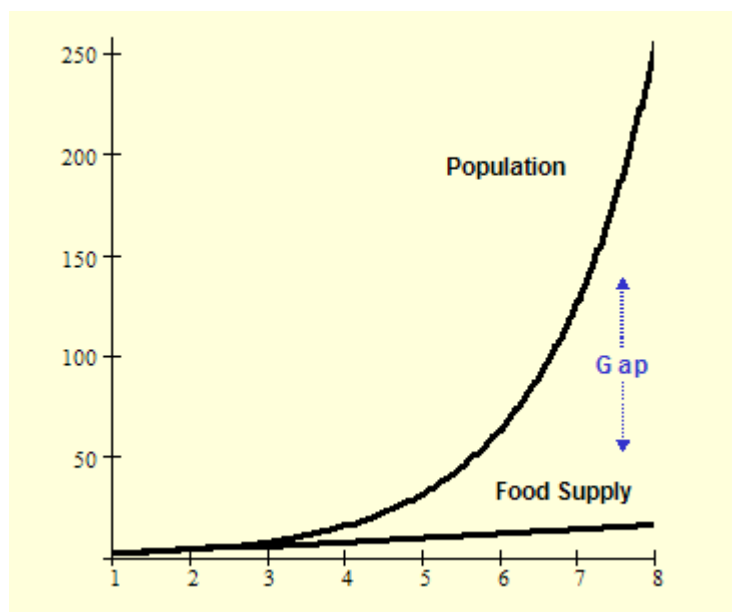


# Cancer is First and Foremost About the Growth of Cell Populations

The importance of the word *population* cannot be over-emphasized. There is a big difference between a *cancer cell* and a *population* of cancer cells. The properties of populations are different from that of individuals. The failure to recognize and fully accept this difference has caused the problem of cancer to be inadequately defined and has frustrated attempts to specifically cure or control cancer.

One of the most important principles of population growth was discovered by the political economist, Thomas Malthus. In 1798 Malthus published [An Essay on the Principle of Population](#) in which he pointed out the rapidly widening gap that results from the difference between exponential population growth and the arithmetic growth rate for food production. This is illustrated in the graph below:

## The Gap Between Population Growth and Food Production

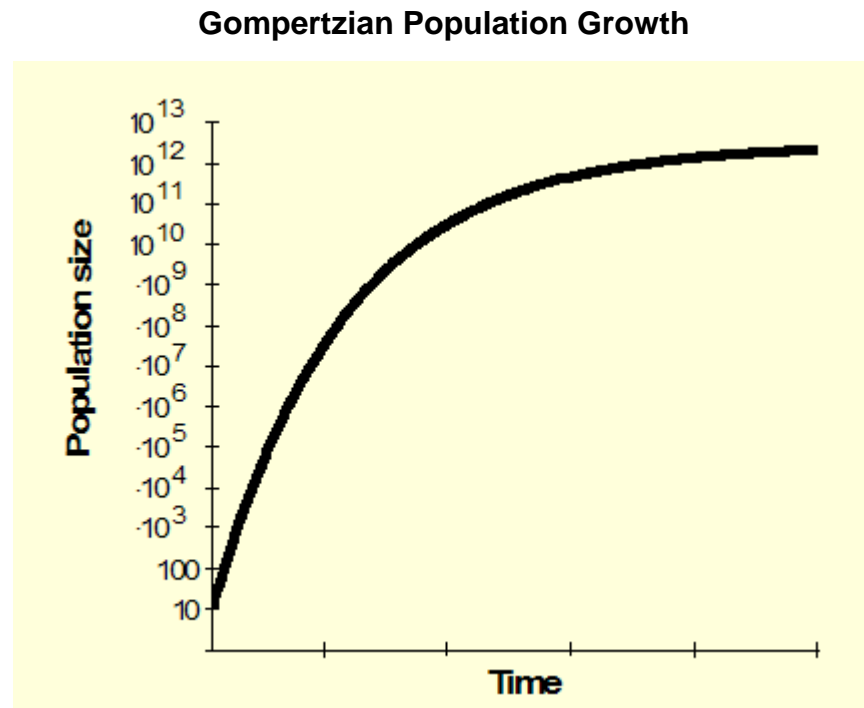


The inevitable consequence of this gap is death and disease, with survival of the fittest and strongest. Cancer cells need oxygen, nutrients and space to grow and survive. The exponential growth potential of cancer cells is necessarily checked. The strongest, best fit, cancer cells survive.

Populations of organisms can grow at an exponential rate for only a short period of time before vital resources such as food and space become growth limiting. After thirty population doublings a single cancer cell, invisible to the eye, can give rise to a pea-sized tumor containing about one billion cells. After 40 population doublings the tumor arising from a single cancer cell would weigh approximately 2 pounds, contain about one trillion cells, and the patient would likely be near death. The time required for a tumor to double in

size depends upon the balance between the rate of cancer cell replication and the rate of cancer cell death.

In 1825, the English mathematician, Benjamin Gompertz, published a formula that accurately described actuarial data for human populations. (1) The growth of a wide range of populations is well described by the Gompertzian formula, which gives a growth curve like that shown below:



It should be noted that the population axis is plotted in the log scale and extends over a range of ten trillion. The growth rate is initially very rapid but decreases as the population size increases. It was recognized about 150 years later that tumor growth is well described by the same type of [Gompertzian growth curve](#). The exact shape depends upon the specifics of the particular tumor.

### **Tumor doubling time**

A typical *potential* doubling time is about five days for many cancers. (2) If all the cells that were produced survived, the weight of the tumor would double every five days. In actuality, most cancer cells die and it generally takes several months for a tumor to double in size. Even in a very slow growing tumor the cancer cells are constantly replaced. The constant turnover of cancer cells, coupled with Malthus's observation that the strong survive, has profound implications.

### **The probability of cancer cell survival**

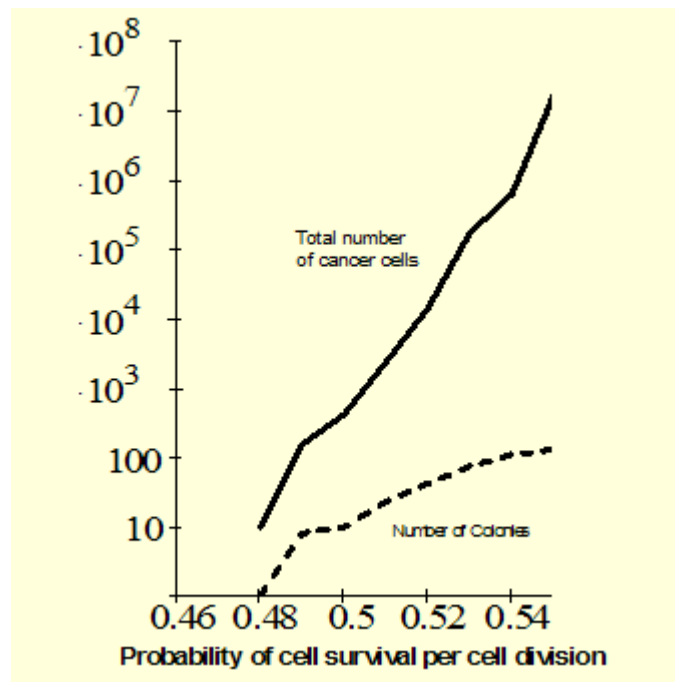
Purely statistical factors can play a major role in the failure of isolated cancer cells to progress to new metastatic tumors. In human cancers the probability of cancer cell survival

is estimated to be in the range of 0.50 to 0.57 per cell division. Cell survival probabilities less than 0.50 would lead to tumor shrinkage or regression. Values greater than 0.57 would give tumor growth rates far in excess of that observed in even the most aggressive human cancers. In other words, almost as often as not, when a cancer cell divides, another cancer cell dies. This has profound, but by no means obvious, implications. At the present time let us consider the consequences of statistical factors on tumor progression and the formation of new metastatic lesions.

Dr. Jules J. Berman and Dr. G. William Moore used Monte Carlo based computer methods to look the influence of the probability of tumor cell survival on tumor growth. (6) Monte Carlo techniques involve using computers and random numbers to solve or simulate mathematical problems.

The graph below is based on their computer-generated data and illustrates the influence of the probability of cancer cell survival per cell division upon tumor cell growth. The graph is based upon the simulated population growth over 100 generations, beginning with 500 individual cancer cells. Each of the initial 500 cancer cells potentially could have given rise to a colony. The number of colonies surviving after 100 generations is shown. The total number of cancer cells in all the colonies, after 100 simulated generations, is also plotted on the graph. It should be noted that the axis for tumor cell and colony number is in log scale and extends over a range of one hundred million.

### Computer Simulation of Population Growth after 100 Generations (Beginning with 500 single cell cancer colonies)



In real tumors, the probability of cancer cell survival per cell division is not a constant, unchanging number. However, the message is clear. Very minor differences in the probability of cancer cell survival over prolonged periods of time can have absolutely

enormous impacts on cancer cell population growth. A tiny sustained increase in the ability of cancer cells to survive can make a huge difference on the course of the disease. Conversely, a tiny sustained decrease in the probability of cancer cell survival can dramatically retard cancer progression. In addition, cancer cells with even a minor survival advantage (over other cancer cells) that is transmitted to offspring will rapidly and almost completely dominate the tumor cell population. The magnitudes of these effects are huge.

## Evolution

The similarities between the behaviors of human population growth as described by Malthus and that of cancer cell growth are not metaphorical. They reflect deep and important underlying principles of nature.

In October 1838, that is, fifteen months after I had begun my systematic inquiry, I happened to read for amusement Malthus on Population, and being well prepared to appreciate the struggle for existence which everywhere goes on from long-continued observation of the habits of animals and plants, it at once struck me that under these circumstances favourable variations would tend to be preserved, and unfavourable ones to be destroyed. The results of this would be the formation of a new species. Here, then I had at last got a theory by which to work. (3)

..... **Charles Darwin**

And so was discovered the single most important principle in all of biology and one of the most important in all of science, Darwin's Theory of Evolution. (Alfred Russel Wallace about the same time reached similar conclusions.)

[Darwin's Theory of Evolution](#) explains how natural selection or "survival of the fittest" can lead to the development of the highly complex structures characteristic of life. Minor random variations that confer a reproductive or survival advantage are naturally selected for and become enriched in the population. New random variations arise and the process repeats. The gradual cumulative effect of a very large number of these selection cycles can generate the complex machinery of life. Evolution is a repetitive, iterative process. The output from one cycle becomes the input for the next. The net result is the development of a population that is increasingly well adapted for survival and reproduction in its environment. In the process, highly complex, ordered structures and functional machines such as life forms can emerge.

## Evolution is not just about dinosaurs and of ages long past

Evolution is typically considered to require very long periods of time, millions to hundreds of millions of years. This is true if you're talking about drastic change. It took about 600 million years for multi-cellular organisms to evolve into humans. However, evolution is a continuous process. It occurs on a daily basis. It is readily observed when large populations of organisms, (millions to billions of organisms) are subjected to a severe selective

pressure. For example, exposing bacteria to penicillin causes massive death and the destruction of sensitive organisms. The few variant bacteria, perhaps one out of one million, that are resistant to the penicillin survive and repopulate. The resulting population that grows can then thrive in the presence of penicillin that so readily poisoned and killed the prior generation. Expose this penicillin-resistant population of bacteria to a second antibiotic such as tetracycline and the same process is repeated. The net result is a population that has evolved resistance to both penicillin and tetracycline. In short order, by repeating the process, super-germs that are resistant to multiple antibiotics can evolve.

The evolution of antibiotic resistance is a major problem in medicine today. According to the CDC there are approximately 67,000 deaths in the U.S. every year from bacteria that are resistant to multiple antibiotics. According to the World Health Organization there are about 2 million deaths each year for TB. Approximately 4% of these are due to TB germs that are resistant to multiple antibiotics.

The evolution of drug resistant strains of AIDS virus is especially rapid for two reasons. First, the error rate in the replication of the AIDS virus is very high. Second, very large numbers of viral particles can be produced every day in a patient. (Approximately 10 billion viral particles) (4) The mutation rate can be so high that essentially every viral particle can be slightly different. (5) The net result is that HIV infection provides a large pool of variants for natural selection to act upon. Drug resistance can rapidly develop. **Cancer cells behave in exactly the same manner.**

It is a tribute to the remarkable genius of Darwin that he recognized that evolution was not dependent upon long periods of time. Darwin writes in Origin of the Species:

The mere lapse of time does nothing, either for or against natural selection. Lapse of time is only so far important, and its importance in this respect is great, that it gives a better chance for beneficial variations arising and of their being selected, accumulated, and fixed.

..... **Charles Darwin**

It is the underlying probabilities that count. In cancer, with billions of cells, each with a large number of mutations, the underlying probabilities strongly favor evolution.

### **Tumor cell evolution**

In 1947, [Dr. Sidney Farber](#) obtained the first remission in childhood leukemia using an anti-folate drug called aminopterin..



**Dr. Sidney Farber** [photo NCI](#)

Bone marrow that had been completely replaced by leukemic cells returned to normal appearance. Kids who were on death's doorstep recovered. Unfortunately the miracle was short lived. Leukemic cells resistant to the drug evolved. The result was invariably fatal. Tumor cell evolution, the fundamental problem of cancer had revealed itself to plain view.

In the early 1950's, [Dr. Lloyd Law](#) one of the great pioneers of cancer research had clearly demonstrated that the problem was [tumor cell evolution](#). He was even able to identify leukemic cells that required the anticancer drug in order to grow. These leukemic cells had evolved the ability to use the poison with impunity to satisfy their nutritional needs. Such is the power of tumor cell evolution.

Tumor cell evolution is not controversial. In 1976, Peter C. Nowell, published a now classic article in the journal [Science](#), [The Clonal Evolution of Tumor Cell Populations](#). In 1998 he was awarded the prestigious [Lasker Award](#) for Basic Medical Research for his contributions on the evolution of cancer.

**Therapy must kill or control an evolutionary population of cancer cells to consistently cure or control cancer.**

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