

Evolutionary Basis of Cancer Metastasis and its Implication to a Lasting Cure

ABSTRACT

Globally, the absolute burden of disease caused by cancers is currently projected to double in the two decades from 2010 to 2030. Observers estimate that there will be 26 million or more new cases a year by 2030, and some 17 million cancer deaths annually. The US president in 1971 Richard Nixon introduced in his State of the Union Address the 'War on Cancer' with the aim to find ways to cure cancer within the next 25 years. A review was done In 1996 the elapsing year and it was discovered that though significant efforts and advances have been made yet we are still in a war with cancer and far away from a definite victory with local invasion, and distant metastasis that is resistant to conventional therapy being the major causes of death. This attitude of cancer cells had been more understood in the light of ecology and evolution in recent years as the Darwinian theory of evolution by natural selection now becomes a theoretical frame work for the study of cancer behaviour. However, the implication of this eye opener to the cure of cancer had to be more highlighted if the 'moon shot' war against cancer as declared by President Obama in 2016 would be successful. More specific choice and scheduling of cancer treatment; selective toxicity, Inhibiting other chemicals or factors that initiate and sustains angiogenesis in cancer cells (tumour or human specific), supporting the immune system, boosting normal cell fitness and Restoring a more normal ecological niche may be the answer we have long sorted for as we strive to find a lasting cure to cancer.

Keywords: Oncology, cancer, metastasis, evolution, ecology, cancer cure, carcinogenesis, moon shot, cancer management

1.0 BACKGROUND TO THE STUDY

It is a social and political fact that cancer is in some respects a special case, and is widely seen as '*the emperor of all modern maladies*' [1]. For many years the main methods of treating cancer were

surgery and radiotherapy. Control of the primary tumour indeed has been a concern, since this is usually responsible for the patient's symptoms. There may be unpleasant symptoms due to local spread, and failure to control the disease locally leads to death. For many tumours, breast cancer for example, the energies of those treating the disease have been directed towards defining the optimum methods of eradication of the primary tumour. It is perhaps not surprising that these efforts, while improving management, have not greatly improved the prognosis because the most important cause of mortality is metastatic spread, [2]. In most cases, metastases have often developed before diagnosis and commencement of treatment. The prognosis is not then altered by treatment of the primary cancer, even though the presenting symptoms may be alleviated. Progress in treatment has been slow but steady, [3]. Precision medicine requires an understanding of cancer genes and mutational processes, as well as an appreciation of the extent to which these are found heterogeneously in cancer cells during tumour evolution. Tumours sequenced at the exome level have been found to harbour anything from merely one or two to thousands of somatic aberrations, ranging from base-pair substitutions to whole-genome doublings, [4].

Tumours accumulate somatic aberrations through an evolutionary process [5]. While the majority of these aberrations are likely to be passenger events that do not provide any selective benefit to the cancer cell, only a small subset represent cancer driver events conferring a selective advantage [6]. Accumulating evidence suggests that not every mutation, whether driver or passenger, will be found in every cancer cell within a tumour [7, 8]. While the types and distribution of mutations across the genome in a cancer cell can be used to decipher the mutational processes that have been active during its evolutionary history [9], the extent of heterogeneity and its dynamics over time can reveal a tumour's life history [10, 8]. The heterogeneity observed within tumours and the myriad of genome instability processes that shape tumour evolution over space and time have important clinical implications and may reflect the mismatch between cost and benefit of some anticancer therapies [11]. Acquired drug resistance is a major limitation for the successful treatment of cancer. Resistance can emerge due to a variety of reasons including host environmental factors as well as genetic or epigenetic alterations in the cancer cells.

Evolution theory has contributed to the understanding of the dynamics of resistance mutations in a cancer cell population, the risk of resistance pre-existing before the initiation of therapy, the composition of drug cocktails necessary to prevent the emergence of resistance, and optimum drug administration schedules for patient populations at risk of evolving acquired resistance, [12]

Obviously, evolution by natural selection is the foundation law of life. We shouldn't be surprised therefore that it has great relevance to cancer. The idea that cancer is fundamentally a process of somatic cell evolution was first advocated in the 1970s. Since then, the concept has been validated and greatly elaborated, highlighting the striking parallels with Darwinian evolution by natural selection in ecosystems. Cancer genomics has provided detailed genetic descriptions and technologies for interrogating single cells and multi-regional small biopsies, revealing space-time genetic diversification of cancer cells and allowing us to infer clonal phylogenies, or evolutionary history. It's a striking fact that every patient's cancer has an individually unique and variegated clonal architecture and evolutionary trajectory. This represents a paradigm shift with major implications for the way we think about the fundamental study of cancer, the emergence of drug resistance and our attempt to control it. This also applies to evolutionary considerations of why humans are so vulnerable to cancer. Evolutionary perspective isn't a sub-topic of cancer sciences - it is a conceptual framework for everything in cancer [13].

This paper will review some of the evolutionary basis of cancer metastasis and discuss its possible implication to cancer cure/ management.

. 2.0 METHODS

Eighty five pertinent literatures by various authors were reviewed from several journals, most of which are recent.

3.0 FINDINGS

3.1 Why Cancer is now very common in Human

Cancer is a name used to describe a large and diverse group of diseases most notably characterized by a rapid increase in the growth and proliferation of certain cells (that have acquired genomic mutations)

and a resultant tumour mass. This malignant tumour mass is distinguished from benign tumours because of the ability to metastasize, i.e. spread to other distant organs [14].

Sporadic tumours, either benign or malignant, can only develop in those tissues or organs that retain regeneration ability, because tumorigenesis requires cell proliferation to fix mutations onto progeny cells [15]. Cancer originates from a single mutation within the genome of a cell. Subsequent accumulation of more mutations can turn a normal cell into an aberrant cell [16].

A mutation in which a tumour suppressor such as p53, Rb or p16INK4a/ p14ARF is knocked down, or an oncogene such as Ras become constitutively active, leads to excessive proliferation of the cell, [17, 18] and with each cell division, the chances of cells acquiring more mutations increases. Eventually, cells accumulate enough mutations to trigger endless Peer review under responsibility of Changing Medical growth and tumour formation [19].

One may further infer that those cell types that have a quicker and more-massive cell turnover may have a higher chance of, and a shorter latent period for, developing neoplasia and thus are collectively referred by us to as “anabolic cell type” [20] The reason behind the contribution of a frequent cell turnover to the easier formation of cancers goes beyond the requirement of cell proliferation to fix mutations onto progeny cells, when thought about from an evolutionary point of view: As we described before [21]. Sequencing the genomic DNA of thousands of samples from different cancer types surprisingly found only 138 genes with driver mutations, i.e. those that drive carcinogenesis [22]. Some of the mutations may already exist in normal cells [23], and are given more changes of expression by our constant civilization in terms of what we eat and the extrinsic factors of the ever changing environmental effect on these mutants.

3.2 Brief Introduction to the Present day Cure or Management of Cancer

The treatment of cancer has undergone evolutionary changes as understanding of the underlying biological processes has increased. Tumour removal surgeries have been documented in ancient Egypt, hormone therapy was developed in 1896 and radiation therapy was developed in 1899. Chemotherapy, immunotherapy and newer targeted therapies are product of the 20th century. As new information about the biology of cancer emerges, treatments will be developed and modified to increase effectiveness, precision, survivability and quality of life [24].

According to WHO [25] the major treatment modalities for cancer requires a careful selection of one or more of the major treatment modalities – surgery, radiotherapy and systemic therapy – a selection that should be based on evidence of the best existing treatment given the resources available. Surgery alone, and sometimes radiation alone, is only likely to be highly successful when the tumour is localized and small in size. Chemotherapy alone can be effective for a small number of cancers, such as haematological neoplasms (leukaemia's' and lymphomas), which can generally be considered to be widespread from the onset. Combined modality therapy requires close collaboration among the entire cancer care team. This then implies that no specific cancer treatment is hard and fast but would require careful study of the specific cancer and may result in a combination of the known methods of cancer treatments.

3.2 Common Treatments for Cancer

The following are the common ways of treating cancer as highlighted by the American Cancer Society [26]:

- **Surgery:** The goal of the surgery can be either the removal of only the tumour, or the entire organ, [27].
- **Chemotherapy:** The main objective in cancer chemotherapy is using anti-cancer drugs to kill the cancerous cells thereby preventing the growth of cancerous tumours. Chemotherapy creates a damaging range of side-effects, and so it is normally given in cycles of treatment which alternate with rest periods, to allow the body to recover [28].
- **Radiation Therapy:** The goal of radiation therapy is to use ionizing radiation to kill as many cancer cells as possible and shrink tumours, while limiting harm to nearby healthy tissue [28].
- **Targeted Therapy:** It constitutes the use of specific agents for the deregulated proteins of cancer cells. Small molecule targeted therapy drugs are generally inhibitors of enzymatic domains on mutated, overexpressed, or otherwise critical proteins within the cancer cell [29]. This is currently a very active research area, two most important aspects are highlighted below:

- **Hormonal therapy:** The growth of some cancers can be inhibited by providing or blocking certain hormones. E.g. prostate cancer and Breast cancer, [28].
- **Angiogenesis inhibitors:** Angiogenesis inhibitors prevent the extensive growth of blood vessels (angiogenesis) that tumours require to survive. One of the main problems with anti-angiogenesis drugs is that many factors stimulate blood vessel growth in cells normal or cancerous. Anti-angiogenesis drugs only target one factor, so the other factors continue to stimulate blood vessel growth. Other problems include route of administration, maintenance of stability and activity and targeting at the tumour vasculature. [30]
- **Immunotherapy:** This is aimed at using diverse set of therapeutic strategies designed to induce the patient's own immune system to fight the tumour [31].

3.3 The Continuous Menace of Cancer

Continuing rapid advances in biomedicine and associated disciplines, including molecular biology, human genetics, health psychology and medical sociology, have led to claims that more has been learned about cancer in the past two decades than in the preceding two thousand years [26]. Yet despite the accelerating progress, cancer remains a major and growing cause of suffering and loss of life throughout the world [32]. There were some 325,000 new cases of cancer diagnosed in Britain in 2013, and about 150,000 deaths recorded. A half of those given an initial cancer diagnosis were aged 70 or over, while just over half of the people who died from cancer in that year were aged 75 or more [33].

At the global level the burden of death and disability neoplastic diseases impose will rise markedly at this time to 2050, unless and until the advances now being made in more affluent nations such as America and Britain (as well as by pharmaceutical and other scientists working in emergent economies like China) can be developed and implemented on a universal basis. World-wide there are presently some 8 million deaths a year due to cancer, and 14 million new cases diagnosed annually [34]. It is however worth stressing that even today in the wealthiest parts of Europe and North America, outlays on cancer care amount to no more than 6-7 per cent of all health spending [35].

Table 1. The percentage of cancer attributable to lifestyle and environmental factors in the UK in 2010

	Men	Women
Tobacco	23	15.6
Diet	11.9	7.2
Overweight	4.1	6.9
Exercise	0.4	1.7
Alcohol	4.6	3.3
Infections	2.5	3.7
Radiation (ionizing)	1.7	2.0
UV light	3.5	3.6
Occupation	4.9	2.4
Breastfeeding + HRT	--	2.8
All	45.3	40.1

Source: Parkin, 2011

Data such as those presented in the Table above indicate that, again with the notable exception of tobacco smoking, it would be wrong to over-state the extent to which modifications in any one life style factor can protect individuals and/or communities from cancer. Yet in aggregate life style changes, especially when combined with the use of vaccination programmes, pre-cancer and early stage disease detection and treatment services, have the potential to reduce to halve the current age standardized cancer death rates [36].

3.5 The Hallmark of Cancer Growth

Tumours are complex tissue aggregates composed of multiple types of cells that interact with each other and surrounding normal body components in order to permit their unrestricted collective proliferation. Understanding the processes involved in the transition from normal to neoplastic cells has been the central aim of most cancer research. In 2000, Hanahan and Weinberg outlined six key hallmarks of cancer [16].

They followed this, eleven years later with a further analysis of the essential characteristics of cancers [19]. These can be characterised as:

1. **Self-sufficiency in Growth Signals:** Normal cells control the production and release of signals

that promote tissue growth. Cancer cells effectively deregulate the latter's availability. This can involve an overproduction of growth factor ligands (binding agents) or receptors, along with the additional production of altered receptors that are no longer ligand-dependant.

2. **Insensitivity to anti-Growth Signals:** Normal cell proliferation is controlled by growth inhibitors that interrupt cell division. Cancers become resistant to growth-preventing signals.

3. **Limitless Replicative Potential:** Healthy mammalian cells typically have a limit of around 60-70 replications before reaching senescence, when they no longer divide. But tumour cells often display an increased production of telomerase, the enzyme that maintains the length of the telomeres that govern cell multiplication.

4. **Evasion of Programmed Cell Death (apoptosis):** Programmed cell death normally causes cells to die if they become abnormal. Cancer cells are able to overcome this, most importantly by evading TP53 which elicits apoptosis in response to DNA damage. The tumour suppressor gene TP53 is mutated in more than half of all cancers in ways that facilitate increased cell growth.

5. **Sustained Angiogenesis (new blood vessel growth):** Cancers can trigger new blood vessel formation to provide a blood supply sufficient for their on-going growth.

6. **Tissue Invasion and Metastasis:** Cancers have the ability to invade surrounding tissues or distant body parts. Metastatic cancers achieve this via cell-cell adhesion molecule (CAM) based mechanisms.

7. **Deregulated 'cellular energetics':** The uncontrolled cell proliferation characteristic of neoplastic diseases requires adjustments to cellular metabolism in order to fuel cell growth and division. Cancer cells often, for instance, employ aerobic glycolysis. In normal cells glycolysis generally occurs in anaerobic conditions.

8. **Genome Instability Leading to Enhanced Mutation Rates:** In cancer cells the surveillance systems that normally monitor genetic integrity and force genetically damaged cells into programmed cell death or senescence become compromised. Mutability can also be achieved through increased sensitivity to mutagenic agents.

9. **Avoiding Immune Destruction:** In cancers immune editing results in neoplastic cells being able to evade immune surveillance.

10. Tumour-promoting Inflammation: Cancerous lesions contain infiltrations of cells from both the innate and adaptive immune systems. Inflammation is an enabling characteristic of cancers because it facilitates the supply of bioactive molecules such as growth and pro-angiogenic factors and extracellular matrix modifying enzymes in the tumour microenvironment. Inflammatory cells may also release mutagenic chemicals that accelerate evolution toward heightened states of malignancy.

3.6 Metastasis

Metastasis refers to the dissemination and growth of neoplastic cells in an organ distinct from that in which they originated [37, 38]

It is well known that the body attempts to mobilize macrophages or other predatory immune cells as scavengers to remove cancer cells. What is unknown is whether it is the weaker (loser) or the stronger (winner) cancer cells that are scavenged first. Moreover, sometimes the scavenger engulfs a cancer cell but is unable to digest it, resulting in a hybrid (or fusion) cell that gains metastatic ability [39]. This mechanism for acquiring metastatic ability via fusion with another cell [40], especially with an immune cell that can travel freely, was already proposed one century ago [39] and observed 40 years ago [41] and has received ample evidence. Sometimes metastases still occur years after the primary tumour had been surgically removed at its very early stage. One possibility is that some cancer cells had already been transported to other sites by predatory immune cells. What remains unclear is whether it is the winner or the loser cancer cells that may have a better ability to resist digestion by the scavengers and further utilize the scavengers' property of evading the body's surveillance to gain metastatic ability.

Metastasis-favouring mutations certainly occur first in some cells of the primary tumour to allow the cells later to break away from the tumour mass and lodge in another body site. In addition, the differences in mutations between primary and metastatic or between therapy-sensitive and -resistant tumours are probably quantitative rather than qualitative. A mutation is detected because it appears in more cells, which is in turn because of the clonal expansion during natural selection [21]

3.7 Ecology and Darwin's Evolutionary Perspective in Cancer Growth

Modern cancer biology and genomics have validated cancer as a complex, Darwinian, adaptive system [42, 43]

The classic model of carcinogenesis describes multiple, successive clonal expansions driven by the accumulation of genomic changes or 'mutations' that are preferentially selected by the tumour environment [44, 45, 46]

Genome instability processes result in an elevated rate of somatic aberrations, ranging from point mutations to chromosomal and whole-genome doublings. This instability can contribute to intratumour heterogeneity by providing a pool of mutations upon which selection can act in a given micro environmental context [10]

In cancer patients there exist much collaboration among different cell types, especially when a mend is involved [47], as summarized by [48]. First, cancer cells recruit normal stromal cells to establish cancer niches, as exemplified by tumour angiogenesis [49]. Second, cancer cells collaborate with each other [50], which is evident not only in vivo, as in their collective invasion in patients [51] and clonal cooperation in animals [52, 53], but also in vitro as demonstrated by the fact that many cancer cell lines cannot survive in a culture dish when cells are seeded in a very low density [54].

Figure1: Darwin's Evolution Tree



Figure 1. Darwin's branching evolutionary tree of speciation from his 1837 notebook [55].

3.7.1 Ecology and Darwin's Natural Selection

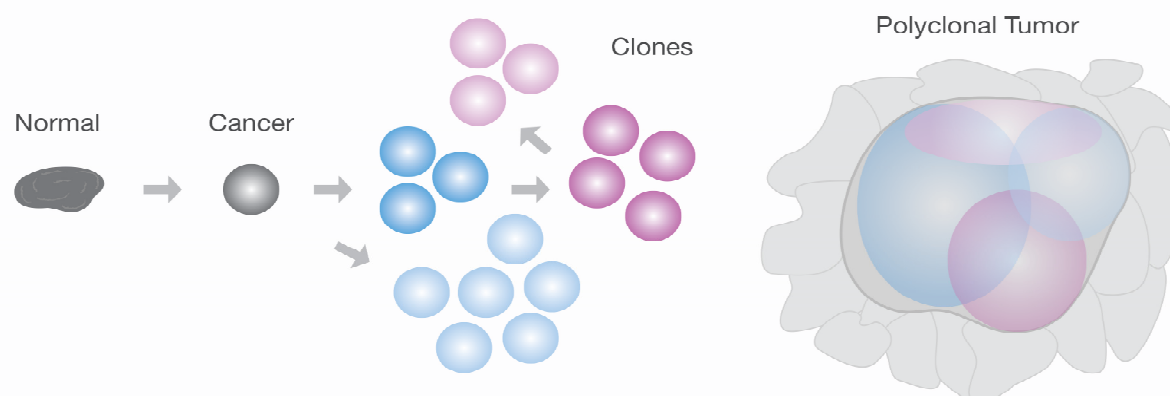
Natural selection is actually a course of clonal expansion of those cells that have functional gain of oncogenes and/or functional loss of tumour suppressor genes, either of the two rendering the cells

growth- or survival-advantage in their particular microenvironments. Therefore, a best known molecular profile of cancer cells, i.e. functional gain of survival- or growth sustaining oncogenes and functional loss of differentiation sustaining tumour suppressor genes, is actually a result of natural selection from numerous mutations that emerge randomly and stochastically. Restated more clearly, these common alterations of cancer are not the drivers of cancer formation or progression as regarded by the mainstream of cancer research [22, 56] but, instead, are the results of natural selections from numerous mutations occurring as happenstances. However, selection has to wait for its chance, i.e. wait until an advantageous mutation or even a set of synergistic mutations have emerged, and God knows how long it will take. Therefore, functional gain of an oncogene or functional loss of a tumour suppressor gene, and the ensuing selection via clonal expansion, take a long time and occur as an evolution, which is another reason why sporadic cancer formation takes many years [21]

Carcinogenesis is a course of sequential gene mutations that confer onto the cell growth advantage and thus are called “drivers”, although different cell types have different successions of driver mutations [22]. Carcinogenesis as a continuous process is well known to result in cells of greater and greater malignancy, manifested as invasion to the surrounding tissue, metastasis to distant body sites, and resistance to therapies. These occur presumably because individual cells accumulate more DNA mutations, which in turn is because the cells progressively lose their DNA damage response and their DNA repair mechanisms, and thus have ever greater difficulty in repairing continually emerging mutations. Natural selection ensues to select, from all these mutations, those with growth- or survival advantages, usually occurring in oncogenes or tumour suppressor genes (Figure 2). This type of selection somewhat resembles organismal development during Darwinian selection in Mother Nature. However, Mother Nature changes only very slowly, over millions of years and thus organismal evolution also occurs slowly. In contrast, the larger and larger tumour mass and the reciprocally weaker and weaker patient’s health together change the cancer’s microenvironment more and more rapidly, and thus cell clones with greater and greater diversity are selected more and more quickly. Actually, the tissue environment can change in just minutes or hours, especially in the presence of therapies, requiring cancer cells to change accordingly, as it is a matter of life or death for them. For instance, the friendly environment around cancer cells is immediately shifted to a very hostile one during radiation therapy, in

less than the second needed to switch on the radiation device. The cancer cells have to immediately mobilize their wherewithal to adapt to the vicious environment; likely with quicker, non-genetic approaches first, such as protein phosphorylation or RNA editing. It can be imagined that some cancer cells may choose to phosphorylate an oncoprotein while other cells cannot do so, because the gene coding for the kinase or the oncoprotein is mutated or silenced, and thus choose to edit another gene's mRNA instead [57]. These disparities are collectively manifested as heterogeneity of survived cells and selected clones. Moreover, this somatic cell evolution occurs in an asexual manner, as it increases the cellular heterogeneity by mutation loads as shown in figure 2 below.

Figure 2: Intratumour Heterogeneity



Source: [58] Figure 2 represents Intratumour heterogeneity. The progressive accumulation of somatic mutations results in an heterogeneous polyclonal tumour in which different clones may respond differently to treatment.

This is in contrast to the sexual propagation in which sex functions to purge altered genome to maintain the species identity, as explained later. Because of this fundamental difference, asexual propagation of cells widens heterogeneity of the progenies, whereas sexual propagation maintains the species no matter how many generations have passed [58] the microenvironment may be changed in just a second, and thus cancer cells accordingly have to equip themselves with some quick response mechanisms. Some of these mechanisms may be maintained for a long time, and may or may not be succeeded by a relatively stable epigenetic mechanism but will eventually be superseded by mutation as a permanent mechanism.

Secondly, although a primary tumour mass has been detected for all mutations needed for a phenotype of more malignancy, it does not mean that there has been a cell that bears all these mutations. The tumour still needs time to allow some individual cells to accumulate all the mutations required for the presentation of a more aggressive phenotype. Equipping a single cell with all the required mutations is just the phase I of the evolution, which will be followed by a phase II that is the natural selection via clonal expansion of this cell to present its particular phenotype, such as chemo-resistance. A mutation is detected because it appears in more cells, which is in turn because of the clonal expansion during natural selection [21].

3.7.2 Cell War; Possible Targets for Cure

Several cancers are highly curable, such as testicular cancer and gestational choriocarcinoma, likely because they arise without lengthy selection and progression, as inferred by [59].

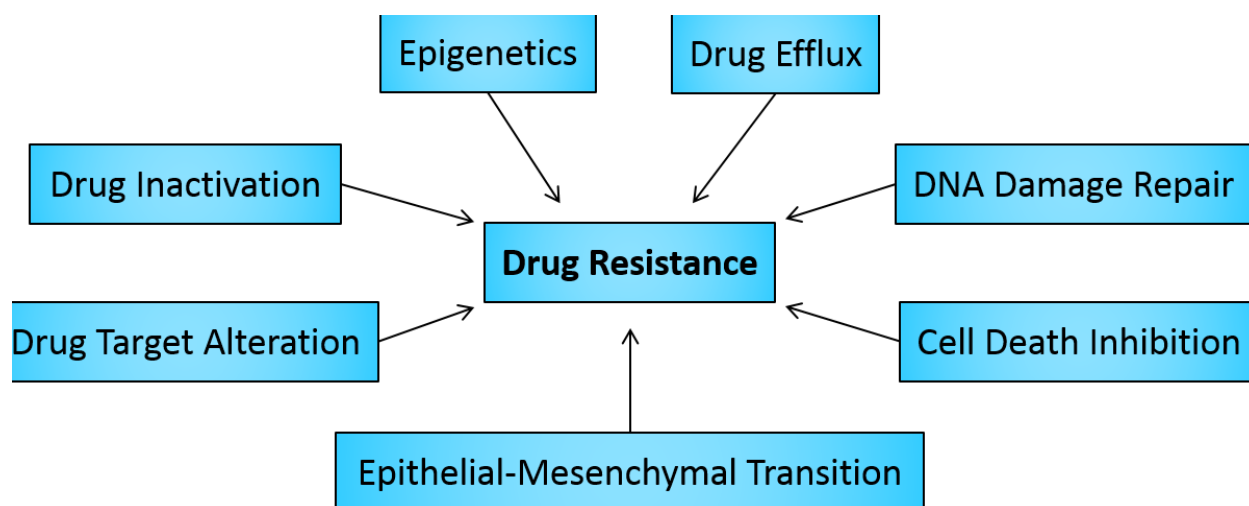
There are also many fights among different cell types. Normal cells that surround cancer cells battle the cancer, at least at early carcinogenic stages, for the fitness of the patient as a whole [60, 61] Even in cell culture, the media that have been used to culture normal cells have been found to contain factors such as cytokines or microRNAs that can kill or inhibit cancer cells, which somewhat resembles an antibiotic secreted by a bacterium to kill another microorganism in the nearby. For instance, normal mammary [62] or prostate [63] epithelial cells release such factors to the media to kill or inhibit breast or prostate cancer cells, respectively. If these observations are directly translated to clinical oncology, probably in the patients with an early breast or prostate cancer, their sera still favour the patients' health by containing cancer cell specific killing or inhibiting components released from the normal cells. These data dovetail with the so-called "neighbouring suppression" notion proposed 50 years ago, which says that normal cells can cause growth inhibition of neighbouring premalignant cells [64], probably by arresting them at the G2/M phase of the cell cycle [65]. For survival, the premalignant, probably also early malignant, cells need to find a way, such as having some additional genetic or epigenetic change, to desensitize such inhibition. Once having progressed to an advanced stage and having become dominant, cancer cells may also release factors into the blood that can eliminate normal cells in the same and other organs or tissues [66]. Cachexia, i.e. wasting syndrome, is probably one manifestation. From an ecology point of view, these complex interactions among different cell types make sense, and breaking their balances may

make one cell type dominant while others become extinct, which provides us with opportunities for cancer prevention and therapy. Cancer cells not only collaborate with each other as above mentioned but also compete with each other for resources [67], which may be due to, and is also one reason for, the intra-tumour heterogeneity [68]. From the viewpoint of cell-autonomy, invasive and metastatic cells are considered stronger than the others because they are more aggressive and perverse. However, from a viewpoint of biological dispersal, the winners in the cell competition are less motivated to relocate to other habitats since they adapt to the environment very well and have the privilege of the first use of nutrients and oxygen, whereas the losers may die if they do not relocate [69]. Therefore, it is possible that cells invade to the surrounding tissue or metastasize distantly because they have lost out in the competition with other cells and are forced to leave [70]. This possibility deserves exploration, not only because it may provide us with a new slant to understand cancer but also because cells have other reasons for dispersal, including changes in metabolisms [71, 72], and the winner cells may disperse as well if new habitats provide an even better living environment. From this point of view, the invasive or metastatic cells are actually weaker, although they later acquire competence in the incursive or the metastatic site where they develop colonies within which new rounds of cell-competition occur, resulting in new losers and winners. If this is the case, we may be able to kill those initial cells with invasive or metastatic potential within the primary tumour, such as by helping the winner cells to weed out the losers or by quickly depriving them from all resources before they disperse. Alternatively and conversely, slightly alleviating their hardship by providing them with basic resource may also retain them in the primary tumour without thinking of relocation to new habitats [73; 74, 75].

3.8 Resistance to Cancer Therapies

Every individual carries a unique set of inherited germ line mutations. As cancer progresses, additional somatic mutations and genomic rearrangements accumulate, [8]. These changes can trigger drug resistance and metastasis [55]. Late stage cancers often consist of polyclonal tumours, (see figure3) where each clone has a unique set of mutations, unique pathology, and unique drug responses, [76, 77]

355 **Figure 3: Factors Responsible for Drug Resistance**



356
357 Source [78]

358 Acquired drug resistance is a major limitation for the successful treatment of cancer. Resistance
359 can emerge due to a variety of reasons including host environmental factors as well as genetic or
360 epigenetic alterations in the cancer cells. Evolutionary theory has contributed to the understanding of the
361 dynamics of resistance mutations in a cancer cell population, the risk of resistance pre-existing before the
362 initiation of therapy, the composition of drug cocktails necessary to prevent the emergence of resistance,
363 and optimum drug administration schedules for patient populations at risk of evolving acquired resistance,
364 [78] Factors of the host organism such as poor absorption and rapid metabolism can reduce the total
365 concentration of the drug in the gastrointestinal tract blood stream or the tumour itself; this mechanism is
366 often referred to as intrinsic resistance. In addition mechanical or biochemical factors may present
367 challenges to the delivery of drugs into tumours. Alternatively, cancer cells may evolve specific genetic
368 and/or epigenetic alterations that allow them to escape from treatment. Some of these alterations, such
369 as loss of a cell surface receptor or transporter and over expression or alteration in the drug target, lead
370 to resistance against only a small number of related pharmacological agents. For example, over
371 expression of EGFR has been associated with resistance to the EGFR-inhibitor cetuximab [79]

372 Generally, cancer is not noticed by patients until it has gotten to a late stage and metastasis had
373 begun. At this stage, there are very few things health care givers can do. Surgeons may try to remove the
374 tumour mass surgically and administer chemotherapy and radiation, but apart from the side effects these
375 techniques have on normal cells, chemotherapy is not very effective in completely wiping out cancer cells,

because in a given tumour, there are different types of cancer cells with different kinds of mutations. Indeed, cancer tumours do not contain homogenous cancer populations; rather they contain heterogeneous cancer populations (refer to figure 3), [80]

Cancers have the ability to develop resistance to traditional therapies, and the increasing prevalence of these drug resistant cancers necessitates further research and treatment development.

3.9 Eco-evolutionary Approach to Cancer Cure

Recommended Eco-evolutionary (ecology and evolutionary) approach to cancer cure shall be summarized with the two Figures below after which It's implication to major health care providers involved in the care of cancer patients will be highlighted as well.

Figure 4: Cancer malignancy

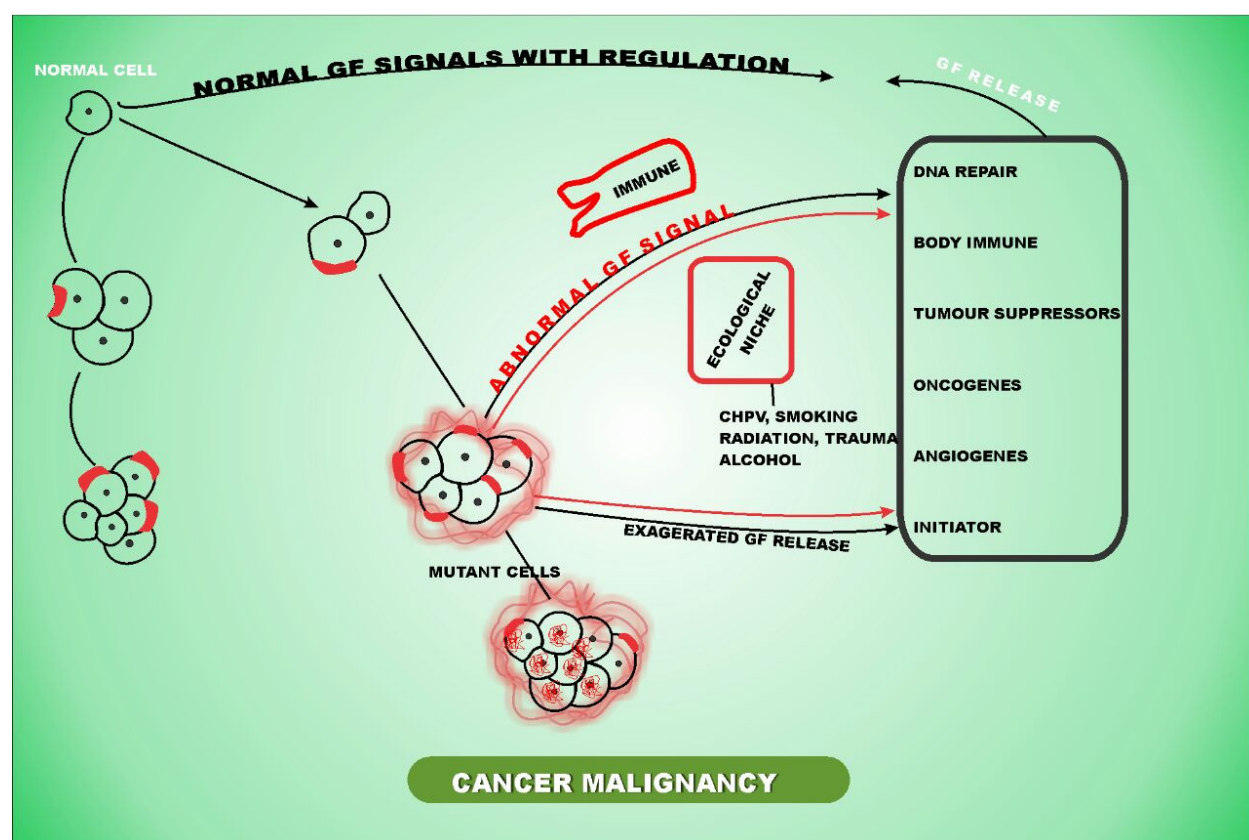


Figure 4 above explains and summarizes the major processes of cancer malignancy as it relates to ecology and evolution. The 'red spots' on each cells represents a mutation, the thicker it became represents more mutation. The red colour surrounding the cells labelled as mutant cells represents an ecological niche initiated by the red rectangle right beside it that favours natural selection of mutant cell

for the next cell division. GF means (growth factors). The big black rectangle represents the body's pool or system that comprises factors for control of normal cell division. The little red cone represents a weak immune system that can't attack mutant cells.

Figure 5: Eco-evolutionary Perspective of Cancer cure

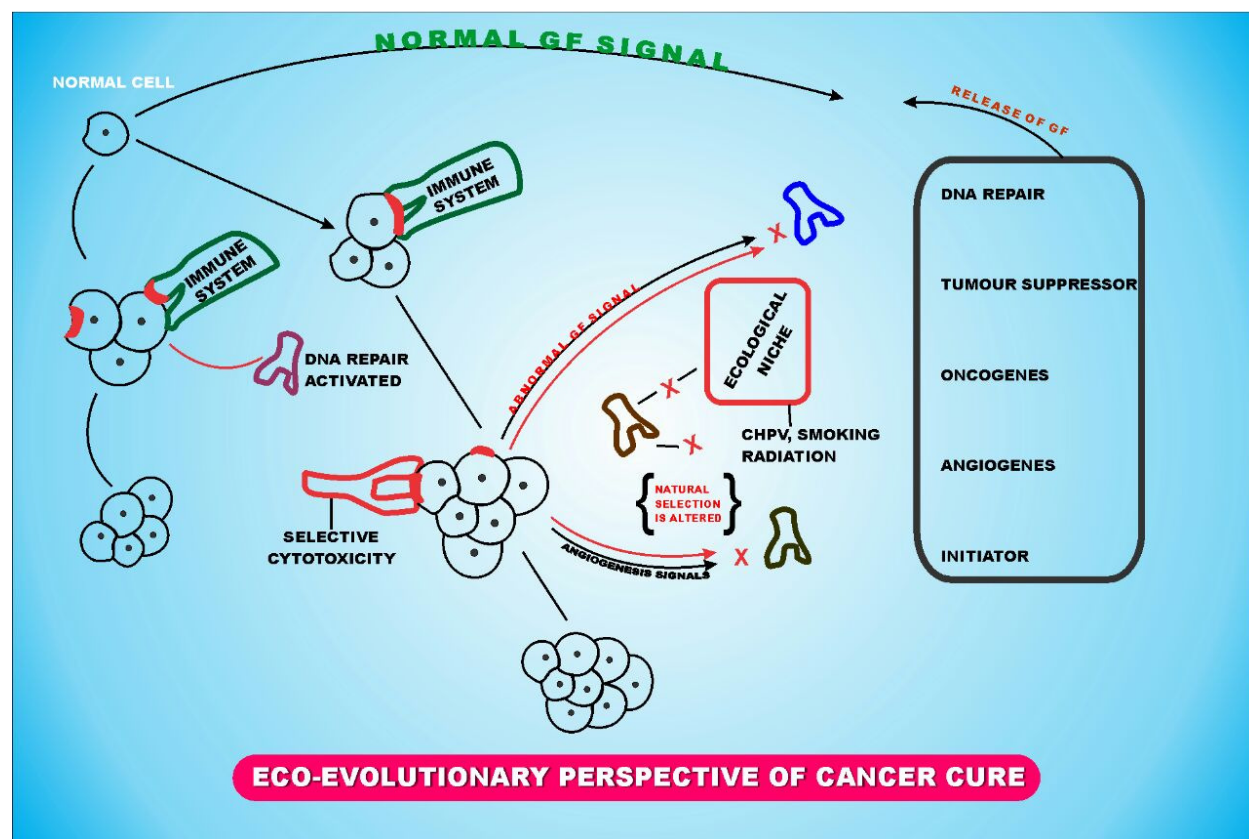


Figure 5 above represents the eco-evolutionary perspective of cancer cure. It shows generally, the different areas to be targeted in order to bring a lasting solution to cancer. The gamma shapes represents drug targets. The first black gamma shaped represent a target to block negative ecological influence on the cells niche (influences such as smoking, Human Papilloma Virus [HPV], alcohol, radiation etc.); with this, natural selection of mutant cells is altered. The second black gamma shape represents the drug target that blocks angiogenesis signals from the mutant cells (Only few angiogenesis signals from cancer cells or its surrounding had been discovered). The blue gamma represents drug target that blocks abnormal Growth factor (GF) release signals. The pink gamma represents drug target that enhance DNA repair mechanism. The red gamma shaped represents a drug target involved in selective toxicity. The green gamma represents a strengthened or boosted immune system attacking mutant cells.

These approaches can be summarized under the following listed targets:

- I. Improved and more specific choice and scheduling of cancer treatment
- II. Attack the cancer (by selective toxicity)
- III. More research into other chemicals or signalling technique that is either tumour specific or specific to the normal cells. For instance, other chemicals or factors that initiate and sustain angiogenesis in cancer cells.
- IV. Support the immune system
- V. Boost normal cell fitness
- VI. Restore a more normal ecological niche

3.9.1 Implication to Nursing

Whatever treatment would be used to treat a particular cancer in a patient had to be carefully considered and the patient must have been planned for the intervention even before any treatment commence. Even if the treatment had to be only surgery or surgery along-side with chemotherapy; the patient and his relatives had to have all these care or procedures explained to them and a date given for commencement with credible follow-up. Fortunately most of these is the function of the nurse rendering care to the patient. According to [81], achieving good cancer outcomes depends on individual, family and community abilities to act appropriately on risk related information. The capacities needed to overcome the shock of receiving a diagnosis of a potentially fatal illness and to cope with the longer term stresses of treatment and survival after life changing events play an essential role in optimising therapeutic results. Simply instructing patients about accepting treatments is no substitute for working with them and respecting each individual's freedom to choose how they should face serious illness and defend their own best interests [82]

3.9.2 Implication to Medicine and Surgery

Several interventions should be considered as the case may be one after the other or it runs concurrently depending on the kind of tumour and the site. No sole method of intervention should be trusted by care givers because the behaviours of neoplastic growths which might however escaped most if not all our diagnostic measures. According to [82] treatment realities mean that there can never be a single, low cost, 'magic bullet' technical solution to overcoming all the challenges that cancer presents.

Likewise, for health professionals concerned with protecting, treating and supporting people experiencing cancer, minimising harm today demands models of practice far removed from traditional paternalistic patterns of care. [81] Stated that in future decades combinations of innovative medicines coupled with enhanced radiological and surgical interventions will, , mean that many more individuals with advanced cancers will be cured, or enabled to live with them in a fulfilling manner, provided research investment levels are maintained.

3.9.3 Implication to Pharmacy/Pharmacology

New areas (As seen in the above Figure) in which cancer can be managed with minimal side effects should be looked into majorly by Pharmacist and Pharmacologist. However, it is still the responsibility of every other aspect of science. As NHS England's October 2014 *'Five Year Forward View'* [83] highlights, from a strategic perspective achieving improved cancer outcomes will depend on both widening and deepening cancer prevention, detection and treatment. 'Widening' in this context means involving every member of the population more effectively in their own protection and care, and when appropriate in that of others close to them.

3.9.4 Implication to other Allied Health professionals

All allied health professionals are to join in this big 'war against cancer' as stated by the US president Richard Nixon in 1971 [84]. *'Winning the cancer war'* in the twenty first century will in part require reforming health care cultures which discourage the reporting of 'minor' symptoms that can be indicative of serious disease. All cancers are most effectively treated at an early stage. But there is also a need for better therapies (including specific cancer typing) and supportive care for people with more advanced and metastatic cancers [81]. More research areas like other initiating factors of angiogenesis should be given attention and grants should be channelled towards understanding some other chemicals or signalling factors that makes cancer thrive and so difficult to combat. The psychosocial aspect of the cancer patient should also be considered. Grants should be available for the purchase of drugs or better still the drugs made available in a subsidized rate. [85] Stated that a number of observers appear to believe that the costs of improving cancer care are threatening to become unaffordable in richer as well as poorer nations.

4.0 Conclusion

A lot of work had been done on trying to understand the mechanism of operation of neoplastic growth especially its behaviour at the later stage called metastasis responsible for most death in cancer patients. More so, the 20th century had witnessed the re-awakening of the Darwin's theory of natural selection especially as it applies to neoplastic growth. However, most literatures had not really been able to pin point which direction is next now in the war against cancer. As most scientist now struggle to find a lasting cure to cancer however the aspect of 'minimal side effects should also be taken into consideration. These few reviewed literatures had been able to update our understanding and as well pave way by proposing the possible means by which cancer can be properly eradicated especially when each proposed point is meticulously considered. It include: Improved and more specific choice and scheduling of cancer treatment, Attack the cancer (by selective toxicity), More research into other chemicals or factors that initiate and sustains angiogenesis in cancer cells (Tumour or human specific), Support the immune system, Boost normal cell fitness and Restore a more normal ecological niche. I believe with this we are a step closer to winning the war against cancer.

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