This first chapter of the book aims to set the scene on issues pertaining to cancer epidemiology, as well as the socioeconomic and molecular basis of the disease. It will clearly demonstrate various aspects of cancer initiation. Cancer, as a disease, is often different from other diseases in that it has various reasons why it can be initiated. It has often been thought off as a genetic disease, as an infectious disease, even as an inflammatory disorder, and has shared many similarities with all of them. However, cancer is a very complex disorder, or group of disorders in fact, that are very much dependent on all of the above as we will see later on. However, it is also very much related to our environment, the cultural and socioeconomic aspects of our life, even the *place* where we live and the *time* of our lives. As you will see in this chapter, contrary to popular belief, cancer is a disease that takes a very long time to develop. So, if we can only extend this process a bit further, we will all be suffering from old age before we have to encounter cancer. And though it may be frightening to know that in many of us cancer has started years before we ever find out, it is always reassuring to discover that there are things we can do to slow this process or even avoid it in our lifetime. It is reassuring to know that by changing our habits, our diet and behaviour, we can, more often than not, postpone this disease perhaps indefinitely. The socioeconomic and molecular basis of cancer will be discussed in this first chapter, together with some indication of the world cancer incidence and the 'time' and 'place' distribution of the disease, also hoping to shed light on some of the differences between parts of the population.

1

Socioeconomic and molecular basis of cancer

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1.1 Introduction

Cancer is a disease that is characterized by the slow rate at which it develops. This might seem at odds with our experience of seeing people diagnosed with a cancer seeming, for the most part, to have a short life expectancy. However, the clinical stage of most cancers is literally the 'tip of the iceberg', because the cancer will have been growing undetected for many years in the early stages of its natural history.

As we have come to understand more about the phenomenon of cancer at both the biological and epidemiological level it has become apparent that there are two main factors that influence the risk of developing cancer – *time* and *place*.

The importance of *time* can be seen by looking at the age-specific mortality of cancer at all sites in men and women (Figure 1.1). The age-specific rates of different cancers display similar patterns (with the notable exception of some childhood cancers such as neuroblastoma), namely, the incidence is very low until about 40 years of age and then displays a dramatic rise thereafter. This overall pattern is driven by the profiles of some of the major cancers – the age-specific incidence of colorectal cancer rises relentlessly with age (Figure 1.2). However, within this overall pattern there are some significant differences for particular cancer sites. For example, the incidence of ovarian cancer in women shows a peak at age 70–80 with a noticeable decline thereafter (Figure 1.3). Somewhat more spectacularly, the peak incidence of testicular cancer is seen in men at around age 40 with

The Cancer Clock Edited by Sotiris Missailidis

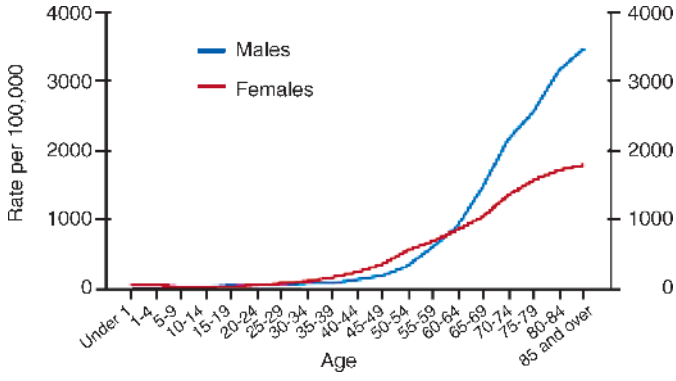


Figure 1.1 Age-specific mortality from all cancers (excluding non-melanoma skin cancer), England and Wales, 1997. Data from *Cancer trends in England and Wales 1950–1999 (Studies on Medical and Population Subjects No. 66)* Stationery Office, 2001. Reproduced under the terms of the click-use licence

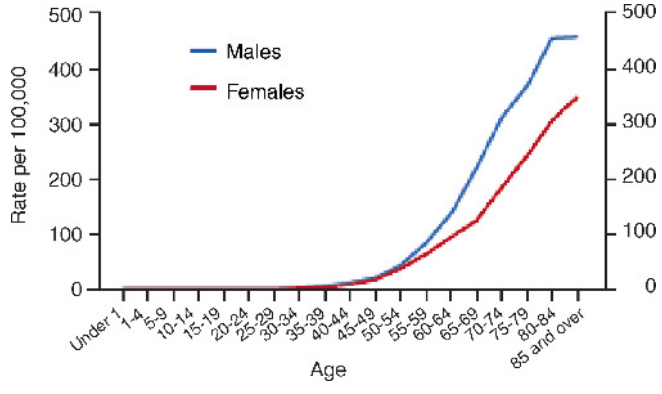


Figure 1.2 Age-specific incidence of colorectal cancer, England and Wales, 1997. Data from *Cancer trends in England and Wales 1950–1999 (Studies on Medical and Population Subjects No. 66)* Stationery Office, 2001. Reproduced under the terms of the click-use licence

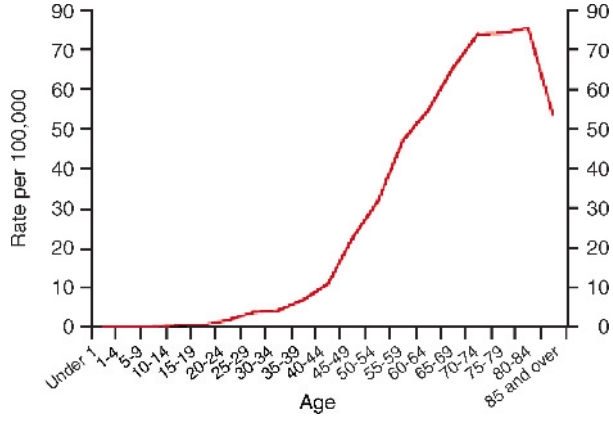


Figure 1.3 Age-specific incidence of ovarian cancer in women, England and Wales, 1997. Data from *Cancer trends in England and Wales 1950–1999 (Studies on Medical and Population Subjects No. 66)* Stationery Office, 2001. Reproduced under the terms of the click-use licence

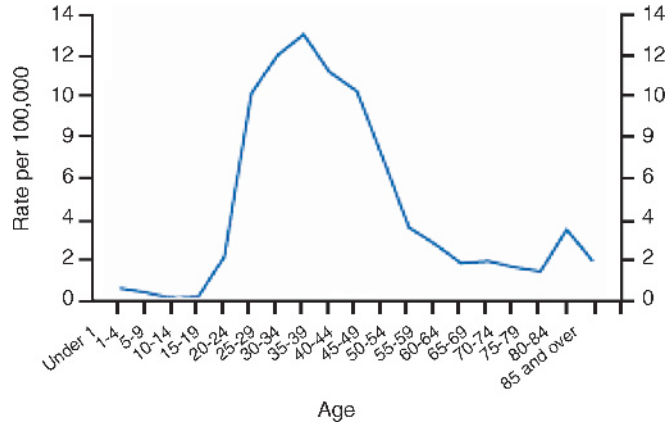


Figure 1.4 Age-specific incidence of cancer of the testis in men, England and Wales, 1997. Data from *Cancer trends in England and Wales 1950–1999 (Studies on Medical and Population Subjects No. 66)* Stationery Office, 2001. Reproduced under the terms of the click-use licence

the incidence at age 70 being not much more than that for young men (Figure 1.4). These exceptions are probably linked to hormonal effects that change throughout lifetime. Note also that the incidence rates (as incident cases per 100 000 individuals of the population, shown on the vertical axes) vary greatly between the different cancers.

So far we have discussed *time* as it is measured in epidemiological studies. There is another way in which time is important in the cancer process and that is at the molecular and biological level. One of the best characterized cancer progressions is that of colorectal cancer, for which the key molecular steps have been identified. Vogelstein and colleagues at Johns Hopkins University in Baltimore have built up a picture of the natural history of colorectal cancer that can be summarized in a diagram that has become affectionately known as a 'Vogelgram' (Figure 1.5). Colorectal cancers are believed to develop over the course of 20–40 years as a consequence of the episodic accrual of specific mutations in oncogenes such as *KRAS* (*Kirsten Ras*) and tumour suppressor genes such as *APC* (a gene first identified in the hereditary susceptibility to adenomatous polyposis coli) and *TP53* (a gene encoding for the p53 tumour suppressor

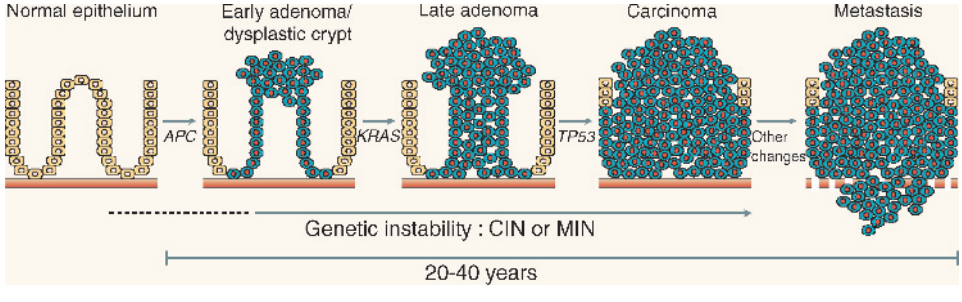


Figure 1.5 A step-wise model of colorectal tumorigenesis developed by Vogelstein and colleagues. Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Cancer *3*, 695–700 © 2003

protein). These mutations arise within the tumour in a characteristic sequence. A single cell acquires a mutation in one such gene, and this mutation soon reaches fixation because of the growth advantage it provides to the cell. Genetic instability is thought to occur somewhere during the process of colorectal tumorigenesis to accelerate the rate of mutations in dividing cancer cells. Each of the individual mutations is itself a rare event. For a cancer to progress to the clinical stage, a progenitor cell, or clone of cells, would have to accumulate three or more of these mutations. It is the time that it takes for such a 'jackpot' of rare mutations to occur in sporadic cancers that probably explains why it can take up to 40 years for a cancer to develop. Some evidence for this comes from studies of rare inherited genetic disorders such as the Li–Fraumeni and Lynch syndromes that predispose to the virtually certain development of cancers in early life. In such syndromes mutations in key genes are inherited in the germline so that every cell in the body contains mutated *APC* or *TP53*. This circumstance vastly increases the likelihood that a subsequent rare somatic mutation will occur in an already mutated cell.

We now turn our attention to the role of *place* in influencing cancer risk. The incidence of many cancers varies greatly from country to country and from region to region (Figure 1.6). One possible explanation of this could be that variations in the genetic make-up of different populations would lead to differing susceptibilities to cancer. Alternatively, variations in exposure to environmental carcinogens, or

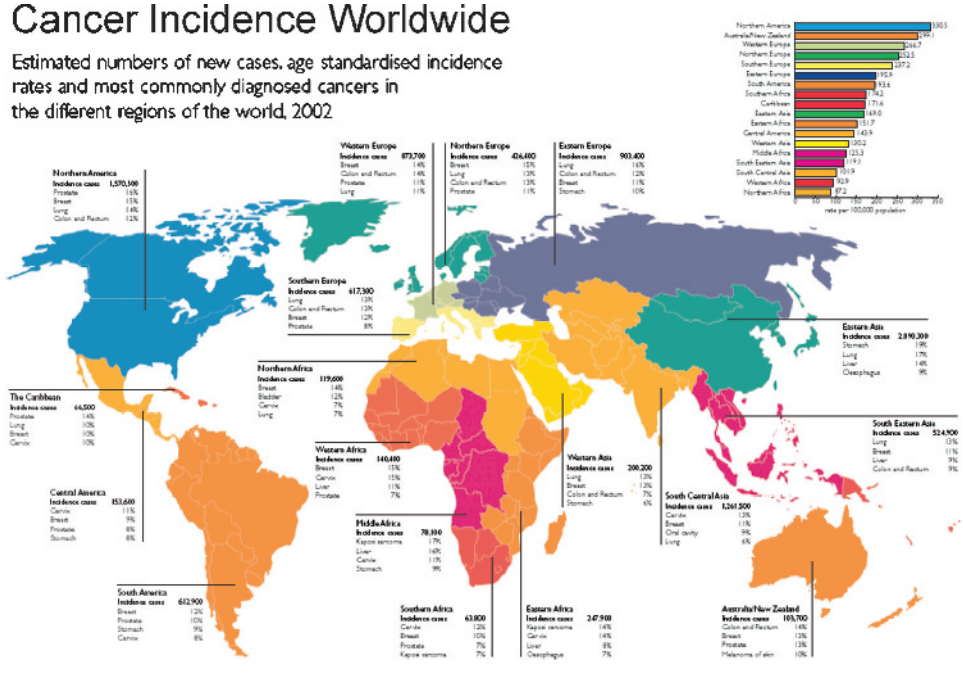


Figure 1.6 The variation in incidence of cancers at major sites around the world. (Figure reproduced from http://info.cancerresearchuk.org/cancerstats/geographic/world/?a=5441; accessed 20 April 2007) used with permission

differences in lifestyle because of the range of cultural profiles around the world, might lead to differences in cancer risk. Studies of migrant populations offer the possibility to examine the contributions of these alternative explanations. The genetic profile of individuals within a migrant population will not change within one generation, or within several generations for that matter. In contrast, exposures to environmental carcinogens will change immediately upon arrival and lifestyle changes will follow as assimilation of migrants into a new culture occurs. Thus, cancer risks driven predominantly by genetic factors would show little if any change in migrant populations, whereas those influenced by environmental or lifestyle factors would reflect the changes in the profile of exposures. The available evidence suggests that most cancer risks fit the environmental/lifestyle model of causation rather than the genetic model.

Migrant studies provide compelling evidence that cancer risk is principally determined by environmental factors, including diet. Patterns of cancer among migrant groups, as they move from country to country, often change faster than those within any country. Patterns of diet also change over time as a result of migration, sometimes dramatically.

A classic example of changes in cancer risk, in both directions, for different cancers is found in Japanese migrants to Hawaii (Figure 1.7). Japanese women living in Japan typically have a high risk of stomach cancer and an almost three times lower risk of breast cancer. The first generation of Japanese migrants in Hawaii showed a halving of their stomach cancer risk and an almost trebling of their breast cancer risk. By the second generation the Japanese–Hawaiians had a stomach cancer risk one-third that of women in Japan but a breast cancer risk that was four times higher. In a number of migrant studies a similar pattern has been seen with incoming migrants 'adopting' the profile of

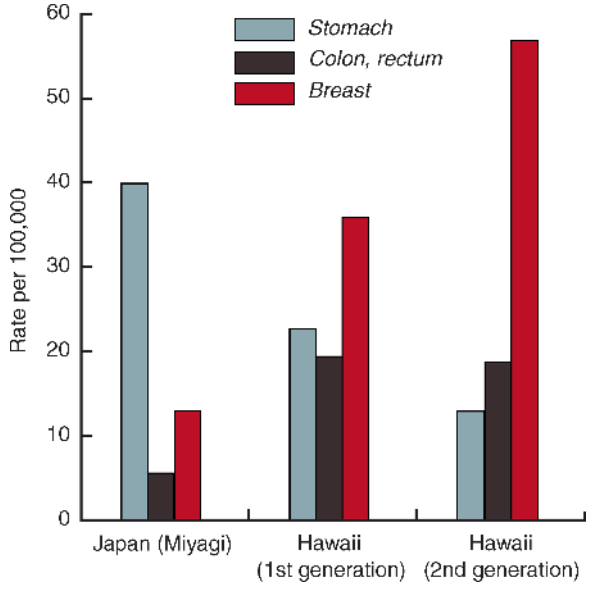


Figure 1.7 Cancer incidence for three sites in Japanese women by generation in Hawaii and Japan, 1968–1977. *WCRF/AICR Report 'Food, Nutrition and the Prevention of Cancer: A Global Perspective'* 1997. Fig. 1.1.20 Washington DC: American Institute for Cancer Research (Source: used with permission)

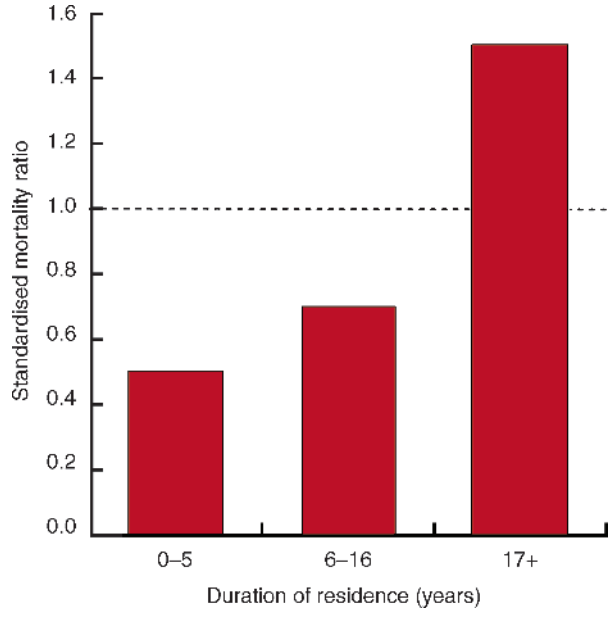


Figure 1.8 Breast cancer mortality ratios for Italian women migrants by duration of residence in Australia, 1962–1971. *WCRF/AICR Report 'Food, Nutrition and the Prevention of Cancer: A Global Perspective'* 1997. Fig. 1.2.21. Washington DC: American Institute for Cancer Research (Source: used with permission)

cancer risks of the indigenous populations. The rapidity with which cancer risks change is illustrated by a study of breast cancer mortality in Italian women migrants in Australia. Changes in rates of cancer mortality could be seen as soon as 5 years after the arrival of migrants in the host country (Figure 1.8).

In the discussion so far of the effects of *time* and *place* on cancer risk we have hinted at a number of environmental, lifestyle and dietary factors as causative, or aetiological agents. We will now turn our attention to a more detailed discussion of the role of certain factors in the determination of cancer risk.

1.2 Diet and cancer

Human beings need to consume a certain amount of food and water each day in order to acquire the basic energy required to keep the system going, as well as obtain the raw materials essential for building and repairing cellular components. The sheer quantity of food consumed by an average British family during a year in the late 1980s is rather impressive (Figure 1.9).

Until quite recently, the 'normal' diet was assumed to be either largely neutral in its effects on cancer risk or, for the most part, beneficial or protective. The role of diet in some other chronic diseases, such as diabetes and coeliac disease, had been long recognized as being linked to the presence of particular food components interacting with a defective metabolic function. In the case of cancer, the available evidence suggested that some cancers were linked to the presence of contaminants of man-made or natural origin. However, despite the public concern about cancer risk from pesticides, arising in

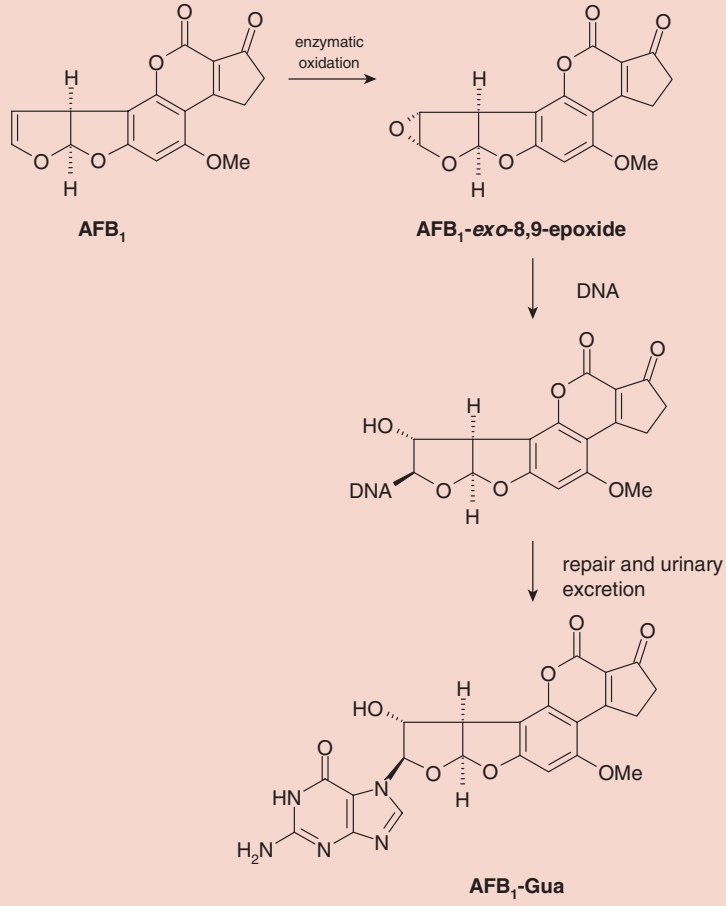
Figure 1.9 Food consumed by a British family in the 1980s during a year (image from Open University ST240 Our Chemical Environment, course book 3. Copyright © The Open University)

large part from the publication of Rachel Carson's book *Silent Spring* in the 1960s, there is little, if any, evidence that the use of pesticides raises the risk of cancer. This is not to say that pesticides are not toxic or carcinogenic, for many of them are, but the reality of the situation is that the levels of pesticide residues in foods are so low that, for all practical purposes, these exposures do not add perceptibly to the burden of cancer. It is important to note that this conclusion is not based on the extrapolation of data obtained in experimental animals to the human situation but on large epidemiological studies where pesticide exposures were assessed and for which data on cancer outcome were available. Notwithstanding, there is evidence that occupational exposure to pesticides in agricultural workers working with high volumes of concentrated pesticide solutions does lead to a somewhat increased risk of developing non-Hodgkin's lymphoma. Perhaps this is as good an example as any of the well-known aphorism – 'it is the dose that makes the poison' – attributed to the wonderfully named 16th century physician Philippus Aureolus Theophrastus Bombastus von Hohenheim (aka Paracelsus, 1493–1541).

In contrast, there is evidence that exposure to certain naturally occurring toxins, at levels consumed in the diet, does lead to a significantly increased risk of cancer. The aflatoxins, for example, are a group of fungal metabolites that are found in foodstuffs contaminated with *Aspergillus* fungi. The fungal contamination occurs when the susceptible foodstuffs

(maize and groundnuts) are stored in warm and humid climates. There has been concern for a long time that human exposure to aflatoxins is a major risk factor for liver cancer but the epidemiology has been confounded by the risks of the same disease due to hepatitis infections. The distinctive chemical structure of aflatoxins has enabled the development of various assays capable of measuring human exposure to these carcinogens. The assays are based on the measurement of urinary metabolites as well as products of the interactions between aflatoxin and proteins or DNA (protein or DNA adducts; Box 1.1).

Box 1.1 Metabolic activation of aflatoxin B_1 (AFB_1) to a reactive epoxide that binds to DNA, giving rise to a major DNA adduct (aflatoxin B_1-guanine) that is repaired and excreted in urine



The demonstration that DNA adducts and other measures of aflatoxin exposure could really contribute to human risk assessment came with the results of a large prospective cohort study in south-east Asia. Between 1986 and 1989, 18 244 men (aged 45–64 years) were recruited into a cohort which was followed up with respect to the occurrence of hepatocellular carcinoma. At recruitment into the study each subject was interviewed, using a questionnaire, for details of dietary and other past exposures. Samples of blood and urine were also collected and stored for future analysis for a number of markers. Over the following years, 55 cases of liver cancer and 267 matched controls were collected and analysed as a nested case-control study. The presence of any urinary biomarker of aflatoxin exposure indicated a four-fold elevated risk of liver cancer. The presence of urinary aflatoxin B1-guanine (AFB1-Gua), derived from the breakdown of specific liver DNA adducts, was linked to an almost eight-fold increase in risk. The combination of urinary AFB1-Gua and specific urinary metabolites of aflatoxins indicated a ten-fold increase in risk. The study also allowed an analysis of the effect of hepatitis. Previous exposure to hepatitis B results in the presence of antibodies to a surface antigen (HBsAg) that can be detected many years after the infection and this antibody is, therefore, a biomarker of the past infection. The simultaneous presence of markers of exposure to aflatoxin and hepatitis indicated an almost 60-fold increase in the risk of developing liver cancer. Interestingly, a classic epidemiological analysis of the questionnaire data for the cases and controls failed to reveal the same effects.

This study dramatically demonstrated the value of using biomarkers of exposure to an environmental carcinogen as means to identify risk factors for a disease outcome with much greater sensitivity than traditional methods of epidemiological enquiry. Having established that certain biomarkers of aflatoxin exposure did indeed have good predictive value for the disease outcome, there are now efforts to use them to evaluate the effect of intervention studies using a drug, oltipraz, which is known from animal studies to reduce the risk of liver cancer caused by aflatoxins.

Whilst the story of aflatoxins and liver cancer is a good example of the identification of a particularly potent foodborne carcinogen, much of the cancer risk associated with diet has proved much more difficult to characterise. There are several problems associated with the study of diet and cancer. First, establishing exactly what constitutes an individual's diet is not as easy to determine as might be thought. Surprisingly, people are very unreliable in their recollection, even within the past 24 hours, of what they ate, particularly with respect to portion size. Studies using biomarkers of protein and salt intake have shown how inaccurate a 24-h dietary recall questionnaire can be. From a practical standpoint, a diet diary, in which all types of food and the quantities consumed are recorded, has been shown to provide an acceptably complete account of what a person really has eaten. Moreover, the use of photographic prompts for portion size has been shown to provide a quantitatively accurate measure of the amount consumed. You may not, however, be surprised to hear that, in the absence of such approaches, people tend to overestimate how much fruit and vegetables they have eaten and underestimate their consumption of meat. Second, it is not particularly obvious what it is about a particularly dietary component that is important for its effect on cancer risk. For

example, with respect to meat consumption, is it important to know how the meat was prepared? – was it processed with the addition of additives such as nitrite, leading to the formation of nitrosamines? – was it cooked at a high temperature, leading to the production of mutagenic pyrolysis products? – or is the protein content an important source of precursors for endogenous processes that lead to mutagen formation? Similarly, for fruit and vegetables – is it the frequency and type of fruit/vegetable that is important? – is it the vitamin C/E content? – or, is it the amount of fibre that is important? Third, the level of cancer risk associated with dietary components is usually not very large. This is perhaps not surprising. If a food was strongly associated with cancer, this would have been recognized long ago and its use would have been avoided. This is certainly the case with other chronic and acute diseases – particularly if the cause of the problem is related to food being mouldy or tainted. Thus, the study of links between diet and cancer require large groups of people to be followed over many years (10–20 or more years). Such studies are expensive and do not yield many results in the early stages. However, several large studies were set up in the late 1980s – the Nurses' Health Study in the US and the European Prospective Investigation on Diet and Cancer (EPIC) – and are now beginning to yield important results. The scale of these studies is truly vast – in the second stage of the US Nurses' Health Study there were over 110 000 volunteers and in the entire EPIC cohort there were over 500 000 people recruited. The size of these prospective studies means that nested case–control studies with high statistical power for particular endpoints can be carried out within the cohort. The use of stored biological samples (notably blood and urine) adds further power to these studies, as biomarkers provide objective measures of dietary components. Furthermore, because the studies are prospective, the dietary questionnaires and biological samples were collected when the volunteers were healthy. If such markers are predictive of subsequent cancer risk they have the potential to be used in future studies where dietary interventions designed to reduce cancer risk can be tested.

Examples of the kind of results that can be obtained using the large cohort studies include the links between meat and colorectal cancer, and, saturated fat and breast cancer.

There has been much controversy as to whether high meat intake increases risk of bowel cancer. In the EPIC study, it has been found that high dietary fibre intake lowers and high meat intake increases risk of bowel cancer. However, there is an interaction between the different foods. Meat intake increases cancer risk only in those people with low intakes of dietary fibre; high dietary fibre or high fish intake appear to protect against the effects of meat intake and risk of bowel cancer.

In a study based on 13 000 women participants in EPIC, it was found that those who ate the most saturated fat were almost twice as likely to develop breast cancer as those who ate the least. Saturated fats are found mainly in full-fat milk, meat, and products such as biscuits and cakes. In the past, many large studies have failed to find a link between fat intake and breast cancer, possibly due to imprecise methods. The EPIC participants were asked to complete a detailed food diary over the course of 7 days. Even the brand of food was recorded so that the nutritional content could be worked out more precisely. It was found that women who ate more than 90 g of fat per day have twice

the risk of developing breast cancer as women who ate less than 40 g of fat per day. Two-thirds of a pint of full-fat milk contains 16 g of fat, whereas the same volume of semi-skimmed milk contains 7 g of fat.

In 1997 the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) published an influential report entitled *Food, Nutrition and the Prevention of Cancer: A Global Perspective*. The WCRF/AICR report summarized the large amount of data on diet and cancer and drew conclusions on which six main dietary recommendations are based. These can be summarized as follows:

1. Choose a diet rich in a variety of plant-based foods.
2. Eat plenty of vegetables and fruits.
3. Maintain a healthy weight and be physically active.
4. Drink alcohol in moderation, if at all.
5. Select foods low in fat and salt.
6. Prepare and store foods safely.

These recommendations are broadly similar to those that have been made by the World Health Organization, the US National Cancer Institute and a number of cancer research organizations worldwide.

The decade following the 1997 WCRF/AICR report there has been much further work on the links between diet and cancer. Body mass and physical activity are things that are likely to emerge as important factors for cancer risk and some of the earlier conclusions about fruit and vegetables may be revised in the light of new information, particularly from recently concluded prospective studies of large cohorts.

We began this section by noting that human beings need to eat food and drink water regularly to maintain good health. Although we can try and optimize our diet so that it is compatible with acceptable nutritional requirements, as well as carrying the minimum attainable risk of cancer, there really is no practical alternative to eating food in order to obtain the main macro- and micro-nutrients. There are however a number of 'optional extras' that we consume which affect cancer risk in a substantial way and which would be possible, in principle, to substantially reduce or completely eliminate from our lives: alcohol and tobacco.

1.3 Alcohol and cancer

The consumption of alcoholic beverages is something that almost all societies have indulged in, from the earliest recorded times. It is likely that the production of alcoholic

beverages was an accidental discovery made in several parts of the world at different times. Once the pleasurable and potent effects of alcoholic drinks were discovered, their consumption became a regular feature of social gatherings. Drinking patterns – overall level of alcohol consumption, choice of alcoholic beverages, differences by sex and age and temporal variations – differ among and within societies. Recorded consumption tends to be higher in societies with populations of European origin and lower in Muslim societies. In most of the developed countries, the majority of adults consume alcoholic beverages, at least occasionally.

Alcoholic beverages are produced from raw materials by fermentation. The predominant types of commercially produced alcoholic beverages are beer, wine and spirits. The main components of all alcoholic beverages are ethanol and water; beers also contain substantial amounts of carbohydrates. Furthermore, many compounds have been identified as common to all alcoholic beverages and are present in different quantities, depending on the beverage. Some components and occasional contaminants include known and suspected carcinogens. Beers and wines, however, also contain vitamins and other nutrients which are usually absent from distilled spirits. Despite the differences in concentration, the average intake of ethanol per drink is approximately constant across beverage types.

Alcohol is rapidly converted in the liver to acetaldehyde and then to acetate, in which form it is excreted in urine. These metabolic steps are carried out by specific enzymes (protein-based molecules with the ability to act as biological catalysts and facilitate reactions in the body), namely alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). Acetaldehyde is not a complete carcinogen in experimental animals, but it exhibits potent co-carcinogenic effects when administered with other chemicals such as nitrosamines. Furthermore, acetaldehyde is a very reactive molecule and binds covalently to proteins and DNA (Figure 1.10, Box 1.2). People who lack the enzyme ALDH, or express it at low levels or inactive forms, exhibit symptoms of acute toxicity to acetaldehyde, such as flushing, following consumption of alcoholic beverages. There is considerable variation between various populations in the expression of ALDH and this may contribute to differences in the risk of cancer linked to alcohol.

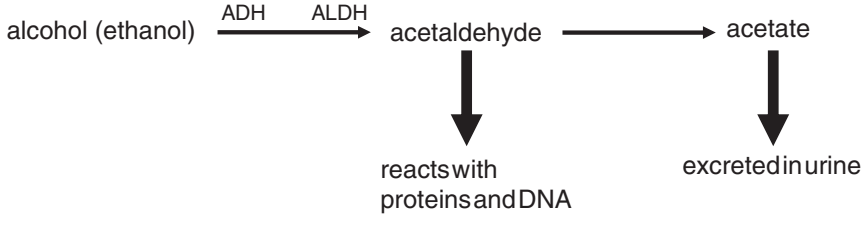
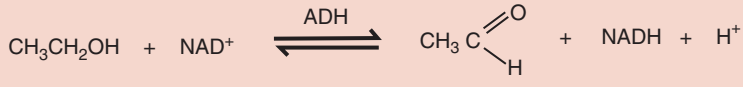


Figure 1.10 Summary of the metabolic and biochemical pathways of alcohol (ethanol)

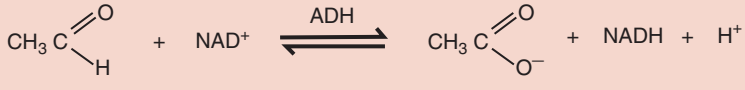
Box 1.2 Alcohol metabolism in the body

The metabolism of ethanol in the presence of nicotinamide adenine dinucleotide (NAD) takes place with the assistance of the enzyme alcohol dehydrogenase (ADH) as shown in the following reaction:



ethanol **acetaldehyde**

Acetaldehyde, a substance even more toxic than ethanol, is quickly converted by another liver enzyme, called aldehyde dehydrogenase (ALDH), to acetate, a normal, non-toxic metabolite in humans. Non-metabolized acetaldehyde can interact with proteins and DNA and form adducts. It is also responsible for some of the obvious effects of alcohol, such as blushing. The metabolic reaction of acetaldehyde to acetate also needs NAD for its completion:



acetaldehyde **acetate**

Acetate is finally broken down into carbon dioxide and water and is eliminated, mainly through the kidneys in the urine but also through the lungs.

Epidemiological studies clearly indicate that drinking of alcoholic beverages is causally related to cancers of the oral cavity and pharynx (excluding the nasopharynx), larynx and oesophagus. Alcoholic beverages are also causally linked to liver cancer, with the relationship being most evident in cirrhosis. There is no indication that these effects are dependent on type of beverage. The available evidence indicates an increased risk for cancers of the breast, colon and rectum, whereas there is little evidence to suggest a causal role for drinking of alcoholic beverages in stomach and pancreatic cancer.

The link between alcohol consumption and breast cancer in women has been a subject of controversy for a number of years. This is because many studies have failed to give conclusive results, although there has been evidence of small but consistent increases in risk of cancer. There have been several attempts to merge the available epidemiological results into one large dataset – this is the technique of meta-analysis. By and large, such meta-analyses have reached the same conclusion that there is a dose-dependent increase in risk of breast cancer that does not show a threshold. On average, consumption of each additional 10 g ethanol/day was associated with risk higher by 10 per cent. Risk did not differ significantly by beverage type or menopausal status. Because of the widespread consumption of alcohol, even at modest levels, this low risk contributes to a large number of breast cancer cases at the population level.

Red wine and cancer prevention

Alcohol, itself, has been shown in various studies to increase cancer risk. However, there has also been good news for moderate consumers of alcohol. Drinking a glass of an alcoholic drink a day has been shown to have a beneficial effect on cardiovascular disease and decrease the risk for Alzheimer's and dementia at old age. Besides that, alcohol, even though only in particular form and indirectly, has been shown to have protective properties against cancer.

Red wine has been found to be a rich source of antioxidants (compounds that protect the cells from oxidative damage caused by free radicals) in the form of polyphenols. These are compounds that are in the skin and seeds of the grapes. However, during the wine-making process, the alcohol dissolves the polyphenols from the skin and seeds of the fruit and into the wine. Red wine is much richer in polyphenols than white wine, due to the making process that requires the removal of the skins after the grapes are crushed in the white wine.One particular type of polyphenol compound, resveratrol, is present in red wine, as is in grapes, raspberries and other plants. This compound has shown significant antitumour and cancer preventive activity in experimental animals and human tumour cell cultures. Furthermore, resveratrol has been found to reduce inflammation, which often increases the risk of cancer or is used by cancer for growth and metastasis (see Chapter 5). Thus, resveratrol has been shown to have both preventative properties against the initiation of the disease, but it can also inhibit cancer promotion and progression.

Research has shown that drinking a glass of red wine a day reduces the risk of prostate cancer by half, with even stronger effects against the most aggressive forms of the disease. Consumption of four glasses of wine per week can reduce the cancer risk of aggressive forms of prostate cancer by 60 per cent. Furthermore, epidemiological studies in regions of France, where the consumption of red wine is higher, have confirmed a reduced cancer incidence associated with red wine drinking.
Thus, although alcohol itself can increase the risk of cancer, and any cancer prophylactic properties are related to non-alcoholic substances, a glass of red wine a day can not only be an enjoyable experience and help one relax at the end of a longday, but it can ultimately assist in the control of some of the major disease of our time, such as cardiovascular and mental illnesses, and confer protection against cancer initiation and progression.

1.4 Tobacco and cancer

Smoking of tobacco is practised worldwide by over one thousand million people. However, while smoking prevalence has declined in many developed countries, it remains high in others and is increasing among women and in developing countries. Between one-fifth and two-thirds of men in most populations smoke. Women's smoking rates vary more widely, but rarely equal male rates. Tobacco is most commonly smoked as cigarettes, both manufactured – which are a highly sophisticated nicotine delivery system – and hand-rolled. Pipes, cigars, bidis and other products are used to a lesser extent or predominantly in particular regions. Cigarettes are made from fine-cut tobaccos that are wrapped in paper or a maize leaf. Cigars consist of cut tobacco filler formed in a binder leaf and with a wrapper leaf rolled spirally around the bunch. Bidis (smoked in India) contain shredded tobacco wrapped in non-tobacco leaves.

The peak of tobacco consumption in the USA occurred around 1960, but the peak of lung cancer deaths followed some 20 years later in men and is just becoming apparent in women. The 20-year lag between the consumption peak and cancer peak in men is characteristic of the time it takes for cancer to manifest itself as a clinical disease (see above). The difference between the peak cancer death rates for men and women is due to the fact that women began smoking cigarettes in the USA somewhat later than men (Figure 1.11). One of the most remarkable trends in disease over the 20th century was that in 1900 stomach cancer was the leading cause of cancer deaths in men and lung cancer was a comparatively rare condition (Figure 1.12). The gradual decline of stomach cancer over the past century has been called 'the great unplanned triumph of cancer epidemiology' because it is still not quite clear why it occurred. Unfortunately, it has been supplanted by 'the great unplanned disaster in cancer epidemiology' which is the lung cancer epidemic of the 20th and 21st centuries. In women, lung cancer took over from breast cancer as the leading cause

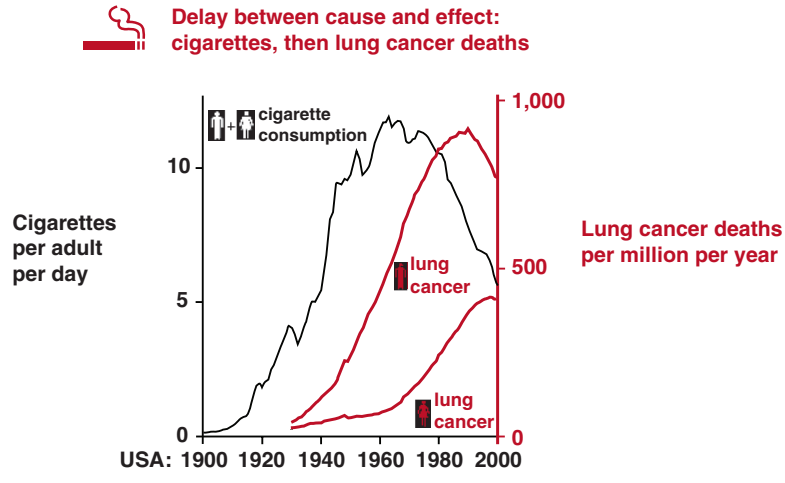


Figure 1.11 The relationship between cigarette smoking and lung cancer in US men and women over time (*Source*: www.deathsfromsmoking.net)

of cancer in 1990 – perhaps 'a great unplanned triumph of equal opportunity in disease provision' (Figure 1.13).

The link between tobacco and cancer was first identified in the 1930s in Germany and then studied in detail by Ernst Wynder in the US and Richard Doll in the UK in the late 1940s. Wynder asked a few simple questions to lung cancer patients and discovered that most of them were smokers. Many subsequent epidemiological studies have confirmed that 95 per cent of lung cancer deaths occur in smokers.

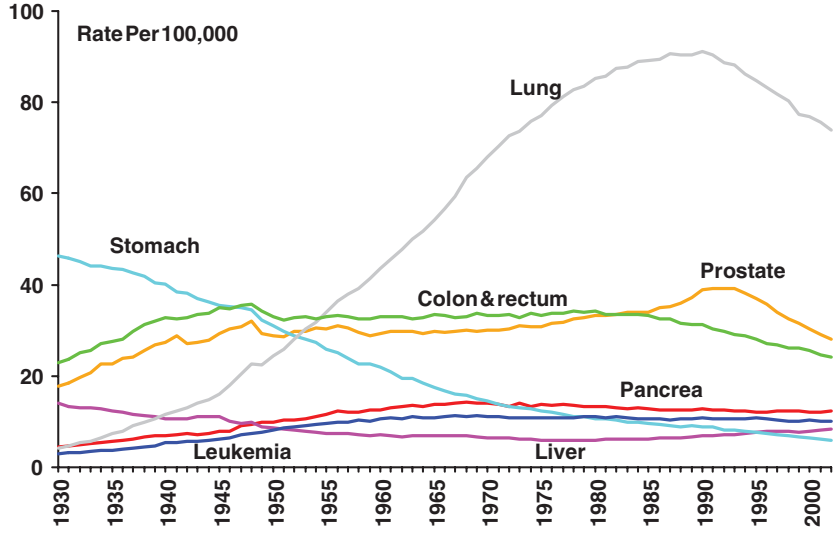


Figure 1.12 Cancer death rates, for men, US, 1930–2002 (*Source*: American Cancer Society. *Cancer Facts and Figures 2007* Atlanta: American Cancer Society, Inc.)

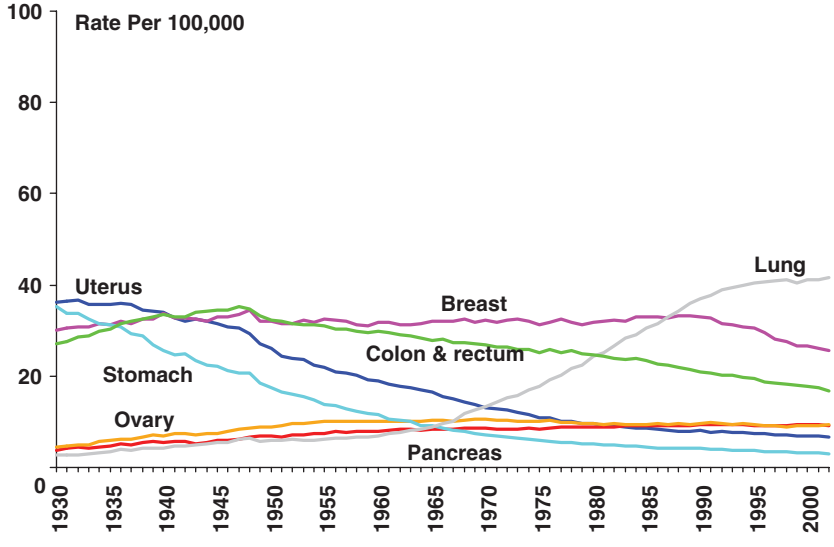


Figure 1.13 Cancer death rates, for women, US, 1930–2002 (*Source*: American Cancer Society *Cancer Facts and Figures 2007* Atlanta: American Cancer Society, Inc.)

Yet, most smokers do not die of lung cancer. This apparent paradox is due to such factors such as individual susceptibility to the development of cancer and death from other common, non-cancer, causes. Much of the detail of what we know about the links between tobacco and cancer has come from a study in a cohort of British doctors begun in 1951 by Richard Doll and colleagues. Doll recruited 34 439 male British doctors in a prospective study. Information about their smoking habits was obtained in 1951, and periodically thereafter; cause-specific mortality was monitored for 50 years. As more than 80 per cent of the doctors smoked at the time of recruitment, it took only a few years of follow-up to confirm the link between tobacco use and lung cancer. In the subsequent decades of follow-up more cancers were shown to be linked to tobacco use, including bladder cancer. The prospective design of the British doctors' study also revealed the sustained difference in numbers of years of life lost between lifelong non-smokers and continuing smokers (Figure 1.14). However, it was also possible to show that the benefits of stopping smoking could even be seen at age 55–64 in lifelong smokers. There are even larger benefits to be gained from stopping smoking at earlier ages.

By reviewing a large number of epidemiological studies carried out in many parts of the world, a World Health Organization expert working group came to the conclusion that tobacco use is causally associated with cancers at many sites in addition to lung, including oral cavity, pharynx, larynx, oesophagus (squamous-cell carcinoma and adenocarcinoma), pancreas, urinary bladder, renal pelvis nasal cavities and nasal sinuses, stomach, liver, kidney (renal-cell carcinoma), uterine cervix and myeloid leukaemia.

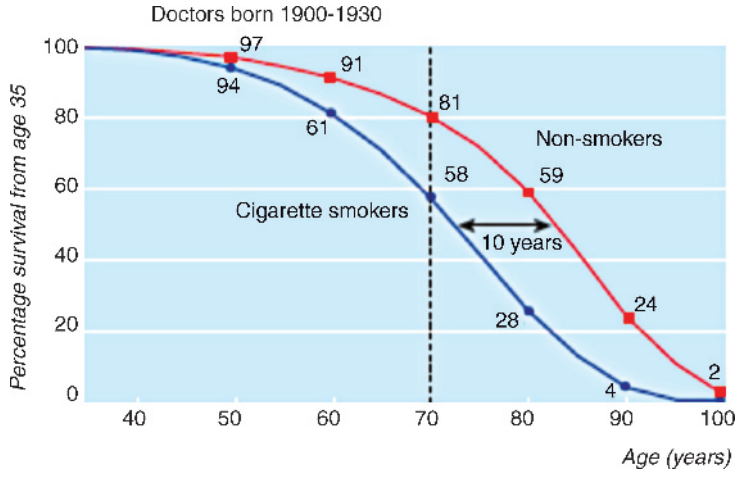


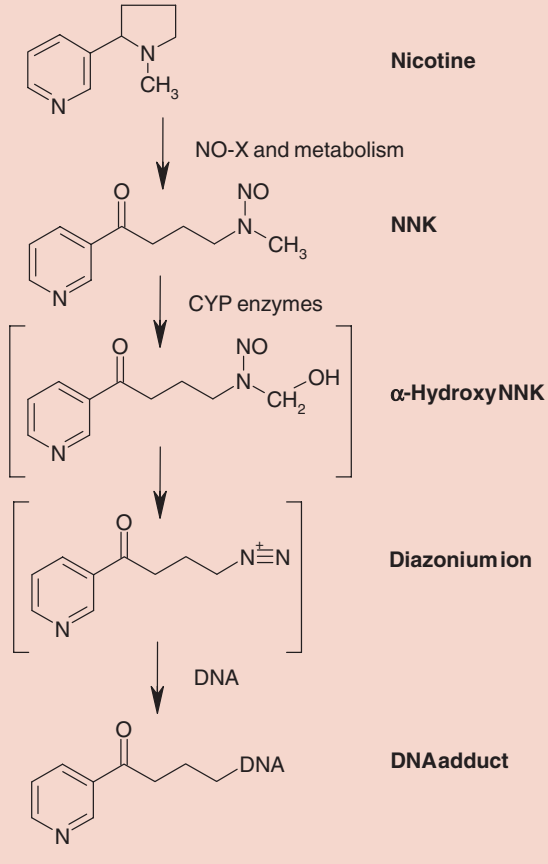
Figure 1.14 Survival from age 35 for continuing cigarette smokers and lifelong non-smokers among UK male doctors born 1900–1930, with percentages alive at each decade of age (*Source*: Doll *et al.* BMJ, 2004 *328*, 1519–1528. Reproduced with permission from BMJ Publishing Group)

The chemical composition of tobacco smoke, although influenced by the specific manner in which individuals smoke, is primarily determined by the type of tobacco. It is also influenced by the design of the smoking device or product and, for cigarettes, by the presence or absence of filters, and by other factors including ventilation, paper porosity and types of additives. As a result, concentrations of individual chemicals in smoke vary. Analysis of the ways in which people smoke modern cigarettes shows that the actual doses of nicotine, carcinogens and toxins depend on the intensity and method of smoking and have little relation to the stated tar yields. The total volume of smoke drawn from cigarettes as a result of specific smoking patterns is the principal determinant of dose to the smoker. All presently available tobacco products that are smoked, deliver substantial amounts of established carcinogens to their users. More than 60 known carcinogens are present in tobacco smoke, including polyaromatic hydrocarbons such as benzo[*a*]pyrene and formaldehyde and the radioactive isotope polonium 210.

Active smoking raises the concentrations of carbon monoxide, benzene and volatile organic compounds in exhaled air. The concentrations of urinary metabolites of some important tobacco smoke carcinogens and related compounds are consistently higher in smokers than in non-smokers. These include metabolites of benzene, a known carcinogen in humans, as well as metabolites of several carcinogens that cause lung tumours in rodents. Binding to blood proteins by carcinogens present in tobacco smoke has been demonstrated to occur at significantly higher levels in smokers than in non-smokers. This binding results in the formation of adducts, which are derived from various compounds including aromatic amines (e.g. 4-aminobiphenyl), polycyclic aromatic hydrocarbons (e.g. benzo[*a*]pyrene), tobacco-specific nitrosamines (e.g. 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone), benzene, acrylamide and acrylonitrile.

Much early work on tobacco carcinogenesis concentrated on carcinogens that had been identified in occupational or environmental situations. It appeared to be the case that the various nicotine delivery systems that characterized tobacco use were perhaps a more efficient way of delivering such carcinogens to the lung. However, it has recently become apparent that derivatives of the main tobacco alkaloids themselves may be responsible for the particular carcinogenesis of tobacco. Nicotine is probably responsible for the addictive properties of tobacco but does not cause cancer itself. However, during the tobacco curing process, as well as during the process of smoking and chewing of tobacco, nicotine is converted to derivatives such as *N*-nitrosonornicotine (NNN) and a related compound known as NNK. Once in the body, NNK is further metabolized to an unstable metabolite (α-hydroxy) that spontaneously decomposes to a highly reactive species (diazonium ion) that binds covalently to DNA to give characteristic DNA adducts (Box 1.3).

Box 1.3 The connection between nicotine and DNA damage related to tobacco use



Smoking-related DNA adducts have been detected by a variety of analytical methods in the respiratory tract, urinary bladder, cervix and other tissues. In many studies, the levels of carcinogen-DNA adducts have been shown to be higher in tissues of smokers than in tissues of non-smokers. Some, but not all, studies have demonstrated elevated levels of these adducts in the peripheral blood and in full-term placenta. Smoking-related adducts have also been detected in cardiovascular tissues. Collectively, the available biomarker data provide convincing evidence that carcinogen uptake, activation and binding to cellular macromolecules, including DNA, are higher in smokers than in non-smokers.

1.5 Conclusions

We began this chapter by a consideration that *time* and *place* are two factors that have a great influence on cancer risk. The slow pace of the development of cancer means that the longer that you live the greater your chance of developing cancer. If the process of cancer can be slowed down or reversed, it probably will not matter how many deleterious mutations have been acquired in various genes because the clinical stage of the disease will be delayed and some other, more acute, form of death will intervene. Overall, much of the available evidence suggests that most cancers are preventable. As Doll and Peto have observed: 'Death in old age is inevitable, but death before old age is not'. The notion of *place* being important in the development of cancer is not to suggest that one's physical location on the planet has perforce an influence on cancer risk, except perhaps in the special case of ultraviolet light and sun exposure-related skin cancer, where latitude of habitation is a risk factor. Rather, the place of habitation has an important impact on the cultural and environmental milieu, which manifests itself in diet and lifestyles that do impact directly on cancer risk.

Despite public concern over environmental pollutants and contaminants as causes of cancer, there is little evidence that they are responsible for much of the burden of cancer. One of largest preventable causes of cancer is tobacco. The link between tobacco use and lung cancer is now so well defined that it is possible to predict that tens of millions of smokers and other tobacco users worldwide will die of cancer over the next 40 years. This epidemic would be entirely preventable if it were not for two addictions. The first is the now well-established nicotine addiction that keeps tobacco users hooked and the second is that large income flows into national treasuries from tobacco excise duties. The consumption of alcohol in its various forms is now so well integrated into many societies that it will be difficult to eliminate. The experience of the US during the prohibition era highlights the difficulties of separating drinkers from their source of alcohol. The widespread consumption of alcohol and use of tobacco are two 'natural experiments' that show that human beings are not resistant to the carcinogenic affects of these two exposures.

Diet is also a major source of cancer risk – but, unlike tobacco and alcohol, also has the potential to lower cancer risk providing that the balance between nutritional requirements and the unavoidable intrinsic risks of dietary components can be found. Because all of us need to eat on daily basis, the reduction of even very small cancer risks, and the enhancement of small benefits, associated with food will have a significant effect on

cancer risks for many people. However, unlike the situation with cardiovascular disease, where readily measurable risk markers such as blood pressure and serum cholesterol are available, there are currently no widely usable markers of diet-related cancer risk. For the foreseeable future, governments and other organizations will have to continue to give the best possible advice to the public on lowering cancer risk without any measure, at the individual level, of the efficacy of any intervention.

1.6 Self-assessment questions

Question 'Cancer is a disease of old age'. In what ways is this statement *not* true?

Answer

(i) for most cancers the incidence rate begins to increase from about 40 years of age

(ii) there are a number of cancers that occur in children

(iii) the of rate testicular cancer peaks in young adult men

Question What are the two major risk factors for liver cancer in south-east Asia?

Answer Exposure to dietary aflatoxins and infection with hepatitis viruses.

Question What is the major difference between approaches to managing possible cancer risks related to pesticides and diet?

Answer Pesticides can, at least in principle, be removed from our environment whereas dietary patterns can only be altered.

Question If smoking causes cancer why don't all smokers get cancer?

Answer Individual variations in susceptibility to the development of cancer and variations in metabolic profiles mean that a proportion of smokers will not develop cancer during their lifetime

Question Why did the rate of lung cancer peak in women 20 years after that of men?

Answer Women began to smoke at a comparable rate to men after a delay of about 20 years

1.7 Further reading and resources

Note: Wherever possible, in addition to the literature citations, the URLs for appropriate websites are given. As the homepages for the various organizations are likely to be more stable than individual pages this is what is provided. Details correct as of January 2007.

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