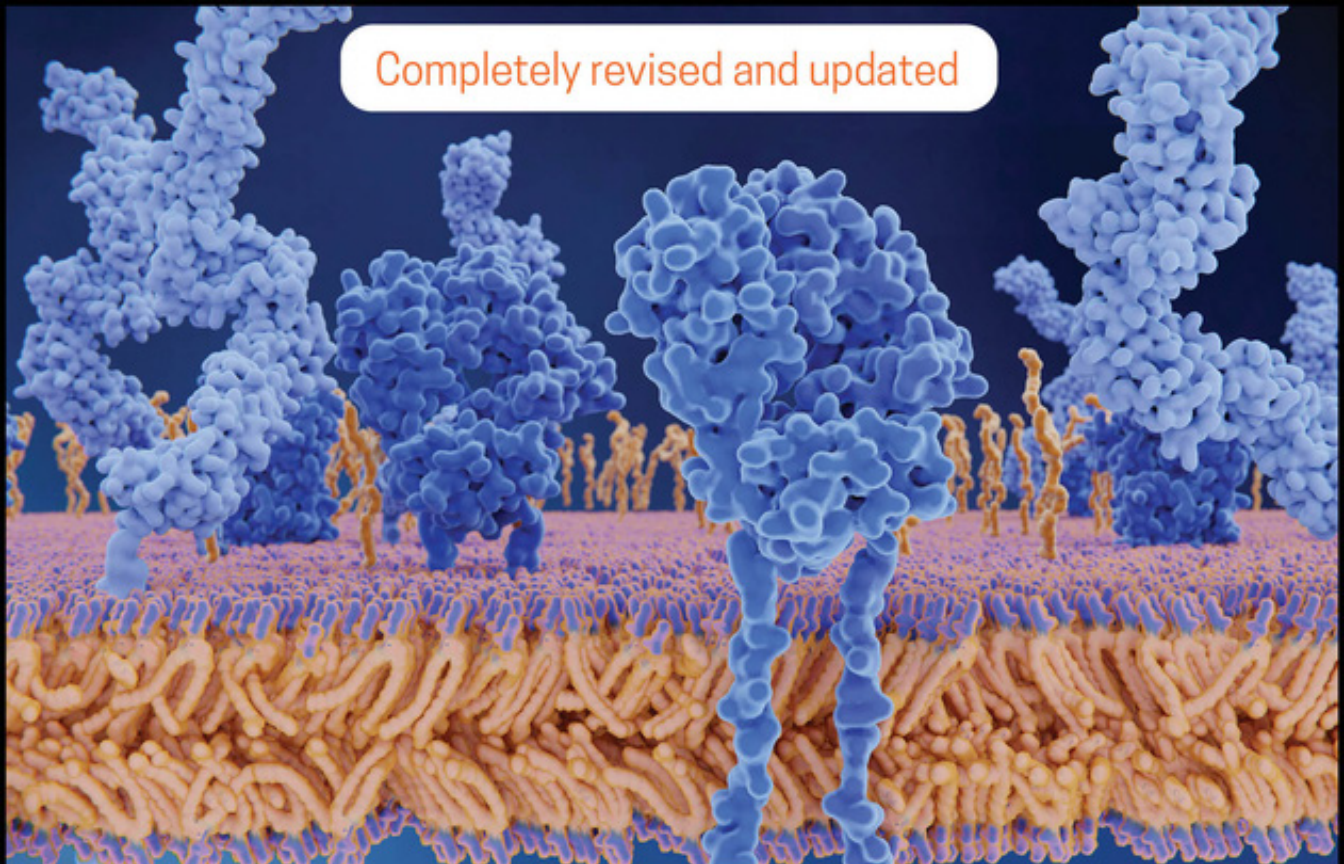




Completely revised and updated

Second Edition

A Beginner's Guide to
**Targeted Cancer
Treatments and
Cancer Immunotherapy**

Elaine Vickers

WILEY

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to Targeted Cancer
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and critiqued this edition. They are: Maggie Uzzell, Joanne Bird, Anne Croudass, Karen Turner, Ben Hood, Chloe Beland, Miranda Payne, Nick Duncan, Clayton Wong, and Philip Dean.

As with the first edition, special thanks go to Ruth McLaren. Ruth was the person who first suggested I should teach nurses and other health professionals as my full-time occupation. Without her, my business and my book might never have happened.

Praise for the First Edition

"I wish this book had existed when I began my career in oncology research. It gives an excellent background to proteins within cancer cells and healthy cells as well as microenvironment differences in cancers. Reading this book gave me even deeper insight into some of the studies I had previously worked on. The writing style and presentation of material is very easy to follow and well organized."

**–Dr Ben Hood, Cancer Research
Consultant Nurse, Sir Bobby Robson
Cancer Trials Research Centre**

"Well done on such a massive undertaking and a really, really useful book. I've learned a lot as I've read it."

**–Dr Sue Brook, Associate Medical
Director, Ellipses Pharma**

"Very impressive! Supportively written, this will become the "go-to book" for any health care professional wanting information on targeted treatments in cancer."

**–Daniel Collins, Deputy Chief
Pharmacist, Liverpool Women's
NHS Foundation Trust**

"As a healthcare professional, I need to know how the drugs I administer to my patients are acting in the body, how they are designed to fight cancer, and to be able to answer the

sometimes-difficult questions that patients ask. This book helps me to do this with confidence. It is complicated in parts because the science is complicated, but written in a way that all those working in the field of cancer care will be able to understand, with knowledge that they can apply to practice. Fabulous illustrations throughout the book and a very logical format make this text accessible to all."

**–Nikki Hayward, Skin Cancer CNS
team lead, Buckinghamshire
Healthcare NHS Trust**

"What an amazing achievement! Patients and healthcare professionals will be delighted to discover a book that makes incomprehensible concepts accessible, interesting, and logical."

**–Heather Phillips, Research Delivery
Manager, NIHR**

"Really wonderful, so nicely written, exactly what I had been looking for. We are in the very early stages of developing an NIH/NCI grant proposal related to technology that helps clinicians easily align their patients' variants with potential treatment options, and Dr. Vickers' book was absolutely invaluable at opening my eyes to the complexity and the possibilities."

**–Bob Dolin, Senior Informaticist,
Elimu Informatics**

I recommend this book to all of my students who wish to further develop their knowledge of some of the targeted therapies used to treat cancer. The book is well written which strengthens its use as a reference and it is also

a book which readers can use to check their understanding of these treatments. It contains excellent illustrations.

**–Maggie Uzzell, The Royal
Marsden School**

About the Author



Elaine Vickers has been a cancer educator and writer for over twenty years. Since setting up her company, Science Communicated Ltd (sciencecommunicated.co.uk), Elaine has developed a wide range of study days, courses, and teaching materials that explain cancer biology and the science behind targeted cancer treatments and immunotherapies.

Each year, Elaine teaches hundreds of cancer nurses, doctors, and allied cancer professionals working in the United Kingdom. She also presents a regular program of in-person study days for the Royal Marsden Conference Centre in London and speaks at numerous cancer conferences in the United Kingdom and Europe. In recent years, Elaine has expanded her reach by delivering online courses and creating educational videos and webinars. She has also worked with an animator to create animations that explain cancer and cancer treatments.

Elaine has a degree in Medical Science from the University of Birmingham and a PhD in Molecular Biology from the University of Manchester. Her goal is to unravel the complexities of cancer biology and new cancer treatments and make these topics interesting and accessible to nonscientists.

Elaine considers herself incredibly lucky to live in Manchester with her husband Rowan and her little dog CJ.

How to Use This Book

I wrote the first edition of this book when I couldn't find a resource that would cover all the topics I was teaching on without overwhelming the reader with scientific detail. I felt what was missing was a single book that brought together sufficient information on cancer biology to explain the promise and the limitations of the latest cancer treatments.

Since the first edition was published in 2018, a lot has changed, particularly in the realm of immunotherapy. Thus, in this edition, I have expanded the early chapters to incorporate greater detail on the relationship between cancer and our immune system. I have also vastly expanded the information on immunotherapy. In this edition, immune checkpoint inhibitors have their own chapter. I also devote a second chapter to explanations of the science behind many other immunotherapy approaches.

As with the first edition, although I have called this book "A Beginner's Guide ..." I do include a lot of science. I also don't try to hide the complexity of the subjects I am attempting to describe. However, I hope that by providing illustrations and including lots of background information in the first two chapters, you can follow the rest of the book.

You'll also notice that I don't describe any advances in radiotherapy or surgery, and I provide very little information on chemotherapy and hormone therapy. I made this choice

because I am a molecular biologist, and I wanted to focus my attention on where I feel I have the most to offer: explaining the science behind targeted therapies and immunotherapies for cancer.

One challenge I had when writing this book was the rapid pace of cancer research and drug development. Although I have done my best to provide up-to-date information, this will no doubt be quickly eroded by the creation of new treatments and new approvals in the months and years to come. I apologize if any drug or bit of science you are interested in – from a professional or personal standpoint – isn't included. I hope that because I have focused on the mechanisms of action of new treatments rather than their stage of development, you will find this book relevant to you.

Another decision I made when writing the book was to provide only passing information on the degree of benefit offered by the treatments mentioned. I made this choice because the difference a treatment makes is context- and disease-specific. For example, a treatment that provides only a modest extension in survival times in people with relapsed, advanced disease may be able to cure people who have early-stage, newly diagnosed disease. As a molecular biologist interested in explaining how treatments work, I decided this level of detail was beyond the scope of this book. For similar reasons, I don't generally provide

information about which countries a treatment is licensed in or for which patients.

I have presumed that when you open this book, you will be approaching the subject from one of four perspectives:

1. Because you're interested in a **specific treatment** and want to learn more about it. If that's the case, you might want to start with the index and look it up by name.
2. Because you're involved in caring for people affected by a **certain type of cancer** and want to know about the relevant treatments. If so, you might wish to turn to chapter seven first.

3. Because you'd like to know about treatments that **have a specific target**, such as CDK inhibitors, or that **have a particular mechanism**, such as vaccine-based treatments. If that's you, then chapters 3–6 will likely contain the information you're after.

4. Or, if you're relatively new to the topics covered in this book, I would advise you to begin at the beginning and go from there!

Whatever your reason for reading this book, my sincere hope is that you will find it useful and interesting.

CHAPTER 1

An Introduction to Cancer Cell Biology and Genetics

IN BRIEF

I find it impossible to describe how targeted cancer treatments work without mentioning what it is they target. And when I try to explain what it is they target, I find myself going back to the beginning and explaining where cancers come from, what faults they contain, and why they behave as they do. And, to explain that, I need to explain concepts such as DNA damage, oncogenes, tumor suppressor genes, and the hallmarks of cancer cells.

In recent years, we've also made great progress in using a patient's immune system to treat cancer using immunotherapy. When explaining how immunotherapies work, I find it useful to offer at least a brief description of our immune system and the ways in which cancer cells and white blood cells interact. Armed with this knowledge, various strategies to use the immune system to destroy cancer cells begin to make sense.

In this chapter, my goal is to bring together much of this background knowledge. I hope it will provide you with a useful foundation that enables you to understand individual targeted therapies and immunotherapies that I mention in later chapters.

First, I run through the causes and consequences of DNA mutations in cells. I describe how even just a handful of mutations can force a healthy cell to become a cancer cell.

I also describe the cancer microenvironment – the cells and structures that cancer cells live alongside, including white blood cells of our immune system. Cancer cells have the ability to exploit their local environment and, in many instances, manipulate it. I explain what impact this has when doctors come to treat people with the disease.

In addition, I tackle topics such as genome instability and intratumoral heterogeneity. Perhaps these are topics that right now don't mean anything to you, and you're unsure of why you need to know about them. But it's only through understanding these concepts that you can appreciate the limitations of targeted (and standard) cancer treatments and grasp the potential of immunotherapy. It is also important to understand why cancer spreads and how cancers evolve and change over time.

I then turn my attention to the unique properties of hematological cancers. I describe some of the types of mutation that drive their behavior and talk about why these mutations occur. I also explain their greater vulnerability to immunotherapy compared to solid tumors.

Finally, I wrap up the chapter with a brief overview of why cancer is so difficult to treat successfully and why so many people currently cannot be cured.

1.1 INTRODUCTION

This book is about the science that lies behind targeted cancer treatments and cancer immunotherapies. Almost without exception, **these treatments work by attaching to, or blocking the actions of, proteins**. So, to understand these treatments, it's first of all essential to understand what proteins are, how they work, and how the proteins found inside and on the surface of cancer cells differ from their healthy counterparts.

For this to make sense to you, I need to explain the different types of DNA damage that cancer cells contain, **because a cell's DNA is its instruction manual telling it how to make proteins**. If we know what DNA damage a cell contains, this will tell us what faulty proteins it's making. And if we know what faulty proteins it's making, we will have a better idea of which treatments might work against it.

So, **this chapter contains lots of information about cancer cells, DNA, and proteins**. However, even in this chapter, I've made some assumptions about what you do and don't know. For example, I've assumed that you have a rough idea of what DNA is and how cells use their DNA to make proteins. If you're not familiar with these concepts, I would recommend first taking a look at the Appendix, which contains a list of reading materials about cells, DNA, chromosomes, genes, and proteins. When you've had a look at that, you'll be ready to read further.

This chapter doesn't exclusively focus on individual cancer cells and their faults.

Cancer cells don't live alone, nor are tumors a homogenous mass of identical cancer cells.

Instead, cancer cells live among other types of cells, such as fibroblasts, fat cells, and numerous types of white blood cells. This composition changes over time and also in response to treatment. In addition, cancer cells themselves evolve and change over time, and this has an enormous impact on the effectiveness, or not, of many treatments.

In this chapter, I'll also provide you with some background information about **how cancer cells relate to, and influence, our immune system**. Why it is, for example, that in some people their immune system reacts strongly against their cancer cells, while in another person their immune system seems to essentially shrug its shoulders and carry on as normal. I'll also pay special attention to T lymphocytes (T cells), which are at the heart of many different forms of immunotherapy.

Some of the information in this chapter is relevant to all cancers, wherever they occur in the body and whatever type of cell they developed from. However, there are some features of hematological cancers (such as leukemias and lymphomas) that set them apart from solid tumors like breast or bowel cancer. Some of this difference comes down to the mutations that drive hematological cancers, but some of it is due to their accessibility to drugs, and to healthy white blood cells.

Along with the chapter that follows (which is all about the two main groups of cancer treatments in this book: monoclonal antibodies and kinase inhibitors), this chapter hopefully

provides you with all the background information you need to make sense of the rest of this book.

1.2 DNA DAMAGE IS THE CAUSE OF EVERY CANCER

Our cells' DNA is essentially a huge instruction manual telling our cells what proteins to make, how to make them, when to make them, what to do with them, and when to destroy them. In turn, the proteins our cells make dictate their behavior. For this reason, **if you damage a cell's DNA, it is likely to make the wrong, or damaged, versions of proteins**, leading to abnormal behavior (see Figure 1.1).

Cancer starts to develop when a single cell accumulates DNA damage to several important genes. This damage causes the cell to

make faulty proteins that force it to behave abnormally. To result in cancer, the cell also needs to overcome whatever hostile forces are exerted by its environment and by neighboring cells. Thankfully, this normally doesn't happen. Instead, **a cell that finds its DNA damaged usually tries to repair the damage, or it self-destructs** through a process called apoptosis.¹ **Or, if the cell doesn't kill itself, it's usually kept in check by its environment or destroyed by white blood cells.** But, if a damaged cell survives, and if it avoids or overcomes its hostile neighbors, it might ultimately multiply and cause us to develop cancer.

Over the past 40 years or so, scientists have been gradually uncovering which gene mutations cause cancer. Genes only take up about 1%–2% or so of our cells' total DNA, so it's this DNA they have focused on [1].

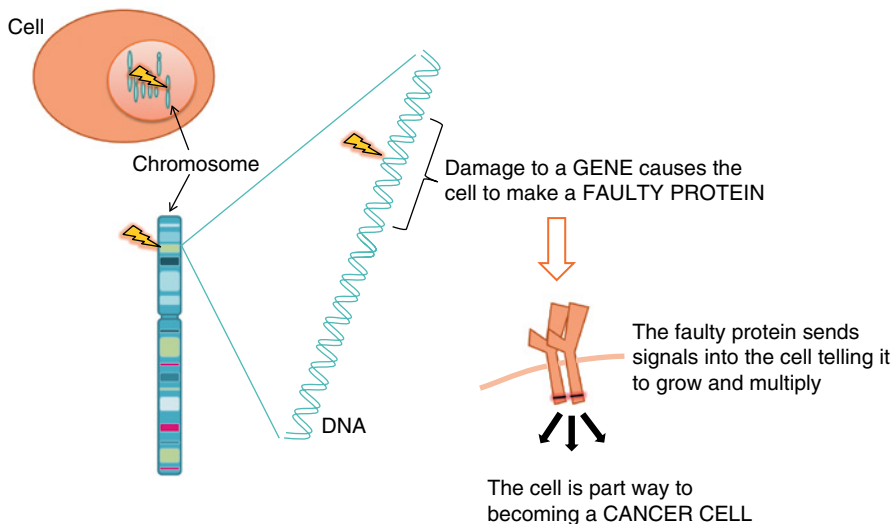


Figure 1.1 Gene mutations cause the production of faulty proteins. Chromosomes are long lengths of DNA found inside the nucleus of each cell. Within our chromosomes are regions of DNA called genes. These are stretches of DNA that contain the instructions to make proteins. If a gene is affected by a mutation (represented by a lightning bolt), the cell might then make a faulty protein. In this example, the faulty protein is a cell surface receptor that gives the cell a continuous signal to grow and multiply.

¹ Apoptosis is also referred to as “programmed cell death.”

Box 1.1 The names of genes and their proteins

As you read this book, you might notice that protein names are written normally but that gene names are written in italics. For example, the *HER2* gene contains the instructions for making HER2 protein. You might also notice that sometimes the gene and the protein have different names. An example of this is the *TP53* gene, which contains the instructions for making a protein called p53. It's also possible for a gene to contain the instructions for making more than one protein. For instance, the *CDKN2A* gene (sometimes referred to as the *CDKN2A* locus) contains the instructions for making several proteins, two of which are called p16^{INK4a} and p14^{ARF}.

To add to the confusion, some genes and proteins have more than one name. For example, the *HER2* gene is also called *ERBB2* and *NEU*. The reasons behind the various names often have a lot to do with what organism or group of cells the gene/protein was discovered in; if it's similar to another gene/protein that has already been discovered; what role the gene/protein is thought to play in the cells or organism it was found in; and whether or not abnormalities in the gene/protein cause disease. For example, HER2 stands for "human epidermal growth factor receptor-2," because it's similar in structure to HER1 (although we usually refer to HER1 as the EGF receptor or EGFR). *HER2* is also called *ERBB2* because a very similar gene, called *ERBB*, was discovered in a disease-causing virus called the avian erythroblastosis virus. *HER2* is also called *NEU* because a faulty version of it can cause a cancer called neuroblastoma in rodents.

A final point to note is that gene names are often written in capital letters, whereas protein names aren't. But this convention isn't always adhered to.

(What exactly the rest of our cells' DNA is for is a matter of continued debate among scientists.)

Through initiatives such as The Cancer Genome Atlas [2] and the International Cancer Genome Consortium [3], hundreds of scientists have amassed an incredible catalog of information about the thousands of different DNA mutations cancer cells contain [4, 5]. They've also discovered that **different types of cancer differ from one another in terms of the mutations they contain and the treatments they respond to**. In addition to these differences, we know that important similarities can exist between cancers that arise in different organs. For example, the cancer cells of some breast

cancers overproduce² a protein called HER2, and the same is true of the cancer cells in some stomach cancers and other cancer types [6].

Because there's lots I want to say about the DNA mutations found in cancer cells, I'm going to split it up into different topics. First, I'll talk about what **causes the DNA mutations** found in cancer cells (Section 1.2.1). Then I'll describe what **types of mutation** occur (see Section 1.2.2), how the **number and pattern of mutations** in cancer cells varies (see Section 1.2.3), and **which mutations have the greatest effect on cell behavior** (see Section 1.2.4). Then I'll talk about some of the most **common gene mutations** in cancer cells and what impact they have (Section 1.2.5).

² Scientists generally talk about proteins being "overexpressed" rather than "overproduced," but they essentially mean the same thing.

All this information is gradually helping scientists create the new, more targeted cancer treatments described in this book.

1.2.1 Causes of DNA Mutations

There are many different reasons why our cells' DNA gets damaged. Much of this damage is **natural and unavoidable**, whereas some of it is down to our **lifestyle, behaviors, exposures, geographical location**, and even **local customs**.³ We can also **inherit** damaged DNA from our parents. Depending on what sort of data scientists look at (e.g., whether they examine individual cells or whole organs or tissues, or look at populations of people in different countries), they end up drawing very different conclusions about what proportion of cancers could be avoided [7–10]. So, although I've listed some of the causes of DNA damage later, and in Figure 1.2, I haven't

tried to pin down exactly how many cancers are caused by each one.⁴

Unavoidable Causes of DNA Damage

1. The byproducts of chemical reactions.

Unfortunately for us (and for all living things), **our cells' DNA gets damaged every second of every day**. Scientists think that even without the influence of external factors, each of our cells sustains damage to its DNA roughly 20,000 times each day [15].

Much of this damage is caused by the products of chemical reactions that are essential to keep us alive. For example, many of our cells' important chemical reactions produce oxygen free radicals⁵ – high-energy oxygen atoms that essentially bash into and break DNA [16]. Our cells contain well over 100 different DNA repair proteins to fix this damage [17]. But sometimes they

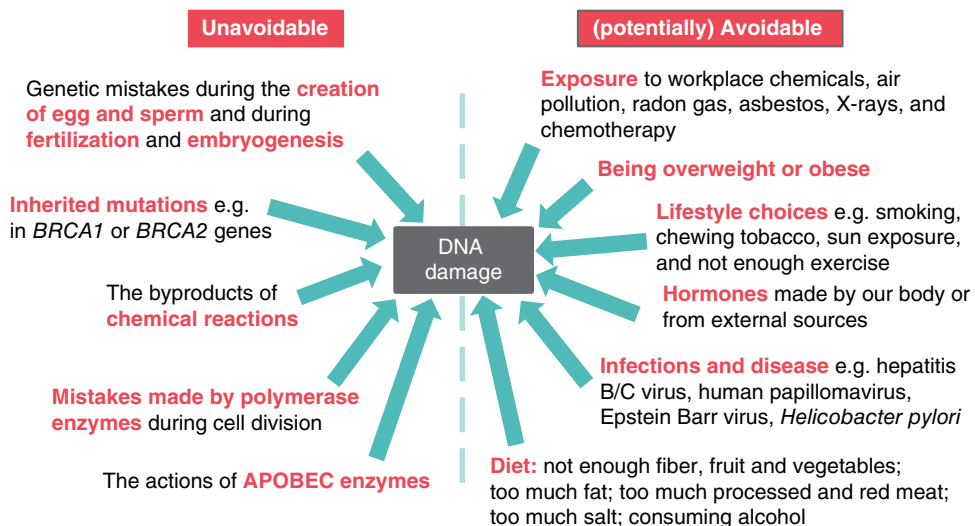


Figure 1.2 Some of the causes of DNA damage. *Source:* Adapted from Ref. [11–14].

³ For example, in countries like Iran, people are used to drinking much hotter tea than people do in the United Kingdom, and this has been linked to a higher incidence of esophageal cancer.

⁴ If you do want to learn more about what you can do to reduce your risk, I would recommend looking at the Cancer Research UK website: <http://www.cancerresearchuk.org/about-cancer/causes-of-cancer/cancer-be-prevented>.

⁵ These are also called reactive oxygen species – ROS.

fail to spot all the damage, or they simply can't keep up.

2. Cells make mistakes as they multiply.

Tissues that need to renew and replenish their cells often (such as the lining of our bowel, our skin, and those that comprise our immune system) are at the highest risk of cancer⁶ [9, 18–20]. This is because for a cell to multiply, it has to make a complete copy of all of its DNA – all 3000 million base pairs of it. The enzyme that copies DNA, called DNA polymerase, although spectacularly fast and accurate, does occasionally make mistakes [18]. Therefore, **cells that need to multiply often are at a greater risk of becoming cancer cells** than cells that rarely, if ever, multiply.

3. The actions of APOBEC enzymes.

APOBEC⁷ enzymes are a family of proteins that our cells use to help protect them from viruses. **APOBEC enzymes attack viruses** by introducing mutations into their DNA. However, if an uninfected cell accidentally makes APOBEC enzymes, the enzymes will attack the cell's own DNA and introduce lots of mutations that could cause cancer [19]. Also, after a cell has become a cancer cell, APOBEC enzymes continue to add more and more damage to the cell's genes [20].

4. Inherited mutations. Some people are **born with DNA faults** that put them at a higher risk of cancer. Sometimes the fault has been passed down from generation to generation, with many family members affected. For example, actress and film director Angelina Jolie has inherited a fault in one copy of her *BRCA1* gene (we inherit two copies of each

gene). Because this fault is shared by many of her relatives, she lost her mother, grandmother, and aunt to cancer [21]. Faults in high-risk genes such as *BRCA* genes are relatively rare, but they can have an enormous impact on a person's cancer risk. More commonly, subtle variations in many genes will combine to affect our risk.

Faults can also arise in an egg or sperm; if the faulty egg or sperm goes on to create an embryo, this fault will be present in every cell. Or, the fault might occur later, as the growing embryo is developing. For example, faults that occur in an embryo's white blood cells as its immune system forms can cause infant or childhood leukemia [11].

Potentially Avoidable Causes of DNA Damage

1. Lifestyle and exposures.

Cells that are exposed to high levels of **carcinogens** (anything that causes cancer is called a carcinogen) are particularly vulnerable to becoming cancer cells. This includes cells that line our lungs, skin, bowel, and stomach. Carcinogens include various constituents of cigarette smoke, alcohol, UV light from the sun or from sunbeds, radiation from X-rays, some viruses, asbestos, and food toxins [13].

Our cancer risk is also linked to our **diet** (including our consumption of fruit and vegetables, red and processed meat, salt, and fiber), our level of **physical activity**, and our **weight**. This is a huge topic. If you would like to learn more, I suggest looking at the Cancer Research UK [22] and American Cancer Society [23] websites.

⁶ If this seems like a simple and straightforward association, don't be fooled. There is huge controversy around the exact relationship between cancer risk and tissue renewal, number of stem cells, and DNA damage by environmental versus natural mechanisms. I've supplied a handful of references if you want to explore further.

⁷ In case you're curious, APOBEC stands for apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like.

- 2. The influence of sex hormones.** When discussing the causes of cancer, we shouldn't ignore the influence of sex hormones such as **estrogen, progesterone, and testosterone**. These tiny, fat-soluble chemicals encourage cells that contain receptors for them to survive, grow, and multiply (estrogen can also cause DNA damage [24]). Cancers that develop from hormone-sensitive tissues in the breast and prostate often retain their sensitivity to hormones. These cancers often respond to treatments that block the production of hormones in the body or that block the impact of hormones on cancer cells.

The risk of various cancers, including breast, ovarian, and endometrial cancer, is linked to a person's exposure to sex hormones such as estrogen. Reproductive factors (such as age of menarche⁸ and menopause, along with the number of pregnancies and length of time they breastfed) and bodyweight affect a person's lifetime exposure to estrogen and thus also influence their cancer risk [25].

- 3. The influence of inflammation.** For many people, their cancer diagnosis was preceded by **years of inflammation, infection, or irritation** [26]. For example, people with a chronic hepatitis B or hepatitis C virus infection are at high risk of liver cancer, whereas people with inflammatory bowel disease are at an increased risk of bowel cancer [27, 28]. It seems that the presence of white blood cells in a tissue can increase the DNA mutation rate in the tissue's cells and encourage the cells to multiply, raising the risk of cancer [28].
- 4. Cancer treatments. Most chemotherapies and radiotherapy work by causing so much DNA damage** that cancer cells die. However, not every cell is killed. Cells that

sustain damage to their DNA and yet survive may later become cancer cells. Because of this, people treated for cancer sometimes develop second cancers months or even many years later [29, 30].

Causes of DNA Mutations – Summary

Our risk of cancer in any particular place in our body is therefore a combination of the following [8–10]:

- The natural rate that the cells multiply in that tissue.
- The extent to which DNA polymerase, oxygen free radicals, and APOBEC enzymes have caused mutations in the tissue's cells (the amount of damage will gradually increase as we age).
- Our biological sex and our inherited genetic makeup.
- Our lifestyle and behaviors (which will be hugely impacted by our cultural background, physical location, personal choices, and opportunities).
- Our cells' exposure to carcinogens, hormones, and factors that cause inflammation.

Cancer Research UK estimates that **around 4 in every 10 cases of cancer diagnosed in the United Kingdom are potentially preventable** through changes to lifestyle, behaviors, exposures, and weight [31, 32]. However, we cannot influence factors such as the activity of APOBEC enzymes or the accuracy of DNA polymerase. As I said before, estimating what proportion of cancers can be prevented is an incredibly contentious topic, and estimates vary widely depending on how the research was done [7].

1.2.2 Types of DNA Mutations

DNA mutations come in many forms. For the sake of simplicity, I'm going to split them into two groups: (1) mutations affecting long

⁸ The age at which a girl has her first period.

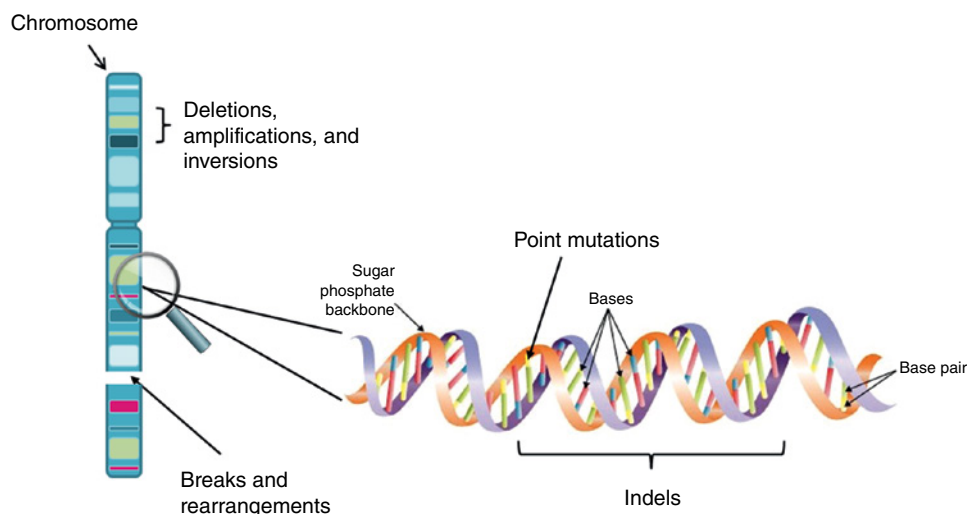


Figure 1.3 DNA damage can come in many forms. Deletions, amplifications, and inversions can affect tens of thousands of DNA bases at a time. Breaks and rearrangements affect whole chromosomes. Smaller-scale mutations include point mutations (insertions, deletions, or substitutions) affecting a single DNA base. Insertions and deletions that involve up to 1000 DNA bases are called indels. *Source:* Adapted from Ref. [33], the image of DNA double helix was created by the Genomics Education Programme and licensed under the Creative Commons Attribution 2.0 Generic license. <https://www.flickr.com/photos/genomicseducation/13081113544/> Image of magnifying glass from pixabay.com.

stretches of DNA and whole chromosomes and (2) mutations affecting under 1000 DNA base pairs (see Figure 1.3).

Mutations Affecting Long Stretches of DNA and Whole Chromosomes

For a start, **many cancers are aneuploid** – that is, the cells contain the wrong number (i.e., not the normal 23 pairs) of chromosomes [34]. Often, there is evidence that at an early point in the cancer’s development, its entire genome – all 46 chromosomes – have been duplicated (called **whole-genome doubling** [35]). In addition, chromosomes often show signs of having shattered into small pieces and then been stitched back together in a haphazard fashion – called **chromothripsis** [36, 37]. These types of DNA damage are no doubt important. However, it’s not always clear what impact they have on cancer cells, nor what we could do about them in terms of offering better treatments. Because detecting

these types of DNA damage doesn’t generally help doctors decide what treatment to give to their patients, I’m not going to talk about them further.

What can be more helpful is detecting chromosome faults such as translocations, inversions, insertions, deletions, and amplifications.

Chromosome Translocations and Rearrangements

A chromosome translocation is when two chromosomes break, and the cell accidentally sticks them back together incorrectly (see Figure 1.4). Chromosomal rearrangements are similar, but both breaks occur in a single chromosome. More often than not, the chromosomes break in regions that don’t contain any genes (remember that the information to make proteins only takes up 1% or so of our chromosomes). However, **sometimes translocations and rearrangements do affect genes**, and this can have dire consequences.

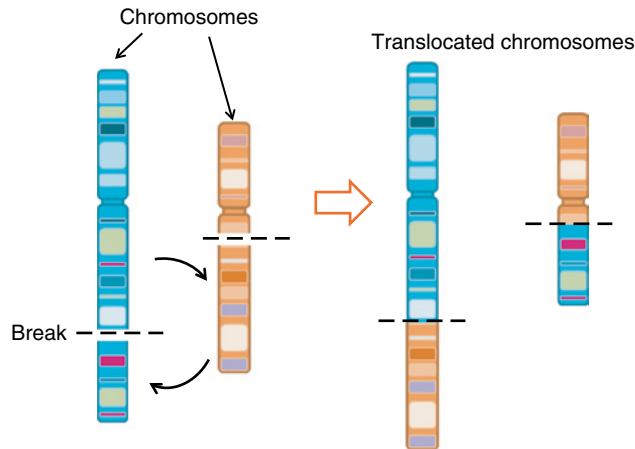


Figure 1.4 A chromosome translocation. Two chromosomes (colored turquoise and orange) break. The cell attaches them back together incorrectly. If the chromosomes have broken where genes are located, this may result in two genes from different chromosomes becoming fused together on the same chromosome (a gene fusion).

For example, the cancer cells of chronic myeloid leukemia (CML) almost always contain a translocation in which chromosome 9 and chromosome 22 have broken and been stitched back together incorrectly. This causes the *BCR* gene on chromosome 22 to become fused together with the *ABL* gene on chromosome 9. The fusion of these two genes causes the cell to make a Bcr-Abl **fusion protein** (a protein made using the information in the fusion gene), which forces the cells to grow and multiply [38, 39].

In some other cancers, you find translocations and gene rearrangements in which a control region from one gene (a promoter or enhancer⁹) has become fused to the protein-coding region¹⁰ of a second gene. This has often happened during the development of prostate cancer and some forms of blood cancer such as non-Hodgkin lymphomas and myeloma (sometimes called multiple myeloma).

In prostate cancer, the rearrangement often involves the *ERG* and *TMPRSS2* genes on chromosome 21. The rearrangement places the promoter from the *TMPRSS2* gene (a gene that is always active in prostate cells) next to the protein-coding region from a powerful, pro-growth protein called *ERG* [40] (see Figure 1.5). The consequence of this mutation is the massive overproduction of ERG protein, which forces the prostate cell to multiply.

Chromosome Insertions

An insertion is when **part of one chromosome is inserted into another chromosome** (Figure 1.6). It can also occur when part of a chromosome is reinserted back into the chromosome it came from, but in the wrong place. An example is the “internal tandem duplications” affecting the *FLT3* gene, which are found in the cancer cells of around a third of people with acute myeloid leukemia (AML) [41].

⁹ The Khan Academy website has a nice description of gene regulation: <https://www.khanacademy.org/science/ap-biology/gene-expression-and-regulation/regulation-of-gene-expression-and-cell-specialization/a/overview-of-eukaryotic-gene-regulation>.

¹⁰ That is, the part of the gene that contains the instructions to make a protein.

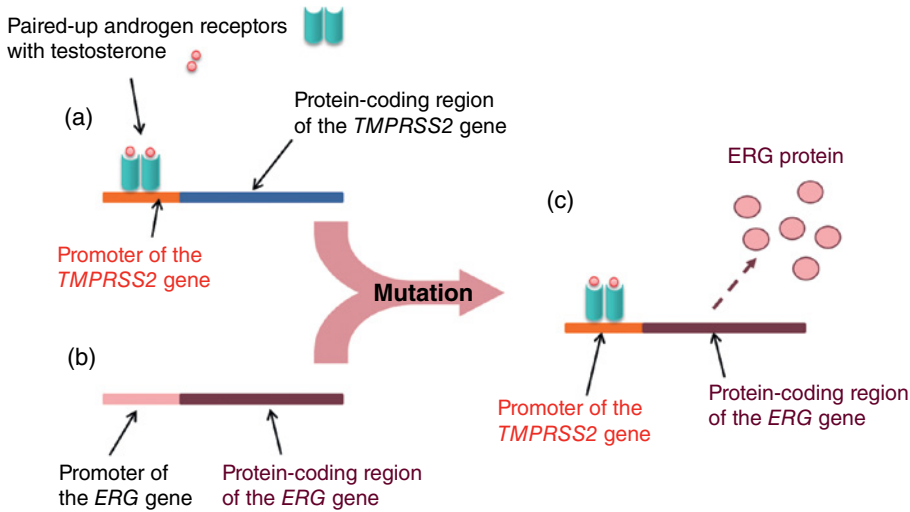


Figure 1.5 The TMPRSS2-ERG gene fusion often found in prostate cancer cells. (a) In healthy prostate cells, androgen receptors pair up due to the presence of testosterone. Paired-up receptors then attach to the *TMPRSS2* gene promoter and cause the cell to produce TMPRSS2 protein. (b) Prostate cells only rarely produce ERG because the *ERG* gene does not contain attachment sites for androgen receptors. (c) 50% of prostate cancers contain a mutation that puts the protein-coding region of the *ERG* gene under the control of the promoter from the *TMPRSS2* gene. This mutation causes the cell to overproduce ERG protein, which in turn forces the cell to multiply. *Source:* Adapted from Ref. [40].

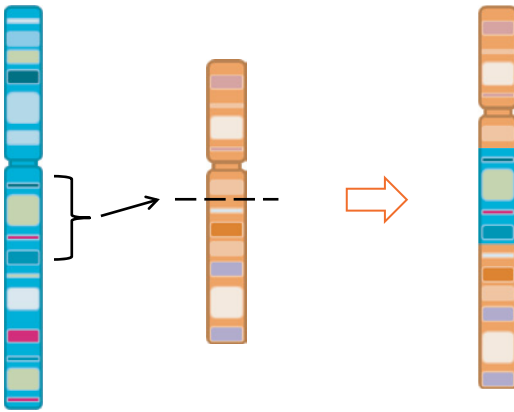


Figure 1.6 A chromosome insertion – part of one chromosome is inserted into another chromosome (as shown) or back into the chromosome it came from.

The insertion involves part of the *FLT3* gene, which is copied and reinserted back into the original gene. This causes the cell to make an extra-large, overactive version of FLT3 protein, which can be blocked with FLT3 inhibitors (see Section 3.6.8 for more on this).

Chromosome Deletions

Not surprisingly, a chromosome deletion is when **part of a chromosome gets deleted** (Figure 1.7a). An example is the deletion of the part of chromosome 17 that contains the *TP53* gene – this is often referred to as del(17p). *TP53* is a vital tumor suppressor gene that prevents faulty cells from becoming cancer cells (there is more about *TP53* in Sections 1.2.5 and 4.7). The loss of *TP53* means that part of the cell's protection against cancer has gone.

Chromosome Inversions

Inversions (Figure 1.7b), in which **part of a chromosome is cut out, flipped over, and then reinserted**, can also disrupt genes. For example, an inversion of part of chromosome 2 is found in about 4%–7% of non-small cell lung cancers (NSCLCs; this is the most common type of lung cancer). The inversion joins together the *ALK* gene with part of the *EML4* gene, creating an uncontrollable ALK fusion

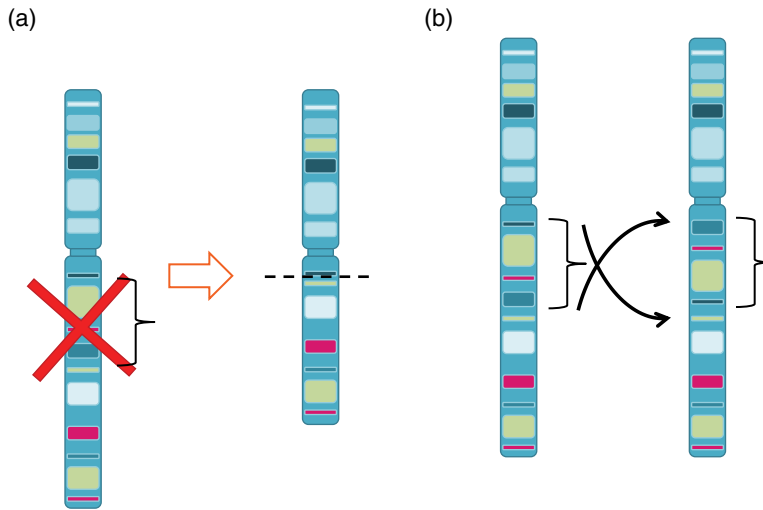


Figure 1.7 Chromosome deletions and inversions. (a) In a chromosome deletion, part of a chromosome is (not surprisingly) deleted. (b) Chromosome inversion – a segment of the chromosome is cut out, flipped over, and inserted back into the chromosome.

protein that forces the cells to multiply [42]. (For more about *ALK* mutations in lung cancer, and *ALK* inhibitors, see Section 3.6.5.)

Gene Amplification

Gene amplifications occur when a cell's DNA replication machinery **accidentally makes extra copies of a region of a chromosome** that contains one or more genes (see Figure 1.8). As a consequence, the cell overexpresses¹¹ the proteins made from the amplified genes. A common amplification is that of the *HER2* gene (also referred to as *NEU* or *ERBB2*), which is amplified in about 15%–20% of breast cancers [43].

Point Mutations and Indels

A point mutation is when **one DNA base is accidentally added, deleted, or swapped** for a different one. The term “indel” is used to refer to **small insertions and deletions affecting fewer than 1000 DNA base pairs**. Most point

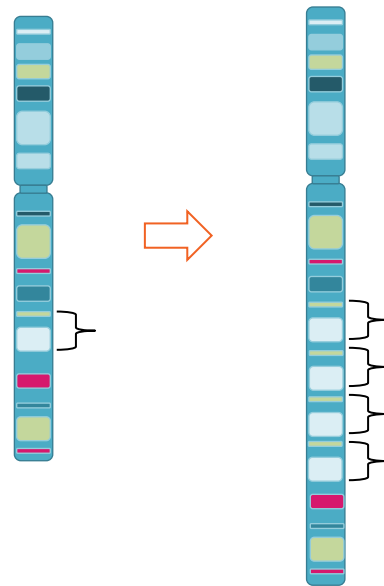


Figure 1.8 Gene amplification. The cell accidentally makes extra copies of a section of a chromosome. The duplicate segments are inserted into other chromosomes or back into the same chromosome.

¹¹ When a cell uses the information in a gene to make the corresponding protein, that gene is “expressed.” So, if a gene is said to be overexpressed, that means that more of the corresponding protein is being made than is normal.

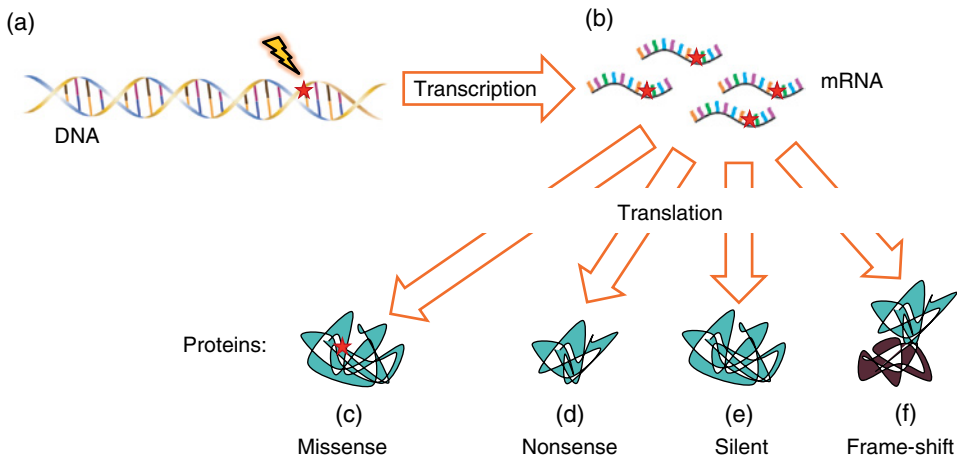


Figure 1.9 Point mutations. A point mutation (shown by a red star) is when one DNA base is added, deleted, or swapped for a different one in the cell's DNA. (a) If the mutation is in a gene, the mutation will be copied into the mRNA (b) and it may alter the resulting protein. The consequence might be that (c) due to a **missense mutation**, the protein made by the cell differs from the normal version of the protein by one amino acid, (d) a **nonsense mutation** in the DNA introduces a stop signal into the mRNA, and the cell makes an extra-short (truncated) protein, (e) a **silent mutation** has no impact on the protein produced, and (f) a **frameshift** mutation causes the cell to make a very different protein compared to the normal protein, which is only partly the same as the original. *Source:* DNA image from Pixabay. mRNA image by Christine I Miller, licensed under the Creative Commons Attribution-Share Alike 4.0 International license.

mutations and indels have no impact on the cell, as they occur outside of genes. However, if a mutation (such as a base substitution, addition, or deletion) occurs within a gene, it can have various consequences (see Figure 1.9).¹² Point mutations are classed as missense, nonsense, or silent, depending on what consequence the mutation has on protein production. They are also classified as “in-frame” or “frameshift” mutations [44]. All of these terms are explained in greater detail later.

Just one extra piece of information before I move on: The unmutated, normal version of any gene is often referred to as the “wild-type” version of that gene.

Missense and Nonsense Mutations

If one DNA base is substituted for a different one, this might change a single codon. As you might already know, proteins are constructed from long chains of 20 different amino acids. Each **set of three bases** (called a **codon**) in the mRNA strand tells the ribosome what amino acid to add next to the protein it's making.¹³

In a missense mutation, the change in a codon means that the **protein made from that gene differs by one amino acid** from the normal protein (Figure 1.9c) [44]. Two examples are the faulty version of the B-Raf protein (called V600E), which is often found in the

¹² If you need a refresher on gene transcription and translation at this point, I suggest taking a look at some of the resources suggested in the Appendix.

¹³ If you're struggling to make sense of this, I would suggest looking at the Appendix and learning a bit about gene transcription and translation.