УДК 61.618.19

ENGLISH VERSION: ENVIRONMENTAL CONDITIONALITY OF BREAST CANCER MORBIDITY IN WOMEN RESIDING IN INDUSTRIALIZED AREAS*

Pyatchanina T.V., Ohorodnyk A.N., Dvorschenko O.S., Zarytska M.Y.

R.Ye. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology, National Academy of Sciences of Ukraine, Kyiv, Ukraine

The role of factors of environmental conditionality of breast cancer in women living in the ecologically polluted areas of Ukraine and other former USSR republics of the European part is highlighted. Regulatory parameters are presented for the main environmental pollutants with etiopathogenetic role in the development of breast cancer.

Keywords: environment, risk factors, breast cancer, ionizing radiation, pollutants, chemical carcinogens.

Introduction

Global processes associated with the development of technology and industries have led to intense pollution, including pollution with carcinogenic substances of the environment, which adversely affects health of the population and contributes to the occurrence of cancer. Of all malignant neoplasms (MNs), breast cancer (BC) is most commonly diagnosed in women (140 out of 184 countries): in the United States (2014), the highest standardized incidence rate was reported 32% of all newly diagnosed MN cases among women (103 cases per 100,000); in the Western Europe the incidence is much lower, with France featuring the highest rate (86 per 100,000); in Eastern Europe the number of cases of breast cancer among all MNs is less: 21% in Poland and the Czech Republic, and 17% in Belarus (92.8 per 100,000) [48]. According to descriptive epidemiology, breast cancer in Ukraine occupies the first place in the MN morbidity structure of the female population (72.3 per 100,000) and mortality (32.3 per 100,000) (data as of 2014) [3]. The leading place of breast cancer in the structure of MN morbidity and mortality among the female population of Ukraine has turned it from a purely medical condition to a complex medical and social problem.

The world practice has proved the consistency of predictive models of breast cancer risk constructed primarily with account for age-appropriate indicators, race, personal and family history, reproductive factors, number of breast biopsies, bad habits, etc. [15, 67]. However, such predictive models have limitations as they do not include the contribution of regional environmental patterns in the formation of cancer pathology in the form of the whole spectrum of etiologic factors, which is especially important for the industrialized cities with a high level of anthropogenic pollution. In view of the existing epidemiological evidence of environmental conditionality of breast cancer occurrence [46], this feature greatly reduces the potential for assessing the individual risk in the areas with varying carcinogenic loads.

The aim of the study is to review the literature on the regional ecological characteristics of the formation of cancer-causing environmental factors and their role in the occurrence of breast cancer.

Materials and findings

Data of a number of international organizations, including WHO, World Cancer Research Fund (WCRF), US National Cancer Institute (NCI), International Agency for Research on Cancer (IARC) [62, 69] suggest a direct involvement of the combined effects of environmental carcinogens (physical, such as UV and ionizing radiation, and chemical, such as polycyclic aromatic hydrocarbons (PAHs), nitrogen oxides, asbestos, heavy metals, pesticides, dioxins) in the occurrence of 70-80% of all MN cases.

In the human life environment, hundreds of chemicals – inducers of tumor growth are found, 14 of them, including PAHs and nitrosamines are considered to be substances with the greatest degree of carcinogenic risk, 61 substances are considered to be potentially dangerous in this respect. Twenty three manufacturing processes (steel, carbon, aluminum, rubber, etc.) are associated with the development of MNs in humans [63, 64]. Among chemical environmental carcinogens causing high risks of breast cancer, the most important are: PAHs, nitrosamines [41, 68], heavy metals, pesticides, dioxins, polychlorinated biphenyls, and solvents [62].

In Ukraine [11, 16], as a result of industrial and agricultural production and increased number of cars, 6.8 mln tons of chemical pollutants were discharged in the atmosphere in 2014, which is 15% more than in 2010. On a per capita basis, 15 kg of pollutants were discharged in Ukraine, while in the Donetsk region, which is one of the most polluted, this number was 332 kg per capita. A high proportion of gross emissions of chemical pollutants is recorded in the industrialized areas: Donetsk, Dnepropetrovsk, Lugansk, Zaporizhya (30.1-117.5 t/km^2); the lowest levels (7.2-7.9 t/km^2) are typical for the northern regions: Chernihiv, Volyn, and Zhytomyr [37]. The large industrialized cities of the Eastern and Southern regions (Donetsk, Odessa, Lugansk), as well as Kyiv feature the highest overall rates of air pollution which exceed the maximum permissible concentration (MPC) by 1.6-3.5 times. The Northern and Western regions of Ukraine are characterized by the lowest rates of total pollution, which do not exceed MPC.

In line with the level of pollutants, the level of substances that cause high risks of MN is also several

* *To cite this English version: Pyatchanina T.V., Ohorodnyk A.N., Dvorschenko O.S., Zarytska M.Y. Environmental conditionality of breast cancer morbidity in women residing in industrialized areas // Problemy ekologii ta medytsyny. - 2015. - Vol 19, № 1-2. - P. 17 -21.*

times higher than normal in the air of industrialized cities in Ukraine. For example, the contents of BP – an indicator of carcinogenic PAHs (MPC:1×10^{-6} mg/m^3) is by 4-15 times higher than the permissible level in Donetsk, Odessa, Lugansk, Dnepropetrovsk, Kremenchug, Kyiv; formaldehyde level is 2.0-7.6 times higher than MPC in Kyiv, Odessa, Simferopol, Donetsk, Lugansk; phenol level in Odessa, Donetsk, and Kyiv (2.0-2.3 times MPC); ammonia level in Donetsk, Kyiv, Vinnitsa (1.5-2.8 times MPC), nitrogen dioxide level exceeds MPC 1.8-2.3 times in the cities of Donetsk, Odessa, Kyiv, nitrosodimethylamine (NDMA) level, which is a well known inducer of breast carcinogenesis, ranges from 1×10^{-4} to 8.6×10^{-6} mg/m^3 in Dnepropetrovsk, Kremenchug and Kyiv (in the absence of the reference value) [16].

In the post-Soviet states, the lack of modernization of obsolete technologies in industry and outdated regulatory framework contributes to the further growth of the volume of unsafe wastes in the environment and increased levels of MPC in industrialized regions. This situation is typical for all the former republics of the European part of the Soviet Union. For example, in 2014 the volume of pollutant emissions into the air of Belarus amounted to 462,800 tons, which means an average of 46.16 kg per capita. The largest the shares of pollutant emissions are in the Vitebsk and Gomel regions – 22% in each (102,000 – 103,000 tons), in Minsk region – 16% and Mogilev region – 11%. The most polluted city in Belarus is Novopolotsk with 52,000 tons of emissions per year, or 498 kg of emissions on a per capita basis [17].

As a result of technological processes of processing and storage, as well as contamination due to widespread distribution, sources of PAHs in the human body include water and food, specifically oils, fats, smoked meat products. WHO recommends that BP intake with food should be strictly limited to the amount of 0.36 g/day, with an average acceptable level of 0.05 mg/day. About 1% of PAHs entering the body are associated with the consumption of drinking water. BP content in drinking water should not exceed 0.7 mg/l [55]. Regulation of the European Commission determines that the content of BP in vegetable oils and fats should not exceed 2 mg/kg; in smoked products 5 mg/kg; in cereals, including infant formulas, up to 1 mg/kg [25].

The level of BP resulting from the thermal treatment of cocoa beans in chocolate should not exceed 0.63 mg/kg (according to Ukrainian standards, this number is 2 mg/kg, and the content of BP is regulated only in sunflower oil). Tea (dry matter) contains 2.7 – 63 mg/kg (it should be noted that the only 1.6% of PAH gets into tea as a beverage). The BP content in meat after heat treatment should not exceed 4 mg/kg. Its content should be limited to 5.5 mg/kg in chickens and to 62.6 mg/kg in grilled meat [8, 27, 28]. According to EU standards, BP level in vegetable oil is limited to 2 mg/kg.

In the list of environmental contaminants with a high potential risk of causing breast cancer, dioxins (DOs) rank rather high. Dioxins comprise two classes of organochloride compounds containing more than two hundred substances, of which 17 are considered toxic. One of the DOs – 2,3,7,8-tetrachlorodibenzo-p-dioxin (THHD) – is classified as a carcinogen by the US Environmental Protection Agency and IARC. Based on its mechanism of biological action, it is classified as an endocrine disruptor [45, 46]. At present, there are conflicting epidemiologic data on the direct role of DOs in breast carcinogenesis [57, 58, 61, 66]. However, in animal models (rats, mice, hamsters), THHD has been proved to act as an inductor and promoter of carcinogenesis with an estrogen-dependent mechanism of action [51]. It has been confirmed that DOs are able to accumulate in the fatty tissue of human breast in case of elevated exposure [43].

DOs form as a result of production processes in the pulp and paper; woodworking and metal industries, in chlorination of drinking water and biological wastewater treatment. In addition, DO emissions from the combustion of municipal solid wastes are one of the main and the most hazardous sources for the population. Also, DOs are consumed with food, accumulate in fatty tissue, are transmitted along the food chains, and have a long half-life of 7 to 11 years [56].

During the last three decades, as a result of numerous state regulatory actions, the DO levels in food and in the environment of economically developed countries in Europe and the United States tend to reduce, although today more than 95% of US citizens have detectable DO levels in the body; and older people have statistically higher values compared to younger people, which probably reflects the low DO levels in the environment today [42]. For example, in the atmospheric air of the populated areas in US, permitted DO content is 0.02 pg/m^3, in water 0.013 pg/L, in soil of farmlands 27 ng/kg, and in food 0.001 ng/kg. In Germany, water: 0.01 pg/L, soil: 5 mg/kg; standards for food and air are not established. In Italy, air of populated areas: 0.04 pg/m^3, water: 0.05 pg/l, soil: 10 mg/kg; allowable concentrations for food are not established. These DO levels are significantly lower than the MPC in the former Soviet Union. In the territory of the Customs Union, the following MPC levels are established for DOs: air: 0.5 pg/m^3, water: 20 pg/l [7], foods: 0.1×10^{-5} – 0.3×10^{-5} mg/kg [10].

It should be noted that there are no laboratories in Ukraine for the detection of low concentrations of DOs. This fact, along with the widely-accepted practice of burning municipal waste in the settlements, increases the degree of uncontrollability of the environmental situation [33]. At the same time, there are data showing a high (5.88-fold) concentration compared with the average urban rates, incidence of breast cancer in Kyiv (Ukraine), among residents of a 2-km zone around the waste incineration plant [23].

Transition metals are classified as carcinogens with respect to humans. Based on their mechanism of action, they are classified as endocrine disruptors [47]. There is experimental evidence of estrogenic effect of these metals on the breast tissues. Heavy metals, being accumulated in breast tissues, cause molecular damages that play a role in the development of carcinogenesis; namely, they modulate the processes of antioxidant protection, gene expression, signal transduction, cell proliferation, differentiation, and apoptosis [47, 65].

In today's world, the impact of heavy metals on human beings has increased dramatically in line with the exponential growth of their industrial (mining, casting, and steel manufacturing), agricultural, domestic and technological (pharmaceuticals) use. Arsenic (As), cadmium (Cd), nickel (Ni), copper (Cu), chromium (Cr), zinc (Zn) are currently among the most hazardous carcinogenic metals, prolonged exposure to which increases the risk of breast cancer. Higher concentrations of these metals are found in serum samples from women diagnosed with breast cancer and breast tumor biopsy specimens, compared with levels in normal breast tissue of women [53]. The increased (by 15-25% compared to control) content of heavy metals, such as Fe, Zn, Cu, Cr, Ni and Pb, in breast tumor tissue was found in women living in ecologically contaminated areas of Ukraine [26].

Human exposure to Cd is possible as a result of occupational activity in the mining, metallurgical industry and manufacture of batteries, pigments, stabilizers, and alloys [30]. But still, the main sources of Cd in a human body include cigarette smoke, drinking water and food (leafy vegetables, potatoes, grains, seeds, liver, kidneys, as well as crustaceans and mollusks). Cd-high foods can considerably increase its concentration in the tissues of the body, which can be assessed by the measurements of the levels in the blood (reflecting the recent exposure, for example, due to smoking) or urine (reflects chronic loads). Cd levels vary considerably in the environment of various regions across the world: serious Cd pollution of rivers, lakes, coastal waters and groundwater sources exist in China, India, Pakistan, Thailand, Nigeria, and Russia. However, in developed countries, there is also some pollution of coastal waters and large areas of farmlands (US, Canada, China) due to the use of phosphate fertilizers and manure [2].

Prolonged exposure to Cd can lead to varying forms of cadmium intoxication, and increase the risk of breast cancer. This is especially true for the Eastern countries [40, 70]. There is a large body of experimental evidence of the accumulation of Cd in biological fluids, tissues and breast tumors of women, as well as women with addictions or living in polluted areas [26, 50].

WHO and the UN Food and Agriculture Organization have established the following maximum permitted Cd levels: 0.003 mg/l for drinking water, 0.01-0.4 mg/m^3 for air [12], 0.05 – 0.2 mg/kg for food [14].

In Ukraine MPC for Cd in water is set at 0.001 mg/l, in soil at 1.0 mg/kg. For food, the following hygienic standards for the levels of Cd are established (mg/kg of wet weight): meat, bread: 0.05; grains, vegetables, fruits, milk: 0.03 [8]. The average daily intake of Cd in the human body must not exceed the values that give the levels of 4.7 mg/L in urine and 0.05 g/l in the blood [32].

Pb is one of the most toxic metals. It is included in the list of priority pollutants by several international organizations, including WHO, UNEP, the United States Agency for the Control of Toxic Substances and Disease, and other regulatory government agencies in various countries. The main sources of Pb in the air, water and soil include: ferrous and non-ferrous metallurgy, mining and refining, chemical and coking industries, thermal power plants, and motor vehicle emissions. Natural sources of Pb in clude its fields, where from Pb enters the environment through weathering and leaching. In a human body, the main routes for Pb intake are inhaled and oral route [20].

It is believed that the widespread contamination of the soil and drinking water sources with Pb, along with other industrial metals, contribute to the increased incidence of breast cancer. There are epidemiological studies of the link between the high content of Pb in hair samples of patients diagnosed with breast cancer. Also, there is experimental evidence of the occurrence and accelerated growth rate of breast tumors in mice in conditions of chronic exposure to low levels of Pb. Besides, Pb has been shown to decrease the antitumor effect of selenium, whose anti-oxidant properties are well known [39].

In Ukraine, MPC for Pb in water is 0.03 mg/l; in soil 20 mg/kg; in food 0.1- 1.0 mg/kg [5, 45]. According to the current state standards for the content of Pb in food, its content should not exceed 0.3 mg/l for beverages; 0.1 mg/l for drinking water; about 2.5 mg/kg for solids food, about 8 mg/kg for fruits and vegetables (on a dry matter basis) [14, 47]. The allowable daily intake of Pb in the human body must not exceed the amount which is recorded at 0.2 mg/l of blood, 50 g/l in urine [32].

It is known [49, 52] that ionizing radiation (IR) under certain conditions can increase the risk of breast cancer. Breast is one of the most radiosensitive organs. The degree of its sensitivity depends on the intensity of the proliferative processes: the risk increases when a woman with hormonal imbalance (menarche, pregnancy and lactation, menopause) is exposed to irradiation. Breast cancer can be induced by doses less than 0.5 Sv, while the irradiation dose of 1 – 3 Sv increases the risk by 60% [60] both as a result of the body's direct exposure to IR and indirectly; i.e. as a result of disturbed endocrine balance [24].

An average natural background radiation dose, to which the world's population is exposed annually, is approximately 2.4 mSv/year [59]. In Ukraine, according to the Standards of Radiation Safety (NRBU 97) [19], the recommended effective dose is 1 mSv/year. However, the extrapolation of data from epidemiological studies suggests that life-long exposure to this dose of IR leads to 65 cases of leukemia and 495 cases of other forms of MN per 100,000; that is, IR may be responsible for 4-5% of all MNs [69].

It has been established that the increased IR level and radioactive contamination from the Chernobyl disaster and the combined effect of environmental risk factors play a significant role in the CIS countries. According to some estimates, over 10 years after the accident, the population in the affected areas has been exposed to an average whole-body radiation dose of 33 mSv [36]. For comparison: residents of some countries, where there is a high natural background radiation (Brazil, India, Iran), are exposed to 100-200 mSv in 20 years, which is not associated with any increase in the incidence of breast cancer.

In 1986-1987, an increase in the incidence of breast cancer in a limited cohort of women – participants of liquidation of the aftermath of the Chernobyl accident – was reported. Since 1997, an increase in the incidence of breast cancer in women who were evacuated from the exclusion zone has been registered. The incidence of breast cancer in women exposed to the factors of the zone of radioactive contamination after the accident increased dramatically: in 1986, there were 21.8 cases per 100,000; in 2010, this number was 34.7 [34].

In Belarusian women who participated in the liquidation of the aftermath of the Chernobyl accident in 1988-2010, the incidence of breast cancer significantly increased in each 5-year age group, beginning from 35 years of age. The average age of the onset of breast cancer in 1993-2003 was 62.6 years, in 2005 – 63.9 years, in 2009 – 64 years, and in 2010 – 64.5 years. In the Gomel region, which was the most contaminated as a result of the Chernobyl accident, the number of cases of breast cancer is higher compared to other regions [18, 29].

Thus, the growing industrialization and urbanization leads to intensive pollution with carcinogens of the air, soil, water, and food. Besides, the degree of hazard of the environmental risk factor increases as a result of simultaneous synergistic effects of various contaminants. Such an effect is materialized in the long-term consequences in the form of cancer pathology, particularly in the regionally-conditioned increase in the incidence of breast cancer. In Ukraine, there is a clear upward trend in breast cancer incidence along the geographic vectors directed from the West to the East and from the North to the South. However, there are also some differences in the breast cancer incidence within a single administrative-territorial unit (region), one of which is the difference in the incidence rates of urban and rural populations. On the other hand, it is possible to see the unidirectional trends in the incidence of breast cancer among the urban population of the regional centers of geographically remote regions of Ukraine [24]. For instance, according to data from the National Cancer Registry of Ukraine (2014), the highest incidence rates of breast cancer (per 100,000) are observed in the industrialized regions: Kyiv city – 87.8, Kirovograd region – 85.3, Kharkiv region – 83.0, Zaporizhia region – 81.5, while in the environmentally friendly areas the incidence rates of breast cancer are the lowest: Zakarpattya region – 49.0, Ivano-Frankivsk region – 50.4, Volyn region – 51.6, as compared to Ukraine's average incidence of 72.3 [3].

Conclusions

The results of analysis of literature warrant the conclusion that it is needed to assess the role of environmental risk factors in the occurrence of breast cancer, taking into account the regional specifics of their formation, general patterns of the concomitant action of physical and chemical agents of carcinogenic nature, and predicted cancer risk. It is also essential to develop the ways and means for its prevention/reduction as part of the primary prevention framework.

The development of models able to predict the risk of breast cancer based on the use of risk factors, reflecting the state of the hormonal status of a woman must take into account the prognostic significance of regionally-conditioned carcinogenic environmental factors, which will help to individualize the recommendations for oncological vigilance and screening activities.

References

1. Antipova S.I., Gender issues in Belarus Oncology / S.I. Antipova, V.V. Antipov, N.G. Shebeko // Medical News. - 2013. – No. 3. – P. 31–41.
2. Bukharitsin P.I., Assessment of the current state of water resources of the continental regions of the globe // Geology, Geography and Global Energy. - 2011. – No. 1 (40). – P. 121–132.
3. Bulletin of the National Cancer Registry No. 16. – Cancer in Ukraine 2012-2013. / National Cancer Institute, Kyiv, 2015. – 127 p.
4. Emissions of pollutants into the air in the Russian Federation [Electronic resource]. – Access: http://www.gks.ru/wps/wcm/connect/rosstat_main/rosstat/ru/statistics/environment/, free. – (Date of retrieve: 11.03.2003).
5. GOST 3034-84, 3210-85, 42-128-4433-87 "Maximum permissible concentrations of harmful substances in soils." – [Electronic resource]. – Access: http://agromage.com/stat_id.php?id=577 – (Date of treatment: 15.02.2003).
6. GN No. 187 dated 06.11.2008 "Maximum permissible concentrations (MPCs) of the mobile forms of chromium, zinc and cadmium in the soil (land) of various functional areas of human settlements, industry, transport, communications, energy, defense and other purposes. – [Electronic resource] – Access: http://www.busel.org/texts/cat2na/id5qwmfng.htm – (Date of retrieve: 11.02.2003).
7. GN 1.1.725-98. List of substances, products, production processes, domestic and natural factors, which are carcinogenic for humans. – Publishing house: Science, 1998. – 27 p.
8. DSP No. 201-97. State sanitary rules of protection of atmospheric air in populated areas from contamination by harmful chemical and biological agents. – Publishing house: Science, 1997. – 34 p.
9. WHO report on the situation in the area of non communicable diseases in the world, 2010 – 2013 – 184 p.
10. Uniform sanitary/epidemiological and hygienic requirements for goods subject to sanitary/epidemiologic supervision (control) dated 02.03.2011. – No. 571. – 1011 p.
11. Zvyagintsev A.V. Hazard assessment of air pollution of industrial cities of Ukraine / A.V Zvyagintsev. // Geotechnical Mechanics. - 2013. – No. 109. – P. 233.
12. Cadmium[Electronic resource]. – Access: http://www.euro.who.int/__data/assets/pdf_file/0016/123073/AQG2ndEd_6_3Cadmium.PDF, free. – (Date of retrieve: 5.04.2015).
13. Kiriushin V.A., Motalova T.V., Safonkin S.V. Chemical Toxicology: hazardous materials and activities in the centers of chemical damage. – Ryazan: Russian State Medical University, 2004. – 163 p.
14. Codex Alimentarius [Electronic resource]. – Access: http://www.codexalimentarius.org, free. – (Date of retrieve: 11.03.2003).
15. Kuligina E.Sh. Epidemiological and molecular aspects of breast cancer / E.Sh. Kuligina // Practical Oncology. - 2010. – V. 11. – No. 4. – P. 203–216.
16. National Report on the State of Environment in Ukraine in 2011. – K.: Ministry of Ecology and Natural Resources of Ukraine, 2012. – 258 p.
17. National Statistical Committee of the Republic of Belarus [Electronic resource]. – Access: http://belstat.gov.by/ofitsialnaya-statistika/otrasli-statistiki/okruzhayuschaya-sreda/, free. – (Date of retrieve: 11.03.2003).
18. Neumerzhitsky V.A. The relative risk of breast cancer with concurrent somatic pathology in female liquidators of the Chernobyl accident / V.A. Neumerzhitsky, T.A. Kozlov, K.V. Moschik // Medical News. - 2003. – No. 6. – P. 66–68.
19. NRBU-97. State Hygienic standards. Radiation Safety Standards of Ukraine dated 01.12.97. – K.: Naukova Dumka, 1998. – 121 p.
20. Review of the problem of environmental pollution with cadmium, lead and mercury, 2008. – [Electronic resource]. – Access: http://www.who.int/ifcs/documents/forums/forum6/eco_accord_ru.pdf, free. – (Date of retrieve: 04.01.2015).
21. Evaluation of the risk of breast cancer [Electronic resource]. – Access http://www.womenshealthsection.com/content/print.php3?title=gyno018&cat=41&lng=russian, free. – (Date of retrieve: 11.03.2003).
22. The list of maximum permissible concentrations (MPC) and approximate permissible concentrations (APC) of chemical substances: hygienic standards 2.1.7.12-1-2004. Minsk, 2004. – 48 p.
23. Prodanchuk N.G. The role of organochlorines in the formation of breast pathology / N.G. Prodanchuk, R.A. Moiseenko // Modern Problems of Toxicology. - 2010. – No. 1. – P. 7–16.
24. Reichman Y.G. Theoretical Foundations of Cancer Prevention, 2009. – 350 p.
25. Commission Regulation (EC) No. 1881/2006 setting the maximum levels for certain contaminants in food stuffs. – Official Journal of the European Union, 2006. – 28 p.
26. Romanyuk A.M. Morphological and biochemical characteristics of breast cancer in terms of pollution with salts of / A.M. Romaniuk, M.S. Lyndin // Bulletin of Biology and Medicine Problems. - 2014. – Issue 4 – Vol. 1 (113). – P. 318–322.
27. Sanitary Standards SanPiN 42-128-4433-87 "Sanitary standards of permissible concentrations of chemicals in

the soil." – Publishing house: State Statistics Committee, 1987. – 37 pp.
28. Sanitary Rules SanPiN 4630-88 "Sanitary rules and norms for surface waters protection from pollution." – M., 1988. – 59 p.
29. Sosnovskaya E.Y. The risk of developing breast cancer after exposure to ionizing radiation from the Chernobyl disaster / E.Y. Sosnovskaya, O.F. Semenenko, A.A. Silina // Medical News. - 2006. – No. 3. – P. 31–36.
30. Suleimanov E.V. Korshunov A.O. Modern Environmental Problems. – Nizhny Novgorod: Nizhny Novgorod State University, 2012. – 29 p.
31. Technical Regulations of the Customs Union 021/2011 "On Food Safety" , 2011. – 242 p.
32. Toxic trace elements and heavy metals (Hg, Cd, As, Li, Pb, Al). [Electronic resource]. – Access http://www.helix.ru/kb/item/06-232, free. – (Date of retrieve: 25/02/2015).
33. Chasova E.V. Dioxins as an environmental hazard / E.V. Chasova, L.D. Ermak // Vesnik KTU. Technical Sciences – 2010. – Issue. 25. – P. 158–165.
34. Chumak AA Health effects of the Chernobyl disaster in Ukraine. – Chernobyl: Ecology, Man, Health. / Coll. materials. – M.: Nuclear Safety Institute, 2006. – P. 60–64.
35. Shamrai OV Malignant neoplasms: territorial and socio-medical aspects / O.V. Shamrai, P.Y. Odarchenko // Vinnytsya: “Publishing House of Vinnytsya”, 2002. – 78 pp.
36. Shamrai O.V. Hygienic assessment of regional ecological characteristics of the environment and their role in the formation of regional differences in cancer pathology of the population of Ukraine: author's abstract of the Ph.D. thesis. Techn. Sciences. – D., 2003. – 17 p.
37. Schwager O.V. Hygienic evaluation of carcinogenic air pollution of cities with varying profiles of industry / O.V. Schwager, I.O. Chernichenko // Protection of the Environment and Health. Proceedings. – 2013. – No. 3. – P. 9–13.
38. Akesson A. Long-term dietary cadmium intake and postmenopausal endometrial cancer incidence: a population-based prospective cohort study / A. Akesson, B. Julin // Cancer Res, 2008. – 68. – P. 6435–6441.
39. Alatise O. Lead exposure: a contributing cause of the current breast cancer epidemic in Nigerian women / O. Alatise, G. Schrauzer // Biol Trace Elem Res. – 2010. – 136(2). – P. 127–139.
40. Bettina J., Alicja W. Dietary Cadmium Exposure and Risk of Postmenopausal Breast Cancer: A Population-Based Prospective Cohort Study // Cancer Res. - 2012. – 72. – P. 1459–1466.
41. Collins J. Body mass index and serum ch6lorinateddibenzo-p-dioxin and dibenzofuran levels / J. Collins, K. Bodner // Chemosphere. - 2007. – 66. – P. 1079–1085.
42. Dip R. Genetic reprogramming of human mammary cells by environmental carcinogens released into breast milk. / R. Dip, T. Buerin // Chimia. - 2008. – 62. – P. 410–416.
43. Hankinson S. Endogenous estrogen, testosterone and progesterone levels in relation to breast cancer risk. / S. Hankinson, A. Eliassen // The Journal of Steroid Biochemistry and Molecular Biology. - 2007. – 106. – P. 24–30.
44. Health assessment document for 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds // US Environmental Protection Agency Office of Health and Environmental Assessment, Office of Research and Development. – Vol. 13. – Washington, 1994.
45. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 1-83. Lyon France, 2006. – Eng., Fran. [Electronic resource]. – Access: http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php, free. – (Date of retrieve: 12.03.2015).
46. Kortenkamp A. Are cadmium and other heavy metal compounds acting as endocrine disrupters. // Metal Ions in Life Sciences. - 2011. – 8. – P. 305–317.
47. Latest world cancer statistics. International Agency for Research on Cancer, 2013. -№223. [Electronic resource]. – Access: http://globocan.iarc.fr/Default.aspx – (Date of retrieve: 11.03.2003).
48. Little JB Radiation carcinogenesis / Carcinogenesis. - 2000. – No. 21(3). – P. 397–404.
49. Loreta Strumylaite, Algirdas Bogusevicius, Olegas Abdrachmanovas, Dale Baranauskiene, Rima Kregzdyte, Darius Pranys, Lina PoskieneCadmium concentration in biological media of breast cancer patients // Breast Cancer Research and Treatment. – 2011. – Vol. 125. – Issue 2. – P. 511–517.
50. Mastalers P. The true story of DDT, PCB and dioxins. – Wroclav : Wyd. Chemiczne, 2005. – P. 165
51. Otto G. Raabe Ionizing Radiation Carcinogenesis. INTECH Open Access Publisher, 2012. – P. 299–348.
52. Pasha Q. Comparative evaluation of trace metal distribution and correlation in human malignant and benign breast tissues. // Biological Trace Element Research Stephen Juma Mulware. The Mammary Gland Carcinogens: The Role of Metal Compounds and Organic Solvents. International Journal of Breast Cancer, 2013. – P. 10
53. Polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofurans. Vol. 69. Lyon, France: IARC Press, 1997. – P. 333–344.
54. Polynuclear Aromatic Hydrocarbons. In: Guidelines for Drinking-water Quality, 2nd ed. Vol. 2. Health Criteria and other Supporting Information . – 2003. – P. 32
55. Prashant S. Dioxins sources and current remediation technologies – a review. // Environment International. - 2008. – Vol. 34. – Is. 1. – P. 139–153.
56. Revich B. The dioxin pollution as a risk of development female breast cancer. / B. Revich, T. Ushakova // Organohalogen compounds, Russia. - 2002. – Vol. 59. – P. 361–364.
57. Revich B. Dioxin exposure and public health in Chapaevsk, Russia. // Chemosphere. - 2001. – Vol. 43. – P. 951–966.
58. Pukkala E. Breast cancer in Belarus and Ukraine after the Chernobyl accident. [Electronic resource]. – Access:http://onlinelibrary.wiley.com/doi/10.1002/ijc.21885/epdf – (Date of retrieve: 11.03.2015).
59. Russo J. Developmental, cellular, and molecular basis of human breast cancer / J. Russo, Y. Hu // J. Natl. Cancer Inst. Monogr. - 2000. – Vol. 27. – P. 17–37.
60. Reynolds P. Adipose levels of dioxins and risk of breast cancer. / P. Reynolds, S. Hurley // Cancer Causes Control. - 2005. – 16(5). – P. 525–535.
61. State of the Science of Endocrine Disrupting chemicals, 2012. [Electronic resource]. – Access: http://www.who.int/ceh/publications/endocrine/en/ – (Date of retrieve: 11.03.2015).
62. Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures / IARC Monogr Eval Carcinog Risks Hum. - Lyon, France, 2010. – Vol. 92. – 853 p.
63. Some industrial chemicals / IARC MonogrEvalCarcinog Risks Hum. – Lyon, France, 2000. – Vol. 77. – 573 p.
64. Stephen J. The Mammary Gland Carcinogens: The Role of Metal Compounds and Organic Solvents. [Electronic resource]. – Access: http://dx.doi.org/10.1155/2013/640851 – (Date of retrieve: 21.03.2015).
65. Warner M. Serum dioxin concentrations and breast cancer risk in the Seveso women's health study. / M. Warner, B. Eskenazi, P. Mocarelli // Environ Health Perspect. - 2002. – Vol. 110. – P. 625–628.
66. Weir R. Risk factors for breast cancer in women / R. Weir, P. Day, W. Ali // NZHTA Report. - 2007. – 10(2). – 361 p.
67. Welsch CW Host factors affecting the growth of carcinogen-induced rat mammary carcinomas: a review and tribute to Charles Brenton Huggins. Cancer Res., 1985. – 45. – P. 3415–3440.
68. World Cancer Report. Edited by Bernard W. Stewart and Christopher P. Wild. – [Electronic resource]. – Access: http://apps.who.int/bookorders/anglais/detart1.jsp?codlan=1&codcol=76&codcch=31 – (Date of retrieve: 30.03.2003).

Матеріал надійшов до редакції 03.06.2015