Breast cancer risk in Ukrainian women exposed to Chornobyl fallout while pregnant or lactating: standardized incidence ratio analysis, 1998 to 2016

Vibha Vij (vibha.vij@nih.gov)
National Cancer Institute https://orcid.org/0000-0002-1411-0257

Victor Shpak
Institute of Endocrinology and Metabolism

Galyna Zamotayeva
Institute of Endocrinology and Metabolism

Less Lapikura
Institute of Endocrinology and Metabolism

Anton Ryzhov
National Cancer Registry of Ukraine

Evgeniy Gorokh
National cancer Registry of Ukraine

Rui Zhang
National Cancer Institute Division of Cancer Epidemiology and Genetics

Kiyo Mabuchi
National Cancer Institute Division of Cancer Epidemiology and Genetics

Mark P Little
National Cancer Institute Division of Cancer Epidemiology and Genetics

Vladimir Drozdovitch
National Cancer Institute Division of Cancer Epidemiology and Genetics

Konstantin Chizhov
National Cancer Institute Division of Cancer Epidemiology and Genetics

Sergii Masuik
Institute of Endocrinology and Metabolism

Dale Preston
Hirosoft International, California

Mykola Tronko
Institute of Endocrinology and Metabolism, Kiev

Elizabeth K Cahoon
National Cancer Institute Division of Cancer Epidemiology and Genetics

---

Research Article

Keywords: breast cancer, radiation, Ukraine, Chornobyl, Chornobyl, pregnancy, lactation, breastfeeding

Posted Date: April 7th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1506950/v1

Abstract

Background

The radiation-related risk of breast cancer among women following the Chornobyl accident remains uncertain. During pregnancy, there is rapid cell proliferation in the breast while radioactive iodine from fallout exposure can concentrate in lactating breast tissues.

Methods

We conducted a standardized incidence ratio (SIR) analysis of breast cancer in a cohort of 2,631 women who were lactating and/or pregnant at any time during the two-month period of radioiodine fallout (April 26, 1986 - June 30, 1986). There were 37,151 person-years of follow-up, and 26 incident breast cancers were identified through linkage with the National Cancer Registry of Ukraine. Breast cancer rates among pregnant or lactating women were compared to the general population rates, and SIRs were adjusted for oblast, urban/rural, age, and calendar year.

Results

The SIR was non-significantly elevated for women lactating at the time of accident (SIR = 1.30, 95% CI: 0.40; 3.01), but not for women initiating lactation within the two months of the accident (SIR = 0.82, 95% CI: 0.32; 1.65) or women pregnant at the time of the accident (SIR = 0.75, 95% CI: 0.44; 1.18).

Conclusions

The increased SIR for breast cancer among lactating women is consistent with the results of a similar study in Belarus and indicates the need to quantify the radiation risk of breast cancer in a larger study of women lactating during the period of fallout exposure.

Introduction

Breast cancer is a leading cancer and cause of death among women in many countries, including Ukraine[1, 2]. While breast tissue is known to be radiosensitive [3, 4], limited epidemiological data is available for breast cancer risk from environmental exposure to radiation after nuclear accidents. The accident at the Chornobyl (Chernobyl) nuclear power plant (NPP) in northern Ukraine that occurred on April 26, 1986 resulted in a massive release of contaminants including Iodine-131 (^{131}I), which has a half-life of eight days, in addition to longer-lived cesium isotopes[5, 6]. Rapid cell proliferation during pregnancy and radioactive iodine accumulation in the lactating mammary gland suggest that exposure to fallout during these two reproductive periods may increase breast cancer risk [7].

Studies of breast cancer incidence following the Chornobyl accident have focused on female liquidators (cleanup workers), evacuees of the exclusion zone, and women residing in areas contaminated by fallout.

Increased breast cancer risks have been reported among female liquidators when compared to the general population [8]. In a recent ecological study in Belarus and Ukraine, Zupunski and colleagues reported no increase in breast cancer incidence in contaminated areas [9]. However, this study did not include individual breast doses, and did not account for reproductive factors aside from age. Epidemiological data for women that were either pregnant or lactating at the time of radiation exposure are sparse. Cahoon and colleagues were the first to examine rates of breast cancer among women residing in contaminated regions in Belarus who may have been exposed to Chornobyl fallout during these reproductive periods, finding a significantly increased breast cancer risk among women lactating, but not pregnant at the time of the accident[10]. However, the limited sample size in that study underscores the need for additional data in this potentially vulnerable population.

The objective of this study is to compare the rates of breast cancer among women in Ukraine who were exposed to Chornobyl fallout while pregnant or lactating to the rates in the general population. National cancer registry data and well-established long-term thyroid screening cohorts of individuals exposed to Chornobyl fallout as children and *in utero* were used to examine whether mothers of these subjects were at increased breast cancer risk.

Materials And Methods

Study population

Our study cohort included mothers of subjects derived from two existing cohorts: the Ukrainian-American thyroid cohort (UkrAm) and the Ukraine In-utero (UkrIU) cohort. Detailed descriptions of these two cohorts are given elsewhere [11–13]. At the time of the accident, in both cohorts, subjects and mothers of the subjects resided in the most radioactively contaminated areas of northern oblasts (an oblast is an administrative area similar in size to a state or province) of Ukraine, mainly Chernihiv and Zhytomyr[14]. The study population includes 2,631 mothers of infants aged 0–6 months at the time of the accident or women who were pregnant at the time of the accident and were breast-cancer free at study entry (Fig. 1). The reasons for exclusion (in series) included missing or incomplete data on mother (n = 36), low expected frequency of breastfeeding because child was 6 months or older (n = 220), non-residence in Zhytomyr and Chernihiv oblasts (n = 138), death (n = 6) or diagnosis with breast cancer (n = 4) before start of follow-up.

Pregnancy and lactation status

Questionnaire data collected from UkrAm subjects was used to assess whether their mothers were nursing at the time of the Chornobyl accident and to estimate the thyroid dose from ^{131}I intake. A parent or a close relative was interviewed for the UkrAm subjects that were younger than 10 years at the time of accident. UkrIU mothers were administered questionnaires to assess both pregnancy and nursing status at the time of the Chornobyl accident in order to determine UkrIU study eligibility and to estimate fetal and infant thyroid dose from ^{131}I. Because of the short physical half-life of ^{131}I (eight days) radioiodine exposure over the two-month period of April 26 - June 30, 1986 was considered the critical exposure period.

Our cohort of 2,631 women consisted of 1,809 pregnant women (all mothers of the UkrIU subjects) and 822 lactating women. Among lactating women, there were 218 UkrAm mothers that were already lactating at the time of the accident. UkrIU mothers who were both pregnant and lactating during between April and June 1986 were categorized into the lactating group because of their potentially higher exposure to the mammary gland due to ^{131}I intake.

Breast cancer incidence

Breast cancer incidence was ascertained through linkage with the National Cancer Registry of Ukraine (NCRU) from 1990 to 2016. The NCRU is a nationwide population-based cancer registry that monitors cancer incidence and mortality and represents a network of regional population-based cancer registries (PBCR) in Ukraine's administrative regions. The NCRU depends on mandatory reporting of cancer diagnoses by local medical practitioners to regional oncological institutions (oncological dispensaries). The data collected by each regional PBCRs are then submitted annually to the central unit of the NCRU operating in the Department of the National Cancer Institute of Ukraine. Established in 1988, the database reached near-universal coverage by 2000. Ryzhov et al reported on the quality of the data in the NCRU and noted that the incidence data are in accordance with international cancer registry standards with respect to timeliness, completeness, validity, and comparability [15]. Information collected includes the patient's last, first and patronymic names, date of birth, sex, place of residence, date and place of cancer diagnosis, methods used for the basis of diagnosis, cancer diagnosis coded according to International Classification of Diseases (ICD) and ICD-O-3 classification, and follow-up information including migration and date of death.

An electronic database containing demographic data (last, first and patronymic names, patronymic name, date of birth, address of residence) for mothers of UkrAm and UkrIU cohort subjects was created and linked with the NCRU data for identification of breast cancer cases. The linkage procedure was based on a computerized deterministic record linkage technique with probabilistic elements incorporating a set of comparison functions using last, first and patronymic names, date of birth, and complete residential address. Each computer link was also reviewed by the team of Ukrainian researchers. Breast cancer cases with confirmed identities were included in the study. Corresponding census-based population counts were obtained from the State Statistics Service of Ukraine[16].

Statistical analysis

Study entry dates of January 1, 1998 and January 1, 2003 were selected for mothers of the UkrAm and UkrIU subjects, respectively, to minimize selection bias because these were the dates when full-scale screening in the respective cohorts began. We followed the study population from study entry until the earliest of (i) date of first breast cancer diagnosis, (ii) date of death or migration out of the country, or (iii) closing date of linkage with the cancer registry (12/31/2016).

We created person-event time tables for the study population stratifying person-years and breast cancer cases by pregnancy/lactation status (lactating in period April-June 1986, pregnant but not lactating in period April-June 1986), attained age (10-year categories from age 30 to 79 years), oblast of residence at the time of study entry (Zhytomyr and Chernihiv), urban/rural residence at the time of study entry, and calendar period of follow-up (1998–2002, 2003–2011, and 2012–2016). We calculated standardized incidence ratios (SIR) by dividing the number of observed cases by the number of expected cases based on national cancer incidence rates,

stratified by oblast, urban/rural, age, and calendar period using identical categories. All statistical tests were two-sided with $p \leq 0.05$ considered to be statistically significant. Model parameters and 95% confidence intervals (CIs) were estimated using Epicure [17].

Results

There were altogether 37,151 person-years at risk and 26 incident breast cancer cases identified in the study cohort during up to 18 years of follow up (Table 1). The median age of study subjects at time of the accident was 24 years (range: 16 to 45) and the median attained age was 55 years (range: 39 to 76). At the time of study entry, roughly half of women in the study were residents of Chernihiv oblast (51%) and most lived in rural settings (58%). For pregnant women, all of whom were mothers of the UkrIU cohort subjects, we found an SIR of less than unity (0.75, 95% CI: 0.44; 1.18) (Table 1). There was no significant heterogeneity in the SIRs across the categories of age at time of accident, calendar year, attained age, urban/rural residence, or oblast (Zhytomyr vs. Chernihiv) in this group.

Table 1. Breast cancer standardized incidence ratio estimates by selected characteristics in women exposed while pregnant or lactating to Chornobyl fallout while residing in Ukraine.

	Pregnant during April-June, 1986					Lactating during April-June, 1986				
	PYRs	Women	Obs	Exp	SIR (95% CI)	PYRs	Women	Obs	Exp	SIR (95% CI)
Total	24,856	1,809	16	21.29	0.75 (0.44, 1.18)	12,295	822	10	10.43	0.96 (0.48, 1.68)
Study										
UkrAm						4,040	218	4	3.08	1.30 (0.40, 3.01)
UkrIU	24,856	1,809	16	21.29	0.75 (0.44, 1.18)	8,255	604	6	7.35	0.82 (0.32, 1.65)
Age at time of accident										
15-19	3,388	244	1	1.95	0.51 (0.03, 2.26)	1,174	79	0	0.67	
20-24	9,440	684	7	7	1.00 (0.43, 1.93)	4,752	314	2	3.43	0.58 (0.10, 1.80)
25-49	12,029	881	8	12.34	0.65 (0.30, 1.21)	6,368	429	8	6.34	1.26 (0.58, 2.35)
Calendar year										
1998-2002						1,086		0	0.56	
2003-2011	16,097		11	12.03	0.91 (0.47, 1.57)	7,300		5	5.66	0.88 (0.32, 1.90)
2012-2016	8,759		5	9.27	0.54 (0.19, 1.16)	3,909		5	4.21	1.19 (0.43, 2.55)
Attained age										
30-39	1,913		0	0.62		1,219		0	0.42	
40-49	12,412		9	9.38	0.96 (0.46, 1.73)	5,830		3	4.41	0.68 (0.17, 1.76)
50-59	9,087		7	9.42	0.74 (0.32, 1.44)	4,431		6	4.53	1.32 (0.53, 2.68)
60-69	1,413		0	1.84		796		1	1.05	0.95 (0.05,

										4.20)
70-80	31		0	0.04		18		0	0.02	
Urban status at first screening										
Rural	14,311	1,045	10	10.27	0.97 (0.49, 1.71)	7,233	473	4	5.2	0.77 (0.24, 1.79)
Urban	10,545	764	6	11.02	0.54 (0.22, 1.10)	5,062	349	6	5.24	1.15 (0.46, 2.32)
Oblast at first screening										
Zhytomyr	12,342	900	8	9.84	0.81 (0.37, 1.51)	5,694	391	3	4.77	0.63 (0.16, 1.63)
Chernihiv	12,514	909	8	11.45	0.70 (0.32, 1.30)	6,601	431	7	5.66	1.24 (0.53, 2.39)

Abbreviations: PYRs, person-years; Obs, number of observed cases; Exp, number of expected cases; SIR, standardized incidence ratio; CI, confidence interval, UkrAm, Ukraine-American Thyroid Disease Study; UkrIU, Ukraine In Utero Study.

* Adjusted for oblast, urban status, attained age group (10-year categories from 30 to 79 years), and calendar year categories (1998-2002, 2003-2011, 2012-2016). Entry date for UkrAm is 1/1/1998 and for UkrIU 1/1/2003 with exit at earliest date of breast cancer diagnosis, date of death, or date of linkage with the cancer registry (12/31/2016). Time-dependent variables for calendar year and attained age do not include number of subjects. P for heterogeneity non-significant for study, urban status, or oblast for either exposure group. P for trend non-significant for age at time of accident, calendar year, and attained age for either exposure group.

For lactating women, the breast cancer risk was close to unity (SIR = 0.96; 95% CI: 0.48; 1.68) for UkrAm and UkrIU mothers combined. However, the SIR for UkrAm mothers (who were lactating at the time of the Chornobyl accident) was higher than unity (SIR = 1.30; 95% CI: 0.40, 3.01), while lower than unity for UkrIU mothers (who initiated lactation within 2 months of the accident) (SIR = 0.82; 95% CI: 0.32, 1.65). The difference in the two SIRs was not significant (p for heterogeneity = 0.48). No significant heterogeneity was observed in SIRs for lactating women across the categories of age, calendar year, urban/rural residence, and oblast, but we noted higher SIRs for those exposed at age 25 years or older and women residing in Chernihiv oblast.

Discussion

In this cohort of Ukrainian women exposed to Chornobyl fallout during pregnancy and lactation, we found a non-significantly elevated breast cancer risk for women in Ukraine who were lactating at the time of the Chornobyl accident when compared to the general population. There was little indication of excess risk among women initiating lactation within the two months of the accident or women pregnant at the time of the accident. This study of breast cancer in Ukrainian women was conducted following a similar study of

pregnant and lactating women residing in Belarus. Our findings are broadly similar to those of the Belarus study, though the estimated elevation in the risk for lactating women was somewhat less than that seen in that study [10].

In both the Ukrainian and Belarussian studies, the highest breast cancer risks were found for mothers who were lactating at the time of the accident. As in the Belarussian study, the SIR was lower for mothers who started lactation within the two-month window of April 26-June 30, 1986, than for mothers who gave birth following the accident. We found little indication of elevated breast cancer risk for women who were pregnant in either study population. Although the SIR in the UkrAm women lactating at the time of the accident did not reach statistical significance, the consistency in the SIR patterns by pregnancy/lactation status in both Ukrainian and Belarussian women is noteworthy. This suggests that women residing in the areas most affected by the Chornobyl accident offers a unique opportunity to investigate effects of radioiodine exposure at these important reproductive stages.

The female breast undergoes dramatic changes in size, shape, and function during puberty, pregnancy, lactation, and postmenopausal regression [18]. Exposure to ionizing radiation around the time of menarche has been associated with markedly increased breast cancer risks in the Japanese atomic bomb survivors [19] and among women under 13 years exposed to Chornobyl fallout in Bryansk, Russia [20]. Both puberty and pregnancy are marked by rapid cell proliferation [21], however, we did not find increased risk of breast cancer among women pregnant at the time of the accident. One possible reason for the null finding could be low exposure levels in this group, similar to the general population. The majority of the affected population was exposed to low doses of ionizing radiation due to intake of short-lived radioisotopes of iodine, ^{131}I, external irradiation to gamma-emitting radionuclides deposited on the ground, and ingestion of long-lived ^{134,137}Cs[5]. Between 1986 and 2016, the mean cumulative breast dose of 5.7 mGy was reported in Ukraine, with the maximum dose of 54 mGy in Narodychi rayon of Zhytomyr oblast[9].

Several studies have demonstrated ^{131}I uptake in lactating breasts following therapeutic radioiodine [22–25] treatment. Active iodide transport occurs in the lactating mammary gland and is secreted into breast milk used by the nursing newborn for the biosynthesis of thyroid hormones [26–28]. Increased ^{131}I exposure in the lactating group of women may explain why risks were highest in this group.

The most important limitation of this study is the lack of individual estimates of radiation dose. This study is therefore fundamentally ecological in design and the possibilities of bias in such studies are well known [29]. Known breast cancer risk factors such as age at menarche, parity, and age at first birth could not be controlled for. In addition, women that may relocate or die before the cancer reporting process is either initiated or completed are sometimes not recorded in the cancer registry data and may be missed in our data. Our study had small sample size that resulted in limited power to examine associations by reproductive stage, age at exposure, calendar year, and oblast.

The results of this study in combination with those of a similar study from Belarus, suggest that ^{131}I exposure could be an important contributor to breast cancer risk in lactating women. Future well-powered studies examining breast cancer risk among women exposed during radiosensitive reproductive periods and with individual dose estimates are necessary to quantify any increased risk. Such studies are important from both

public health perspective as well as to monitor long-term effects of radiation in the context of potential future radiological and nuclear disasters.

Abbreviations

SIR	standardized incidence ratio
CI	confidence interval
NPP	nuclear power plant
UkrAm	Ukrainian-American thyroid cohort
UkrIU	Ukraine In-utero
PBCR	population-based cancer registries
NCRU	National Cancer Registry of Ukraine
ICD	International Classification of Diseases
mGy	milligray

Declarations

This research was supported by the Intramural Research Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services through the contracts HHSN261201800762P and 7591020C00008 between the National Cancer Institute, National Institutes of Health (USA) and the Science and Technology Center in Ukraine (STCU).

Financial interests: The authors declare they have no actual or potential competing financial interests.

Ethics Approval: Thisstudy was reviewed and approved by the Ethics Committee at Institute of Endocrinology and Metabolism, Kiev, Ukraine.

Consent to participate: Informed consent was obtained from all individual participants included in the study

References

1. *Cancer in Ukraine, 2018-2019. Ukrainian cancer registry statistics, 2020.* Volume 21: Bulletin of National Cancer Registry of Ukraine (English). Accessed 15 July 2021

2. Ryzhov, A., et al., *Recent cancer incidence trends in Ukraine and short-term predictions to 2022.* Cancer Epidemiol, 2020. **65**: p. 101663.

3. Ronckers, C.M., C.A. Erdmann, and C.E. Land, *Radiation and breast cancer: a review of current evidence.* Breast Cancer Res, 2005. **7**(1): p. 21-32.

4. Gilbert, E.S., *Ionising radiation and cancer risks: what have we learned from epidemiology?* Int J Radiat Biol, 2009. **85**(6): p. 467-82.

5. UNSCEAR, *Sources and Effects of Ionizing Radiation.* Volume II: United Nations Scientific Committee on the Effects of Atomic Radiation, 2011**.**

6. IAEA, *Environmental Consequences of the Chernobyl Accident and their Remediation: Twenty Years of Experience.* Report of the Chernobyl Forum Expert Group 'Environment', 2006. **8**.

7. Cahoon, E.K., *Commentary: Breast cancer risk among women exposed to fallout after the Chernobyl accident.* Int J Epidemiol, 2020. **49**(2): p. 456-458.

8. Prysyazhnyuk, A.Y., et al., *Epidemiology of Breast Cancer in Ukraine with Consideration of the Factors of the Chornobyl Accident.* Probl Radiac Med Radiobiol, 2019. **24**: p. 150-168.

9. Zupunski, L., et al., *Breast cancer incidence in the regions of Belarus and Ukraine most contaminated by the Chernobyl accident: 1978 to 2016.* Int J Cancer, 2020.

10. Cahoon, E.K., et al., *Breast cancer risk in residents of Belarus exposed to Chernobyl fallout while pregnant or lactating: standardized incidence ratio analysis, 1997 to 2016.* Int J Epidemiol, 2021.

11. Tronko, M.D., et al., *A cohort study of thyroid cancer and other thyroid diseases after the chornobyl accident: thyroid cancer in Ukraine detected during first screening.* J Natl Cancer Inst, 2006. **98**(13): p. 897-903.

12. Stezhko, V.A., et al., *A cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident: objectives, design and methods.* Radiat Res, 2004. **161**(4): p. 481-92.

13. Hatch, M., et al., *A screening study of thyroid cancer and other thyroid diseases among individuals exposed in utero to iodine-131 from Chernobyl fallout.* J Clin Endocrinol Metab, 2009. **94**(3): p. 899-906.

14. Likhtarov, I., et al., *Thyroid cancer study among Ukrainian children exposed to radiation after the Chornobyl accident: improved estimates of the thyroid doses to the cohort members.* Health Phys, 2014. **106**(3): p. 370-96.

15. Ryzhov, A., et al., *Evaluation of data quality at the National Cancer Registry of Ukraine.* Cancer Epidemiol, 2018. **53**: p. 156-165.

16. *All-Ukrainian population census*. State Statistics Service of Ukraine; Available from: http://www.ukrstat.gov.ua/.

17. Preston, D.L., et al, *Epicure Risk Regression and Person-Year Computation Software: Command Summary and User Guide. .* Ottowa, Canada: Risk Sciences International, 2015.

18. Russo, J. and I.H. Russo, *Development of the human breast.* Maturitas, 2004. **49**(1): p. 2-15.

19. Brenner, A.V., et al., *Incidence of Breast Cancer in the Life Span Study of Atomic Bomb Survivors: 1958-2009.* Radiat Res, 2018. **190**(4): p. 433-444.

20. Rivkind, N., et al., *Female breast cancer risk in Bryansk Oblast, Russia, following prolonged low dose rate exposure to radiation from the Chernobyl power station accident.* Int J Epidemiol, 2019.

21. Macias, H. and L. Hinck, *Mammary gland development.* Wiley Interdiscip Rev Dev Biol, 2012. **1**(4): p. 533-57.

22. Bakheet, S.M. and M.M. Hammami, *Patterns of radioiodine uptake by the lactating breast.* Eur J Nucl Med, 1994. **21**(7): p. 604-8.

23. Bakheet, S.M., J. Powe, and M.M. Hammami, *Unilateral radioiodine breast uptake.* Clin Nucl Med, 1998. **23**(3): p. 170-1.

24. Basu, S. and S.H. Moghe, *Unusual unilateral breast (131)I uptake related to breastfeeding practice.* Clin Radiol, 2009. **64**(7): p. 743-4.

25. Robinson, P.S., et al., *Iodine-131 in breast milk following therapy for thyroid carcinoma.* J Nucl Med, 1994. **35**(11): p. 1797-801.

26. Carrasco, N., *Iodide transport in the thyroid gland.* Biochim Biophys Acta, 1993. **1154**(1): p. 65-82.

27. Stubbe, P., F.J. Schulte, and P. Heidemann, *Iodine deficiency and brain development.* Bibl Nutr Dieta, 1986(38): p. 206-8.

28. Mountford, P.J., et al., *Transfer of radioiodide to milk and its inhibition.* Nature, 1986. **322**(6080): p. 600.

29. Greenland, S. and J. Robins, *Invited commentary: ecologic studies–biases, misconceptions, and counterexamples.* Am.J.Epidemiol., 1994. **139**(8): p. 747-760.

Figures

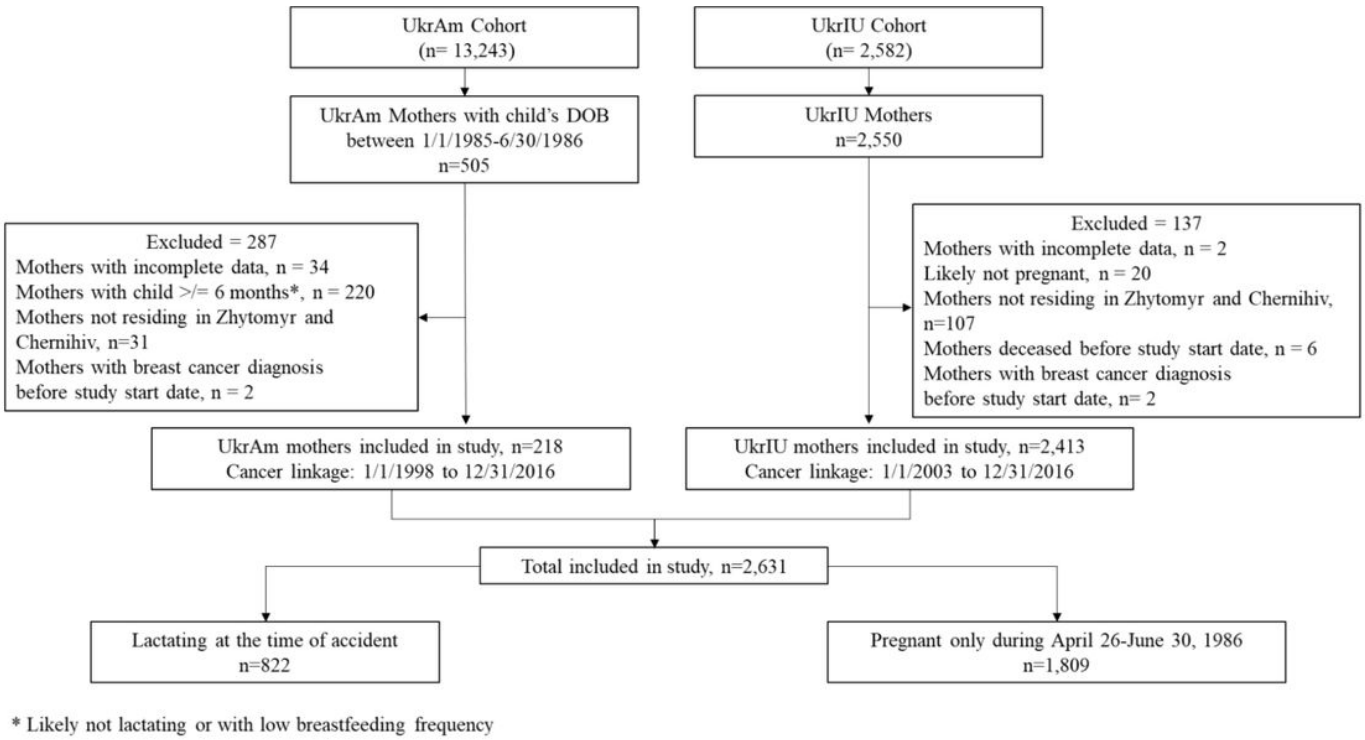

Figure 1

Flowchart of participants in the study of breast cancer among Ukrainian women exposed to Chornobyl fallout while pregnant or lactating, 1998–2016. UkrAm, Ukrainian-American Cohort; UkrIU, Ukrainian In Utero Cohort