

# 1 Painting a Clear Picture

Once upon a time it was fair to say that most people knew little of science. After all, scientists spent years learning their job so it's clearly tough-going and, by and large, the rest of the world could get by knowing nothing of superconductivity or the origins of the universe. But increasingly our daily lives have come to be dominated by science, and part of that revolution has been the ever-expanding reach of television and the Internet as sources of information. It's as though, unwittingly, we've all signed up to the Open University. And, it should be said, when it comes to science this has all been helped by a growing awareness among those in the trade that they have an obligation to let the world know how they while away their days.

High time too, I say – but all might not agree. Friends of mine who are general practitioners tell me that increasingly folk turn up to their surgeries fully armed with a diagnosis of their perceived condition, courtesy of the Internet. I can see that being forced to wonder why you spent years slogging through medical school could be rather dispiriting but, as I point out, setting the personal aside, you have to concede that people being willing and able to teach themselves has to be a step forwards for civilization.

That's as may be, but in science, and especially in biology, there is almost always another side to any argument. Alexander Pope, in his 1709 essay, noted that 'A little learning is a dangerous thing', and that 'shallow draughts intoxicate the brain'. Wise words, and with them in mind let's make a start on

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understanding cancer by looking at some critical questions that often cause confusion – and not just for non-scientists!

As we launch ourselves into this story, there's one thing we all might agree on: cancer is complicated. However, and you might find this surprising, what emerges from short answers to a handful of rather obvious questions is that cancer is a great paradox. On the one hand, it is indeed mind-boggling – which is why clinicians will almost never say 'This will work' with regard to treatments. But, when you cut to the heart of the matter, cancer is very simple – that is, it's easy to grasp the key points and thus to see how, in principle, to go about dealing with it. It's only then that the going gets tough as our ingenuity is tested by the immense weight of evolution that underlies the disease.

### What is Cancer?

A three-word answer to this most basic of questions is 'Cells behaving badly'. More scientifically, it's a group of cells somewhere within an animal that are reproducing (i.e., making more of themselves) either faster than they should or in a place where they should not be. Put another way, these cells have lost control of their capacity to divide. The result is that the cells grow and divide to make more copies of themselves, paying no heed to normal controls. The resulting unruly mass of cells constitutes a tumour. This word comes from the Latin for 'swelling' – that is, an abnormal growth. It's used interchangeably with 'cancer' and 'neoplasm' (new growth), and all three words mean much the same. Tumours may grow relatively quickly or very slowly, but to expand significantly food and oxygen are required – just like for any other cell in the animal body. To achieve growth, tumours can release chemical signals that switch on growth in nearby blood vessels. New 'sprouts' penetrate into the tumour cell mass. The whole ensemble is now primed to take off: to expand regardless of the best interests of its host. Most ominously of all, by acquiring its own blood supply the tumour now has a conduit and cancer cells can be carried the circulatory system to any part of the body. Cells may also be carried by the lymphatic system but, whatever the means of transport. The process of tumour cells spreading to other places is called metastasis and it's critical because it results in over 90 per cent of deaths due to cancer.

## What Causes Cancer?

Perhaps the most frequently asked question about cancer. In today's world most of us can come up with a quick answer: mutations – that is, damage to our genetic material, otherwise known as DNA. The term DNA has, of course, passed into common speech as we have all learned more and more about the science of molecular biology. That's good, because it means we don't need to use its full name (deoxyribonucleic acid) when, in Chapter 4, we come back to this wondrous molecule that is the eternal language of the living cell and look at how it works and the many ways in which it can be 'damaged'. The key point for now is that what we inherit comes in the form of DNA – a gigantic chemical molecule made of four types of unit joined together. The units are bases (abbreviated as A, C, G and T), and it is their sequence that encodes genetic information.

The term 'genome' was invented in 1920 to describe the entire genetic material of an organism – thus, in humans that includes the DNA in the nucleus of our cells (almost all our DNA) and a tiny amount in mitochondria, membrane-bound units in cells often called the powerhouse of the cell. It's mitochondria, and hence mitochondrial DNA, that are passed almost exclusively from mother to offspring in the egg.

Within the length of DNA there are blocks called genes, which carry specific, functional units of heredity. The study of genes and genetic variation is called genetics. The study of the genome is called genomics. Before you ask, the Danish botanist Wilhelm Johannsen is credited with coining the word 'gene' ('gen' in Danish and German) in 1909. Because cancers arise from changes in genetic material, they are 'genetic diseases'. That doesn't make them unique: about 6,000 other genetic disorders are known. What is unique about cancers is that almost all need mutations in several genes to get them started and keep them going. Thus, the vast majority of cancers arise from the combined effects of mutated genes. We should note that about 20 per cent of cancers are initiated by infection but, ultimately, these too acquire mutations that drive tumour development.

Given that they are genetic diseases, you might suppose that cancers could be passed from one generation to another through defective genes – and indeed

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they can. As long ago as 1820, a Stourbridge doctor, William Norris, described a family in which individuals from several generations had developed the same form of cancer. This inference that some families might be predisposed to cancer was extended by the extraordinary French physician Paul Broca who, in 1866, suggested it might be possible to inherit breast cancer. He'd looked at his wife's family tree and noted that 10 out of 24 women, spread over four generations, had died from that disease and that there had been cases of other types of cancer in the family as well. We know now, of course, that a changed (mutated) form of a gene passed from generation to generation was almost certainly responsible for the suffering of this family.

One consequence of the rise of the 'media' is that breast cancer genetics has in recent times come into the spotlight, with the much-publicized saga of Angelina Jolie, the American actress. Jolie's mother and maternal grandmother had both died of ovarian cancer, and her maternal aunt from breast cancer – a family history that persuaded Jolie to opt for genetic testing that indeed revealed she was carrying a mutation in one of two genes named *BRCA1* and *BRCA2* (the acronyms come from BREast CANcer type 1 and type 2, so named because they were the first major genes to be identified, in 1990 and 1994, as associated with hereditary breast cancer). *BRCA* genes are mutated in about 10 per cent of breast cancers and 15 per cent of ovarian cancers. The National Cancer Institute estimates that 'about 12% of women in the general population will develop breast cancer sometime during their lives'. By contrast, a recent large study estimated that about 72 per cent of females who inherit a harmful *BRCA1* mutation and about 69 per cent with a harmful *BRCA2* mutation will develop breast cancer by the age of 80.

These estimates prompted Jolie to have a preventive double mastectomy, thereby reducing her risk to less than 5 per cent. The 'Angelina effect' saw a doubling in the number of women being referred for genetic testing for breast cancer mutations in the months after she revealed her story. A study in 2020 concluded that screening entire populations for *BRCA* mutations, rather than only those with a strong family history of breast or ovarian cancer, could prevent millions of breast and ovarian cancer cases

worldwide. For the UK the estimate was that about 10,000 deaths from these cancers would be prevented.

Breast cancers are an enormously varied set of diseases, and as such they're a challenge even to classify, let alone to treat. The recent rapid progress in DNA sequencing has led to a new genome-based classification system but there is still strong reliance on the traditional prognostic and predictive factors, notably what's called hormonal status – meaning the presence on the surface of the tumour cells of protein receptors to which the hormones oestrogen and progesterone attach, together with the presence or otherwise of the human epidermal growth factor receptor 2 (HER2). One significant sub-group has no detectable levels of these proteins. These are called triple-negative breast cancers (TNBCs), and they make up 10–15 per cent of breast cancers. They are very aggressive cancers (i.e., have a poor prognosis), known for some years to disproportionately affect young women of African origin – they are about twice as common in African Americans as in European Americans. Sequencing has revealed that mutations in *BRCA1* are present in most (69 per cent) TNBCs in females of European origin. But here's a very odd thing: African American women have a low *incidence* of *BRCA1* mutations (less than 20 per cent – incidence being the number of new cancers occurring in a population per year), despite the fact that they are relatively prone to TNBC. This implies, of course, that if *BRCA1* isn't doing the driving there must be other potent drivers for TNBC in this group.

These examples clearly show that cancer can 'run in families' and the estimate is that 10–30 per cent of cancers arise from inherited genetic damage. However, the majority occur as the result of accumulated DNA damage as we pass through life. In other words, cancers are, by and large, diseases of old age. In the UK and the USA about 70 per cent of all newly diagnosed cancers occur in people aged 60 or over. Knowing the rate at which we collect mutations, it's easy to work out that if we lived to be 140 years old we'd all have a cancer of some sort. 'Thank heavens we don't have to worry about that yet' is a perfectly reasonable reaction, but there's an important point here, namely that the fact of the inevitability of cancer (if we live long enough) tells us that it's an in-built feature of life. It may be difficult to deal with, but it's not something freaky and weird. It arises because our

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DNA is not made of stone: it's mutable and hence vulnerable, as indeed it must be, for without its plasticity there would be no evolution.

### Are All Cancers Equally Bad?

We've just noted that the critical event in terms of potential lethality is the acquisition of metastatic capacity: the tumour is no longer self-limiting in terms of growth, it can invade adjacent tissues and spread to distant sites. In short, it's become malignant. However, it may have occurred to you that if cancer cells have to do 'something' to become malignant, it is quite likely that many of them won't bother. Indeed, a lot of them do just that (nothing, that is) and we've known since early in the twentieth century that mini-tumours can form and then stop growing, remaining static as 'dormant tumours'. The most likely reason is that they are not able to flip the switch that turns on the growth of new blood vessels.

It has transpired from autopsies of road traffic accident victims that many, perhaps all, adults are wandering around carrying dormant tumours – clumps of about 100,000 cells – in a variety of organs and tissues. Sometimes called *in-situ* tumours, these microscopic growths would normally never be detected – it just happened that accidental deaths provided tissues for pathological analysis.

The key point here is that these micro-tumours were clearly dormant: their carriers died in accidents and had shown no signs of cancer. Knowing what we do about the time course of cancer development, we can be sure that most of them would not have gone on to produce cancer for many more years, or even decades.

### Malignant versus Benign

We've now met the two ends of the cancer spectrum: dormant tumours that we can ignore and malignant tumours that we ignore at our peril. We should note in passing that malignancy is preceded by a pre-malignant phase, namely groups of cells (lesions) that are not yet cancerous but have the potential to develop into malignant cancer (i.e., become metastatic). One example would be colon polyps, growths on the lining of the colon or rectum that can progress to bowel cancer.

There's one further group of cancers that we need to meet – not least because almost all of us have got some of these too – benign tumours. They are indeed extremely common. For example, in 9 out of 10 women it's possible to detect changes in breast tissue that are benign and not dangerous. Fibroids are another type of abnormal growth: they occur in the uterus and are also typically benign. And that's the most important thing about benign tumours: they're not malignant – that is, they can't invade surrounding tissues and therefore do not spread. Benign tumours can arise in any tissue, the most common being lumps of fat called lipomas and, in general, they are fairly harmless. They're usually surrounded by a membrane, a sort of sac that helps to prevent them from spreading. They tend to grow very slowly, but they can reach the size of a grapefruit. The only real problem comes if they press on other tissues (e.g., blood vessels or the brain). That may require surgical treatment, but the good news is that once removed they usually don't return.

One other way in which they can have harmful, indirect effects is by growing in tissues that make hormones, such as the adrenal glands or the thyroid. When this happens, the tumours are derived from cells of the tissue and you might guess that the extra growth would give rise to abnormal levels of the hormones normally made by those glands. They're often symptom-free and only detected by chance (say, from a blood test).

An obvious thought is that, if the evolution of malignant cancers is driven by picking up changes in DNA, perhaps benign growths don't arise from mutations but are just caused by, say, a local imbalance in growth factors – chemical signals that turn on cell proliferation. As ever in cancer, it's not that simple. Mutations that in some tissues are associated with malignancy also pop up in benign tumours and in normal tissue, which tells us that knowing the mutational state of genes doesn't enable you to say for sure whether a growth will become malignant. We're stuck with what, as this story unfolds, you will come to recognize as a typical cancer problem. The difference between benign and malignant tumours is critical: one of them can kill you. But even with the all-conquering power of modern molecular biology that we will come to

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shortly, we are yet to define precisely what it is that converts a relatively harmless abnormal growth into the fatal variety.

### Warts and All

I suspect everyone will have noticed that human beings tend to come adorned with a variety of moles, birthmarks and warts. Try as you might, it's hard not to ask yourself sometimes whether these things, that are undoubtedly unusual growths, are some form of cancer – and if they are, what should be done about them. Relax. The answers are almost always 'no' and 'nothing'. If you want to be pedantic, as abnormal growths of skin they are indeed 'neoplasms', but the best thing is to forget about them or, if they're Angelina Jolie's mole or Mikhail Gorbachev's port-wine stain, turn them into an adornment. Sometimes these oddities will disappear of their own accord, as often happens with 'strawberry marks' usually found on the face. Otherwise, if they are a cosmetic concern, it's often possible to reduce their prominence by laser treatment.

One other abnormality you may acquire is a cyst. These are not benign tumours but are closed sacs of cells containing liquid or semi-solid material that can form almost anywhere and can be removed by surgery.

You probably spotted another reference to the enigma of cancer a few lines ago in 'almost always', and, although we'll return to this point later, we need a word about moles before we get to warts. These are birthmarks, called nevi, the most common form being a growth of melanocytes in the outer layer of the skin. These cells make melanin – a skin pigment that gives a dark colour to hair, skin and eyes. Moles are therefore benign clusters of pigmented skin cells. Normally no more than decorative, just once in a while a mole can kick off into something nasty and turn into a fully malignant tumour. No need for panic, however, for that almost always requires us to give it a helping hand – usually by lying in the sun without any protection, that is, by exposing it to ultraviolet radiation. Hence the widely publicized advice to use sun cream. Regardless of sun or creams, the essential thing is to consult a doctor if one of your moles changes appearance – gets blacker, starts growing, itching or bleeding. At that point the problem can be resolved by surgical removal of the offending



spot. We'll return to the other scenario later, when we look at drug treatments for malignant melanoma.

The key thing that distinguishes birthmarks and moles from warts is that warts are caused by viral infection. That means we aren't born with them, but most of us get them at some point, often before we are 20 years old. More often than not they disappear of their own accord, although they may take years to do so. Usually they form on the hands or feet or in the anogenital area. Palmar warts occur on the palm of the hand; plantar warts, otherwise known as verrucas (*verruca plantaris*), on the soles of the feet. It's worth noting that warts are *not* the same as the irritating condition known as athlete's foot (*tinea pedis*), which is a fungal infection of the skin between the toes.

Warts are caused by infection with human papillomavirus (HPV), which means they are contagious. There are over 100 different types of HPV, giving rise to variant forms of warts in the outer layer of skin (epidermis) where the virus causes excessive amounts of a protein called keratin to be made. Once infected, you can't get rid of HPV. Nevertheless, most warts can be treated either chemically or by freezing (cryosurgery), burning (cauterization) or laser treatment.

### Why Do Some Children Get Cancer?

They're very unlucky. Either they've inherited a powerful cancer-driving mutation in the DNA they received from a parent, or they acquired such a mutation in the womb. When our very young are stricken it is, of course, especially shattering, so it's worth pointing out that childhood cancers are very rare – less than 1 per cent of all cancers. In the UK the yearly incidence is about 1 child in 500 under the age of 14 – around 1,900 in total with just over 200 deaths. The corresponding US figures are just over 11,000 new cases with 1,200 deaths. The most common childhood cancer affects the blood cells (acute lymphoblastic leukaemia). For this disease the wonderful advances of the last 50 years have seen the cure rate soar to 90 per cent from about 50 per cent in the mid-1970s.

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### How Many Different Cancers Are There?

There are over 100 different types of cancer that can be identified by examining cells from the tumour. Cancers are usually described by the part of the body from which they originated (liver, lung, etc.). However, as we shall see when we look at the molecular picture, that classification is beginning to be replaced by a genetic definition – that is, on the basis of specific mutations.

A further classification is based on the type of cell from which the tumour formed. The three main groups are as follows:

1. Carcinomas – cancers derived from epithelial cells. Skin is made of epithelial cells (epithelial cells are what you scrape off the inside of your cheek) but they also form the lining of all your organs – throat, intestines, blood vessels, etc. Cancers that arise in this type of epithelia are called adenocarcinomas. Carcinoma *in situ* is a pre-malignant change that happens in many cancers in which cells proliferate abnormally within their normal location: the epithelial cells show many malignant changes but have not invaded the underlying tissue. Ductal carcinoma *in situ* (DCIS) is one of the two most common forms of breast cancer, characterized by abnormal proliferation in the wall of the milk ducts. It carries a risk of developing into the invasive ductal carcinoma (IDC) form in which the cells are malignant. The majority of cancers (85 per cent) are carcinomas (e.g., breast, prostate, lung, colon).
2. Sarcomas involve connective tissue – that is, bone and soft tissues such as muscles, tendons and blood vessels. They are much rarer than carcinomas, accounting for less than 1 per cent of cancers, and are not thought to have a pre-malignant (*in situ*) phase.
3. Leukaemias (liquid cancers or blood cancers) and lymphomas are two groups of cancers arising in blood cells. Leukaemias affect bone marrow, whereas lymphomas arise in lymph node cells. The word ‘leukaemia’ comes from the Greek for ‘white’ (*leukos*) and ‘blood’ (*haima*). White blood cells are sometimes called leukocytes but, as that term covers all white cells, including lymphocytes, it’s apt to be a bit confusing. Lymphomas are cancers of lymphocytes, the cells of the immune system that fall into the two main classes of T cells and B cells. The two major