

## Damaging Your DNA: New Interpretations of Mortality Differentials

Written by Stephen Richards.

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### Introduction

Many factors are known to explain mortality differentials: smoking, gender, diet, occupation and - most obviously of all - age. This article will show that these factors have a partial interpretation based on damage to your DNA.

### A quick science lesson

DNA is the code for building all known living organisms on Earth. DNA (or *deoxyribonucleic acid* to its friends) is a quite remarkable chemical. It is made up from four building blocks, known as bases. These bases are labelled A, C, G and T after their full names: adenine, cytosine, guanine and thymine. A sequence of bases makes a gene, and a collection of genes form a recipe for making a protein. Proteins make us what we are: our flesh made of proteins, but proteins also act as enzymes and catalysts in many of the important bio-chemical reactions that take place in our bodies.

### Inheritance - Part I

For most people, the word 'genetic' is associated with the genes they inherited from their parents. When it comes to mortality, people intuitively look at their parents' and relatives' mortality to draw conclusions about themselves. This is sound science, too, since a number of serious diseases have at least a partial genetic basis: from sickle-cell anaemia to heart disease and some cancers. Adverse mortality from an inherited pre-disposition to certain diseases is relatively well-understood.

However, people also draw positive conclusions about their own longevity if their parents or grandparents are particularly long-lived. Again, this has a sound basis in science: the studies of Leonid Gavrilov and Natalia Gavrilova found that having a long-lived mother reflects positively on your own longevity prospects. As with almost all aspects of mortality work, there are important gender differentials: Gavrilov and Gavrilova found that the effect of having a long-lived father is twice as strong as that of having a long-lived mother.

### Inheritance - Part II

Gavrilov and Gavrilova also found a further aspect to inheritance and mortality: damaged DNA passed on to offspring. Such damage is specifically to the germ-line cells (sperm and ova) of parents, and it mainly occurs after reaching adulthood. As a result, the parents themselves need not suffer any consequences of these damaged genes, since their own bodies were 'built' using the original, undamaged genes. There are, however, consequences for the offspring, since they start life with bodies built using a damaged DNA 'blueprint'.

In particular, Gavrilov and Gavrilova found that the age of a father at conception played a strong negative role in longevity,

particularly for daughters. Having an older father at conception - say over age 55 - will reduce a woman's life expectancy by several years, even after controlling for a variety of other factors such as relative wealth and social status. Recent work by biologists suggests that the mutation rate in male germ-line cells (i.e. sperm) is up to *five times* that of female cells (i.e. ova). While some mutations can be beneficial, most are not.

Clearly, damage to your DNA is something to be taken very seriously indeed. Damaged DNA could mean the failure of important cell processes, or could even lead to cancer and early death. As it happens, the DNA in each cell of your body is damaged hundreds of times a day. These so-called 'pre-mutagenic events' are a result of normal metabolism, and the body has a variety of mechanisms constantly at work to repair this DNA damage. Thanks to the expanding field of molecular genetics, many of the mortality differentials long-known to actuaries can now be partially explained in terms of damaged DNA.

### Smoking

Smoking is probably the most obvious factor for adverse mortality. What is perhaps less obvious is that smoking inflicts extensive DNA damage. Tobacco smoke contains over two hundred chemicals known to cause cancer, known as carcinogens. The precise mechanism whereby cancer starts is not yet fully understood, but many of the chemicals in tobacco smoke are known to damage cellular DNA. For example, a study in the US-based *Journal of the National Cancer Institute* found that the rate of DNA alteration in lung tissue was not just higher for smokers, but very much higher for people who started smoking at a young age. These DNA mutations are permanent and forever increase the likelihood of developing lung cancer.

Smoking is also known to cause DNA damage elsewhere in the body, for example in cervical cells which can lead to cervical cancer. Tobacco smoke also contains chemicals in a group called the *polycyclic aromatic hydrocarbons*, which can lead to specific genetic mutations in a gene known as 'p53'. p53 plays an important role in suppressing tumours and, significantly, mutations in this gene are present in around half of all major human tumours.

All in all, smoking is perhaps the biggest source of DNA damage in the developed world. Smoking is well-known as a cause of higher mortality, even if the route of 'DNA damage' is less widely understood.

### Diet

Diet is also well-known as a factor in health and mortality, but it is less commonly understood to have a role in perhaps one third of all human cancers. Food can potentially damage your DNA in two ways: both in the things you eat (toxins and carcinogens), but also in the things you do *not* eat.

The most obvious mechanism for your food to damage your DNA is through the presence of mutagenic chemicals. Some food additives are thought to cause DNA mutation: azo dyes, for example. However, even chemicals from 'natural' sources can be a problem: high levels of sugar (sucrose) can also cause DNA damage in

the large intestine, for example. Also, over-cooking food such as fish, poultry, or meat until it is charred changes ordinary proteins and amino acids into substances called *heterocyclic amines*. These are potent DNA-altering mutagens, which certainly makes this author think more carefully about summer barbecues. High levels of beef consumption - whether over-cooked or not - are also associated with DNA damage to cells in the large intestine, particularly fried beef.

The risk of DNA damage posed by the things you eat is not trivial. However, this pales next to the DNA damage you can do by what you do *not* eat: the deficiency of key vitamins and micro-nutrients 'mimics radiation in damaging DNA', according to Bruce Ames in his landmark paper, *Micronutrient deficiencies: A Major Cause of DNA Damage*. Normal cellular processes produce so-called 'free radicals', chemicals which damage DNA through oxidation. A whole class of compounds called 'anti-oxidants' can combat these free radicals and thus reduce the damage to cell DNA. Many anti-oxidants are commonly available in the 'right' foods: Vitamins C and E, for example, and more exotic-sounding ones like lycopene (found in tomatoes).

Although some food supplements are marketed as 'pure' in a particular anti-oxidant, their effect may fall some way short of what consumers expect. Firstly, you have to have a broad basket of anti-oxidants in order to benefit from any given one. Simply supplementing one anti-oxidant in isolation may not reduce DNA damage by much, since DNA-repair is often a sequence of reactions, with each step requiring a quite separate anti-oxidant. Secondly, while many anti-oxidants are impaired or destroyed by cooking, some - such as lycopene - are paradoxically more 'bio-available' *after* cooking the food which contains them.

Happily, no-one should fear that they are condemned to fun-free foods: cocoa liquor contains beneficial *phenols*, and eating plain chocolate raises the level of this type of anti-oxidant in the body. Red wine, too, contains resveratrol, a *polyphenol* found in the skins of red grapes. This author is notably keener on getting his resveratrol from *Chateauneuf du Pape*, rather than mere grapes.

Tea also contains phenols, and green, black and oolong teas are all associated with reduced DNA damage. Perhaps surprisingly, coffee has also been shown to inhibit DNA damage in a number of experiments. There is an exception to this, however: a Japanese research team isolated a chemical in *instant* coffee which causes single-strand breaks in DNA (hands up those who went to the coffee machine before sitting down to read this article).

One major dietary component of excess mortality is alcohol consumption, and here, too, there is an interpretation based on molecular genetics. Alcohol metabolism occurs within the liver, and free radicals are by-products of this metabolism. Fortunately for moderate drinkers, significant oxidative stress (i.e. DNA damage) only appears to occur above a threshold concentration of alcohol. The implication is that the liver is well-able to deal with those free radicals, providing they are not produced at the rapid rate implied by high levels of alcohol consumption. This is one reason why binge

drinking is so much more harmful than drinking the equivalent amount of alcohol over a longer period of time.

In the developed world, diet is perhaps second only to smoking in its association with DNA damage. Both smoking and diet are so-called 'lifestyle factors' in that they are linked to behavioural choices. In one sense, these forms of DNA damage are voluntary.

## Gender

It has long been known that there are strong mortality differentials between men and women. In humans, males differ from females in having the shorter Y-chromosome instead of a second X-chromosome. This is the beginning of several major biological reasons why males have a higher mortality rate than females.

Firstly, in terms of genetic inheritance, a male needs to inherit only one deleterious recessive gene on the X-chromosome to inherit an ailment, whereas a female must inherit two. A recessive gene can only be 'expressed' if it either faces another similar gene on the other chromosome, or if there is no other chromosome. It is this latter case which often applies to males: any deleterious gene in the wrong place on the X-chromosome will not have anything to 'dominate' it on the shorter Y-chromosome opposite. Males are thus more at risk of inheriting genetic disadvantage. The classic example of this is the prevalence of hæmophilia amongst male descendants of Queen Victoria, whereas female descendants are largely unaffected, even if they have the gene.

Secondly, certain hormones in the human body have the unfortunate side-effect of causing damage to DNA. One particular example is oestrogen, which breaks down into powerful oxidants, i.e. free radicals. In particular, it is 'unopposed' oestrogen which is the source of trouble. One possible route to DNA damage for men is through the falling level of testosterone at older ages: as the balance changes in favour of oestrogen, increasing levels of DNA damage may occur in male bodies which are not 'designed' for high oestrogen levels. Unopposed oestrogens are also a risk factor for post-menopausal women on hormone-replacement therapy (HRT).

Although being male is not in any sense to be 'damaged' in terms of DNA, testosterone does cause the production of *low-density lipoprotein* (or LDL, the bad kind of cholesterol) in the human liver. Cardio-vascular disease is still the major cause of late-life mortality in both men and women, but there are complex interactions with hormones such as testosterone and oestrogen. The different balance of these between men and women would appear to 'program' males for higher rates of cardio-vascular mortality at all ages.

## Occupation

The job you do can also be a factor in determining how much genetic damage you receive. This can be through the continued exposure to chemicals, e.g. in dry-cleaning, film-developing or other industrial chemical processes. A particular risk factor for DNA damage lies with occupations linked with smoke or burning, e.g. coke-oven workers.

One other route to DNA damage is through exposure to certain metal compounds which induce DNA damage. Curiously, the

metal compounds themselves are only mildly 'genotoxic', and their main role in damaging DNA seems to lie in the disruption of the natural DNA repair mechanisms, rather than directly causing additional initial damage.

Alternatively, mutation-inducing radiation can be the factor for some occupations, for example mine workers or people working near X-ray machines. A powerful, yet oft-overlooked, source of ionising radiation is the sun itself, so occupations which lead people to spend a lot of time in the open air can be a source of DNA damage. Lip and skin cancers are noticeably more common in people with outdoor occupations, for example.

It is also known that occupations with exposure to dust, small particles, asbestos or irritants suffer higher mortality than office-based occupations. Such materials cause irritation and one consequence of this is greater frequency of inflammation, which one would not ordinarily link to DNA damage. In fact, inflammation activates oxidant-generating enzymes which produce a variety of free radicals. The resulting DNA damage contributes to the multi-stage process of carcinogenesis.

### **Old Age**

There are a wide variety of contributing factors which make the rate of mortality increase with age. One of these is simply being old: the longer an organism has been around, the greater the DNA damage it has accumulated. Humans are particularly long-lived animals, and they are subject to quite a high mutation rate. Furthermore, the body's ability to repair DNA damage weakens with age, thus permitting increasing numbers of mutations to go uncorrected. As a result, old age can itself be viewed as a cause of unrepaired DNA damage.

The immune system of the human body also loses effectiveness with increasing age. The body becomes less able to distinguish between 'self' and 'non-self', and false attacks on one's own body tissue causes more frequent inflammation, which is a route to DNA damage.

Reduced immune-system function also leads to more frequent infection, and the root of nearly one-fifth of cancers lies with infectious agents. Over half of these are caused by viruses, which can either directly or indirectly damage DNA. The obvious route is for the virus to cause prolonged inflammation, which damages DNA indirectly as described above. However, several viruses cause direct damage by inserting, deleting, or otherwise modifying the host DNA. Examples of such 'vandal viruses' include hepatitis B and human papillomavirus.

Old age therefore sees a vicious circle: reduced immune-system and reduced DNA-repair functions, which both lead to greater DNA damage. This damage leads, in turn, to further-reduced DNA-repair and immune-system functions. This self-reinforcing and accelerating process may be a partial explanation as to why mortality rates increase so rapidly at older ages.

### **Conclusion**

Many factors have long been known to explain mortality differentials, amongst which are smoking, gender, diet, occupation and old age itself. These factors have at least a partial explanation based

upon DNA damage. Many of these factors are lifestyle-related: people cause substantial DNA damage to themselves through their everyday choices of work, food, drink and smoking habits.

**Stephen Richards** is a member of the CMIB Mortality Sub-Committee. He is writing in a personal capacity and the views expressed here are not those of the CMIB.