Are certain types of cancer the result of random mutations “bad luck”?
Or cancer risk is heavily influenced by environmental-lifestyle factors?

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Most cancer risk factors were identified in the past decades by specialized epidemiological studies. The most important are: Ageing; Tobacco use; Dietary factors; Physical inactivity; Obesity; Hormones, Sexual behaviour; Sunlight exposure; Alcohol consumption; Chronic inflammation; Occupational carcinogens; and Genetic factors. A paper by Tomasetti and Vogelstein (*Science* 347:78-81, 2015) led to assertions that certain forms of cancer are mainly the result of “bad luck”, and suggested that these types would be relatively resistant to prevention efforts.....
Are certain types of cancer the result of random mutations “bad luck”?  
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Athanasis Valavanidis  
Department of Chemistry, National and Kapodistrian University of Athens, University  
Campus Zografou, 15784 Athens, Greece

Abstract

Most cancer risk factors were identified in the past decades by specialized epidemiological studies. From global and national statistical evidence the major risk factors of cancer to humans are: Ageing; Tobacco use (active and passive smoking); Unhealthy Dietary factors; Physical inactivity; Overweight and obesity; Hormones, sexual behaviour; Radiation and sunlight exposure; Alcohol consumption; Chronic inflammation; Occupational carcinogens; Genetic factors. Cancer is the result of accumulation of DNA damage through incomplete repair because of ageing and may lead to mutagenesis and initiation of carcinogenic mechanisms. A paper by Tomasetti and Vogelstein (Science 347:78-81, 2015, from Johns Hopkins University, USA) projected with data the argument that differences in inherent cellular processes (normal stem-cell division in healthy tissue) are the chief reason that some tissues become cancerous more frequently than others. This paper led to assertions that certain forms of cancer are mainly the result of “bad luck”, and suggested that these types would be relatively resistant to prevention efforts. The question of random mutations and “bad luck” on cancer brought the question of prominence of environmental (extrinsic) versus inherited (intrinsic) causes of cancer. Scientists supported until now that environmental factors and lifestyle causes were supposed to be responsible most types of cancer and were preventable through healthier diet style, cessation of smoking and better diagnosis and . The new hypothesis caused many comments and rebuttals by other experts of cancer. Data presented (Wu et al., 2016) argued that the models that were used suggested that mutations during cell division rarely build up to the point of producing cancer, even in tissues with relatively high rates of cell division. In almost all cases, the team found that some exposure to carcinogens or other environmental factors would be needed to trigger disease. This review presents the main arguments supporting “bad luck” and the counter arguments for extrinsic or environmental causes of cancer and comments from well known scientists. Also, the most important causes of cancer, such as diet, tobacco use, obesity, lack of physical activity, alcohol consumption, exposure to sunlight, infectious agents are described with recent literature studies and epidemiological evidence. Additionally, scientific evidence on the campaign “war on cancer” in the developed countries, to diagnose, treat and cure cancer is making steady progress in the last decades.
Introduction: What are the most important cancer risk factors

Epidemiological studies are the primary type of research that analyse mortality data and identify cancer risk factors. Cancer epidemiologists investigate and record data for a long period of time at large groups of people and compare those who develop cancer with those who don’t. These studies may show that the people who develop cancer are more or less likely to behave (lifestyle) in certain ways or to be exposed to certain carcinogenic substances than those who do not develop cancer. It has been estimated that 1/3 burden of cancer in developed and developing countries can be traced to modifiable health behaviours that increase one’s risk of disease.1-3

From global and national statistical evidence in the last decades, the major risk factors to cancer incidence and mortality in humans are:

a. Advancing Age; it is the most important risk factor for cancer overall. Statistical data from National Cancer Institute (NCI, USA): Surveillance, Epidemiology, and End Results program, established that the median age of a cancer diagnosis is 66 years and 25% of new cancer cases are diagnosed in people aged 65 to 74,

b. Tobacco use (active and passive smoking),

c. Dietary factors (risk increases with poor or insufficient diet in fruit, vegetables, fibre and vitamins, excess consumption of animal fat and red/processed meat, salted and smoked foods ),

d. Physical inactivity, lack of exercise,

e. Overweight and obesity,

f. Radiation and sunlight exposure (UV, mainly skin cancer)

g. Alcohol consumption,

h. Chronic inflammation,

i. Exposure to cancer causing substances (occupational, environmental, car exhaust, urban air pollution, indoor smoke-stoves in unventilated rooms, etc),

k. Genetic factors, inherited faulty genes [Inherited genetic mutations play a major role in about 5-10% of all human cancers].

These extrinsic (environmental) and intrinsic factors for cancer risk have large impacts on the incidence of other major diseases, such as cardiovascular disease (CDV), stroke, diabetes, and osteoporosis. Scientists have been argued that 50% of all cancers in industrially developed and affluent societies could be avoided by nonsmoking, reducing alcohol consumption, weight control and physical activity, a plant-based diet, and breast-feeding. Scientists and medical practitioners in cancer diagnosis, treatment and prevention agree that the most important cancer risk factors for humans are: Age, Tobacco smoke (active, passive), Diet, Obesity and Lack of exercise, Alcohol, Cancer-Causing Substances (occupational, environmental), Chronic Inflammation, Hormones Immunosupression, Infectious Agents, Radiation, Sunlight (especially UV radiation).

Cancer is a genetic disease caused by certain changes to genes that control the way human cells function, how they grow and divide. Cancer is caused by changes (mutations) to the cellular DNA within cells. The DNA inside a cell is packaged into a large number of individual genes, each of which contains a set of instructions telling the cell what functions to perform, as well as how to grow and divide. Mutations cause errors in the instructions that can cause the cell to stop its normal function and may allow a cell to become cancerous. Normal cells know when to stop growing whereas cancer cells lose the controls (tumour suppressor genes) that tell them when to stop growing. A mutation in a tumour suppressor gene allows cancer cells to continue growing and accumulating.

Recent scientific debate. Are certain forms of cancer the result of “bad luck”?

All multicellular aerobic organisms use oxygen for fundamentals metabolic cellular mechanisms, electron transport processes and important physiological
functions. But in the process, a small part of oxygen and nitrogen free radicals and Reactive Oxygen Species (ROS) are leaked in mitochondrial reactions, in tissues and organs. These intracellular oxidative species play an important physiological role but also exert on a daily basis damaging oxidative reactions which produce oxidative stress. This free radical attack has exogenous or endogenous (intracellular) origin. All eukaryotic cells withstand and counteract free radicals and ROS occurrence by the use of several antioxidant enzymatic defense mechanisms (glutathione, superoxide dismutase, catalase, peroxidases, etc) and free radical scavengers (small antioxidant molecules, vitamins C and E, uric acid, etc). Despite all these protective mechanisms DNA and RNA oxidative damage is happening on a daily base. But cells are using sophisticated and elaborate DNA repair enzymatic mechanisms which repair damaged DNA. The outcome of this dynamic equilibrium is usually the induction of oxidatively induced lesions, double strand breaks, and certain mutations. The accumulation of DNA damage through misrepair or incomplete repair because of ageing may lead to mutagenesis and initiation of carcinogenic mechanisms. In the last decades there is substantial accumulation of knowledge and evidence on the mechanisms and involvement of intracellular oxidative stress and DNA damage in human malignancy. These damages have evolutionary origins. Some specific DNA damage can be used as cancer biomarkers (such as 8-hydro-2’-deoxyguanosine). 

In 2015, an article in the prestigious American journal Science (Tomasetti and Vogelstein, Science 347:78-81, 2015, the first a mathematician and the second a cancer expert in Johns Hopkins University, USA) projected an argument that differences in inherent cellular processes are the chief reason that some tissues become cancerous more frequently than others. This paper led to assertions that certain forms of cancer are mainly the result of “bad luck”, and suggested that these types would be relatively resistant to prevention efforts.

In their article Tomasetti and Vogelstein argued that some human tissue types give rise to human cancers millions of times more often than other types. The lifetime risks of cancer of many different types is strongly correlated (high correlation coefficient, 0.81) with the total number of divisions of the normal self-renewing cells maintaining that tissue’s homeostasis. These results according to the two scientists suggest that only 1/3 of
the variation in cancer risk among tissues is attributable to environmental factors (i.e. are preventable) or inherited predispositions. The argument is that Intrinsic factors, inherent cellular processes, are the chief reason that some biological tissues or organs become more frequently cancerous. The argument is that in every instance of cell division there is an additional risk that DNA will be incorrectly copied, leading to mutations — some of which could contribute to cancer.  

The question of random “bad luck” on cancer brought the question of prominence of environmental (extrinsic) versus inherited (intrinsic) causes of cancer. Vogelstein and Tomasetti argued that stem cell divisions in healthy cells and random mutations (or what we can call “bad luck”) accumulated and became the drive for the development of cancer in different tissues. The implication to this hypothesis is that cancer diseases will be harder to prevent. The “bad luck” proposal sparked controversy and confusion among cancer experts.

In 2017 the same research team (Johns Hopkins University, Kimmel Cancer Centre, Baltimore, USA) behind the previous study (2015) has taken their analysis further, publishing their findings in the high-profile journal Science. And as the first paper caused quite a stir, it’s no surprise that the results have been picked up in the media again.

The researchers in their new paper back up their previous conclusions, adding further evidence to their mathematical theory that cancer risk is most strongly associated with how quickly specialized stem cells, replicate. They predict that mutations in 2 in 3 cancers are ‘due to bad luck’, which they define as the random genetic mistakes that occur naturally in cells as they divide, and may lead to cancer. The researchers looked at data from 32 types of cancer in patients from 69 countries. And they tried to link cancer-causing genetic faults (mutations) to different causes: inheritance, lifestyle/environment, and (the one they focus on) random errors that occur when cells divide. “As a mathematical exercise to study mutations in cancer, the 2017 paper is well done and interesting,” says Professor Richard Gilbertson, director of Cancer centre in Cambridge (UK). “But we have to remember that this study uses existing data to generate a correlation and hypothesis – it’s not a definitive answer to a very complex problem.” But one of the biggest problems, Gilbertson says, is that trying to get a clear answer of cause and
effect from the analysis might oversimplify things. They’ve taken an approach focused too heavily on mutations, and while mutations are very important for cancer, the disease can’t be boiled down solely to specific mutations,” [Walsh M. Reports that cancer is ‘mainly bad luck’ make a complicated story a bit too simple. Science blog, 24.3.2017, Cancer Research UK].

Many cancer experts took part in the following debate. Other scientists have agreed that the complicated nature of cancer makes it tricky to reduce multiple cases of cancer to single cause. They noticed that “… any model attempting to fully describe cancer risk needs to take into account a variety of extrinsic factors that influence cancer development and progression of tumours without inducing gene mutations (inflammation, immune response and tumour microenviroment) [http://scienceblog.cancerresearchuk.org/2017/03/24/reports-that-cancer-is-mainly-bad-luck-make-a-complicated-story-a-bit-too-simple/ ].

The debate of “bad luck” hypothesis in cancer risk

The debate on the subject of ‘bad luck’ continue. In 2016 a scientific article by Wu, Powers, Zhu and Hannun (Nature 529: 43-47, 2016, from Stony Brook University, New York), questioned with facts the initial argument that there are high unavoidable intrinsic cancer risk factors due to the “bad luck” hypothesis. They provided evidence that intrinsic risk factors contribute only modestly (less than ~10-30% of lifetime risk) to cancer development. They showed that the rates of endogenous mutation accumulation by intrinsic processes are not sufficient to account for the observed cancer risks and concluded that cancer risk in humans is heavily influenced by extrinsic (environmental) factors which can be prevented (such as smoking, diet, exposure to occupational carcinogens, etc).12

The debate on the hypothesis of “bad luck” cancer risk on intrinsic factors and their role in prevention of cancer morbidity and mortality attracted the attention of many scientists worldwide.13 Opinions of other scientists and cancer specialists appeared in the most important scientific cancer journals. “There’s no question what’s at stake here,” said in an interview, John Potter of the Fred Hutchinson Cancer Research Center (Seattle, Washington), who studies causes of
cancer. “This informs whether or not we expend energy on prevention.” The scientists from Stony Brooks university Wu, Hannun and colleagues rebutted the hypothesis by using other lines of evidence to try to pinpoint the contribution of environmental (extrinsic) factors to cancer risk to humans.\(^\text{12}\) They looked at epidemiological data showing that, for example, people who migrate from regions of lower cancer risk to those with higher risk (for example, emigrants from Japan in the USA) soon develop disease at rates consistent with their new environment (exposed to different diet and other extrinsic factors). The authors also examined patterns in the mutations associated with certain cancers; ultraviolet light, for example, tends to create a tell-tale signature of mutations in DNA. And they used other mathematical models, expanding the data set used in the earlier work to include prostate and breast cancer — two of the most common cancers.\(^\text{13}\)

The scientists (Wu et al., 2016) argued that the models that were used suggested that mutations during cell division rarely build up to the point of producing cancer, even in tissues with relatively high rates of cell division. In almost all cases, the team found that some exposure to carcinogens or other environmental factors would be needed to trigger disease. Tomasetti counters that he never intended to explain why cancers develop. His analysis, he says, was based on normal stem-cell division in healthy tissue and was meant to explain only why some cancers are more prevalent than others. He also argues that the models created by Wu, Hannun and colleagues make too many assumptions and fail to incorporate some features of tumour growth.\(^\text{13}\)

Both solid tumours and leukaemias show considerable histological and functional heterogeneity. It is widely accepted that genetic lesions have a major role in determining tumour phenotype, but evidence is also accumulating that cancers of distinct subtypes within an organ may derive from different ‘cells of origin’. These cells acquire the first genetic hit or hits that culminate in the initiation of cancer. The identification of these crucial target cell populations may allow earlier detection of malignancies and better prediction of tumour behaviour, and ultimately may lead to preventive therapies for individuals at high risk of developing cancer.\(^\text{14}\) The Nature (2016) article included a series of Tables and Figures with extended data on epidemiological studies for extrinsic risk.\(^\text{14}\)
Table 1. Epidemiological studies on the extrinsic risks of various cancers (extended data 2).

https://www.nature.com/articles/nature16166/tables/2  and  


<table>
<thead>
<tr>
<th>Cancer Types</th>
<th>Extrinsic risk</th>
<th>Examples of potential extrinsic risk factors*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>substantial</td>
<td>Oral contraceptive, hormone replacement therapy, lifestyle (diet, smoking, alcohol, weight)</td>
</tr>
<tr>
<td>Prostate</td>
<td>substantial</td>
<td>Diet, obesity, smoking</td>
</tr>
<tr>
<td>Lung</td>
<td>&gt;90%</td>
<td>Smoking; air pollutant</td>
</tr>
<tr>
<td>Colorectal</td>
<td>&gt;75%</td>
<td>Diet, smoking, alcohol, obesity</td>
</tr>
<tr>
<td>Melanoma</td>
<td>65-86%</td>
<td>Sun exposure</td>
</tr>
<tr>
<td>Basal cell</td>
<td>~90%</td>
<td>UV</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>~80%</td>
<td>HBV, HCV</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>65-80%</td>
<td>H. pylori</td>
</tr>
<tr>
<td>Cervical</td>
<td>~90%</td>
<td>HPV</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>~75%</td>
<td>Tobacco, alcohol</td>
</tr>
<tr>
<td>Esophageal</td>
<td>&gt;75%</td>
<td>Smoking, alcohol, obesity, diet</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>~70%</td>
<td>HPV</td>
</tr>
<tr>
<td>Thyroid</td>
<td>&gt;72%</td>
<td>Diet low in iodine, radiation</td>
</tr>
<tr>
<td>Kidney</td>
<td>&gt;58%</td>
<td>Smoking, obesity, workplace exposures</td>
</tr>
<tr>
<td>Thymus</td>
<td>&gt;77%</td>
<td>Largely unclear</td>
</tr>
<tr>
<td>Small intestine</td>
<td>&gt;61%</td>
<td>Diet, smoking, alcohol</td>
</tr>
<tr>
<td>Extramedullary non-Hodgkin's lymphoma (NHL)</td>
<td>&gt;71%</td>
<td>Chemicals, radiation, immune system deficiency</td>
</tr>
<tr>
<td>Testis</td>
<td>&gt;45%</td>
<td>Largely unclear</td>
</tr>
<tr>
<td>Anal and anorectal cancers</td>
<td>&gt;63%</td>
<td>HPV, smoking</td>
</tr>
</tbody>
</table>

Another Table of extended data that was added in the article by Wu et al. (Nature, 2016) to support their argument.
Table 2. Extended Data Table 3: Percentages of intrinsic versus extrinsic MS (mutational signatures) with known and unknown causes in different cancer types (Wu et al, Nature 2016)

From: Substantial contribution of extrinsic risk factors to cancer development

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Intrinsic MS</th>
<th>Extrinsic MS - Known</th>
<th>Extrinsic MS - Unknown</th>
<th>Extrinsic MS - Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>65.8</td>
<td>34.2</td>
<td>0</td>
<td>34.2</td>
</tr>
<tr>
<td>AML</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bladder</td>
<td>14.2</td>
<td>71.2</td>
<td>14.6</td>
<td>85.8</td>
</tr>
<tr>
<td>Breast</td>
<td>35.5</td>
<td>60.1</td>
<td>4.4</td>
<td>64.5</td>
</tr>
<tr>
<td>Cervical</td>
<td>25.3</td>
<td>74.7</td>
<td>0</td>
<td>74.7</td>
</tr>
<tr>
<td>CLL</td>
<td>76.7</td>
<td>23.3</td>
<td>0</td>
<td>23.3</td>
</tr>
<tr>
<td>Colorectal</td>
<td>17.1</td>
<td>66</td>
<td>16.9</td>
<td>82.9</td>
</tr>
<tr>
<td>Esophageal</td>
<td>48</td>
<td>25.3</td>
<td>26.7</td>
<td>52</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>53.8</td>
<td>0</td>
<td>46.2</td>
<td>46.2</td>
</tr>
<tr>
<td>Glioma-Low Grade</td>
<td>9.2</td>
<td>2.8</td>
<td>88</td>
<td>90.8</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>24.9</td>
<td>75.1</td>
<td>0</td>
<td>75.1</td>
</tr>
<tr>
<td>Kidney Chromophobe</td>
<td>17.4</td>
<td>37.5</td>
<td>45.1</td>
<td>82.6</td>
</tr>
<tr>
<td>Kidney Clear Cell</td>
<td>66.5</td>
<td>4.1</td>
<td>29.4</td>
<td>33.5</td>
</tr>
<tr>
<td>Kidney Papillary</td>
<td>0</td>
<td>15.7</td>
<td>84.3</td>
<td>100</td>
</tr>
<tr>
<td>Liver</td>
<td>10.9</td>
<td>21.3</td>
<td>67.8</td>
<td>89.1</td>
</tr>
<tr>
<td>Lung Adenocarcinoma</td>
<td>9.1</td>
<td>73.8</td>
<td>17.1</td>
<td>90.9</td>
</tr>
<tr>
<td>Lung - Small Cell</td>
<td>0</td>
<td>92.8</td>
<td>7.2</td>
<td>100</td>
</tr>
<tr>
<td>Lung-Squamous</td>
<td>0</td>
<td>47</td>
<td>53</td>
<td>100</td>
</tr>
<tr>
<td>Lymphoma B-cell</td>
<td>46.3</td>
<td>33.4</td>
<td>20.3</td>
<td>53.7</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>48.4</td>
<td>0</td>
<td>51.6</td>
<td>51.6</td>
</tr>
<tr>
<td>Melanoma</td>
<td>7.2</td>
<td>90.9</td>
<td>1.9</td>
<td>92.8</td>
</tr>
<tr>
<td>Myeloma</td>
<td>0</td>
<td>19.9</td>
<td>80.1</td>
<td>100</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>53.2</td>
<td>0</td>
<td>46.8</td>
<td>46.8</td>
</tr>
<tr>
<td>Ovarian</td>
<td>36.6</td>
<td>63.4</td>
<td>0</td>
<td>63.4</td>
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<tr>
<td>Pancreatic</td>
<td>49.9</td>
<td>50.1</td>
<td>0</td>
<td>50.1</td>
</tr>
<tr>
<td>Pilocytic Astrocytoma</td>
<td>82.5</td>
<td>0</td>
<td>17.5</td>
<td>17.5</td>
</tr>
<tr>
<td>Prostate</td>
<td>32.2</td>
<td>10.2</td>
<td>57.6</td>
<td>67.8</td>
</tr>
<tr>
<td>Stomach</td>
<td>22.3</td>
<td>6.1</td>
<td>71.6</td>
<td>77.7</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0</td>
<td>39.7</td>
<td>60.3</td>
<td>100</td>
</tr>
<tr>
<td>Uterine</td>
<td>10.7</td>
<td>65.5</td>
<td>23.8</td>
<td>89.3</td>
</tr>
</tbody>
</table>

*Intrinsic mutational signatures (MS) includes signatures 1A/B, and extrinsic MS includes signatures 2–21, R1–R3, U1 and U2, excluding signature 11 for Temozolomide, an alkylating agent used for chemotherapy. The blue, yellow and red colours highlight cancers that are have substantial extrinsic risk proportions based on epidemiological data, MS with known causes and MS with unknown causes, respectively. Data from the supplementary figs 59–88. Reference. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature 500, 415–421 (2013).
Some specialists in cancer prevention welcome the *Nature* paper because of fears that the public — and possibly also funders of scientific research — might conclude that prevention efforts are not worthwhile, Prof. Edward Giovannucci, who is well known researcher on cancer prevention at the prominent Harvard University T. H. Chan School of Public Health in Boston, Massachusetts (USA) took part in the debate of “bad luck” in lifetime cancer risk. Prof. Giovannucci stated “…the paper by Tomasetti and Vogelstein demonstrated a high correlation coefficient of 0.81 between estimated lifetime normal renewing cell (stem cell) divisions among tissues in the body and the lifetime cancer risk in that organ. This finding has been interpreted frequently to suggest that if 2/3 of cancers arise primarily through normal proliferation then environmental and hereditary factors combined could explain only 1/3 of cancers. Yet, the pool of dividing stem cells is what risk factors act upon; it is unlikely that risk factors and proliferation act completely independently and are simply additive; thus, there is no constraint that stem cell proliferation and environmental/genetic attributable risk sum to 100%. The cancers illustrated to represent lifetime risk in the paper by Tomasetti and Vogelstein all implicitly incorporate risk factors common in the USA (example, obesity, physical inactivity, tobacco, alcohol, diet, infectious agents). In fact, there is little evidence that a cancer would exceed a substantial rate, such as greater than 1% lifetime risk, in the absence of an important risk factor. Relatively high rates of cancer (eg, > 1% lifetime risk) only seem to occur in organs when strong risk factors (example, 10- to 20-fold) are superimposed on relatively high stem cell division. In organs with low stem cell divisions, the lifetime cancer risk will typically be very low. The major types and most abundant cancers in a given population will arise from tissues that have relatively high stem cell division rates and that have a high prevalence of strong relevant risk factors…”.

The debate continued with some scientists publishing their opinion on the subject on the Tomasetti and Vogelstein hypothesis. “…they argued that lifetime cancer risk for particular tissues is mostly determined by the total number of stem cell (SC) divisions within the tissue, whereby most cancers arise due to “bad luck”—mutations occurring during DNA replication. In our opinion the poorly substantiated
estimations of SC division parameters and assumptions that oversimplify somatic evolution prevent such a conclusion from being drawn”.  

Another group of scientists noted “…Deciphering the relative contribution of intrinsic (e.g., genetic) and extrinsic (e.g., lifestyle, environmental) risk factors in cancer development is crucial for strategizing cancer prevention. The recent publication by Wu and colleagues in Nature (2016) appears as an important contribution to the debate previously initiated by Tomasetti and Vogelstein in Science (2015), who proposed that 2/3 of cancers can be attributed to random mutations and hence 'bad luck'. By contrast, Wu and colleagues, using four lines of evidence, suggest that cancer risk is dominated by extrinsic factors, and intrinsic risk factors only contribute marginally. The debate remains open, and an approach focusing on the evolutionary ecology of organs could provide crucial insights”.

A scientist from Russia (Blokhin Cancer Research Center, Moscow, with expertise in Oncology) noted “…Contrasting opinions on the role of extrinsic and intrinsic factors in cancer etiology [Tomasetti, C., and Vogelstein, B. (2015) Science, 347, 78-81; Wu, S., et al. (2016) Nature, 529, 43-47] variously define priorities in the war on cancer. The correlation between the lifetime risk of several types of cancer and the total number of divisions of normal self-renewing cells revealed by the authors has given them grounds to put forward the "bad luck" hypothesis. It assumes that ~70% of cancer variability is attributed to random errors arising during DNA replication in normal, noncancerous stem cells, i.e. to internal factors, which is impossible either to expect or to prevent. This assumption caused many critical responses that emphasize, on the contrary, the defining role of extrinsic factors in cancer etiology. The analysis of epidemiological and genetic data presented in this work testifies in favour of the "bad luck" hypothesis".

In the last decades the medical and pharmacological advances in the case of human cancer has been directed in worldwide educational campaigns of prevention (changes in lifestyle and diet) and the timely diagnosis in the initial stage of neopastic tumours. So, it is crucial to know how important are the relative contribution of intrinsic (e.g., genetic, inherited) and extrinsic (e.g., lifestyle, environmental) risk factors in cancer development. Researchers have long followed the strategy that in order to achieve a fuller understanding of the causes of cancer
and how can be prevented, it is necessary to study the biochemical and physiological processes involved in the etiology of neoplastic tumours.\textsuperscript{19}

According to other scientists “…The argument based on reproduction of cells and the accumulation of mutations is clearly prone to generating false conclusions. This is consistent with the hypothesis proposed here regarding the limitations of mechanistic research. But the alternative strategy, which in the case of the paper by Wu et al. (\textit{Nature} 2016), refers only to epidemiology, has provided convincing evidence that most cancer is directly related to lifestyle and environmental factors.\textsuperscript{20} The famous 1981 paper of Doll and Peto (JNCI, 1981) established without doubt and was supported later by more epidemiological studies that extrinsic factors (lifestyle and environmental exposures) play an important role in cancer risk. Evidence has accumulated, mostly from cohort studies and case-control studies, demonstrating that excess alcohol and red or processed meat consumption increases the risk of various types of cancer.\textsuperscript{21,22} In the other hand, there are studies for the preventive action of some chemicals in our diet, such as selenium (especially cancer of the lung and prostate) and vitamin D… “.\textsuperscript{23-26}

\textbf{Extrinsic causes of cancer}

\textbf{Tobacco smoking, the leading cause worldwide of human cancer}

Tobacco use is the leading worldwide cause of cancer – and it is avoidable. Cigarette smoking is the most dangerous extrinsic cause of cancer and other diseases. Breathing the smoke of tobacco is the number one risk factor for lung cancer and it is responsible for 87\% of lung cancer deaths worldwide. Tobacco smoking, especially active smoking (compared to passive smoking) is a leading cause worldwide of initiation and promotion of a large number of cancers and of premature deaths. Tobacco causes many types of cancer, such as lung, larynx, mouth, esophagus, throat, breast, bladder, kidney, liver, stomach, pancreas, colon, rectum, cervix, as well as acute myeloid leukemia. Scientific studies established that here are over 60-80 known carcinogens in cigarette smoke, the most important of which are polycyclic aromatic hydrocarbons, N-nitrosamines, aromatic amines, and oxidative stable radical in tar.\textsuperscript{27-31}

It is estimated by WHO that smoking is responsible for 6 million premature deaths from cancer and other diseases every year worldwide (WHO cancer
prevention, http://www.who.int/cancer/prevention/en/). Recent research have established that about 50% of all Americans who keep smoking will die prematurely because of the habit. Each year in the USA 160,000 people die each year from various types of cancer, but in total 480,000 people in the USA die from cancer and other diseases related to tobacco use. Each year smoking causes about 20% of deaths in the USA. People who smoke (cigarettes, cigars or other products) for long period and more than 20 cigarettes per day or who are regularly breath environmental tobacco smoke (also called secondhand or passive smoke) have an increased risk of cancer, especially lung cancer. Studies showed that secondhand smoke in the USA causes more than 7,000 lung cancer deaths (premature) each year.\textsuperscript{32}

The tobacco smoke and the production of some of the most carcinogenic chemical substances many of which are highly oxidative and can damage protein enzymes, cellular membrane lipids and cellular and mitochondrial DNA in the various organs.\textsuperscript{33}

**Smoking cessation and decreased risk of lung cancer**

In the last decade around 35% of males and 6% of females around the world smoke tobacco. The number of adults worldwide who smoke tobacco has decreased in recent years. Awareness of the dangers of smoking, costs, and targeted policies and campaigns have all contributed to this decrease. Many epidemiological studies were contacted in developed countries to establish the reduction of lung cancer risk for people who reduced substantially smoking. For example, an observational population-based cohort study with up to 31 years of follow-up was contacted from the Copenhagen Centre for Prospective Population Studies, which administrates data from 3 longitudinal studies conducted in Copenhagen and suburbs, the Copenhagen City Heart Study, the Copenhagen Male Study, and the Glostrup Population Studies, Denmark. Participants were 11,151 men and 8563 women aged 20 to 93 years, who attended 2 consecutive examinations with a 5- to 10-year interval between 1964 and 1988. The results showed that among individuals who smoke 15 or more cigarettes per day, smoking reduction by 50% significantly reduced the risk of lung cancer.\textsuperscript{34}
Figure 1. Tobacco smoking (active and passive) is considered the most important extrinsic factor for various cancers in humans. It is estimated by WHO that smoking is responsible for 6 million premature deaths from cancer and other diseases every year worldwide.

Another study in the USA on the reduction of smoking among Americans calculated that ~ 795,851 US lung cancer deaths were averted during the period 1975–2000 due to the reduction in smoking habits among the population. These numbers were estimated to represent approximately 32% of lung cancer deaths that could have potentially been averted during the period 1975–2000. This result represents the cumulative impact of changes in smoking behavior since the 1950s in the USA. Expert on cancer support the continued efforts at tobacco control as a critical factor in reducing the burden of lung cancer.35

Tobacco control efforts are having a major impact in USA. A new analysis of cancer data of lung-cancer suggests. The rate of new lung cancer cases (incidence rate) decreased among men and women in the USA from 2005 to 2009, according to a report in this week’s Morbidity and Mortality Weekly Report. The study also found that lung cancer incidence rates went down 2.6% per year among men, from 87 to 78 cases per 100,000 men and 1.1% per year among women, from 57 to 54 cases per 100,000 women. The fastest drop in lung cancer was among adults aged 35-44 years, decreasing 6.5% per year among men and 5.8% per year among women.36

Two large case-control studies were contacted for the 1950-1990 in the United Kingdom (UK). The studies found that for men in early middle age in the UK the prevalence of smoking between 1950-1990 was reduced by 50% but the death rate from lung cancer (at ages 35-45) was reduced even more rapidly, indicating some reduction in the risk for lung cancer among continuing smokers. By 1990
cessation of smoking had almost reduced by 50% lung cancers that would have expected if the former smokers had continued smoking. For men who stopped smoking at ages 60, 50, 40 and 30 the cumulative risks of lung cancer by age 75 were 10%, 6%, 3% and 2%.  

Another large study in the USA used the National Health Interview Surveys which provided cigarette smoking histories for the US adult population in the period 1964-2012. The study estimated that around 17.7 million deaths in the USA were related to smoking. Researchers calculated that tobacco control (intensive campaign for many years to stop smoking among Americans) was estimated to be associated with avoidance of 8 million premature deaths (USA) and an estimated extended mean life span of 19 to 20 years. Although tobacco control represents an important public health achievement in the USA, efforts must continue with the same determination to reduce the effect of smoking on the nation’s death toll.

An epidemiological study in California used age-adjusted incidence rates of lung and bladder cancer (which are caused by smoking) and prostate and brain cancer (which are not) in the San Francisco-Oakland (SFO) Surveillance Epidemiology End Results (SEER) registry and other 8 SEER registries from 1975 to 1999. Cigarette consumption over time was also analyzed and related to lung cancer incidence. The study established that during the first decade, the tobacco control program was associated with about a 6% reduction in lung cancer incidence (state-wide that corresponds to about 11,000 cases avoided). Also, with a three year lag, the incidence of bladder cancer fell by −0.234 (cases/100,000/year)/year. No association of the program was observed on prostate or brain cancers in SFO.

The tobacco control efforts in the last decades in many European countries influence the drop in lung cancer death in the decade 2002-2012. For men, overall lung cancer mortality between 2002 and 2012 decreased by 13.5% in the European Union. Declines of lung cancer deaths were also noted in several countries worldwide.
Diet, obesity and cancer risk to humans

In 2018 a special issue of the Journal of the Journal of Academy of Nutrition and Dietetics (JAND, Elsevier, April 2018) published a series of articles on the association of diet and cancer risk. Research in the last decades established that about 1/3 of cancer cases are linked to dietary and other modifiable risk factors, especially for obesity-related cancers such as breast, colorectal, ovarian, endometrial, kidney, gallbladder, esophageal, and pancreatic cancers. In the special issue of JAND food and nutrition practitioners and other health professionals took an in-depth look at the relationship between nutrition, obesity, and cancer prevention, treatment, and survival and identified research gaps for future prevention research efforts. The leading institution in the US, American Cancer Society (ACS) estimates there will be more than 1.7 million new cases diagnosed in 2018 and around 610,000 cancer deaths in the USA. Studies strongly suggest that diet is associated with cancer and that obesity increases the risk of many types of cancer as well as several chronic diseases, including type 2 diabetes, cardiovascular disease, hypertension, and chronic inflammation.42

Colorectal cancer (CRC) is a global public health problem (the third most common cancer), with an estimated 1.4 million cases diagnosed worldwide in 2012. Scientific evidence suggests that diet play an important role as a primary cause but also for healthy dietary patterns can be important for primary prevention. A recent review synthesized data from dietary patterns studies over a 17 year period (2000-2016) that included 28 cohort and 21 case-control studies. The review established that a "healthy" dietary pattern, generally characterized by high intake of olive oil, fruits and vegetables, whole grains, nuts and legumes, fish and other seafood, milk and other dairy products, was associated with lower colorectal cancer risk. In contrast, the "unhealthy" pattern, characterized by high intakes of red meat, processed meat, sugar-sweetened beverages, salty and smoked food, refined grains, desserts and potatoes was associated with higher CRC risk. However, researchers noted that “...important questions remain about mechanisms underlying differences in cancer risk by sex, life-course timing of exposure to
dietary patterns; interaction of dietary patterns with the microbiome or with lifestyle factors including physical activity; and elucidation of subsite differences of cancer tissues.  

Many studies in the last decade focused on the Mediterranean diet as a dietary pattern that reduces the risk of cancer, especially colorectal cancer. A recent review evaluated the correlation between three components of the Mediterranean diet (olive oil, red wine, and tomatoes) and incidence and progression of colorectal cancer. As such, the research group conducted a literature search using keywords "colorectal cancer," "dietary pattern," "Mediterranean diet," "olive oil," "protective effects," "resveratrol," and "lycopene." Olive oil polyphenols (antioxidants), red wine resveratrol (antioxidant), and tomato lycopene (antioxidant) showed several characteristics in vitro that interfere with molecular cancer pathways. The review identified many clinical studies that reported an association of these diet components with a reduction in cancer initiation and progression.  

Many studies concentrated on the various beneficial effects of The Mediterranean diet on human health. According to a research group the Mediterranean diet (MD) represents a possible therapy for metabolic syndrome, preventing adiposopathy or "sick fat" formation. Recent studies have demonstrated a relationship between cancer and obesity. In the USA (which represents a country with western diet habits, high in red and processed meats, animal fat), diet represents 30-35% of death causes related to cancer, unlike populations living in the Mediterranean area that have a decreased incidence of cancer compared with populations living in Northern Europe or the USA, likely due to healthier dietary habits. The beneficial effect of MD on reducing colorectal cancer risk was proved in pooled analysis of three recent Italian case-control studies.  

Observational studies of the last years provided new evidence that high adherence to a Mediterranean diet (fruits, vegetables, nut, legumes, fish, olive oil, low fat milk and butter) is associated with reduced risk of overall cancer mortality as well as a reduced risk of incidence of several cancer types (especially cancers of
Breast cancer (BC) is the most common cancer worldwide and cause of cancer death in women, accounting for 23% of all cancers and 13.7% of cancer deaths in 2008. Epidemiological evidence suggests that the Mediterranean diet (MD) could reduce the risk of breast cancer (BC). An epidemiological study investigated the association between adherence to the MD and risk of breast cancer among 335,062 women recruited from 1992 to 2000, in 10 European countries, and followed for 11 years on average. The results of the study showed that adherence to a MD (excluding alcohol) was related to a modest reduced risk of breast cancer in postmenopausal women, and this association was stronger in receptor-negative tumours. The results support the potential scope for BC prevention through dietary modification.48

Every 5 years the American Cancer Society (ACS) publishes Nutrition and Physical Activity Guidelines to serve as a foundation for its communication, policy,
and community strategies and, ultimately, to affect dietary and physical activity patterns among Americans. According to ACS the great majority of Americans who do not use tobacco, the most important modifiable determinants of cancer risk are weight control, dietary choices, and levels of physical activity. 30% of the more than 572,000 cancer deaths that occur in the USA each year can be attributed to diet and physical activity habits, including overweight and obesity, while another 1/3 is caused by exposure to tobacco products.  


According to ACS there is great association of body weight and cancer risk. In the USA (representing a developed country with high calorific diets and consumption of red meat and processed meat), it has been estimated that overweight and obesity contribute to 14% to 20% of all cancer-related mortality. Overweight and obesity are clearly associated with an increased risk of developing many cancers, including cancers of the breast in postmenopausal women, colon
and rectum, endometrium, kidney. Also, adenocarcinoma of the esophagus, and pancreas are probably associated with an increased risk of cancer of the gallbladder. Additionally, these cancers may also be associated with an increased risk of cancer of the liver, non-Hodgkin lymphoma, multiple myeloma, cancer of the cervix, cancer of the ovary, and aggressive prostate cancer. Studies showed that abdominal fatness is convincingly associated with colorectal cancer, and probably related to a higher risk of pancreatic, endometrial, and postmenopausal breast cancer.\textsuperscript{50,51}

In the last decade scientists agree that there is clear evidence that bowel cancer is more common among those who eat the most red and processed meat. Processed meat consumption has also been strongly linked to a higher risk of stomach cancer. The WHO (through the specialized institute of cancer, International Agency for Research on Cancer, IARC, Lyon), has classified processed meats – including ham, salami, bacon and frankfurts – as a Group 1 carcinogen which means that there is strong evidence that processed meats cause cancer. Red meat, such as beef, lamb and pork has been classified as a ‘probable’ cause of cancer. These classifications do not indicate the risk of getting cancer, rather how certain we are that these things are likely to cause cancer. Eating poultry (white meat) and fish may help to reduce the risk of bowel, breast and prostate cancer.\textsuperscript{52,53}

**Alcohol consumption and cancer risk**

Alcohol is the common term for ethanol or ethyl alcohol (CH\textsubscript{3}CH\textsubscript{2}OH), a chemical substance found in beer, wine, and alcoholic liquor (distilled spirits, such as gin, whiskey, vodka, etc with 40-80% alcohol proof). Alcohol is produced by the fermentation of sugars and starches by yeast.

Extensive reviews of research studies, showed strong scientific consensus of an association between alcohol drinking and several types of cancer.\textsuperscript{54} In its Report on Carcinogens, the National Toxicology Program (NTP) of the US Dep. of Health and Human Services lists consumption of alcoholic beverages as a known human carcinogen. Also, IARC research places alcohol consumption and its
metabolic substances in the carcinogenic list. Research evidence indicates that the more alcohol a person drinks the higher his or her risk of developing an alcohol-associated cancer. It is estimated that 3.5% (from 2009) of all cancer deaths in the USA (about 19,500 deaths) were alcohol related.

Alcohol consumption has been linked to cancers of the large bowel (i.e., colon and rectum) in both men and women and to breast cancer in women, although these associations have not yet been proven unequivocally. Nevertheless, because these are the two most common types of cancer in developed countries after lung cancer, even a moderate increase in risk may result in a relatively large number of additional cases. The association between alcohol consumption and other types of cancer (e.g., stomach, pancreatic, prostate, and endometrial cancer) is still controversial.

A large number of studies have established that alcohol consumption is linked to an increased risk for various types of cancer. A combined analysis (meta-analysis) of more than 200 studies assessing the link between alcohol and various types of cancer sought to investigate this association in more detail. This meta-analysis found that alcohol most strongly increased the risks for cancers of the oral cavity, pharynx, esophagus, and larynx. Statistically significant increases in risk also existed for cancers of the stomach, colon, rectum, liver, female breast, and ovaries.

Clear patterns have emerged between alcohol consumption and the development of the following types of cancer:

**Head and neck cancer**: Alcohol consumption is a major risk factor for certain head and neck cancers, particularly cancers of the oral cavity (excluding the lips), pharynx (throat), and larynx. The risks of these cancers are substantially higher among persons who consume alcohol and also use tobacco.

**Esophageal cancer**: Alcohol consumption is a major risk factor for a particular type of esophageal cancer called esophageal squamous cell carcinoma.

**Liver cancer**: Alcohol is an independent risk factor for, and a primary cause of, liver cancer (hepatocellular carcinoma).

**Breast cancer**: More than 100 epidemiologic studies have looked at the association between alcohol consumption and the risk of breast cancer in women. A meta-
analysis of 53 of these studies (total of 58,000 women with breast cancer) showed that women who drank more than 45 g of alcohol per day (approximately three drinks) had 1.5 times the risk of developing breast cancer as nondrinkers. The Million Women Study in the United Kingdom (more than 28,000 women with breast cancer) provided a more recent, and slightly higher, estimate of breast cancer risk at low to moderate levels of alcohol consumption: every 10 g of alcohol consumed per day was associated with a 12% increase in the risk of breast cancer.64

Colorectal cancer: Drinking alcohol is associated with a modestly increased risk of cancers of the colon and rectum. A meta-analysis of 57 cohort and case-control studies that examined the association between alcohol and colorectal cancer risk showed that people who regularly drank 50 g or more grams of alcohol per day (approximately 3.5 drinks) had 1.5 times the risk of developing colorectal cancer as nondrinkers or occasional drinkers.65

Alcohol consumption and other types of cancer. Numerous studies have examined the association between alcohol consumption and the risk of other cancers, including cancers of the pancreas, ovary, prostate, stomach, uterus, and bladder. For these cancers, either no association with alcohol use has been found or the evidence for an association is inconsistent.66-68

It must be added here that alcohol as a chemical is not carcinogenic, but inside the human body ethanol (CH₃CH₂OH) is converted (oxidized) into a toxic chemical called acetaldehyde (CH₃CHO). Animal experiments have clearly shown that acetaldehyde, the first metabolite of ethanol oxidation, is carcinogenic. Acetaldehyde can cause cancer by damaging DNA and stopping human body cells from repairing this damage. The IARC, have classified acetaldehyde formed as a result of drinking alcohol as being a cause of cancer, along with alcohol itself. A number of in vitro and in vivo experiments in prokaryotic and eukaryotic cell cultures, as well as in animal models, have identified acetaldehyde as a mutagen and carcinogen. Acetaldehyde causes point mutations in the hypoxanthine–guanosine–phosphoribosyl transferase locus in human lymphocytes, induces sister chromatide exchanges, and gross chromosomal alterations.69,70
Figure 3. Multiple mechanisms are involved in alcohol-mediated carcinogenesis. Among those the action of acetaldehyde (AA), the first metabolite of ethanol oxidation is of particular interest. AA is toxic, mutagenic and carcinogenic in animal experiments. AA binds to DNA and forms carcinogenic adducts. [Seitz HK, Stickel F. Acetaldehyde as an underestimated risk factor for cancer development: role of genetics in ethanol metabolism. Genes Nutr 5(2):121-128, 2010].

Acetaldehyde also causes liver cells to grow faster than normal. These regenerating cells are more likely to pick up changes in their genes that could lead to cancer. Ethanol is broken down mainly by the liver, but lots of other cell types can do this as well. Some of the bacteria that live in our mouths and the linings of our guts are also able to convert ethanol into acetaldehyde. Also, alcohol can increase the levels of some hormones, such as oestrogen. Hormones act as messengers in the body, giving our cells instructions such as when to divide. Unusually high levels of oestrogen increase the risk of breast cancer.  

**Physical inactivity, lack of exercise and cancer risk**

All humans have every day some kind of physical activity. Physical activity can be during their working time, when exercising, performing household chores, and leisure-time activities such as walking, running, tennis, hiking, bicycling, and swimming. Physical activity is defined as any movement that uses skeletal muscles and requires more energy than does resting. Physical activity is essential for people
to maintain a balance between the number of calories consumed and the number of calories used for body metabolism. Excess calories in the body increases oxidative stress, internal temperature and hormonal metabolism. High caloric foods are normally high in animal fats and carbohydrates (sugars) and increased intake of these types of foods increase risk factors for type 2 diabetes, heart disease and cancers. Sedentary lifestyle is associated with increased cardiovascular events. The underlying molecular mechanisms are incompletely understood. Reactive oxygen species (ROS) contribute to endothelial dysfunction and atherosclerosis. An important source of vascular ROS is the NADPH oxidase.73

Making moderate to vigorous physical activity that makes the human body to sweat and the heart to beat faster must be part of the lifestyle of the modern humans. Medical experts propose systematic physical activity as a lifestyle that can lower risk of cancer and that of other chronic diseases, such as heart disease and diabetes. A growing body of research suggests that doing any kind of activity to avoid too much sitting can help lower cancer risk.74,75

Scientific evidence in the last decade indicated that physical activity may reduce the risks of several cancers through other mechanisms, independent of its effect on obesity. For example, physical exercise lowers blood estrogen, thus helping to lower a woman’s breast-cancer risk. Exercise also reduces other cancer-growth factors such as insulin. Even older women need to be concerned about estrogen, because after menopause the hormone is produced by fat cells.76-78

The biological mechanisms by which body weight and physical activity influence cancer risk and patient outcomes are not well understood. Moreover, traditional epidemiologic studies are limited in their ability to determine how strongly these factors influence cancer-related outcomes, because they rely on people’s ability to accurately recall or record their weight at specific ages as well as their dietary intakes and amounts of physical activity over time. Consequently, stronger study designs, such as randomized controlled trials when feasible, and more accurate survey instruments are needed. Scientific evidence is increasing that physical exercise influences other aspects of the cancer experience, including cancer detection, coping, rehabilitation and survival after diagnosis. The National Cancer Institute (NCI, USA) supports research in the laboratory and the clinic to
address these issues, with the goal of ultimately translating the knowledge gained into effective interventions for those at risk of cancer and for cancer survivors.\textsuperscript{79,80}

There is substantial evidence that higher levels of physical activity are linked to lower risks of several cancers.

**Colon cancer:** is one of the most extensively studied cancers in relation to physical activity.\textsuperscript{81} A 2009 meta-analysis examined data from 52 epidemiologic studies that focused the association between physical activity and colon cancer risk. The results showed that most physically active individuals had a 24\% lower risk of colon cancer than those who were the least physically active.\textsuperscript{82} A pooled analysis of data on leisure-time physical activity (activities to improve or maintain fitness or health) from 12 prospective U.S. and European cohort studies reported a risk reduction of 16\%, when comparing individuals who were most active to those where least active.\textsuperscript{83} Incidence of both distal colon and proximal colon cancers is lower in people who are more physically active than in those who are less physically active.\textsuperscript{84,85} Physical activity is also associated with a decreased risk of colon adenomas (polyps), a type of colon polyp that may develop into colon cancer.\textsuperscript{86-88}

**Breast cancer:** Physical exercise and activity contributes in lowering risk of breast cancer. Studies showed that women who are physically active have a lower risk of breast cancer than inactive women. A 2013 meta-analysis of 31 prospective studies, the average breast cancer risk reduction associated with physical activity was 12\%.\textsuperscript{89} Physical activity has been associated with a reduced risk of breast cancer in both premenopausal and postmenopausal women; however, the evidence for an association is stronger for postmenopausal breast cancer.\textsuperscript{90,91} Women who increase their physical activity after menopause may also have a lower risk of breast cancer than women who do not.\textsuperscript{92,93}

**Endometrial cancer:** Many studies have examined the relationship between physical activity and the risk of endometrial cancer (cancer of the lining of the uterus). In a meta-analysis of 33 studies, the average endometrial cancer risk reduction associated with high versus low physical activity was 20\%.\textsuperscript{93} There is some evidence that the association between physical activity and endometrial cancer risk may reflect the effect of physical activity on obesity, a known risk factor for endometrial cancer.\textsuperscript{94-96}
Leisure-time physical activity in a large number of studies (cohort, meta-analyses studies) was linked to reduced risks of esophageal adenocarcinoma, liver cancer, gastric cardia cancer (a type of stomach cancer), kidney cancer, myeloid leukemia, myeloma, and cancers of the head and neck, rectum, and bladder.\textsuperscript{97-100}

A recent large study used data from 1.44 million participating adults. Researchers pooled data from 12 prospective USA and European cohorts studies with self-reported physical activity (questionnaires, 1987-2004). Researchers used multivariable Cox regression to estimate hazard ratios (HRs) and 95% confidence intervals for associations of leisure-time physical activity with incidence of 26 types of cancer. The results showed that leisure-time physical activity is associated with the reduction of risk for most of the cancers.\textsuperscript{101}

The majority of these studies on physical activity and reduction of cancer risk are observational studies. Participants report (annual structured questionnaire) on their physical activity and are followed for years for diagnoses of cancer. Data from observational studies can give researchers clues about the relationship between physical activity and cancer risk, but such studies cannot definitively establish that being physically inactive causes cancer (or that being physically active protects against cancer).

**Sunlight, UV radiation and skin cancer risk**

Skin cancer incidence is the most prevalent form of all cancers in the USA, Australia, Israel and in countries where most people have light skin tone, but it can develop even in persons with dark skin after prolonged exposure to ultraviolet sunlight (UV). Skin cancer is the uncontrolled growth of abnormal skin cells. This rapid growth results in tumours, which are either benign (noncancerous) or malignant (cancerous). Exposure to the sunlight for long time or repeated long periods is the main cause of skin cancer. Also, exposure to sunlamps and tanning booths which give off ultraviolet (UV) radiation can increase the risk. Exposure to UV radiation causes early aging of the skin and skin damage that can lead to skin cancer.\textsuperscript{102}
There are three main types of skin cancer: basal cell carcinoma, squamous cell carcinoma and melanoma. Basal cell and squamous cell cancers are less serious types and make up 95% of all skin cancers. Also referred to as non-melanoma skin cancers, they are highly curable when treated early. Melanoma, made up of abnormal skin pigment cells called melanocytes, is the most serious form of skin cancer and causes 75% of all skin cancer deaths. Left untreated, it can spread to other organs and is difficult to control.

![Basal-cell carcinoma diagram]

**Figure 4.** Basal cell and squamous cell cancers are less serious types and make up 95% of all skin cancers. Melanoma, made up of abnormal skin pigment cells called melanocytes. Melanoma causes 75% of all skin cancer deaths.

It is well known that chronic exposure to ultraviolet (UV) radiation present in sunlight is responsible for the induction of most non-melanoma skin cancer (NMSC) in humans. Recent surveys indicate that around one million new cases of skin cancer are diagnosed each year in the USA, about 70% of which result from repeated exposure of the skin to sunlight. The first step in UV skin carcinogenesis involves the induction of DNA damage. Occasional mistakes during the repair of this damage leads to the incorporation of wrong bases into the genetic material. These types of mistakes often result in mutation leading to loss or inappropriate expression of affected genes. Recent studies indicate that genetic alterations in the p53 tumour suppressor gene play an important role in the development of skin cancer.¹⁰³
Melanoma and non-melanoma skin cancer (NMSC) are now the most common types of cancer in populations with light (white) skin. Both tumour entities show an increasing incidence rate worldwide but a stable or decreasing mortality rate. The rising incidence rates of NMSC are probably caused by a combination of increased sun exposure or exposure to ultraviolet (UV) light, increased outdoor activities, changes in clothing style, increased longevity, ozone depletion, genetics and in some cases, immune suppression. Studies showed that an intensive UV radiation exposure in childhood and adolescence is causative for the development of basal cell carcinoma (BCC) whereas for the aetiology of Squamous Cell Cancers (SCC) a chronic UV exposure in the earlier decades is responsible. Cutaneous malignant melanoma is the most rapidly increasing cancer in white populations. The frequency of its occurrence is closely associated with the constitutive colour of the skin and depends on the geographical zone. The highest incidence rates have been reported from Queensland, Australia with 56 new cases per year per 100,000 for men and 43 for women. Mortality rates of melanoma show a stabilisation in the USA, Australia and also in European countries. Epidemiological studies have confirmed the hypothesis that the majority of all melanoma cases are caused, at least in part, by excessive exposure to sunlight.\textsuperscript{104}

**Concluding remarks**

Cancer is largely a genetic disease, in which a medley of mutations accumulates to the point that a few cells reach a state of unchecked growth. In 2017 Tomasetti and Vogelstein published a second paper supporting their hypothesis of “bad luck” on cancer risk (“Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention”).\textsuperscript{11} Though some of the mutations may be more powerful than others, this new study focuses on apportioning cancer-causing mutations generally to one of three categories. Ultimately, its authors conclude, across 32 cancer types, 66\% of cancer-promoting mutations arise randomly during cell division in various organs throughout life, 29\% trace to environmental causes, and 5\% are inherited. In their new paper (Science 2017\textsuperscript{11}) Tomasetti Vogelstein,
described their effort to untangle cancer’s randomness from inherited or environmental factors like sun exposure and smoking. Various organs contain stem cells, from which many cancers are thought to arise. Key to the pair’s original analysis was how quickly those stem cells are thought to replicate in different organs and how many such stem cells there are. The researchers matched those data against U.S. cancer rates in various tissue types. They found that the more stem cells and the more rapidly a particular organ’s stem cells replicate, the higher the risk of cancer in that tissue. Their conclusion in the 2107 paper was that across 32 cancer types, 66% of cancer-promoting mutations arise randomly during cell division in various organs throughout life, 29% trace to environmental causes, and 5% are inherited. But the new paper (2017) appears unlikely to resolve, and may even reignite, the furor that was lit 2 years ago (Tomasetti C, Li, L, Vogelstein B. Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. Science, 355 (6331),1330-1334, 2017).\textsuperscript{11} Science spoke with some scientists who took issue with the authors’ hard numbers for various reasons. “The idea of viewing cancer as a whole is pretty alien to us, the causes of different types are so different,” says Noel Weiss, an epidemiologist (at the Fred Hutchinson Cancer Research Center in Seattle, Washington)... “what seems random today will not seem so random”\textsuperscript{105}

Many scientists took issue with the paper and how reporters communicated it, in part because they felt it overemphasized the randomness of cancer and downplayed the value of trying to prevent it (early diagnosis, change lifestyle). The study was also widely misunderstood as suggesting that 2/3 of cancer cases were attributable to random mutations. In the 2017 paper the researchers focused on 17 cancers—a mix of common and rare, such as colon cancer and the bone cancer osteosarcoma—for which incidence data were available across 69 countries, and for which they already had information on stem cell numbers and replication rates. They found virtually the same correlation between cancer rates and the rates of stem cell division in those tissues—suggesting that the two-thirds figure holds up globally. Their second question took a different tack. Could they break down the absolute proportion of random mutations driving different cancer types? Teasing out just what proportion of cancer-causing mutations is random had “never been
addressed before,” Tomasetti notes. Along with graduate student Lu Li, the pair applied what was known about inherited contributions and environmental influences on mutation rates. They also drew on the Cancer Research UK database, which has in-depth epidemiological and other data about cancers in the UK. In pancreatic cancer, for example, their results suggested that just 5% of mutations were inherited, 18% were due to environmental factors like smoking, and the remaining 77% were the result of random mutations. For prostate cancer, they estimated that a whopping 95% of mutations that drive the disease were randomly acquired. In all, based on the U.K. data for 32 cancers, the researchers estimated that 66% of mutations driving cancer were due to “bad luck.” (Again, they emphasize, that doesn’t mean two-thirds of cancer cases are from those “bad luck” mutations.) “Of course these are estimates,” said Tomasetti at a press conference on Wednesday. “It’s the best that can be done today. It’s a paradigm shift in how we dealing with the causes of cancer risk”.

But scientists across different specialties offered mixed reviews of the follow up work, and many of their critiques echoed those advanced 2 years ago. “[The authors] make a point that heredity is associated with a certain percentage of cancer, and environment is associated with a certain percent, and this is probably true,” says Anne McTiernan, a physician and epidemiologist at the Fred Hutchinson Cancer Research Center. “But then to assume that the rest is because of stem cell divisions and chance … we just don’t know.” McTiernan was skeptical 2 years ago and remains so now. “I think why people struggle with this, it’s a very reductionist approach to a complex problem,” says Richard Gilbertson, a pediatric oncologist and cancer biologist at the University of Cambridge in the United Kingdom. The genesis of cancer is incredibly intricate and only partially understood, he believes. To make their calculations, the authors had to rely on a number of assumptions, several of which were questioned by outside researchers. For example, Gilbertson says, he doesn’t dispute that mutations in proliferating stem cells are the basis of cancer, and his own experiments in mice support this. But the authors assume that stemness is a “fixed” entity—a cell is either a stem cell or not—and take a “mutation-centric” view to cancer’s genesis, he says. The mice that Gilbertson has studied suggest that the big picture is a lot more complicated. In his lab, cells in,
say, an animal’s liver that have stem cell potential can accumulate mutations but simply sit, harmless—and then, when he induces tissue damage to the organ, those cells “wake up” and turn cancerous. “Stem cell function is fluid, and can be activated by tissue damage independent of mutations,” Gilbertson says. "Understanding the elements that drive cancer, and it's not just mutations, is critical if we are to prevent it."105

Meanwhile the well known epidemiologists Giovannucci and Song (Harvard University published a new article (2016) on preventable cancer risk associated with lifestyle factors in the USA. According to Giovannucci, lifestyle factors are important for cancer development. However, a recent study (Tomassetti, Volgstein) has been interpreted to suggest that random mutations during stem cell divisions are the major contributor to human cancer. In their study estimated the proportion of cases and deaths of carcinoma (all cancers except skin, brain, lymphatic, hematologic, and nonfatal prostate malignancies) among whites in the United States that can be potentially prevented by lifestyle modification. The prospective cohort study analyzed cancer and lifestyle data from the Nurses’ Health Study, the Health Professionals Follow-up Study, and US national cancer statistics to evaluate associations between lifestyle and cancer incidence and mortality. A total of 89,571 women and 46,339 men from 2 cohorts were included in the study: 16,531 women and 11,731 men had a healthy lifestyle pattern (low-risk group), and the remaining 73,040 women and 34,608 men made up the high-risk group. The study calculated the population-attributable risk (PAR) by comparing incidence and mortality of total and major individual carcinomas between the low- and high-risk groups. Also, they assessed the PAR at the national scale by comparing the low-risk group with the US population. The results of the study showed that a substantial cancer burden may be prevented through lifestyle modification. So, they concluded that primary prevention should remain a priority for cancer control.106

For historical reasons, we must refer here in the famous review on the causes of cancer in 1981 (Doll and Peto, JNCI). In late 1980, the famous cancer epidemiologists Sir Richard Doll and Richard Peto (Oxford University, UK) submitted a landmark review of factors known at the time to affect cancer risk.1 The report had been commissioned by the US Congress Office of Technology assessment to
help determine the percentage of cancer because of avoidable causes, and the 117-page document was published in the prestigious Journal of the National Cancer Institute in June 1981 (and in a book under the same title, Oxford University Press). The article became a reference standard when estimates were made of the relative roles of lifestyle vs environmental vs host factors as causes of cancer in the US population. The Doll-Peto article is one of the few, if only, reports in the Journal’s 75 years that was generated by Congressional request. At the time there was considerable controversy over the burden of cancer associated with exposures to various chemicals in the workplace, air and water, in part because of a report by 10 National Institutes of Health researchers submitted to the Occupational Safety and Health Administration (hereafter referred to as the OSHA report) claiming that a minimum of 20% of all cancer deaths in the USA were because of occupational exposures. Doll was the world’s leading cancer epidemiologist of the day, having designed and led some of the original epidemiologic research studies documenting that smoking was the dominant cause of lung cancer and that groups heavily occupationally exposed to asbestos also were at elevated risk of this cancer, but the OSHA report projections seemed too high to the Oxford group. The issue of attribution of risks remained topical, and thus Doll and Peto were invited by congressional representatives to prepare a comprehensive report on the known causes of cancer and the amount of cancer in the United States because of tobacco, occupation, and other known etiologic factors.¹⁰⁷

Doll and Peto did not provide an estimate of genetic contributions to cancer risk, noting that inherited susceptibility, like age, is not avoidable, and they did not provide an estimate of the overall percentage of all cancer deaths attributable to avoidable causes. The sum of their estimates for tobacco, alcohol, diet, and the other specific factors considered comes close to 100%. Doll and Peto noted that there may be overlap in the estimates between some of the causes considered (eg, that smoking and alcohol combine to increase risk of oral, esophageal, and laryngeal cancers), so that removing the influence of one factor may in turn reduce the impact of another. While the article, like similar assessments at the time left the impression that most cancers arise from the environmental and lifestyle exposures described, this likely reflects both the limits of the available scientific evidence and
a desire not to underestimate the impact of any component of cancer risk. Indeed, in a recent investigation Peto concluded that 50% of all cancer deaths in the United Kingdom in 2010 could be accounted for by lifestyle and environmental factors. Inherited factors also clearly play a role, because there are multiple examples where host traits can directly predispose to cancer (eg, as with BRCA mutations and breast and ovarian cancer).107,108

Blot WJ, Tarone RE (Vanderbilt University Medical Center and Vanderbilt-Ingram Cancer Center, Nashville, TN (WJB); International Epidemiology Institute, Rockville, MD) in their paper107 support the fact that large majority of cancers have an external cause or are more likely to be the result of stochastic processes (by chance or “bad luck”, that was the basis of the hypothesis of Tomasetti and Vogelstein). According to their opinion “….Attempting to define a clear dichotomy of “deterministic” (strongly affected by environment or genetic susceptibility) vs “replicative” cancers (related most strongly to random errors during DNA replication), will be difficult, and such a dichotomy may be of questionable value in assessing cancer causation. Multiple genetic changes are involved in the development of a malignancy, and it is likely that many of the changes are random errors, but that some are the result of genetic susceptibility or damage from environmental causes. The organ-specific probabilities both of random mutations and of mutations with genetic or environmental causes likely increase with total number of stem cell divisions, so that mutations of both types would contribute to the observed positive correlation between stem cell divisions and lifetime cancer risk. A simple correlation analysis cannot readily partition the relative contributions of random vs environmental or genetic changes to cancer development. Further, neither mutation rates nor the numbers of lifetime stem cell divisions at various organs or tissues are likely to differ widely among different human populations, and thus even if most mutations in the majority of cancers are the result of random replication errors, the large geographic variation in cancer rates observed at most organs suggests that the percentage of cancers arising entirely by such random errors in the United States is relatively low….”107
References

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