyle into account. Including counties in southern Sweden would not have provided any extra information on ^{137}Cs exposure, because of very low fallout, but could have instead resulted in an increased risk of confounding. We were able to avoid misclassification of individuals by using the personal identity numbers to match data in various registers. The accuracy regarding histologically verified diagnoses in the National cancer Registry is high, and validation studies have shown the completeness of malignancies to be above 96%.[50,51] The precision in the results was increased by including only individuals with no previous cancer diagnosis at baseline, as secondary cancer caused by treatment with cytostatic drugs and/or radiation, possibly could mask any effect from the Chernobyl fallout. Similarly, a matched control with a cancer diagnosis prior to that of the case was removed and a new control randomly selected. Finally, our dose model is generic and can be applied to other populations to give additional information on dose response at low protracted doses for future pooling of data. As the programming code is publically available it can be modified and used in other settings (https://github.com/absorbedDose/absorbedDose).

The main limitation we have identified is that adjustment for *a priori* confounding factors was not sufficient, as we identified hunter status as a strong confounding factor in combination with low regional background cancer incidence. This combination was particularly prevalent in the county of Norrbotten and resulted in inflated risk estimates when analyzing all 9 counties. We also assumed that all hunters have the same diet of game over time, which is a simplification that will affect the dose assessment. Also, we were only able to identify hunters in 1986, not able to include new hunters with a license of a hunting weapon registered after 1986. However, not including hunter household status in our dose model could have led to miscalculation of the internal dose since the proportion of male hunters varied between the counties, from 2.5% in Västmanland to 8.3% in Norrbotten.[46] Our dose model suffers from a lack of individual shielding factors for snow cover at the dwelling coordinate (f_{snow} by county), and lack information of information on those working outdoors who have a lifestyle involving more outdoor activities, as all individuals were assigned the same time fraction spent outdoors (f_{out} 0.2). However, outdoor lifestyle was taken into account to some extent by matching for age and adjusting for rural habitat. Although the contribution from terrestrial gamma radiation to the external dose was not taken into account in our study design, it will only be a potential confounding factor if it has a positive or negative correlation to ^{137}Cs fallout. Adjusting our risk estimates by highest educational level during the follow-up period might have resulted in some remaining confounding from socioeconomic factors, but this would have influenced our risk estimates only if such factors were also correlated with ^{137}Cs exposure.

CONCLUSIONS

Our results of this study clearly show the importance of scrutinizing the results, as any epidemiological study in low-radiation-dose research might suffer from uncontrolled confounding, that cannot be accounted for in the initial design of the statistical analysis. Therefore, we consider our risk estimates obtained from the post hoc analysis of 7 counties to be more reliable. Significant adjusted HR per mGy for all cancer sites combined only remained in males when analyzing 7 counties. Taking into account both the adjusted HRs and the results from the analysis in deciles, our results suggest an association between the low-dose-radiation from the Chernobyl NPP accident and cancer in the colon, pancreas, and stomach, respectively, in males but only lymphoma in females. However, caution should be exercised in the interpretation of our results as the absorbed doses are extremely low, and there could still be uncontrolled confounding moderating the risk estimates. Future studies of nonhunting households are warranted.

CONFLICTS OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest with regard to the content of this report.

ACKNOWLEDGMENTS

We acknowledge Katja Gabrysch, Uppsala Clinical Research Center for developing the R-program used for the calculation of organ doses.

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