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Role of Epidemics in Cancer Evolution

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ABSTRACT

Cancer is an evolutionary process and its research has attracted experts from a broad range of disciplines. A physically integrated team of interdisciplinary scientists can produce an integrative oncology view of cancer progression. Examining mathematical models of oncology and validating their findings by experimental and clinical observations seems to be a promising way forward, provided that the models portray correct molecular dynamics. A quick overview of different cancer types, different treatment strategies at different stages is provided in this letter, by keeping in view the epidemiological behaviour of this class of diseases.

Keywords: Stochastic processes; Evolutionary dynamics; Epidemiology; Heterogeneity; Genotypes

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INTRODUCTION

Cancer is mainly caused by changes in tumor defenselessness genes commonly known as tumor suppressor genes (TSGs). TSGs inactivation can lead to oncogenesis, a process through which healthy cells are altered into cancerous cells. These genes have ability to cause hereditary insecurity. There are more than 200 types of cancer and it is mainly associated with Age, Alcohol, Cancer-causing Substances, Chronic inflammation, Diet Hormones, Immunosuppression, Infectious Agents, Obesity, Radiation, Sunlight, Tobacco and many more. Cancer is a disease that occurs when cells in our body are damaged. These cells can begin to grow and divide abnormally and escape our body's normal control processes. These abnormal cells are cancer cells. Cancer cells can grow together as masses called tumors which replace normal cells in tissue or organs. These cells can interfere with the normal functioning of the organ where they arose, and they can also spread to surrounding tissue or through the blood and lymph tissue to other organs. Cancer usually develops slowly often involving multiple steps, over a period of several years. Cancer can usually be treated. Staging is helpful in describing about cancer location, where cancer has spread

and whether other organs are affected by it or not. A cancer staging is based on size and extension of the primary tumor in accordance to the cancerous cells behavior. TNM System is usually used to describe a cancer stage. Each type of cancer has a specific TNM system. T in TNM stands for tumor, N stands for Node and M stands for Metastasis. The alphabet T plus a number (0 to 4) describes the location and size of tumor. A larger tumor will receive high number. The alphabet N plus a number (0 to 3) describes the presence of cancer in lymph nodes. Large number of lymph nodes having cancerous cells will receive high number. The alphabet M describes about the spread of cancer to other parts of the body. If cancer is spread to other organs it is named as M1 otherwise M0.

TNM results are used to determine the stage of cancer for each person. There are total 5 stages named as 0, I, II, III and IV. Stage 0: Cancers can still located in the place they started and have not spread to nearby tissues in this stage. This type of cancer is often highly curable, usually by removing the entire tumor with surgery.

Stage I: This stage is usually a small cancer or tumor that has not grown deeply into nearby tissues. It also has not spread to the lymph nodes or other parts of the body. It is often called early-stage cancer.

Stage II: This stage is usually small but bigger than stage I cancer. In this case, cancer has been spread to nearby lymph nodes.

Stage III: This stage indicates larger cancers or tumors that have grown more deeply into nearby tissue. They may also spread to other than nearby lymph nodes but not to other parts of the body.

Stage IV: This stage means that the cancer has spread to other organs or parts of the body. It may also be called advanced or metastatic cancer. TNM staging system is usually used for the description of solid tumours like colon, breast and lung cancers. Other staging systems are used to determine the other types of cancer. Only 'T' description of the TNM system applies to brain tumor as they do not spread outside the brain. Blood cancers and childhood cancers cannot be described under TNM system. Figures 1 and 2 present different occurrences and mortality rates relative to different cancer types and sex.

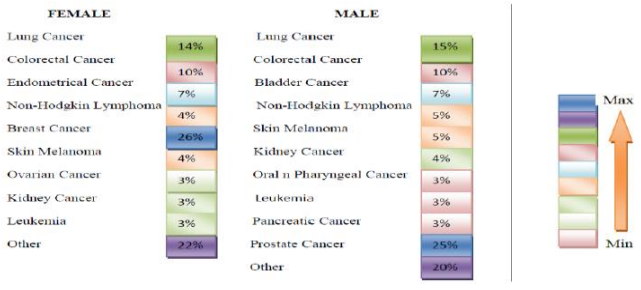

Figure 1. Illustration of cancer occurrence (male and female) in USA in 2016

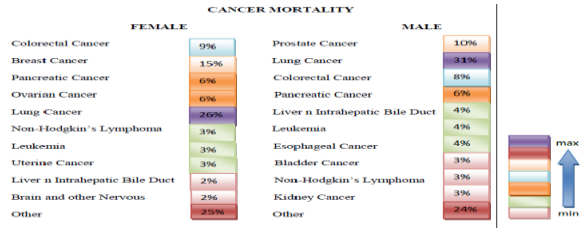

Figure 2. Cancer mortality rates (male and female) in USA in 2016 (wikipedia.org wiki Epidemiology of cancer)

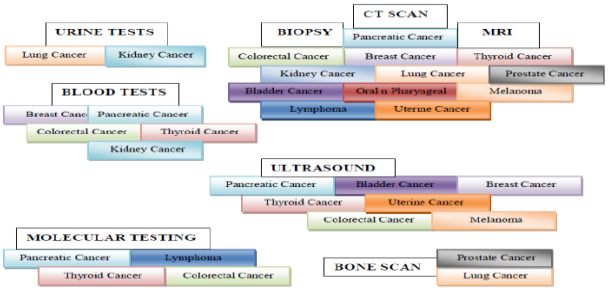

Figure 3. Cancer types and different treatment strategies

In addition to TNM system other information is also used to determine the chance of recovery and to decide which treatment can be used for different cancers. Grade explains about similarity of cancer cells with healthy cells under a microscope. It helps in predicting how quickly the cancer will spread. Tumor markers and Tumor genetics also help in predicting the spread of cancer. Different techniques are used for the diagnosis of cancer. Some of the techniques are MRI, Urine tests, CT scan, Biopsy and Ultrasound. In MRI tests, magnetic fields are used to give detailed images of the body. In CT scan, X-rays are used to give 3-dimensional picture of the body. These pictures are combined into cross-sectional and detailed view that shows tumors. Both MRI and CT-scan is used to measure the size of tumor and identifies enlarged lymph nodes which indicate that cancer has spread. In ultrasound, sound waves are used to give picture of internal organs. The treatment of cancer includes Surgery, Radiation therapy, Chemotherapy, Immunotherapy and targeted therapy. The goal of surgery is to completely remove tumor and the surrounding lymph nodes. In Radiation therapy high energy x-rays or other particles are used to destroy cancerous cells. In Chemotherapy drugs are used to destroy cancer cells, usually by ending the cancer cell's ability to grow and divide. The combination of chemotherapy and radiation therapy can sometimes control tumor growth, and it is more effective than giving either of these treatments alone. Targeted therapy is a treatment that targets the cancer specific genes, proteins, or the tissue environment that contributes to cancer growth and survival. This type of treatment blocks the growth and spread of cancer cells. Immunotherapy, also called biologic therapy, is designed to boost the body's natural defense to fight the cancer. It uses materials made either by the body or in a laboratory to improve, target, or restore immune system function. Figure 3 shows different treatment strategies for different types of cancer. In the field of computational biology, much advancement has been achieved during the past decade. Mathematical models and computational techniques are available in recent literature [1,2], however, in this letter, we aim to present some important aspects of the population dynamics of cancer.

Heterogeneous Effects

In heterogeneous population, every individual has different value for the characteristic which you want to study. Heterogeneous populations are very common in real life, e.g. patients having same disease may differ with many factors including diagnostic test results, medical histories and demographics. While in homogenous population, every individual has same characteristic which you want to study.

For most of the cancer studies, the word "heterogeneity" is used to express the variability with respect to attributes of individuals that affect their mortality [3]. This concept of heterogeneity is closely linked with the concept of selection (the selection process is explained in section 1.2). Because of the effects of selection, the

patterns of "death rate" in a heterogeneous population can differ qualitatively from the patterns of mortality in the constituent sub-populations. While conducting cancer studies, detailed understanding of heterogeneity is necessary, since a false assumption (that observed patterns for the entire population are true for the sub-population or at individual level) may lead to wrong inference. Such incorrect inferences may produce erroneous policy recommendations, because the effect of an intervention usually depends on the behavior and response of individuals.

In addition, heterogeneous studies are more challenging, i.e. "rates for homogeneous groups often follow simpler patterns than composite population rates" and thus heterogeneous pattern identification is difficult and sometimes impossible. In 1970's [4] mathematical models were used to simplify the analysis of heterogeneous populations. Lou [5] addressed some challenging aspects of the modelling of heterogenous population.

The death and birth rate of every population (of animals or human beings) contributes in its epidemiology. The entire population of a specific study can further be divided into subgroups based on their age groups. Let be the group name for *i* number of population subgroups. A subgroup's rate of death or exit is often measured by the relative force of mortality or hazard rate, φ. At age *x* and time *t* φ(*x*,*t*) is the proportion of the subgroup born *x* years ago that is surviving at time *t* and the birth year. In equation 1, the variables are continuous. In a homogeneous population, all individuals of age *x* during one year of study face the same hazard rate *p*(*x*,*t*), on the contrary, a heterogeneous population consists of various homogeneous sub-populations. In the extreme case, when the population size is small, or the disease studied is rare, each homogeneous sub-population consists of a single individual. Consider the system of equations:

$$\phi(x,t) = \frac{\frac{dp(x,t)}{dt}}{p(x,t)}, t = t_0 + t \ (1)$$

$$\xi(0) = \frac{n_1}{n_1 + n_2} \ (2)$$

$$\xi(x) = n_1 \frac{p_1(x)}{n_1 p_1(x) + n_2 p_2(x)}, x > 0 \ (3)$$

And, after simplification, leads to:

$$\xi(x) = \xi(0) \frac{p_1(x)}{\xi(0) p_1(x) + [1 - \xi(0)] p_2(x)} \ (4)$$

$$\phi(x) = \xi(x)\phi_1(x) + [1 - \xi(x)]\phi_2(x) \ (5)$$

Supposing first sub-group weaker $\phi_1(x) > \phi_2(x) \ \forall \ x$:

$$p_i(x) = e^{-\int_0^x \phi_i(t)dt}, i = 1,2 \ (6)$$

For cancer studies, we have considered an example to elaborate the technique used in the literature for the heterogeneous population. Testicular-cancer, for example, is more common than prostate-cancer at younger ages but less common at older ages. Does this imply that any particular individual is more likely to die from testicular-cancer in youth and from prostate-cancer in old age? Not necessarily, as illustrated by Figures 1a and 1b. These hazard lines produce the apparent crossover in mortality rates shown in Figure 4: the calculations are based on equations (1-6). The data is based on information provided by Cancer Research UK.

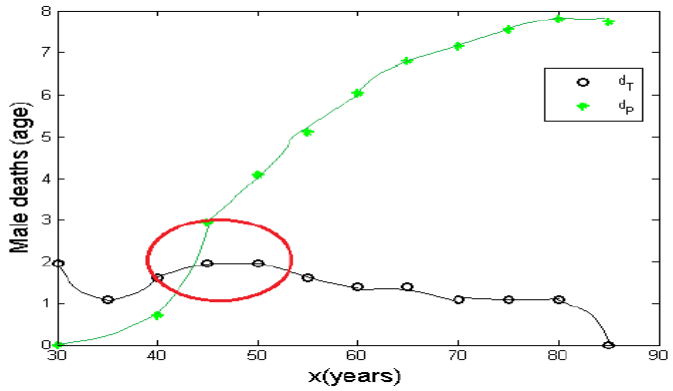

Figure 4. Observed mortality rates for two causes of death may appear to intersect (red); d_T and d_P shows the number of deaths caused by testicular-cancer and prostate cancer respectively

Epidemiological Evidence

The variation in the cancer statistics, drawn from different parts of the world makes its understanding and cure more challenging. This dynamic response is not only attributable to genetic characteristics of different populations but also associated with environmental exposures.

Natural selection is a process by which some organisms have a chance of reproducing and surviving than others due to genotypic changes that are better adapted to the environment. There are three types of natural selection i.e. Directional selection, Disruptive selection and stabilizing selection. Directional selection is a type of natural selection in which one phenotypic trait is favored over other phenotypic traits. The frequency of favored trait and its allele increases over time while the frequency of non-favored traits and their alleles decrease, causing allele frequencies to shift in one direction. Stabilizing selection is a type of selection in which average values of a trait are favored against the extremes of a trait. As a result the frequency of extreme traits decreases and the frequency of average traits increase. Disruptive selection is opposite of stabilizing selection.

Migration is the movement of groups, populations or individuals. In genetic terms, migration enables gene flow. Gene flow is the movement of genes from one population into another. If two populations have distinct gene frequencies and if selection is not operating, gene flow will quickly cause the gene frequencies of distinct populations to converge.

Mutation is a change in DNA sequence which often results due to environmental factors or due some other changes, when DNA is copied. Two main types of mutations are spontaneous mutations and frame shift mutations.

Spontaneous mutations occur randomly, during cell division, in DNA whereas Frame Shift mutation occurs when nitrogen base is deleted or inserted into the DNA sequence.

For a long time mutations have been considered to be the main mechanism by which cancer arises; or, more accurately, they have been considered to be necessary but not sufficient for carcinogenesis, but the role of selection of mutated cell has not been clearly investigated. Mutations are not likely to be the only mechanism to explain geographic variation and incidence changes in migrants. An alternative model is mutation plus selective pressure over mutated cell clones.

In short, it is necessary to understand the epidemiology of cancer due to the following reasons:

- Highly penetrant mutations explain only 5-10% of all cancers, while geographic variation is-for instance, for melanoma or oesophageal cancer, up to 1:200;
- Low-penetrant gene variants (polymorphisms) are only weakly associated with cancer risk;
- For most cancers, the risk of migrants tends to approach that of the population to which they migrate, sometimes as soon as in the first generation [6].

Prostate Cancer is second most common cancer in men worldwide. Highest incidence of prostate cancer and breast cancer was in Oceanic and northern America; and lowest incidence in Asia and Africa. In more developed countries, there were 5.9 million women who had survived breast cancer for at least 5 years; the figure for less developed countries was 3.7 million. In Tables 1 and 2, we have provided statistics for three types of cancer. The variation portrays the epidemiological effects. Some results are presented in the form of pie chart (Figure 5).

Table 1. Annual incidence rates of Prostate and Breast Cancer in different areas of world [7]

High risk areas		**Low risk areas**	
Prostate cancer			
France	227-234	USA	98-102
Sweden	119-123	Denmark	90-97
Australia	115-121	Belgium	89-92
Ireland	114-123	Estonia	88-94
Breast cancer			
Belgium	110-115	USA	92-97
Denmark	105-109	Ireland	92.3-92.4
Iceland	96-99	Italy	91-94
UK	95-97	Malta	85-88

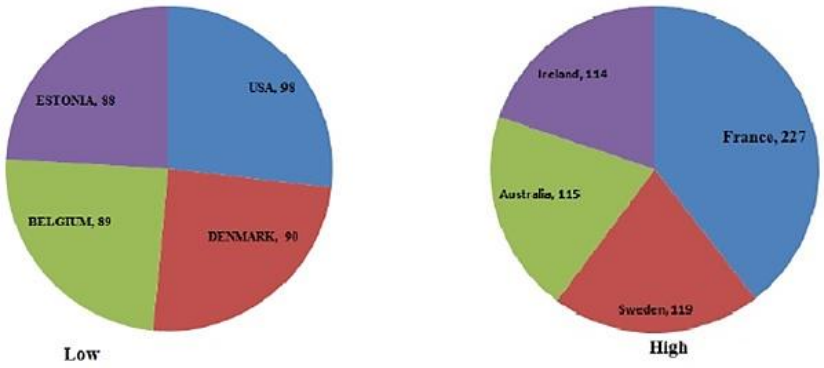

Figure 5. Low versus High rates of PCa cases as per data provided

Table 2. Annual incidence rates of prostate cancer and testicular cancer in different parts of the world per 100,000 men [8,9]

High risk areas		**Low risk areas**	
Testicular cancer			
Germany	Oct-14	Lithuania	2.1-3.4
Hungary	09-Dec	Ukraine	2.0-3.9
Ireland	9.6-13.4	Spain	1.7-3.6
Norway	Aug-13	Moldova	1.7-3.1
Slovenia	08-Dec	Greece	1.5-4.2
Prostate cancer			
France	227-234	USA	98-102
Sweden	119-123	Denmark	90-97
Australia	115-121	Belgium	89-92
Ireland	114-123	Estonia	88-94

Genomic cancer evolution studies have been reported in the literature [10] (and the references therein), the resulting computational models are promising to help in developing therapeutic strategies which cause delay in tumour evolution [11].

Cancer can arise not only as effect of a “mutant phenotype” [12], but actually of a “mutator phenotype” [13]. The selective pressure over mutants and, even more, mutator cells, is likely to be crucial in explaining the role of environmental exposures.

Darwin’s research on different species of the world was based on the phenotypes of different species. The clear understanding of “responses to somatic selection” (including clonal adaptation, diversification and extinction) was made possible with the advancement in the mathematical theory of Darwinian dynamics. This theory can be implemented to analyze the cancer initiation and progression [12]. As the selection of certain genotypes was favorable in specific environments and not in others, similarly, the selection of cells carrying certain mutations can

lead to a greater incidence of cancer under specific environmental circumstances. Comparative analysis of cancer cell phylogenies could reveal which molecular changes occurring during neoplastic progression facilitate the development of invasive, metastatic and resistant cell phenotypes. Incorporation of biological markers into epidemiological research and development of genetic epidemiology may lead to better understanding of this evolving subfield of oncology.

CONCLUSIONS

Genetic and epigenetic variability among people lead to differences in susceptibility and makes cancer diagnosis and therapies difficult and sometimes ineffective. Tumors develop in different organs and tissues of the body, and cancers deriving from the same tissue can be stratified into disease subtypes based on differences in gnomic measurements [14]. Therefore, the cancer research and its population dynamics at cellular, subcellular and genomic level is a vast field of research. We have made an attempt to highlight some important features of this field of research. This article provides:

- An insight of important mathematical techniques to obtain population dynamics of cancer cells.
- It also explains the epidemiology of cancer, in a simple way with useful examples.
- It outlines the role of genomic cancer evolution studies, in the field of oncology.

With advancement in the field of oncology, the percentage of cancer survivors has increased all over the world. Nevertheless cancer survivors from one particular cancer type are at increased risk to other diseases including different cancers, cardiovascular disease, diabetes, osteoporosis and many more. Lifestyle factors, such as a healthy diet, regular exercise, stress control, and smoking cessation may prevent these conditions. More research is necessary to develop interventions that can effectively promote cancer awareness and accelerate robust cures.

DECLARATIONS

Competing Interests

All of the authors declare that there is no conflict of interest.

Availability of data and materials

Not applicable

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REFERENCES

[1] S Javed; A Sohail; K Maqbool; SI Butt; QA Chaudhry. *Complex Adaptive Systems Modeling*. **2017**, 5(1), 12.

[2] A Sohail; ZW Li; M Iftikhar; M Mohamed; OA Beg. *J Mech Med Biol*. **2017**, 17(4), 1750067.

[3] JS Krinsley. *Mayo Clin Proc*. **2003**, 78, 1471-1478.

[4] JW Vaupel; KG Manton; E Stallard. *Demography*. **1979**, 16(3), 439-454.

[5] Y Lou. *Tutorials Math Biosci*. **2008,** 171-205.

[6] MR Greenberg. Urbanization and cancer mortality: the United States experience 1950-1975. **1983**.

[7] RL Siegel; KD Miller; A Jemal. *CA Cancer J Clin*. 2016, 66(1), 7-30.

[8] Aua 2016: Prostate cancer 2016: Worldwide epidemiology trends-session highlights. Tech Rep.

[9] International agency of research in cancer. Tech Rep.

[10] X Wu; P Northcott; A Dubuc; AJ Dupuy; DJ Shih; H Witt; S Croul; E Bouffet; DW Fults; CG Eberhart; L Garzia; T Van Meter; D Zagzag; N Jabado; J Schwartzentruber; J Majewski; TE Scheetz; SM Pfister; A Korshunov; XN Li; SW Scherer; YJ Cho; K Akagi; TJ MacDonald; J Koster; MG McCabe; AL Sarver; VP Collins; WA Weiss; DA Largaespada; LS Collier; MD Taylor. *Nature*. **2012**, 482(7386), 529-533.

[11] B Zhao; JR Pritchard; DA Lauffenburger; MT Hemann. *Cancer Discov*. **2014**, 4(2), 166-174.

[12] DJ Weisenberger; KD Siegmund; M Campan; J Young; TI Long; MA Faasse; GH Kang; M Widschwendter; D Weener; D Buchanan; H Koh; L Simms; M Barker; B Leggett; J Levine; M Kim; AJ French; SN Thibodeau; J Jass; R Haile; PW Laird. *Nat Genet*. **2006**, 38(7), 787-93.

[13] LA Loeb; JH Bielas; RA Beckman. Cancer Res. **2008**, 68(10), 3551-3557.

[14] Y Kuang; JD Nagy; SE Eikenberry. Introduction to mathematical oncology. CRC Press. **2016**.