

The high cancer incidence in young people in Italy: do genetic signatures reveal their environmental causes?

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Abstract

The increased incidence of cancer in children and adolescents registered in Italy in the last few decades is one of the highest amongst Western countries. The causes are difficult to identify, but recent daily news and some epidemiological surveys, such as the 'Sentieri' study, suggest that environmental pollution has an important role. In the past 20 years, epigenetic studies have described how the changes induced by the cell microenvironment on the non-coding parts of the genome can heavily influence gene function, contributing to the carcinogenesis process. Connecting links amongst the external environment, cellular microenvironment and functional epigenetic and genetic mutations promote carcinogenesis. Today, the whole genome sequencing techniques for human cancers can help to formulate a map of mutational signatures in individual tumours, and a list of mutational fingerprints showing exposure to specific environmental mutagens is being developed. Determining the ethical, legal and economic consequences of known cancer causative agents in young people will be a crucial step for a serious reconsideration of primary prevention.

KEY WORDS: neoplasms; primary prevention; carcinogens, environmental; epigenomics; DNA mutational analysis

Riassunto

L'aumento dell'incidenza dei tumori nei bambini e negli adolescenti registrato in Italia negli ultimi decenni è un fenomeno preoccupante perché tale riscontro resta uno dei più elevati fra i Paesi occidentali. Non è facile stabilire con certezza quali possano esserne le cause, tuttavia i recenti resoconti di cronaca e diversi rilievi epidemiologici come i risultati dello studio Sentieri, indicano un ruolo importante dell'inquinamento ambientale. Da quasi un ventennio l'epigenetica studia come le modificazioni indotte dal microambiente cellulare sulle parti non codificanti del genoma possano influenzare in modo importante la funzionalità dei geni, contribuendo al processo di cancerogenesi. Esiste, quindi, un anello di congiunzione fra l'ambiente esterno, il microambiente cellulare e le mutazioni funzionali oltre che genetiche che possono favorire o determinare la cancerogenesi. Oggi, le moderne tecniche di sequenziamento dell'intero genoma possono disegnare vere e proprie mappe complete delle firme genetiche nei singoli casi di tumori. La descrizione delle prime firme mutazionali in tumori umani indicanti l'esposizione a specifici agenti mutageni ambientali è già iniziata. Le implicazioni etiche, legali ed economiche che ne deriveranno costringeranno a considerare con forza la prevenzione primaria.

TAKE-HOME MESSAGE

In Italy, childhood cancer exhibits one of the highest incidences in the Western world, perhaps related to environmental causes. Genetic signatures of specific environmental mutagens may trigger ethical, legal and economic implications and lead to a renewed push for primary prevention in oncology.

Competing interests - none declared.

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A scientific report on the causes of human cancer published by Tomasetti and Vogelstein in the journal *Science* in January 2015 has received widespread media coverage, as it focusses on an unusual topic. Using a mathematical model that estimates the number of somatic mutations in tumours of self-renewing tissues, the authors claim that the most cancers in the world would be due to chance, or in other words, to 'bad luck' [1]. This hypothesis, which makes primary prevention in oncology illogical, has been strongly contested by experts worldwide. In particular, the International Agency for Research on Cancer (IARC) has pointed to numerous methodological limitations and biases in the report's analysis, as well as serious contradictions compared to well-known epidemiological evidence [2]. Currently, the daily news reports indicating strong links between environmental pollution and increased incidence of serious chronic degenerative diseases and cancers are increasing [3]. The latest air pollution report from the European Environment Agency estimates that in Italy, there are 59,500 premature deaths per year due to exposure to fine particulate matter (PM_{2,5}). The Italian National Institute of Statistics (ISTAT) found that the total number of deaths in our country in the first eight months of 2015 increased by 11.3% (about 45,000 units) compared to the same period in 2014; this increase has especially affected females and the weakest populations – the elderly and children. The recent update on the epidemiological situation in the 55 municipalities defined by the Italian Law 6/2014 as 'Land of Fires' in the Campania region describes an increased number of child hospitalisations in the first year of life for all type of cancers, with an excess of central nervous system tumours at the age of 0–14 years [4]. Furthermore, Italy uses more pesticides in agriculture than all other European countries do, thereby exposing child health to an extremely high risk that is now widely documented [5]. A worrying aspect of the relationship between pollution and health concerns the unborn, children and teenagers, who are much more

sensitive to pollutants than adults for both physiological and behavioural reasons. Their health, which may already be heavily affected in utero or even in the parents' gametes in preconceptional stage, is influenced by not yet fully functioning detoxification mechanisms, and because, for the same weight, they consume greater quantities of air, water and food than adults do. Several reports in the literature have linked environmental causes with a wide range of serious childhood diseases, such as hormonal disorders (especially in the thyroid); an increased risk of birth defects, including cryptorchidism and hypospadias; autoimmune disorders; diabetes; obesity; asthma; neurological disorders with cognitive deficits; and behavioural disorders [6, 7]. Compared to the prevalence of all these pathologies, the incidence of cancer shows smaller numbers but can be easily detected by cancer registries.

The increasing number of paediatric and adolescent cancers in Italy seems to be one of the most important issues of the last decades, although in the reports by epidemiological experts, these data are rarely linked to environmental causes. However, in our country, despite a growth slowdown in 2003–2008, the incidence rate for all cancers at the age of 0–19 years (175.4 cases per million/year in children and 270.3 in adolescents) remains one of the highest in the Western world. In 1998–2002, there was an increased incidence of 2% per year for all childhood cancers (0–14 years), whereas the European and US averages recorded in the same period rose by 1.1% and 0.6%, respectively. The highest increases were recorded in children under 1 year of age (+3.2% per year) and those aged between 10 and 14 years (+2.4%) [8]. In 2003–2008, the rate of incidence of childhood cancer in Italy appeared to be stationary but maintained higher values than in other Western countries. In addition, the cancer incidence in adolescents (15–19 years) did not increase further in the same period, but considering the entire decade from 1998 to 2008, there was an annual increase of 2%, mainly due to increased incidences of Hodgkin's lymphomas, thyroid

cancers and melanomas in women [9].

Complex epidemiological studies will be required to determine the causes of cancer incidence in young people with high probability; however, such research will certainly be long and expensive. Still, a lot of currently existing data indicate that environmental pollution is an important risk factor [10]. In particular, the 'Epidemiological Study of Residents in National Priority Contaminated Sites' (SENTIERI project), carried out in the period 1995–2009 in 44 polluted Italian sites (SIN) inhabited by about 5.5 million people – of whom about 1 million are under the age of 20 years – has also reported data concerning childhood health. The study found that 3332 children died from any cause in the first year of life versus an expected number of 3206 (+126) [11]. More specifically, in the 23 SIN covered by cancer registries, the cancer incidence evaluated from 1995 to 2009, was +9% in males and +7% in females compared to the geographic areas of reference [12]. Amongst the most impressive data are those that concern Taranto, where the study of mortality in 2003–2008 saw an increase of +35% of deaths from all causes in children under 1 year of age, an increase of +71% in perinatal mortality and an increase of the incidence rate of +30% for all cancers in the whole population versus the reference areas [13].

The incidence of cancer and degenerative diseases continues to increase worldwide, with even higher rates in developing countries. Land degradation and conditions of poverty, as well as the low level of schooling of the population, are generally associated with an increase in these diseases [14]. The highest price in terms of health is paid by children; living in polluted and degraded environments, members of this population sustain damage that will affect their existence and their entire lives: the most recent EUROSTAT data, while confirming a further increase in life expectancy (80.3 and 85.2 years respectively for men and women) for Italy, indicate a strong decrease in life expectancy 'free from diseases' for the past decade. Children born in Italy in 2013 had a 'disease-free' life expectan-

cy that was decreased to 61.8 years for males and 60.9 for females (for those born in 2004, the figures were 68.7 and 71 years, respectively). These decreases of 6.9 years (males) and 10.1 years (females) mean that the Italian values are now well below the European average [15].

Since the beginning of the 2000s, numerous scientific reports have been addressed to the study of epigenetics; along with genetics, this has assumed an important role in knowledge concerning the onset of many chronic diseases, including carcinogenesis [16]. The epigenetic modifications affecting non-coding parts of the genome are able to modulate gene functions via overexpression or silencing in a continuous exchange of information and adaptation to the surrounding environment of cellular life [17]. The control of cell functions plays a special role in inducing severe damage during the critical moments of the physiological development of the body (embryo, foetus, childhood, adolescence); if epigenetic changes are transmitted by parents with their gametes, they may also affect the health of subsequent generations [18].

The exchange of messages passing through the external environment to the cellular microenvironment, and finally to the DNA, is functional, dynamic and reversible; this provides evidence that the quality of environmental components in which we live, namely soil, water and air, has a direct impact on human health. Environmental pollution causes serious harm to living organisms, but those who sustain the most damage are the most vulnerable individuals, who are at risk of serious effects from conception [19]. Unfortunately, the most striking aspects of the link between the environment and health are the increasing incidence of cancer and of chronic degenerative diseases, which occur at an increasingly early age in the most polluted areas and particularly affect children, adolescents and young adults [20, 21]. Today, the simultaneous evaluation of genetic and epigenetic arrangements, obtained from circulating tumour cell DNA, can provide information on the development and progression of cancer;

moreover, the whole-genome sequencing of human tumours has shown distinct patterns of mutation that point to the causal origins of cancer, suggesting the concrete hypothesis that each mutagen induces a characteristic 'mutational signature' [22, 23].

The convergence of genetic alterations with the epigenetic backgrounds due to micro-environmental conditions of metabolic re-programming can promote aberrant transcriptional programmes of activation and maintenance in cancer cells that are similar to those seen in stem cells [24]. The DNA of circulating cancer cells has been shown to provide information on the development and progression of the tumour and its epigenetic mechanisms, thereby distinguishing between contributing factors and intrinsic (mutations) or extrinsic factors (microenvironment). In the case of brain tumours, this could soon lead to the description of a complex epigenomic mapping [24]. The identification of correlations between specific mutational signatures in human cancers and exposure to environmental mutagens has already begun [25]: the slight differences in mutational signature amongst the various components of tobacco smoke in lung tumours, the fingerprints due to ultraviolet light damage in skin cancers and the individual losses in mismatch repair mechanisms are already known [26, 27]. Recently, a high frequency and magnitude of c-MYC amplification and c-MYC protein overexpression in breast cancers due to previous exposure to radiation compared with cases without a radiation aetiology was demonstrated [28]. Analysis of mutational gene expression and of specific epigenetic methylations caused by organic compounds from air pollution, such as PM_{2.5} particulate, have been carried out [29].

Investigations of the whole-genome sequen-

cing of thousands of human cancers are now producing catalogues of somatic mutations. Alexandrov et al. published an analysis of 4 938 362 mutations from 7042 types of cancer in *Nature* in 2013, in which they extracted more than 20 distinct mutational signatures [30]. These specific signatures of known causes can then be placed in a reference database and provide clear indications for the aetiology of cancer. The origins of many types of cancer that are suspected to be caused by yet unidentified environmental causes can finally be discovered, and this will represent a crucial step towards achieving the maximum target of public health in the prevention of cancer [31]. Over the next decade, thousands of whole genomes of the most frequent types of cancer will be examined; this will allow the creation of an exhaustive map of mutational signatures. The map application requires the refinement of existing mathematical methods to examine all known types of somatic mutations accurately; of course, the analysis of these new data will have to be integrated with experimental epidemiological studies [32]. Today, profits can be made from the treatment of advanced cancer because of the incentives derived by the interaction between the patent system and the drug approval process; such economic incentives encourage young researchers to focus on cancer treatment rather than prevention [33]. However, mutational signatures may lead to a different balance in the allocation of resources. In the near future, leaving aside the idea of 'bad luck', the cause or main causes that led to tumour development in each individual may be determined. Ethical, legal and economic implications will accrue, and finally, society will be forced to pursue the necessary actions for a real and renewed primary prevention.

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