An Overview of Research Activities in the Former Soviet Union and a Summary of Results: Thyroid Cancer and Childhood Leukemia Following The Chernobyl Accident

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It is a pleasure to have this opportunity to briefly describe the research activities a team of investigators at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle have been engaged in for more than a decade to investigate the occurrence of thyroid cancer and childhood leukemia in persons exposed to the radiation released from the Chernobyl Power Station accident on April 26, 1986.

Beginning in the Spring of 1990, the Fred Hutchinson Cancer Research Center established communication with the leadership of the National Center for Hematology in Moscow as part of an effort to provide a bone marrow transplant to one of the helicopter pilots who worked in the initial days after the Chernobyl accident to try to bring the explosion and fires under control. As a result of this activity, a small group of scientists at the Hutchinson Center began to explore the feasibility of initiating population-based epidemiologic studies related to radiation exposure from Chernobyl. For approximately two years we spent considerable time developing relationships and assessing the resources available for conducting population-based research in what was then the Soviet Union.

Largely as a result of these efforts, in 1993 the International Consortium for Research on the Health Effects of Radiation (ICRHER) was formed to initiate a series of international collaborative studies investigating the health effects of radiation exposure resulting from the Chernobyl accident. This consortium was funded by the Office of Naval Research. The focus of the Consortium was to study the potential effects of radiation exposure in children and young adults in the areas of Ukraine, Belarus and Russia most heavily contaminated by radiation from the Chernobyl accident. The U.S. team based at the Fred Hutchinson Cancer Research Center has been responsible for studies in the Russian Federation, and has undertaken a number of studies in the Bryansk Oblast, which is the region of Russia most heavily contaminated by fallout from the Chernobyl accident. The most important and significant components of this collaborative work are three case-control studies of thyroid cancer in Russia and a three republic leukemia case-control study in Russia, Belarus, and Ukraine.

Close working relationships are now well-established with three teams of investigators in Russia. One team, under the leadership of Prof. Anatoly Tsyb and Dr. Valery Stepanenko, is based at the Medical Radiological Research Center in Obninsk. This group provides expertise in: 1) radiation dose estimation using physical dose reconstruction methods, including a field investigation unit; 2) clinical field investigations; and 3) molecular biology. The second team, under the leadership of Drs. Anatoly Proshin and Nikolay Rivkind, is based at the Bryansk Diagnostic Center. This group provides expertise in: 1) epidemiology and clinical field investigation; 2) identification of cancer cases from the population-based Bryansk Oncology Registry; and 3) access to the Bryansk Institute of Pathology, which maintains the repository of diagnostic materials for all of the Bryansk Oblast. The third team comprises a Data Coordination Office in Moscow, under the direction of Dr. Sergei Kulikov. This team provides centralized data management and analysis capabilities as well as information technology support for all three Russian teams. As a result of our ongoing collaborative efforts, the capability to conduct all phases of population-based epidemiologic studies to investigate radiation health effects is now firmly established for the population in the Bryansk Oblast.

The Seattle-Russian team has completed two population-based case-control studies of thyroid cancer in people who were under age 20 and residents of Bryansk at the time of the accident. The first study was conducted in the eight most highly contaminated regions of the Bryansk Oblast, and included diagnoses from the time of the accident through September 1997. A total of 26 cases of thyroid cancer were identified and were confirmed by an independent pathology review. All 26 cases were located and agreed to participate. Controls were identified from the Russian State Medical Dosimetrical Registry, which comprises a population roster of individuals who resided in these eight contaminated raions at the time of the accident.

A very unique and important aspect of this study, which distinguishes this study from most other efforts to date, is that we attempted to estimate an individual thyroid radiation dose for each case and control in the study. We used a physical dose reconstruction approach for this purpose (1), although we also experimented with biologically-based approaches in earlier aspects of the feasibility stages of the project. This approach is based primarily on measurements that were taken shortly after the accident, including measurements of I-131 in human thyroids and a number of environmental measurements taken in dozens of settlements throughout the Oblast.

To individualize the dose estimates for participants in this study we collected two kinds of information. First, we administered a personal interview to obtain details of each participant's residence history and dietary history after the accident, as well as special precautions they might have taken to avoid exposure. Second, we collected a series of physical samples from each person's home, including building materials, soil, water, and food. These items provided important additional information regarding dose and dose rate to supplement the settlement measurements used in developing the dose estimation models.

Results of this study, published in *Radiation Research* in 2004 (2), indicate that the risk of thyroid cancer was significantly increased in a dose-dependent manner among residents of the heavily contaminated regions of Bryansk Oblast of the Russian Federation who were exposed as children and adolescents to radiation fallout from the Chernobyl accident. Table 1 displays the estimated odds ratios (ORs) for the three upper dose quartiles, compared to the first quartile, adjusting for the possible confounding effects of the matching factors. The OR increases for each successive quartile, and is very large (44.7) and statistically significant for the highest quartile of radiation dose. Based on a loglinear dose-response model that treated estimated radiation dose as a quantitative (continuous) variable, there was a statistically significant trend of increasing risk of thyroid cancer with increasing estimated thyroid radiation dose (Table 2, one-sided $p = 0.009$). Although the dose-response was slightly stronger among females than males (and statistically significant), there was no significant difference in the dose-response relationship according to gender (two-tailed $p = 0.62$). There was little difference between the estimated dose-responses of those born before 1983, compared to those born during 1983-86 (p = 0.93). Although the regression coefficient was particularly large for the seven matched sets with case's age ATA six or older, the variation of the regression coefficient among the three age groups was not statistically significant (p = 0.15).

These were the first results to quantify the extent of excess risk of thyroid cancer in relation to radiation exposure from Chernobyl based on individual estimates of radiation dose to the thyroid, and to demonstrate a dose-response relationship based on such estimates. They are also the first findings from a study of this type among residents exposed in the Russian Federation. These findings are consistent with the evidence from descriptive studies of an increased number of cases of thyroid cancer in areas most highly contaminated by fallout from Chernobyl.

The second study expanded the investigation to include the remaining, less contaminated regions of the oblast and case accrual was extended to September 1998. Controls from the additional regions were selected from rosters constructed from polyclinic records serving the oblast, which constitutes a complete list of the population at risk from these areas. In this phase, 40 of 42 cases contacted participated (95%), as did 80 of 88 controls (91%). Thus, a total of 66 cases and 132 controls were included in the two studies combined. Interviews were conducted using a set of data collection forms developed and tested by the International Consortium. Individual radiation doses to the thyroid were estimated for all cases and controls enrolled in the study.

The results of this second study, currently *in press* in *Radiation Research* (3), extend and confirm previously reported results that thyroid cancer risk significantly increased in a dose-dependent manner among residents of the Bryansk Oblast of the Russian Federation who were exposed as children and adolescents to radiation fallout from the Chernobyl accident. Table 3 displays the estimated odds ratios (ORs) for the three upper dose quartiles, compared to the first quartile, adjusting for the possible confounding effects of the matching factors. The OR increases for each successive quartile, and is very large (13.04) and statistically significant for the highest quartile of radiation dose, but with a wide confidence interval (2.18, 77.8). Based on a loglinear dose-response model that treated estimated radiation dose as a quantitative (continuous) variable and ignoring dose uncertainties, the risk of thyroid cancer increased significantly with estimated thyroid radiation dose, with estimated regression coefficient $\hat{\beta}_{\log l} = 1.54 / \mathrm{Gy}$ and 95% confidence interval 0.50 - 4.50/Gy (Table 4). This relationship did not differ significantly by gender (p=0.89) or year of birth (p=0.50). The regression coefficient was 2.90/Gy for those less than 2 years old ATA, 0.02/Gy for ages 2-5 ATA, and 5.81/Gy for ages 6+ ATA. For the linear dose-response model, again ignoring the dose uncertainties, the estimated ERR was 48.7/Gy with 95% confidence interval ranging from 4.8/Gy to 1151/Gy. Adjusting for uncertainty roughly tripled the magnitude of the estimated dose-response, increasing the regression parameter in the loglinear model from 1.5/Gy to 3.8/Gy and the estimated ERR in the linear model from 48.7/Gy to 138/Gy (Table 3).

These findings are also consistent with the evidence from descriptive studies of an increased number of cases of thyroid cancer in areas most highly contaminated by fallout from Chernobyl, and with the results of two case-control studies in Belarus and one other in Russia. The results also suggest that previously reported estimates of the risk of thyroid cancer in Belarus and Russia following exposure in childhood to fallout from Chernobyl may have significantly underestimated the magnitude of the radiogenic risk since they did not account for the uncertainties in dose estimates.

You will note two points in particular about these completed studies of thyroid cancer. One is that we elected to study persons who were young at the time of the greatest exposure (the time of the accident). This is because such individuals were likely to have the highest thyroid dose per unit exposure, and because they are likely to be more sensitive to the effects of such exposure than persons exposed at older ages. Second, our initial efforts focused on the eight most highly contaminated regions the Bryansk Oblast. This was partly due to the desire to capture persons exposed to the highest doses, and also partly due to the resources available for identifying cases and controls in the population.

The Seattle-Russian team is currently conducting a third case-control study of thyroid cancer in the Bryansk Oblast of Russia, which will investigate the occurrence and molecular characteristics of thyroid cancer in residents of the oblast who were up to 50 years of age at the time of the accident. The study will: 1) characterize cases of thyroid cancer according to specific molecular markers, and investigate whether the presence of such markers is associated with individual thyroid radiation dose from the Chernobyl accident; 2) investigate whether age-at-exposure dependent radiation dose response for thyroid cancer differs between cancers that are positive versus negative for the molecular markers; and 3) investigate whether the presence of these same molecular markers is associated with clinical outcome. The thyroid study is progressing well and is on schedule to be completed in about two years.

In addition, investigators at the FHCRC have been funded to conduct a related study of gene amplification, based on the thyroid cancer cases in the on-going case-control study. The primary objectives of this study are to detect DNA copy number deviations, and to determine whether copy number deviations are associated with radiation dose in a dose-dependent manner.

A second major accomplishment of the ICRHER has been the completion of a three-country population-based case-control study which investigated whether the occurrence of acute leukemia is increased among children who were *in utero* and under six years of age at the time of the Chernobyl accident. Confirmed cases of leukemia diagnosed from April 26, 1986 through December 31, 2000 in contaminated regions of Belarus, Russia and Ukraine were included in this study. Two controls were matched to each case on sex, birth year and residence. Accumulated absorbed radiation dose to the bone marrow was estimated for each subject. This is the first reported population-based study of childhood leukemia among persons exposed to radiation from the Chernobyl accident conducted in contaminated regions of Ukraine, Belarus, and Russia using a common methodology and based on individual estimates of radiation dose.

There are two principal findings from this study, published recently in the *International Journal of Epidemiology* (4). First, the magnitude of the radiation doses received by study participants was relatively low. Table 5 summarizes the distribution of total estimated radiation dose to the bone marrow calculated using the common methodology, for each country separately and for all countries combined. Overall, the mean dose was higher among cases (10.8 mGy) than controls (6.3 mGy). Mean doses were similar in Belarus and Russia, and there was little difference between cases and controls in these two countries. In contrast, the mean dose for cases in Ukraine was substantially higher (10.1 mGy) than for controls (3.5 mGy), and was somewhat lower than for cases and controls in Belarus and for controls in Russia. There was less difference in median doses between cases (0.9 mGy) and controls (0.7 mGy), and median doses were considerably lower than the means, reflecting a highly skewed distribution of doses. Median doses were lowest in Ukraine (0.5 mGy for cases and 0.4 mGy for controls) and highest in Belarus (5.6 mGy for cases and 5.0 mGy for controls).

Second, there was an overall significant increase in leukemia risk associated with increasing radiation dose to the bone marrow. Analyses of the radiation dose response are summarized in Table 6. Using <1.0 mGy as the baseline category, the odds ratio for acute leukemia was estimated as 1.46 and 2.60 for doses of 1.0 – 4.999 mGy and ≥ 5 mGy, respectively, for all republics combined. In Ukraine the odds ratio in the highest dose category was 3.50 with 95% confidence interval (CI) that excludes the value of 1.0 (1.995 – 6.15). The odds ratios for ≥ 5 mGy were also greater than 1.0 for both Belarus and Russia, although the corresponding CIs included 1.0. Based on the loglinear model for the odds ratio, leukemia risk increased significantly with increasing radiation dose for all republics combined (one-tailed p-value=0.0030). This is largely accounted for by the significant dose response in Ukraine (p=0.005). Although the heterogeneity of dose response among the three republics was not statistically significant (p=0.26), the estimated regression coefficient for Ukraine was roughly five times greater than the estimate for Belarus. The dose response was not statistically significant in either Belarus (p=0.33) or Russia (p=0.57).

Taken at face value, these results are difficult to interpret. The findings suggest that prolonged exposure to very low radiation doses may increase leukemia risk as much as or even more than acute exposure. However the large and statistically significant dose response might be accounted for, at least in part, by an overestimate of risk in Ukraine. It is unclear whether the results are due to a true radiation-related excess, a sampling bias in Ukraine, or some combination thereof. The lack of significant dose responses in Belarus and Russia cannot convincingly rule out the possibility of an increase in leukemia risk at low dose levels.

The Seattle-Russian team is currently working on the development of two new research initiatives. Exposure to ionizing radiation is well documented as a cause of breast cancer in women. Populations exposed to radiation from the Chernobyl Power Station accident in April 1986 provide a powerful and unique opportunity to conduct a study of radiation-related breast cancer. Persons living in the path of radioactive fallout from the accident were exposed to a mix of radionuclides over an extended period, resulting in relatively low whole body radiation doses delivered at relatively low dose rates. As a result of our ongoing collaborations, it is possible to initiate studies of radiation-related breast cancer that have until now primarily been investigated by extrapolation from effects observed at high doses and dose rates. A sufficient period of time has elapsed since the accident for radiation-induced breast cancer to appear. To date there have been no descriptive or analytical studies of breast cancer risk in populations exposed to radiation from Chernobyl published in the peer-reviewed literature, although there have been reports of increasing incidence rates of breast cancer since the accident in areas of Ukraine and Belarus contaminated by fallout from Chernobyl.

We have proposed a study that will take advantage of a unique set of circumstances and opportunities to address the limitations in knowledge of low dose radiation effects on breast cancer risk. The overall purpose is to investigate whether individual radiation dose to the breast from the Chernobyl accident is associated with breast cancer risk. Further, we propose to investigate whether the association with radiation dose differs according to specific characteristics of breast cancer, and will evaluate the relationship of breast cancer phenotype and genotype to radiation dose by comparing rates of inactivating genetic or epigenetic changes in selected DNA repair genes to radiation dose. This is a novel approach that has not been attempted in any population-based epidemiologic studies of environmental radiation exposure and breast cancer to date. It is expected to provide new insights into the biological mechanisms associated with increased breast cancer risk from radiation exposure, particularly in subsets of people characterized by defects in DNA repair capacity.

The Seattle-Russian team has now completed two phases of a case-control pilot study of breast cancer in women resident in the Bryansk Oblast at the time of the accident. In summary, the experience gained in performing this pilot study has demonstrated that it will be feasible to successfully conduct the proposed study, based largely on procedures and methods developed and used in the previous studies of thyroid cancer and childhood leukemia. An application for funding of this study is currently under review at NIH.

The Seattle-Russian team is also exploring the feasibility of initiating a study to investigate whether the risk of stillbirth in a population of Russian women has been increased by the exposure to fallout from the Chernobyl accident. Our group is currently designing a pilot study to test the feasibility of conducting a case-control study of stillbirth in the Bryansk Oblast. Women will be selected from residents of the Bryansk Oblast, Russia who were *in utero* or were young children at the time of the Chernobyl accident in April of 1986. The data collected for the study will include information from personal interviews, from analysis of environmental samples, from review of existing pathology materials from the stillbirth cases, and from investigation of medical records. Maternal blood samples and placental tissue will be collected at labor and delivery. The ultimate goals of the pilot study are to establish the ability to identify pregnant women at increased risk of experiencing stillbirth, and to further understand the mechanisms by which stillbirth occurs. If successful, we plan to develop an application for funding a full-scale case-control study. Results from the proposed research have a very high potential for yielding etiologic and clinical information that may prove to be effective in the identification of subgroups of women at greatest need for specific preventive interventions and specialized clinical care. Results from the proposed study could have practical significance in developing alternative, practical preventative interventions for stillbirth and other adverse pregnancy outcomes. The information gained from this investigation will help us further understand the long-term health effects on a population exposed to radiation fallout.

In summary, we have been able to establish and maintain a strong and ongoing collaborative relationship between investigators in the U.S. and three sites in Russia. Over more than a decade this collaboration has resulted in the successful completion of case-control studies of thyroid cancer and childhood leukemia, and the conduct of pilot studies of breast cancer and congenital malformations. Considerable effort has been made to establish detailed research procedures and protocols, and to develop a variety of data collection instruments. An administrative framework and infrastructure has been established for basic operational functions such as communications and transfers of funds and materials. This established collaborative structure has produced important new information on the effects of radiation exposure from the Chernobyl, and forms the basis for expanding this research to investigate other disease outcomes, such as breast cancer and congenital malformations.

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Table 1. Estimated odds ratios and 95% confidence intervals by quartile of estimated thyroid radiation dose [1].

Median (Min – Max) Dose (mGy)	No. (%) Of Cases	No. (%) Of Controls	Odds Ratio[2]	95% Confidence Interval
23 (3 – 60)	4 (15%)	16 (31%)	1.00	---
139 (66 – 240)	5 (19%)	14 (27%)	1.65	0.32 – 8.50
427 (290 – 600)	4 (15%)	16 (31%)	3.05	0.42 – 22.1
1049 (610 – 2730)	13 (50%)	6 (12%)	44.7	3.30 – 604

[1] Quartiles of estimated thyroid radiation doses were calculated using data for all 78 cases and controls combined

[2] Adjusted for sex, year of birth, raion, and type of settlement by conditional logistic regression

Table 2. Results of radiation dose-response analyses using a loglinear model.

Analytic Group	Number of Matched Sets	Estimated Regression Parameter [x 10^3] (95% Confidence Interval) [1]	One-tailed p-value [2]
All Cases	26	1.65 (0.10, 3.20)	.009
Gender			
Female	13	2.06 (-0.23, 4.35)	.023
Male	13	1.27 (-0.75, 3.29)	.087
Year of Birth			
1972-1982	10	1.82 (-2.35, 5.99)	.20
1983-1986	16	1.63 (-0.00, 3.29)	.014
Age ATA [3]			
< 2	10	2.67 (0.08, 5.26)	.006
2 – 5	9	0.30 (-1.58, 2.18)	.38
6+	7	5.27 (-1.73, 12.3)	.039

[1] The regression parameter is the coefficient, β, of dose in the loglinear dose response model log OR(d) = βd, where OR(d) is the odds ratio for dose d relative to dose 0. Since thyroid cancer is a rare disease, OR(d) closely approximates the relative risk at dose d. So, for example, based on the overall estimate of .00165, the estimated odds ratio (and relative risk) of thyroid cancer for the controls' median dose of 180 mGy is exp(.00165×180) = 1.35, with 95% confidence interval 1.20 – 1.78. Estimation of β was adjusted for matching on sex, year of birth, raion, and type of settlement by conditional logistic regression.

[2] P-value based on likelihood ratio test.

[3] Each matched set was classified according to the case's age at the time of the accident (ATA).

Table 3. Estimated Odds Ratios and 95% Confidence Intervals by Quartile of Estimated Thyroid Radiation Dose[a]

Median (Min – Max) Dose (Gy)	No. (%) Of Cases	No. (%) Of Controls	Odds Ratio[b]	95% Confidence Interval[b]
0.0018 (0.00014 – 0.0058)	15 (23)	35 (27)	1.00	---
0.0089 (0.0059 – 0.0205)	13 (20)	36 (27)	1.13	0.46 – 2.77
0.068 (0.0206 – 0.284)	17 (26)	33 (25)	4.42	1.01 – 19.3
0.610 (0.285 – 2.73)	21 (32)	28 (21)	13.04	2.18 – 77.8

[a]Quartiles of estimated thyroid radiation doses were calculated using data for all 198 cases and controls combined.

[b]Adjusted for sex, year of birth, raion, and type of settlement by conditional logistic regression, and ignoring uncertainties of estimated doses.

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Table 4. Estimates of Dose-Response Regression Parameter without and with Adjustment for Dose Uncertainties

	Estimate (Gy^{-1})	95% Confidence Interval[a]	One-sided P-value[a]
Loglinear Model			
Unadjusted	1.54	(0.50, 4.50)	0.00006
Adjusted	3.84	(1.19, 13.9)	0.00006
Linear Model			
Unadjusted	48.7	(4.8, 1151)	0.00013
Adjusted	138	(-0.36, 5.4×10^{8})	0.039

[a]Confidence interval and one-sided p-value estimated from bootstrap. See Appendix for a description of the bootstrap method.

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Table 5. Estimated Radiation Doses, by Republic and Case-Control Status

	Belarus				Russia				Ukraine				Combined			
Estimated Total Dose (mGy)	Case (N = 114)		Control (N = 221)		Case (N = 39)		Control (N = 78)		Case (N = 268)		Control (N = 536)		Case (N = 421)		Control (N = 835)	
Minimum	0.10		0.04		0.40		0.19		0.00		0.00		0.00		0.00	
Maximum	144.88		186.19		88.89		202.38		390.58		265.33		390.58		265.33	
Median	5.61		5.02		1.38		1.09		0.50		0.39		0.93		0.65	
Mean	12.81		11.74		9.97		10.49		10.12		3.46		10.84		6.30	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
< 1.0	26	23	57	26	17	44	34	44	176	66	409	76	219	52	500	60
1.0 – 4.999	26	23	53	24	10	26	25	32	47	18	85	16	83	20	163	20
≥ 5.0	62	54	111	50	12	31	19	24	45	17	42	8	119	28	172	21

Table 6. Radiation Dose-Response Results

Estimated Total Dose (mGy)	Belarus Odds Ratio[a]	Belarus Confidence Interval	Russia Odds Ratio[a]	Russia Confidence Interval	Ukraine Odds Ratio[a]	Ukraine Confidence Interval	Combined Odds Ratio[a]	Combined Confidence Interval
< 1.0	1.00	---	1.00	---	1.00	---	1.00	---
1.0 – 4.999	1.28	(0.60, 2.70)	1.00	(0.28, 3.50)	1.49	(0.92, 2.43)	1.46	(0.998, 2.12)
≥ 5.0	1.58	(0.74, 3.36)	6.00	(0.45, 79.75)	3.50	(1.995, 6.15)	2.60	(1.70, 3.96)
Loglinear regression coefficient, mGy^{-1}[b] (95% CI)	0.0024 (–0.0082, 0.0131)		-0.0027 (–0.0315, 0.0261)		0.0123 (0.0030, 0.0215)		0.0081 (0.0023, 0.0139)	
One-tailed P-value	P = 0.33		P = 0.57		P = 0.005		P = 0.0030	
Estimated ERR/Gy[c] (95% CI)	4.09 (N. E., 37.7)		-4.94 (N. E., N. E.)		78.8 (22.1, 213)		32.4 (8.78, 84.0)	

[a]Adjusted for matching
[b]Regression coefficient (β_{logl}') in loglinear model for odds ratio of disease as function of dose, estimated with adjustment for matching.
[c]ERR/Gy = excess relative risk per Gy ($\beta_{lin}'/1000$), estimated for linear model for odds ratio of disease as function of dose, estimated with adjustment for matching. 95% CI is based on profile likelihood. N. E. = not estimable.