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Late Cancer-Related Health Effects in the General Population:

# Leukemia and Breast Cancer

*November 1st, 2016 Gilbert W. Beebe Symposium on 30 Years After the Chernobyl Accident*

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# Outline

- Why an interest in leukemia and breast cancer after the 1986 Chernobyl accident?
- General population studies of breast cancer risks
- General population studies of leukemia risks among those exposed *in utero,* children and adults
- Thoughts on CLL radiogenicity
- Remaining knowledge gaps on radiation risks of leukemia
- Future directions

# Why an interest in leukemia and breast cancer after the 1986 Chernobyl accident?

***Study of survivors of atomic bombings in Hiroshima and Nagasaki***
***Life Span Study (LSS) N=86,572***

- **20 years after the bombings:** The only significant consequences were increases in cataracts, leukemia and thyroid cancer
- **30 years:** A significant increase in solid cancers
- **50 years[1]:**
  - An unexpected increase was found in non-cancer diseases.
  - Solid cancers observed over 50 years: 10,127; due to radiation: **479 (4.7%)**
  - Leukemia observed over 50 years: 296; due to radiation: **93 (31.4%)**
- **65 years: Leukemia and breast cancer** form only a small fraction of the accepted total radiation-related health detriment

[1]Preston et al. 2004

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# Groups affected by the Chernobyl accident

**Table D9. Number of people in the Chernobyl registries**

| *Registration category* | *Belarus (2005)* | *Russian Federation (2006)* | *Ukraine (2006)* |
|---|---|---|---|
| Group 1: Emergency and recovery operation workers | 72 362[a] | 186 395 | 229 884 |
| Group 2: Evacuees from the exclusion zone | 5 951 | 9 944[b] | 49 887 |
| Group 3: Residents of the contaminated regions | 1 513 826 | 367 850 | 1 554 269 |
| Group 4: Children born to parents of above three groups | 17 914[c] | 35 552[d] | 428 045 |
| Total | 1 610 053 | 599 741 | 2 262 085 |

[a] As of 2005 in contrast to table B1 where the data for Belarus are presented as of 1996.
[b] For Russia, the number of both evacuees from 1986 and some migrants from later years is presented.
[c] Children born to parents included in groups 1–3.
[d] Children born to recovery operation workers only.

**Group 1:** Total Emergency (600) and clean-up workers (530,000)

**Group 2:** Total Persons evacuated from contaminated areas in 1986 (116,000)

**Group 3:** Total Persons who continue to live in contaminated areas (6,400,000)

UNSCEAR 2008 Report, Vo. II, Annex D

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# Predicted Number of Cases and Deaths From Breast Cancer In Europe Up To 2065

| Country group | Average whole-body dose (mSv) 1986–2005 | Population (in millions) in 1986 | Leukemia | | | | Breast cancer | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | From radiation | 95% UI | From other causes | AF to 2065 | From radiation | 95% UI | From other causes | AF to 2065 |
| Incidence | | | | | | | | | | |
| 1 | 0.1 | 274.8 | **200** | 50–900 | **2,800,000** | 0.01% | **350** | 100–1,000 | **14,600,000** | 0.00% |
| 2 | 0.3 | 158.5 | **500** | 100–2,000 | **1,600,000** | 0.03% | **800** | 300–2,400 | **7,200,000** | 0.01% |
| 3 | 0.7 | 73.1 | **400** | 150–1,300 | **600,000** | 0.07% | **800** | 350–1,900 | **2,600,000** | 0.03% |
| 4 | 1.8 | 54.6 | **800** | 250–2,100 | **400,000** | 0.20% | **1,500** | 700–3,000 | **1,500,000** | 0.10% |
| 5 | 6.1 | 11.2 | **500** | 150–1,400 | **75,000** | 0.66% | **1,000** | 500–2,000 | **200,000** | 0.50% |
| Total | 0.5 | 572.2 | **2,400** | 700–7,700 | **5,475,000** | 0.04% | **4,450** | 1,900–10,400 | **26,100,000** | 0.02% |
| Mortality | | | | | | | | | | |
| 1 | 0.1 | 274.8 | **150** | 30–700 | **2,100,000** | 0.01% | **100** | 50–350 | **4,900,000** | 0.00% |
| 2 | 0.3 | 158.5 | **300** | 80–1,400 | **1,170,000** | 0.03% | **300** | 100–800 | **2,500,000** | 0.01% |
| 3 | 0.7 | 73.1 | **300** | 100–900 | **400,000** | 0.07% | **300** | 100–700 | **900,000** | 0.03% |
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| 5 | 6.1 | 11.2 | **350** | 100–1,000 | **50,000** | 0.70% | **600** | 300–1,300 | **130,000** | 0.46% |
| Total | 0.5 | 572.2 | **1,650** | 500–5,400 | **3,995,000** | 0.04% | **2,100** | 900–4,900 | **9,130,000** | 0.02% |

Group 4 (1–2 mSv): Belarus (Brest region), Finland, Russian Federation (Orel and Kaluga regions), Ukraine (city of Kiev, Chernigov region, rest of country).
Group 5 (≥3 mSv): Belarus (Gomel and Mogilev regions), Russian Federation (Bryansk and Tula regions), Ukraine (Kiev, Rivno and Zhytomir regions).

About **1,000 extra breast cancer cases** over life among 11.2 million people

Cardis et al. 2006

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# Breast cancer following exposure from Chernobyl

I. Ecological Studies

| Reference | Country | Results |
|---|---|---|
| Prysyazhnyuk (2002) | Ukraine | Significantly increased incidence compared to the general population |
| Prysyazhnyuk (2014) | Ukraine | No increase in incidence compared to the general population |
| Ostapenko (1998) | Belarus | Increase in risk over time |
| Dardynskaia (2006) | Belaurs | No increase in Gomel (high contamination) compared to Vitebsk (low contamination) |
| Pukkala (2006) | Ukraine, Belarus | Increase in risk, significant during the period 1999-2001 |

**TABLE 2 – RELATIVE RISK (RR) OF BREAST CANCER IN UKRAINE, BY ANNUAL ESTIMATED DISTRICT-SPECIFIC CUMULATIVE DOSE (LAGGED BY 5 YEARS) AND CALENDAR PERIOD**

| Period | Dose category (mSv) | Number of cases | RR | 95% CI | *p*-value |
|---|---|---|---|---|---|
| 1986–1991 | <5.0 | 6,151 | 1 | – | |
| | 5.0–19.9 | 8 | 0.94 | 0.46–1.94 | 0.87 |
| 1992–1996 | <5.0 | 5,643 | 1 | – | |
| | 5.0–19.9 | 126 | 1.17 | 0.94–1.46 | 0.15 |
| | 20.0–39.9 | 36 | 1.58 | 1.08–2.33 | 0.02 |
| 1997–2001 | <5.0 | 5,995 | 1 | – | |
| | 5.0–19.9 | 122 | 1.32 | 1.05–1.65 | 0.02 |
| | 20.0–39.9 | 7 | 0.75 | 0.35–1.63 | 0.47 |
| | 40.0+ | 22 | 1.78 | 1.08–2.93 | 0.02 |

**TABLE I – RELATIVE RISK (RR) OF BREAST CANCER IN BELARUS, BY ANNUAL ESTIMATED DISTRICT-SPECIFIC CUMULATIVE DOSE (LAGGED BY 5 YEARS), AGE AT EXPOSURE AND CALENDAR PERIOD**

| Period | Dose (mSv) | All women | | | | Women aged less than 45 at the time of the accident | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Number of cases | RR | 95% CI | *p*-value | Number of cases | RR | 95% CI | *p*-value |
| 1986–1991 | <5.0 | 3,255 | 1 | – | | 759 | 1 | – | |
| | 5.0–19.9 | 36 | 0.86 | 0.61–1.22 | 0.40 | 10 | 1.06 | 0.54–2.07 | 0.87 |
| | 20.0–39.9 | 5 | 1.89 | 0.75–4.75 | 0.17 | 1 | 2.18 | 0.28–17.2 | 0.46 |
| 1992–1996 | <5.0 | 2,774 | 1 | – | | 1,104 | 1 | – | |
| | 5.0–19.9 | 532 | 1.08 | 0.97–1.20 | 0.17 | 171 | 0.95 | 0.77–1.16 | 0.59 |
| | 20.0–39.9 | 120 | 1.00 | 0.81–1.23 | 0.9 | 35 | 0.84 | 0.56–1.27 | 0.41 |
| 1997–2001 | <5.0 | 2,616 | 1 | – | | 1,226 | 1 | – | |
| | 5.0–19.9 | 901 | 1.14 | 1.04–1.25 | 0.005 | 445 | 1.16 | 1.00–1.36 | 0.05 |
| | 20.0–39.9 | 181 | 1.17 | 0.98–1.40 | 0.08 | 67 | 1.01 | 0.72–1.41 | 0.96 |
| | 40.0+ | 34 | 2.24 | 1.51–3.32 | <0.0001 | 17 | 3.33 | 1.71–6.50 | 0.0004 |

Pukkala et al. 2006

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# Breast cancer following exposure from Chernobyl

II. Analytical Studies

| Reference | Country | Results |
|---|---|---|
| **Hatch (2014)** | **Ukraine** | **No increase in incidence compared to the general population (n=5 among N=13,203 over 1998-2009)** |
| **Ostroumova (2016)** | **Belarus** | **No increase in incidence compared to the general population (n=5 among N=11,970 over 1997-2011)** |

# Breast cancer following exposure from Chernobyl

**Conclusions:**

- No consistent increase
- No individual radiation doses in ecological studies
- Only thyroid doses in descriptive studies; possible screening bias
- Limited statistical power due to small number of cases

# Why leukemia?

- Radiosensitivity and carcinogenicity of the immature cells of bone marrow (Law of Bergonie and Tribondeau)[1]
- The highest risk per unit of radiation dose among all radiation-induced cancers[2]
- The shortest latency period (2-5 years)[2,3]
- Those exposed at younger ages have higher risk[2,3]

[1] Bergonie J. and Tribondeau L. Comptes-Rendus des Séances de l'Académie des Sciences 143 (1906).
[2] UNSCEAR 2000 Report. Vol. II: Effects.
[3] Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation (BEIR VII -phase II), National Research Council, 2005.

# General population studies

- ***Studies of those exposed in utero***
- ***Studies of those exposed as children***
- ***Studies of those exposed as adults***

# 30 years after the Chernobyl accident

## *What do we know about the long-term health risks?*

- **Risk projection studies:**
  - Cardis et al., 1996. From a presentation to the WHO Expert Group "Health" for the UN Chernobyl Forum, 2011.
    - ➢ Predictions of deaths from leukemia

| Population | Period | Background number of deaths | | Predicted lifetime excess | | |
|---|---|---|---|---|---|---|
| | | Number | % | Number | % | AF |
| **Group 1:** Liquidators, 1986-7 | Lifetime | 800 | 0.4 % | 200 | 0.1 % | **20 %** |
| **Group 2:** 1986 Evacuees | Lifetime | 500 | 0.3 % | 10 | 0.01 % | 2 % |
| **Group 3:** | | | | | | |
| Residents of SCZ's | Lifetime | 1 000 | 0.3 % | 100 | 0.04 % | 9 % |
| Residents of other contaminated areas | Lifetime | 24 000 | 0.3 % | 370 | 0.01 % | 1.5 % |

About **700 extra leukemia deaths** over life among 5.6 million people

*- about 200 among the 600 000 cleanup workers*

*- about **500 in the general population** (~400 among most heavily exposed)*

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    - estimated that about **9 to 10,000 deaths from leukemia and solid cancers** might be expected over life in the most exposed populations in Ukraine, the Russian Federation and Belarus.

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About **500 extra leukemia cases** over life among 11.2 million people

Cardis et al. 2006

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# Leukemia following exposure from Chernobyl *in utero*

## I. Ecological Studies

| Reference | Country | Results |
|---|---|---|
| **Petridou (1996)** | **Greece** | **Increased risk** |
| **Steiner (1998)** | **Germany** | **No increase in risk** |
| **Ivanov E. (1998)** | **Belarus** | **No increase in risk** |
| **Noshchenko (2001)** | **Ukraine** | **No increase in risk** |
| **Parkin (1996)** | **Europe** | **No increase in risk** |
| **Busby (2009)** | **Europe** | **Significantly increased risk?** |

- External gamma radiation due to ground deposition of radionuclides and internal radiation from radionuclides incorporated by the mother.
- Chernobyl contamination highest in Greece and Austria outside the FSU.

# Leukemia following exposure from Chernobyl *in utero*

I. Ecological Studies

**Conclusions:**

- No consistent increase
- No individual radiation doses
- Limited statistical power due to small number of cases
- Questionable methodological approaches in some studies

# Leukemia following exposure from Chernobyl *in childhood*

I. Ecological Studies

| Reference | Country | Results |
|---|---|---|
| **Parkin (1993, 1996)** | **Europe** | **No increase in risk** |
| **Ivanov E. (1993, 1996)** | **Belarus** | **No increase in risk** |
| **Gapanovich (2001)** | **Belarus** | **No increase in risk** |
| **Ivanov V. (2002, 2003)** | **Russia** | **No increase in risk** |

# Leukemia following exposure from Chernobyl in *childhood*

## II. Analytical Studies

| Reference | Country | Results |
|---|---|---|
| Noshchenko (2002), children 0-20 yrs | Ukraine | Mean dose=4.5 mSv. Increased risks only for ALL diagnosed 1993-1997 in males with doses>10 mSv |
| Davis (2006), *in utero and* children <6 years | Belarus, Russia, Ukraine | Median BMD<10 mGy. ERR/Gy=32.4 (8.78–84.0), significant only in Ukraine. Potential sampling bias. |
| Noshchenko (2010), children 0-5 years | Ukraine | Significantly increased risks, ERR/Sv=22.0 (9.9, 50.0) |
| Hatch (2014), children 0-18 years | Ukraine | A non-significant increasing trend of leukemia compared to the general population (based on 6 cases in Ukraine and 5 in Belarus) |
| Ostroumova (2016), children 0-18 years | Belarus | |

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# Leukemia following exposure from Chernobyl *in*

## II. Analytical Studies

**Conclusion** Taken at face value, these findings suggest that prolonged exposure to very low radiation doses may increase leukaemia 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. Therefore, we conclude this study provides no convincing evidence of an increased risk of childhood leukaemia as a result of exposure to Chernobyl radiation, since it is unclear whether the results are due to a true radiation-related excess, a sampling-derived bias in Ukraine, or some combination thereof. However, the lack of significant dose–responses in Belarus and Russia also cannot convincingly rule out the possibility of an increase in leukaemia risk at low dose levels.

| | Belarus | | Russia | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Estimated total dose (mGy)** | Odds Ratio[a] | 95% CI | Odds Ratio[a] | 95% CI | Ratio[a] | 95% CI | Ratio[a] | 95% CI |
| <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 per mGy[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 (NE–37.7) | | −4.94 (NE) | | 78.8 (22.1–213) | | 32.4 (8.78–84.0) | |

[a] Adjusted for matching.

[b] Regression coefficient ($\beta_{log}$) 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. NE = not estimable.

Ukraine had positive sign association largely due to the 2 raions in Zhytomyr

Davis et al. 2006

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# Leukemia following exposure from Chernobyl *in adults* residing in contaminated areas

I. Ecological Studies

| Reference | Country | Results |
|---|---|---|
| Bebeshko (1997) | Ukraine | Increase in risk over time not related to level of contamination |
| Ivanov V. (1997) | Russia | No increase in risk |
| Prisyazhniuk (1991, 1995) | Ukraine | No increase in risk |
| Auvinen (2014) | Finland, 3.8 mln | No increase in risk comparing to 1986-1987 committed dose <0.1 mSv |

# Leukemia following exposure from Chernobyl *in adults* residing in contaminated areas

**Conclusions:**

- Increases in incidence reported, but not related to contamination levels
- Methodological limitations
- No individual radiation doses
- Limited statistical power due to small number of cases

# Limitations of ecological studies

- Quality of the registry data changes over time
  - Eg., percentage of leukemia cases of ‘unspecified’ type, of cases diagnosed from bone marrow or peripheral blood, of cases registered from death certificates only
- Geographical differences in cancer registration
- Problems with denominators (population data)
- ‘Screening bias’ in detecting cases in high-dose areas
- Heterogeneity of accident-related radiation doses
- Not possible to adjust the radiation-leukemia association for confounders and effect modifiers

# Empirical studies of leukemia

- Advantages: No need for extrapolation
- Disadvantages:
  - Lack of statistical power
  - Individual doses not available
  - Ecological doses in ecological designs with the results applicable only to groups and not to individuals
  - Screening bias (overestimate of the measure of effect)

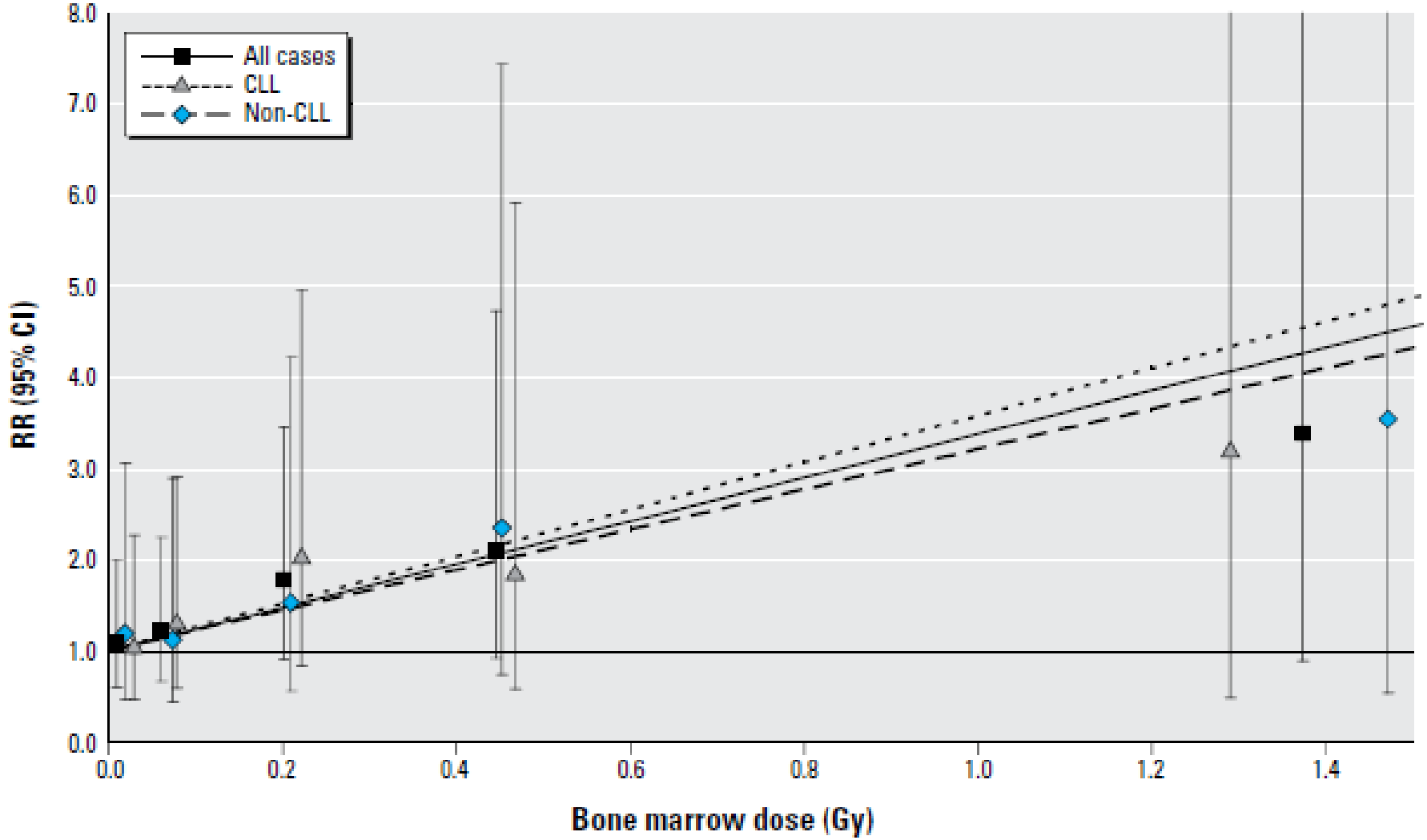


**Figure 1.** RRs (95% CIs) of leukemia by categories of radiation dose and fitted linear dose–response models. For display purposes, we added offsets to category mean doses on the abscissa coordinate to separate the overlapping estimates (10 mGy for non-CLL and 20 mGy for CLL analyses, respectively).

Zablotska et al. Env Health Perspect 2013.

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# Comparisons with other studies

## Incidence studies

*significant at p<0.05

| Study cohort | Follow-Up | Cohort | ERR/Gy (95% CI) | |
|---|---|---|---|---|
| | | | CLL | NHL |
| Chernobyl cleanup workers from Ukraine (Zablotska et al. 2013) | | | n=65 | - |
| | 1986-2006 | 110,645 | 2.58 (0.02, 8.43)* | - |
| Chernobyl cleanup workers from Belarus, Russia and Baltic countries (Kesminiene et al. 2008) | | | n=21 | n=20 |
| | 1993-2000 | ~146,000 | 4.7 (<0, 76.1) | 28.1 (0.9, 243)* |
| A-bomb survivors study (Hsu et al. 2013) | | | n=12 | n=402 |
| | 1950-2001 | 113,011 | 6 (0.3, 31)* | 0.46 (-0.08, 1.29) |
| U.K. radiation workers (Muirhead et al. 2009) | | | n=128 | n=305 |
| | 1955-2001 | 174,541 | -0.12 (-1.42, 2.71) | 1.28 (-0.38, 4.06) |
| Techa River cohort (Davis et al. 2015) | | | n=27 | - |
| | 1953-2007 | 28,223 | 0.10 (<0, 1.20) | - |
| Wismut uranium workers (Mohner et al. 2010) | | | n=159 | - |
| | 1953-1990 | 360,000 | 1.95 (-0.86, 4.99) | - |

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# Survival after CLL diagnosis

## 5-year survival rate

- US in 2004:
  - **< 65 years old:** 83%
  - **65 years and older:** 68%
- Chernobyl cleanup workers in 2010:
  - 48%
  - 39%

Finch et al. 2016

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# CLL characteristics

| | USA, Europe and Australia | Chernobyl cleanup workers |
|---|---|---|
| **Proportion of all leukemia incident diagnoses:** | • 40% | • 56% |
| **Age of diagnosis:** | • Median: 70 years | • 57 years |
| | • <65 years ~25% | • 84% |
| | • 50 years ~6% | • 22% |
| | | • Study enrolled only males who were <60 years during Chernobyl cleanup work |
| **Chemotherapy** | • ~50% with a community referral base | • 86% |

Mulligan et al. *in* Advances in the Treatment of B-cell Chronic Lymphocytic Leukaemia., Keating MJ and Tam CS, Editors; 2012.

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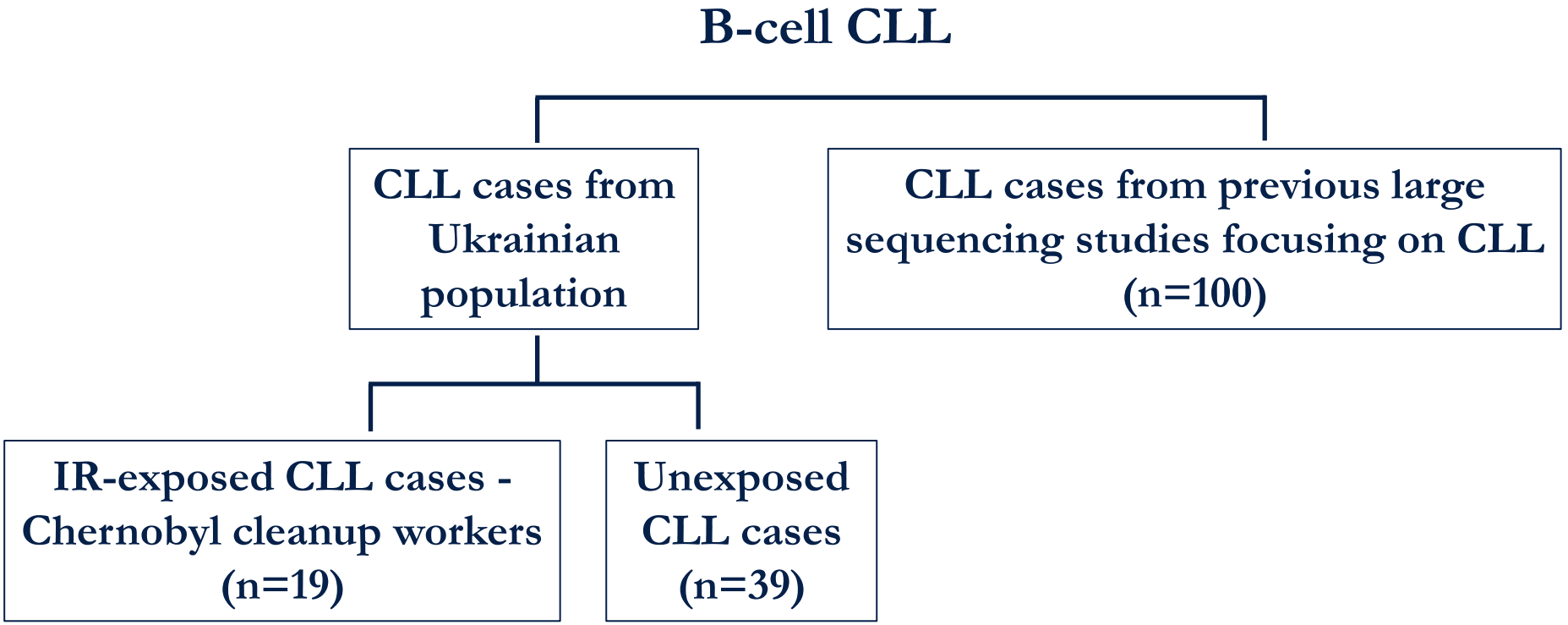
# Genetic Study Design




matched on age; males only

Ohja et al. 2016 *in preparation*

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# Approach

| | |
|---|---|
| **Somatic mutations** | Targeted deep sequencing in 530 genes found predominantly mutated in various cancers (UCSF500 panel) |
| **Copy number alterations** | By aligning off- target reads from targeted sequencing hg19 reference genome - CNVkit software, GISTIC & CopywriteR |
| **Pathways analysis with recurrently mutated genes** | Predominant pathways perturbed by acquired somatic lesions – Go gene analysis |
| **Mutation signature Analysis** | Non-native matrix factorization method (NMF) |
| **Telomere length (TL)** | Estimated using Tel-Seq algorithm |

Ohja et al. 2016 *in preparation*

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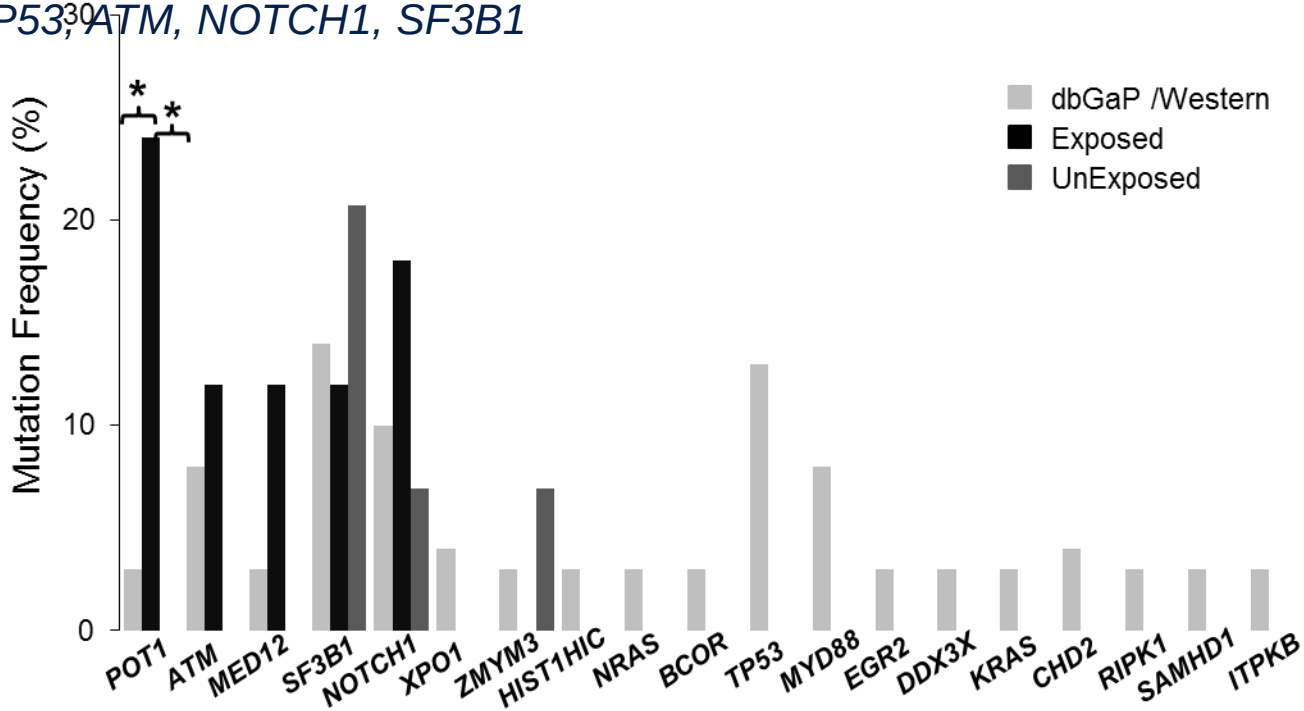
# Results

## Somatic mutations (mutation prevalence of driver mutations)

- **Total mutations:** Similar in Exposed, Unexposed, and Western cases, ~8, p>0.2
- **Exposed: POT1 (21%)**, *NOTCH1* (16%), *RB1 (*16%), and *ATM, APC, MED12, SF3B1, KMT2C* (2% each).
- **Unexposed: SF3B1 (17%)**, *NOTCH1* (10%), *TP53, XPO1 and ZMYM3 (5% each)*
- **Western: SF3B1 (14%)**, ***TP53 (13%)***, *NOTCH1* (10%), *ATM and ZMYM3 (7.5% each)*
  - ***Literature:*** *TP53, ATM, NOTCH1, SF3B1*

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# Results

## Copy number alterations (CNAs)

- **Equal** prevalence in Exposed, Unexposed, Western cases

## Total number of lesions (mutations & CNAs)

- In Exposed cases was strongly **associated with type of work performed in the Chernobyl zone** (p=0.013), number of doctor visits prior to diagnosis, and several time-dependent variables (combined R-square= 0.96). Progressively stronger association of total lesions with radiation dose of **increasing latency periods** (p=0.11 for lag=15 years) was observed.

## Pathways analysis with recurrently mutated genes

- **No statistically significant clustering of genes** was identified.

## Mutation signature

- Due to small mutation load, the signature **could not be extracted** with high confidence.

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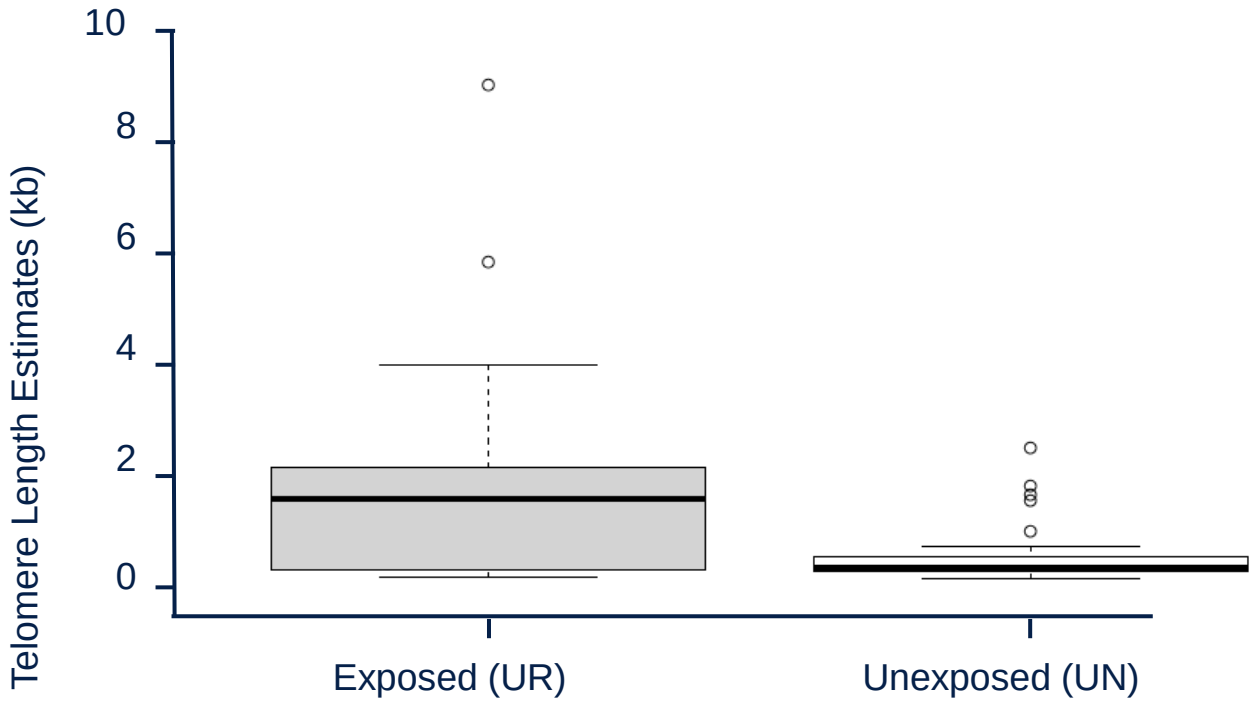
# Telomere length in Ukrainian CLL cases: Chernobyl cleanup workers *vs.* general population

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# Summary of findings

## Genetic studies

- **Significantly longer** TL in Exposed compared to Unexposed cases (p=0.009, adjusted for age).
- Lifestyle risk factors such as alcohol consumption and smoking, and type of cleanup work performed **associated with differences in TL**.
- POT1 mutation prevalence **increased with increasing TL**
- POT1 mutation was also **associated with poorer patient survival**
- **Similar findings in recent Western CLL studies**

**Genetic Variation Associated with Longer Telomere Length Increases Risk of Chronic Lymphocytic Leukemia**

Juhi Ojha[1,2], Veryan Codd[3,4], Christopher P. Nelson[3,4], Nilesh J. Samani[3,4], on behalf of the ENGAGE Consortium Telomere Group*; Ivan V. Smirnov[5], Nils R. Madsen[1], Helen M. Hansen[1], Adam J. de Smith[2], Paige M. Bracci[2], John K. Wiencke[1,6], Margaret R. Wrensch[1,6], Joseph L. Wiemels[1,2,6], and Kyle M. Walsh[1,7]

Cancer Epidemiology, Biomarkers & Prevention

Ohja et al. 2016 *in preparation*

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# Potential problems with previous studies

- **Under-ascertainment:** Diagnosis of B-cell malignancies is complex; some of the most prevalent subtypes frequently have a benign course. Thus, patients may die from other causes of death.
  - E.g., 38% lower incidence in studies based on death certificates compared to incidence studies (Richardson et al, 2005)
- **Under-reporting:** Lower incidence rates of CLL in the cancer registry compared with the hospitals, particularly among patients diagnosed at older ages and with early stage disease, even in a country with universal health care
  - E.g., 38% higher incidence of CLL in the Central Arkansas Veterans Healthcare System database than that reported to the central tumor registry (Zent et al, 2001)
  - E.g., 12% under-ascertainment of CLL in the population-based cancer registry compared with the hospitals during 1964–2003 in Sweden (Turesson et al, 2007)
- **Mis-identification/competing causes:** Secondary cancers frequently follow CLL incidence
  - E.g., 34% of CLL patient deaths had the second malignancy recorded as the primary cause of death on death certificates (Kyasa et al, 2004)
- **Low incidence in Asian populations:**
  - Low incidence of CLL in the Japanese vs. Western populations (2-3%, Finch et al. 1969, Matsuda et al. 2013 vs. 40%, Dores et al. 2007)

# Remaining Knowledge Gaps

1. Are increased CLL risks due to radiation? – **High probability**
   - Somatic mutations of POT1 and TL → Need further studies
2. Due to Ukrainian genetics? → NOT likely, need further studies
   - Due to interaction and activation of previously dormant pathways? What are these pathways?
3. Due to lifestyle factors? → NO
4. Due to active screening? → NO
5. Is radiation-related CLL more aggressive or in any way different from the typical CLL? → Appears to be more aggressive

# Future directions

- Genetic studies
  - Mutations in telomere-related genes may be critical to radiation-associated leukemogenesis
  - The relationship between telomere maintenance, radiation exposure, and CLL prognosis merits further investigation
- Pooled analysis of cleanup workers
  - Modifying effects of time since exposure and age at exposure?
- Studies of cancer and non-cancer diseases in the general population affected by the Chernobyl accident
  - Follow-up through Chernobyl Registries
  - Linkage with the Cancer Registries
  - Estimation of relevant individual-level doses

# Principal Collaborators

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  - **Head of Hematology Group: I. Dyagil**
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