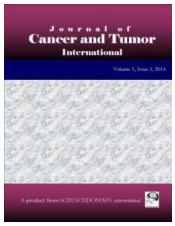

Journal of Cancer and Tumor International
4(4): 1-16, 2016; Article no.JCTI.27710
ISSN: 2454-7360

SCIENCEDOMAIN *international*
www.sciencedomain.org

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

Emmanuel O. Adesuyi[1*], Doubra A. Obaila[1] and Mojisola A. Aladeyelu[1]

[1]Institute of Nursing Research, (INRFCNSWZ), Nigeria.

Authors' contributions

The main author designed, analyzed, interpreted and prepared the manuscript. The co-authors assisted in other aspect of the research.

Article Information

DOI: 10.9734/JCTI/2016/27710
Editor(s):
(1) Rafael Roesler, Cancer Research Laboratory, University Hospital Research Center, Federal University of Rio Grande do Sul, Brazil.
(2) Sung-Chul Lim, Industry-Academic Cooperation Foundation, Chosun University, South Korea.
Reviewers:
(1) Vasa Jevremovic, American Northwest University, USA.
(2) Roland Sennerstam, Karolinska Hospital and Karolinksa Institute, Sweden.
(3) S. N. Nagendra, Scintilla Academy for Applied Sciences' Education & Research, USA.
(4) Felisbina Queiroga, Uniersity of Trás-os-Montes and Alto Douro, Portugal.
Complete Peer review History: http://www.sciencedomain.org/review-history/17156

Review Article

Received 15th June 2016
Accepted 30th August 2016
Published 7th December 2016

ABSTRACT

This review is intended to take us through a journey on how cancer had been treated and highlight the paradigm shift in understanding its treatment since adoption of evolution concept and hope to point to a possible future breakthrough in cancer management. Researchers estimate there will be 26 million or more new cases a year by 2030, and some 17 million cancer deaths yearly. The US president in 1971 Richard Nixon proposed the war on cancer in a bid to find lasting cure to cancer in the space of 25 years. An evaluation was carried out after 25 years, which, showed that although there had been major breakthrough in the battle against cancer yet the war continues and we are not yet close to 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 framework 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. Early diagnosis taking into cognizance polyploidy parameters, 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

**Corresponding author: Email: cyrusunikmedicalgroup@gmail.com;*

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. BACKGROUND TO THE STUDY

The fact that cancer is the leader of all modern maladies when viewed in certain ways is not an issue to quibble on [1]. Over the years, the most common ways of treating cancer had been surgery and radiotherapy. Focusing on inhibiting and complete eradication of the primary tumour had been a major concern because it is the major cause of the patient's symptom. Local spread of the tumour may cause unbearable symptoms and the inability to eradicate the primary tumour may cause death. In several tumours like the breast cancer, the focus of treating the tumour had been channelled towards identifying the best method of eradicating the primary tumour. Although this method had greatly improved the management of the disease yet the prognosis had been odious since the major cause of death is metastasis, [2]. Most of the time the primary tumour would have metastasize even before it is detected and treatment commenced. The future outcome is therefore not affected by treating the primary tumour though the primary complaint of the patient had been solved. Obviously, treatment had proceeded on a slow but steady pace, [3].

Understanding mutation, cancer genes and their extent of heterogeneous expression in cancer cells during cancer evolution is the onus of precision medicine. Thousands of somatic aberrations such as missing/substituting base pairs and duplication of whole genome had been observed in sequenced tumours [4].

Evolution had been the major means for acquisition of somatic aberrations [5]. Most of these aberrations may probably be events (passengers) that do not favour cancer cells during natural selection, only few referred to as driver events favours the cancer cells during natural selection [6]. There are evidences that depict that cancer cells do not contain all kinds of mutation (passenger and driver events) [7,8]. Although the characteristics of a mutation in the genome of a cancer cell can reveal the active process of mutation in its evolutional journey [9], the life history of tumours can be gotten from the measure of its heterogeneity and behaviour [10,8]. The clinical implication in relation to efficiency of anticancer therapies of this behaviours and heterogeneity as it orchestrates tumour evolution with respect to time is very essential [11]. Drug resistance accumulated overtime is a major hindrance to the successful treatment of cancer. Environmental factors of the host and epigenetic changes in cancer cells can initiate resistance. The dynamics of resistant mutation in tumour cells had been understood in the light of evolutional theories. We have also been able to understand how possible it is for resistance to develop even before the commencement of therapy, drugs that may prevent resistance and treatment schedule of patients with tendency of developing resistance [12].

Obviously, evolution by natural selection is the bedrock of life as its relevance to cancer can't be underestimated. Somatic cell evolution as a fundamental process of cancer formation was first opined in the 1970s' and supported ever since as it elaborately demonstrate its agreement with natural selection in Darwin's theory of evolution. Gadgets for detailed analysis of cells and biopsies showing several genes in cancer at a particular time have been made possible through cancer genomics. We must note that every patient's cancer has a unique clonal architecture and evolutional makeup. This then alters our perception of the basic study of cancer, initiation of drug resistance and our various methods of controlling. It also explains why human beings are vulnerable to cancers. Evolutionary basis of cancer is therefore a conceptual framework of every study 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. METHODS

Eighty five pertinent literatures by various authors were reviewed from several journals, most of which are recent. These literatures were sought using the keywords "cancer and

evolution," "cancer cureand evolution," "evolutionary measure of understanding and treating cancers," "evolutionary basis of metastasis," "Darwin's natural selection and cancer. We searched PubMed, academia and research gate for articles addressing evolution and cancer. The reference sections were reviewed of identified articles to locate additional publications not found in our initial search. Each article was reviewed noting its date of publication, geographic location, and study type, use of qualitative and/or quantitative methods, and key results and conclusions. It was then assigned to one of three mutually exclusive content categories, based on the authors' primary focus.

3. FINDINGS

3.1 Why Cancer is now Very Common in Human

Cancer is a disease characterized by speedy proliferation and replication of cells that have accrued mutations in their genome, which now results in a tumour mass. Metastasis is what differentiates a benign tumour from a malignant one [14].

Cell proliferation is essential in tumorigenesis because mutations had to be fixed into progeny cells especially in cells that retain the ability to regenerate. This then leads to the formation of benign or malignant sporadic tumours [15]. One single mutation in a genome may initiate cancer. Accommodation of additional mutations is what makes the normal cell an aberrant cell [16].

Mutation of p53, Rb or p16INK4a/ p14ARF tumour suppressors and Ras oncogene results in the proliferation of the cells excessively [17,18] with possibility of accommodating additional mutations in every cell division. Cells soon or later accommodate myriads of mutation to trigger endless peer review under responsibility of changing medical growth and tumour formation [19].

This further suggests that quick turnover cells with short latent period may have higher probability of developing neoplasia [20]. The reason why these quick turnovers develop into tumours is more than inability of cell proliferation to repair mutation in progeny cells from an evolution perspective [21]. Thousands of DNA samples sequenced from several kinds of cancers found only 138 genes that drives 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 had undergone evolutionary changes due to an increased knowledge about biological concept of tumorigenesis. It started with evidences of tumour removal by surgical intervention in ancient Egypt. 1896 and 1899 respectively witnessed the advent of hormone and radiation therapy. Newer therapies such as immunotherapy, chemotherapy, and other specific therapies were inventions of the 20th century. Increase in knowledge about cancer biology will lead to the development of new approaches to treatment and thus increases the chances of survival for cancer patients [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. 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.

3.3 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 the removal either 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 recover [28].
- **Radiation Therapy:** The main objective of radiation therapy is to shrink tumours by destroying a considerable number of cancer cells and at the same time ensure little or no damage is done to close by healthy tissues [28].
- **Targeted Therapy:** It constitutes the use of specific agents against certain molecules (usually deregulated proteins) of cancer cells. [29]. This is currently a new trending 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:** Drug targets that prevent the proliferation of blood vessels (angiogenesis) required for the survival of tumours. One of the major challenges facing the use of angiogenesis inhibitors in clinical settings is the several known and unknown factors that initiate the proliferation of blood vessels both in normal and cancer cells. The present anti-angiogenesis drugs were made to target just one of the factors, thereby leaving other factors to complement for the absence of the attacked factor. Other challenges includes: specifically targeting the cancer vasculature, sustaining the drug action and drug administration route [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].

3.4 The Continuous Menace of Cancer

The following disciplines in biomedicine: molecular biology, human genetics, health psychology, and medical sociology had experienced a very rapid and continuous growth, which have led to more knowledge about cancer in the past two decades than in the preceding 200 centuries [26]. Although this increasing progress is laudable, yet cancer remains a leading cause of suffering and death throughout the world [32]. In 2013, 325,000 new cases of cancer were diagnosed in Britain, with 150,000 recorded deaths. Half of the diagnosed persons were 70 years of age and above, while just over half of the deaths due to cancer in that year were recorded in individuals 75 years of age and above [33].

Globally, it has been predicted that the burden of death and disability on populace of the world will remarkably rise from now to 2050, unless the breakthroughs now recorded amidst scientists working in affluent nations like Britain and US and upcoming economies like China can be developed and implemented on a universally. Presently there are 8 million recorded deaths per year due to cancer and 14 million new diagnosed cases yearly throughout the world [34]. It is however; worthy of note that countries with high economy like Europe and North America spends 6-7 per cent of all health spending on cancer care [35].

The data presented in the Table 1 with the exception of tobacco smoking showed that, it would be wrong to over-state the level of effect life style modifications can have on a person or community in relation to prevention of cancer. In contrast, life style changes, mostly when it is in combination with the use of vaccination, early diagnosis, and treatment, have the capacity to reduce to halve the current age standardized cancer death rates [36].

3.5 Metastasis

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

The body in the course of removing cancer cells mobilizes macrophages or other immune factors for surveillance. The unknown thing here is who is usually detected first, the weaker cancer cell that loses in the cell war, or the stronger ones that won the battle. Moreover, sometimes after being engulfed by scavengers, the cancer cell remains undigested resulting in hybrid (fusion) with the ability to metastasis [39]. Cancer's ability to become metastatic through fusion with other cells including the immune cells, which gives it the transporting capacity, was proposed 100 years ago. [40,39] and examined 40 years ago

with ample evidence [41]. At times metastasis is seen to have occurred years before even with very early removal of the primary tumour. This may be because of possible transportation of cancer cells (loser and winner cells) to other parts of the body by surveillance immune cells. However, we are left with the question of which of the two (winner or loser cells) has the better capacity to evade capture by this surveillance immune cells and then uses this tactic to escape the body's surveillance and invade other sites in the body.

Mutations favouring metastasis occurs first in some cells of the primary tumour to accommodate for breaking away tumour cells from the tumour mass and their residence in another body site. Furthermore, the disparities that are observed in mutations occurring in primary, metastatic, therapy sensitive and resistant tumours are considered quantitative rather than qualitative since mutation is easily detected by its appearance in more cells, due to clonal expansion by natural selection [21].

3.6 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 leads to an increased rate of somatic aberrations, which varies from minor to chromosomal mutations then to whole genome duplication. This instability may add to heterogeneity within the tumour by supplying diverse of mutations that can confer selection benefits to the cancer cells within its microenvironment [10].

Different cell types in a cancer patient interact [47,48]. They begin by recruiting normal stromal cells in a bid to create their own cancer ecological niche initiated by tumour angiogenesis [49]. Then collaborates with each other [50], evidently seen in their collective invasion, *in vivo*, *in vitro* [51], and clonal cooperation in animals [52,53] since there is a lower survival rate of many cancer cells seeded in a very low density in a culture dish [54].

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

Factors	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)

3.6.1 Ecology and Darwin's natural selection

Functional gain of oncogenes and functional loss of tumour suppressor genes are cogent steps in clonal expansion through natural selection, either of the two offers cell growth the survival advantage in its specific microenvironment. Therefore, as natural selection is established by several random and stochastic mutations it in turn results in the most basic molecular profile of cancer cells, which includes functional gain of oncogenes and functional loss of tumour suppressor genes. More precisely, the drivers of cancer formation or progression are not really these common alterations stated above [22,56] but rather, the products of natural selections from the several mutations occurring as happenstances. More so, selection depends on chance, as it had to wait for a mutation or sets of synergistic mutations that offer an advantage to its choice of selection and only God can tell how long that will take. This then mean that natural selection in evolution as it occurs by clonal expansion after a functional gain of oncogene and a functional loss of tumour suppressor takes a very long time and may be the reason why cancer formation takes many years [21].

Carcinogenesis is a process of sequential gene mutations that offers advantage called drivers to the growth of cells although sessions of driver mutations differs with the different cell types [22]. Carcinogenesis is a continuous process known to result in cells of greater malignancy, which invades the surrounding tissue, metastasis to distant body sites, and resist therapies. These may be because of the accumulation of more DNA mutations by each cell as the cells gradually loses their DNA damage response and

repair mechanism and thus are unable to repair the continuous emerging mutations. Natural selection ensures selection is made from all these mutations especially the ones with growth or survival advantages (Fig. 2). This selection process in one way resembles Darwin's illustration of selection in Mother Nature at organismal development. However, the slowness of the changes in Mother Nature like millions of years may also mean slowness in organismal evolution. On the contrary, a continuous increase in the size of the tumour mass, and weakness in the patient's health rapidly changes the cancer's microenvironment. As a result, cell clones with greater diversity are selected more and quickly. Although, the tissue environment can change in the shortest time, especially in the presence of therapies, which in turn changes cancer cells, as it is a struggle for survival. For instance, the one-time friendly environment around cancer cells suddenly becomes hostile during radiation therapy. This then necessitates an immediate response from the cancer cells in a bid to adapt to the new hostile environment some of which could be non-genetic approaches, such as protein phosphorylation or RNA editing. Electronic imaging showed that some cancer cells chose to phosphorylate an oncoprotein while others cannot do this because of mutation of the gene coding kinase or oncoproteins and therefore proceeds to edit another gene's mRNA instead [57]. The beauty of these disparities is seen collectively displayed as heterogeneity of eventually selected clones that survived. More so, as shown in Fig. 2 increase in cellular heterogeneity by mutation as seen in somatic cell evolution occurs in an asexual manner.

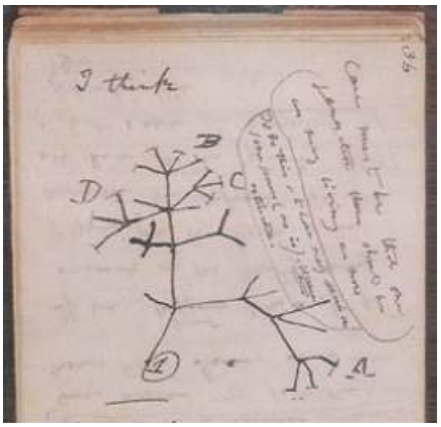

Fig. 1. Darwin's evolution tree
Darwin's branching evolutionary tree of speciation from his 1837 notebook [55]

In sexual propagation, sex functions to purge altered genome and maintain the species identity no matter how many generations had passed. Heterogeneity is therefore widened due to these basic differences [58]. We must understand that even though a primary tumour mass has virtually been detected for all mutations needed for a phenotype of more malignancy, no cell has been discovered to bear all these mutations without a length of time. Since time is still needed for individual cells of the tumour to accumulate all the mutations required for presenting more aggressive phenotype. Equipping a single cell with all the required mutations is just the first phase of evolution which will be proceeded by natural selection (phase II) by clonal expansion of this equipped cells to present certain phenotypes such as drug resistance [21].

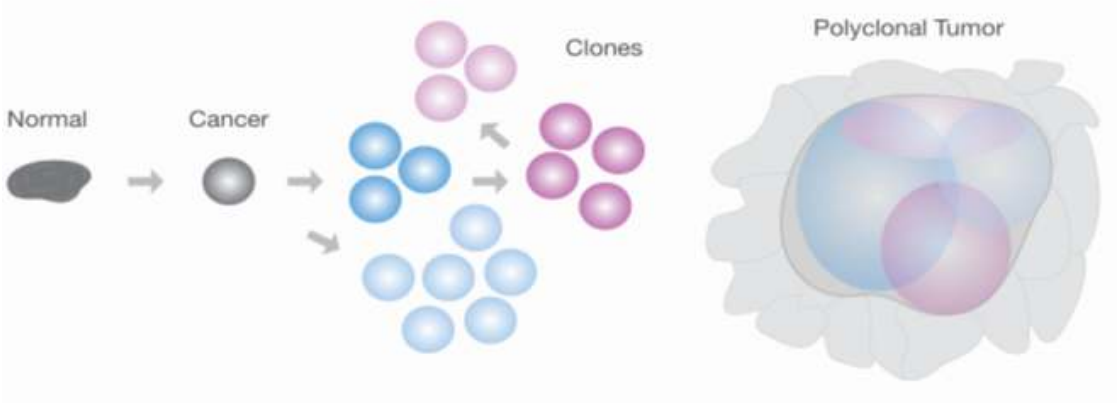

Fig. 2. Intratumour heterogeneity
Fig. 2 represents Intratumour heterogeneity. The progressive accumulation of somatic mutations results in a heterogeneous polyclonal tumour in which different clones may respond differently to treatment. Source: [58]

3.6.2 Polyploidization

Polyploidization is an important evolutionary force which refers to the increase in genome size caused by the inheritance of an additional set (or sets) of chromosomes. It is a process where two or more genomes are brought together into the same nucleus, usually by hybridization followed by chromosome doubling. This duplicate chromosomes may emerge from related or the same individual species (autopolyploid) or from hybrids (allopolyploids). This represents one of the most dramatic mutations known to occur [59].

Deficiencies resulting in abortive cell cycles including cell fusion, endoreplication and abortive phagocytosis, are the major mechanism of polyploidization. Unregulated endoreplication favours the growth of cancer cells thereby accommodating chromosomal instability. This is one of the way in which cancer is connected to polyploidy [60]. This process (endoreplication) can either promote or inhibit cancer growth with respect to tissue microenvironment and genetic makeup [61].

Instant phenotypic effects are observed in individuals with genomic changes. These instantaneous changes may permit evolutionary trends that were not initially possible. Polyploidization may also initiate more changes in the structure of the genome producing generations of polyploidy with several variations not present in diploid genomes. Tetraploidy had been proposed to be an intermediate stage in certain cancers resulting in structural changes that hinders the normal control of cell proliferation [62].

- **Tetraploidization:** Cancer development occurred in a stepwise model from diploid → tetraploid → aneuploidy cells, corresponding to a sequence of normal acinar cells to hyperplasia to dysplasia and ultimately to invasive cancer. Tetraploidization refers to genome doubling. It can initiate chromosomal instability, possibly because of the doubled chromosome mass and supernumerary centrosomes. Aneuploidy karyotypes are formed when a persistent chromosomal instability eventually gives way. The both of them are commonly observed in cancers. Of recent, an increase in the number of chromosomes had been proposed to promote cell transformation and thus result in an aneuploidy tumour. Most malignant tumours have been found to have an abnormal karyotype with multiple structural and numerical aberrations of chromosomes – so-called aneuploidy [63].

The following may be explained by tetraploid: centrosomes are frequently seen in cancer cells, tetraploidy is common especially in the early stages of tumour growth, and tumour cells had usually contained very high chromosome numbers often difficult to explain. Unscheduled tetraploidy can arise by one of three main mechanisms: cell fusion, mitotic slippage or a failure to undergo cytokinesis, [62]. The tetraploid intermediate model shows that defect in some genes can result in tetraploidization, which in turn leads to aneuploidy and tumorigenesis. In fact, mutations in some well-known oncogenes have recently been shown to induce tetraploidization. Interestingly, tetraploidization of primary cells was discovered in patients diagnosed with Gardner syndrome several years ago [64]. Gardner syndrome occurs by hereditary mutation although now referred to as familial adenomatous polyposis [65].

Cancer cells can fuse with normal cells (stromal, epithelial, macrophages), and with other cancer cells. Depending on the cell type in the fusion event, the hybrid has novel properties [66] and increased heterogeneity [67]. Polyploid giant cells (PGCCs) are chemo-resistant cells resulting from the fusion of cancer cells [68]. This fusion with macrophages can initiate cancer metastasis [69]. Polyploidy cells contain abnormal chromosomes that make it quite unstable and suggest its connection to disease like cancer [67]. Aneuploidy is commonly seen in human cancer, which refers to cells carrying abnormal number of chromosomes resulting from several proliferations of polyploids [62]. Tetraploidization refers to the doubling of genomic codes that have acquired chromosomal instability and majorly found in colorectal cancer. [70].

An elevated level of tetraploidy was previously reported in women diagnosed by the Papanicolaou smear as Atypical Squamous Cells of Undetermined Significance (ASCUS) and in combination with Human Papilloma virus (HPV)-positive cells [71], and might represent a conserved reaction to stress caused by the HPV infection or by fusogenic proteins. This study is of particular interest because diagnosis

of pancreatic cancer frequently identifies aneuploid tumours because the tumour is first apparent when liver metastasis is established [72].

3.6.3 Cell war; possible targets for cure

Several cancers such as testicular cancer and gestational choriocarcinoma are curable because they arise without lengthy selection and progression, as inferred by [73].

There is war among different cell types. The cancer cells are being fought by the normal cells surrounding it for fitness of the patient at the early stage of the tumour growth [74,75]. Cytokines or microRNAs can kill or inhibit cancer cells by secreting substances similar to antibiotic secreted by a bacterium to kill another microorganism. This have been found in media used to culture normal cells. Let us assume the normal mammary or prostate epithelial cells release this kind of factors to the media to kill or inhibit breast or prostate cancer cells, respectively. If we consider these observations in clinical oncology and if the proposition is true then the serum of the patient should contain these factors that inhibits or kills cancer cells thereby favouring the patient's health especially at the early stage of the disease [76,77]. This proposition is in consonance with the neighbouring suppression concept opined 50 years ago, which stated that the growth of neighbouring potential malignant cells can be hindered by normal cells [78], by probably stopping them at the gap 2 phase of the cell cycle [79]. In order to survive, the premalignant cells and may be the malignant ones too had to neutralize such inhibition by acquiring additional genetic or epigenetic changes. As soon as the cancer cells becomes dominant by progressing to the advanced stage they may also begin to release factors into systemic circulation that can eliminate normal cells in the affected cell and other tissue or organ [80]. Cachexia, or muscle wasting, could be one of the manifestations. These complex interactions among the different cell types is worthy of note when viewed from an ecological point as it could be inferred that a breakage in the balance of these interactions will make one cell type dominate and extinct the other which suggests a possible way of cancer prevention and cure.

Although these cancer cells collaborate as above mentioned, yet they also struggle with each other for sustaining resources [81], which may be due to heterogeneity [82]. Metastatic cells are more agile because of their aggressiveness when viewed from the platform of cell-autonomy. However, from biological dispersal point of view, the cells that win in the competition have no compelling reasons to relocate since they now have access to the oxygen and nutrient in that habitat and are well adapted to it, whereas death may ensue if the losers do not relocate [83]. Therefore, it is logical to assume that defeat from the cell competition war initiates near and distant metastasis and the loser cells are forced to leave their present habitat to surrounding tissues for survival [84]. This assumption deserves exploration as it provides us with new clues to understand the behaviour of cancer cells and highlights other possible reasons like metabolic changes for cancer cell dispersal [85,86]. There is also a possibility of dispersal of winner cells if the new habitat has a better living condition. Considering this, the metastatic cells are weaker and may later gain competence at the metastatic site as they develop colony where a new platform of war (cell competition) is staged leading to new set of winners and losers. If this is true, then there is the possibility of destroying the pioneering cells with invasive tendencies within the primary tumour by assisting the winner cells to clear off the losers or better still by quickly cutting them off all resources before they disperse. In another way, tentatively easing their sufferings by supplying them with nutrients for a while so they could stay within the primary tumour without thinking of relocating would improve the patient's prognosis if surgery is done at this stage to remove the primary tumour [87,88,89].

3.7 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 Fig. 2) where each clone has a unique set of mutations, unique pathology, and unique drug responses, [90,91].

Drug resistance in cancer cells may occur because of factors, which includes the host environment and genetic or epigenetic alterations. Acquisition of this resistance had been a major limitation to success in cancer cure. The theories of evolution had made it possible for us to understand the dynamics of

resistance mutations, possibility of pre-existing resistance even before commencing treatment, the composition of essential drugs that may prevent the initiation of resistance, and accurate scheduling for drug administration to people at risk of possible acquired resistance [92]. Factors of the host organism such as poor absorption and rapid metabolism can reduce the total concentration of the drug in the gastrointestinal tract blood stream or the tumour itself; this mechanism is often referred to as intrinsic resistance. In addition, mechanical or biochemical factors may present challenges to the delivery of drugs into tumours. Alternatively, cancer cells may evolve specific genetic and/or epigenetic alterations that allow them to escape from treatment. Some of these alterations, such as loss of a cell surface receptor or transporter and over expression or alteration in the drug target, lead to resistance against only a small number of related pharmacological agents. For example, over expression of EGFR has been associated with resistance to the EGFR-inhibitor cetuximab [93].

Generally, patients do not detect tumours until it later stage when metastasis had commenced. During this period, there is a poor prognosis of the condition. Surgical removal of the tumour mass may be attempted followed by chemotherapy and radiotherapy. Tumour mass are not made up of homogenous cancer populations but rather heterogeneous cancer populations (Fig. 3) [94].

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.

3.8 Eco-evolutionary Approach to Cancer Cure

Recommended Eco-evolutionary (ecology and evolutional) 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.

Fig. 4 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.

Fig. 4 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. Early diagnosis taking into cognizance polyploidy parameters.
II. Improved and more specific choice and scheduling of cancer treatment
III. Attack the cancer (by selective toxicity)
IV. 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.
V. Support the immune system
VI. Boost normal cell fitness
VII. Restore a more normal ecological niche.

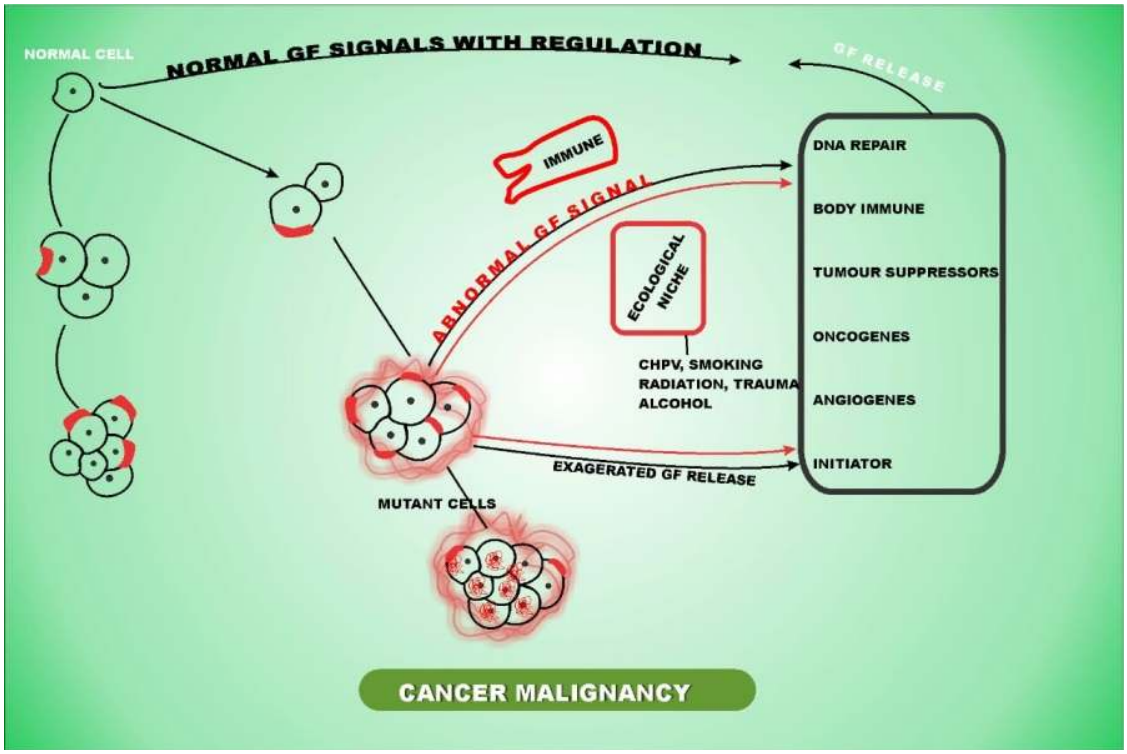

Fig. 3. Cancer malignancy

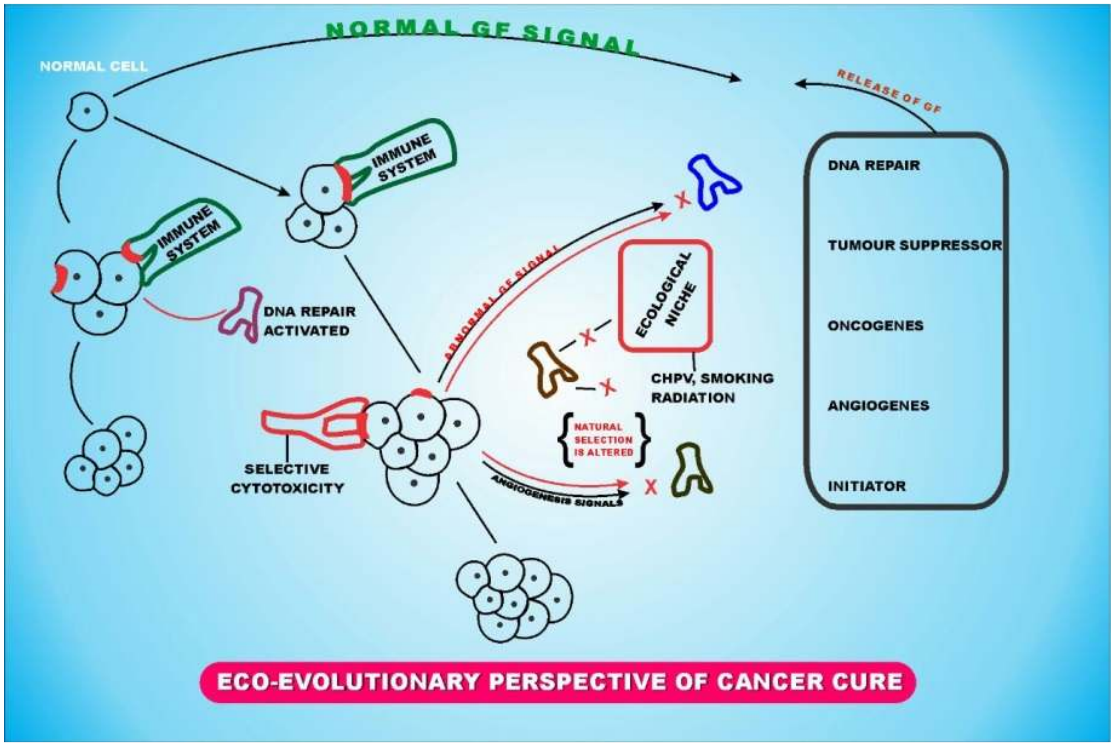

Fig. 4. Eco-evolutionary perspective of cancer cure

3.8.1 Implication to early diagnostic evaluation

Understanding the evolutionary trend in the life cycle of neoplasia is pertinent in the early diagnosis of tumours and may be a life-saving technique for cancer patients. The behaviour of cancers from an evolutionary point of view may be considered as future signals or biomarkers to early diagnosis and treatment of cancers. The study of polypoidy especially tetraploidization and aneuploidy could also be considered as parameters or indexes for detecting certain cancers in time. For instance, spontaneous tetraploidization of primary cells from patients diagnosed with Gardner syndrome was observed several decades ago [64]. The diagnosis of pancreatic cancer also frequently identifies aneuploid tumours because the tumour is first apparent when liver metastasis is established [72]. Most malignant tumours have been found to have an abnormal karyotype with multiple structural and numerical aberrations of chromosomes – so-called aneuploidy. [63]. This study could therefore shed more light on how certain cancers could be diagnosed early before they get out of hand.

3.8.2 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 are the function of the nurse rendering care to the patient. According to [95], individual, family, and community abilities to take quick and meaningful actions on risk related information determines good cancer outcome achievement. The various groups must first overcome the shock of receiving a diagnosis of a potentially fatal illness like cancer; prepare to cope with the longer-term rigour of treatment and survival after the many activities during the course of treatment. We cannot substitute merely instructing or persuading the patient to consent to treatment with respecting their right to choose how to face the serious illness before them and our cooperation with them in defending their interest [96].

3.8.3 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. Caregivers should trust no sole method of intervention because the behaviours of neoplastic growths, which might however escaped most if not all our diagnostic measures. According to [96] challenges that cancer presents cannot be absolutely overcome by one way or one method technical solution. Also, models of practice far better than the traditional pattern of care should be embraced by health professionals concerned with protecting, treating and supporting cancer patients. [95] proposed that many individuals with more advanced cancers will be cured by combinations of therapies such as innovative medicine, radiology ad surgery in decades to come if the level of investment into research is maintained.

3.8.4 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 [97] suggested that widening and deepening cancer prevention, detection and treatment will improve cancer outcomes. Widening and deepening means getting every members of the population involved in the three methods stated above.

3.8.5 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 [98]. Reformation of health cultures that stands against reporting of minor symptoms that may suggest a serious sickness may be a step towards w*inning the big war against cancer* in the twenty first century as most cancers are most effectively treated at the early stage. However, there may also be need for more effective therapies with the advancement of technology and supportive care for patients with advanced metastatic cancers [95]. 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. [99] discovered that some of his respondents do believe that the financial implication for treating cancer is gradually becoming unaffordable in both developed rich and poor nations.

4. 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, which is 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, 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: Early diagnosis taking into cognizance polyploidy parameters, 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.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Mukherjee S. The emperor of all maladies: A biography of cancer. Clays Ltd; 2011.
2. Available:http://www.slideshare.net/parichayrao/cancer-and-its-management-7-ed2015-jeffrey-tobias-and-daniel-hochhauser
3. Jeffrey T, Daniel H. Cancer and its management. 6th ed. Blackwell Publishing; 2010.
4. Nicholas M, Swanton C. Biological and therapeutic impact of intratumor heterogeneity in cancer evolution. Cancer Cell. 2015;27. Elsevier Inc. Available:http://dx.doi.org/10.1016/j.ccell.2014.12.001
5. Nowell PC. The clonal evolution of tumor cell populations. Science (New York, NY). 1976;194:23–28.
6. Kandoth C, McLellan MD, Vandin F, Ye K, Niu B, Lu C, Xie M, Zhang Q, McMichael JF, Wyczalkowski MA, et al. Mutational landscape and significance across 12 major cancer types. Nature. 2013;502: 333–339.
7. Swanton C. Intratumor heterogeneity: Evolution through space and time. Cancer Res. 2012;72:4875–4882.
8. Yates LR, Campbell PJ. Evolution of the cancer genome. Nat. Rev. Genet. 2012; 13:795–806.
9. Helleday T, Eshtad S, Nik-Zainal S. Mechanisms underlying mutational signatures in human cancers. Nat. Rev. Genet. 2014;15:585–598.
10. Burrell RA, McGranahan N, Bartek J, Swanton C. The causes and consequences of genetic heterogeneity in cancer evolution. Nature. 2013a;501:338–345.
11. Fojo T, Mailankody S, Lo A. Unintended consequences of expensive cancer therapeutics-the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity: The john conley lecture. JAMAO Tolaryngol. Head Neck Surg. Published; 2014. Available:http://dx.doi.org/10.1001/jamaoto.2014.1570.
12. Jasmine F, Franziska M. Evolution of acquired resistance to anti-cancer therapy. Journal of Theoretical Biology. 2014;355: 10–20. Available: www.elsevier.com/locate/yjtbi
13. Centre for evolution and cancer. The Institute of Cancer Research, London; 2015. Available:http://www.icr.ac.uk/Media/centres-...

14. Sylvia OI. Cancer stem cells may contribute to the difficulty in treating cancer. Elsevier B.V Genes & Diseases. 2016;3:7e10.
Available:http://dx.doi.org/10.1016/j.gendis.2016.01.001
15. Lou X, Zhang J, Liu S, Xu N, Liao DJ. The other side of the coin: The tumor-suppressive aspect of oncogenes and the oncogenic aspect of tumor-suppressive genes, such as those along the CCND-CDK4/6-RB axis. Cell Cycle. 2014;13(11): 1677-1693.
16. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100:57e70.
17. Sherr CJ. Principles of tumor suppression. Cell. 2004;116:235e246.
18. Weinberg RA. The biology of cancer. 2nd ed. New York, USA: Garland Science, Taylor and Francis Group LLC; 2013.
19. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell. 2011; 144:646e674.
20. Jia QW, Chen XH, Jia YP, Dou XX, Ezeogu L, Xu NZ, et al. Is type 2 diabetes one of such aging phenomena that lack an irreversible structural change? J Diabetes & Metab. 2015;6:6:543.
DOI: 10.4172/2155-6156.1000543
21. Zhang J, Lou XM, Zellmer L, Liu SQ, Xu NZ, Liao DJ. Just like the rest of evolution in Mother Nature, the evolution of cancers may be driven by natural selection, and not by haphazard mutations. Oncoscience. 2014;1(9):580-590.
22. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr., Kinzler KW. Cancer genome landscapes. Science 2013;339(6127):1546-1558.
23. Martincorena I, Roshan A, Gerstung M, Ellis P, Van LP, McLaren S, et al. Tumor evolution. High burden and pervasive positive selection of somatic mutations in normal human skin. Science. 2015; 348(6237):880-886.
24. Sudhakar A. History of cancer, ancient and modern treatment methods. Journal of Cancer Science and Therapy. 2009; 01(02):1-4.
25. WHO Cancer Treatment; 2016.
Available:http://www.who.int/cancer/treatment/en/
(Retrieved 31st March 2016)
26. American Cancer Society. The history of cancer; 2014.
27. Subotic S, Wyler S, Bachmann A. Surgical treatment of localised renal cancer. European Urology Supplements. 2012; 11(3):60–65.
DOI: 10.1016/j.eursup.2012.04.002
ISSN: 1569-9056
28. Cancer Management.
Available:www.wikipedia.com/management
(Retrieved 4th May 2016)
29. Duarte FJ (Ed.), Tunable Laser Applications (CRC, New York); 2009. Chapters 5, 7, 8.
30. Kleinman HK, Liau G. Gene therapy for antiangiogenesis. J. Natl. Cancer Inst. 2001;93(13):965–7.
DOI: 10.1093/jnci/93.13.965
PMID: 11438554
31. Damodar S, Terunuma H, Abraham S. Autologous Immune Enhancement Therapy (AIET) for a case of Acute Myeloid Leukemia (AML) - Our experience. Pasrm. 2006-001.
32. Stewart BW, Wild CP. World cancer report; 2014.
Available:http://www.academia.edu/10233879/Ov...
33. Moller H, Flatt G, Moran A. High cancer mortality rates in the elderly in the UK. Cancer Epidemiology. 2011;35:407-12.
34. International Agency for Research on Cancer. Globocan 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012.
35. Sullivan R, Peppercorn J, Sikora K, Zalcberg J, Meropol NJ, et al. Delivering affordable cancer care in high-income countries. The Lancet Oncology. 2011;12: 933-80.
36. Parkin DM, Boyd L, Darby S, Mesher D, Sasieni P, Walker L. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. British Journal of Cancer. 2011;105.
37. Fidler IJ. Critical determinants of metastasis. Semin. Cancer Biol. 2002;12: 89–96.
38. Nguyen DX, Bos PD, Massague J. Metastasis: From dissemination to organspecific colonization. Nature Rev. Cancer. 2009;9:274–284.
39. Pawelek JM. Fusion of bone marrow-derived cells with cancer cells: Metastasis as a secondary disease in cancer. Chin J Cancer. 2014;33(3):133-139.
40. Goldenberg DM. Horizontal transmission of malignancy by cell-cell fusion. Expert Opin Biol Ther. 2012;12(Suppl 1):S133-S139.

41. Goldenberg DM, Pavia RA, Tsao MC. In vivo hybridisation of human tumour and normal hamster cells. Nature. 1974; 250(5468):649-651.
42. Merlo LM, Pepper JW, Reid BJ, Maley CC. Cancer as an evolutionary and ecological process. Nature Rev. Cancer. 2006;6: 924–935.
43. Pepper J, Scott Findlay C, Kassen R, Spencer S, Maley C. Cancer research meets evolutionary biology. Evol. Appl. 2009;2:62–70.
44. Jemal A, et al. Cancer statistics, 2008. CA Cancer J. Clin. 2008;58:71–96.
45. Stratton MR. Exploring the genomes of cancer cells: Progress and promise. Science. 2011;331:1553–1558.
46. Nowell PC. The clonal evolution of tumor cell populations. Science. 1976;194:23–28.
47. Marin A, Martin M, Linan O, Alvarenga F, Lopez M, Fernandez L, et al. Bystander effects and radiotherapy. Rep Pract Oncol Radiother. 2015;20(1):12-21.
48. Ebos JM. Prodding the beast: Assessing the impact of treatment-induced metastasis. Cancer Res. 2015;75(17): 3427-3435.
49. Kareva I. What can ecology teach us about cancer? Transl Oncol. 2011;4(5):266-270.
50. Korolev KS, Xavier JB, Gore J. Turning ecology and evolution against cancer. Nat Rev Cancer. 2014;14(5):371-380.
51. Friedl P, Locker J, Sahai E, Segall JE. Classifying collective cancer cell invasion. Nat Cell Biol. 2012;14(8):777-783.
52. Polyak K, Marusyk A. Cancer: Clonal cooperation. Nature. 2014;508(7494):52-53.
53. Cleary AS, Leonard TL, Gestl SA, Gunther EJ. Tumour cell heterogeneity maintained by cooperating subclones in Wnt-driven mammary cancers. Nature. 2014; 508(7494):113-117.
54. Zhu S, Wang J, Xie B, Luo Z, Lin X, Liao DJ. Culture at a higher temperature mildly inhibits cancer cell growth but enhances chemotherapeutic effects by inhibiting cell-cell collaboration. PLoS One. 2015;10(10): e0137042.
55. Caldas C. Cancer sequencing unravels clonal evolution. Nat Biotechnol. 2012;30: 408-410.
56. Weinberg RA. Coming full circle-from endless complexity to simplicity and back again. Cell. 2014;157:267-271.
57. Avesson L, Barry G. The emerging role of RNA and DNA editing in cancer. Biochim Biophys Acta. 2014;1845:308-316.
58. Heng HH, Stevens JB, Bremer SW, Liu G, Abdallah BY, Ye CJ. Evolutionary mechanisms and diversity in cancer. Adv Cancer Res. 2011;112:217-253.
59. Sarah P. Otto. The evolutionary consequences of polyploidy, cell 131, November 2, 2007 ©2007 Elsevier Inc. DOI: 10.1016/j.cell.2007.10.022
60. Fox DT, Duronio RJ. Endoreplication and polyploidy: Insights into development and disease. Development. 2013;140:3–12. [CrossRef] [PubMed]
61. McClendon AK, Dean JL, Ertel A, Fu Z, Rivadeneira DB, Reed CA, Bourgo RJ, Witkiewicz A, Addya S, Mayhew CN, et al. Rb and p53 cooperate to prevent liver tumorigenesis in response to tissue damage. Gastroenterology. 2011;141: 1439–1450. [CrossRef] [PubMed]
62. Storchova Z, Pellman D. From polyploidy to aneuploidy, genome instability and cancer. Nat. Rev. Mol. Cell Biol. 2004;5: 45–54.
63. Zuzana Storchova, Christian Kuffer. The consequences of tetraploidy and aneuploidy. Journal of Cell Science. 2008; 121:23.
64. Danes BS. Gardner syndrome-increased tetraploidy in cultured skin fibroblast. J. Med. Genet. 1976;13:52-56.
65. Rusan NM, Peifer M. Original CIN: Reviewing roles for APC in chromosome instability. J. Cell Biol. 2008;181:719-726.
66. Mohr M, Zanker KS, Dittmar T. Cancer (stem) cell differentiation: An inherent or acquired property? Med. Hypotheses. 2015;85:1012–1018. [CrossRef] [PubMed]
67. Coward J, Harding A. Size does matter: Why polyploid tumour cells are critical drug targets in the war on cancer. Front. Oncol. 2014;4:123. [CrossRef] [PubMed]
68. Zhang S, Mercado-Uribe I, Xing Z, Sun B, Kuang J, Liu J. Generation of cancer stem-like cells through the formation of polyploid giant cancer cells. Oncogene. 2014;33: 116–128. [CrossRef] [PubMed]
69. Seyfried TN, Huysentruyt LC. On the origin of cancer metastasis. Crit. Rev. Oncog. 2013;18:43–73. [CrossRef] [PubMed]
70. Daniel Bastida-Ruiz, Kylie Van Hoesen, Marie Cohen. The dark side of cell fusion. Int. J. Mol. Sci. 2016;17:638.
71. Olaharski AJ, Sotelo R, Solorza-Luna G, Gonsebatt ME, Guzman P, et al.

Tetraploidy and chromosomal instability are early events during cervical carcinogenesis. Carcinogenesis. 2006;27: 337-343.

72. Roland B Sennerstam, Jan-Olov Strömberg. Hyperdiploidy tetraploidization and genomic instability in breast cancer–a case report study. J Carcinogene Mutagene. 2013; 4:2.
Available:http://dx.doi.org/10.4172/2157-2518.1000144
73. Blagosklonny MV. NCI's provocative questions on cancer: Some answers to ignite discussion. Oncotarget. 2011;2: 1352-1367.
74. Wagstaff L, Kolahgar G, Piddini E. Competitive cell interactions in cancer: A cellular tug of war. Trends Cell Biol. 2013; 23(4):160-167.
75. Vivarelli S, Wagstaff L, Piddini E. Cell wars: Regulation of cell survival and proliferation by cell competition. Essays Biochem. 2012;53:69-82.
76. Furuta S, Jeng YM, Zhou L, Huang L, Kuhn I, Bissell MJ, et al. IL-25 causes apoptosis of IL-25R-expressing breast cancer cells without toxicity to nonmalignant cells. Sci Transl Med. 2011; 3(78):78ra31.
DOI: 10.1126/scitranslmed.3001374
77. Kosaka N, Iguchi H, Yoshioka Y, Hagiwara K, Takeshita F, Ochiya T. Competitive interactions of cancer cells and normal cells via secretory microRNAs. J Biol Chem. 2012;287(2):1397-1405.
78. Stoker M. Regulation of growth and orientation in hamster cells transformed by Polyoma virus. Virology. 1964;24:165-174.
79. Flaberg E, Markasz L, Petranyi G, Stuber G, Dicso F, Alchihabi N, et al. High-throughput live-cell imaging reveals differential inhibition of tumor cell proliferation by human fibroblasts. Int J Cancer. 2011;128(12):2793-2802.
80. Aktipis CA, Nesse RM. Evolutionary foundations for cancer biology. Evol Appl. 2013;6(1):144-159.
81. Kareva I, Morin B, Castillo-Chavez C. Resource consumption, sustainability, and cancer. Bull Math Biol. 2015;77(2):319-338.
82. Knauss S, Klein A. From aneuploidy to cancer: The evolution of a new species? J Biosci. 2012;37(2):211-220.
83. Taylor TB, Johnson LJ, Jackson RW, Brockhurst MA, Dash PR. First steps in experimental cancer evolution. Evol Appl. 2013;6(3):535-548.
84. Pienta KJ, Robertson BA, Coffey DS, Taichman RS. The cancer diaspora: Metastasis beyond the seed and soil hypothesis. Clin Cancer Res. 2013;19(21): 5849-5855.
85. Chen J, Sprouffske K, Huang Q, Maley CC. Solving the puzzle of metastasis: The evolution of cell migration in neoplasms. PLoS One. 2011;6(4):e17933.
DOI: 10.1371/journal.pone.0017933
86. Aktipis CA, Maley CC, Pepper JW. Dispersal evolution in neoplasms: The role of disregulated metabolism in the evolution of cell motility. Cancer Prev Res (Phila) 2012;5(2):266-275.
pii: 2014 0219
DOI: 10.1098/rstb.2014.0219
87. Aktipis CA, Boddy AM, Jansen G, Hibner U, Hochberg ME, Maley CC, et al. Cancer across the tree of life: Cooperation and cheating in multicellularity. Philos Trans R SocLond B BiolSci. 2015;370:1673.
88. Amend SR, Pienta KJ. Ecology meets cancer biology: The cancer swamp promotes the lethal cancer phenotype. Oncotarget. 2015;6(12):9669-9678.
89. Walther V, Hiley CT, Shibata D, Swanton C, Turner PE, Maley CC. Can oncology recapitulate paleontology? Lessons from species extinctions. Nat Rev Clin Oncol. 2015;12(5):273-285.
90. Gerlinger M, Rowan AJ, Horswell S, Larkin J, Endesfelder D, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med. 2012;366:883-892.
91. Landau DA, Carter SL, Stojanov P, McKenna A, Stevenson K, et al. Evolution and impact of subclonal mutations in chronic lymphocytic leukemia. Cell. 2013; 152:714-726.
92. Jasmine Foo, Franziska Michor. Evolution of acquired resistance to anti-cancer therapy. Journal of Theoretical Biology. 2014;35510–20.
93. Schulte A, Liffers K, Kathagen A, Riethdorf S, Zapf S, et al. Erlotinibresistance in EGFR-amplified glioblastoma cells is associated with up regulation of EGFRvIII and PI3Kp110delta. Neuro Oncol. 2013; 15:1289–1301.

94. Marjanovic ND, Weinberg RA, Chaffer CL. Cell plasticity and heterogeneity in cancer. Clin Chem. 2013;59:168e179.
95. Gill J, Sullivan R, Taylor D. Overcoming Cancer in the 21st Century. UCL School of Pharmacy Embargoed until 00.01 hours Wednesday 14 January 2015
96. Kantarjian H, Zwelling L. Cancer drug prices and the free-market forces. Cancer 2013;119:3903–3905.
97. NHS. Five year forward view; 2014b.
98. Surveillance, epidemiology and end result program. Cancer facts and the war on cancer; 2002.
99. Chalkidou K, Marquez P, Dhillon PK, Teerawattananon Y, Anothaisintawee T, Gadelha CAG, Sullivan R. Evidence-informed frameworks for cost-effective cancer care and prevention in low, middle, and high-income countries. The Lancet Oncology. 2014;15:e119-e31.

© 2016 Adesuyi et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/17156