1.1

The Global Burden of Cancer

In order for us to understand cancer and its treatment it is obviously important to define what is meant by the term ‘cancer’. The word is credited to Hippocrates, the Greek physician (460–370 BC), who used the words *carcinos* and *carcinoma* to describe non-ulcer and ulcer-forming growths. These words in Greek derive from the word for crab, and their use is believed to be due to the fact that the spreading nature and cellular projections of the growths observed were reminiscent of the shape of a crab. Later changes resulted in the use of the words *cancer* (Latin for crab) and *oncos* (Greek for swelling) to describe tumours, terms attributed to the Roman physicians, Celsus (28–50 BC) and Galen (130–200 AD), respectively. Interestingly, we still use all of these words to define malignancy, to discuss a tumour’s histological appearance, and as a description for medical specialists in this area (oncologists).

Although described as a single condition, cancer is actually a family of hundreds of different diseases. The distinction between the different types of cancer is extremely important since their treatment, management, and outcomes for the patient are very diverse (as we shall see in the later sections). Additionally, even within a single cancer ‘type’ there are significant issues with regards to treatment options and patient prognosis, as individual cancers of the same type can behave very differently from one another. The same can be said for the global distribution of cancer; there are different profiles of cancer types in different geographical regions, with different causative factors, different treatment options and successes, and different prognostic and survival rates. Invariably, across the globe, some cancer types and some patients will achieve some degree of remission, and some will be cured, but others will not, with treatment in their case focusing on extending life expectancy.

Cancer is a major worldwide public health problem, as indicated by the World Health Organization (WHO) identifying cancer as one of four leading threats to human health and development (the others being cardiovascular disease, chronic respiratory diseases, and diabetes) in 2008 [1]. In 2012, cancer incidence\(^1\) was estimated at 14.1 million people, cancer mortality\(^2\) was predicted at 8.2 million deaths, and cancer

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1. Incidence is the number of new cases arising in a given time period in a specified population, presented as the absolute number of cases annually or the ‘age-standardised’ rate per 100,000.
2. Mortality is the number of deaths in a given time period in a specified population, presented as absolute number of deaths annually or the ‘age-standardised’ rate per 100,000.
prevalence\(^3\) was estimated at 32.6 million people [2]. When we just consider these numbers it is difficult to appreciate the scale of the problem, and it is therefore important to put this into context. For instance, in 2012 the estimated population of the world was 7.05 billion people, and the risk of dying\(^4\) from cancer before age 75 was 10.5% [2].

Cancer is not a modern disease, being first identified and described around 5,000 years ago. What may be unexpected is that the frequency and occurrence of cancer are higher nowadays than about a century ago despite significant advances in cancer diagnosis, treatment, and management over this period. So how can that be? Are we seeing an increase in cancer cases? Are we really making progress with the treatment of these diseases? The answers to these questions relate to the way we consider and view cancer, and have a direct relationship to factors and successes outside of the cancer field.

A major contributory factor in cancer appearing to become an increasing cause of mortality over the past century is our achievements in the treatment of other life-threatening diseases. In the early 1900s cancer accounted for a small proportion of deaths, with the majority of deaths being due to infectious diseases such as pneumonia, tuberculosis, and polio. Since this time, medical progress and improvements in public health and hygiene have led to the significant reduction and elimination of infection as a major cause of death. This effect can be observed if we compare differences in cancer incidence and mortality in different regions of the world, particularly developed versus developing countries. In the developed countries of Europe, treatment for infectious diseases is highly successful and cancer appears to be a major mortality factor, for example mortality rates are greater than 150 per 100,000 and incidence rates are greater than 300 per 100,000 in Northern and Western Europe. We can compare this to the developing countries of Middle and Northern Africa, where infectious diseases are a major factor and treatment success is poor; here cancer mortality rates are below 90 per 100,000 and incidence rates are below 130 per 100,000 (Figure 1.1.1).

As we can clearly see from Figure 1.1.1, the incidence of cancer is highest in Australia/New Zealand, but is also higher than the global rate (World) in Europe and North America. The mortality rates (which are dictated by the most prevalent cancers found in each of the regions) partly reflect the incidence rates, but notable exceptions are Melanesia (Western Pacific), which has an incidence rate below the global average, but a mortality rate near the top, and its near neighbours Australia/New Zealand, which have the highest incidence per 100,000 but are below global average mortality. The most common cancer-related death in Australia is lung cancer (19%), followed by bowel cancer (11%); in Melanesia, cervical, breast, liver and lip/oral cavity cancers are the most common causes of cancer-related death (10%). Another significant factor which is related to the apparent increase in the rates of cancer in modern times is the fact that, as a population, we are living longer, with a subsequent steady increase in the global population; better lifestyles and disease management have resulted in improved life expectancy. In 1970 the median age\(^5\) of the global population was 22 years, which increased to 29 years by 2010 and is predicted

\(^3\) The number of people diagnosed with cancer in the preceding 5 years who were still alive in 2008.

\(^4\) In other words, at current cancer rates, just over 10 in every 100 newborn babies would be expected to die from cancer by the age 75.

\(^5\) The age that divides a population into equal halves.
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to reach 38 years by 2050. Additionally, the number of people aged 60 years and over in 2050 is predicted to increase threefold, to 2 billion. With respect to cancer, by 2030 it is predicted that, annually, there could be 27 million new cancer cases and 17 million cancer-related deaths worldwide. Our extended life expectancy and improved cancer survival prevalence rates are thus an indirect consequence of the elimination of other life-threatening diseases, which has propelled cancer into the top four major health concerns.

Figure 1.1.1 Estimated age-standardised (a) cancer incidence and (b) cancer-related mortality rates per 100,000 population in regions of the world in 2012 [3]. Northern Europe incorporates the UK and Scandinavia; South-Central Asia incorporates Iran, Iraq, Afghanistan, Pakistan, and India; Eastern Asia incorporates China, Taiwan, Japan, North Korea, South Korea, and Mongolia; South-eastern Asia incorporates Laos, Myanmar, Philippines, Thailand, Vietnam, Malaysia, Singapore, and Indonesia. Source: Torre 2012 [3].
But why are the number of cancer cases apparently rising? If we accept that the increased percentage of deaths attributable to cancer is due to a shift in the dynamic balance because of significantly reduced figures for other diseases, such as infection, then should we not just see a reduced number of total deaths reported, but with approximately the same number of cancer-related deaths? Although in principle this point should be true, what it fails to account for is the fact that, as a population, we are living longer. We know that there is a significant correlation between increasing age and the number of cancer cases, for which the underlying principles will be discussed later. Put simply, the continued growth and ageing of the World population means that people are around longer and so there is a greater opportunity for cancer to develop. Taken together, we can appreciate that these underlying factors have propelled cancer to become a major health concern globally. Nevertheless, recent studies have begun to indicate improvements in combating cancer as a consequence of improved lifestyle, earlier detection, or better treatments. For instance, the overall risk in Europe for being diagnosed with cancer has now reportedly stabilised relative to previous years (estimated at an age-standardised rate of 356 people per 100,000), and the overall risk of dying from cancer has shown a decline (estimated to be 168 per 100,000, with variations dependent on tumour type and country) [4].

We now know that cancer is a major disease, with clear global differences in terms of incidence, survival, and related-deaths. However, it is worthwhile at this point to fly a flag of caution in relation to this data, with particular reference to evaluation and interpretation. In the previous section it was identified that cancer incidence is stabilising and cancer deaths are declining in Europe, which is true based on the data presented. While this overarching change is positive, it does not identify data for specific cancers or European countries, and does not report the degree by which the risk of cancer-related mortality varies between these factors. This highlights a major consideration when evaluating or analysing cancer data, particularly in the extraction of the specific information you require. As with all things, the quality and utility of the information gained is only as good as the data entered into the system. We are by no means suggesting that this data is uninformative, misleading, or indeed incorrect, but merely indicating the caution that should be adopted when considering this task. Careful thought and consideration must be applied when drawing conclusions from these observations because of inter-country differences in data reporting, documentation, reporting practices, and pathological evaluations. It should be no surprise that the majority of reported studies concentrate on developed areas, such as Europe and the USA, where there are dedicated and well-developed cancer registries and standardised reporting structures for cancer. Therefore, in order to make valid conclusions and comparisons, it is important to confirm data reliability and that appropriate analyses and statistical evaluation have been applied, to ensure the figures are not skewed by confounding factors. Incomplete documentation, such as the description of ‘lung cancer’ without specification of histological type, has significant implications for reporting and consequent analyses. Similarly, there can be a lack of follow-up data or inconsistencies in reporting structures between one area and the next. Nevertheless, when used correctly, this data is invaluable in assessing the causative and progressive factors associated with a particular cancer type, and more importantly from a pharmaceutical perspective, for evaluating treatment options and successes.
Over the past 40 years cancers affecting the lung, breast, bowel, stomach, and prostate were the types most commonly diagnosed, with varying levels of treatment success and prognostic outcomes. This has not changed significantly, with the most common cancers globally being lung, female breast, colorectal, and prostate, accounting for close to four in ten cancers (Figure 1.1.2) [2,5]. If we consider Europe alone, the situation is slightly different, with cancers of the female breast, colorectal region, prostate, and lung representing almost half of the overall burden of cancer in this region [4]. The differences in cancer types are a reflection of the different geographical and environmental factors across the World, with stomach being a top-four cancer type globally, but not in Europe, probably reflecting dietary factors in Asia. The higher incidence of prostate cancer in Europe, as opposed to the global picture, may also reflect dietary and lifestyle factors in developed versus developing regions of the World. This gender-specific cancer also feeds into differences reported globally, wherein the incidence of cancer per se is more than a fifth higher in males than females, with male and female incidence rates varying by three- to four-fold across different regions of the globe. In a similar pattern to that observed globally for cancer incidence there are also marked differences with respect to cancer deaths. The four most common cancer types in relation to cancer-related deaths globally are lung, stomach, liver, and colorectal, which are responsible for 45% of global cancer mortality. This pattern is again different when analysed specifically for the UK, where lung, colorectal, breast, and prostate cancers account for almost half of the total number of cancer-related deaths.

Figure 1.1.2 Estimates of the 20 most commonly diagnosed cancers Worldwide in 2012 (http://globocan.iarc.fr/Pages/fact_sheets_population.aspx). CNS, central nervous system.
The incidence of cancer in a particular region, country, or culture can be used to indicate or outline potential underlying contributory factors to those specific cancers. In simple terms, we could attribute variations in cancer incidence between different populations or geographical regions purely on genetic differences between these varying populations. However, we now know that this viewpoint is too simplistic and there is a second contributory dimension involving the variation in environmental factors and subsequent exposure profiles of the inhabitants. There is now a clear argument to directly link specific environmental, dietary, recreational and industrial factors to the development or promotion of cancer based upon comparisons of cancer incidence in different geographical regions. For instance, a high incidence of liver cancer was previously identified in Mozambique, which was suggested to be due to a dietary factor of some sort. One possible cause identified related to the way in which peanuts were stored, which permitted growth of aflatoxin mould. In the years and decades following a change in practise for peanut storage, the incidence of liver cancer declined in this region, strongly supporting a link between these factors. This example provides a straightforward indication of the existence of cancer-causing (carcinogenic) factors, but pessimistically could also indicate a genetic link related to food intolerances or other risk factors specific to this population.

A stronger validation for the co-existence of genetic and environmental risk factors for cancer development is provided through studies of migrant populations. This is easily evaluated through the study of cancer incidence in immigrants who have settled with a new lifestyle in a new country. One such example, in support of the promotion of cancer development by environmental factors, is the fact that Japanese immigrants in the USA were shown to have a similar incidence of colon cancer to Americans, but five times that of those still living in Japan, indicating an environmental driver for colon cancer development over that provided by the genetic background. Conversely, stomach (gastric) cancer is reportedly higher in Japan than the UK or USA. At face value it could be claimed this is due to the different genetic profiles of these populations. However, in reality, studies of the incidence of gastric cancer of Japanese individuals relocated from Japan to the USA supported the environmental contribution to cancer development. Within one to two generations, the incidence of gastric cancer in the Japanese-American population shifted towards that of America. In this case, the carcinogenic factor was believed to be due to a change in salt preservation of food, which was high in Japan in comparison to the USA.

Whereas (unfortunately) it is not within the scope of this particular section to describe a multitude of risk factors, it is pertinent to briefly discuss tobacco smoking and its clear links to the development of cancer, particularly lung cancer. Tobacco smoking is unquestionably a major environmental and carcinogenic risk factor for lung cancer, both directly to the smoker and indirectly to bystanders in the form of passive smoke. The global frequency of lung cancer has increased more than tenfold since 1930, making this cancer the leading cause of cancer death in Europe in 2012 and the most common malignant disease in the World for several decades. This rise in lung cancer incidence is directly attributable to increased use of tobacco, particularly cigarettes [4]. However, an important criterion when comparing the effect of an agent upon cancer development is the time taken for the effect to be observed. In this case, there is an approximately 20-year lag in the relationship between incidence
of people smoking and the development of lung cancer. This lag-time is a reflection of the cellular basis of cancer development (which we will discuss later), involving a multistep developmental process and the requirement for specific hallmarks of cancer to be satisfied. The existence of a lag-time is evident through studies of differences in smoking habits within a specific population, which in the case of smoking and lung cancer can be evaluated via comparison of males and females. Whereas tobacco smoking in males began to increase around the First World War (1910s to 1920s), it only really became popular in females during and after the Second World War (1940s). Whereas the incidence of lung cancer in males began to increase in the 1930s to the 1940s, that in females increased around the 1960s, reinforcing an approximately 20-year lag period.

In recent years a clear shift has been made in many populations from the smoking of cigarettes towards the use of electronic cigarettes, primarily on the communicated improved health benefits of the latter over the former, and improved awareness of cancer risk factors associated with smoking. It will be interesting to see if this manifests in a reduction in lung (and other smoking-related) cancers over time.

As you will now appreciate, there is a huge level of complexity and uncertainty about the factors contributing to cancer, and widespread differences in the prevalence and aetiology of specific cancer types. However, based upon the information discussed above, we now understand there are multiple external factors driving the development of cancer. On face value this would strongly imply a direct causative relationship between these carcinogenic (cancer-causing) factors and the development of cancer. Is this not true? It is without doubt that there is an environmental link in cancer development, with many epidemiological studies providing strong evidence in support. The remaining pieces in the puzzle are, therefore, whether these carcinogenic factors are actually causative, catalysts of the disease process, central and indispensable factors, or purely coincidental to the whole process. Second, it remains to be shown how these carcinogenic factors actually manifest themselves in the alteration of cell behaviour (how they become tumourigenic and malignant). The answer is actually fairly straightforward (now many studies over many years have been conducted): cancer is a consequence of genetic change and reprogramming of cell behaviour, and these carcinogenic factors drive and/or promote these changes. This, therefore, implies that the environmental and carcinogenic contributors are predominantly catalysts and promoters for cancer development.

Although it is clear that environment and lifestyle are major contributors and risk factors for cancer development, it is all too easy to describe many practices, activities, and environmental parameters as being tumourigenic or carcinogenic. Consequently, we must be realistic about these causative factors for cancer. Cancer of the colon, for example, showed a rise in developed countries in the later part of the 20th century. This has been linked to a decline in healthy diets, an increase in take-away and convenience foods, and a subsequent increase in obesity. In support of this, it is now well reported that diets low in fruit and vegetables, and high in red meat, processed food, and fat result in an increased risk of colorectal cancer [4]. However, the rise in colorectal cancer over the same time period would also support a relationship between this cancer to the invention and use of the personal computer and electronic games machines. Whereas a clear link can be seen between colon cancer and diet, it is unlikely that the use of the personal computer is the major causative factor for this disease (although a lack of exercise,
parallel consumption of unhealthy snacks, and computer-related dormancy could be contributory factors!). Consequently, risk factors and carcinogenic stimuli have also to be biologically (or scientifically) plausible. The caveat, as can be drawn from the colorectal-electronic gaming relationship, is that the risk–disease link is commonly not linear or straightforward, with several additional contributory or supporting factors also playing a role in the complex intertwined pathogenic networks. In this particular case, there is a lot to be said for exercise and physical activity, a balanced diet, fresh fruit and vegetables, and weight management. In reality, this is not a new concept, reflecting normal practices from the earlier parts of the 20th century. The underlying culprit could thus be assumed to be changes in lifestyle, social environment, retail convenience, and attitudes over the past 50 or so years.

As well as linking particular risk factors to specific cancer types, a change in the incidence of cancer in a particular population also provides clues to its aetiology. This is especially so for ‘rare’ cancers which may appear in greater numbers in a particular place or sub-population. An example would be several cases of acute leukaemia occurring in close proximity in a particular town within a short space of time, indicating a strong environmental or personal exposure factor, such as radiation.

The important message from these epidemiological studies (and several thousand more) is the relationships between human cancers and environmental risk factors, suggesting that many cancers could, in principle, be prevented through identification, elimination, and modification of causative carcinogenic factors. This ‘preventative’ approach to cancer has probably become the highest priority initiative in the cancer research field over the past couple of decades, and remains so to this date. Based on this, can we therefore prevent cancer developing in the first place? Before answering this question it is important to consider the role environmental factors play in the process. Based on the assumption that environmental factors play a major role in approximately 75% of all cancers, a baseline intrinsic (genetic) cause of cancer must indeed exist. This would suggest that we can, at least, reduce the rate of cancer development through control of risk factors, potentially to a rate wherein an individual dies of another factor before the cancer is detectable or problematic. However, there is strong evidence to suggest environmental factors primarily promote and accelerate cancer development rather than cause the initiating event, especially when we remember cancer is a genetic disease. This latter concept would thereby support the hypothesis that the multistep nature of carcinogenesis is merely fuelled by environmental factors, with the cancer developing eventually (albeit potentially beyond the lifetime of the individual). So to address the question ‘Can we completely prevent cancer formation?’ we need to consider the ‘cancer initiating’ genetic event, the pre-existence of genetic changes, and the contribution of environmental carcinogenic factors, but in essence the answer is a combination of yes and no.

Cancer awareness and prevention is also now becoming a major initiative through health-promotion campaigns, improved education of public health practitioners, and the changing role of the health practitioner within the community setting.

While it is clear that tackling cancer worldwide will remain one of the major challenges in the 21st century, in addition to preventative strategies, advances in diagnosis and treatment will also hopefully significantly reduce the impact of these diseases.
References


