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Chornobyl 30 years later: Radiation, pregnancies, and developmental anomalies in Rivne, Ukraine

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ABSTRACT

In the 30 years since the Chornobyl nuclear power plant disaster, there is evidence of persistent levels of incorporated ionizing radiation in adults, children and pregnant women in the surrounding area. Measured levels of Cesium-137 vary by region, and may be influenced by dietary and water sources as well as proximity to nuclear power plants. Since 2000, comprehensive, population-based birth defects monitoring has been performed in selected regions of Ukraine to evaluate trends and to generate hypotheses regarding potential causes of unexplained variations in defect rates. Significantly higher rates of microcephaly, neural tube defects, and microphthalmia have been identified in selected regions of Ukraine collectively known as Polissia compared to adjacent regions collectively termed non-Polissia, and these significantly higher rates were evident particularly in the years 2000–2009. The Polissia regions have also demonstrated higher mean whole body counts of Cesium-137 compared to values in individuals residing in other non-Polissia regions. The potential causal relationship between persistent ionizing radiation pollution and selected congenital anomaly rates supports the need for a more thorough, targeted investigation of the sources of persistent ionizing radiation and the biological plausibility of a potential teratogenic effect.

1. Introduction

This report presents data on patterns and population-based rates of congenital anomalies (CA) in the Rivne Province of Ukraine inclusive of the region known as Polissia (P), a large area of wetlands contaminated by Chornobyl (Chernobyl in Russian) with ionizing radiation (IR). This ongoing investigation, initiated in the year 2000, seeks to clarify teratogenic impacts, in particular those associated with IR, and builds on previous reports covering this topic (Yuskiv et al., 2004; Wertelecki, 2010, 2014, 2016).

During the 1996 International Congress of Human Genetics, the senior author moderated a satellite conference "Chornobyl – Implications of a Decade" concerned with teratogenic and mutagenic risks posed by exposures of large populations to Chornobyl IR (Widney, 1996). A plan was formulated and submitted for consideration by the Ukrainian Ministry of Health proposing creation of a population-based CA surveillance system. The plan was to establish a system that would uphold international standards to document CA rates and that would qualify Ukraine to join both EUROCAT, a European Network of Population Based Registries for the Epidemiologic Surveillance of Congenital Anomalies, as well as the International Clearing House for Birth Defects Surveillance and Research (ICBDSR) network (Wertelecki, 2006). The plan was endorsed by Ukrainian authorities; to expedite implementation, a network of Ukrainian and international experts in this field was established (OMNI-Net for Children) and was registered in Kyiv, Ukraine, as a not-for-profit organization. Since the year 2000, population-based CA surveillance has been ongoing in Rivne and the neighboring Volyn provinces in Ukraine. This system has been

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utilized to examine trends in CAs over time, as well as associations of specific CA rates with region of residence. In particular, the system has been used to generate hypotheses regarding regional variations potentially due to persistent IR pollution.

The vast region of forested wetlands known as Polissia (P), extends eastward from Poland along the northern regions of five Ukrainian provinces along the Belarus border toward Russia. The northern half of the Rivne province is Rivne P and individuals in its native population (Polishchuks) are viewed as an ethnic group of Ukrainians with characteristics of a population isolate. The forested wetlands in P are largely unsuitable for the development of urban centers and for agriculture. Polishchuks, for the most part, live in small villages, often isolated by floods, severe winters and a general lack of roads. Often, family surnames are characteristic of particular villages (isonomy). Polishchuks subsist on a diet of homegrown foods, stock, and wild fish, game, mushrooms and berries. The majority of Polishchuks consume water from shallow wells and use local wood for cooking and heating (Dancause et al., 2010).

The other regions in Rivne (not-P) are fertile prairies and its ancient population, similar to those in the adjoining Volyn and Khmelnytsky provinces (Fig. 1). The fallout from Chornobyl primarily impacted P, in particular its most northern regions. In not-P, the fallout was characterized as negligible. Across P, there are scattered IR “hot spots,” and IR soil levels also change as a consequence of forest fires and dust (Fig. 1). The index of the radioactive isotope Cesium-137 (Cs-137) transfer from soil to biota in P is among the highest in Ukraine which augments the IR risks to humans who are consuming forest products from these areas (Likhtarev et al., 1996, 2000).

In addition, in Rivne, there are two nuclear power plant complexes (NPP); one located in P within the urban zone of Kuznetsovsk city in Volodymyrets county. Another NPP is situated in the Khmelnytsky province and adjoins the capital city Ostroh in Ostroh county, both of which are located in not-P. The effluent waters from the cooling ponds of both NPPs rejoin local rivers that flow northward across P toward the river Prypiat that flows eastwards toward the Chornobyl site (Fig. 1).

In our initial report, we demonstrated elevated neural tube defect (NTD) population-based rates in Northwest Ukraine (Rivne and Volyn provinces combined) (Yuskiv et al., 2004). These observations were confirmed by a second report solely focused on the Rivne province. Also noted were elevated rates of microcephaly (MIC) and/or microphthalmia (mOPH), in particular in P (Wertelecki, 2010). A third report noted the persistence of the elevations of these three CA which we referred to as core-CA. In addition, a relatively high number of instances of conjoined twins (CTW) and teratomas (TER) was noted along concurrent with a predominance among females in cases of CTW, NTDs and perhaps isolated MIC.

Also included were preliminary results of analyses of whole body counts (WBCs) of incorporated Cs-137 measured in residents from these areas. These analyses demonstrated that the highest levels of incorporated IR among ambulatory patients were in the north-P region (Wertelecki et al., 2014). Subsequently, selected analyses subdivided the Rivne province into three regions: north-P, central-P and not-P. A 2016 report focused primarily on patterns of WBCs and concurrent CA rates in all counties in Rivne. Analyses of archived WBCs demonstrated that five years after Chornobyl, diminished WBC levels were noted which thereafter remained stable. However, since 2010, WBC data have shown that in P, incorporated levels of Cs-137 may be rising (Wertelecki et al., 2016).

The purpose of this new descriptive analysis is to further explore trends in specific CA rates over time and by regions in the Rivne province, and to examine these in the context of trends in WBC data in P and not-P regions of the Rivne province in Ukraine, specifically among pregnant women.

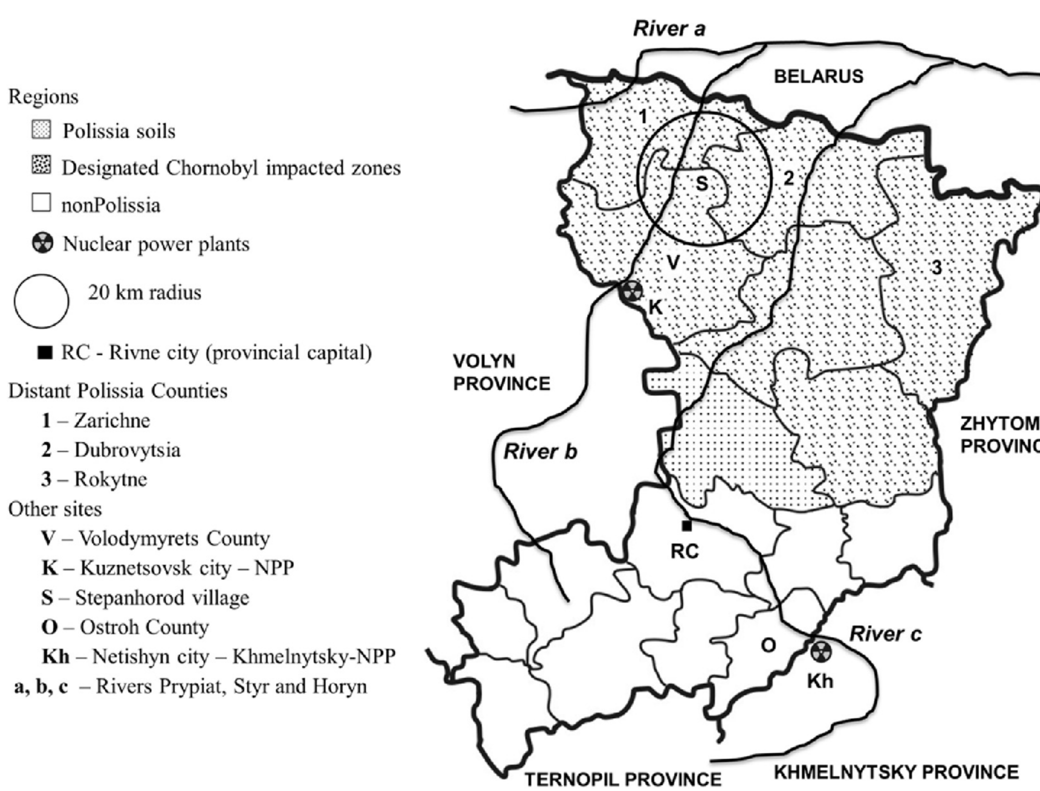

Fig. 1. Schematic map of Rivne Province and Environs.

2. Methods

2.1. Population-based ascertainment and classification of congenital anomalies (CA)

OMNI-Net population-based CA surveillance rests on a mandated birth document produced by neonatologists and in instances of stillbirth, by obstetricians. The report consists of two parts: the first concerns information about parents, the pregnancy and the status of the newborn and the second concerns infants with visually evident CAs. The birth document provides information for local purposes and also fulfills the required data-points for inclusion in international networks of CA monitoring systems. Developmental markers and the presence/absence of particular CAs are recorded. Copies of each report are reviewed by OMNI-Net trained clinicians who may recall or refer mothers and infants for further evaluation. In Rivne, Volyn and Khmelnitsky provinces, as mandated by the Ministry of Health (notification 140-1/decree #290, December 13, 1999), the birth report replaces aggregate birth reports in use elsewhere in Ukraine. The birth document provides the data for a Provincial Neonatal Population Registry, and the CA data from those reports is aggregated in a provincial population-based birth defect database. The process promotes close partnerships and links components of public health, neonatology and pediatric services and OMNI-Net partners while upholding national, EUROCAT and ICBDSR methodologies (EUROCAT, 2013; ICBDSR, 2016).

Following birth, OMNI-Net clinicians engage in further active ascertainment of CA during the first year of life of the infant through bi-annual clinical examinations of orphans and children under state care as well as reviews of records of medical genetics clinics, fetal ultrasound examinations, petitions for terminations of pregnancies, neonatal, infant and pediatric deaths, hospital admissions, and clinics frequented by children with CA and developmental disabilities (Wertelecki et al., 2014).

In this report, we focus on the following CA categories: NTDs (excluding encephaloceles (EN)) which are subdivided into cephalad-NTD or spinal-NTD; MIC which is strictly defined as head circumference three or more standard deviations below the mean for sex and gestational age of the infant using standard growth curves; microphthalmia (mOPH) or anophthalmia confirmed by autopsy (necessary to differentiate severe degrees of microphthalmia) with or without associated MIC; teratomas (TER); conjoined twins (CTW); and omphalocele (OM).

Definitions of terms used in this report are as follows: core-CA refers to the trio of NTD, MIC and mOPH. The term blastopathy refers to core-CA, TER and CTW. The term teratothanasia refers to spontaneous demise of embryos or fetuses that is attributed to CA. For purposes of comparison, rates of isolated cleft lip and/or palate (CL/P) are included in this investigation as representing a CA that has had relatively stable rates over time in P, not-P and other regions in Europe. Sex prevalence is presented as male-female proportions (M-F) or whenever a group includes 10 or more of known sex, a M:F ratio is calculated.

Rates unless stated otherwise, are calculated per 10,000 live births. Counts represent unduplicated individuals with CAs ascertained during the first year of life. Individuals with multiple CAs are counted once and are included in the first applicable CA category in the list of all CA.

2.2. Ionizing radiation (IR)

Data on IR levels in residents in P and not-P were obtained from the Rivne Provincial Diagnostic Center (RPDC) in Rivne Province where patients in the region receive a wide variety of medical diagnostic services. Upon registration, RPDC ambulatory patients sign a global informed consent to obtain clinical services including WBCs of incorporated levels of Cs-137. Patients are informed that participation in WBC procedures is voluntary. In addition, they are advised about the risks of radiation exposure, and the RPDC staff counselled those with elevated WBCs steps that they can use to reduce exposures to nuclides. The consent form of individuals under the age of 18 years is signed by parents or legal guardians. The consent form outlines protection of personalized data in accordance with Law No. 2297-VI, updated in 2010 (Law of Ukraine 2297-VI, 2016). Additional data on IR levels were obtained from archived WBCs measured using equivalent procedures to those of RPDC in ambulatory patients served by the Rivne Chornobyl Dispensary (RCD). In some analyses, the seven county P region was further subdivided into north-P (three northern counties) and central-P (the remaining counties).

In both locations, WBCs of Cs-137 were recorded by two spectrometers incorporated into a chair provided to RPDC and RCD by Provincial Public Health authorities. Procedures, technical training, and yearly calibrations were provided by the Kyiv Metrology Center and Ecology Institute. The detection limit of both spectrometers was under 100 becquerels (Bq) (Kyiv Metrology Center, 2016; SVITCH-M3 “SKRINNER”, 1992; Vasylenko et al., 2013).

For purposes of this report, four WBC data sets were analyzed: the first represented RCD recordings obtained between 1993 and 1994; the second represented RPDC recordings from the period 2001 to 2010; the third represented recordings by RPDC for pregnant women from 2011 to 2014; and the fourth were RCD recordings from 2012 to 2013. The adult ambulatory cohort in these datasets includes patients older than 19 years of age; the pregnant woman cohort includes those between the ages of 20 and 34 years of age and whose body weight ranged from 45 to 85 kg. WBCs under 100 Bq were excluded from analyses.

2.3. Statistical analysis

Descriptive rates, frequencies, means and proportions, as well as temporal trends were presented for illustration. Where formal statistical comparisons were made between groups, logistic regression was used to calculate odds ratios (ORs) and there 95% confidence intervals (CIs) (SPSS Statistics Version 22.0, IBM, 2013).

To determine correlations between average WBCs and CA rates in relatively small geographic regions, a pilot analysis of two clusters of villages in P was conducted. Each cluster (designated A and B) was composed of villages within a radius of 20 km. The centroid villages of cluster-A and cluster-B were excluded from the analyses. Within each cluster, villages were further divided into those with mean WBC measurements above or below 4000 Bq. Those villages at or above the cutoff were designated as high; those below the cutoff designated as low. Rates of the core-CAs were calculated for the high and low groups and within each of the two village clusters.

De-identified data that were approved and available for surveillance purposes were used for these analyses. The Lviv National Medical University Committee on Human Rights and Human Research reviewed OMNI-Net procedures and data confidentiality to insure that Ukrainian, international and U.S. standards were met (Wertelecki et al., 2014). The Lviv committee is registered with the U.S. Office of Human Research Protections.

3. Results

3.1. Live birth and infant mortality trends

Live births in Rivne declined immediately and steadily after the

1986 Chornobyl disaster until reaching a nadir in 2001; when compared to 1986, their number was reduced by 51%, and 46% in Polissia (P) and Rivne as a whole, respectively. During 2012 compared to 1986, the number of live births was still lower than in years prior to the disaster, by 31% and 17% in P and Rivne overall, respectively (See Supplemental Fig. SF1 and Supplemental Table S1).

From 1981 to 2010 the infant mortality rates in north-P were consistently higher than in central-P or not-P. During every successive five-year period the rates in north-P, central-P and not-P decreased with the sole exception in north-P during 1991–1995 when infant mortality rates rose. Compared to 1981–1985, the 2006–2010 rates were lower by 35%, 47% and 39% in north-P, central-P and non-P, respectively (See Supplemental Table S2).

The number of unduplicated individuals with selected CAs in P and not-P, detected during the first year of life during the 2000–2009 and 2010–2014 periods is shown in Table 1. Cumulative rates in four time intervals (2000–2004, 2000–2006, 2000–2009, and 2000–2014) inclusive of M-F proportions are shown in Supplemental Table S3.

Table 1
Temporal contrasts within Polissia and not-Polissia for the number of observed unique individuals with selected congenital malformations, 2000–2009 and 2010–2014.

Category	Polissia					not-Polissia				
	2000–2009		2010–2014		Total	2000–2009		2010–2014		Total
	N	Rate	N	Rate	Rate	N	Rate	N	Rate	Rate
Live births	72,376		42,210			73,058		43,746		
Neural tube defects (NTD)[a]	173	23.9	71	16.8	21.3	105	14.4	74	16.9	15.3
Cephalad	71	9.8	28	6.6	8.6	45	6.2	29	6.6	6.3
Anencephaly	37	5.1	24	5.7	5.3	29	4.0	22	5.0	4.4
Isolated	34	4.7	23	5.4	5.0	28	3.8	19	4.3	4.0
Non-NTD malformations	3	n/c	1	n/c	n/c	1	n/c	3	n/c	n/c
Cranio-inien-rachis-schises	34	4.7	4	n/c	3.3	16	2.2	7	n/c	2.0
Isolated	23	3.2	3	n/c	2.3	12	1.6	6	n/c	1.5
Other malformations	11	1.5	1	n/c	1.0	4	n/c	1	n/c	n/c
Spina bifida cervico-thoracic[b]	17	2.3	11	2.6	2.4	4	n/c	9	n/c	1.1
Isolated	14	1.9	9	n/c	2.0	4	n/c	7	n/c	0.9
Other malformations	3	n/c	2	n/c	n/c	0	n/a	1	n/c	n/c
Spina Bifida lumbo-sacral[c]	74	10.2	32	7.6	9.3	52	7.1	35	8.0	7.4
Isolated	66	9.1	24	5.7	7.9	46	6.3	35	8.0	6.9
Other malformations	7	n/c	8	n/c	1.3	6	n/c	0	n/a	n/c
Spina bifida site unknown	11	1.5	0	n/a	1.0	4	n/c	1	n/c	n/c
Spina Bifida combined	102	14.1	43	10.2	12.7	60	8.2	45	10.3	9.0
Encephalocele	16	2.2	8	n/c	2.1	15	2.1	10	2.3	2.1
Isolated	12	1.7	4	n/c	1.4	11	1.5	10	2.3	1.8
Syndromes	3	n/c	3	n/c	n/c	0	n/a	0	n/a	n/c
Other malformations	1	n/c	1	n/c	n/c	4	n/c	0	n/a	n/c
Microcephaly[d]	44	6.1	36	8.5	7.0	24	3.3	37	8.5	5.2
Isolated	14	1.9	10	2.4	2.1	8	n/c	11	2.5	1.6
Syndromes	15	2.1	17	4.0	2.8	14	1.9	19	4.3	2.8
Other malformations	15	2.1	9	n/c	2.1	2	n/c	7	n/c	n/c
Microphthalmos[e]	18	2.5	6	n/c	2.1	6	n/c	4	n/c	0.9
Isolated	8	n/c	4	n/c	1.0	4	n/c	3	n/c	n/c
Syndromes	3	n/c	1	n/c	n/c	1	n/c	0	n/a	n/c
Other malformations	7	n/c	1	n/c	n/c	1	n/c	1	n/c	n/c
Omphalocele[f]	13	1.8	29	6.9	3.7	25	3.4	11	2.5	3.1
Isolated	5	n/c	17	4.0	1.9	17	2.3	7	n/c	2.1
Syndromes	2	n/c	3	n/c	n/c	1	n/c	0	n/a	n/c
Other malformations	6	n/c	9	n/c	1.3	7	n/c	4	n/c	0.9
Gastroschisis	17	2.3	11	2.6	2.4	23	3.1	5	n/c	2.4
Isolated	16	2.2	11	2.6	2.4	22	3.0	5	n/c	2.3
Other malformations	1	n/c	0	n/a	n/c	1	n/c	0	n/a	n/c
Urinary bladder exstrophy[g]	8	n/c	1	n/c	n/c	5	n/c	1	n/c	n/c
Isolated	8	n/c	1	n/c	n/c	4	n/c	1	n/c	n/c
Other malformations	0	n/a	0	n/a	n/c	1	n/c	0	n/a	n/c
Conjoined twins[h]	2	n/c	0	n/a	n/c	5	n/c	1	n/c	n/c
Isolated	2	n/c	0	n/a	n/c	3	n/c	1	n/c	n/c
Other malformations	0	n/a	0	n/a	n/c	2	n/c	0	n/a	n/c
Teratomas[i]	6	n/c	5	n/c	1.0	4	n/c	2	n/c	n/c
Sacro-coccygeal	6	n/c	2	n/c	n/c	3	n/c	2	n/c	n/c
Isolated	6	n/c	2	n/c	n/c	3	n/c	2	n/c	n/c
Isolated cleft lip with/without palate	55	7.6	25	5.9	7.0	57	7.8	37	8.5	8.0

Abbreviations: n/a, not applicable; n/c, not computed.
[a] Excludes encephalocele.
[b] Includes one instance of a child with fetal alcohol spectrum disorders (FASD) in not-P.
[c] Includes one instance of FASD in P.
[d] Includes 47 instances with FASD (22 in P and 25 in not-P); excludes 3 instances with holoprosencephaly (2 in P and 1 in not-P).
[e] Excludes 5 instances with holoprosencephaly (3 in P and 2 in not-P), 1 instance counted as NTD (P), and 5 instances counted as microcephaly (4 in P and 1 in not-P).
[f] Excludes 17 instances counted as NTD (12 in P and 5 in not-P), 2 counted in microcephaly (1 in P and 1 in not-P), and 3 counted as microphthalmia (2 in P and 1 in not-P).
[g] Excludes 2 instances counted as NTD (both in P).
[h] Excludes 2 instances counted as NTD (both in P).
[i] Excludes 1 instance with holoprosencephaly (in P).

3.2. Core CA and blastopathies

Rates of the blastopathies (CTW and TER) and their female prevalences in P, and not-P, and for comparison, in the neighboring Volyn and Khmelnytsky provinces between 2000 and 2013 are illustrated in Table 2. In Table 3, rates of the core CAs NTD, MIC and mOPH between 2000 and 2009 and between 2010 and 2014 in P and not-P are shown. Overall rates of core CAs were significantly higher in P than not-P for NTDs specifically in the 2000 to 2009 period (OR 1.65, 95% CI 1.31, 2.13), for total MIC (OR 1.85, 95% CI 1.13, 3.09), for total mOPH (OR 3.02, 95% CI 1.24, 8.33), and for the combined total MIC + mOPH (OR 2.09, 95% CI 1.36, 3.27). Isolated instances of these CA were likewise more frequent in P although the comparison did not reach statistical significance. In the 2010 to 2014 period, OR for these same defect categories approximated 1. In contrast, rates of encephalocele (EN) and CL/P were virtually as frequent in P as in not-P (See Supplemental Table S4).

3.3. Neural tube defects (NTDs)

As shown in Table 4, the NTD rates in P decreased from 25.6 to 16.5 between the 2001–2005 and the 2011–2014 time periods. In not-P, the rates remained constant at 16.0 and 16.7 in those same time periods.

The impact of prenatal diagnosis and subsequent elective termination on NTD rates and possible region-specific differences is of interest. In Rivne, during 2000–2014 among 231,390 gestations, 423 were associated with an NTD, of which 363 were detected prenatally by ultrasonography, 248 were terminations of pregnancy and 111 were live born. The rapid growth of prenatally detected CAs is similar in P and not-P – from 2000 to 2004 compared to 2010–2014, prenatal detection of NTDs rose from 68% to 94% in P and in not-P from 80% to 92%. Overall, in P and not-P, between 2000 and 2014, the prenatal detection rate of NTDs was 83% and 89% and the rate terminations of pregnancies following prenatal detection was 64% and 74%, respectively (See Supplemental Table S5).

An additional analysis of 221 instances of isolated spinal-NTD in Rivne confirmed a higher prevalence in P (56%). In addition, 10% in P and 6% in not-P of such pregnancies did not result in live births due to spontaneous demise of the embryo or fetus. Infant mortality among live borns with spinal-NTD was 19% and 15% in P and not-P, respectively. The remainder of spinal-NTD impacted pregnancies were medically terminated, 39% in P and 60% in not-P (data not shown). This contrast is not thought to reflect any difference in

Table 2
Conjoined twins and teratomas in three adjoining Ukrainian Provinces (2000–2013).[a]

Category	Rivne		Volyn	Khmelnytsky	All	
	Polissia	not-Polissia				
	N (rate)	N (rate)	N (rate)	N (rate)	N (rate)	M:F
Live births	106,438	108,190	187,483	161,104	563,215	1.07
Conjoined twins	4 (0.38)	6 (0.55)	4 (0.21)	4 (0.25)	18 (0.32)	[b]
All teratomas[c]	12 (1.13)	6 (0.55)	14 (0.75)	13 (0.81)	45 (0.80)	0.31
Sacro-coccygeal	8 (0.75)	5 (0.46)	13 (0.69)	10 (0.62)	36 (0.64)	0.41

Abbreviations: M, males; F, females; U, unknown sex.
[a] Khmelnytsky includes only 2002–2013 data.
[b] 7 MM, 6 FF, 5 UU sets.
[c] Includes one instance of a neck teratoblastoma in Polissia and another sacro-coccygeal teratoblastoma in Volyn Province.

Table 3
Core CA in Polissia and not-Polissia in Rivne province (2000–2014).

Category	2000–2009			2010–2014			Total		
	Polissia	not-Polissia	OR (95% CI)	Polissia	not-Polissia	OR (95% CI)	Polissia	not-Polissia	OR (95% CI)
Live births	72,376	73,058		42,210	43,746		114,586	116,804	
NTD total	173	105	1.65 (1.31, 2.13)	71	74	0.99 (0.72, 1.38)	244	179	1.39 (1.15, 1.69)
NTD cephalad	71	45	1.59 (1.10, 2.33)	28	29	1.00 (0.59, 1.69)	99	74	1.36 (1.01, 1.85)
Microcephaly total	44	24	1.85 (1.13, 3.09)	36	37	1.01 (0.63, 1.60)	80	61	1.34 (0.96, 1.87)
Microcephaly isolated	14	8	1.77 (0.74, 4.44)	10	11	0.94 (0.39, 2.26)	24	19	1.29 (0.70, 2.38)
Microphthalmia total	18	6	3.03 (1.24, 8.33)	6	4	1.56 (0.43, 6.25)	24	10	2.45 (1.19, 5.35)
Microphthalmia isolated	8	4	2.02 (0.61, 7.69)	4	3	1.38 (0.29, 7.41)	12	7	1.75 (0.69, 4.72)
MIC + mOPH total	62	30	2.09 (1.36, 3.27)	42	41	1.06 (0.69, 1.64)	104	71	1.49 (1.11, 2.03)
MIC + mOPH isolated	22	12	1.85 (0.92, 3.86)	14	14	1.04 (0.49, 2.21)	36	26	1.41 (0.85, 2.36)

Abbreviations: NTD, neural tube defects; MIC, microcephaly; mOPH, microphthalmia.

Table 4
Neural tube defects temporal changes, Rivne province, 2001–2014.

Category	Polissia			not-Polissia			Rivne province		
	Live births	NTD[a]		Live births	NTD[a]		Live births	NTD[a]	
	N	N	Rate	N	N	Rate	N	N	Rate
2001–2005	33,950	87	25.6	33,749	54	16.0	67,699	141	20.8
2006–2010	39,939	81	20.3	41,328	55	13.3	81,267	136	16.7
2011–2014	33,953	56	16.5[b]	35,262	59	16.7	69,215	115	16.6
Total	107,842	224	20.8	110,339	168	15.2	218,181	392	18.0

[a] Excludes encephaloceles.
[b] This rate is statistically significantly lower ($p < 0.01$) than the 25.6 rate recorded during 2001–2005.

rates of prenatal detection but rather to be largely a reflection of cultural differences acceptance of induced abortions by rural populations in P.

Finally, regarding possible differential prevention of NTDs and other defects through folic acid supplementation, in a sample of 4817 pregnant women in Rivne who were asked about periconceptional vitamin supplement consumption, a small proportion reported consuming supplements at the time of conception when protection against folate-sensitive NTDs could be realized; these proportions, however, were similar in P (7%) and not-P (5%) (data not shown).

3.4. Teratothanasia

Another possible contributor to regional differences in CA rates among live born infants is spontaneous loss of malformed fetuses or infants (teratothanasia). In Rivne, the proportion of live born infants with cephalad-NTD was 0.6% compared to 44.3% among all instances of spinal-NTDs (2000–2013). The corresponding frequencies of stillbirths were 19% and 4.7%, respectively. The surveillance data proved unsuitable to determine the impact of spontaneous or induced abortions.

3.5. Comparisons with CAs elsewhere in Europe

To compare CAs in Rivne with those reported by EUROCAT, the Rivne rates were adjusted to reflect CA counts instead of unique individuals. In Table 5 are presented informal comparisons illustrating that NTD as well as cephalad-NTD rates in Rivne (in P and not-P) were among the highest reported in Europe (2005–2012 period). Otherwise, the highest NTD and cephalad-NTD rates were those noted in regions of the U.K. Rates of MIC in P also were among the highest in Europe. The rate of mOPH in P was also among the highest in Europe. The average rate of CTW reported by 40 CA monitoring systems and full members of EUROCAT was 0.19 compared to 0.47 in Rivne (Table 2). The next six highest rates ranging from 0.23 to 0.49 were reported from the UK. A comparison of CTW rates reported during the 2000–20012 period by 40 full members of EUROCAT showed the same mean rate of 0.19 and that the six highest rates after Ukraine were noted in the same regions of the UK. The rate of CL/P in P is nearly the same as in Wales and Wessex in the U.K. and similar to the average rate reported across Europe.

3.6. Radiation

Patterns of incorporated Cs-137 by mean WBC in the four cohorts are presented Table 6, illustrating the sharp decrease in WBC levels recorded in years following the 1993–1994 period. WBC levels were higher among males than females, presumably a reflection of their higher average body weights. However, the Bq/kg levels were also higher among males, an indication perhaps of contrasts of physiologic body-water content between sexes.

The accrual of greater body mass during childhood growth was reflected in higher WBC with increasing age. As illustrated in Fig. 2, in P the WBC nearly doubled every successive five years of age until the age of 20 and thereafter WBCs remained relatively stable. Among young adults (ages 20–34) and older adults (ages of 35 or older) there were inconsistent contrasts. The mean WBCs were generally higher in males and pregnant women compared to those of females in general.

There was a consistent difference, independent of sex or age, between mean WBCs recorded during the 2010–2014 period and those recorded during the 2000–2004 period, with the later period means being higher. The mean WBCs recorded during the intervening 2005–2009 were intermediate. Within P, the highest mean levels of WBC in pregnant women and women in general were recorded in the three most northern counties (north-P). In central-P the WBC recordings were lower but still much higher than in not-P (Table 7).

To assess to what extent longer time of exposure to Cs-137 may result in cumulative WBCs, comparisons of recordings of younger and older pregnant women were examined (Supplemental Table S6). The WBC patterns across age groups were similar.

Table 5
Congenital anomalies rates in Rivne and Europe.[a]

Categories	Births	NTD	Cephalad-NTD	MIC	mOPH	CL/P
Rivne (2000–2014)	232,770	20.28	7.43	6.19	1.98	10.40
Polissia (P)	115,246	23.25	8.59	7.12	2.86	9.89
not-Polissia (not-P)	117,524	17.36	6.30	5.28	1.11	10.89
Selected EUROCAT registries (2005–2012)[b]						
Northern England (UK)	266,965	14.80	6.18	1.46	0.67	10.49
Wales (UK)	279,411	13.67	4.97	4.80	1.54	10.88
East Midlands & South Yorkshire (UK)	586,611	11.97	5.22	1.07	0.32	8.68
Wessex (UK)	237,933	11.73	5.88	1.34	0.63	10.93
Thames Valley (UK)	240,687	11.51	5.11	1.04	0.71	8.64
South West England (UK)	395,882	11.34	4.47	4.34	1.06	8.64
Norway	487,216	9.26	3.28	0.51	0.72	12.15
Antwerp (Belgium)	164,269	8.64	2.80	3.23	1.10	11.63
Wielkopolska (Poland) (2005–2010)	233,615	7.96	0.86	1.50	0.98	9.25
Valencia region (Spain) (2007–2012)	314,704	6.13	2.35	4.19	1.05	5.50
Tuscany (Italy)	243,252	6.00	2.18	0.66	0.74	5.06
Hungary	762,875	5.90	1.53	1.89	1.10	7.77
Dublin (Ireland)	209,581	5.63	2.24	2.43	0.91	6.97
Emilia Romagna (Italy)	325,339	5.38	2.09	1.69	1.26	7.07
S Portugal	151,670	2.84	1.19	0.40	0.40	3.89
All 34 EUROCAT full member registries	6,680,502	9.70	3.63	2.81	1.00	8.83

Abbreviations:NTD, neural tube defects; MIC, microcephaly; mOPH, microphthalmos; CL/P, clift lip with/without palate.

[a] Congenital anomaly rates (not unique individuals) per 10,000 pregnancies (inclusive of fetal deaths after the 20th week of gestation, pregnancy terminations, stillbirths and livebirths) observed in P and not-P and reported to EUROCAT by.

[b] 15 selected monitoring systems (based on at least 150,000 births) during the 2005–2012 period. The average rates computed by EUROCAT are based on 34 full member registries. The highest proportion of termination of pregnancies is reported by the registry of Paris which is excluded from the table. EUROCAT occasionally introduces data updates; the data analyzed was last accessed on December 01, 2015. The highest proportion of terminations of pregnancies is in Paris registry, which is excluded from the table.

Table 6
Mean WBC temporal changes in Rivne province, 1993–2014.

Cohorts	Males-females	Polissia				not-Polissia			
		Male		Female		Male		Female	
		Bq	Bq/kg	Bq	Bq/kg	Bq	Bq/kg	Bq	Bq/kg
1993–1994[a]	760–731	13,839	190.1	8981	133.0	2536	32.6	2043	29.9
2001–2010[b]	9192–25594	2640	n/a	2223	n/a	507	n/a	435	n/a
2012–2013[a]	896–886	3842	46.0	2588	35.8	957	11.4	870	11.9
2011–2014[c]	0–4795	n/a	n/a	2549	40.1	n/a	n/a	713	11.2

Notes: n/a, not applicable.
[a] RCD, at least 20 years of age.
[b] RPDC, at least 20 years of age, body weights unavailable.
[c] RPDC, pregnant women, 20–34 years of age and of 45–85 kg body weight.

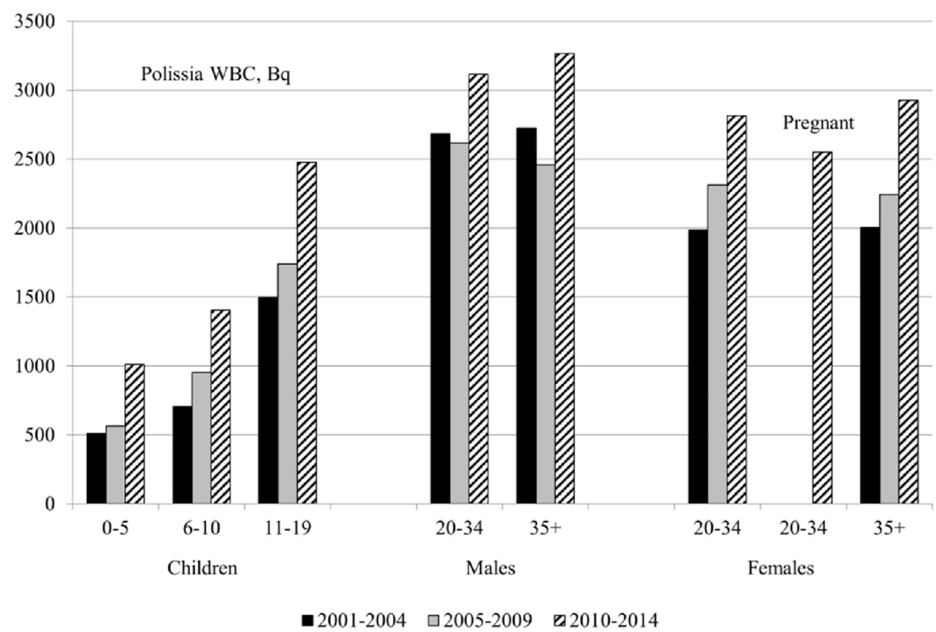

Fig. 2. WBC levels of children, adults and pregnant women recorded during three time periods.

Table 7
Mean WBCs (Bq) of Cs-137 in women, Rivne province.

Area	WBC, Bq[a]			
	Women (2001–2010)[b]		Pregnant (2011–2014)[c]	
	N	Mean	N	Mean
North Polissia	5054	4365	1036	3808
Central Polissia	13,196	1403	1882	1856
not-Polissia	7344	435	1877	713
Rivne province	25,594	1710	4795	1830

[a] Excludes individuals with <100 Bq WBC.
[b] Excludes individuals under 20 years of age.
[c] Includes only individuals of 20–34 years of age and of 45–85 kg body weight.

Variation in the rates of the selected CAs by mean WBCs were examined within two groups of clustered villages (Group A vs. Group B) in Polissia categorized as having mean WBC's of pregnant women that were either high or low 2001–2010. Among 7 Group A sites classified as high, mean WBC in pregnant women was 4729 Bq, and among 13 Group B sites designated high, mean WBC in pregnant women was 4696 Bq. In contrast, in 36 Group A sites designated as low, mean WBC among pregnant women was 2703 Bq, and in 20 Group B sites classified as low, mean WBC in pregnant women was 2942 Bq. NTD frequency among the high WBC groups within both clusters of villages (46.0 and 22.7, respectively) was greater than in either cluster of villages classified as having low WBCs (15.5 and 15.0, respectively). The validity of this approach and observed contrasts are being further tested. (Supplemental Table S7).

4. Discussion

A previous analysis of 2000–2002 of combined data from Rivne and Volyn provinces detected elevated rates of NTD. (Yuskiv et al., 2004). Thereafter, analyses focused mainly on observations in Rivne. An analysis of 2000–2006 Rivne data showed statistically significantly higher rates and female prevalence of NTD in P than in not-P. The frequency of microcephaly (MIC), conjoined twins (CTW) and teratomas (TER) appeared to be elevated and was also associated with female prevalence. These observations called attention toward blastopathies, a category of CA detectable during blastogenesis prior or during early embryonal implantation and known to be prevalent among females. (Tables 1 and 2 in Wertelecki, 2010). An analysis of 2000–2009 data demonstrated the persistence in P of statistically significantly higher rates of NTD, MIC and/or mOPH. Encephaloceles (EN) however were neither prevalent in P nor among females. In subsequent analyses, EN were reported separately from NTD.

A nutritional dietary survey of pregnant women residing in P, indicated that the daily average consumption by pregnant women was a source of 268 Bq of Cs-137, a level above the officially recommended upper limit of 210 Bq. Other investigators estimated the average dietary intake in P of Cs = 137 at at 571 Bq (Table 9 in Wertelecki et al., 2014; Dancause et al., 2010; Shiraishi et al., 2008). Also noted in that time was that prenatal alcohol was an unlikely the primary cause of the higher rates of the core CAs in P.

Another pilot study indicated that in addition to Cs-137, stems of potato plants from P also incorporated 90-Sr. A preliminary analysis of 1156 WBCs obtained from pregnant women residing in P and not-P showed that 48% and 0.1% of women respectively, had WBCs that exceeded the upper recommended limit of Cs-137 of 3700 Bq set for subjects under 15 years of age. Concerning the high sensitivity of rapidly developing embryonic tissues to IR damage, even the 3700 Bq limit is likely to be too high to prevent IR teratogenic impacts. The fourth analysis of 2000–2013 data was focused on IR, in particular WBC of 2073 and 1419 pregnant women residing in P and not-P, respectively. That analysis included county by county WBC levels and core-CA rates (Figs. 1-3 and Table 1 in Wertelecki et al., 2016).

4.1. Blastopathies

The notion "blastopathy" refers to alterations during blastogenesis and early stages of embryonal implantation manifested as monozygotic twinning, CTW, TER, NTD, "celosomias" (failures of anterior body wall closures) and other alterations of morphogenesis. In this report we have applied the term to CTW, TER, NTD, and MIC as a group. However, these and broader associations of blastopathies, including prevalence among females, were observed by a number of pioneers of Human Teratology (Lary and Paulozzi, 2001; Shaw et al., 2003; Szabo et al., 2010). From a variety of perspectives, reports preceding our investigations noted similar associations of twinning, CTW, cephalad-NTD, body wall schises, TER, NTD/OM dyads, exstrophies, among other associations (Czeizel and Opitz, 1981; Schinzel et al., 1979; Opitz et al., 2002; Martinez-Frias et al., 1997, 2000, 2001; Garabedian and Fraser, 1994; Carmi and Boughman, 1992; Phelan and Hall, 2006; Warkany, 1971; Pauniaho et al., 2013; Forrester and Merz, 2006; Tapper and Lack, 1983; Calzolari et al., 1997; Casale et al., 2004; Curry et al., 2006; Du Plessis et al., 1974; Edmonds and Hawkins, 1941; Fraumeni et al., 1973; Lee et al., 1999; Rogers, 1976; Spencer, 2001; Windham and Sever, 1982). A detailed review inclusive of potential pathogenesis and etiology implications are found in a previous report (Wertelecki et al., 2014).

4.2. Rivne in the context of Europe

To compare CA in Rivne with those reported by EUROCAT, the Rivne rates were adjusted to reflect CA counts instead of unique individuals. The rate of CTW in Rivne (0.47) was higher than those in Volyn (0.21) and Khmelnytsky (0.25) provinces. The average CTW rate reported by 43 CA European monitoring systems to EUROCAT was 0.19 for the periods of 2000–2012 and 2005–2012. The highest rates after those in Rivne were reported from the UK and were higher than in Volyn and Khmelnytsky provinces. An analysis of prevalence of CTW reported by 12 European surveillance systems to ICBDSR noted prevalence rates ranging from 0.03 to 0.32 noted in Finland. Three monitoring systems with the largest number of surveyed births (over 2 million each) reported prevalence ranging from 0.08 to 0.15. Another study of 73 sets of CTW and concurrent CA unrelated to the site of the union, noted an association with NTD and abdominal wall defects among 9.9% and 3.6% of instances respectively (Mutchinick et al., 2011). In Rivne, among 10 CTW pairs, one of the co-twins had a spinal-NTD and in another pair, one co-twin had an OM.

As illustrated in Table 5, NTD rates in Rivne were among the highest reported in Europe (2005–2012 period); and rates of MIC and mOPH in P were also among the highest in Europe. The average rate of CTW reported by 40 CA monitoring systems and full members of EUROCAT was 0.19 compared to 0.47 in Rivne. In contrast, the rate of CL/P in P was nearly the same in Rivne as the average rate reported across Europe.

4.3. Neural tube defects (NTD) excluding encephaloceles (EN)

The 2000–2014 NTD rates in Rivne were consistently statistically significantly higher in P than in not-P. Over four time periods, the NTD rates fluctuated between 21 and 25 and in not-P between 14 and 18. The proportions of cephalad-NTD in P and not-P were similar and fluctuated in a narrow range of 41–52% in P and 41–48% in not-P. These patterns documented by monitoring over a 15-year span 114,586 infants in P and 116,804 in not-P are indicative of the stability of the data. However, analyses of large numbers and broad time periods may obscure more recent time trends. An analysis of 2011–2014 observations demonstrated that the NTD rate in P fell to 16.8. To what extent this decrement will persist will be determined by the ongoing CA monitoring process.

Differences in prenatal detection of NTD associated with terminations of pregnancy or prevalence of pre-conception consumption of folic acid supplements in P vs. not-P are modest. To gage burdens in P and not-P associated with NTD, an analysis of 221 instances of isolated spinal-NTD in Rivne confirmed a higher prevalence in P (56%) among which 51% were live born, 4% were stillborn and 6% were spontaneous abortions. The corresponding proportions in not-P, were 34%, 4%, and 2%, respectively. These proportions also illustrate the high frequency of termination of pregnancies following the prenatal ascertainment of NTD. However, the higher proportion of livebirths in P does not implicitly reflect lower rates of prenatal detection, it is more likely that it is a reflection of parental decisions to continue NTD gestations to term. In P and not-P, 19% and 15% of NTD live born died within the first year of post-natal life. Importantly, the monitoring system in place in Rivne allowed for capture of all of these data.

4.4. Microcephaly (MIC), microphthalmia (mOPH), holoprosencephaly (HOLOP)

In P, instances of MIC, either overall or those not associated with mOPH nor HOLOP were statistically significantly more frequent in P than in not-P and likewise instances of mOPH that were not associated with MIC nor HOLOP. The overall rate of MIC in P and not-P was 7.2 and 5.3 respectively. In contrast the average rates reported in Europe were 1.9. Our strict definition of MIC precludes inclusion of milder instances of MIC and milder reduction of head circumferences. While MIC is a known feature of FASD, the corresponding rates of FASD in P and not-P were not different: 1.9 and 2.1. These rates, although based on fairly small number of observations, do not suggest that alcohol teratogenesis accounts for the differential prevalence of MIC in P.

Neither MIC nor mOPH are clinical entities and often represent complex CA due to multiple teratogenic factors including IR and alcohol. Concurrent MIC and mOPH associations with HOLOP are frequent and most often associated with recognizable malformation syndromes. The relative rarity of non-syndromic MIC suggests that an analysis of observations in the adjoining provinces could be informative. However, in our view, regional contrasts of access to advanced technologies required for accurate diagnoses are significant and diminish the value of inter-provincial comparisons. A preferable alternative to increase the number of observations is an investigation of at-birth occipito-frontal circumferences (OFC) of infants gestated in diverse counties and clusters of villages where instances of NTD, MIC and mOPH and FASD are well-documented and WBC data for pregnant women can be linked to infant outcomes. Prior pilot investigations suggested that modest reductions of OFC may be detected in IR-impacted counties, an observation that calls for confirmatory expanded studies (Wertelecki et al., 2014).

4.5. Ionizing radiation (IR)

Following the 1986 Chornobyl disaster, USSR authorities, with participation of international agencies, relied on nuclide soil measurements as a basis to define regions by degrees of IR contaminations. For reasons beyond the scope of this report, Rivne was excluded from such studies. In 1991, after the Ukrainian independence, it became clear that P in Rivne is among the most IR impacted regions in the country attributable in part to its soils greater propensity to release nuclides to the food chain alluded to earlier (Decree 106, 1991; Likhtarev et al., 1996, 2000; Zamostian et al., 2002). Numerous radiation "hot-spots" across P, forest fires, dust and annual floods, add to the complexities and accuracy of regional characterization of IR pollution of soils. An optimal direct measurement is WBC expressed in Bq units, in this analysis emitted by incorporated Cs-137. Our analyses of WBCs showed that Cs-137 incorporated by residents was highest in the three northern counties in P (north-P), followed by those residing in other P counties (central-P). The WBC levels in central-P, although lower than in north-P were several folds higher than among residents in not-P. These contrasts were evident among ambulatory patients of any age and sex as well as among pregnant women. These observations along with previous findings (Wertelecki et al., 2016), fully justify the imperative that prospective investigations of 137-Cs WBC temporal trends are needed.

4.6. Rivne in perspective

Shortly after the 1986 Chornobyl disaster, a series of clinical reports noted clusters of CA in regions impacted by the Chornobyl fallout. A large substantive 1999 investigation in regions of Western Europe, quite distant from Chornobyl, did not demonstrate an impact of IR fallout on CA rates and likely was conducive for other studies showing impacts to be dismissed (Dolk et al., 1999). The International Atomic Energy Agency (IAEA) implicitly endorsed by the World Health Organization (WHO) declared that "*Because of the relatively low dose levels to which the populations of the Chernobyl affected regions were exposed, there is no evidence or any likelihood of observing decreased fertility among males or females in the general population as a direct result of radiation exposure. These doses are also unlikely to have any major effect on the number of stillbirths, adverse pregnancy outcomes or delivery complications or the overall health of children*." (IAEA, 2006). The accent on "*no evidence*" and an implicit opinion that investigations of such matters were not indicated, is perhaps among the reasons for the lack of other substantive population-based investigations of CA rates upholding international standards in regions proximal to Chornobyl. Persistent public concerns of potential impacts of IR, including a chronic epidemic of CAs in Ukraine prompted agencies to brand such concerns as radiophobia. However, as pointed out by a review by Bromet et al. (2011), mental health effects are viewed as some of the most significant public health concerns related to Chornobyl.

The circumstances alluded to above, call for our reports to highlight the credibility of the observations by stressing their persistence and inclusion of extensive companion Data Supplements sufficient to facilitate independent interpretations. Supporting observations by previous independent investigators of associations of higher rates of CA with exposures to relatively low levels of IR were reviewed in our 2014 and 2016 reports (Wertelecki et al., 2014, 2016). Reports concerned with Chornobyl IR impacts on health in Rivne include observations of higher rates of radiation-induced leukemia among children aged 0–5 years, and for adolescents to develop depression and suicide ideations, thyroid nodules and cancer (Contis and Foley, 2015, Noshchenko et al., 2010). A report by the Ministry of Health of Ukraine and National Academy of Medical Sciences asserts that separate research and monitoring is needed to "control internal radiation formation in residents of some areas of the Rivne province" referring to Polissia. The report also notes recent rising trends of levels of WBC in P (Vasylenko et al., 2013).

4.7. Study limitations and strengths

The strengths of this study include the extensive standardized surveillance program for CAs in the regions under study with comprehensive information on prenatal diagnosis, terminations, spontaneous abortions and stillbirths, as well as active ascertainment up through the first year of life. Other strengths include the ability to examine temporal and regional trends and availability of WBC data collected concurrently and on an ongoing basis. The specific findings with respect to strength, consistency, specificity, temporality and biological plausibility support the possibility that the relationship between WBCs and selected CAs may be causal. The associations of higher population rates of five categories of CA and higher WBC in P are strong and persistent. The main limitation of the study is the lack of individual level linked WBC and CA data, leading to the need to follow up on ecological associations with purposefully designed studies.

4.8. Conclusion and prospects

The strong persistent association of higher rates of core-CA and WBC in P compared to not-P is virtually demonstrated. The altered CA patterns in P are unlikely to be due to primary teratogenic alcohol impacts. Causal prospective investigations are warranted with emphasis on pregnancy outcomes in the context of WBC of women residing in small clusters of study-villages across north-P and control-villages in not-P; growth and development of children; diets; and 137-Cs and 90-Srs contents in water, food sources and home-grounds.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmg.2016.09.019.

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Supplemental Figures and Tables

Figure SF1. Annual Number of Live and Stillbirths in Rivne Province, Ukraine, and the Polissia Region of the Rivne Province, 1980-2012

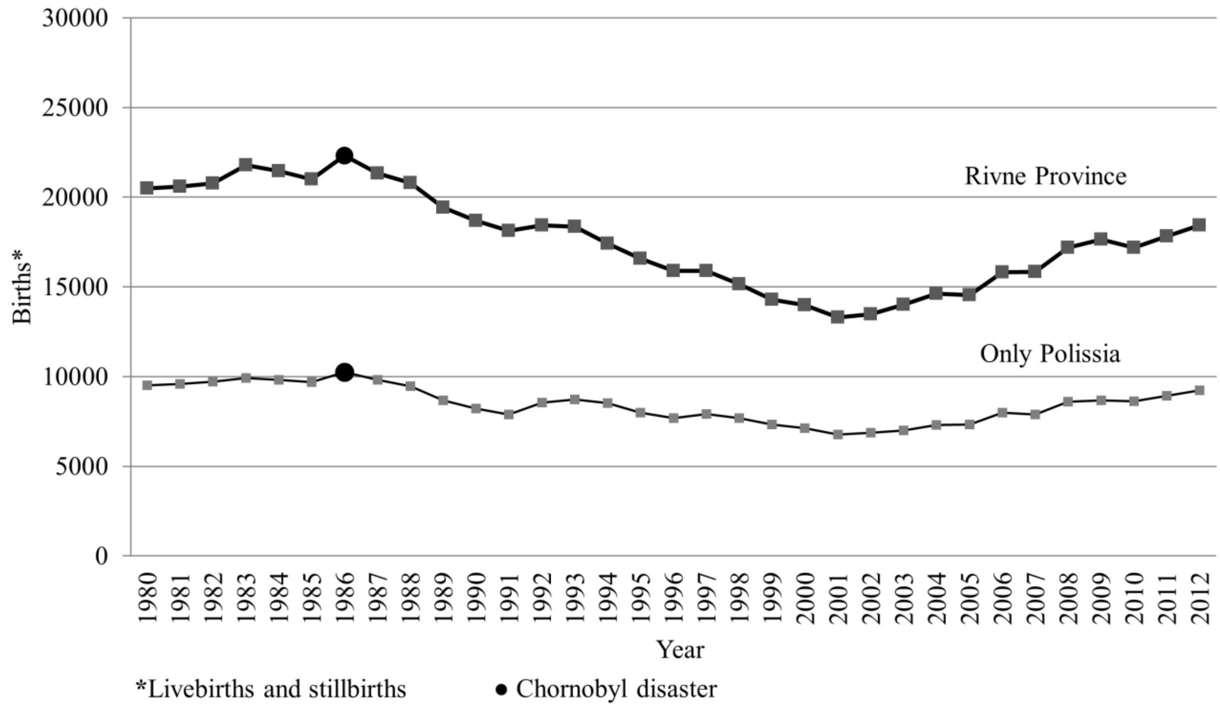

Table S1. Annual Number of Live and Stillbirths in Rivne Province, Ukraine, and Annual Number and Percent in the Polissia Region of Rivne Province, 1980-2012

Year	Total	Polissia	% in Polissia
1980	20500	9524	46.46
1981	20597	9600	46.61
1982	20767	9725	46.83
1983	21786	9917	45.52
1984	21449	9813	45.75
1985	20989	9688	46.16
1986	22323	10244	45.89
1987	21322	9810	46.01
1988	20789	9450	45.46
1989	19421	8674	44.66
1990	18694	8211	43.92
1991	18125	7895	43.56
1992	18444	8549	46.35
1993	18350	8726	47.55
1994	17424	8512	48.85
1995	16585	8000	48.24
1996	15882	7681	48.36
1997	15880	7923	49.89
1998	15157	7673	50.62
1999	14279	7323	51.29
2000	13983	7115	50.88
2001	13310	6779	50.93
2002	13476	6876	51.02
2003	14020	6995	49.89
2004	14612	7306	50.00
2005	14548	7320	50.32
2006	15817	7992	50.53
2007	15848	7891	49.79
2008	17188	8590	49.98
2009	17643	8678	49.19
2010	17191	8629	50.19
2011	17811	8934	50.16
2012	18432	9236	50.11

Table S2. Infant Mortality Rates per 1,000 Live and Stillbirths in North, Central and Not Polissia Regions of Rivne Province, Ukraine, 1981-2010

Period	North Polissia	Central Polissia	not-Polissia	North Polissia vs. not-Polissia			
				OR[2]	P-value (1-tail)	P-value (2-tail)	CL[3]
1981-1985	17.89	15.51	15.52	1.16	0.0229	0.0459	1.00, 1.33
1986-1990	15.93	13.65	14.50	1.10	0.1164	0.2328	0.94, 1.28
1991-1995	16.55	13.69	13.50	1.23	0.0066	0.0133	1.04, 1.44
1996-2000	14.05	12.96	13.80	1.02	0.4382	0.8764	0.85, 1.22
2001-2005	12.10	9.27	10.57	1.15	0.1012	0.2023	0.93, 1.41
2006-2010	11.57	8.82	9.53	1.22	0.0269	0.0537	0.99, 1.48

(1) Data from Rivne Province Vital Statistics Center; rate per 1,000 live births. (2) OR, odds ratio. (3) CL, confidence limits.

Table S3. Population Rates of Five Congenital Malformations in Males and Females from Polissia (P) and not-Polissia (not-P) during Four Time Periods from 2000 to 2014.

Category	2000-2002				2000-2006				2000-2009				2000-2014			
	N		Rate		N		Rate		N		Rate		N		Rate	
	Polissia	not-Polissia	Polissia	not-Polissia	Polissia	not-Polissia	Polissia	not-Polissia	Polissia	not-Polissia	Polissia	not-Polissia	Polissia	not-Polissia	Polissia	not-Polissia
Live births	19968	19399			48392	47891			72376	73058			114586	116804		
Males	10288	9996			25089	24660			37575	37716			59187	60132		
Females	9671	9390			23293	23217			34790	35326			55383	56651		
Neural tube defects(1)	42	35	21.0	18.0	120	76	24.8	15.9	173	105	23.9	14.4	244	179	21.3	15.3
Males	19	8	9.5	4.1	43	27	8.9	5.6	66	38	9.1	5.2	87	59	7.6	5.1
Females	17	12	8.5	6.2	58	26	12.0	5.4	80	38	11.1	5.2	118	70	10.3	6.0
Cephalad NTD	22	17	11.0	8.8	51	34	10.5	7.1	71	45	9.8	6.2	99	74	8.6	6.3
Males	8	1	4.0	0.5	15	8	3.1	1.7	21	11	2.9	1.5	26	14	2.3	1.2
Females	12	5	6.0	2.6	26	12	5.4	2.5	35	15	4.8	2.1	48	25	4.2	2.1
Spinal NTD	20	18	10.0	9.3	69	42	14.3	8.8	102	60	14.1	8.2	145	105	12.7	9.0
Males	11	7	5.5	3.6	28	19	5.8	4.0	45	27	6.2	3.7	61	45	5.3	3.9
Females	5	7	2.5	3.6	32	14	6.6	2.9	45	23	6.2	3.1	70	45	6.1	3.9
Encephaloceles	5	4	2.5	2.1	11	10	2.3	2.1	16	15	2.2	2.1	24	25	2.1	2.1
Males	0	2	n/a	1.0	2	3	0.4	0.6	4	5	0.6	0.7	9	10	0.8	0.9
Females	4	0	2.0	n/a	6	1	1.2	0.2	9	3	1.2	0.4	11	5	1.0	0.4
Microcephaly(2)	9	6	4.5	3.1	23	17	4.8	3.5	44	24	6.1	3.3	80	61	7.0	5.2
Males	6	4	3.0	2.1	12	7	2.5	1.5	20	12	2.8	1.6	40	35	3.5	3.0
Females	3	2	1.5	1.0	11	10	2.3	2.1	24	12	3.3	1.6	40	26	3.5	2.2
Isolated	4	2	2.0	1.0	9	5	1.9	1.0	14	8	1.9	1.1	24	19	2.1	1.6
Males	2	2	1.0	1.0	2	2	0.4	0.4	3	3	0.4	0.4	11	9	1.0	0.8
Females	2	0	1.0	n/a	7	3	1.4	0.6	11	5	1.5	0.7	13	10	1.1	0.9
Microphthalmos(2. 3)	5	2	2.5	1.0	10	2	2.1	0.4	18	6	2.5	0.8	24	10	2.1	0.9
Males	2	2	1.0	1.0	4	2	0.8	0.4	8	3	1.1	0.4	13	4	1.1	0.3
Females	3	0	1.5	n/a	6	0	1.2	n/a	10	3	1.4	0.4	11	6	1.0	0.5

Isolated	1	0	0.5	n/a	4	0	0.8	n/a	8	4	1.1	0.5	12	7	1.0	0.6
Males	0	0	n/a	n/a	1	0	0.2	n/a	5	1	0.7	0.1	8	2	0.7	0.2
Females	1	0	0.5	n/a	3	0	0.6	n/a	3	3	0.4	0.4	4	5	0.3	0.4
Omphaloceles(4)	2	3	1.0	1.5	8	14	1.7	2.9	13	25	1.8	3.4	42	36	3.7	3.1
Males	1	2	0.5	1.0	5	4	1.0	0.8	10	10	1.4	1.4	23	11	2.0	0.9
Females	1	0	0.5	n/a	1	3	0.2	0.6	1	5	0.1	0.7	6	6	0.5	0.5

Abbreviations: n/a, not applicable. (1) Excludes encephaloceles; includes 2 instances in conjoined twins in P (2003 + omphalocele, 2012); (2) excludes holoprosencephaly; (3) excludes one instance in P counted in NTD (2000), 5 instances counted in microcephaly (P - 4: 2004, 2008, 2009, 2010; not-P: 2001); (4) excludes 17 instances counted in NTD (P - 12: 2001, 2003 - 2, 2004, 2005 -2, 2006, 2007, 2008 - 2, 2011, 2013; not-P - 5: 2000, 2006, 2008, 2009, 2010), 2 instances counted in microcephaly (P: 2008, not-P: 2009), 3 instances counted in microphthalmia (P: 2005, 2012; not-P: 2001).

Table S4. Encephaloceles (2000-2014)

Category	Polissia		not-Polissia		Rivne Province	
	N	Rate(1)	N	Rate(1)	N	Rate(1)
Occipital	19	1.7	16	1.4	35	1.5
Syndromic(2)	5	n/c	n/c	n/c	5	n/c
not-Occipital	5	n/c	9	n/c	14	0.6
All	24	2.1	25	2.1	49	2.1

Abbreviations: n/c, not computed. (1) Live births: 231,390 in Rivne; 114,586 in P; and 116,804 in not-P. (2) In P are included one instance of Klippel-Feil complex; two siblings with Meckel-Gruber complex and two siblings with suspected Knobloch syndrome.

Table S5. Neural Tube Defects(1) in Polissia (P) and not-Polissia (not-P) - Prenatal Diagnosis (PrDx) and Terminations of Pregnancies (ToP), 2000-2014

Region	Years	Live births (LB)	NTD total (Rate)	PrDx (%)	PrDx+ToP (%)	No PrDx (%)	LB+NTD (%)
P	2000-2004	33700	88 (26.1)	60 (68.2)	41 (68.3)	28 (31.8)	29 (33.0)
	2005-2009	38676	85 (22.0)	76 (89.4)	48 (63.2)	9 (10.6)	22 (25.9)
	2010-2014	42210	71 (16.8)	67 (94.4)	40 (59.7)	4 (5.6)	23 (32.4)
Total P		114586	244 (21.3)	203 (83.2)	129 (63.6)	41 (16.8)	74 (30.3)
not-P	2000-2004	33205	54 (16.3)	43 (79.6)	30 (69.8)	11 (20.4)	13 (24.1)
	2005-2009	39853	51 (12.8)	49 (96.1)	37 (75.5)	2 (3.9)	8 (15.7)
	2010-2014	43746	74 (16.9)	68 (91.9)	52 (76.5)	6 (8.1)	16 (21.6)
Total not-P		116804	179 (15.3)	160 (89.4)	119 (74.4)	19 (10.6)	37 (20.7)
Total		231390	423 (18.3)	363 (85.8)	248 (68.3)	60 (14.2)	111 (26.2)

(1) Excludes encephaloceles.

Table S6. Pregnant women[1] (2011-2014) - Mean 137-Cs Whole Body Counts and Specific Activity (Bq/kg) by Age and Region in Rivne Province

Age (Years)	Region	N	Bq			Bq/kg		
			Mean	SD	SE[2]	Mean	SD	SE [2]
20-22	Polissia	733	2511	2242	82.8	41.0	37.8	1.4
	not-Polissia	447	677	602	28.5	11.1	9.5	0.4
23-25	Polissia	787	2539	2166	77.2	40.7	35.5	1.3
	not-Polissia	488	732	612	27.7	11.6	9.4	0.4
26-28	Polissia	640	2495	2039	80.6	39.0	33.5	1.3
	not-Polissia	423	749	839	40.8	11.7	12.3	0.6
29-31	Polissia	455	2625	3123	146.4	40.0	44.3	2.1
	not-Polissia	317	709	517	29.0	10.9	8.4	0.5
32-34	Polissia	303	2667	2839	163.1	39.2	40.7	2.3
	not-Polissia	202	678	504	35.5	10.3	8.4	0.6
All	Polissia	2918	2549	2408	44.6	40.1	37.7	0.7
	not-Polissia	1877	713	645	14.9	11.2	9.9	0.2

Abbreviations: SD, standard deviation; SE, standard error. (1) Includes pregnant women weighing from 45 to 85 kg gestating a single fetus and whose initial WBCs register at least 100 Bq, subsequent WBC recordings are excluded; (2) SE = SD/sqrt(N).

Table S7. WBCs and CAs in Two Clusters of Villages in Polissia

Category	Live Births[1]	WBC[2], 2001-2010		Congenital Anomalies[3], 2000-2014				
	N	N	Mean Bq	NTD[4]	NTD Rate	FASD[5]	MIC	CL/P
WBC >4000 Bq								
Group A ”high” (7 sites)	1304	33	4729	6	46.0	0	0	2 (15.3)
Group B “high” (13 sites)	3087	194	4696	7	22.7	4 (13.0)	4 (13.0)	2 (6.5)
WBC <4000 Bq								
Group A “low” (36 sites)	9040	369	2703	14	15.5	3 (3.3)	6 (6.6)	8 (8.8)
Group B “low” (20 sites)	3989	359	2942	6	15.0	6 (15.0)	1 (2.5)	2 (5.0)

Abbreviations: NTD, neural tube defects; FAS, fetal alcohol syndrome; MIC, microcephaly; CL/P, cleft lip with/without palate. (1) 2000-2014 data. (2) Women of 20-34 years of age whose WBC is at least 100 Bq. (3) Unique individuals. (4) Excludes encephaloceles. (5) 2000-2013 data.