Cancer Epidemiology 50 (2017) 132–136

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Review article

An epidemiologic perspective on the stem cell hypothesis in human carcinogenesis

David Schottenfeld

Department of Epidemiology, School of Public Health, University of Michigan, United States

ARTICLE INFO

Keywords:
Random DNA replication errors
Stem cell properties
Progenitor cells
Epigenetic events
Hierarchy of causal risk factors
Population attributable fractions

ABSTRACT

Background: Tomasetti and Vogelstein have hypothesized that the patterns of cancer incidence in various cells and tissues are highly correlated with the estimated lifetime number of stem cell divisions. The authors reviewed the risks in tissues of 17 types of cancer from the United States and 69 additional countries. Positive correlations were observed consistently between the tissue − specific cancer incidence and the estimated lifetime number of stem cell divisions. The authors concluded that approximately two-thirds of global cancer incidence may be attributed to random DNA replication errors.

Methods: An epidemiologic perspective is presented that may serve as a counterpoint in interpreting organ-specific cancer risks. The unifying nature of the Tomasetti/Vogelstein hypothesis must be viewed in the context of diverse and contrasting global trends and patterns of types and "causes" of cancers that are closely linked with economic development and cultural lifestyle practices. The presentation is organized by reviewing the global burden of cancer; concepts of causal inferences and counterfactual assumptions; multifactorial causes of hepatocellular carcinoma and a hierarchy of causes that varies internationally; tobacco carcinogenesis and the multiplex associations with 19 cancer sites and tissues; profile in contrasts in transit through the small and large intestine.

Observations and conclusions: It is readily recognized that DNA replication errors and number of stem cell divisions may vary in individuals and populations due to external environmental genotoxic chemicals and biologic agents, and internal hormonal and metabolic factors. There is a striking contrast in the risk of adenocarcinoma in the small intestine with that in the large intestine. Tomasetti and Vogelstein indicated that the cumulative number of divisions of stem cells over a lifetime in normal epithelial mucosal cells from colorectal cancer patients was 4 time greater than in the epithelial tissue from patients with adenocarcinoma of the small intestine. Their conclusion would suggest a "seed" and "soil" interaction rather than exclusively the independence of either component. Namely, that the contrasting physiological, biochemical, microbial and immunological features in the lumen and on the mucosal surface of the large intestine, in contrast to that in the small intestine, would foster molecular genetic and epigenetic events that are advantageous to neoplasia in the large intestine.

Tomasetti and Vogelstein [1,2] have hypothesized that the patterns of cancer incidence in various cells and tissues are highly correlated with the estimated lifetime number of stem- cell divisions. Each somatic stem- cell division entails a risk of random mutations. Namely, "approximately three mutations occur every time a normal human stem cell divides." The variable number of divisions appears to be a major determinant of differences in cancer risks in different organs. In their most recent paper, Tomasetti and Vogelstein reviewed the risks of 17 types of cancer in 69 countries, in addition to their prior analysis of the U.S. population. The median correlation coefficient of lifetime risk of cancer in each tissue with that tissue's reported number of stem cell divisions was 0.80 (95% CI = 0.67, 0.84). The linearity of the positive correlations was observed consistently among the countries studied. The estimated proportion of total variation in the cancer incidence explained by the independent variable x, or number of stem cell divisions, may be estimated by r^2 or 0.64 (0.45, 0.71). The authors concluded that approximately two-thirds of global cancer incidence may be attributed to random DNA replication errors. Environmental and inherited factors that vary widely among individuals and populations can increase the mutation rate and number of stem-cell divisions. As stated in their 2017 publication: "Our results are fully consistent with epidemiological evidence on the fraction of cancers in developed countries that are potentially preventable through improvements in the environment and lifestyle."

E-mail address: daschott@umich.edu.

http://dx.doi.org/10.1016/j.canep.2017.09.001
Received 11 July 2017; Received in revised form 5 September 2017; Accepted 5 September 2017

1. Histogenesis of adult or tissue stem cells

Adult stem cells are observed in close association with differentiated cells of a given tissue. They are normally located within specialized tissue microenvironments or "stem cell niches" composed of stromal cells and paracrine signaling factors. Stem cells exhibit properties of "self-renewal" and "asymmetric division". Self-renewal signifies that in the mitotic activity of stem cells there is resistance to genetic and epigenetic mechanisms that trigger senescence or a permanent state of cell cycle arrest. Asymmetric division results when a stem cell divides into one daughter cell that remains a stem cell, while the other daughter cell proceeds along some differentiating pathway. The homeostatic balance between self-renewal and differentiation is essential for physiologic maintenance of the architecture and functioning of adult organs and tissues [3,4]. Although adult somatic stem cells have the potential to proliferate actively, they are relatively dormant in their microenvironment. Stem cell quiescence may be viewed as an evolutionary conserving mechanism that modulates stochastic events of cell replication and the acquisition of tumorigenic mutations.

2. Cancer stem cells

Cancer stem cells are a selective clonal subset of tumor cells that have escaped various cell regulatory mechanisms including terminal differentiation, and yet have retained the self-renewing properties and proliferative potential of adult stem cells. As defined by the American Association for Cancer Research, a cancer stem cell (CSC) is "a cell within a tumor that possesses the capacity to self-renew and to cause the heterogeneous lineages of cancer cells that comprise the tumor" [5]. By maintaining at least some of the properties of their tissue of origin, CSCs give rise to tumors that phenotypically share in their morphologic features and pattern of expression of tissue-specific genes. Two models of carcinogenesis have been proposed. A "stochastic model" proposes that neoplasia evolves potentially in any somatic cell through a sequence of mutational and epigenetic events that are amplified by selective clonal growth. In contrast to the stochastic model, the "CSC model" hypothesizes that the cellular origin of cancer resides in tissue stem or progenitor cells that possess or acquire the property of self-renewal [6,7]. The neoplastic evolution from normal tissue cells is signaled by the loss of homeostatic mechanisms that regulate mitotic activity and differentiation. A contemporary view would tend to combine biologic features advanced by both experimental models.

Epigenetic mechanisms that have been demonstrated to impact cancer etiology and progression have been reviewed by Feinberg et al. [8]. As stated by Feinberg et al., "genetic mechanisms are not the only path to gene disruption in cancer." Epigenetic events are composed of potentially heritable alterations in gene expression that do not entail a structural change in DNA sequencing. Epigenetic mechanisms are increasingly being viewed as alternatives to mutations and chromosomal alterations in disrupting gene function. Epigenetic mechanisms (e.g., DNA hypomethylation, hypermethylation of specific genes, chromatin alterations, and loss of imprinting) are essential for normal function and development of human cells and tissues, as well as for maintenance of tissue-specific gene-expression patterns. Feinberg et al., proposed an "epigenetic progenitor cell model" as a strategic step in human carcinogenesis. Progenitor cells are progeny of tissue-specific stem cells with limited potential for self-renewal. The proposed tumorigenic event is a polyclonal epigenetic disruption of stem/progenitor cells mediated by aberrant regulation of tumor-progenitor genes. Epigenetic events are stochastic, discrete and heritable, may confer the propensity for aberrant growth, and may be influenced by environmental factors.

3. The global burden of cancer

The global burden of cancer has exhibited striking differences in cancer patterns between the industrialized high-income countries and low-and middle-income countries (LMICs). In 2012, the World Cancer Report estimated that there were approximately 14 million cancer cases and 8 million cancer-related deaths. By 2020, the projected global cancer mortality will exceed 10 million cancer-related deaths.

Data on the burden of cancer from most LMICs are of limited quality. When population cancer registries are not available, death certificate data have served as the basis for total and cause-specific cancer mortality for 25%–50% of the LMICs [9]. Approximately two-thirds of cancer deaths were registered in LMICs that comprised at least 80% of the world's population [10,11]. The increasing cancer mortality burden in LMICs may be attributed to increasing urbanization accompanied by increasingly sedentary lifestyles, and expansion of the population age distribution at risk. Important environmental and behavioral risk factors contributing to the global cancer burden included exposures to various forms of tobacco, ethanol, increasing prevalence of obesity, and cancer-causing infectious agents. The proportion of global incident cancers attributable to infectious agents has been estimated as 16.7%, although the proportion varied geographically; the attributable fraction for LMICs varied from 20% to 30%, in contrast to ≤5% to ≤10% estimated for the highly industrialized countries. Of the 14 million cancer cases diagnosed in 2012, approximately 2.3 million were comprised of cases attributable to infectious agents. Infections caused by the gram-negative bacterium Helicobacter pylori, hepatitis B virus (HBV), hepatitis C virus (HCV), and the human papillomaviruses accounted for more than 90% of cases attributable to infectious agents [12,13].

Among the LMICs, the high incidence cancers included oral and pharyngeal, liver, esophageal (squamous-cell), stomach, lung and uterine cervical carcinomas, and HIV-associated cancers as Kaposi sarcoma and non-Hodgkin lymphoma. Uterine cervical cancer was the third leading cause of cancer-related deaths in LMIC women. High-income countries reported the highest incidence rates for all sites combined, as well as for lung, colorectal, breast and prostate carcinomas.

In their review of the United Kingdom in 2010 by Parkin et al., 14 lifestyle and environmental risk factors, namely tobacco smoke, ethanol, obesity and overweight, physical inactivity, dietary factors including red and processed meat, cancer causing infectious agents, occupations, ionizing and solar radiations and exogenous hormones, were associated with 45% of cancer cases in men and 40% in women [14].

4. Causal inferences and counterfactual assumptions

"The goal of most modern epidemiologic studies is to quantify the causal effect of a given exposure and outcome of interest, estimated by a measure of association." (Savitz DA and Wellenius GA, 2016) [15].

Tomasetti and Vogelstein have described a biologic mechanism of tissue-specific stem cell replication patterns that are positively correlated and universally applicable in comprehending the diversity of organ-specific cancer risk patterns. The unifying nature of their hypothesis must be viewed in the context of diverse and contrasting global trends and patterns of types and "causes" of cancers that are closely linked with economic development and cultural lifestyle practices. The framework for causal inference has evolved from the use of classic criteria or guidelines for judging probable cause articulated by Sir Austin Bradford Hill in 1965, or as presented in 1964 by the Advisory Committee to the Surgeon General [16,17]. An alternative model for causal analysis in epidemiologic studies, previously explored in agricultural and economic studies, and in the observational studies in sociology and psychology, is the counterfactual or potential outcomes framework. The interpretation of population attributable fractions in causal modeling reflects a counterfactual assumption, namely that the effects observed in exposed persons had they not been exposed, would have been comparable to that observed in the referent unexposed group. This conceptual interpretation is analogous to a cross-over design in randomized clinical trials in which each participant serves as