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EDITORIAL

# What Do We Know 40 Years After Nixon Declared the 'War on Cancer'? On the Origin, Prevention and Treatment of Cancer

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**Abstract** Evolutionary principles suggested by Darwin and Wallace some 150 years ago can provide insights into the origins of cancer. Moreover, they can form a basis for answering the question implicitly posed when Nixon declared the war on cancer in 1971: Can we actually 'cure' cancer? As explained lucidly by Greaves in 2001, necessary keys to evolution and thus for the origin of species, including ours, are changes of genes or mutations; but changes of genes are also necessary links in the causal chains which lead to cancer. In effect, cancer is therefore, according to Greaves, an 'evolutionary legacy'. Intriguingly, the realization that cancer is a consequence of changes in genes which are *conditiones sine qua non* for evolution suggests a mutation paradox on an evolutionary scale: in individuals, mutations may have devastating adverse health effects, including cancer. Populations, however, as a whole can be expected to benefit ultimately from changes of genes to better adapt to environmental challenges. On the basis of premises from evolution theory, it remains for us to interweave growing insights into evolutionary principles with realistic objectives for the primary prevention of and, where the latter fails, coexistence with cancer so that what we do for patients can become more of an art rather than a war.

> Nothing in biology makes sense except in the light of evolution.
> -Dobzhansky, 1937 [1]

> There has not been, is not, and probably will not ever be, a cancer-free utopia.
> -Greaves, 2000 [2]

## Introduction

Four decades ago, Nixon declared war on cancer [3] and the terminology of 'fighting' cancer is certainly martial in tone. To call it a war may not be entirely wrong. Cancer can be conceptualised as a growth or cell chaos where tissues and organs may become the target of invasion. It seems as simple as that: cancer cells do not obey certain rules. They affect cellular crosstalk adversely and violate bilateral coexistence when cell inhibitory signals are ignored by unduly insensitive neighbouring cells.

We all know that cancer kills. Realistically, from what we know today, primary prevention of cancer and some coexistence with this highly heterogeneous disease—as paradoxical as this may sound—should be(come) our realistic objectives. But let us proceed step by step.

## Discussion

### Nixon's 1971 Declaration of the 'War on Cancer'

When Richard Nixon signed the National Cancer Act on December 23 of 1971 [3], implicitly declaring war on cancer, he launched an intensive campaign to find a 'cure' [4] for one of the leading causes of death in the U.S. and elsewhere [1].

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Scientific reasons as to why this ambitious goal was not reached at the individual level were exemplified in *Nature* by Dr. Gatenby [5]. Importantly, the author's invocation of 'evolutionary dynamics of tumours' to explain why we may have to accept *control*, rather than *cure*, also suggests that society will never be able to rid itself of cancer at the population level. Achieving the latter could, at least in theory, make both control and cure superfluous and their distinction academic. However, the following insights into the origin of the majority of cancers and evolutionary principles of tumours make two key points clear: in evolutionary terms, we have to accept our unavoidable coexistence with cancer. In practical terms, we should target primary prevention and control, not 'cure', of tumours, in individuals and populations.

## On the Origin of Cancer

In 2000, Mel Greaves [2] illustrated that when we grapple with cancer we are actually dealing with evolution and its very principles. On the basis of Darwinian insights, what may be called the 'Greaves rationale' holds that when we try to understand cancer, we are actually looking at a necessary condition for evolution, namely changes in genes. Genetic variations are *conditiones sine qua non* for cancer. In other words, without changes in genes, there would be no cancer. However, without changes in genes, there would also be no 'us' – it's as simple as that. Granted, in our short-term judgement, some effects of changes in genes certainly disallow our appreciation—after all, cancer kills. And yet, on an evolutionary scale, genetic variation is a key to the survival of species, including humans. We do need genetic variation to adapt to, and to ultimately survive, under changing environmental conditions. In other words: not only is the elimination of changes in genes impossible but, soberingly, it would actually be unwise to pursue that goal since genetic change has been—and will continue to be—the major driving force for adaptive evolution of all life forms, humans not exempted. Without genetic variability we may, theoretically, no longer suffer from growth chaos, such as cancer, but equally clearly without mutations enabling at least some of us to adapt to and survive in a world of changed environmental conditions we would, sooner or later, face unsurmountable problems [2]. Overall, therefore, there can be no doubt that the 'Greaves rationale' is correct: 'no changes in genes→no cancer'. And yet, 'no changes in genes→no evolution→no us.'

Remarkably, there is an analogy to Rose's famous 'prevention paradox' [6]: a preventive measure, which brings much benefit to the population may offer little to each participating individual. In a similar vein, we are facing a 'mutation paradox' with regard to cancer. Clearly, in individuals, mutations may have devastating adverse health effects such as cancer, which can kill. But, equally clearly, future generations are likely to benefit in the long run from the changes which occur in genes, for instance arising as a result of mutations [7].

## On the Art of Our War on Cancer

Now, since Gatenby and Greaves, among others, have lucidly and authoritatively conceptualised cancer in evolutionary contexts and as an 'evolutionary legacy' [2], it should come as no surprise that tumours have been documented as early as in dinosaurs [8]. Thus, because of their extreme antiquity, and in view of the evolutionary background, we should not expect to be able to ever eradicate cancer in the future. To complicate things further, being the result of individual changes in genes that add up and do—or do not—turn into an overt cancer, no two cancers will ever be exactly the same. This explains key limitations to cancer therapy – what may work well in one case may have no positive effect in another case, or in fact could make the situation even worse. Therefore, reductionist expectations in the functional role of one or more genes or mutations in addition to having too much hope for a 'golden bullet' cure for many—or even all—cancers seem to be a recipe for failure.

Clearly, it is necessary to gain a better understanding of some of the causes which may be amenable to our doing in order to prevent and possibly intervene in as many cases as possible. Equally clearly, it is important to recall that cancer is characterised by a growth chaos or a growth disorder which we understand better after decades of extensive research, but certainly not well enough to date. In statistical terms, cancer—fortunately—comprises a very unlikely cascade of events, which affect most or all hallmarks of cancer. To appropriately understand 'cancer', Hanahan and Weinberg [9] have suggested that 'a succession of genetic changes, each conferring one or another type of growth advantage, leads to the progressive conversion of normal human cells into cancer cells.' The authors showed that tumour progression is similar to Darwinian evolution as each genetic change provides a growth advantage to one or more cells. According to their review (as of August 22, 2012, cited 10,166), anticancer defence mechanisms fail. In effect, individual cells acquire some or all of the following six capabilities, namely self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis and tissue invasion and metastasis.

In terms of possible prevention strategies, a combination of exogenous (environmental) and endogenous (genetic) factors determine the susceptibility to and development of many cancers. Greaves refers in his aforementioned book [2] to estimates by Doll and Peto that up to 90 % of cancers were attributable to environmental causes and thus as many as nine out of ten cases could be preventable. Indeed, with particular regard to what (co-)determines cancer, it has been suspected for decades that the genetic make-up which we

inherit is important, but not nearly as important as factors in the environment we are exposed to and which increase the risks of DNA damage and pave roads to cancer throughout our lives [2]. Since the year 2000 this is no longer a hunch or an educated guess: a landmark investigation [10] (as of August 22, 2012, cited 1,393 times)—based on the analysis of data from 44,000+ pairs of Scandinavian twins provided robust empirical evidence that environmental, and not inherited, factors (co-)determine the vast majority of cancers in humans. Since then, the race should have intensified to identify more carcinogenic culprits, such as smoking and asbestos, in occupational and environmental settings. As a basis for primary prevention, we should systematically establish the role of a given factor in the chain of causation that leads to cancer and find ways to avoid and act on it [11].

Taken together, therefore, Nixon was far too optimistic 40 years ago when he signed the National Cancer Act into law and boldly declared, 'I hope in the years ahead we will look back on this action today as the most significant action taken during my administration.' [3] In our view, it is not only unrealistic to find a 'cure' [4] for cancer, but it is also a strain on both financial resources and ethical provisions. The conventional wisdom that 'prevention is better than cure' is now more important than ever as we realise that in most cases we have no means to cure [11]. If, however, there is no effective way to cure, this may actually shift considerable focus on primary prevention, i.e. we should strive for means to avoid the very development of cancer in the first place.

Strategy-wise, as the environment plays the key role in the causation of most cancers [10], the identification of (co-)determining exogenous factors which lie on causal chains that lead to cancer could promise effective prevention in many cases. Moreover, insights into the links between specific environmental factors and cancers could promise targeted means to intervene and alter the course of disease in other cases. Gatenby's suggestion [5] with regard to individual patients to strive for some form of coexistence with cancer rather than attempting to cure by vain attempts to eradicate the cancer, ought in fact be extended to populations as a whole. Indeed, according to Darwinian rationale, in populations, coexistence with mutations (and thus cancers) is not only unavoidable, it is a necessity.

Ultimately, interweaving growing insights into the intrinsically beautiful facets of evolution with realistic objectives for a coexistence with—and wherever possible primary prevention of—cancer, should allow us to turn what we can actually do for patients into an art rather than a war.

## On the Ethics of the War on Cancer

This brings us to advice provided by Horrobin in the early 2000s. This fine thinker enjoyed a prolific life, balancing work with patients and work in science with Karl Popper, Sir John Eccles and many more luminaries. Due to his own cancer, Horrobin was familiar with the parallel universes of a doctor and researcher and of a cancer patient, when he published a personal paper in the Lancet in 2003 [12]. There he *inter alia* advocated that 'patients with lethal diseases want to get better, not to have their lives extended by a few weeks or months at great cost in toxicity and time in treatment.' Now, this can tell us something with regard to the cancer studies we do and the treatments we offer. Personally, we see two sets of imperatives:

First, we must improve primary prevention, implying that there could be much less cancer cases in the first place. Indeed, if we aim to transform the war on cancer into the art of preventing and coexisting with cancer, we need to ask ourselves: How can we effectively identify, and thereafter avoid, the predominant factors in the environment that (co-)determine the development of cancer?

Second, for those cases which we fail to prevent, we must find answers: What is an acceptable ratio between how well a patient lives and for how long, when the loss in quality of life may become an almost unbearable price? To facilitate decisions for or against treatment, both patients and their doctors could benefit from adequate information regarding the following questions: How long would we treat and what would the treatment be like? What would be a realistic chance regarding any benefit? What are the associated risks, i.e. what harm can the treatment do? But most importantly, do patients want this type of information at all? Perhaps the most difficult question to answer remains: When is enough, enough?

## Conclusions

On the basis of premises from evolution theory, cancer is and will remain an evolutionary legacy. We cannot—and ultimately we should not—rid ourselves of changes of genes which are driving forces for both, evolution and cancer. In effect, the realisation that cancer is a consequence of changes in genes which are *conditiones sine qua non* for evolution suggests a mutation paradox on an evolutionary scale: in individuals, mutations may have devastating adverse health effects, including cancer. But populations as a whole can be expected to ultimately benefit from changes of genes to better adapt to challenges provided by natural and anthropogenic environments. Given that no two cancers will be the same, primary prevention—rather than a utopian cure of cancer—at the population level should be our primary objective. Overall, therefore, Nixon was over-optimistic when he signed the National Cancer Act and initiated what is referred to as the 'war on cancer'. Not only is it unrealistic to find a 'cure' [4] for cancer, but it is also a strain on both financial resources and ethical provisions. As we understand more and more that in most cases there is no effective way to cure [11], this should shift considerable focus on primary prevention, i.e. we should strive for means to avoid the very development of cancer as much as possible. At the

individual level, it remains for us to interweave growing insights into evolutionary principles with realistic objectives for the primary prevention of and, where the latter fails, coexistence with cancer so that what we do for patients can become more of an art rather than a war. With regard to the ethics of our war on cancer, we should find answers to a host of specific questions to ultimately avoid overtreatment of cancer where there is no realistic reason to have hope.

**Conflict of Interest** The authors declare that they have no competing interests.

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