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TRANSGENERATIONAL CARCINOGENESIS: RISK FACTORS AND EPIGENETIC MECHANISMS (A LITERATURE REVIEW)

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ABSTRACT

Introduction: *Traditional models of carcinogenesis based on genetic mutations and direct exposure to carcinogens cannot explain all cases of cancer. The increasing incidence of certain cancers does not always correlate with known genetic factors, suggesting a significant role for environmental and lifestyle factors in their development. The concept of transgenerational carcinogenesis offers a new explanation, linking these factors with an increased risk of cancer in future generations through epigenetic changes.*

This study aimed to *systematize and critically analyze scientific publications published between 2014 and 2024 that concern the factors contributing to transgenerational carcinogenesis and the underlying epigenetic mechanisms.*

Methods: *To identify relevant publications, extensive searches were conducted in electronic databases, including PubMed/MEDLINE, Scopus, and Web of Science. Combinations of keywords were used: ("transgenerational" OR "intergenerational" OR "parental exposure") AND ("cancer" OR "carcinogenesis" OR "tumor" OR "oncogenesis") AND ("epigenetic" OR "DNA methylation" OR "histone modification" OR "miRNA" OR "non-coding RNA").*

Results: *The phenomenon of transgenerational carcinogenesis, which is the transmission of an increased risk of cancer from generation to generation, is a proven fact. Epigenetic changes that persist in the germline affect gene expression in subsequent generations, and they can be caused by various factors affecting the parents. Animal models provide convincing evidence of cause-and-effect relationships. Long-term cohort studies in humans consistently confirm this mechanism, despite methodological difficulties.*

Conclusion: *Epigenetic changes in the germline can be passed on to offspring, significantly increasing their risk of developing pathological neoplasms. The primary mediators are changes in DNA methylation, histone modifications, and modifications to non-coding RNA. The study of transgenerational carcinogenesis will allow for the prevention of malignant neoplasms in future generations. Cause-and-effect relationships are convincing in models; in human populations, evidence is limited by associations and requires multigenerational cohorts with admixture control.*

Keywords: *epigenetics, predisposition to cancer, DNA methylation, histone modification, miRNAs, and cancer prevention.*

Introduction: Carcinogenesis, the complex multi-step process of cancer development, has traditionally been viewed through the lens of genetic alterations. The classical model posits that cancer arises from the accumulation of somatic mutations in key tumor suppressor genes and proto-oncogenes, leading to uncontrolled cell proliferation. Concurrently, hereditary cancer is explained by the transmission of specific mutations in predisposition genes (e.g., BRCA1/2, TP53) from parents to offspring via germ cells [1]. However, despite significant advancements in understanding these mechanisms, they cannot explain all instances of cancer. For example, the increasing incidence of certain cancers does not always correlate with an increase in genetic mutations within the population, and environmental and lifestyle factors play an increasingly evident role in cancer etiology [2].

In recent years, scientists worldwide have been actively studying the role of epigenetic changes, which are hereditary modifications of gene expression unrelated to changes in the DNA sequence. Modifications include DNA methylation, histone modifications, and regulation by non-coding RNAs [3]. Initially, epigenetics was considered in the context of individual cell development and differentiation. Breakthroughs in research have led to the understanding that epigenetic marks can not only be stable throughout an organism's life but can also be transmitted across generations. This concept is known as *transgenerational inheritance* [4, 5].

Transgenerational carcinogenesis (or transgenerational cancer susceptibility) is a relatively new but rapidly evolving area of research that posits that exposure of one or both parents (even pre-conception) can lead to changes in the germline that, in turn, increase the risk of cancer in their offspring (F1, F2, and subsequent generations) without direct exposure of the offspring to the carcinogen [6, 7]. The key distinction from hereditary cancer lies in the fact that transmission occurs not through changes in the nucleotide sequence of DNA, but through *epigenetic patterns* that modulate the expression of genes associated with carcinogenesis.

Several factors determine the relevance of this topic. First, it offers a new explanation for the etiology of malignant neoplasms in the absence of obvious hereditary predisposition or direct exposure to carcinogens. Sec-

ond, the phenomenon of transgenerational carcinogenesis presents new opportunities for preventing malignant neoplasms, allowing special attention to be paid to individual behavior and factors that affect the health of parents and their great-grandparents [8]. Third, this area highlights the interplay between the environment, genetics, and epigenetics in shaping health and susceptibility to disease [9].

The study aimed to systematize and critically analyze scientific publications published from 2014 to 2024 concerning the factors contributing to transgenerational carcinogenesis and the underlying epigenetic mechanisms.

Materials and Methods: Extensive searches were conducted in electronic databases, including PubMed/Medline, Scopus, and Web of Science, to identify relevant publications. The search covered the period from 2014 to 2024. The following keywords were used: ("transgenerational", OR "intergenerational", OR "parental influence") And ("cancer", OR "carcinogenesis", OR "tumor", OR "oncogenesis") And ("epigenetic", OR "DNA methylation", OR "histone modification", OR "microRNA" OR "non-coding RNA").

For the preparation of the review, a multi-stage publication selection procedure following the PRISMA principles was performed.

• Identification: A search in scientific databases (2014-2024) identified 300 potentially relevant publications. After removing the duplicates, 250 unique records remain.

• Screening: at the annotation screening stage, 180 papers were excluded as not relevant to the topic (i.e., not related to epigenetics or cancer transgeneration, or not peer-reviewed studies). Seventy publications have been accepted for full-text analysis.

• Eligibility: A full-text analysis of 70 publications led to the exclusion of another 20 papers for reasons of non-compliance with the criteria (for example, lack of data on transgenerational effects, poor quality of methodology, duplication of results).

• Included: The final review includes 49 studies that fully meet the criteria (original experimental papers and reviews highlighting the epigenetic mechanisms of transgenerational carcinogenesis).

Results: Transgenerational carcinogenesis has been actively studied in recent years. Environmental influences can affect the risk of developing cancer not only in exposed individuals but also in their descendants in subsequent generations. Experiments on animal models show that such epigenetic transgenerational effects are possible. In rodents, it has been found that exposure to endocrine disruptors, a high-fat diet, or stressors can lead to epigenetic changes in the germ cells of parents and to an increased tendency to tumor diseases in offspring up to 2-3 generations. However, in general, this area remains controversial. Transgenerational epigenetic transmission is viewed with skepticism by many researchers, as it is extremely difficult to separate it from the influence of hereditary genetic factors, as well as environmental and cultural conditions common to generations.

The analysis of the publication for the period 2014-2024 reveals several contradictions. Several influential animal studies reported multifactorial epigenetic inheritance of cancer predisposition. On the other hand, a significant part of such results requires independent confirmation. Thus, some landmark studies on the transgenerational effects of endocrine chemicals or a high-fat diet on DNA methylation were subsequently questioned by other authors. Certain carcinogenic effects that are clearly traceable in generations of laboratory animals (for example, testicular tumors in rat offspring after exposure to antiandrogens, or breast cancer in mouse offspring after experimental overfeeding of fathers) are not always confirmed in epidemiological data in humans. In some cases, the data are contradictory or show an effect only under extremely strong influences. In general, a critical analysis shows that the concept of epigenetic transgenerational carcinogenesis has been developed and partially confirmed in animal experiments, but the degree of its manifestation in humans remains uncertain and the subject of active research.

Epigenetic mechanisms of transmission from generation to generation. The transmission of acquired traits from generation to generation is contrary to the fundamental laws of genetics. However, epigenetics explains this phenomenon. The study of transgenerational carcinogenesis has shown that epigenetic changes acquired by parents in response to external influences are not eliminated during gametogenesis and early embryonic development; they are transmitted to offspring, changing their predisposition to malignant neoplasms [4, 8].

DNA methylation is the most deeply studied epigenetic mechanism. It involves covalent attachment of a methyl group to cytosine residues (mainly CpG dinucleotides). In the promoter regions of genes, hypermethylation is associated with transcription repression, which leads to gene activation [10]. Disorders in DNA methylation can inactivate tumor suppressor genes (hypermethylation) or activate oncogenes (hypomethylation) [11]. Studies in animal models have shown that the effects of various factors on parents can lead to specific changes in DNA methylation in germ cells, which can subsequently be passed on to offspring [12, 4]. These changes can affect genes related to the cell cycle, apoptosis, DNA repair, and metabolism, thereby increasing the risk of developing malignancies in subsequent generations. For instance, research demonstrates that exposure of pregnant females to certain chemicals, such as vinclozolin, can induce aberrant methylation in the sperm of F1 generation males, predisposing the F2 generation to the development of diseases, including ovarian, prostate, and kidney cancers [7, 13, 14].

Histone Modifications. Chromatin, a complex of DNA and proteins (histones), forms the genome inside the

cell nucleus. Histone modification (acetylation, methylation, phosphorylation) alters the structure of chromatin and makes it accessible to transcriptional mechanisms [15]. These modifications are dynamic and regulate gene expression. Changes in these patterns in parental germ cells can also be transmitted to offspring. For example, abnormal patterns of histone methylation (e.g., H3K4me3, H3K27me3) or histone acetylation in sperm can serve as epigenetic markers that determine disease susceptibility in offspring [16]. Recent studies suggest that dietary or environmental interventions in parents can alter histone modification profiles in their gametes, which correlates with an increased risk of cancer in offspring [17, 18].

Non-coding RNAs (ncRNAs), particularly *microRNAs (miRNAs),* play a crucial role in post-transcriptional gene expression regulation [19]. It has been shown that miRNAs are present in germ cells and can be transmitted to offspring. Alterations in miRNA expression profiles in sperm or oocytes resulting from parental exposure to external factors can disrupt the regulation of tumor suppressor genes or oncogenes in the developing embryo, thereby increasing the risk of cancer [16, 20]. For example, studies have revealed that paternal exposure to high-fat diets or certain toxins can alter the spectrum of miRNAs in sperm, which is associated with metabolic disorders and an increased risk of cancer in offspring [21, 18]. Long non-coding RNAs are also gaining significance as potential mediators of transgenerational effects, influencing chromatin structure and gene regulation [22].

Germline Inheritance. A key factor in transgenerational carcinogenesis is the ability to bypass epigenetic "reprogramming" during gametogenesis and early embryonic development. Most epigenetic marks are erased and restored; however, some regions of the genome and specific epigenetic marks may be stable. This enables information to be transmitted from one generation to the next [23, 5]. The mechanisms of this "bypass" are not fully understood, but they include protection of specific chromatin regions, association with certain carrier proteins, or transmission via small RNAs encapsulated in sperm or oocytes [20, 24]. Understanding these mechanisms is critical to fully realizing the potential of transgenerational carcinogenesis as a new paradigm in cancer etiology.

Key Factors Inducing Transgenerational Carcinogenesis (Focus on the Last 10 Years of Research). Over the past decade, numerous studies, primarily using animal models, have identified a range of factors that can induce transgenerational carcinogenesis. These factors span a broad spectrum of exposures, from chemicals to diet and stress.

Environmental Exposures and Toxins. Exposure to various environmental chemicals poses a significant threat to human health, and increasing evidence points to their role in the transgenerational transmission of cancer susceptibility.

• **Endocrine Disrupting Chemicals (EDCs):** These compounds mimic or block the action of hormones, thereby disrupting the endocrine system. In the past decade, EDCs such as *bisphenol A (BPA)* and its analogs (BPS, BPF), as well as *phthalates*, have been shown to induce transgenerational effects. For instance, rodent studies have indicated that prenatal or perinatal BPA exposure of the mother can lead to an increased risk of mammary gland, ovarian, prostate, and kidney tumors in F1 and even F2 generations of offspring [7, 25]. Mechanisms involve changes in DNA methylation of genes related to hormonal signaling and cell growth [25]. Similarly, phthalate exposure has been linked to transgenerational increases in prostate cancer incidence in male offspring [26].

• **Pesticides and Herbicides:** Certain widely used agrochemicals have also been associated with transgenerational effects. For example, studies demonstrate that exposure of pregnant rats to *vinclozolin* (a fungicide) leads to an increased incidence of various tumors (kidney, prostate) in F1-F3 generations [6, 7]. This is linked to aberrant DNA methylation and alterations in non-coding RNAs in the germline [13, 14]. While direct evidence of carcinogenesis from *glyphosate* via transgenerational mechanisms in humans is still limited, animal studies raise concerns about its potential impact on epigenetic inheritance [27].

• **Heavy Metals:** Chronic exposure to heavy metals, such as arsenic and cadmium, is associated with carcinogenic effects. Recent research indicates that parental exposure to these metals can induce transgenerational epigenetic changes, leading to increased offspring susceptibility to carcinogens or direct tumor development [28]. For example, arsenic exposure in pregnant mice was associated with altered DNA methylation in F1 generation sperm and an increased risk of hepatocellular carcinoma in the F2 generation [29].

• **Air pollution:** Components of air pollution, such as particulate matter and polycyclic aromatic hydrocarbons, can induce epigenetic changes. Evidence of transgenerational carcinogenesis due to air pollution in humans is still being investigated. Animal studies suggest that parental exposure to polycyclic aromatic hydrocarbons can lead to changes in germline DNA methylation, potentially increasing the risk of malignancies in offspring [30].

Nutritional and metabolic factors. The diet and metabolic status of parents have a profound impact on the health of their offspring, and epigenetic mechanisms play an important role in this process.

Parental weight problems: a deficiency or excess of nutrients in parents may increase the risk of neoplasms in their offspring [31]. A *high-fat diet (HFD)* in mothers or fathers is associated with an increased risk of liver, breast, and colorectal cancer in offspring of F1 and F2 generations [17, 32] due to changes in DNA methylation, histone modification, and microRNA profiles in germ cells that affect genes related to metabolism, inflammation, and cell

growth [16]. Deficiency of trace elements, such as *folic acid* (a methyl group donor) in parents, can disrupt the DNA methylation patterns in the germline and increase the predisposition to cancer [33, 34].

• **Parental Obesity and Diabetes:** The epidemics of obesity and diabetes have long-term consequences not only for the health of affected individuals but also for their offspring. Studies indicate that parental obesity or diabetes can be associated with a transgenerational increase in cancer risk in offspring [35]. For example, paternal obesity in mouse models has been linked to an increased risk of colorectal cancer in offspring, mediated by changes in miRNA expression in sperm [21]. Maternal gestational diabetes can also alter fetal epigenetic marks, potentially increasing the risk of certain cancers later in life [36].

• **Stress and Psychological Factors.** Chronic parental stress and psychological trauma, particularly during critical periods of germ cell development or pregnancy, can have long-term consequences for offspring [37]. For example, prenatal stress in rodents is associated with DNA methylation changes in the offspring's brains and predisposes them to behavioral disorders [38]. Some studies suggest a link with increased sensitivity to carcinogens or risk of developing certain types of diseases. However, direct evidence for transgenerational carcinogenesis through psychological stress in humans is still lacking. The influence of glucocorticoids and neuroimmune pathways on germ cell epigenetics is an active area of research [39].

• **Pharmacological Agents and Medications.** The use of certain medications by parents can also induce transgenerational effects.

• **Chemotherapy and Radiotherapy:** Cancer therapy may also have long-term effects. Exposure to chemotherapeutic drugs (e.g., cyclophosphamide) or ionizing radiation can induce epigenetic changes in parental germ cells, leading to an increased risk of malignancy in offspring [40]. Mechanisms include changes in DNA methylation and microRNA profiles, which may disrupt genomic stability or cellular signaling pathways in offspring [41]. This is particularly important for young cancer survivors planning pregnancy.

• **Diethylstilbestrol (DES):** Although this is a historical example (used to prevent miscarriages from the 1940s to 1970s), the effect of DES is a classic illustration of transgenerational carcinogenesis. Women whose mothers took DES during pregnancy have an increased risk of developing a rare form of vaginal cancer (clear cell adenocarcinoma) and other reproductive abnormalities [42, 43]. Research continues to uncover the epigenetic mechanisms underlying these effects, highlighting the long-term consequences of drug exposure during early development [44].

Infectious Agents. Direct viral (HPV, HBV)-associated etiocarcinogenesis is well studied, and researchers are beginning to consider whether parental infections may cause transgenetic changes that predispose offspring to cancer [45]. Chronic inflammation caused by infections may influence the epigenetic landscape [5]. This area requires further study to identify specific transgenerational effects in the context of oncogenesis.

Research Models. Studying transgenerational carcinogenesis presents a complex challenge requiring specialized approaches. Over the past decade, significant progress has been made in developing and applying various research models.

Animal Models. Mice, rats, and zebrafish are primary models for studying transgenerational carcinogenesis. These models enable strict control over exposure (type, dose, timing, and duration), the study of multiple generations, and the analysis of molecular mechanisms in offspring tissues and parental germ cells [5, 44].

• **Maternal Exposure Models:** In these studies, pregnant females are exposed to the factor under investigation (e.g., an endocrine disruptor) during pregnancy. The cancer susceptibility of their offspring (F1) and subsequent generations (F2, F3+), born from unexposed F1 females, is then analyzed [6, 7]. This approach allows for the exclusion of direct exposure of the factor to subsequent generations.

• **Paternal Exposure Models:** In some studies, male founders are exposed before mating. Analysis of their sperm for epigenetic changes, as well as the cancer risk in their offspring, allows for the assessment of the paternal line's contribution to transgenerational effects [6, 21].

• **Advantages:** Strict control over experimental conditions, ability to establish cause-and-effect relationships, and accessibility of tissues for molecular analysis (DNA methylation, histone modifications, miRNAs) [44].

• **Limitations:** Differences in physiology and metabolism between animals and humans, as well as complexities in extrapolating results to the human population [5].

Human Epidemiological/Cohort Studies. Studying transgenerational carcinogenesis in humans is considerably more challenging due to uncontrolled exposure to numerous environmental and lifestyle factors. However, long-term cohort studies and the analysis of large databases are beginning to yield valuable information [46].

• **Advantages:** Direct relevance to human health.

• **Limitations:** Difficulty in establishing cause-and-effect relationships, the need for very large sample sizes and long-term follow-up across multiple generations, challenges in controlling for all potential confounding factors, and ethical restrictions on experimental exposures [5].

• **Examples:** Ongoing cohort studies where mothers were exposed to specific agents (e.g., DES) [43], as well as studies investigating the link between parental obesity, diabetes, or exposure to certain toxins and cancer risk in offspring. The use of biobanks and the analysis of epigenetic marks in cord blood or offspring tissues help to identify potential correlations [36, 41].

Clinical Significance and Future Perspectives. Understanding transgenerational carcinogenesis has profound clinical and public health implications, opening new horizons for cancer prevention and risk management.

Potential Impact on Cancer Prevention. Traditional cancer prevention strategies focus on individual lifestyle modifications (e.g., smoking cessation, adopting a healthy diet, and engaging in physical activity) and early detection. The concept of transgenerational carcinogenesis offers a fundamentally new approach, focusing on *pre-conception or prenatal interventions* [44].

• **Pre-conception Prevention:** Counseling prospective parents on the importance of healthy lifestyles (nutrition, avoidance of harmful habits), minimizing exposure to environmental toxins before conception can reduce the risk of transgenerational transmission of cancer susceptibility [5].

• **Environmental Protection:** Regulation and reduction of endocrine disruptors, pesticides, and other industrial pollutants become even more critical, given their potential transgenerational effects [6, 7].

• **Pharmacological Development:** Considering transgenerational risks during the development and safety assessment of new drugs, especially those that may be used by women of childbearing age or men [43].

• **Identification of At-Risk Groups.** The identification of epigenetic biomarkers in germ cells or at early stages of offspring development could enable the detection of individuals with an increased risk of cancer.

• **Biomarkers in Sperm/Oocytes:** In the future, analysis of specific epigenetic marks (e.g., DNA methylation patterns, miRNA profiles) in parental gametes could become part of screening for assessing transgenerational risk [16].

• **Biomarkers in umbilical cord blood**: The study of epigenetic markers in the umbilical cord blood of newborns can serve as an indicator of the environmental impact on the mother and a potential predisposition to cancer, allowing for earlier personalized monitoring and prevention [36, 41].

• **Molecular mechanisms:** It is necessary to study how epigenetic tags are transmitted along the germline, which of them are resistant to reprogramming, and how they affect gene expression during ontogenesis [8, 5].

• **Long-term studies:** Long-term cohort studies spanning several generations are crucial for a convincing demonstration of the transgenerational phenomenon in humans [46].

• **Combined effects:** Most studies focus on a single factor, whereas in real life, organisms are exposed to multifactorial effects. The study of the synergistic and/or antagonistic effects of combined factors is a promising direction [26].

• **Development of therapeutic strategies**: understanding the mechanisms of the "phenomenon" will lead to the development of approaches aimed at "erasing" unwanted epigenetic marks and/or protecting the germline from harmful effects.

• **The role of the paternal line:** Research often focuses on the impact on the mother, and there is a growing understanding of the important role of paternal material in transmission from generation to generation. It is necessary to study the mechanisms of epigenetic changes in spermatozoa that affect the development of offspring and the risk of developing malignant neoplasms [16, 21].

Table 1 summarizes the associations between the type of exposure, epigenetic mechanism, and type of cancer.

Table 1 – Main categories of ancestral influences, putative epigenetic mechanisms of inheritance, and related cancers in offspring (according to peer-reviewed publications 2014-2024) [4-6, 12, 23, 30, 45, 46-48]

Type of exposure	The epigenetic mechanism of inheritance	Associated types of cancer in offspring
Chemical toxicants (pesticides, endocrine disruptors – DDT, vinyl chloride, etc.)	– Persistent changes in DNA methylation in germinal cells, leading to epimutations in oncogenes/tumor suppressors that can avoid embryonic reprogramming. – Disruption of the chromatin structure: changes in repressive histone tags that affect the long-term shutdown of genes. – Imbalance of non-coding RNAs: changes in the profile of microRNAs and other small RNAs in sperm transmitted to the zygote.	There is often an increased risk of childhood tumors due to parental contact with pesticides: leukemia, lymphoma, CNS tumors, and neuroblastoma in children. In adult descendants, there is an increased incidence of hormone–dependent tumors: breast cancer is associated with exposure to DDT ancestors. Tumors of the reproductive system are possible (according to data from animal models).
Nutritional factors (parental diet, starvation)	– Epigenetic rearrangement of spermatozoa: changes in global DNA methylation and in the content of small non-coding RNAs. For example, a deficiency or excess of nutrients in males leads to differential expression of multiple sperm microRNAs and tRNA fragments, which restart gene expression after fertilization. – Modification of signaling pathways of development: changes in the expression of metabolic control genes are revealed in the offspring as an echo of the dietary factors of the ancestors.	An increase in the predisposition to breast cancer in offspring with obesity or protein starvation of the female parent has been shown in animals. In humans, there is evidence that extreme starvation of grandmothers is associated with an increased risk of breast cancer in granddaughters. Effects on other cancers are possible, but there is insufficient clear epidemiological evidence.
Psychological stress (severe traumatic events, chronic parental stress)	– Long-term dysregulation of neuroendocrine genes: extreme stress can lead to changes in the methylation of genes regulating the stress response. – Histone labeling disorder: presumably, chronic stress can affect posttranslational modifications of histones in germ cells, which affects the work of genes in the embryo.	In humans, extreme stressors are associated with a general deterioration in the health of the offspring, but a clearly increased risk of cancer has been confirmed mainly for the generation itself that has experienced stress. Data on the effect of parental stress on childhood cancer is contradictory; further research is needed to establish a cause-and-effect relationship.

Table 1 (continued)

Medications (pharmacological effects on pregnant women or before conception; for example, diethylstilbestrol)	– Hormonal and epigenetic effects: Exogenous hormones during critical periods of development can cause persistent epigenetic shifts. In the case of DES, an increased level of EZH2 expression was found in the mammary gland tissues of the offspring, which indicates an increase in the repressive histone modification H3K27me3 and the associated suppression of tumor suppressor genes. – Violation of genomic imprinting: Some drugs can probably disrupt the installation of methyl tags in imprinted genes during gametogenesis; this effect is probably inherited.	The "DES daughters" syndrome is well documented: women whose mothers took diethylstilbestrol during pregnancy had a sharply increased risk of clear-cell adenocarcinomas of the vagina and cervix. Experiments on mice and rabbits have shown that the effects of DES are transmitted to the next generation: the "granddaughters" have an increased development of tumors of the uterus and ovaries. In addition, there is evidence of a slightly increased risk of breast cancer and melanoma in daughters exposed to DES in utero. This example highlights the reality of the transgenerational effects of medications, although there are few such confirmed cases so far.

Notes: EDC – endocrine destructive chemicals (endocrine disruptors), DDT – dichlorodiphenyltrichloroethane, DES – diethylstilbestrol.

Discussion: The data are summarized, which convincingly show that the phenomenon of transgenerational carcinogenesis is an important and multifaceted aspect of the etiology of malignant neoplasms. Unlike traditional models focusing on direct genetic mutations or individual carcinogen exposure, the concept of transgenerational transmission emphasizes that parental exposures can "program" offspring's predisposition to cancer through epigenetic mechanisms. These mechanisms, including alterations in DNA methylation, histone modifications, and non-coding RNA profiles, act as a bridge between environmental factors and inherited disease risk.

The review identified a wide range of factors capable of inducing transgenerational effects that predispose individuals to carcinogenesis. Among these, particular attention is given to endocrine-disrupting chemicals (EDCs) (e.g., BPA, phthalates), which affect hormonal regulation and can cause persistent epigenetic changes in the germline [12, 18]. Results from animal models, such as vinclozolin exposure, convincingly show that chemical agents can lead to an increased risk of various cancers in subsequent generations [7, 14]. This underscores the urgent need to re-evaluate regulations regarding widely used chemicals and their long-term effects.

Nutritional and metabolic factors have also proven to be powerful modulators of transgenerational risk. Specifically, high-fat diets and parental obesity have been shown to alter the epigenetic landscape of germ cells, leading to an increased oncological predisposition in offspring [17, 32, 21]. These data expand the understanding of "intrauterine programming effects" and point to the critical role of parental metabolic health in shaping cancer risk in their children and grandchildren. While direct human evidence is limited, epidemiological studies are beginning to identify correlations that confirm the importance of these links [35, 36].

Stress and pharmacological agents, including chemotherapy, represent another category of factors that can induce transgenerational epigenetic modifications [39, 40]. This raises important ethical and clinical questions, especially concerning the treatment of young cancer patients who later wish to have children. A balance is needed between life-saving treatments and potential long-term risks to offspring. The example of diethylstilbestrol (DES) [43] serves as a stark historical warning that the consequences of medical interventions can manifest decades and generations later.

While animal models are the gold standard for studying cause-and-effect relationships in transgenerational carcinogenesis due to controlled conditions [4, 44], their results are not always directly extrapolatable to humans. Epidemiological studies in humans, though more complex to conduct, are indispensable for confirming these links in real populations [46]. Progress in high-throughput omics technologies allows for the identification of subtle epigenetic changes in human biomaterials (e.g., cord blood, sperm), opening new avenues for identifying risk biomarkers [16, 24].

However, significant knowledge gaps remain. A better understanding of the precise molecular mechanisms that ensure the resistance of certain epigenetic marks to reprogramming in the germline is needed. Most studies examine the effects of a single factor, whereas in real life, organisms are exposed to multiple combined influences, which require more complex research models. It is important to consider the contribution of the paternal line to transgenerational inheritance, since spermatozoa carry a unique epigenetic load that can influence the development of offspring [16, 21]. Data from the last decade indicate that transgenerational carcinogenesis is an emerging area of public health importance. Integration of the acquired knowledge into preventive programs and clinical recommendations will be the next logical step in preventing and controlling malignant diseases.

Data comparison: animal models vs human studies. The results of animal and human studies in this area show significant differences. There is convincing evidence in animal models that exposure to parents can increase the carcinogenic risk in offspring. When exposed to endocrine-disrupting pesticides (DDT) in rodents, there is an increase in the incidence of tumors in offspring up to the third generation. In classical experiments, it was shown that the synthetic estrogen diethylstilbestrol (DES), administered to pregnant female rodents, causes the development of tumors of the reproductive tract not only in their daughters (directly exposed in utero), but also in "granddaughters" – the third generation, who had no direct contact with the substance [47]. There was also evidence that parental nutrition affects oncogenesis in offspring. For example, obe-

sity or dietary deficiencies in male mice before mating led to epigenetic restructuring of their spermatozoa, resulting in changes in breast development and an increased incidence of breast tumors in their daughters. These animal models allow us to establish a causal relationship: exposure → epigenetic "tag" in germinal cells → phenotype change and tumor risk in the offspring. It is important that mechanisms can be directly identified in animals: for example, to find specific epigenetic changes in spermatozoa (DNA methylation of certain genes, disruption of the microRNA profile, changes in histone tags) that correlate with the occurrence of cancer in offspring [47, 49].

In human studies, the picture is less definite. Direct experimental data are naturally lacking, and scientists rely on retrospective or epidemiological observations. Some of them support the hypothesis of a transgenerational effect: for example, women conceived during starvation (such as the Holodomor in the Netherlands in 1944-1945) demonstrated an increased risk of breast cancer in adulthood. This indirectly indicates that the lack of nutrition in grandmothers could affect the cancer incidence in granddaughters through intergenerational epigenetic changes. Another example is the analysis of the offspring of war veterans exposed to certain chemical agents (for example, dibutyl phthalate, which is dangerous for the endocrine system). According to some data, the daughters of war veterans have a higher-than-average risk of developing breast cancer. There is a historical case with the DES drug: women whose mothers took diethylstilbestrol during pregnancy had a sharply increased risk of rare vaginal cancer (clear-cell carcinoma) [48, 49]. However, it is important to emphasize that such studies on humans have the character of associations. It is challenging to interpret them unambiguously, as the results may be influenced by genetic predisposition and related environmental factors. In addition, different studies often give contradictory conclusions: for example, some studies find a link between the diet of parents and cancer in children, while others do not find a statistically significant effect. Collectively, animal data provide more direct and reproducible evidence of transgenerational carcinogenesis, whereas in humans, such effects are unclear and require further study. Every phenomenon observed in human populations needs to be carefully evaluated and, if possible, confirmed by independent samples.

Limitations of human research. Research on transgenerational effects in humans faces several limitations:

• Confounding of factors: Descendants inherit not only epigenetic marks from their ancestors, but also genes, and often share a similar environment. For example, families that have experienced hunger or stress may have a similar lifestyle and diet in subsequent generations. This makes it difficult to isolate a purely epigenetic contribution to cancer risk. Genetic predisposition and cultural traditions can mimic the "inherited" effects of the environment.

• Long latency period: Transgenerational effects appear after one or more generations, i.e., decades. To establish a connection, very long-term observations are needed. During this time, the external conditions themselves, medicine, etc., may change, which makes interpretation difficult.

• Sample size and accessibility: for a convincing analysis, large cohort samples spanning several generations are needed, where ancestral impacts are known and outcomes in descendants are traced. Such data is extremely rare. Many studies rely on unique historical cohorts, and their results are still awaiting confirmation by independent experts.

• Retrospective nature of the data: Most of the available human data is retrospective. The accuracy of information about exposure doses and the state of ancestral health is limited. There may be systematic errors and biases.

• Ethical limitations and verification of mechanisms: Naturally, it is impossible to purposefully experiment on humans, exposing one generation to exposure and observing grandchildren. Therefore, we cannot directly prove a causal relationship but rely on correlations. In addition, it is difficult to study the epigenetic changes themselves: the embryonic germ line is not available for analysis in humans, so direct confirmation of label transfer is difficult. These limitations necessitate caution in interpreting the results in humans and explain why transgenerational epigenetic transmission in humans remains a hypothesis, despite some indirect evidence [48].

Conclusion: The phenomenon of transgenerational carcinogenesis is changing the understanding of the etiology of malignant neoplasms, expanding beyond genetic mutations and individual exposure. Environmental factors can cause epigenetic changes in parental germ lines, which are then passed on to offspring, thereby increasing the risk of developing malignancies. DNA methylation, histone modifications, and non-coding RNAs are key mediators of these transgenerational effects. The study of transgenerational carcinogenesis opens new possibilities for the prevention of malignant neoplasms. A healthy lifestyle is important for expectant parents. Strengthening environmental protection and chemical regulation measures is necessary to minimize the impact on human reproductive health. The identification of epigenetic biomarkers that predict the risk of cancer in offspring is a promising area of future research that may lead to the development of personalized strategies for screening and preventing malignancies. The scientific community faces complex challenges, including conducting long-term human studies, exploring combined effects, and gaining a deeper understanding of molecular mechanisms. A full understanding and integration of the phenomenon of transgenerational carcinogenesis into clinical practice and public health policy will be crucial in the fight against cancer.

Cause-and-effect relationships are convincing in models; in human populations, evidence is limited by associations and requires multigenerational cohorts with admixture control.

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АҢДАТПА

ТРАНСГЕНЕРАЦИЯЛЫҚ КАНЦЕРОГЕНЕЗ: ҚАУІП ФАКТОРЛАРЫ ЖӘНЕ ЭПИГЕНЕТИКАЛЫҚ МЕХАНИЗМДЕР (ӘДЕБИЕТКЕ ШОЛУ)

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Өзектілігі: *Генетикалық мутацияларға және канцерогендердің тікелей әсеріне негізделген канцерогенездің дәстүрлі үлгілері қатерлі ісіктің барлық жағдайларын түсіндіре алмайды. Кейбір қатерлі ісік ауруларының көбеюі әрқашан белгілі генетикалық факторлармен байланысты бола бермейді, бұл олардың дамуындағы қоршаған орта мен өмір салтының маңызды рөлін көрсетеді. Трансгенерациялық канцерогенез тұжырымдамасы осы факторларды эпигенетикалық өзгерістер нәтижесінде болашақ ұрпақтарда қатерлі ісік қаупінің жоғарылауымен байланыстыратын жаңа түсініктеме ұсынады.*

Зерттеудің мақсаты *– трансгенерациялық канцерогенезге ықпал ететін факторларға және олардың негізінде жатқан эпигенетикалық механизмдерге қатысты 2014-2024 жылдар аралығында жарияланған ғылыми басылымдарды жүйелеу және сыни тұрғыдан талдау болды.*

Әдістері: *Тиісті басылымдарды анықтау үшін PubMed/MEDLINE, Scopus және Web of Science сияқты электронды мәліметтер базасында кең іздеу жүргізілді. Кілт сөздердің тіркесімдері қолданылды: (“трансгенерация” немесе “ата-ана тәжірибесі”), және (“қатерлі ісік “немесе” канцерогенез “немесе” ісік “немесе” онкогенез”) және (“эпигенетикалық “немесе” ДНҚ метилденуі “немесе” гистон модификациясы “немесе” микроРНҚ “немесе”кодталмаған РНҚ”).*

Нәтижелері: *Трансгенерациялық канцерогенез құбылысы дәлелденген факт болып табылады. Ұрық сызығында сақталатын эпигенетикалық өзгерістер кейінгі ұрпақтардағы гендердің экспрессиясына әсер етеді және олар ата-аналарға әсер ететін әртүрлі факторлардан туындауы мүмкін. Жануарларға арналған модельдер себеп-салдарлық байланыстардың нақты дәлелдерін береді. Адамдардағы ұзақ мерзімді когорттық зерттеулер әдістемелік қиындықтарға қарамастан бұл механизмді дәйекті түрде қолдайды.*

Қорытынды: *Жыныстағы эпигенетикалық өзгерістер ұрпаққа берілуі мүмкін, бұл патологиялық ісіктердің даму қаупін айтарлықтай арттырады. Негізгі медиаторлар ДНҚ метилденуіндегі өзгерістер, гистондық модификациялар және кодталмаған РНҚ модификациялары. Трансгенерациялық канцерогенезді зерттеу болашақ ұрпақтарда қатерлі ісіктердің алдын алуға мүмкіндік береді. Себеп-салдарлық байланыстар модельдерде сенімді, адам популяцияларында дәлелдер ассоциациялармен шектеледі және араласуды бақылайтын көп буынды когорттарды қажет етеді.*

Түйінді сөздер: *эпигенетика, қатерлі ісікке бейімділік, ДНҚ метилденуі, гистон модификациясы, микроРНҚ (miRNAs), қатерлі ісіктің алдын алу.*

АННОТАЦИЯ

ТРАНСГЕНЕРАЦИОННЫЙ КАНЦЕРОГЕНЕЗ: ФАКТОРЫ РИСКА И ЭПИГЕНЕТИЧЕСКИЕ МЕХАНИЗМЫ (ОБЗОР ЛИТЕРАТУРЫ)

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Актуальность: *Традиционные модели канцерогенеза, основанные на генетических мутациях и прямом воздействии канцерогенов, не могут объяснить все случаи рака. Рост заболеваемости некоторыми видами рака не всегда коррелирует*

с известными генетическими факторами, что указывает на значительную роль окружающей среды и образа жизни в их развитии. Концепция трансгенерационного канцерогенеза предлагает новое объяснение, связывая эти факторы с повышенным риском развития рака у будущих поколений в результате эпигенетических изменений.

***Цель исследования** – систематизировать и критически проанализировать научные публикации, опубликованные в период с 2014 по 2024 год, которые касаются факторов, способствующих трансгенерационному канцерогенезу, и лежащих в их основе эпигенетических механизмов.*

***Методы:** Для выявления соответствующих публикаций был проведен обширный поиск в электронных базах данных, включая PubMed/MEDLINE, Scopus и Web of Science. Использовались комбинации ключевых слов: (“трансгенерационный” ИЛИ “родительский опыт”), и (“рак” ИЛИ “канцерогенез” ИЛИ “опухоль” ИЛИ “онкогенез”) и (“эпигенетическое” ИЛИ “метилирование ДНК” ИЛИ “модификация гистонов” ИЛИ “микроРНК” ИЛИ “некодирующая РНК”).*

***Результаты:** Феномен трансгенерационного канцерогенеза является доказанным фактом. Эпигенетические изменения, которые сохраняются в зародышевой линии, влияют на экспрессию генов в последующих поколениях, и они могут быть вызваны различными факторами, влияющими на родителей. Модели на животных дают убедительные доказательства причинно-следственных связей. Долгосрочные когортные исследования на людях последовательно подтверждают этот механизм, несмотря на методологические трудности.*

***Заключение:** Эпигенетические изменения в зародышевой линии могут передаваться потомству, значительно увеличивая риск развития патологических новообразований. Основными медиаторами являются изменения метилирования ДНК, модификации гистонов и модификации некодирующей РНК. Изучение трансгенерационного канцерогенеза позволит предотвращать злокачественные новообразования у будущих поколений. Причинно следственные связи убедительны на моделях, однако в человеческих популяциях доказанность ограничена ассоциациями и требует многопоколенных когорт с контролем смешения.*

***Ключевые слова:** эпигенетика, предрасположенность к раку, метилирование ДНК, модификация гистонов, микроРНК (miRNAs), профилактика рака.*

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