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Cancer incidence in a male adult population in relation to estimated protracted colon dose – A nested case control study in Northern Sweden after the Chernobyl Nuclear Power Plant accident

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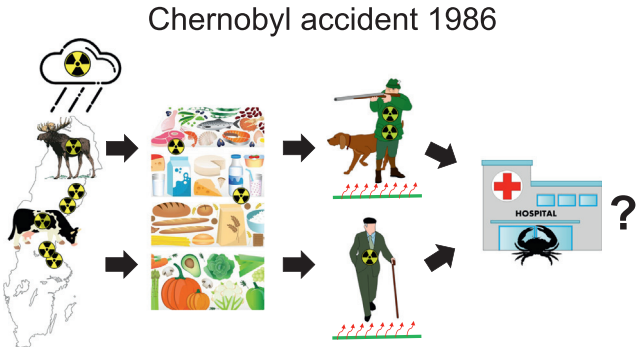
HIGHLIGHTS

- Algorithm for calculation of external and internal colon absorbed radiation dose.
- Hunters have higher colon absorbed dose than non-hunters after Chernobyl in Sweden.
- Positive Hazard Ratio per mGy in some cancer sites associated with radiation
- Classifying cancer sites associated with radiation is a valuable research tool.

GRAPHICAL ABSTRACT



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ABSTRACT

Introduction: Uncertainty in the dose-response of low dose radiation raised concern of an increased cancer incidence in Sweden after the Chernobyl Nuclear Power Plant (NPP) accident.
Material and methods: A closed cohort was created of all males ≥18 years of age living in the Northern Sweden in 1986. In total 826,400 individuals were enrolled including 40,874 hunters. A nested case-control design was used with five controls randomly selected for each cancer case matched on year of diagnosis and year of birth. Individual absorbed colon dose was calculated 1986 to 2015. Allowing for a 5-year latency period Hazard Ratios (HR) per mGy with 95% Confidence Intervals (95% CI) were calculated in a conditional logistic regression adjusted by rural/non-rural living, length of education and pre-Chernobyl cancer incidence 1980 to 1985. A total of 127,109 cancer cases occurred from 1 January 1991 to 31 December 2015. Cancer was classified in: 1) Organ-specific (stomach, colon, liver, lung, prostate, urinary bladder, thyroid and leukaemia), 2) Other and 3) Not previously associated to ionizing radiation.
Results: The average colon dose in cases was 1.77 mGy compared to controls 1.73 mGy. Hunters average colon dose was 2.32 mGy. Organ-specific cancers showed the highest HR per mGy both in the full cohort, adj HR 1.019 (1.014–1.024) and the hunter subcohort, adj HR 1.014 (1.001–1.027) during follow-up 1991 to 2015. Other cancer and Not previously associated with ionizing radiation showed lower HR per mGy. Therefore, the adj HR per mGy for Total cancer, 1.013 (1.009–1.017) was explained by Organ-specific cancer. Increased adj HR per mGy was seen in stomach, colon and prostate cancer, respectively in the full cohort and lung cancer in hunters.
Conclusions: Some cancer sites previously associated with ionizing radiation showed a positive adjusted HR per mGy both in the full cohort and in the hunter subcohort.

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1. Introduction

The largest nuclear power plant accident in the world hitherto occurred on 26 April 1986 at 1.24 a.m. A steam explosion at reactor 4 in the Chernobyl nuclear power plant (NPP) in Ukraine resulted in a total release of 5300 PBq of radioactive material (excluding noble gases) into the atmosphere during a 10-day period (United Nations Scientific Committee on the Effects of Atomic Radiation, 2000). The radioactive cloud reached Sweden and was first indicated by a gamma monitoring station at the southern tip of the island of Öland southeast of Sweden, which recorded an increased dose rate at 7 p.m. on 27 April (Kjelle, 1986). Out of the total released ^{137}Cs (85 PBq) from the Chernobyl NPP accident 5% (4.25 PBq) was deposited in Sweden in the ensuing days, especially during a heavy rainfall on the coastal area north of Stockholm, 28–29 April 1986 (Mattsson and Moberg, 1991; United Nations Scientific Committee on the Effects of Atomic Radiation, 2000). The deposition of ^{137}Cs was unequally distributed over Sweden with remaining deposition of ^{137}Cs from the atmospheric nuclear weapons tests of 2–3 kBq/m^2 up to more than 100 kBq/m^2 after the Chernobyl NPP accident (Andersson, 2007). After the Chernobyl NPP accident, the Swedish Food Agency introduced reference levels of ^{137}Cs to 300 Bq/kg to all foodstuff produced in Sweden or imported (Statens livsmedelsverk, 1986). However, the consequences were drastic for reindeer herders when 78% of the slaughter meat had to be discarded exceeding 300 Bq/kg in 1986/1987 (Åhman, 2005). As a result, an additional recommendation of a maximum of 1500 Bq/kg was introduced in 1987 for game, venison (mainly reindeer meat), wild berries, mushrooms, freshwater fish and nuts sold to the public. As these food items gives a small contribution to the yearly effective dose it was still believed that the target of a 1 mSv/year could be fulfilled with this new reference level (Livsmedelsverket, 2020; Statens livsmedelsverk, 1987). However, hunters were identified as a vulnerable group escaping the food restrictions as relying partly on contaminated game for food consumption. Due to the elevated ^{137}Cs concentration in reindeer meat and food from the forest ecosystem, the Swedish Radiation Safety Authority, together with the Swedish Defence Research Agency (FOI) launched a measurement program in 1996. Reindeer herders and several hunting communities in Sweden were regularly surveyed by whole-body counting (Ågren, 1998; Rääf et al., 2006).

Epidemiological studies on cancer after the Chernobyl NPP accident, outside the former USSR, has been hampered by comprehensive methods estimating the internal dose in the total population. Although a positive association of ground deposition of ^{137}Cs (kBq/m^2) as proxy of the absorbed dose and total cancer has been seen in Northern Sweden, conclusions of a causal relationship could not be made (Tondel et al., 2004; Tondel et al., 2006; Alinaghizadeh et al., 2016). Therefore, our research group has developed methods for dosimetry for time-integrated external and internal dose to the population in Sweden after the Chernobyl NPP accident based on the municipal measurement system and the whole-body measurements (Jönsson et al., 2017; Rääf et al., 2019; Tondel et al., 2017). In a pilot study we could identify a difference in lifetime effective doses to the members of hunter families, with county averages of 8.3 mSv in Västernorrland, 4.7 mSv in Uppsala and 4.1 mSv in Gävleborg, respectively. The lifetime dose was inversely associated with age in 1986 with a maximum dose of 11.9 mSv in the county of Västernorrland, the county in Sweden with the highest average deposition of ^{137}Cs. Our estimate in these three counties was that about 75% of the total lifetime effective dose in hunters was from internal dose, which can be translated into almost 30% in the general population in these three counties (Tondel et al., 2017). Based on this pilot study we conducted an epidemiological study in the 9 northern-most counties in Sweden during the follow-up period from 1986 to 2015. An overall increased risk of cancer was identified for male hunters compared to male non-hunters, but an association could not be identified to the deposition of ^{137}Cs from the Chernobyl NPP accident in these counties (Tondel et al., 2020). However, because the exposure classification was too crude it could not exclude such association. Therefore, we decided to explore the dose-response in one cohort of all adult males and a separate analysis only in hunters. There is a challenge in modelling protracted exposure to ionizing radiation and subsequently analyse cancer incidence. A nested case control design was chosen to analyse the relationship between absorbed colon dose and various sites of cancer in adult males and separately in hunters to better elucidate potential relationship comparing dose response in cancer sites previously known to be associated with radiation. The advantage of analyzing a subcohort of hunters separately is that lifestyle is expected to be similar regardless of ^{137}Cs deposition. The aim of our study is to explore a more comprehensive exposure model with our cancer incidence data to study the relationship of absorbed dose and cancer incidence.

2. Material and methods

2.1. Population

The study design is taking the advantage of merging two closed cohorts (here called full cohort) with previously published results, consisting of all male persons ≥18 years of age in 28 April 1986 living in the 9 northernmost counties in Sweden (Tondel et al., 2020).

From Statics Sweden (SCB) we retrieved information on all individuals living in these 9 counties by 31 December 1986. In the population registry at SCB all individuals have a unique social identity number and information on the county where they live. SCB also keeps registries on date of emigration and date of death that can be linked to the data set. The Swedish National Land Survey has assigned each inhabitant in Sweden an annually updated dwelling coordinate. These dwelling coordinates can then be used to link the population registry to the digital map of the ^{137}Cs, hence creating an individual deposition value of ^{137}Cs at each dwelling. SCB has also provided data on rural and non-rural residence at each dwelling. The definition of rural and non-rural (including urban) areas was created by SCB in the year 1960 and updated every fifth year by SCB. The definition of rural residence is a population centre having less than 200 inhabitants where the population centre is defined as a congregation of buildings with the largest distance between buildings being 200 m (Statistics Sweden, 1986). Hence, rural residence is a very sparsely populated area and non-rural residence is a mixed category including both urban and semi-urban residence.

A total of 1,113,564 males of all ages lived in the counties of Norrbotten, Dalarna, Södermanland, Jämtland, Västmanland, Gävleborg, Västerbotten, Uppsala and Västernorrland in 1986. The final closed cohort for analyses included 826,400 persons i.e. ≥18 years of age in 28 April 1986 after excluding duplicates of re-used social identity numbers (n = 834), missing information on dwelling coordinates (n = 4943), having a cancer diagnosis between 1958 and 27 April 1986 (n = 17,553) and persons <18 years age in 28 April 1986 (n = 264,739), with or without a combination of these excluding factors.

In Sweden, all hunters need a licence for their hunting weapon, issued and registered by the Swedish National Police Agency, and registered under the social identity number. This register from 1986 was linked to the population registry data base by SCB. The total number of male hunters in the 9 counties was 41,378. Hence, the final cohort for further analyses consisted of male hunters (n = 40,874) and male non-hunters (n = 785,526) ≥18 years of age with no known cancer prior to the estimation of the colon dose from 28 April 1986 to 31 December 2015. Allowing for a latency period of almost 5 years a total of 764,040 including 40,543 hunters were left for the epidemiological analysis after excluding people who emigrated (n = 4006), died (n = 47,671) and/or had a diagnosis of cancer (n = 20,209) before start of follow-up at 1 January 1991.

2.2. Exposure assessment

Life-time total absorbed colon dose (mGy) was calculated for each individual up to the year of first cancer, death, emigration whatever came first, or up to being alive without cancer 31 December 2015. The following equation was used to calculate the time-integrated total colon dose as a sum of

external and internal colon dose with parameter values given in Tables 1 and 2.

$$D_{colon}\left(t, age, A_{esd,loc}, A_{esd,county}\right) = A_{esd,loc} \bullet d_{Cs} \bullet \varnothing_{K/H}(600keV) \bullet f_{snow} \bullet k_{SEQ,colon} \int_{t0}^{t} r(t)$$

$$\bullet k_{SEQ,sex}(age) \cdot \left(f_{out} + (1 - f_{out}) \bullet f_{shield}\right) dt + A_{esd,county} \bullet T_{ag,\ max} \bullet \int_{t0}^{t} \left(\left(1 - e^{\frac{-\ ln\ (2)}{t1} \bullet t}\right) \bullet \left(c_1 \bullet e^{\frac{-\ ln\ (2)}{t2} \bullet t} + c_2 \bullet e^{\frac{-\ ln\ (2)}{t3} \bullet t}\right)\right) \bullet f_{sex}$$

$$\bullet \left(k_{colon,int,Cs\ -\ 137} \cdot e_{Cs\ -\ 137}(w(age(t))) + k_{colon,int,Cs\ -\ 134} \bullet FR \bullet e^{\left(\frac{ln\ 2}{T,Cs\ -\ 137} - \frac{ln\ 2}{T,Cs\ -\ 134}\right) \bullet t} \bullet e_{Cs\ -\ 134}\left(w(age(t))\right)\right) dt$$

Table 1
Description of and reference to parameters used to calculate total colon absorbed dose (mGy).

Parameter	Description (unit)
D_{colon}	Absorbed dose to colon (mGy)
$A_{esd,\ loc}$	Equivalent surface deposition at the dwelling coordinate of ^{137}Cs (kBq m^{-2}), decay corrected to the time of the fallout event. This quantity is proportional to the total ground deposition density, A_{tot} (kBq m^{-2}) of ^{137}Cs by a factor of 1.6 and was obtained through airborne gamma spectrometry mapping by SGU in Sweden, as described by Byström (2000). The definition of A_{esd} refers to Isaksson et al. (2019).
$A_{esd,\ county}$	Average ^{137}Cs deposition (kBq m^{-2}) in each county from Table 2.
d_{Cs}	Empirical correlation factor (=1.02 mSv y^{-1}/kBq m^{-2}) between the so-called surface equivalent deposition, A_{esd}, of fresh fallout from the Chernobyl accident in Sweden and the ambient dose rate 1 m above ground, taken from Rääf et al. (2020).
$\varnothing_{K/H}(600keV)$	Ratio between air kerma rate and ambient dose equivalent rate 1 m above ground for an infinite uniform surface deposition of gamma emitters with photon energy 600 keV (mGy mSv^{-1}). A value of 0.83 has been used, taken from ICRU report 47 (International Commission on Radiation Units and Measurements, 1992).
f_{snow}	Snow cover shielding factor (unity) averaged over the whole year for ambient dose rate 1 m above ground. Snow cover correction for the studied counties is given in Table 2.
$k_{SEQ,colon}$	Organ absorbed dose rate in colon per unit kerma rate 1 m above ground for a ground deposition with a penetration depth of 0.5 g cm-1 in soil for an adult male. In our study, a value of 0.6855 for males have been taken from Zankl et al. (2002).
r(t)	Time-dependent function describing the decrease in external ambient dose rate 1 m above ground, normalized to the maximum initial dose rate following a nuclear power plant fallout corresponding to a Chernobyl-like wet deposition at remote locations from the release point. Apart from external gamma contribution from ^{134}Cs and ^{137}Cs, corresponding contributions from gamma emitters, such as ^{131}I, ^{132}I, ^{132}Te, and ^{140}Ba, are included. A time-dependent function composed of four components was taken from Rääf et al. (2020), with time constants expressed in terms of y^{-1}. $r(t) = 0.96 \cdot e^{-36.9 \cdot t} + 0.10823 \cdot e^{-2.45 \cdot t} + 0.0796 \cdot e^{-0.668 \cdot t} + 0.0314 \cdot e^{-0.126 \cdot t}$.
$k_{SEQ,colon}$ (age)	Age dependent dose conversion factors between absorbed dose to colon and air kerma rate in air 1 m above ground for males, $k_{SEQ,colon}$, are based on computer simulations by Becker et al. (2012). $k_{SEQ,colon}(age) = \{[1.46665 + (-40 * (0.002577) - 1200 * (-0.36^{-4})] * x + (0.002577) * x^2 + (-0.36^{-4}) * x^3\} / 1.01185$
f_{out}	Time fraction spent outdoors for an individual residing in a temperate climate zone. Typical values range between 0.1 and 0.2 for Northern European populations (Andersson, 2007; World Health Organization, 1999). A value of f_{out} = 0.2 was used in this work.
f_{shield}	Shielding factor for indoor stay, ranging between 0.10 and 0.40 for Northern European houses. A value of f_{shield} = 0.4 from Finck (1992) was used in this work.
t_{acc}	Time over which the radiation exposure is integrated (y).
$T_{ag,max}$	Maximum aggregated transfer factor aggregated over all radioecological transfer pathways. This parameter determines the magnitude of the time-dependent transfer, $T_{ag}(t)$ (Bq/ kg)/(kBq m^{-2}), from regional-average equivalent surface deposition to whole-body concentration of ^{134,137}Cs in residents. A value of $T_{ag,max}$ of 11 for the general population was assumed, and a value of 29.3 (Bq/ kg)/(kBq m^{-2}) for hunters and their family members from Isaksson et al. (2019).
t_1, t_2 and t_3	Time constants of radioecological transfer depending on type of population. Values used here are t_1 = 1.0 y, t_2 = 0.75 y, and t_3 = 15 y. Values for other types of populations can be found in Isaksson et al. (2019).
c_1 and c_2	Coefficients of amplitude of radioecological transfer depending on type of population. Values used here refer to urban populations in Scandinavia and are c1 = 1.0 and c2 = 0.10. Values for other types of populations can be found in Isaksson et al. (2019).
t	Time in years.
f_{sex}	Male = 1.0
$k_{colon,int,Cs-134}$	Ratio between organ-absorbed dose and the average whole-body absorbed dose incurred by a uniformly distributed internal contamination of ^{134,137}Cs. Values of 1.00 for ^{137}Cs and 1.05 for ^{134}Cs were taken from Rääf et al. (2020).
$k_{colon,int,Cs-137}$	
e_{Cs-137}(w (age(t)))	Body weight dependent conversion factor between average absorbed dose to whole-body per unit ^{137}Cs concentration in humans. The value is assumed to be = 0.0014·w(age(t))$^{0.111}$, see Rääf et al. (2020).
FR	Isotopic ratio ^{134}Cs/^{137}Cs at the time of initial fallout. A value of 0.56 was used for Swedish Chernobyl fallout, see Rääf et al. (2020).
$T_{1/2,Cs-137}$	Physical half-life of ^{137}Cs: 30.2 years.
$T_{1/2,Cs-134}$	Physical half-life of ^{134}Cs: 2.06 years.
e_{Cs-134}(w (age(t)))	Body weight dependent conversion factor between average absorbed dose to whole-body per unit ^{134}Cs concentration in humans. The value is assumed to be = 0.00164·w(age(t))$^{0.188}$, see Rääf et al. (2020).
w(age(t))	Body mass (kg) as a function of age as described in Rääf et al. (2020). w(age) = −0.0000021·age^6 + 0.0002623·age^5 − 0.011799·age^4 + 0.2305·age^3 − 1.8759·age^2 + 8.0766·age + 3.8872 (age < 20 y) w(age) = 78 kg (age ≥ 20 y)

2.3. Cancer statistics

The cancer registry at the National Board of Health and Welfare began registration of cancer in 1958 and have since the start consistently coded cases according to the International Classification of Diseases, version 7. The primary objective in BEIR VII was to review all relevant epidemiologic data to assess the cancer risk at low-dose radiation exposure (National Research Council (U.S.) and Committee to Assess Health Risks from Exposure to Low Level of Ionizing Radiation, 2006). Using BEIR VII, table 12D-3, all malignancies could be coded in three categories: 1) Organ-specific BEIR VII, 2) Other BEIR VII and 3) Cancer not regarded as caused by ionizing radiation (Not in BEIR VII), respectively. There is firm epidemiological support for an association between ionizing radiation in the so-called Organ-specific cancer category (stomach, colon, liver, lung, prostate, urinary bladder, thyroid and leukaemia) and in the group of Other cancer (Table 3). By using the unique social identity number registered with Statistics Sweden cancer in each person could accurately be retrieved. It was also possible to exclude cancer diagnosis before start of follow-up 28 April 1986 to avoid cancer prone individuals or cancer treatment (cytostatics, radiation treatment) to obfuscate a potential relationship with the absorbed colon dose.

2.4. Statistical methods

Due to protracted exposure during follow-up 1 January 1991 to 31 December 2015 a nested case-control design was chosen. For each cancer case

Table 2
County average surface equivalent deposition of ^{137}Cs in kBq/m^2 (A_{esd}) 1 May 1986 and shielding factor for snow cover by county (F_{snow}) used to calculate total colon dose.

County	A_{esd}	F_{snow}
	kBq m-2	
Uppsala	15.18	0.90
Södermanland	5.04	0.90
Västmanland	10.90	0.90
Dalarna	2.45	0.85
Gävleborg	13.11	0.85
Västernorrland	27.87	0.84
Jämtland	6.35	0.84
Västerbotten	14.36	0.84
Norrbotten	2.05	0.81
Västra Götaland	1.87	0.97
Gotland	3.14	0.97
Skåne	1.76	0.97
Kronoberg	1.61	0.90
Jönköping	1.75	0.90
Halland	1.79	0.97
Örebro	1.93	0.90
Blekinge	1.96	0.90
Värmland	2.04	0.85
Kalmar	2.05	0.90
Östergötland	2.18	0.90
Stockholm	2.58	0.90
Kristianstad	1.76	0.97
Älvsborg	1.87	0.97
Skaraborg	1.87	0.97

occurring in the follow-up period (n = 127,109) five controls (n = 635,542) were randomly selected from the study base (n = 764,040) matched on year of diagnosis and year of birth. Cases and controls could therefore be treated identical when calculation the duration of exposure. Each control had no prior cancer diagnosis and was alive at time of year of diagnosis of the case. Hence, a control could be selected several times if it fulfilled these criteria. During the follow-up 63% of all cases could be classified as Organ-specific, 30% Other cancer according to BEIR VII and 7% cancer cases not radiation associated in BEIR VII (Table 3).

For analysis of the subcohort of hunters an identical procedure was performed within the study base of hunters (n = 40,543) resulting in 8964 cases of cancer and 44,820 controls. Hazard Ratios (HR) with 95% Confidence Intervals (95% CI) were calculated in a conditional logistic regression using the Cox proportional hazard survival model in SAS®, statistical package, version 9.4. HR were calculated in quintiles based on number of cancer cases after calculating the colon dose in cases and controls, using the first quintile as reference category and presented in graphs by average colon dose in each quintile. The average absorbed colon dose in each quintile was 0.30, 0.57, 1.17, 2.23, and 4.41 mGy for the total cohort and 0.28, 0.49, 1.22, 2.96, and 6.68 mGy for hunters, respectively for the follow-up period 1991 to 2015. HR were also calculated using a linear model with total absorbed colon dose per milliGray (mGy) as a continuous variable, expressed as HR per mGy. The material was analyzed in birth cohort tertiles based on year of birth at start of follow-up 1 January 1991: 1890–1926 (n = 250,755), 1927–1939 (n = 257,880) and 1940–1968 (n = 254,016).

As each case of cancer was matched to a control on year of birth, age was not considered as asserting confounding (crude HR). To account for urban lifestyle, socioeconomic status and pre-Chernobyl total cancer incidence as potential confounding factors all risk estimates were adjusted by these three factors in the model (adjusted HR). In the cohort 194,915 persons could be classified as having a rural and 567,736 persons having a non-rural habitat in 1986. Length of education was used to indicate socioeconomic status and data was provided by Statistics Sweden to categorize education into three levels in 1990: low ≤9 years (369,522), middle 10–12 years (n = 253,444), high >12 years (n = 109,770) of education and missing (n = 29,915), respectively. The total cancer incidence as a county average 1980 to 1985 from National Board of Health and Welfare database was used in the model to control for potential confounding from the pre-Chernobyl cancer incidence by county (https://sdb.socialstyrelsen.se/if_can/val.aspx).

Two time periods were analyzed 1991 to 2015 and 2011 to 2015, respectively. For the first time period all cases of cancer (n = 127,109) and controls (n = 635,542) were used in the analyses. For the second time period an identical matching procedure were performed in all living individuals without cancer diagnosis prior to 31 December 2010 (n = 487,765). Hence, the latency period for the second follow-up period from 1 January 2011 to 31 December 2015 can be regarded as an analysis with 25 years of latency period.

Our study was approved by the regional ethics committee in Uppsala (Reg. No. 2014/184 with the extension Reg. No. 2014/184/1).

3. Results

The average colon dose was slightly higher for cases 1.77 mGy compared to controls 1.73 mGy (Table 4). Hunters had a higher average colon dose 2.32 mGy compared to the full cohort 1.73 mGy (Table 5). The average internal dose (^{134}Cs + ^{137}Cs) for hunters, 1.30 mGy constituted 56% versus 0.68 mGy or 39% in the full cohort. Since hunters only constitute a small proportion of all adult males they only contribute marginally to the colon dose in the full cohort.

Crude and adjusted HR (95% CI) for total cancer indicated a small positive dose-response with a plateau and weak confounding 1991 to 2015 (Fig. 1). The dose-response for hunters 1991 to 2015 seemed more obvious in the adjusted HR although only significant in the highest quartile (Fig. 2).

Organ-specific cancers showed the highest HR per mGy of total colon dose in both time periods adj HR 1.019 (1.014–1.024) 1991 to 2015 and

Table 3
Number of malignancies in the 9 counties 1 January 1991 to 31 December 2015. Classification in radiation associated and not radiation associated malignancies according to BEIR VII (National Research Council (U.S.) and Committee to Assess Health Risks from Exposure to Low Level of Ionizing Radiation, 2006).

Radiation-associated				1991–2015	
		Cancer sites	ICD-7 (male)	n	%
Yes	Organ-specific BEIR VII	Stomach	151, 1510, 1511, 1518, 1519	3657	2.88
		Colon	1530, 1531, 1532, 1533, 1534, 1536, 1538, 1539	8775	6.90
		Liver	1550	1604	1.26
		Lung	1620, 1621	9082	7.15
		Prostate	177	46,521	36.60
		Urinary bladder	1810, 1816	8143	6.41
		Thyroid	194	428	0.34
		Leukaemia	2040, 2044, 2047, 2049, 2050, 2051, 2059, 2060, 2061, 2069, 2070, 2071, 2072, 2073, 2079	1683	1.32
Yes	Other BEIR VII	Remainder	all other ICD-7 codes	38,346	30.17
No	Not in BEIR VII	Male breast	170, 1701, 1702, 1707, 1708, 1709	164	0.13
		Lymphoma	2001, 2002, 2003, 201, 2021, 2022	4753	3.74
		Other leukaemia	2024, 203, 2041, 208, 209	3953	3.11
	Total cancer			127,109	100.00

Table 4
Absorbed colon dose (mGy) from 28 April 1986 to 31 December 2015 by cases of cancer and controls, respectively.

		Absorbed colon dose (mGy) 1986–2015						
		Mean	SD	Median	p5	p95	Min	Max
Cases (n = 127,109)	Cs-134 internal	0.17	0.18	0.15	0.03	0.38	0.02	1.36
	Cs-137 internal	0.53	0.62	0.40	0.07	1.40	0.04	6.24
	Total external	1.07	1.16	0.57	0.14	3.35	0.00	12.11
	Sum (int + ext)	1.77	1.67	1.20	0.27	4.96	0.09	13.81
Controls (n = 635,542)	Cs-134 internal	0.17	0.17	0.15	0.03	0.38	0.02	1.36
	Cs-137 internal	0.51	0.59	0.39	0.07	1.39	0.04	6.24
	Total external	1.05	1.16	0.53	0.14	3.35	0.00	12.06
	Sum (int + ext)	1.73	1.65	1.15	0.26	4.91	0.09	14.10

Table 5
Absorbed colon dose (mGy) from 28 April 1986 to 31 December 2015 for cases and controls in the full cohort and hunters, respectively.

		Absorbed colon dose (mGy)						
		Mean	SD	Median	p5	p95	Min	Max
All (n = 762,651)	Cs-134 internal	0.17	0.17	0.15	0.03	0.38	0.02	1.36
	Cs-137 internal	0.51	0.59	0.39	0.07	1.39	0.04	6.24
	Total external	1.06	1.16	0.54	0.14	3.35	0.00	12.11
	Sum (int + ext)	1.73	1.66	1.16	0.26	4.92	0.09	14.10
Hunters (n = 53,784)	Cs-134 internal	0.29	0.38	0.15	0.03	1.36	0.02	1.36
	Cs-137 internal	1.00	1.36	0.45	0.08	4.51	0.04	6.24
	Total external	1.03	1.17	0.47	0.14	3.41	0.00	10.29
	Sum (int + ext)	2.32	2.57	1.19	0.26	8.33	0.11	13.81

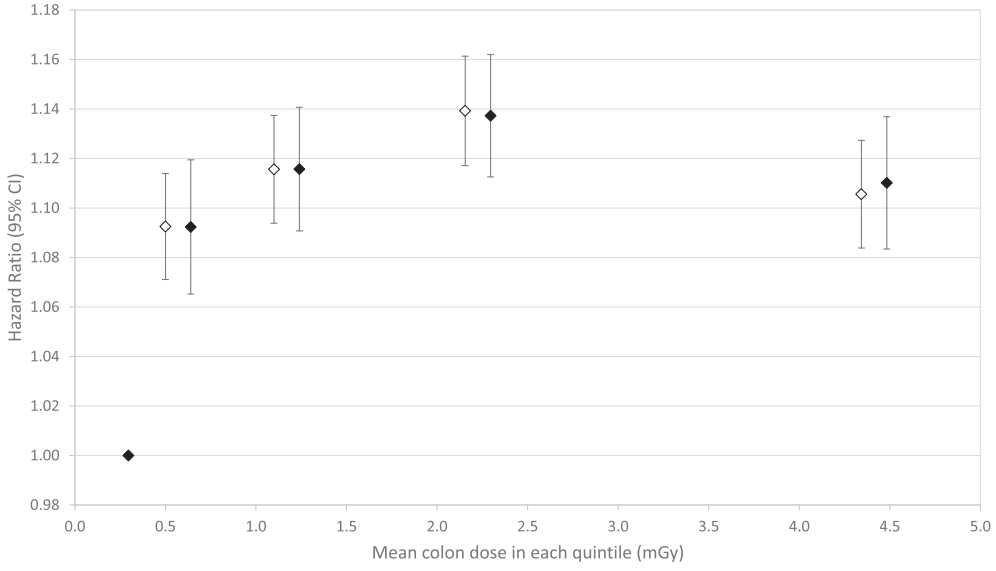

Fig. 1. Total cancer in full cohort. Hazard Ratio (HR) in quintiles, with lowest quintile as reference category, is given with 95% Confidence Intervals (95% CI) for the follow-up period 1 January 1991 to 31 December 2015. Crude HR (open diamond) and HR adjusted by urban lifestyle, socioeconomic status and pre-Chernobyl total cancer incidence (filled diamond).

adj HR 1.022 (1.013–1.032) 2011 to 2015, respectively. Other cancer and not in BEIR VII showed lower, but similar HR per mGy for these time periods. Therefore, the statistically significant HR per mGy for Total cancer was explained by Organ-specific cancer (Table 6). In hunters, an almost identical pattern was seen with the highest adjusted risk HR per mGy seen in Organ-specific cancers (Table 7). The adjusted HR per mGy was consistently lower suggesting a slight positive confounding from rural/non-rural, education and pre-Chernobyl cancer incidence. Analyzing by birth cohort did not change these patterns with Organ-specific showing the highest adj HR per mGy in all the comparisons of birth cohorts without identifying any pattern of susceptible specific birth cohort (data not shown).

Within the category of Organ-specific cancers, significant increased adj HR per mGy was seen in stomach adj HR per mGy 1.032 (95% CI 1.008–1.056), colon 1.024 (1.009–1.038), prostate cancer 1.022 (1.016–1.029) in the full cohort and lung cancer 1.043 (1.006–1.081) in hunters. Considering the confidence intervals, no additional Organ-specific cancers showed a statistically significant HR per mGy (Figs. 3 and 4).

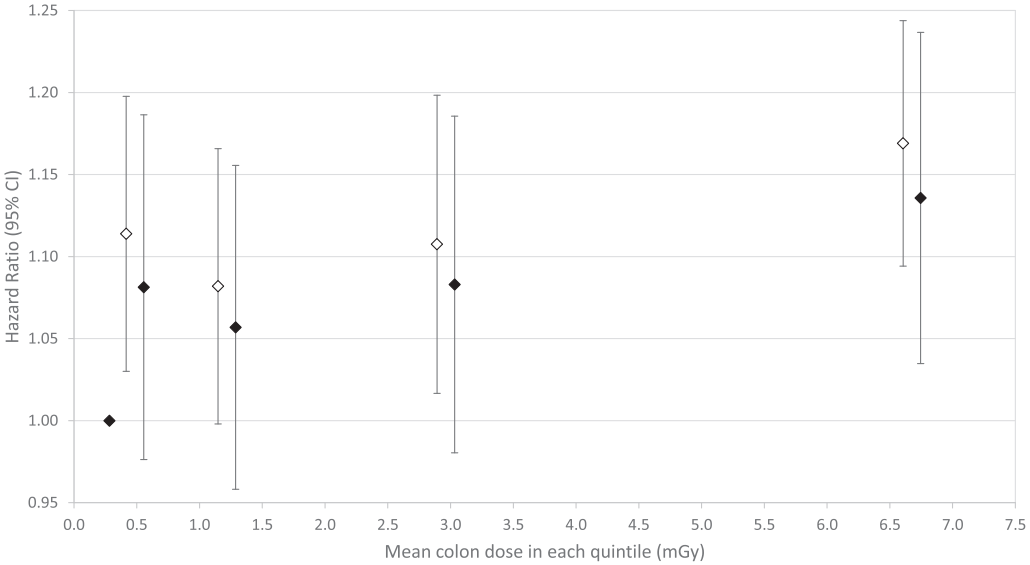

Fig. 2. Total cancer in hunters. Hazard Ratio (HR) in quintiles, with lowest quintile as reference category, is given with 95% Confidence Intervals (95% CI) for the follow-up period 1 January 1991 to 31 December 2015. Crude HR (open diamond) and HR adjusted by urban lifestyle, socioeconomic status and pre-Chernobyl total cancer incidence (filled diamond).

Table 6
Cancer classification according to BEIR VII for the full cohort. Hazard Ratio (HR) per mGy total colon dose is given with 95% Confidence Intervals (95% CI). Two follow-up periods 1 January 1991 to 31 December 2015 and 1 January 2011 to 31 December 2015, respectively.

		HR per mGy (95% CI)			
Time periods		Organ-specific	Other cancer	Not in BEIR VII	Total cancer
1991–2015	Crude	1.019 (1.014–1.023)	1.010 (1.003–1.016)	0.999 (0.985–1.013)	1.015 (1.011–1.018)
	Adjusted[a]	1.019 (1.014–1.024)	1.002 (0.995–1.009)	1.002 (0.987–1.017)	1.013 (1.009–1.017)
2011–2015	Crude	1.023 (1.015–1.033)	1.004 (0.991–1.018)	0.979 (0.952–1.007)	1.015 (1.008–1.022)
	Adjusted[a]	1.022 (1.013–1.032)	0.997 (0.984–1.011)	0.969 (0.941–0.998)	1.011 (1.004–1.019)

[a] Adjusted by urban lifestyle, socioeconomic status and pre-Chernobyl total cancer incidence.

Table 7
Cancer classification according to BEIR VII for hunters. Hazard Ratio (HR) per mGy total colon dose is given with 95% Confidence Intervals (95% CI). Two follow-up periods 1 January 1991 to 31 December 2015 and 1 January 2011 to 31 December 2015, respectively.

		HR per mGy (95% CI)			
Time periods		Organ-specific	Other cancer	Not in BEIR VII	Total cancer
1991–2015	Crude	1.016 (1.005–1.028)	1.017 (1.001–1.033)	1.007 (0.970–1.046)	1.018 (1.009–1.027)
	Adjusted[a]	1.014 (1.001–1.027)	1.008 (0.991–1.026)	0.994 (0.953–1.036)	1.013 (1.003–1.022)
2011–2015	Crude	1.035 (1.013–1.059)	0.999 (0.965–1.035)	0.943 (0.870–1.023)	1.020 (1.001–1.038)
	Adjusted[a]	1.033 (1.008–1.059)	0.988 (0.950–1.027)	0.923 (0.845–1.007)	1.013 (0.993–1.033)

[a] Adjusted by urban lifestyle, socioeconomic status and pre-Chernobyl total cancer incidence.

4. Discussion

The average time-integrated absorbed colon dose, during 30 years after the Chernobyl NPP accident, to the individuals in our cohort is low, even after considering the maximum colon dose of 14.10 mGy. Assuming that the average colon absorbed dose of 1.73 mGy is delivered relatively homogeneously to the whole body, the effective dose will be numerically similar, it can be compared to the annual Swedish average from the natural background radiation of 1.12 mSv, excluding radon contribution (Åkerblom et al., 2005). The average colon dose in hunters were higher and dominated by internal exposure compared to the full cohort. As we in our study have included not only the three most contaminated counties, but instead all 9 counties, the lower average absorbed colon doses in all hunters in our study do not contradict previous findings (Tondel et al., 2017). Few studies have investigated internal radiation dose in hunters after the Chernobyl NPP accident. In the Czech republic a small group of hunters have been followed 1999 to 2015 with an estimated annual committed effective dose of 0.010–0.052 mSv and in Germany a maximum annual effective dose of 0.035 mSv was calculated after whole body counting in hunters and probands 2018 to 2020 (Škrkal et al., 2017; Meisenberg and Gerstmann, 2021). A few hunters consuming predominantly wild boar meat the first year after the Fukushima accident had a committed effective dose of 1 mSv, about half of the time-integrated average absorbed total colon dose in our hunters 1986 to 2015 (Hayano et al., 2013). The Swedish hunter's exposure can also be compared with a maximum estimated effective dose, in an area with the highest ^{137}Cs deposition in Poland, after the Chernobyl NPP accident where the doses to hunters did not exceed 0.13 mSv per year after 2012 (Oloś and Dołhańczuk-Śródka, 2021). In

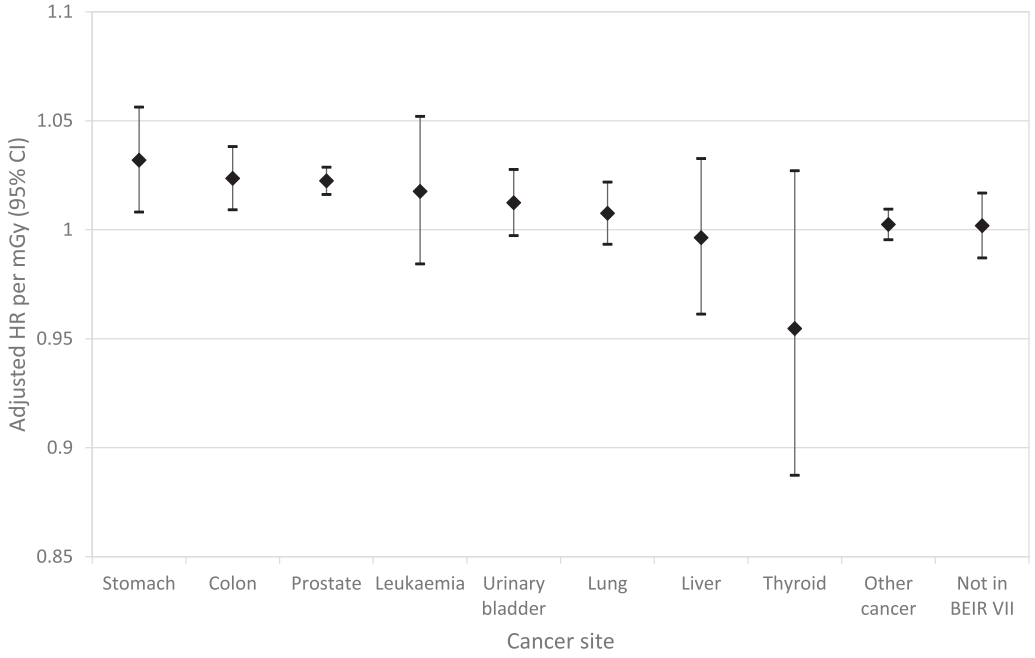

Fig. 3. Organ specific cancer according to BEIR VII, other cancer and Not in BEIR VII presented in the full cohort. Follow-up period from 1 January 1991 to 31 December 2015. Hazard ratio (HR) adjusted by urban lifestyle, socioeconomic status and pre-Chernobyl total cancer incidence per mGy total colon dose.

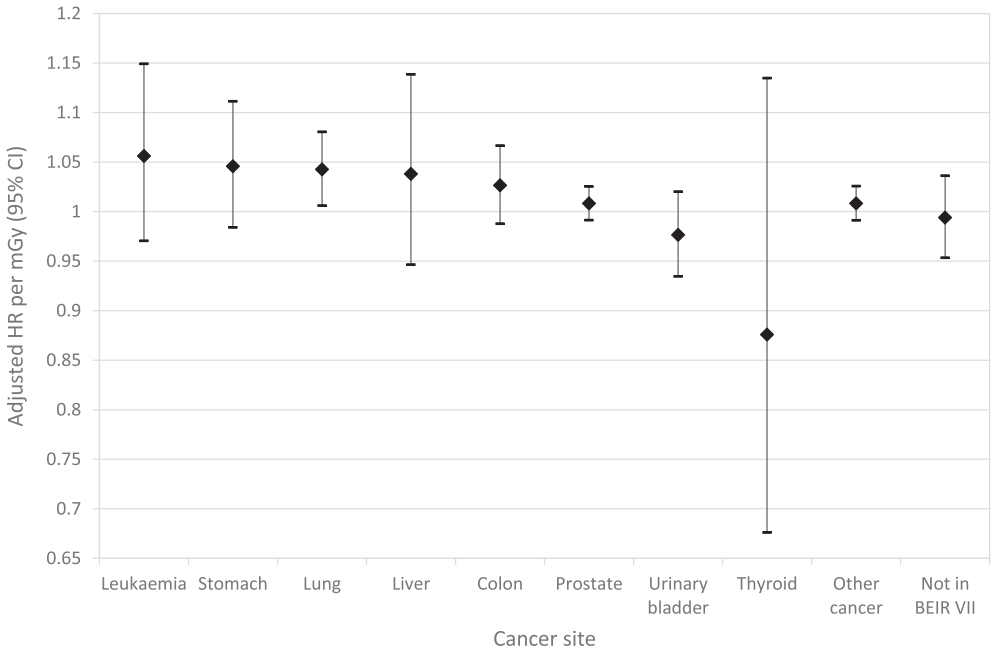

Fig. 4. Organ specific cancer according to BEIR VII, other cancer and Not in BEIR VII presented for hunters. Follow-up period from 1 January 1991 to 31 December 2015. Hazard ratio (HR) adjusted by urban lifestyle, socioeconomic status and pre-Chernobyl total cancer incidence per mGy total colon dose.

Norway whole body counting was performed on a small group of farmers-hunters with annual dose of 0.37, 0.57 and 0.67 mSv for the years 1987, 1988 and 1989, respectively (Strand et al., 1992).

In epidemiological studies on external ionizing radiation the red bone marrow dose (Gy) has often been used to estimate the dose-response relationship with leukaemia, but for solid cancers the colon dose (Gy) has been assumed to better representing the exposure to the whole body. The INWORKS is a cohort of workers in the nuclear industry in France, the United Kingdom, and the United States and the absorbed dose to the red bone marrow has been calculated for each individual (average 15.9 mGy) to study the relationship with leukaemia, lymphoma, and multiple myeloma, respectively (Leuraud et al., 2015). In another study of INWORKS cohort the colon dose (average 22.8 mGy in males) was used as a proxy to represent the exposure to the rectum, peritoneum, bone/connective tissue and remainder (Richardson et al., 2018). Colon dose has also been used in epidemiological studies on diagnostic X-ray, average population cumulative colon dose 12.6 mSv in males up to 50 years of age (Marant-Micallef et al., 2019). Thus, in our study we have chosen the absorbed dose to the colon to represent the external contribution to the average whole-body dose, not only because used in prior studies but also relying on the

relatively uniform body organ exposure to radiation from both external and internal Chernobyl sources in our studied cohort.

Moreover, epidemiological cancer research in protracted low dose radiation exposure has often relied only on the external absorbed dose ignoring the contribution from the internal dose (e.g. Alinaghizadeh et al., 2016; Auvinen et al., 2014; Tondel et al., 2004; Tondel et al., 2006; Tondel et al., 2020). Unfortunately, only a few studies have tried to estimate the absorbed doses after internal contamination, but attempts have been made in the Techa River cohort and after diagnostic nuclear medicine procedure, respectively (Degteva et al., 2009; Marant-Micallef et al., 2019). The total stomach dose in the Techa River follow-up was 52 mGy with a statistically significant linear dose-response for all solid cancer and in diagnostic nuclear medicine the average population cumulative colon dose was 0.75 mSv in males up to 50 years of age with estimated 0.5% of all new cancer cases annually attributed to diagnostic medical ionizing radiation, respectively (Davis et al., 2015; Marant-Micallef et al., 2019). Using existing organ dose coefficients for colon made it possible for us to calculate the internal absorbed colon dose as a proxy for the whole body and convenient to add with the external colon dose creating a total absorbed colon dose in mGy. Overall, the total absorbed colon dose in our study was one order of magnitude lower than in other similar epidemiological studies with thoroughly assessed radiation doses.

If the linear no-threshold (LNT) hypothesis holds, a priori finding was confirmed that adjusted HR per mGy absorbed colon dose was increased both in the full cohort and in the hunter subcohort. This increased HR explains the overall increased HR per mGy seen in Total cancer and is somewhat leveled out by no increase seen in Other cancer and in Not in BEIR VII radiation associated cancer. Advantages of using the second time window of follow-up from 2011 to 2015 is both that the surviving cohort has attained maximum time-integrated dose, but also because it allows to study cancer sites with longer latency. The pattern of dose-response relationship is almost identical in the last 5 years of follow-up compared to 1991 to 2015 and therefore does not refute the hypothesis. We would be reluctant to translate our risk estimates outside our dose-range with a potential risk of multiplying errors resulting in far-reaching conclusions. The adjusted HR per mGy in the total cohort and for all type of cancer incidence during the follow-up period from 1991 to 2015 is 1.013 (1.009–1.017) i.e. a point estimate about 32 times higher than the corresponding HR for mortality in the Life Span Study (Nakashima, 2015). Our risk estimate with a HR of 1.013 is to some extent influenced by the increased HR in the second quintile and therefore probably overestimate the overall risk when applying a linear function. However, adjustment for various potential confounding factors did not change the patterns when total cancer incidence was analyzed in quintiles. Therefore, we have not able to identify why there is a relatively steep increase from first to second quintile. An alternative could have been to analyse the data with a non-linear model that could have fit the data better, but then we could not have been able to compare the results with other risk estimates. To allow comparison the Excess Relative Risk (ERR) in the Life Span Study (LSS) has been converted to HR = ERR + 1. However, for the low-dose region below 50 mSv the upper confidence limit for solid cancer mortality the LSS will almost reach the lower confidence limit in our study, but in the follow-up period 2011 to 2015 the lower confidence limit will overlap with a HR 1.011 per mGy (1.004–1.019). Moreover, the ERR values of cancer mortality is assumed to be somewhat less than that for cancer *incidence* which has been used to calculate our adjusted HR (Table 6).

In the 8 cancer sites within the Organ-specific group, stomach, colon and prostate cancer showed increased HR per mGy in the full cohort, but only lung cancer showed a significant HR per mGy in hunters. A similar finding with increased colon cancer has been seen in women in Finland after the Chernobyl NPP accident with an Excess Rate Ratio of 0.06 (95% CI 0.02–0.11) per mSv, but not for other cancer sites (Auvinen et al., 2014). However, the dose assessment in the Finnish study only relied on external dose for the first year post-accident when we instead used time-integrated absorbed colon dose considering both internal and external contribution to the colon dose.

The strength of our study is the size and the detailed time-integrated dose assessment on individual level including both internal and external absorbed dose, taking into account also hunter status. Including only male adults will minimize the possibilities of family members, as partners or children, consuming the game resulting in misclassification of exposure. The high resolution from the aerial measurements of ^{137}Cs made it possible for us to achieve a detailed dose assessment for the external colon dose. The relatively large database on whole body counting was essential for relatively accurate predict internal colon dose. Expressing the cancer risk by HR per mGy, was justified by the LNT-model, but had also support in our quintile analysis (ICRP, 2007). Moreover, the linear statistical model enabled us to use the full dose range with dose as a continuous variable, not restricted and sensitive to defining dose categories including creating a reference category. A similar statistical method has recently been used when analyzing childhood cancer in relation to background radiation, including the contribution from ^{137}Cs fallout in Switzerland from the Chernobyl NPP accident. In the Swiss study, the Hazard Ratio per 1 mSv increase in cumulative dose of external background radiation was higher than in our study, and estimated to be 1.04 (95% CI 1.01–1.06) for all cancer combined (Mazzei-Abba et al., 2021). Adjustments for a priori confounding factors had minimal impact on the HR in our study suggesting a small remaining influence from unidentified confounding factors affecting the overall result. Studying the population in Northern Sweden could to some extent take geographical difference in lifestyle, excluding larger cities in South Sweden, into account and at the same time achieve a maximum contrast in radiation dose. Including counties in South Sweden would not have given any extra information of ^{137}Cs exposure, but instead expanded the non-exposed group including geographical distributed risk factors. The population registries are of high quality in Sweden and by using the individual social identity number as a matching variable in the registries we could avoid misclassification of individuals. Another strength is the accuracy regarding histological verified diagnosis in the cancer registry where validation studies has shown a completeness of malignancies over 96% (Mattsson, 1984; Barlow et al., 2009). Precision has been increased in the study design by excluding persons free of cancer at baseline which avoids a potential secondary cancer caused by treatment of cytostatics and/or radiation, hence with a risk of masking an effect from ^{137}Cs. Moreover, our dose model can be used in other populations to give additional information on dose-response at low protracted doses for future pooling of data to achieve higher statistical power.

The limitation in our study is mainly lack on information about lifestyle in the individuals i.e. we assume that all hunters have the same diet of game over time. This could result in a misclassification in the internal dose assessment, however most probably random. We only take into account hunters in 1986, excluding new hunters. If male relatives eat game meat from the hunters they will not be included in the hunter category, but most probably at an ignorable proportion in the full cohort. Due to low numbers of female hunters we decided to limit our study to the male population. Our model for individual dose estimations also suffers from lack of individual shielding factors for snow cover (f_{snow} by county) and building material (f_{shield} 0.4 for all), to some extent compensated by the division in rural and non-rural living with more snow cover and higher proportion of the population living in wooden houses in the rural areas resulting in less and more shielding, respectively. All individuals have been assigned to the same time fraction spent outdoor (f_{out} 0.2) ignoring people working outdoors and a life-style with more outdoor activities, but studying our two cohorts separately and also by division in rural habitat can probably to some extent adjust for this potential confounding. Moreover, contribution from terrestrial gamma radiation is not taken in account when calculating the external absorbed colon dose, a potential confounding factor if there is a positive or negative correlation to the ^{137}Cs fallout. In the relation between radiation dose and thyroid cancer we ignored the absorbed dose contribution from ^{131}I to the thyroid, however radioiodine would not significantly have contributed to the absorbed colon dose influencing other cancer sites. Potential confounding factors could be various socioeconomic factors reflecting lifestyle that might have influenced some cancer sites and assert

confounding, but only if such factors also would correlate with ^{137}Cs exposure.

5. Conclusions

The total colon dose was low compared to other epidemiological studies that have included internal contamination. Nevertheless, a dose dependent increased risk of Organ-specific cancer was identified both in the full cohort an in hunters explaining the increased HR per mGy seen in Total cancer during the follow-up period from 1991 to 2015. Almost the same pattern could be seen in the second time-window 2011 to 2015 supporting a potential contribution of radiation dose to the increased cancer incidence. Unless not explained by remaining confounding our risk estimates are somewhat higher, but after considering the confidence limits, probably consistent with the LSS findings, but only in the low dose interval in that cohort. The increased risk of stomach, colon and prostate cancer, considered as cancer sites associated with radiation, could be attributed to the radioactive fallout from the Chernobyl NPP accident, and therefore warrants further investigation. The lack of statistical significant increased risk in other cancer sites, previously associated with radiation, could theoretically be explained by low statistical power.

The slightly higher HR per mGy in hunters, but with larger statistical uncertainties could be explained either by low statistical power in hunters, misclassification of exposure resulting in attenuated risks, preventive factors in the hunters lifestyle, or merely that the results found in the total cohort could be explained by uncontrolled confounding. However, of those potential confounding factors we could adjust for it showed weak confounding. In cancer sites not regarded as associated with ionizing radiation there was no identified cancer risk, as the a priori assumption, giving additional support to the finding of a possible radiation effect in Organ-specific cancer. Our study has also illustrated the importance of analyzing cancer sites separately instead of lumping together into larger groups like total cancer. Finally, all our findings need to be interpreted with caution taking into account the limitations inherit in all epidemiological studies at low doses.

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CRediT authorship contribution statement

Martin Tondel: Conceptualisation, Methodology, Validation, Investigation, Resources, Writing – Original Draft, Writing – Review & Editing, Visualization, Supervision, Project administration, Funding acqusition.

Tobias Nordquist: Methodology, Software, Validation, Formal analysis.

Mats Isaksson: Conceptualisation, Methodology, Software, Validation, Investigation, Resources, Writing – Review & Editing.

Christopher Rääf: Conceptualisation, Methodology, Software, Validation, Investigation, Resources, Writing – Review & Editing.

Robert Wålinder: Conceptualisation, Methodology, Validation, Resources, Writing – Review & Editing.

Declaration of competing interest

The authors have no competing financial interests.

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