International Social Science and Humanities Studies
ISSN 2768-105X
Vol. 4, No. 3, 2024
Published by STSL Press

Original Paper

Environmental Epigenetic Signatures can Explain the Increased Incidence of Cancer in Young People and Open up New Ways to Primary Prevention

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Abstract

Tumor incidence in Italy and in the world, although decreasing in the last decades for some types of neoplasms, overall continues to show growing trends and, recently, a worrying increase in the incidence of cancer in childhood and young people has been described. In the XX century the entire Western world has suffered the release into the environment of an ever-increasing number of harmful and carcinogenic substances which have polluted air, water and food, progressively exposing the latest generations. Epigenetics, directly influenced by the external environment, plays an important role in carcinogenesis: methylations, despite being in non-coding structures, modify the functionality of genes by increasing or decreasing their expression and also demonstrating a capacity for transgenerational transmission which can have repercussions in children, adolescents and young adults. Thanks to Artificial Intelligence (AI), more and more epigenetic methylations sites related to specific environmental causes are being identified, increasing our knowledge and the possibility of developing increasingly effective therapies. These "Epigenetic Signatures" will also be able to provide fundamental as well as ethical, legislative and perhaps even legal indications to set up a renewed Primary Prevention.

Keywords: Young People Cancer, Environmental Pollution, Epigenetic Signatures, Primary Prevention

Take-Home Message: The growing worldwide incidence of cancer in younger generations may be linked to environmental pollution. Epigenetic mutations, influenced by the external environment, can sometimes be carcinogenic and have transgenerational capabilities. The numerous “epigenetic signatures” linked to specific etiological environmental causes, now easily identified with Artificial Intelligence, can lead to a renewed Primary Prevention.

Introduction

Environmental pollution certainly has an important impact on carcinogenesis [1, 2]. Influences from the external environment promote epigenetic DNA alterations regulating or altering the functionality of genes [3, 4]. In our DNA there are numerous genes affecting cell proliferation, differentiation, and immune regulation, essential for life and development in the fetal and infantile period. In adults, their overexpression or silencing can result in the formation and growth of tumors: this way, they can act as oncogenes or tumor suppressors [5]. Epigenetic mutations, due to changing environmental influences, can be transitory and reversible, but can also persist over time and be transmitted from parents to children [6, 7]. Since the 1950s, environmental pollution has progressively increased due to the abnormal emission of combustion products, the sometimes excessive use of pesticides and herbicides, the production of ever new synthetic substances and perhaps also due to an increased exposition to electromagnetic fields [8]. The incidence of cancer in the world has been increasing in parallel with

environmental pollution, with some exceptions due to primary prevention (e.g. fight against smoking) or secondary prevention (early diagnosis; e.g. screening mammography and Pap-Test) (9,10). For some years now, in the Western world, a worrying increase in tumors has been reported in the younger generations (children, adolescents, young adults) who have evidently been exposed to ever-increasing pollution since conception and childhood (11). In the last decade, epigenetics has highlighted specific potentially harmful and/or carcinogenic methylations related to single molecules of substances present in the environment (12, 13). These epigenetic signatures, linked to the formation, growth and/or aggressiveness of cancer, enhance our chances of fighting tumors by designing potentially effective targeted therapies, but can also revolutionize primary and secondary prevention by facilitating screening and indicating the carcinogenic or co-carcinogenic agents in the tumors of individual patients (14).

Environmental Pollution and Tumors

Environmental carcinogenesis has always been the subject of epidemiological research which, through case-control studies and subsequent meta-analyses, has indicated the possible causes. However, traditional epidemiological studies risk being increasingly inadequate in reliably identifying the etiological factors responsible for the increase in cancer incidence: prospective studies are time-consuming, expensive, and, in the now globalized world, will be increasingly difficult to select those exposed from those who are not exposed to any given pollutant. On the other hand, retrospective studies provide data that is a few decades old, often representing a situation that no longer exists and, in any case, require other confirmatory studies. Furthermore, the limitations of epidemiological research in trying to define causal relationships of cancer also collide with the multifactorial nature of tumor etiology (15).

However, only thanks to these studies was IARC able to classify numerous environmental factors and causes as "certainly carcinogenic to humans (class 1)": arsenic, heavy metals, fibers, dust, dioxin and dioxin-like chemicals, PAH (polycyclic hydrocarbons aromatics), and many more (16, 17). In 2013, due to the link between combustion products and atmospheric particulate, "air pollution" was also classified in class 1 (18). Well conducted epidemiological evidence is numerous and irrefutable. With respect to this, the latest report (the sixth) of the SENTIERI study, which has been evaluating, for almost twenty years, the health risk of the approximately 6 million Italians residing in the most polluted sites in the country, and still largely to be decontaminated, found in the period 2013 -17 a mortality risk greater than the national average of 2.6%. The data remained almost identical to that of the previous period 2006-13 (2.7%) and malignant tumors represent the largest percentage (56%). Furthermore, in 43% of the contaminated areas, an excess of hospitalizations was found in the pediatric-adolescent age group (0-19) and in young people (20-29) for congenital malformations in the first year of life, genital anomalies and frequent damage to fertility in both sexes and also tumors (19). In the literature, associations are reported between exposure to PM_{10} and $PM_{2.5}$ found in city air and lung, but also brain and breast tumors, and to NO_2, increases the risk of serious cardio-respiratory diseases and premenopausal, but not postmenopausal, breast cancers (20, 21, 22).

A recent leading confirmation of the relationship between air pollution and tumors was published by Cazzola Gatti et al. in 2023: with the help of AI, mortality from 23 types of cancer in all Italian regions and provinces were compared against 35 sources of pollution and against 7 socioeconomic variables (including lifestyles). Mortality from cancer was significantly higher in the areas with the greatest pollution, even after adjusting for where socioeconomic variables and lifestyle and by far the most harmful source turned out to be air quality (23).

Not without discussion, IARC has classified other sources of pollution as "probable and/or possible" carcinogenic: these include, for example, various pesticides/herbicides and exposure to electromagnetic fields (24, 25). Data from single studies on animals and crops and the subsequent meta-analyses reporting a clear relationship between exposure to pesticides and predominantly hematological, neurological, gastrointestinal tumors and melanomas were not deemed sufficient to revise this position (26, 27). Similarly, neither the demonstration of risk of brain tumors due to electromagnetic radio frequency fields (RFF) from the use of mobile phones (28), nor the worrying data reported from the exposure of RFF in laboratory animals were sufficient to change the classification of “possible carcinogenic” (class

3) [29, 30]. INCRIP (International Commission on Non-Ionizing Radiation Protection) proposed new prospective studies, knowing full well that exposure to REFs, which have reached frequencies billions of times higher than natural ones, in this globalized world appears increasingly difficult to select exposed from non-exposed [31].

Young Person Cancers in Italy and Worldwide

More and more young people are getting cancer around the world: a strong global increase in cancers in people under 50, with the highest rates in North America, Australia and Western Europe [32, 33]. In the USA, in the period 1990-2019, young people with cancer increased by 79% [34]. In Italy, the number of people aged 15-39 with cancer has doubled in 24 years (from approximately 10,000 in 2019 to 20,000 in 2019). The latest generations have increased the incidence of major cancers compared to any previous generation since the beginning of the century and, according to current data, this trend could remain high for decades [35]. To explain the phenomenon, changes in lifestyle have been indicated: poor physical activity, obesity, changes in diet, etc. [36]. However, it can also be hypothesized that the cause of this increase is exposure, during fetal development, childhood, adolescence and young adulthood, to chemical pollutants and radiations released into the environment in ever-increasing quantities since the middle of the last century [13]. Lorenzo Tomatis already in 1979 without yet having any notions of epigenetics, had predicted, that the last two generations, who lived with this greater exposure to pollutants since birth, were also affected by any transgenerational mutations transmitted by their parents [37]. Already in the first decade after 2000, worrisome data from case-control epidemiological studies were published describing a statistically significant association between pesticide exposure of both parents before conception and childhood leukemia (HR: 1.74) and/or maternal exposure during pregnancy (HR: 2.19) [38]. Similarly, a meta-analysis of 20 studies in children and young adults between 1974 and 2010 reported that exposure of both parents to pesticides increased the risk of brain tumors (from +30% to +53%) [39]. These observations were then expanded and confirmed in case-control studies and meta-analyses published more recently in 2019 and 2021, supporting the transgenicity of epigenetic mutations [40, 41, 42].

Epigenetics and Cancer

Epigenetics studies the influence on non-coding DNA structures determined by the cellular context, which in turn is in direct contact with the external environment [43, 44]. All harmful or non-harmful environmental agents cause DNA methylation alterations which can be reversible but can also persist over time and can be potentially transmitted from parents to offspring [45, 46]. Epigenomic dynamics are an essential cofactor of cellular adaptation to the external environment, producing various biological effects, including the onset of degenerative diseases and susceptibility to cancer [47]. Studies on the effects of epigenetic mutations have highlighted that, like aging, exposure of parents to chemical substances (smoking, pesticides and herbicides, polluted air, etc.) can also increase the risk of their offspring developing cancer as well as metabolic, cardiovascular and neurological diseases [48]. In animal models, exposures to toxic substances (e.g. dioxin) have determined mutagenic effects on the sperm epigenome, causing intergenerational transmission mechanisms in spermatozoa [49]. In the 2022 Recillas-Targas Overview we read: *"Cancer is a complex disease caused by genetic and epigenetic alterations in the control of cell division. Findings from the field of cancer genomics and epigenomics have increased our understanding of the origin and evolution of tumorigenic processes, greatly advancing our knowledge of the molecular etiology of cancer"* [50].

Epigenetic Signatures

The epigenetic alterations and the genetic mutations present in a tumor genome can be considered potential markers of cancer development and/or progression and constitute a true hallmark of its etiology [43]. Since they occur in specific genomic loci, their identification can represent a signature of the external factor and cofactor molecules that caused and/or favored the progression of that cancer [44]. Epigenomic mutations can also affect the immunogenicity of both healthy and tumor immune cells, resulting in immunosuppression and/or tumor immune escape [51, 52], and are also inheritable: this way, as Emma Whitelaw and Virginia Hughes had already imagined, the exposome of the ancestors can influence the health of the offsprings [53, 54]. This has been demonstrated in experimental animals, where paternal epigenetic factors influence the hereditary traits of offspring through sperm, and mothers act as

a modulating factor in determining their impact on their development (49). Some lifestyles (cigarette smoking) and exposure to toxic and carcinogenic substances by parents before conception and by mothers during pregnancy increase the risk that their offspring will develop cardiovascular, neurological, and metabolic pathologies, as well as childhood and youth cancers (45, 55). The mutational signatures have gradually been deciphered in the last decade (56, 57) and in vitro exposure tests to several carcinogens on mouse embryonic fibroblasts precisely showed the identity of the mutational signatures observed in human tumors (58). Specific differences in mutational signatures of various tobacco smoke components in human lung tumors are described (59), and epigenetic signatures of ultraviolet radiation in skin tumors are well recognized (60, 61). A breast tissue signature linked to breast carcinogenesis in female populations professionally exposed to pesticides is described (62). Specific epigenetic methylations caused by carcinogenic compounds in air pollution have been found for lung cancer and exposure to $PM_{2.5}$ (20). This association is also described for breast, ovarian and endometrial cancers which, however, requires further investigation due to the limited supporting literature, as the authors themselves point out (63). Epigenetic signatures identifying occupational exposures to individual toxic chemicals as mercury, cadmium, chromium, nickel, arsenic, and benzene have been reported (64, 65). The mutational signatures of occupational exposure to pesticides/herbicides in association with UV rays in melanoma are being identified, leading to a molecular subclassification based on a wide range of epigenetic mechanisms (66). Single mutations can influence the expression of many target genes related to the origin of melanoma, angiogenesis, apoptosis, proliferation and potential resistance to treatments (67). The high correlation of female exposure to plasma levels of 14 polychlorinated biphenyl (PCB) congeners and 11 organochlorine pesticides and melanoma indicates that many specific mutations are due to these factors (68). Epigenetic alterations could also promote aberrant transcriptional programs involving tumor immunogenicity and healthy immune cells involved in antitumor responses (69). The first trials combining therapies on immune checkpoint inhibitors with hypomethylating agents demonstrate how immunoediting can significantly increase patients' long-term clinical benefit (70, 71). In addition to introducing increasingly effective therapeutic strategies, epigenetics can also help identify with certainty the etiological relationship between specific environmental causes and the onset and/or progression of cancer.

Discussion and Conclusions

Epigenetics studies how the external environment influences the functionality of our genes. The influence of changing environmental conditions is reversible over time (72), but can persist over time with mutations that can be transmitted from both parents to their children (73). Epigenetics can influence many aspects of health and life, including the rate of aging, sexual orientation (74), the possible onset of autism (75), metabolic diseases and cancer (35, 48). Numerous authors describe a sort of epigenetic clock according to which the association of DNA methylation, premature biological aging and cancer risk may be the basis of the growth of early-onset tumors (47,76, 77). Epigenetic mechanisms of methylation and demethylation are involved in all carcinogenesis phases (66) and these specific alterations can be considered as true biomarkers of environmental agents in the etiology of various types of cancer (67,78, 79). All types of small mutational events constitute the set of signatures directly determined by environmental agents and their whole specific repertoire is being classified (80). The uncertainties of the epidemiological literature on the evidence of carcinogenesis in humans due to numerous polluting factors such as pesticides (81) could be clarified and demonstrated by detecting the various epigenetic marks with the help of AI. The methods of detecting specific epigenetic signatures related to the various polluting molecules involved in carcinogenesis could be able to provide a complete and identifying database of the various etiological causes of cancer (82, 83). Finding the signature of the responsible or co-responsible elements in the histological tissue of each individual patient's tumor could be decisive for creating new therapeutic strategies, to better direct secondary prevention (early diagnosis) (84), but also to identify and remove the etiological causes of that tumor. The ethical and legal implications of these findings could also encourage all the stakeholders to support and finance a renewed primary prevention (recognize the causes of diseases to eliminate or reduce them... for a healthy society) (85, 86).

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