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Non-thyroid cancer in Northern Ukraine in the post-Chernobyl period: Short Report

M Hatch[1,*], **E Ostroumova**[1], **A Brenner**[1], **Z Federenko**[3], **Y Gorokh**[3], **O Zvinchuk**[2], **V Shpak**[2], **V Tereschenko**[2], **M Tronko**[2], and **K Mabuchi**[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

[2]Institute of Endocrinology and Metabolism, Kiev, Ukraine

[3]National Cancer Registry of Ukraine, National Cancer Institute, Kiev, Ukraine

Abstract

The Chernobyl nuclear power plant accident in Ukraine in 1986 led to widespread radioactive releases into the environment - primarily of radioiodines and cesium – heavily affecting the northern portions of the country, with settlement-averaged thyroid doses estimated to range from 10 mGy to more than 10 Gy. The increased risk of thyroid cancer among exposed children and adolescents is well-established but the impact of radioactive contamination on the risk of other types of cancer is much less certain. To provide data on a public health issue of major importance, we have analyzed the incidence of non-thyroid cancers during the post-Chernobyl period in a well-defined cohort of 13,203 individuals who were <18 years of age at the time of the accident. The report is based on Standardized Incidence Ratio (SIR) analysis of 43 non-thyroid cancers identified through linkage with the National Cancer Registry of Ukraine for the period 1998 through 2009. We compared the observed and expected number of cases in three cancer groupings: all solid cancers excluding thyroid; leukemia; and lymphoma. Our analyses found no evidence of a statistically significant elevation in cancer risks in this cohort exposed at radiosensitive ages, although the cancer trends, particularly for leukemia (SIR=1.92, 95% Confidence Interval: 0.69; 4.13), should continue to be monitored.

Keywords

ionizing radiation; Chernobyl accident; cancer incidence; standardized incidence ratio; ecological study

[*]Correspondence to: Radiation Epidemiology Branch, National Cancer Institute, 9609 Medical Center Drive, Bethesda, Maryland 20892, USA. Fax: 240-276-7840; hatchm@mail.nih.gov.

Author Contributions

Drs. Hatch, Ostroumova, Brenner and Mabuchi participated in the design of the study, the statistical analysis and the drafting of the manuscript. Dr. Federenko and Mr. Gorokh provided the cancer incidence data used in the analysis. Mrs. Zvinchuk and Shpak contributed to data analysis and review of the manuscript. Drs. Tereschenko and Tronko reviewed the study design and the draft of the manuscript.

Introduction

The accident at the Chernobyl Nuclear Power Plant on April 26, 1986 contaminated many areas of Ukraine, Belarus and the Russian Federation with a complex mixture of radionuclides, primarily radioiodines and cesium(1;2). Radioiodines concentrate in the thyroid gland, and the main health effect observed to date among those exposed to Iodine-131 (I-131) in fallout at young ages is a striking increase in the incidence of thyroid cancer (reviewed in(1–3)). In addition to internal thyroid irradiation due to I-131, the populations of contaminated areas were exposed to external radiation from radionuclides deposited on the ground and cesium isotopes (Cs-134 and Cs-137) incorporated into locally produced food. Because cesium distributes homogeneously throughout the body and irradiates various tissues and organs, there is a possibility that the incidence of cancers other than thyroid may also have increased after the accident, although the average estimated whole-body doses accumulated over 20 years after the accident are low (< 10 mSv, with a range from a few to hundreds of millSieverts)(4).

A 2006 estimation of the risk for all of Europe projected that in 1986–2006 as many as 1000 cases of thyroid cancer and 4000 cases of other cancers might occur as a result of exposure to Chernobyl fallout(5). In residents of the most exposed areas, there have been reported increases in non-thyroid cancers, including such radiation-related malignancies as leukemia(6;7) and breast cancer(8;9). However, the breast cancer studies are based on group-average trends in cancer incidence, and the case-control results for radiation-induced leukemia in exposed young people may have reflected a sampling bias(3). Other studies of leukemia in childhood (10;11) found no association with radiation from Chernobyl. Studies of leukemia risk in children exposed while *in utero* have also produced conflicting results(12–14). Because the evidence to date regarding a post-Chernobyl increase in risk of non-thyroid cancers is uncertain, it is important to monitor incidence rates for all cancer types to fully characterize the burden of Chernobyl-related diseases over time. Follow-up of those exposed to radioactive fallout at the most susceptible ages is particularly important.

To provide data on an important public health issue, we have analyzed cancer incidence data through 2009 on more than 13,000 residents of the most contaminated regions of Northern Ukraine who were exposed to I-131 from Chernobyl fallout as children or adolescents. Previously we have reported on thyroid cancer cases detected in this cohort during in-depth clinical screening examinations, and have described the strong, linear dose-response relationships for I-131 and thyroid carcinoma(15). Here we focus on non-thyroid cancer in cohort members, using record linkage with the database of the National Cancer Registry of Ukraine (NCRU), and compare the incidence to Ukraine as a whole.

Material and Methods

Study Area

The study area in the heavily affected northern region of Ukraine consists of Chernihiv, Zhytomyr and Kyiv oblasts (an oblast is an administrative area similar in size to a state or province), as well as Kyiv City. This is an area covering approximately 90,000 sq. km, with a population of about 7 million (or 14.6% of all Ukraine). Maps of Cs-37 deposition show that exposure levels throughout the study area are low, with little variation among the oblasts studied. Estimates of region-specific average whole-body doses accumulated over the period 1986–2005 were 1.7 mSv in Chernihiv oblast, 5.7 mSv in Zhytomyr, 3.9 mSv in Kyiv oblast and 1.3 mSv in Kyiv City(16).

Study Subjects

Cohort construction is described in detail elsewhere(17). In brief, the cohort of 13,203 subjects exposed in childhood and adolescence includes individuals who were under 18 years of age on the day of the accident (April 26, 1986); had direct measurements of thyroid radioactivity performed shortly after the accident; resided in Chernihiv, Zhytomyr and Kyiv oblasts or in Kyiv City; and were screened for thyroid disease in 1998, at the first of serial screening examinations designed to detect thyroid disorders in cohort members. *In utero*-exposed individuals were not included in the cohort.

Cancer Incidence Data

Cancer incidence is monitored through regular linkage of the cohort data with data from the National Cancer Registry of Ukraine (NCRU) (http://www.ncru.inf.ua). To increase linkage accuracy, demographic information on cohort members is updated regularly through mail and telephone contacts as well as outreach by local medical personnel. The NCRU, part of the Institute of Oncology of the Academy of Medical Sciences of Ukraine, began in 1988 and by 1997 had reached near universal coverage. The Registry is population-based, relying on mandatory notifications from medical practitioners of all cancers diagnosed in living or deceased patients. To increase accuracy of the linkage, each notification contains demographic data as well as information on cancer diagnosis and is supplemented by clinical data from in-patient charts. The data are entered into a cancer registry at the local level and submitted in electronic form to the NCRU. The vast majority of diagnoses reported to the Registry are confirmed by pathological and morphological findings, with less than 1.5% based on death certificates only. The delay to registration is minimal (~ 95% of cases entered in the year of diagnosis. The NCRU carries out follow-up activities to check on patients' vital status and degree of disability.

We performed a linkage of the cohort data with a sample of data from the NCRU. The Registry sample consisted of 3,836 subjects born in Ukraine in 1968–1987 with a cancer diagnosis established from the earliest date possible to the end of 2009. The linkage procedure was based on a computerized deterministic record linkage technique with probabilistic elements (described in detail in Howe, 1998(18)) which has proved to be a reliable tool for cohort studies requiring linkage with a "live registry". The technique incorporates a set of comparison functions based on the value of each identifier on each record. Through these computerized comparisons, a probability is estimated that matched records are a true link.

We used subjects' gender, full name (last, first, patronymic), date of birth (day, month and year of birth), and complete residential address as link identifiers. For each identifier a weight was assigned and the weights were then summed. All links with a weight suggesting the matched records were a possible link were reviewed manually by a panel of six independent experts, using updated information on key link attributes collected during follow-up of the cohort. Only after manual reviews was a link determined to be ‘true’ or ‘false’.

Statistical Analysis

We calculated person-years at risk from the date of the first screening (the earliest was 14.04.1998) through December 31, 2009, or the earliest of the following: date of cancer diagnosis, date of death, or date of migration. For estimation of the SIRs, we stratified person-years and cancer cases by categories of sex, age at exposure (<10, 10–14, 15+), attained age (5-year groups from 10 to 45), oblast of residence at the time of the accident (Zhytomyr, Chernihiv, Kyiv, including Kyiv City) and calendar time (1998–2002, 2003–2005, 2006–2009). Person-year computations and standardized incidence ratio (SIR) analyses were performed using Epicure software(19).

To estimate the SIR – the ratio of the observed to the expected number of cancer cases - we calculated the number of expected cases for each cancer site or grouping using national sex-, age- and calendar-period-specific rates in the Ukrainian population. SIRs were calculated with 95% confidence intervals (CI) assuming a Poisson distribution of the data. Significance tests for heterogeneity or trend and CIs were determined directly from maximum likelihood analysis; all p-values are derived from two-sided tests, with a p-value of < 0.05 considered statistically significant.

SIR analyses were carried out for three outcome categories: all solid cancers (excluding thyroid) and two groupings of hematopoetic malignancies: leukemia and lymphoma. We also estimated the SIR for breast cancer as a site of major public concern, taking into account only female person-years at risk.

Results

The main characteristics of study subjects are presented in Table 1. Women comprised slightly more than half of the cohort (51%). The mean attained age of subjects in 2009 was 31 years; mean age at the time of the accident was 8 years. Because cohort members were relatively young, losses to follow-up due to death or migration were few (1.7% and 1.8% respectively). At the time of the accident, the majority of cohort members (52.5%) were residents of Chernihiv oblast.

Forty-three incident non-thyroid cancers were identified among the 13,203 members of the cohort exposed to accident fallout in childhood during an average follow-up period of 12 years. The most frequent malignancies were lymphomas (9 cases), cancers of female genital organs (9 cases, including 8 cancers of the cervix uteri), digestive cancers (6 cases), breast (5 cases) and leukemia (5 cases). In addition to the 43 non-thyroid cancers, the cohort also included 45 prevalent and 65 incident thyroid cancers, resulting in a total of 153 cancer cases, out of which 29, or 19%, were solid cancers and 14 (9.2%) were hematological malignancies.

SIR estimates are presented in Table 2. There were no statistically significant findings overall for any of the cancer groupings analyzed. The SIR for the category of solid cancers excluding thyroid was less than 1.00 (SIR=0.73), while the SIRs for leukemia and lymphoma showed modest elevations in risk (SIR=1.92 and SIR=1.23, respectively), with both estimates based on small numbers of cases. Breast cancer incidence was not raised compared to national incidence rates (data not shown).

Table 2 also presents results of SIR analyses stratified by sex, age at exposure, attained age, oblast of residence and calendar time. For solid cancers excluding thyroid, we observed significant heterogeneity in the SIRs by oblast of residence in 1986 (p for heterogeneity = 0.04), mainly due to the higher SIR in Chernihiv oblast (21 cases) compared to the SIRs for Zhytomyr and Kyiv oblasts (8 cases). There was no significant heterogeneity by age at exposure (p=0.09), although the SIR for non-thyroid solid cancer in those 0–9 at the time of the accident (SIR=0.44) was significantly lower than 1.00. Based on a total of five leukemia cases, there was suggestive, non-significant heterogeneity in the SIRs by sex (p=0.08), with females having a higher (and significantly elevated) SIR (4 cases) than males (1 case). While the overall trend with attained age was not significant (p=0.12), the SIR for leukemia in the oldest age group (30–41) was significantly elevated. For lymphoma, as for solid cancers, significant variation was observed for oblast of residency (p=0.05), again with a higher SIR for Chernihiv oblast relative to Zhytomyr and Kyiv oblasts; there was no variation in the SIRs for lymphoma by sex, age at exposure, attained age or calendar time (p>0.5 in each case).

Discussion

In this follow-up of 13,203 individuals from Northern Ukraine who were exposed to Chernobyl fallout at young ages, we found no evidence of a statistically significant overall increase in the incidence of non-thyroid cancers, leukemias or lymphomas compared with national rates. These results are consistent with expectation given the low levels of exposure, young age of study participants, and relatively short follow-up period. There were no unexpectedly large increases in risk found for any of the cancer groupings examined. In addition, the pattern of SIRs for non-thyroid cancers and leukemia by oblast of residence in 1986, did not correlate with the estimates of mean oblast dose, although these are only an indicator of individual exposure.

In the case of leukemia, the cancer seemingly most sensitive to radiation, our SIR analysis did show a modest, statistically non-significant elevation in risk (SIR=1.92), with a wide confidence interval (0.69–4.13) reflecting the small number of cases (n=5). We found that for females the leukemia SIR was significantly greater than 1.00, and was higher than the SIR for males. The observed pattern of leukemia SIRs by age, with the highest SIR in the oldest age group, is inconsistent with the pattern of radiation-related leukemia risk in atomic bomb survivors (decreasing ERR/Gy with increasing age)(20). However, for age at exposure we did observe, as expected, the highest SIR in the youngest age group. We have no data on leukemia in the first decade following the accident, when radiation-related increases would be likely to occur. The data presented here together with the results from earlier studies(6;7;10;11) are inconclusive regarding the leukemogenic effect of radiation exposure in areas contaminated by Chernobyl fallout. However, they do indicate the need for further monitoring.

In spite of some earlier evidence suggesting a post-Chernobyl increase in risk of breast cancer among female clean-up workers(9) and women living in affected regions(8), the SIR for breast cancer in our childhood-exposed cohort was not statistically significantly elevated. However, the women are only in their early 30s and will remain in the pre-menopausal age group for some time, underscoring the importance of further follow-up.

Our study is based on a comparison of post-Chernobyl cancer incidence in cohorts of individuals from areas of Ukraine contaminated by fallout with the sex-, age- and time-specific rates for Ukraine as a whole. A major limitation is the lack of individual estimates of radiation dose so that we are unable to classify study subjects according to levels of exposure. Our statistical power was another major limitation, restricted by sample size, low exposure levels and short follow-up time. We cannot rule out that several significant findings in subgroup analyses, including the lower SIR for non-thyroid solid cancers in the 0–9 age group and the trends with oblast-dose, could be due to chance. The study does have several strengths, however, principally its focus on the cancer experience of the most susceptible age groups from one of the most affected areas. Linkage with the national cancer registry, based on updated cohort information and including a manual review by experts, is another strength. For the period of follow-up beginning in 1998, we believe registry-based case ascertainment to be essentially complete. The high quality of the NCRU has been recognized by its inclusion in the current edition of IARC's "Cancer in Five Continents," a compilation of data from population-based registries worldwide.

Our finding of no statistically significant increase to date in the estimated SIR for non-thyroid cancers or hematologic malignancies should provide some reassurance to concerned residents of the study area. The data revealed no unexpected radiation effect, although statistical power was limited by the cohort' size and the relatively small number of cases. It remains critical to continue surveillance of cancer incidence patterns in these groups – including the trends for leukemia and breast cancer - as the cohort approaches ages when marked increases in cancer incidence are expected.

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Abbreviations

I-131	Iodine-131
NCRU	National Cancer Institute of Ukraine
Cs	Cesium
SIR	Standardized Incidence Ratio

CI Confidence Interval

mSv milliSievert

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Highlights

- First systematic report on non-thyroid cancer incidence post-Chernobyl in Ukraine
- Well-defined cohort exposed at radiosensitive ages
- Cancers ascertained through linkage with high-quality Registry
- No significant increase to date in estimated SIRs
- Trends for leukemia warrant continued follow-up

Table 1

Descriptive characteristics of the cohort of Chernobyl-exposed children and adolescents, northern Ukraine

Characteristics	Number (%)
Cohort size	13,203
Females	6,704 (50.8)
Deceased	251 (1.9)
Lost to follow-up	236 (1.8)
Oblast of residence at the time of the accident:	
- Zhytomyr oblast	3,666 (27.8)
- Kyiv oblast & Kyiv city	2,599 (19.7)
- Chernihiv oblast	6,938 (52.5)
Mean attained age at the end of follow-up (31.12.2009), years	31.4 ± 4.7
Number of non-thyroid cancers (C00 – C96, except C73)	43
Number of person-years	130,475

Table 2

Standardized Incidence ratios (95% CI) for non-thyroid cancers in a cohort of Chernobyl-exposed children and adolescents in comparison to the general population of Ukraine, by selected characteristics, follow-up period, 1998–2009

Parameter	Solid cancers except thyroid (C00–C80 except C73)			Leukemia (C91–C95)			Lymphoma (C81–C90)		
	Obs	Exp	SIR, 95% CI	Obs	Exp	SIR, 95% CI	Obs	Exp	SIR, 95% CI
Total	29	39.8	0.73 (0.49 – 1.03)	5	2.6	1.92 (0.69 – 4.13)	9	7.3	1.23 (0.59 – 2.22)
Gender									
Males	11	14.5	0.76 (0.39 – 1.30)	1	1.5	0.67 (0.04 – 2.93)	4	3.4	1.17 (0.36 – 2.71)
Females	18	25.4	0.71 (0.43 – 1.09)	4	1.1	3.63 (1.13 – 8.44)	5	3.9	1.29 (0.46 – 2.78)
P for heterogeneity[1], df = 1			0.86			0.08			0.88
Age at exposure, yrs									
0 – 9	7	16.0	0.44 (0.19 – 0.84)	3	1.6	1.83 (0.45 – 4.74)	6	4.7	1.28 (0.51 – 2.60)
10 – 14	19	18.2	1.05 (0.64 – 1.59)	1	0.8	1.29 (0.08 – 5.70)	3	2.2	1.37 (0.34 – 3.55)
15 – 18	3	5.6	0.53 (0.13 – 1.38)	1	0.2	5.34 (0.30 – 23.49)	0	0.4	0 (0.00 – 4.46)
P for trend[2], df=1			0.25			0.16			0.64
Attained age, yrs									
12 – 19	1	1.6	0.62 (0.04 – 2.71)	0	0.5	0.00 (0.00 – 3.91)	1	0.8	1.24 (0.07 – 5.44)
20 – 29	12	15.3	0.78 (0.42 – 1.31)	2	1.4	1.45 (0.24 – 4.49)	6	4.4	1.35 (0.54 – 2.74)
30 – 41	16	22.9	0.70 (0.41 – 1.10)	3	0.7	4.08 (1.02 – 10.59)	2	2.1	0.97 (0.16 – 3.01)
P for trend, df=1			0.48			0.12			0.63
Oblast of residency									
Chernihiv	21	19.6	1.07 (0.68 – 1.60)	1	1.4	0.74 (0.04 – 3.25)	7	3.8	1.84 (0.79 – 3.57)
Zhytomyr	4	11.3	0.35 (0.11 – 0.82)	2	0.7	2.70 (0.45 – 8.33)	0	2.1	0.0 (0.00 – 0.93)
Kyiv	4	8.9	0.45 (0.14 – 1.04)	2	0.5	3.95 (0.66 – 12.19)	2	1.4	1.38 (0.23 – 4.26)
P for heterogeneity, df = 2			0.04			0.31			0.05
Calendar time									
1998 – 2002	6	7.5	0.80 (0.32 – 1.62)	0	0.9	0.00 (0.00 – 2.20)	4	2.1	1.91 (0.59 – 4.44)
2003 – 2005	8	10.5	0.76 (0.35 – 1.42)	3	0.8	3.93 (0.98 – 10.20)	1	2.2	0.44 (0.03 – 1.96
2006 – 2009	15	21.8	0.69 (0.40 – 1.10)	2	1.0	2.07 (0.34 – 6.40)	4	3.0	1.35 (0.42 – 3.14)
P for trend, df =1			0.65			0.37			0.86

Abbreviations: Obs – number of observed cases; Exp – number of expected case; SIR –Standardized Incidence Ratio; CI – Confidence Interval.

[1] p for heterogeneity estimated for a model using categories of age at exposure, attained age and calendar year.

[2] p for trend estimated for a model using age at exposure, attained age or calendar year as continuous variables.

95% CI estimated from the maximum likelihood.