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The role of chance in cancer causation

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Summary

In the last years, the discussion about the role of chance in the causation of cancer has generated a large scientific and public debate. The concept that chance, or "bad luck", as responsible for a majority of the variation of cancer incidence, may be misleading, possibly causing an underestimation of the role played by known risk factors. In this commentary we discuss how host and external factors interact with chance in cancer causation in different ways, and provide examples of situations where chance appears to play only a minor role on cancer onset.

1. Introduction

As causal factor for cancer, chance has been described as "bad luck", "intrinsic replicative factor", "unpreventability", "intrinsic random factor" [1, 2] and, specifically for cancers, a "stochastic event" [3].

According to Tomasetti and Vogelstein [4, 5], two thirds of the variation in cancer rates across different tissues and organs could be explained by random mutations occurring during DNA replication, a concept they referred to as "bad luck". However, such hypothesis sparked criticism [6] in the scientific community due to a number of reasons, including: (i) the authors' assumptions, such as the use of mouse data to derive human stem cell division rates [7]; (ii) the emphasis on rare cancers, coupled with the exclusion of common cancer types due the lack of data; and (iii) the possible detrimental effects on public health perspective driven by the article if misinterpreted, suggesting the need for a greater focus on secondary prevention of cancer rather than primary prevention [8]. Besides, in contrast with the "bad luck" hypothesis, subsequent reports confirmed previous evidence that environmental factors play a key role in explaining cancer risk and that the rates of mutation occurring by chance alone cannot explain cancer risk without taking into consideration extrinsic factors [9, 10].

A necessary condition for cancer development is a sequence of genetic mutations [11, 12] escaping DNA-repair systems.

Although chance is considered to play a prominent role in some cases [4], additional factors appear to be crucial in cancer causation, such as the immune system, hereditary factors and the DNA damage response. In addition, the environmental exposure is also known to be involved in cancer occurrence [13, 14]. In this commentary, we discuss how host and external factors interact with chance in cancer causation in different ways. Also, we provide examples of situations where chance plays only a minor role on cancer onset.

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1.1 Environmental factors

Literature accounts many carcinogen agents, which have been deeply studied in relationship to different cancer types and which have been classified by IARC [15]. Known carcinogens include high prevalence factors, such as arsenic, asbestos and tobacco smoking, to low prevalence ones, including infectious agents which are endemic in restricted areas (e.g. Clonorchis sinensis) or chemicals (e.g. aromatic amines) which currently are rarely used, or continue to be used in small subgroups of the population worldwide. Exposure to environmental carcinogens typically leads to cancer in a minor proportion of the exposed subjects. For a given carcinogen, the magnitude of the risk of cancer depends on different exposure-related factors, including dose (cumulative exposure), dose-rate (quantity of exposure within a certain time interval), intensity and duration of exposure, the co-presence of other agents (e.g. mineral dust for radon decay products, where the exposure to α-particles is conditional to mineral dust inhalation [16]) which may reciprocally interact, as well as host-related factors including genetic susceptibility, family history of cancer [17] and chance [3].

Even after prolonged exposure to ascertained carcinogens, the cumulative risk of cancer in the exposed rarely exceeds 25% compared to the unexposed. For example, the absolute risk of lung cancer in heavy, long-term smokers is in the order of 20-30% [18]. However, few examples of circumstances of exposure to environmental carcinogens in which all – or an overwhelming proportion of – the exposed subjects were diagnosed with cancer can be identified. A well-known example is that of occupational exposure to aromatic amines in the dye production industry. Following anecdotal reports and experimental studies in dogs [19], the carcinogenicity of aromatic amines such as 2-naphthylamine and benzidine was demonstrated in the 1950s in a cohort of British chemical workers [20]. The study included 4,622 men employed in 21 plants in which workers were exposed to aniline, benzidine, 2-naphthylamine or 3-naphthylamine. A large excess of bladder cancer was noticed in this cohort, in particular among those exposed to aniline and 2-naphthylamine.

Other studies subsequently reported an increased risk of bladder cancer in workers exposed to 2-naphthylamine, benzidine, and 4-aminobiphenyl [21], with heterogeneity in the risk estimates, likely reflecting different levels of exposure and other possible circumstances. In one of the plants included in the first study, however, all 15 workers involved in the distillation of 2-naphthylamine developed bladder cancer [22]. This result shows that, in exceptional situations of exposure to environmental carcinogens, chance no longer operates, except possibly in determining the timing of cancer onset.

1.2. Hereditary factors

Genetic syndromes with high penetrance are a remarkable example of the different role that chance might play in cancer causation at individual level.

Indeed, a situation in which all the individuals with a specific mutation develop the related disease or phenotype, can be considered an example of exclusion of chance from the etiologic pathway. For instance, as reported by previous studies in mice [23], *Rb1* is the most frequently mutated gene in the pediatric retinoblastoma (Rb), and its loss causes E2F transcription factors to induce proliferation-related genes. Co-deletion of *Pten* with *Rb1* and *Rbl1* in mouse retinal progenitor cells causes fully penetrant bilateral retinoblastomas by 30 days and strongly suppresses Rb/E2F-induced apoptosis [23], while germline mutations in humans lead to 90-95% penetrance [24] and 95% of Rb patients are diagnosed by the age of 5 [25].

Another good example is Multiple endocrine neoplasia type 1 (MEN1), an autosomal dominant disorder characterized by parathyroid, pancreatic islet, and anterior pituitary tumors. The MEN1 gene, a tumor suppressor gene, had been localized to chromosome 11q13. Different studies [26, 27] demonstrated that the penetrance of this disease rises steadily with age, from 7% in the <10-years-old to 100%, by the age of 60.

In these examples of genetic syndromes with high penetrance, the hereditary factor seems to be the only sufficient causal factor for developing a tumor at some point in life, practically excluding the role of chance that would, otherwise, interfere in a proportion of the cases.

However, syndromes caused by genetic variants with incomplete penetrance may also provide valuable examples for the role of factors other than genetics, including chance, in the occurrence of diseases at the individual level. For instance, germline mutations in the Rearranged during Transfection (RET) proto-oncogene are associated with the Multiple endocrine neoplasia type 2 (MEN2) hereditary syndrome, though not all the individuals carrying such mutations develop all cancers and non-neoplastic diseases commonly associated with the syndrome, the most common being medullary thyroid carcinoma and pheochromocytoma [28]. Such phenotypic differences are linked to different mutations in the RET gene, albeit these do not entirely explain interindividual variability [29]. While a need for further genetic events (second-hit) in the RET gene has also been suggested for cancer development, the role of other factors, such as environmental factors, stochastic events involving also epigenetic modifications, may be significant. In addition, the factors leading to this second hit are not known [30], and the role of chance cannot be excluded in this context as well. Similarly, factors determining epigenetic differences which may lead to different phenotypes are not well understood [30-32] and, while one could argue that we still do not have a complete understanding of the individual contributions of genetics and environmental factors, the potential effect of stochastic events cannot be ruled out.

Unlike all the syndromes mentioned above, which are associated with specific types of tumors, Li-Fraumeni syndrome is characterized by the great variability of organs and type of neoplasms involved. This hereditary condition connoted by alterations on p53, one of the main tumor suppressor proteins, is due to genetic mutation on the TP53 allele on chromosome 17.

A large cohort study investigated cancer epidemiological and phenotypical aspects in subjects with p53 mutations. Li-Fraumeni syndrome carries a nearly 100% risk of cancer by age 70, causing leukemia, lymphoma, gastrointestinal, head and neck, kidney, larynx, lung, skin melanoma, ovary, pancreas, prostate, testis and thyroid cancers [33, 34].

An opposite example is Laron syndrome (LS). This disease, also called primary growth hormone resistance, is characterized by congenital deficiency of insulin-like growth factor 1 (IGF1).

A cohort study of 230 LS patients [35], 116 isolated growth hormone (IGH) deficiency patients, 79 patients with Growth-hormone-releasing hormone (GHRH) defects and 113 congenital multiple pituitary hormone deficiency (MPHD) patients reported a surprising low number of cancer cases. In particular, none of the 230 LS patients developed cancer at the time of the study. Knock-out mouse models supported these observations in humans [35]. It appears, therefore, that lack of IGF1 is associated with a null or very low risk of cancer, despite the presence of other environmental, lifestyle, socioeconomic and epigenetic factors.

We must add that studies on LS and cancer incidence [35] are usually characterized by small populations of relatively young patients.

1.3. DNA damage response

As mentioned above, Tomasetti and Volgestein [4] suggested that the lifetime risk of cancer in different tissues is strongly correlated with the total number of divisions of their stem cells, due to driver gene mutations that randomly result from the DNA duplications.

If we took this model literally, we could say that, if cancer does indeed mainly depend on the total number of divisions of stem cells, then taller, bigger individuals, whose cells would have gone through more divisions during the phases of development and generally throughout life, should have higher incidences of cancer. This does indeed appear to be true, with taller, bigger individuals having been proved my multiple studies to have a higher risk of developing various types of cancer when compared to smaller individuals [36], both in the case of humans and in that of animals, for example when considering the different cancer rates between different dog breeds [37].

However, if this applies quite well when considering different individuals within a species, the situation appears different when moving from an animal species to another one: we would expect that bigger animal species, having more cells than smaller ones, and therefore having undergone more cell divisions

throughout their lives in order to reach that number of cells, would also show significantly higher incidences of cancer. However, this is far from being the case, and it seems that, on the contrary, large species of animals show low incidences of cancer, as is the case for whales or elephants [38]. This phenomenon is known as Peto's paradox, and seems to suggest that the role of the total number of stem cell divisions might be essential for the development of cancer in certain single species, but might not be valid across the entire animal kingdom [39].

If we consider elephants, they show a cancer mortality rate of 4,8% [40], lower if compared to the human one (11-39%) [41], despite the fact that elephants can weight up to 100 times more than humans. According to recent studies [40, 42], this seems to be at least partially due to the fact that elephants possess an enhanced DNA damage response mechanism, comprising 20 copies of TP53 encoded throughout their genome. This led to the fact that elephant cells undergo p53-mediated apoptosis at a higher rate in response to DNA damage, when compared to human cells [42]. This seems to show that, even in the case of higher DNA damage, and despite a significantly higher level of lifetime cell divisions, elephant cells are better suited at responding to DNA damage than human ones.

Finally, we could say that, although the gross stochastic effect of DNA replication, and thus chance, could indeed be considered an important contributor to cancer development, one should also take into account the role of processes such as DNA damage repair and antitumoral immunity, which do not depend on chance but, on the contrary, are finalized at reducing the unorderly effects caused by chance.

In fact, out of thousands episodes of DNA damage per stem cell per day, few remain unaddressed by the cellular DNA damage response mechanisms, and are thus potentially lead to mutation in the daughter cells. Even fewer of those mutations will produce neoplastic cells, while most will be neutralized (or, at least kept at bay) by the organism's antitumor immune response [43].

It can be therefore concluded that chance may manifest insofar the organism leaves it the space to do so: in species, individuals or single tissues where DNA damage repair and antitumoral immunity are impaired, the role of chance could be enhanced and the effect of overall divisions on mutations and cancer would be paramount. On the other hand, in cases where the tumoral development can be hindered by DNA damage repair or antitumoral immunity, the role of chance is reduced, and so is the incidence of cancer caused by spontaneous cell divisions.

1.4. The immune system

Another important component playing a crucial role in the development of cancer, is antitumoral immunity. Its important role is clearly shown in small bowel cancer (SBC), which represents an outlier in terms of incidence of neoplasms in humans. In fact, despite the high-replication rhythm of the intestine's epithelium and the large dimension of the organ, the small bowel is rarely affected by cancer, in particular by adenocarcinoma [44], the most common type of cancer in neighboring digestive organs. SBC collectively account for only 2% of cancers of the digestive system.

The SB surface is approximately 15 times larger [45] than that of colon-rectum and even though SBC and colorectal cancer (CRC) share several risk factors [46, 47], the age-standardized rate of SBC in the US is around 20 times lower than that of CRC [48]. Based on these figures, one can estimate that the incidence of SBC is roughly 300 times lower than that of CRC per surface unit.

This epidemiological peculiarity appears to be in contrast with the model proposed by Tomasetti and Vogelstein [4]. In fact, these authors assumed that endogenous mutation rates are nearly identical across all cell types, and therefore the lifetime risk of developing cancer in a particular organ or tissue should correlate with the lifetime number of stem cell divisions in that organ or tissue [4]. According to this model, a tissue whose stem cells undergo a high overall number of divisions would therefore be more likely to develop multiple somatic driver mutations, which in turn would kick off the process of oncogenesis and eventually lead to cancer [4].

One explanation for this phenomenon is the fact that different tissues, and even different cell types within the same tissue, respond differently to DNA damage [49]. For example, SB stem cells appear to

be extremely sensitive to DNA damage and, in experimental settings, undergo massive apoptosis upon low doses of irradiation (1 Gy) [50]; on the contrary, colonic stem cells require eight-time higher level of irradiation in order to undergo apoptosis; they also display a lower expression of p53 and a higher expression of bcl2 compared to SB stem cells [50].

Furthermore, other protective mechanisms and peculiarity of small intestine's mucosa have been hypothesized to exert an anti-cancer effect, including a rapid cell turnover, the relatively small bacterial load, an alkaline environment, the rapid content transit, the low level of activating enzymes of pre-carcinogens and the greater mucosal lymphoid infiltration than in the CR [47, 51, 52]. Moreover, the rapid transit of SB content and the reduced contact time of bowel's mucosa with carcinogens were hypothesized to diminish the risk of cancer compared to CR [51]. In conclusion, the characteristics of the anti-tumoral immunity in these tissues may explain, at least partially, the difference in cancer occurrence between SB and CR. While the immune system's impairment (either dependent from a disease or iatrogenic) increases the risk of cancer occurrence, especially in case of infection-associated neoplasms, the role of chance and its interaction with the anti-tumoral response cannot be excluded.

1.5. Chance, including gene-environment interaction

In the present commentary, we presented examples of conditions in which chance seems to play a minor role in the development of a tumor. Knowing that cancer is a multifactorial disease, and given the presence of chance, it is very difficult to assess which are the necessary causal factors for a specific type of cancer and for a specific patient.

Cancer epidemiology has the valuable ambition to identify and characterize the risk factors of the different types of cancer. To do this, different measures of estimate are used, such as population attributable fraction (PAF). Anyway, such measures apply to the general population – or in more or less large groups of population – rather than on the single individual [53].

A major obstacle in assessing the role of each carcinogenic factor derives from the imprecision of the measures we use to attribute a cancer to a specific event.

If we were able to predict with extreme precision which individual, who has the necessary combination of causal factors, will develop a certain type of cancer, we cannot tell in which moment it's going to happen or if the patient's life is going to be threatened by further diseases. The function of chance in determining the time of onset of a disease is poorly understood. Many other host factors could interact with chance in determining the timing of onset of cancer, including hereditary factors, epigenetics, the immune system and the anti-tumoral response.

Indeed, the increase of probability of an outcome and its anticipation in time are two aspects of the same phenomenon. Our capacity to observe the occurrence of an event is, in fact, determined by the period of observation and by the lifespan of the individual, and it is not possible to know whether a cancer occurring at time t_0 in an exposed individual would have occurred, in the absence of exposure, at time $t_0 + t_1$ or would not have occurred at all. Accelerated failure time models are used to reduce these limitations in the estimation of cancer incidence, survival and onset [54].

Possible examples of chance as "timer" of the onset of a cancer could be some of the high penetrance genetic syndromes cited above, specifically MEN1 and Li Fraumeni syndrome. Patients affected by these conditions have practically 100% probability to develop a tumor, even if with great variability for the age of onset [26, 27, 33, 34]. On the contrary, almost all Rb patients (95%) are diagnosed before 5 years of age; this difference could imply a lesser role of chance or a stronger oncogenic power of the associated genetic mutation of this syndrome.

2. Conclusions

Based on Tomasetti and Volgestein model [4], the effect of chance on cancer causation is expected to increase with age, due to the lifetime number of stem cell divisions and consequently, the accumulation of somatic mutations. Accordingly, there is an increasing trend between age and cancer rate, reaching its peak at 75 to 85 years of age, after which a decrease takes place [55-60]. Even though some possible explanations have been described [58], this phenomenon is still to be completely understood.

However, modern medicine is more and more interested in understanding the causes of cancer, especially when aiming at primary and secondary prevention. In fact, as our knowledge about the other variables grows, the contribution of chance in the causation of cancer reduces. Unlike chance, many carcinogenic factors have been described and are increasingly easier to detect and to remove. In the last years, secondary prevention has been implemented in many countries for breast [61], colorectal [62] and cervical [63] cancer and a significant progress is being made for prevention of liver cancer due to Hepatitis C Virus infection [64, 65], of lung cancer in heavy smokers [66-68] and of Helicobacter pylori-associated gastric cancer [69-71]. Furthermore, several successful interventions in cancer control have been made, such as the introduction of Hepatitis B and Human Papillomavirus vaccinations and of limits of occupational exposure to carcinogens.

From this point of view, public health and occupational medicine play major roles in cancer prevention with benefits in terms of global burden of disease.

Finally, if we were able to prevent any cancer, extending the overall life expectancy, the incidence of many other diseases would probably increase, just because people would live longer enough to develop these other conditions, that are, as cancer, associated with aging. This also applies in reverse; cancer would be more relevant as progress is made in treating or preventing any other disease, leaving cancer the main health focus.

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