

COLLEGIUM RAMAZZINI

MOST TYPES OF CANCER ARE NOT DUE TO BAD LUCK

The Collegium Ramazzini is an international scientific society that examines critical issues in occupational and environmental medicine with a view towards action to prevent disease and promote health. The Collegium derives its name from Bernardino Ramazzini, the father of occupational medicine, a professor of medicine of the Universities of Modena and Padua in the late 1600s and the early 1700s. The Collegium is comprised of 180 physicians and scientists from 35 countries, each of whom is elected to membership. The Collegium is independent of commercial interests

Summary

The Collegium Ramazzini strongly rejects the claim by Tomasetti and Vogelstein that 65% of cancers are due to “bad luck” and result from randomly acquired mutations of the genome (Tomasetti and Vogelstein 2015b). This claim is based on a skewed and highly selective reading of the literature. It examines only a fraction of cancers - 34% - in a single country - the United States (Wild et al. 2015). It ignores enormous differences in cancer incidence and mortality across countries (Wild et al. 2015) (Potter and Prentice 2015). It dismisses abundant clinical and epidemiological research that has discovered scores of environmental and occupational carcinogens to which millions of persons are exposed (Wild et al. 2015). It ignores the very great successes in cancer prevention that have been achieved by controlling exposures to known carcinogens (Ashford et al. 2015; Gotay et al. 2015; Potter and Prentice 2015; Song and Giovannucci 2015; Wild et al. 2015).

The spurious claim of Tomasetti and Vogelstein poses grave danger to public health. It has the potential to undermine governmental programs for cancer prevention and also to discourage individuals from making wise decisions to change lifestyle, diet, and other factors that can reduce exposures to carcinogens.

In rejecting the unsubstantiated claim by Tomasetti and Vogelstein, the Collegium Ramazzini is proud to join the International Agency for Research on Cancer (Wild et al. 2015) and distinguished scientists from around the world (Ashford et al. 2015; Gotay et al. 2015; Potter and Prentice 2015; Song and Giovannucci 2015). We fully endorse the IARC critique of the Tomasetti-Vogelstein report (Wild et al. 2015).

Finally, the Collegium Ramazzini notes that Tomasetti and Vogelstein failed to disclose potentially important financial conflicts of interest (Tomasetti and Vogelstein 2015b).

The Claim is Based on Skewed and Selective Science

The “bad luck” theory of cancer proposed by Tomasetti and Vogelstein ignores current understanding that cancer is a multifactorial disease. The core of their theory consists of an artificial separation of cancer types into those associated with random events related to cell replication and those associated with environmental or inherited risk factors. But genome and environment interact as co-factors, not as mutually exclusive forces, and both almost certainly interact with random events related to cell replication in causing cancer. Therefore their theory is founded on a false and outdated dichotomy (Ashford et al. 2015).

The Tomasetti-Vogelstein analysis examines only a small fraction of all cancers - 34% - in a single country - the United States (Wild et al. 2015)(2). It focuses disproportionately on a few rare malignancies such as osteosarcoma. It fails to include data on many common cancers such as stomach, breast, prostate, cervix, kidney, bladder and lymphoma (Potter and Prentice 2015).

The Tomasetti-Vogelstein analysis ignores enormous differences in cancer rates across countries and populations (Wild et al. 2015) (Potter and Prentice 2015). These differences are not explained by differences in numbers of stem cell divisions. They are due instead to sharp differences across countries in environmental exposures and genetic susceptibility. Forty years ago, Sir Richard Doll studied cancer rates across countries and showed that there is enormous international variation in cancer incidence and mortality (Doll 1972). Doll hypothesized that “age-specific incidence rates [for cancer] could be reduced by 80-90%” by applying knowledge of specific risk factors gained through study of this international variation (Doll 1996).

The Tomasetti-Vogelstein analysis entirely ignores this body of knowledge.

Clinical and Epidemiological Research Has Identified Scores of Environmental and Occupational Carcinogens to which Millions of Persons are Exposed

Since the pioneering observations of Sir Percival Pott, who recognized in 1775 that chronic occupational exposure to soot could cause cancer of the scrotum in chimney sweeps (Pott 1775), numerous specific and potentially preventable causes of cancer have been discovered and confirmed through clinical and epidemiological studies and long term carcinogenicity bioassays on rodents. These include asbestos, aflatoxin, benzene, diesel exhaust, dioxin, ethyl alcohol, ethylene oxide, human papilloma virus (HPV), plutonium, radium, solar radiation, tobacco and vinyl chloride monomer. The International Agency for Research on Cancer currently lists 116 proven (“sufficient”) causes of human cancer and 70 probable causes (IARC)(11).

Despite the fact that hundreds of millions of persons around the world are regularly exposed to these known carcinogens, the Tomasetti-Vogelstein analysis dismisses the significance of carcinogenic exposures in the environment and workplace with the terse statement that environmental carcinogens apply “only to specific populations exposed to potent mutagens or viruses”.

Cancer Caused by Known Carcinogens Can Be Prevented

Preventive actions based on epidemiological and toxicological evidence have successfully prevented hundreds of millions of cancer cases and deaths. These preventive actions have included bans on the use of certain hazardous materials, regulations limiting exposures to

carcinogens in the workplace and controlling emissions to the environment, redesigns of industrial processes, environmental clean-ups and public education.

Evidence-based interventions have successfully limited exposures to many known and probable carcinogens including tobacco, arsenic, asbestos, benzene, vinyl chloride and air pollution (Gee et al. 2013) (12). Tobacco campaigns have saved 8 million lives in the US alone (Holford et al. 2014). Discontinuation of industrial use of aniline dyes in most OECD countries has produced a significant reduction in bladder cancer incidence among textile and dye workers (Clapp et al. 2008). Fifty-five countries have now endorsed the Global Ban of Asbestos thus protecting over 1 billion people against this proven carcinogen.

Failure to prevent exposures to known carcinogens is clearly associated with increased cancer incidence and mortality. The continuing use of asbestos in too many countries around the world is a case in point. Approximately 2 million tons of new asbestos are still produced and used each year, and WHO estimates that about 125 million people continue to be occupationally exposed to asbestos (WHO 2014). The annual burden of cancer deaths due to current occupational exposures to asbestos is estimated to be 100,000–140,000. In Western Europe, North America, Japan, and Australia 20,000 new cases of lung cancer and 10,000 cases of mesothelioma result every year from past exposures to asbestos (Tossavainen 1997). It is estimated that the asbestos cancer pandemic may claim as many as 10 million lives before asbestos is banned worldwide and all exposure is brought to an end (LaDou 2004). These deaths are almost entirely preventable (Ramazzini 2011).

Tomasetti and Vogelstein, ignoring this evidence, attribute to “bad luck” certain type of cancers that are well known to be caused by exposures to environmental carcinogens, including cancers caused by asbestos (lung cancer in non-smokers, ovarian cancer, head and neck cancer, laryngeal cancer)(IARC 2012a), cancers caused by alcohol (esophageal cancer, hepatocellular cancer)(IARC 2012b) and cancers caused by benzene (acute myeloid leukemia) (IARC 2012c).

The False Claims of Tomasetti and Vogelstein Pose Serious Danger to Cancer Prevention

The positions taken by Tomasetti and Vogelstein in their *Science* article (Tomasetti and Vogelstein 2015b) and in subsequent statements to the media (Tomasetti and Vogelstein 2015a) dismiss the significance of efforts by governments to identify and control exposures to carcinogens in the workplace, environment and the food supply. They also diminish the importance of decisions made by individuals to change lifestyles and diets to reduce exposures to known carcinogens. Tomasetti and Vogelstein offer these ill-considered remarks despite the fact that cancer prevention policies have been demonstrated to be both effective and cost-effective (Chokshi and Farley 2012).

The Collegium Ramazzini condemns Tomasetti and Vogelstein’s remarks as dangerous to public health.

Undisclosed Conflicts of Interest

In matters of great importance to science, medicine, public health and policy, the scientific community and the public have a right to know the financial interests of authors (Medicine 2009) (ICMJE), #2952). The Collegium Ramazzini endorses the importance of transparency. The

principle of transparent disclosure is adopted also by the Cochrane Collaboration (Bero 2013) (Lundh et al. 2012), the World Health Organization and many governmental bodies.

In their recent publication in *Science* (Tomasetti and Vogelstein 2015b), Tomasetti and Vogelstein failed to disclose potentially important financial conflicts of interest. Dr. Vogelstein is a founder of Personal Genome Diagnostics, Inc, a company focused on the identification of genetic alterations in human cancer for diagnostic and therapeutic purposes. He is also a member of the Scientific Advisory Board of Inostics, a company that is developing technologies for the molecular diagnosis of cancer using plasma samples (Cavallo 2013) (28). While this potentially relevant information on conflict of interest is missing in the abovementioned paper in *Science* (Tomasetti and Vogelstein 2015b), Vogelstein has previously disclosed this information to the American Society of Clinical Oncology (Cavallo 2013) and also in a recent article in a *Science* journal (Roberts et al. 2012).

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