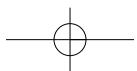
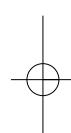
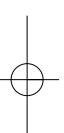


# ESMO handbook of cancer prevention



# ESMO handbook of cancer prevention

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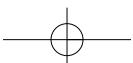
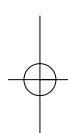
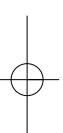
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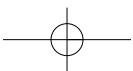
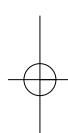
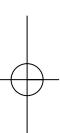


# Foreword

A foreword is a curious entity: first read, last written and usually by someone whose involvement in the preparation of the book has been fairly minimal. Such is the case with this book, but I am nonetheless delighted to be able to introduce it here and to commend authors and editors on the first-rate job they have done. This ESMO *Handbook of Cancer Prevention* follows hard on the heels of the ESMO *Handbook of Principles of Translational Research* and constitutes the fourth volume of a series that has been particularly well received by the oncology community. Part of that reception has been due, I have no doubt, to the quality of the handbooks themselves, but I also feel that the careful choice of subjects – oncologic emergencies, advanced cancer care, translational research, and now cancer prevention – has played a significant part too.

Do we need, at this point in time, to ask why ESMO, an organization for medical oncology has commissioned a book on cancer prevention? I hope not, and I am sure that anyone who takes even a little time with this book will soon come to see why oncologists must take a part in cancer prevention, not just in areas such as the administration of aromatase inhibitors but also in tobacco control, nutrition, and the working environment. Oncologists have the potential to be a large and important group of activists for cancer prevention measures, and faced, as we are daily, with the failure of cancer prevention we have more incentives than many others to see them implemented. Seen in this light, this handbook is both timely and necessary, and it is my sincere hope that you will find it both a practical tool and guide to thinking about this vital subject.

David J Kerr  
ESMO President-Elect



# Cancer epidemiology

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1

## Introduction

Cancer epidemiology studies the distribution of cancer in populations and its changes over time and looks at characteristics of different population groups, not only those who get the disease but also those who do not, to find out how these groups differ.

It evaluates the associations between different exposures and diseases to decide whether the observed relationships are likely to be causal. Its ultimate goal is to identify risk factors that may lead to the introduction of effective preventive measures.

Although cancer epidemiology is not a new science, it has matured only in the last half of the 20th century, when communicable diseases underwent a sharp and sustained fall. The development and growth in the field of vital statistics made it possible to study the patterns of cancer mortality. Unfortunately, mortality data published nowadays by the World Health Organization (WHO) are of different quality and may have several biases:

- coverage of the population is incomplete as mortality rates are implausibly low in some countries
- validity of the cause of death information is low in some countries.

The need for more accurate data on cancer patients and the relatively clear-cut pathological case confirmation led to the development of hospital- and population-based cancer registries.

- Hospital-based registries are concerned with recording of information on cancer patients seen in a particular hospital. The main purpose of such registries is to contribute to patient care by providing readily accessible information on all cancer patients, seen in this hospital, the treatment they had

received, and its result. These registries cannot provide measures of the occurrence of cancer in a defined population, because their catchments population, i.e. the population from which all cases arise, is unknown.

- Population-based registries collect data on all new cases of cancer occurring in a well-defined population over a given period of time. The first population-based cancer registry was established in Connecticut in the United States in 1940 with cases registered retrospectively back to 1935. In Europe, the first registry started to operate in Denmark in 1942; others were set up in subsequent decades, so that by 1955, almost 20 existed in various regions and countries (England and Wales, Slovenia, Finland and other Nordic countries, and few others). In some countries cancer registration is nationwide; in others, cancer registries cover only a proportion of the population. The main role of these registries is the provision of data on cancer incidence and prevalence – for some, also survival and mortality. This activity has placed the population-based cancer registry at the center of monitoring programs for cancer and there are few chronic diseases that are as intensively surveyed and characterized across multiple populations as cancer. Since 1964, the data from all the registries have been brought together in the publication ‘Cancer Incidence in Five Continents’. The 2002 volume was published by the International Agency for Research on Cancer (IARC) in conjunction with the International Association of Cancer Registries and records data for up to 50 types of cancer in 215 populations in 55 countries. Many cancer registries are also able to provide follow-up on patients and thereby generate information on survival. This had led to research that assesses comparative survival outcomes within and between populations, e.g. in the EUROCARE studies.

The observation that cancer incidence is different around the world, that it changes over time, and that migrants from low-risk countries attain the risk of their new country contributed to the idea that cancer is a consequence of several environmental risk factors in the broad sense, including physical, chemical, and biological factors in living and occupational environment as well as behavioral and sociocultural factors (e.g. diet, smoking, alcohol consumption, fertility).

Analytical cancer epidemiology with case-control and cohort studies contributed to current knowledge on several factors implicated in the etiology of cancer. Although several studies were conducted before the 20th century, the growth of these studies began after the Second World War. In 1950, three case-control studies, two from the USA and one from Britain, were published, clearly showing the association (probably causal in nature) between

tobacco smoking and lung cancer. Since then, several studies have confirmed this association and a lot of other agents have been identified as being potentially carcinogenic.

Several studies, published in different parts of the world on various potential cancer risk factors are reviewed by interdisciplinary working groups of expert scientists, gathered by the IARC in the IARC Monographs Program. These groups evaluate the weight of the evidence that an agent (including chemicals, complex mixtures, occupational exposures, physical and biological agents, and lifestyle factors) can increase the risk of cancer. Special scientific criteria have been developed that guide the evaluations and are described in the Preamble to the IARC Monographs. Since 1971, more than 900 agents have been evaluated, of which approximately 400 have been identified as carcinogenic or potentially carcinogenic to humans. The complete list of agents evaluated and their classification is regularly updated and available at <http://monographs.iarc.fr/index.php>. This list is a valuable source of information on carcinogenicity for public health and other scientists and national health agencies to use as scientific support for their actions to prevent exposure to potential carcinogens.

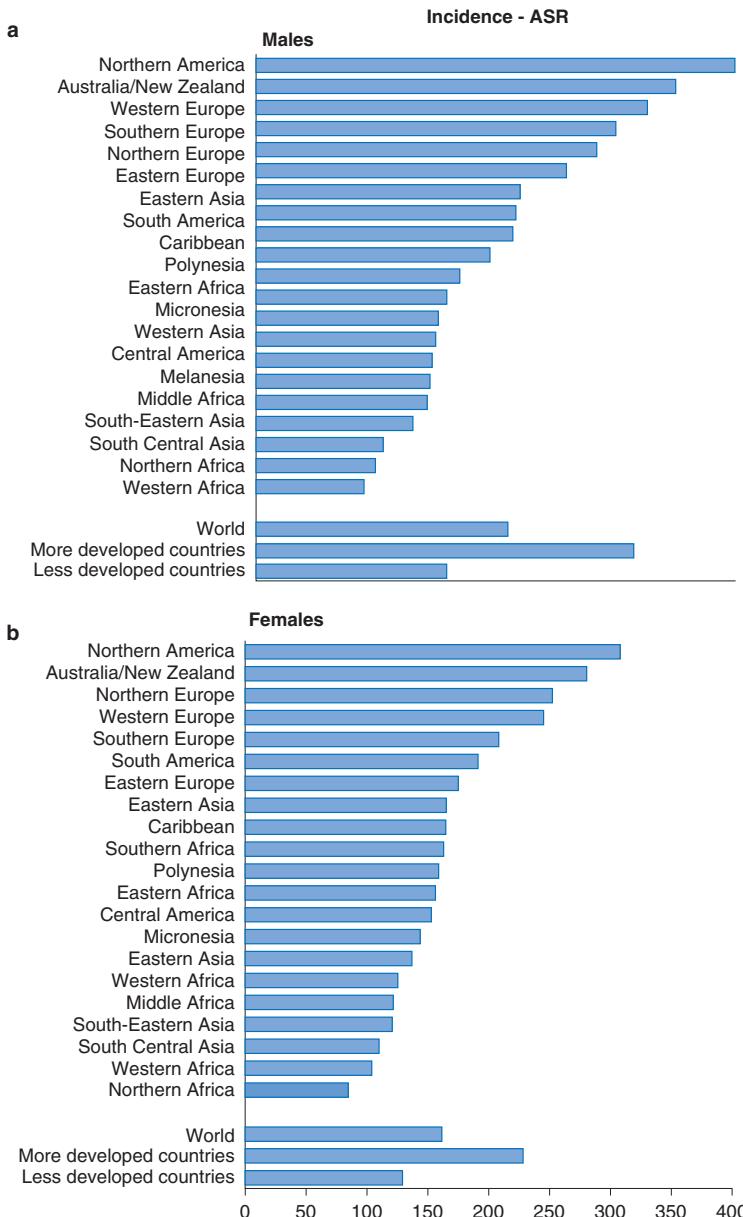
## The burden of cancer worldwide and in Europe

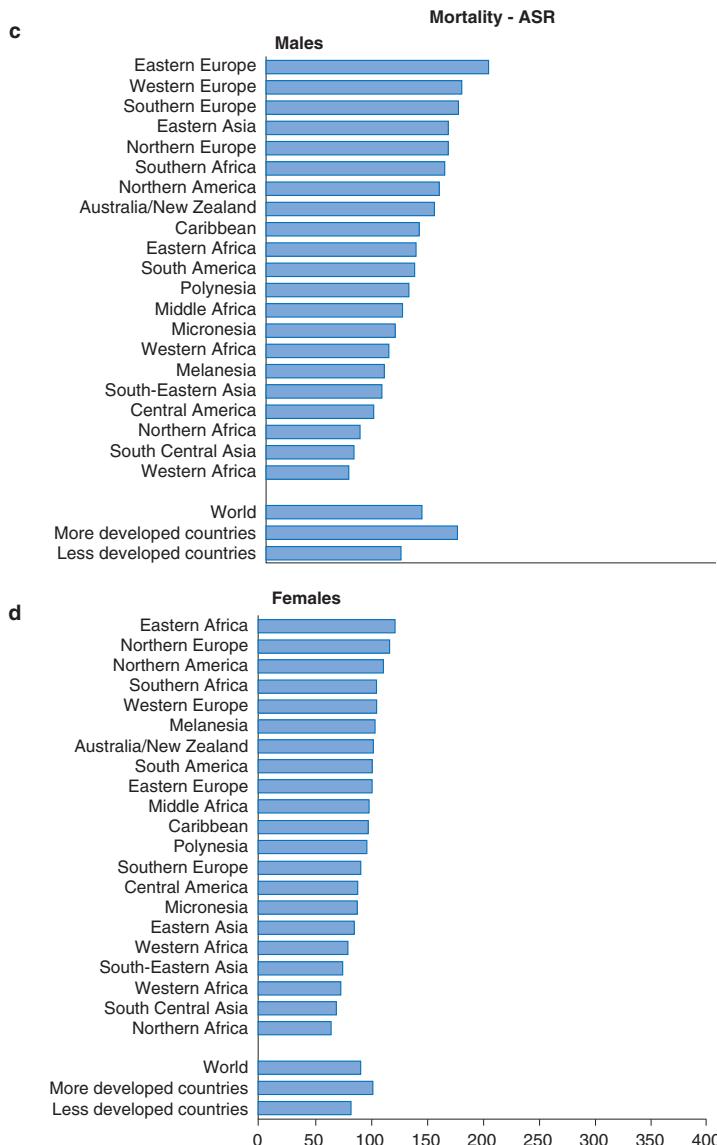
There are great regional differences in cancer incidence and mortality overall and at specific organ sites in the world. A valuable tool to analyze these differences is CANCER Mondial at <http://www-dep.iarc.fr/>. This website provides access to information on the occurrence of cancer worldwide held by the Descriptive Epidemiology Group of IARC in four databases: original and updated data from volumes I to VIII of Cancer Incidence in Five Continents; the WHO Mortality database; and GLOBOCAN 2002. The GLOBOCAN 2002 database presents estimates of the incidence and prevalence of and mortality from 27 cancers for all countries in the world in 2002.

In 2002, there were an estimated 10.9 million new cases (53% among males and 47% among females), 5.1 million in more-developed and 5.8 million in less-developed regions.

Of 6.7 million cancer deaths (57% among males and 43% among females), 2.7 million were in more-developed regions and 4.0 million in less-developed regions. There were an estimated 24.5 million persons living (within 5 years of diagnosis) with all forms of cancer (except non-melanoma skin cancer).

Incidence and mortality rates, standardized to the standard world population in different world regions are presented in Figure 1.1. As age standardization





**Figure 1.1** Estimated age-standardized cancer incidence and mortality rates (ASR) in different world regions in 2002.

eliminates the effect of different age structures in several populations, so the differences in incidence and mortality rates represent differences in risk due to all other risk determinants.

Nearly a third of the world's new cancer cases (excluding non-melanoma cancer) and a quarter of cancer deaths appear in Europe, for which the estimates of incidence and mortality data are available for the year 2006.

Similarly to the whole world, there are regional differences within Europe in terms of incidence and mortality:

- The overall estimated incidence rates in males ranged from nearly 600/100 000 persons in Hungary to 300/100 000 persons in some South and Eastern European countries and from about 400/100 000 persons in Denmark to less than 250/100 000 in Hungary for females after adjusting for the different age structures to a European standard population.
- Mortality rates show variation from nearly 400/100 000 persons to less than 200/100 000 in males and from nearly 200/100 000 to about 100/100 000 in females.

High all-cancer mortality rates for a number of Central and Eastern European countries despite lower incidence reflect the distribution of most frequent cancers and poor survival of these patients. While several published analyses of trends in cancer mortality in Europe over the past 30 years show, that in the majority of countries of the former European Union (EU), the age-standardized mortality from most common cancer sites has fallen since the late 1980s, the situation is less favorable in the majority of Eastern European countries.

## Most frequent cancer types in Europe

Breast, colon and rectum, lung, and prostate were among the most common cancer sites in both sexes in 2006.

- In the last few years prostate cancer has replaced lung cancer at first place in males, followed by colorectal cancer at third place.
- In females, breast cancer was the most common cancer site, followed by colorectal and uterine cancer.

In terms of mortality, lung cancer was still the most common cause of cancer death in both sexes combined, followed by colorectal, breast, and stomach cancer.

## Lung cancer

Lung cancer is still one of the biggest public health problems in Europe, accounting for one-fifth of all cancer deaths. As the most important risk factor for lung cancer is tobacco smoking, trends in lung cancer incidence and mortality reflect the stage of the smoking epidemics in different countries. While in some Western European countries the mortality from lung cancer, especially among younger men has started to decline, due to the modification in the smoking habit from generation to generation, there is an increasing trend in females, especially in Northern Europe.

## Colon cancer

Excess calorie intake and insufficient levels of physical activity leading to obesity clearly increase the risk of colon cancer, and its constant rise in incidence have been observed within populations undergoing economic development. The incidence is high in many Western, but also Central–Eastern European countries, e.g the Czech Republic, Hungary, and Slovakia.

While mortality trends tended to decrease in some of the North-Western countries from the 1990s onwards, they were still in the upward direction in many Central and Eastern European countries.

Besides different lifestyles, these differences may be due also to earlier diagnosis, new treatment modalities and hence better survival in some Western, but not to such an extent in Eastern countries.

As screening for colorectal cancer has been shown to be effective, there is a need for organized programs throughout Europe.

## Breast cancer

Breast cancer was the leading cause of death from cancer in women in Europe.

Genetic factors, including the major susceptibility genes (*BRCA1*, *BRCA2*), may account for up to 10% of breast cancer cases in developed countries, but their prevalence in the population is too low to explain much of the international variation in risk.

The majority must therefore be a consequence of different environmental exposures. This is evident from studies of migrants, which show quite clearly that incidence rises following migration from low to high incidence countries, particularly if this takes place at young ages.

Besides age and sex, the established breast cancer risk factors include previous breast cancer in one breast, family history of breast cancer, fibrocystic disease, and ionizing radiation (the reported range of relative risk estimates of breast cancer is 2.1 to more than 4).

For others, the reported range of relative risk estimates is low, ranging from 1.1 to 2.0. These include hormonal and reproductive factors, such as early age at menarche, late age at menopause, late age at first birth, late age at any birth, nulliparity, current use of oral contraceptives, and hormone replacement therapy.

All these risk determinants are difficult to change, while lifestyle-related factors, such as body mass index, physical activity, diet, and alcohol consumption should be the goal of primary prevention.

The introduction of organized mammography screening programs throughout Europe will lead to a reduction in breast cancer mortality, where the maximum effect is expected from programs with effective quality control.

### **Prostate cancer**

Prostate cancer is a disease predominantly affecting elderly men. In many European countries, the number of deaths is increasing due to aging of the European male population.

### **Cervical cancer**

Mortality from cervical cancer in Europe is much lower than in the developing world, where 80% of all deaths occur. There are great differences in its incidence and mortality between Eastern and Baltic European countries and other European countries, mostly due to different availability of organized screening programs. They reflect the fact that opportunistic screening, as currently present in the majority of these countries, is not effective.

Sexually transmitted infection with some human papillomavirus (HPV) strains is fundamental to the development of cervical cancer and HPV vaccine already available on the market is hoped to reduce incidence in the years to come; however, screening programs will have to remain, as the vaccine does not protect against all HPV strains. Unfortunately, the current high price of the vaccine, especially for the countries with the highest risk, besides some other scientific questions (e.g. most appropriate age for vaccination) are obstacles to its wider use as a public health measure in all selected target age groups.

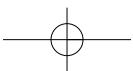
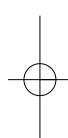
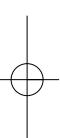
## Conclusion

Cancer epidemiology has contributed to our knowledge on regional differences in cancer burden and time trends across the world and in Europe. It has helped to identify cancer risk factors, lifestyle-related and environmental, including tobacco, alcohol, dietary habits, and pollution of the working and general living environment, that can partially explain these differences and are important for cancer prevention.

The results from the EUROCARE and other studies have revealed great variations in cancer survival among countries in Europe and worldwide that are mostly due to differences in screening, timing of diagnosis, and quality of treatment. All these findings support the need for comprehensive national cancer control programs that extend from primary prevention and screening to management of disease, rehabilitation, and palliative care.

## Further reading

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# Types of prevention: basic concepts

2

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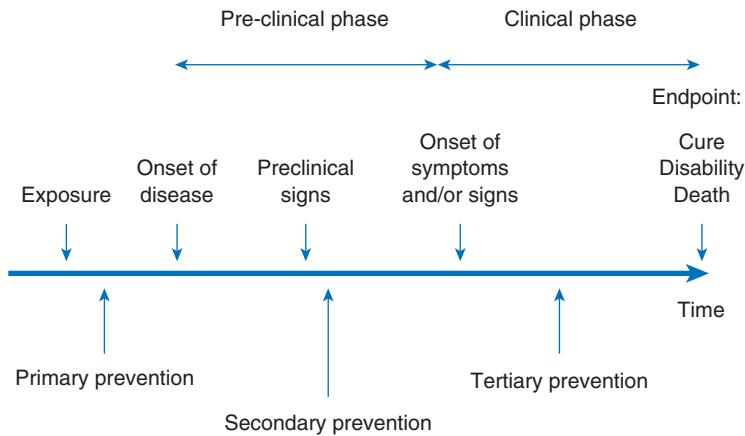
Antwerp, Belgium

## Introduction

Since the beginning of the twentieth century, worldwide collective contributions have led to considerable progress in the prevention of cancer. In the first half of the past century, cancer mortality rose from the ninth to the second most frequent cause of death in the United States. In part this rise could be explained by a population-aging effect, but it also became clear that a changing lifestyle contributed to a great extent to the cancer epidemic. Most striking was the dramatic increase in lung cancer incidence as a consequence of massive adoption of cigarette smoking, first by men and later by women.

In the same period, leading clinicians recognized the importance of early diagnosis and treatment to reduce case fatality and improve cancer survival rates. The first early detection method, a cytological test on a cervical smear for the preclinical diagnosis of (precursor lesions of) cervical cancer was reported in 1943 by Papanicolaou and Traut and it has since been known worldwide as the Pap test. However, it took almost 30 years before the test was generally adopted in population screening programs.

In the second part of the 20th century, the emphasis in cancer control shifted from a curative towards a preventive approach. It became clear that the marked decline in death rates observed in the Western world during the 19th century was mainly due to general improvements in standards of living. As a consequence, it was hoped that specific preventive measures would also influence cancer incidence and mortality rates, as the role of specific medical therapies in cancer control was rather limited. A milestone was the publication by Doll and Peto in 1981 of a table estimating the contribution of different agents to the risk of death by cancer as an indication for the potential of preventive action.



**Figure 2.1** Natural history of disease and the different levels of prevention.

These authors estimated that 30% of all cancer deaths were related to smoking, 35% to diet, and 35% to other causes (e.g. viruses, hormones, radiation, industrial carcinogens). Although the importance of this publication cannot be ignored, the estimations do not take into account multicausality and interactions and are therefore incorrect (the attributable proportions should not add up to 100%).

With respect to early diagnosis, there was growing confusion. Despite the enthusiasm among the advocates for screening, there was also an increasing scepticism:

- lack of evidence based on experimental studies
- reporting of improvement in survival probabilities disregarding the so-called lead-time bias.

Part of this confusion had (and still has) to do with a poor understanding of the concepts of prevention. In the subsequent section, the most important concepts of prevention are discussed.

## Types of prevention

Three levels of prevention are identified, corresponding to the different phases in the natural history of disease (Figure 2.1): primary, secondary, and tertiary prevention.

## Primary prevention

The aim of primary prevention is to reduce the incidence of cancer by controlling (avoiding) exposure to risk factors or by increasing an individual's resistance to these risk factors (by immunization or chemoprevention).

It is clear that the first step in primary prevention is to identify relevant exposures and to assess their impact on the risk of the disease, both at the individual and the population level. Once it has been established that an exposure is causally associated with the disease of interest, it is important to consider methods to either eliminate or reduce this exposure.

The highest impact can be expected from those methods targeting the total population by avoiding the emergence and establishment of the social, economic, and cultural patterns of living that are known to contribute to an elevated risk of disease. This strategy has been labeled 'primordial prevention'.

In many developing countries the basic underlying cause of lung cancer (cigarette smoking) is already present and exposure is increasing even though the resulting epidemic may still be developing. Effective primordial prevention requires strong governmental regulatory and fiscal action to stop the promotion of cigarettes and the onset of smoking.

Primary prevention can focus on the whole population (population strategy) as well as on people at high risk (high-risk population and high-risk individual strategy).

- A high-risk individual strategy, aimed at protecting more susceptible individuals, can be very efficient for people at the greatest risk (e.g. organ transplantation patients are particularly susceptible to non-melanoma skin cancer). However, primary prevention campaigns targeting these people (e.g. organ transplantation patients, involving reduction of sun exposure and sunscreen use), though for them of great benefit, will have only little impact on the overall frequency of occurrence of disease in the total population, because high-risk individuals often only represent a very small fraction of the total population.
- A population strategy is likely to produce greater benefits at the population level and does not require the identification of high-risk individuals. On the other hand, this strategy requires the involvement of large groups of people with a benefit for only relatively few.

It is advisable that intervention studies should be performed before implementing (primary) prevention strategies. These intervention studies should

focus on whether on the one hand the strategy reaches its first objective, i.e. a reduction in exposure and, on the other hand, whether this reduction in exposure leads to a reduction in cancer risk. Quite often, however, the existing evidence of (or belief in) a potential benefit of exposure reduction is so strong that strategies are implemented without performing any pilot studies. In that case it is essential to conduct evaluative studies to ascertain whether the preventive measure has had any positive effect and whether the reduction of an exposure with the aim of a reduction in risk for cancer is not leading to an increase in risk for another adverse health condition.

As stated earlier, a reduction in the incidence of cancer might also be achieved by increasing the individual's resistance to the risk factors by immunization or by chemoprevention.

Considerable effort is now made on the development of vaccines to prevent infection by specific oncogenic infectious agents (human papillomavirus [HPV], hepatitis B virus [HBV]) or to increase the immune response to cancer-specific epitopes. At present many countries are considering the reimbursement of HPV vaccines in young women. Given the current price of the vaccines, cost-effectiveness of such strategies is very unfavorable especially because the benefits of vaccination will only be realized in the distant future and it is very uncertain what the efficacy and cost of a cervical cancer treatment will be at that time.

Cancer-protective effects of chemicals and dietary compounds (e.g. selective estrogen receptor modulators, 5- $\alpha$ -reductase inhibitors, cyclooxygenase-2 [COX-2] inhibitors) have been demonstrated in many high-quality studies. However, at this moment, their general use is limited as a consequence of the important side effects of their daily intake.

### **Secondary prevention**

Secondary prevention aims at detecting cancer at an early stage when treatment is more effective, leading to a higher rate of cure and a reduced frequency of the more serious consequences of disease. When followed by effective treatment, it is possible to prevent the progression of disease and its complications (including death).

One could therefore argue that in fact this 'secondary prevention' is not preventing the occurrence of disease and is therefore a misnomer. Nevertheless, the widespread use and popularity of secondary prevention (instead of 'early detection') and some of the related concepts justify special attention.

Typically, in secondary prevention, the diagnostic procedure is directed at the period between the onset of the disease and the onset of symptoms (approximately the usual time of diagnosis). As a result, the initiative for the diagnostic procedure can be by the individual or by the healthcare provider and in the latter case different strategies are described according to the way asymptomatic people are invited to participate. The invitation procedure can focus on a whole population (screening), on a high-risk subpopulation (targeted screening), or on a high-risk individual (case finding), and each of these procedures has advantages and drawbacks.

Common to all is the fact that in early diagnosis initiated by the healthcare provider, the target is an individual not seeking help for the disease at issue, and this has important (ethical) consequences. For most of the participants there will be no benefit and they will only suffer from possible side effects.

Being already aware of this, in 1968 the World Health Organization (WHO) formulated 10 criteria a disease should meet in order to be suitable for screening (Wilson & Jungner criteria). Many criteria have been proposed since then, but most of them are very similar. As they are quite often inadequately quoted, we present these criteria here in their original form:

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a 'once and for all' project.

In their publication, the authors also discuss criteria for the evaluation of screening tests (case-finding tests): validity, reliability, yield, cost, acceptance, and follow-up services.

Especially with respect to test validity, the publication has had a tremendous influence on the current (lack of) understanding of diagnosis. The test

**Table 2.1**

Screening result	True disease classification of apparently well population	
	Diseased persons	Persons without disease
Positive	With disease and with positive test (true positives)	Without disease but with positive test (false positives)
Negative	With disease but with negative test (false negatives)	Without disease and with negative test (true negatives)
Total	Total unknown cases of disease	Total persons without disease

Sensitivity = diseased persons with positive test/all persons in population with disease.

Specificity = non-diseased persons with negative test/all persons in population without disease.

is extensively discussed as a dichotomized characteristic that leads to four categories of results (Table 2.1).

Consequently, the true diagnostic question ('What is the probability that a person has the disease at issue given the specific diagnostic profile?') has been reduced to the probability of disease in test positives regardless how positive the test result was.

This probability (the so-called positive predictive value) is only the average probability of disease in all test positives and can be far away from the correct probability when taking into account the (known) specific test result.

Screening strategies (and evaluations of screening strategies) that are based on this oversimplified diagnostic concept lead to erroneous results and, as a consequence, to avoidable over- and undertreatment. As an example, it should be clear that a pronounced mammographic finding (big stellar lesion with microcalcifications) has a different probability for breast cancer than a discrete finding. Applying one common approach for reading and referring ('all test positives are equal') is therefore not tenable.

An important consequence of the fact that it is generally accepted that early detection is a kind of ‘prevention’, is the growing belief that it should be considered as a preventive intervention and evaluated as such.

Rather than emphasizing the evaluation of the diagnostic process (validity, reliability, acceptance, yield, shift in stage distribution towards the less advanced stages, and costs in terms of finances and adverse effects), some researchers are convinced that a screening program should be evaluated by intervention studies, preferably randomized controlled trials. These trials should demonstrate whether the screening program is effective in reducing morbidity and mortality from the disease being screened. They forget, however, that ‘early diagnosis’ is at issue and that the consequence of an early diagnosed lesion is an early treatment. It is (fortunately) not common practice to evaluate diagnostic procedures by the outcomes of the following treatments.

Overall evaluations based on randomized controlled clinical trials, comparing screened with unscreened populations with respect to treatment outcomes, have led to confusion and debate (e.g. the debate on the efficacy of breast cancer screening at the beginning of the 21st century).

Early treatment is in general not part of the program but should of course be adequate and lead to an improved case-fatality rate and to a decrease of serious consequences of the disease. The comparison of early-treated with late-treated patients based on survival times is not valid as a result of the so-called lead-time bias (time of progression between the early and late stage). However, it is important that a comparison of health outcomes should be made before even considering any screening program, as it is one of the (most important) criteria that has to be met.

Once the benefits of early treatment are established, it should nevertheless be clear that screen-detected early lesions are not a random sample of all early lesions, especially when screening tests are applied at moderately long intervals. Tumors with a longer preclinical phase are more likely to be detected than fast-growing tumors. As a result of this, cases detected by screening may be those with lesions having a more favorable outcome.

Differences in case-fatality rate between screen-detected cases and other cases may therefore be explained by the selection of less-rapidly fatal cases through screening (so-called length bias). The question is, therefore, whether screen-detected early cases are better off when treated in this early stage compared to a treatment at the moment of clinical symptoms (e.g. leading to a watchful waiting strategy in prostate cancer).

It is obvious that the answer to that question is hard to give, as it would need to compare health outcomes in people complying or not complying with the therapeutic consequences of their positive screening result.

Finally, it is possible that some of the lesions detected by a screening program would never have led to invasive cancer and death as a result of competing risks. This is especially the case when screening is offered to elderly people or when the specific type of cancer has a long preclinical phase, as is the case in prostate cancer.

### Tertiary prevention

Tertiary cancer prevention is usually defined as the prevention of loco-regional relapse and/or metastatic disease after – hopefully curative – primary treatment by surgery or radiotherapy. Tertiary prevention therefore embraces the expanding and important field of adjuvant therapy (chemotherapy, radiotherapy and antiendocrine treatments), prolonging disease-free intervals and even leading to significant overall survival gains in several neoplastic diseases such as testicular cancers, malignant lymphomas, breast and colon cancer and others. Tertiary cancer prevention, especially in the form of adjuvant systemic therapy, is sometimes difficult to distinguish from medical treatment, but – contrary to systemic therapy in manifest, symptomatic disease – is usually confined to a clearly defined and limited pre- and/or postoperative treatment phase of several treatment cycles with subsequent treatment-free regular follow-up of the patient.

Some authors also include rehabilitative measures, leading to improved quality of life, with the term of ‘tertiary prevention’, while experts of WHO call the maintenance of quality of life of the patient by successful prevention of suffering (from pain, disease, and treatment-related side-effects and complications) the ‘fourth level’ of cancer prevention.

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# Methodologies in cancer prevention

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## Introduction

According to the World Health Organization (WHO), from a total of 58 million deaths worldwide in 2005, cancer accounted for 7.6 million (13%). Deaths from cancer are projected to continue rising, with an estimated 9 million people dying from cancer in 2015 and 11.4 million dying in 2030, by which time it will be the leading cause of death.

The high mortality is also accompanied by significant morbidity and cancer has a huge economic burden. It is estimated that 40% of cancers can be prevented by modifying several risk factors. This chapter deals with methodological aspects of assessing risk factors for cancer, cancer prevention strategies, and endpoints in cancer prevention studies.

## Cancer risk factors and risk assessment

### What are risk factors?

Over the years there has accumulated a lot of evidence for association of certain factors that modulate the development of cancer. These are called risk factors.

Risk factors may be:

- Modifiable:
  - behavioral
  - environmental.

- Non-modifiable:
  - biological: age; gender; complexion.
  - genetic.

The effects of risk factors on carcinogenesis are related to:

- duration of exposure to the risk
- quantitative extent of exposure
- cumulative and synergistic effects of other factors
- evolution.

### How are risk factors identified?

Data on risk factors for cancer come from:

- Observational epidemiological studies that show associations between modifiable lifestyle factors or environmental exposures and specific cancers using various statistical methods.
- Randomized controlled interventional trials designed to test whether modification of suggested risk factors actually result in reduced cancer incidence and mortality.
- Prospective studies in animals or in in-vitro cancer models to assess carcinogenic potential of chemicals or to study the influence of exposure to or avoidance of exposure from environmental agents to evaluate future cancer development or progression.
- Molecular genetic studies to identify genetic factors that modulate the development of cancer.
- Assessment of chemical carcinogenicity by biological assays and various predictive models such as tolerance distribution types (like logit, probit, gamma multihit), or mechanistic types (like linearized multistage, multi-stage [Armitage–Doll time to tumor model]), or Cohen and Ellwein biologically based model.

### Quantifying risk from a risk factor

- **Absolute risk** measures the actual cancer risk or rate in a defined population or subgroup. This shows how common a condition is.
- **Lifetime cancer risk** is a person's chance of developing cancer over the course of their life. Very often, 'lifetime' risks assume a person lives to the age of 85.
- **Adjusted rates of risk** are often used (e.g. age-, sex-adjusted rates) to better compare rates over time or among groups by adjusting the data to make the

groups more alike with respect to important characteristics that may affect the conclusions.

- **Relative risk** (RR) compares the risk of developing cancer among those who have a particular characteristic or exposure with those who do not. Relative risk is expressed as a ratio of risks.
- **Odds ratio** (OR) compares the odds of an exposure or characteristic among cancer cases with the odds among a comparison group without cancer.
- **Risk or rate difference** compares the actual cancer risk or rate among two groups of the population, based on an important characteristic or exposure, by subtracting the risks or rates from one another.
- **Population-attributable risk** measures the proportion of cancers that can be attributed to a particular exposure or characteristic.

### **Role of susceptibility and factors influencing individual susceptibility to risks**

The susceptibility of population subgroups to risk factors is identified and quantitatively assessed, on a statistical basis, by relative risk.

Susceptibility may be defined either as:

- Relative risk of developing cancer in those that are exposed to a certain risk factor compared to those not exposed.
- The doses or exposures of a hazardous factor that induce the same response level in different population groups or experimental groups.
- The time period of the effect onset in different equally exposed groups. In this case, a population subgroup is more susceptible than another one, if the onset is significantly earlier in the first with respect to the latter.

Many factors influence an individual's risk of cancer:

- Individual differences concerning the expression of enzymes that metabolize many chemicals involved in carcinogenesis.
- DNA damage and repair kinetics have been shown to have a major role in determining differential susceptibilities to cancer risk, by affecting the capacity of inducing and reducing the mutation rate, and there is a positive and consistent association between reduced DNA repair efficiency and cancer risk.
- The presence of specific inherited changes in relevant genes that code for various regulatory proteins involved in regulation of cell growth, differentiation, and senescence.
- Susceptibility 'acquired' as a consequence of some pathologies, known to increase cancer risk, as, for instance, infection by Epstein–Barr virus, human papillomavirus, hepatitis B and C viruses, previous cancers, or inflammatory diseases such as ulcerative colitis.

## Interplay of environmental and genetic risk factors on cancer development

It is now clear that almost all cancers have genetic factors that play an important role in their causation. External influences interact with the genetic factors in various combinations to initiate and/or propagate the carcinogenetic pathway.

- Both the environmental exposure and the genetic factor are necessary for the induction of the disease.
- The environmental exposure is sufficient to induce the disease and the genetic factor enhances the response to the relevant exposure; the genetic factor itself does not cause any effect.
- The environmental exposure enhances the effect of the genetic factor, which may induce adverse effects even in the absence of the exposure.
- The effect may be caused by either the environmental exposure or the genetic factor; however, the genetic factor increases the effect of the environmental exposure.
- Both factors are sufficient to cause the disease by themselves; however, there is an interaction among them.

## Cancer risk prediction models

It is important to understand that a particular individual's risk of developing a particular cancer is influenced by a complex interplay of several risk factors and this concept has been utilized to develop complex mathematical predictive models based on the presence or absence of individual risk factors.

There are several such risk prediction models for a variety of cancers, the most well known being the Gail breast cancer risk prediction model and the National Cancer Institute (NCI) melanoma risk assessment tool. These provide an important approach to assessing risk and prognosis by identifying individuals at high risk, facilitating the design and planning of clinical cancer trials, fostering the development of benefit-risk indices, and enabling estimates of the population burden and cost of cancer.

Models also may aid in the evaluation of treatments and interventions. Accurately assessing cancer risk in average- and high-risk individuals and determining cancer prognosis in patients are crucial to controlling the suffering and death due to cancer.

However, a calculated 'high risk for cancer' does not necessarily translate into actual development of cancer and cancer can also clearly affect those with 'low risk'.

Also, each model is based on information obtained from a particular population and its validity is generally tested on that population, and thus its applicability is also restricted to individuals from that population alone.

## Endpoints of cancer prevention

### What are endpoints in risk assessment and risk management research?

The final goal in risk assessment or risk management of cancer is to prevent or reduce mortality from cancer, or at least reduce the risk of cancer development.

While ideally all causes of death and perhaps, less suitably, cancer incidence or cancer-related mortality should be the endpoint of studies evaluating prevention strategies, it has to be appreciated that this is rarely feasible.

Carcinogenesis is a protracted process, usually over several years, and makes such a study logistically very difficult. Also, as cancer incidence may be low overall, these studies will need a large number of participants over a long period and thus become very costly. Typically, cancer incidence reduction trials have planned durations of 5–10 years, with anticipated accrual in the tens of thousands of participants.

This has led to the development of surrogate endpoints, which occur early in the carcinogenetic pathway and thus shorten the length of studies looking into cancer prevention or assessment of cancer risk.

### Role of biomarkers in risk assessment and prevention trials

Biomarkers play an increasingly important role in various aspects of assessing genetic and family risks, in non-invasive tests for screening, histological/endoscopic targeting of biopsies in trials, host response for risk stratification, assessing drug metabolism rates, and predicting progression.

The different types of biomarkers are summarized in Table 3.1.

### Problems and issues in using surrogate endpoints in cancer prevention research

- The number of precancerous lesions may far exceed the number of cancers that subsequently develop in the target tissue.
- Although most cancers develop from precancerous lesions, they may also develop independently of such pre-existing lesions.

**Table 3.1** Types of biomarkers as surrogate/intermediate endpoints

Type of biomarker	Major examples
Tissue level phenotypic biomarkers	Dysplasia in Barrett's mucosa, prostatic intraepithelial neoplasia, colorectal adenomas, cervical intraepithelial neoplasia
Cellular biomarkers	Nuclear and nucleolar morphology, mitotic index, DNA ploidy
Genotypic biomarkers	Loss of heterozygosity and gene amplification, either at specific gene loci (for tumor suppressors such as p53 or tumor growth accelerators such as c-erbB2) or at panels of microsatellite loci where mutations indicate increasing genomic instability
Molecular biomarkers	Cellular antigens (PCNA or Ki-67/MIB-1), growth factors (epidermal growth factor; transforming growth factor [TGF], and insulin-like growth factor I)
Apoptosis-related markers	Increased expression of bcl-2
Biomarkers of aberrant differentiation	Changes in G-actin, cytokeratins, and blood group antigens
Biomarkers relating to general changes in cell growth control	TGF $\beta$ , cyclins, p53
Oncogenes associated with carcinogenesis	K-ras, transcription factors myc, fos, and jun
Tissue-related biomarkers	Expression of estrogen receptors in breast, prostate-specific antigen (PSA) in prostate
Drug-related biomarkers associated with chemopreventive activity	Inhibition of ornithine decarboxylase by 2-difluoromethylornithine; inhibition of prostaglandin biosynthesis by non-steroidal anti-inflammatory drugs

- If the putative agent in question exerts its cancer preventive effect at a stage after the formation of a precancerous lesion, these effects will not have been picked up if the endpoint of the study was detection of new or recurrent precancerous lesions.
- It may happen that an agent may reduce the rate of precancerous lesion formation, but may have an accelerating effect on transformation of precancerous lesions to cancer and if the endpoint of studies evaluating such an agent was just precancerous lesion appearance or recurrence rate and not actual rate of cancer formation then a very wrong evaluation of its preventive effect would have been reported.
- Modulation of one or few surrogate biomarker endpoints may actually not have any preventive effect on ultimate carcinogenesis due to the mitigating effect of other variables.
- The shorter duration of studies generally seen with surrogate endpoints may not be sufficient to predict actual effect on cancer incidence or mortality.
- The preventive effect of an intervention on surrogate endpoints may not transpire into actual quality-of-life improvement.
- Adverse effects from long-term use of an agent that had shown preventive effect in short-term surrogate endpoint studies may not be observed in such studies.
- Evidence of benefit established in surrogate endpoint studies in animal models may not translate into similar benefit in actual human studies.

## Cancer prevention programs and how to evaluate preventive programs

Prevention is defined as the reduction of cancer mortality via reduction in the incidence of cancer.

Prevention may be achieved by:

- lifestyle or dietary modifications that reduce exposure to cancer-causing factors
- identifying those individuals with genetic predispositions to cancer formation and screening them for precancerous lesions and early detection of cancers
- chemoprevention with natural or synthetic substances to reduce the risk of developing cancer or to reduce the chance that cancer will recur.

### What are preventive programs?

With the increasing understanding of the models of carcinogenesis and availability of modifiable risk factors, the paradigm shift in approach to cancer management is increasingly from cancer treatment to cancer prevention.

Large programs are being put forward to promote behavioral and non-behavioral changes in the susceptible population to reduce the risk of cancer development or progression. There are two types of cancer prevention clinical trials:

- *Action studies* that focus on individual actions that can prevent cancer, such as quitting smoking
- *Agent studies* that focus on medicines, vitamins, minerals, or food supplements (or a combination of them) that can prevent cancer.

### How does a cancer prevention study evolve into a preventive program?

The basis of all preventive programs is the stepwise translation of basic cellular and molecular biology research through:

- hypothesis development based on risk identification
- methodology development in animal models and in-vitro studies
- controlled intervention trials in very high-risk or affected populations
- trials in populations with moderate to high risk of cancer development
- development of implementation strategies and risk–benefit surveillance
- large-scale national or regional programs for the general population.

### Major steps in developing preventive strategies

- The identification of exposures that may increase cancer risk.
- Utilize national databases to identify populations at risk: e.g. in the United States availability of the Surveillance End Results Registry (SEER), Behavioral Risk Factor Surveillance Survey (BRFSS), National Health Interview Survey (NHIS), National Health and Nutrition Examination Survey (NHANES), National Youth Tobacco Survey (NYTS), and Youth Risk Behavior Surveillance System (YRBSS).
- Identify genetic predispositions to cancers and detection of precursor lesions or early detection of cancer by screening.
- Development of animal models and extrapolation to human cancer prevention.
- Chemoprevention trials in human populations.
- Behavioral interventions trials in prevention by enhancement of behaviors that may reduce cancer risk.
- Creating and maintaining cancer registries and biorepositories of cancer tissues for future research.
- Establishing effective and tailored communication about cancer risks and recommended risk reduction strategies in appropriate and vulnerable populations.

## Types of studies used in assessing cancer risks and prevention strategies

### *Observational studies*

- *Cross-sectional studies*: a population is studied at a certain point in time to assess which individuals have been exposed to a risk factor and which individuals have developed cancer, and to see if there is a link.
- *Cohort studies*: a cohort of people with similar exposure to a risk factor is followed up prospectively to assess the risk of cancer development.
- *Case-control studies*: suitably matched cases with a cancer are compared with those without a cancer to retrospectively compare exposure to a risk factor.

### *Interventional studies*

- *Descriptive studies*: descriptive, uncontrolled studies, based on the experience of individual experts (increasing chance of observational bias) or coming from work based on referral centers (thus having a strong selection bias), and non-population-based registries may yield some information on prevention, but unwarranted inferences are often drawn from such studies because of the absence of an appropriate control group.
- *Randomized controlled trials*: randomized controlled trials are designed to correct for or eliminate selection and other biases when prospectively testing a primary prevention strategy to determine its effect on outcome. Randomized controlled studies may assess the effects of a single agent compared to placebo or the effect of a combination of agents. In studies assessing multiple agents, the various arms of the trial may be of:
  - *Parallel design*: different arms are treated with a single agent and run in parallel.
  - *Cross-over design*: the populations in the arms are swapped over from one agent to another.
  - *Factorial design*: the different arms are treated with the various agents, not only independently but also in combination with each other.
  - *Adaptive phase design*: the different arms being treated with separate agents are periodically assessed at intervals for obvious efficacy or failure and, depending on outcomes, one or more arms may be stopped and the populations in those arms are then redistributed into the remaining arms of the trial.
  - *Case-cohort studies*: cohort studies provide indirect evidence for the effectiveness of primary prevention strategies. Such studies may suggest, but do not prove, a (mortality) reduction effect. The potential for selection and observational bias to invalidate inferences from cohort studies makes these studies weaker than randomized controlled studies as an evidence base for preventive strategies.

## Screening for cancer as a cancer prevention strategy

Screening is a means of detecting disease early in asymptomatic people. Positive results of examinations, tests, or procedures used in screening are usually not diagnostic but identify persons at increased risk for the presence of cancer who warrant further evaluation.

Estimates of the premature deaths that could have been avoided through screening vary from 3% to 35%.

Beyond the potential for avoiding death, screening may reduce cancer morbidity, since treatment for earlier-stage cancers is often less aggressive than that for more advanced-stage cancers.

The performance indicators and risks of screening tests are shown in Table 3.2.

## Interpreting changes in relative survival over time from prevention programs

Increases in survival over time are difficult to interpret.

- They may also result from lead-time bias and overdiagnosis, both of which occur commonly with screening.
- Reductions in incidence rates for late-stage tumors represent a better measure of progress due to screening than 5-year survival trends, although such evidence is less compelling than reductions in mortality.
- Disease-specific mortality has been the most widely accepted endpoint in randomized clinical trials of cancer screening; however, the validity of this endpoint rests on the fundamental assumptions that the cause of death can be accurately determined and that the screening and subsequent treatments have negligible effects on other causes of death.
- In contrast to disease-specific mortality, all-cause mortality depends only on an accurate ascertainment of deaths and when they occur and therefore is not affected by misclassification in cause of death. One major limitation of the all-cause mortality endpoint, however, is that it is unlikely to reveal a statistically significant effect of cancer prevention because this intervention is usually targeted to a disease that causes only a small proportion of all deaths.
- Cancer risk reduction may occur shortly after the reduction or elimination of exposure or after a considerable time period. This raises the question of temporal trend in efficacy assessment of preventive programs.

## Conclusion

The paradigm shift from cancer treatment to cancer prevention is the way forward to reducing cancer-related mortality and morbidity. Identifying risk

**Table 3.2** Indicators of performance and drawbacks of screening tests**Indicators of performance of screening tests**

- **Sensitivity.** The chance that a person with cancer has a positive test
- **Specificity.** The chance a person without cancer has a negative test
- **Positive predictive value.** The chance that a person with a positive test has cancer
- **Negative predictive value.** The chance that a person with a negative test does not have cancer
- **Number needed to screen.** The number of people that must participate in a screening program for 1 death to be prevented over a defined time interval
- **Average life-years saved.** The number of years that an intervention saves, on average, for an individual who receives the intervention. This reflects mortality reduction as well as life extension (or avoidance of premature deaths)

**Major drawbacks of screening tests**

- They may have small risks of serious complications that may be immediate (e.g. perforation with colonoscopy) or delayed (e.g. potential carcinogenesis from radiation)
- A *false-positive* test result, which may lead to anxiety and unnecessary invasive diagnostic procedures with greater risks
- *Overdiagnosis* is the diagnosis of a condition that would not have become clinically significant had it not been detected by screening
- A *false-negative* test may falsely reassure an individual with subsequent clinical signs or symptoms of cancer and thereby actually delay diagnosis and effective treatment

factors for carcinogenesis in general and formulating accurate methods of individual risk assessment are paramount to the development of prevention strategies. Judicious use of surrogate endpoints can facilitate research in cancer risk identification, developing prevention interventions, and screening for early detection of cancer in a suitable population.

The field of cancer prevention is developing rapidly and several prevention programs in common cancer modalities have already been developed and rolled out into the population. These will be discussed in detail in the relevant sections of the book.

## Further reading

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# Obesity and exercising

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## Introduction

The International Agency for Research on Cancer (IARC), after reviewing the epidemiological studies spanning over 30 years, concluded that obesity has a causal link with various forms of cancer (Table 4.1).

It is estimated that obesity-related cancer death kills one in seven men and one in five women in the United States. Similarly, in the European Union, obesity accounts for 4% of cancers in men and 7% of cancers in women. The association between obesity and various cancers is complex. Whereas obesity increases risk of most cancers, size is associated with decreased risk of premenopausal breast and lung cancer.

## Cancer showing a definite association with obesity

### Obesity and breast cancer

In Europe, breast cancer still kills nearly one million women every year despite a recent decrease in mortality trends. The evidence that obesity contributes towards the development of breast cancer in postmenopausal women is overwhelming and indisputable. The attributable risk estimates due to obesity (6–19%) are comparable to those due to a positive family history.

- A one-point gain in body mass index is estimated to increase the risk of postmenopausal breast cancer by 3%.
- Every 5 kg increase in weight increases the relative risk of developing breast cancer in postmenopausal women by 1.08.
- In the United States, obesity accounts for the development of 20% of all postmenopausal breast cancers and 50% of postmenopausal breast cancer deaths.

**Table 4.1** Obesity and various types of cancer

Cancer type	Incidence		Mortality	
	Strength of evidence	Conclusion	Strength of evidence	Conclusion
Breast RR 1.5	Consistent, independent and robust	Increased postmenopausal breast cancer	Modest	Increased recurrence rate
Endometrial RR 3.5	Consistent, independent and robust	Increased risk of cancer throughout life	Inconsistent	Decreased survival Remains to be established
Colorectal RR 2.0 men and 1.5 women	Consistent, independent and robust	Increased risk in men and women on HRT	Inconsistent	Decreased survival Remains to be confirmed
Renal cell RR 2.5	Consistent, independent and robust	Increased incidence in men and women	Inconsistent	Decreased survival Remains to be confirmed
Esophageal RR 3.0	Consistent and robust	Increased incidence in men and women	Modest	Decreased survival
Prostate	Complex and controversial	Remains to be established	Modest	Decreased survival
Pancreatic RR 1.7	Complex and consolidating	Increased incidence in men and women	Inconsistent	Remains to be confirmed

(continued)

*Table 4.1 (continued)*

Cancer type	Strength of evidence		Mortality	
	Incidence	Conclusion	Strength of evidence	Conclusion
Gastric cardia RR 2.0	Complex and consolidating	Increased incidence in men and women	Inconsistent	Remains to be confirmed
Liver RR 1.5–4.0	Complex and consolidating	Increased incidence in men and women	Inconsistent	Remains to be confirmed
Gallbladder RR 2.0	Limited data	Increased incidence in men and women	Limited data	Increased incidence
Lymphoma	Limited data	Increased incidence	Limited data	Increased incidence
Cervix				
Brain				
Connective tissue				

RR, risk ratio; HRT, hormone replacement therapy.

## **Obesity and endometrial cancer**

Case control and cohort studies have shown a consistent and convincing association between cancer of the uterine corpus and obesity. A study of more than 100 000 women at a median follow-up of 4.6 years compared women with a stable weight between age 18 and baseline and those with a weight gain. The risk ratio for endometrial cancer in women with a weight gain of 20 kg or more among never users of menopausal hormone therapy was 5.00 (95% confidence interval [CI] 3.01–9.52). It was concluded that both current adiposity and adult weight gain are associated with substantial increases in the risk of endometrial cancer.

## **Obesity and colorectal cancer**

The incidence of colorectal cancer increases with obesity in men and women. This increased association is consistent in both case control and cohort studies, confirming a higher risk increase in men than women. There has been speculation that altered waist–hip ratio may be the reason for the gender difference in the occurrence of colorectal cancer, but large-scale data have not supported this hypothesis.

## **Obesity and renal cell carcinoma**

Obesity, by an as-yet unexplained mechanism, increases the risk of renal cell carcinoma, especially in women. These data need to be verified in further large-scale studies.

## **Obesity and esophageal adenocarcinoma**

Obesity is considered to increase the risk of esophageal adenocarcinoma indirectly by increasing the prevalence of gastroesophageal reflux disease and its consequent Barrett's esophagus, which is the metaplastic precursor of adenocarcinoma. However, other studies have shown the increased incidence of esophageal carcinoma to be independent of the reflux disease.

## **Cancer showing a modest association with obesity**

Obesity increases the risk of developing pancreatic cancer by two-fold.

The incidence of hepatocellular carcinoma of the liver rises with obesity, but the magnitude of this risk has not been reliably established yet.

Obesity also increases the risk of gastric cardia carcinoma, most likely due to Barrett's metaplasia.

Limited data suggest that obesity may be associated with increased risk of ovarian cancer and cervical cancer as well as connective tissue cancers and lymphoma. Further epidemiological studies are needed to fully define these relationships.

## Cancers showing a negative association with obesity

Several studies have demonstrated an inverse relationship between lung cancer and obesity. This negative effect is explained by the confounding effect of smoking, which is the primary cause of lung cancer and is associated with a low body mass index.

The incidence of premenopausal breast cancer is shown to be lower in obese women. It is suspected that anovulatory cycles in premenopausal obese women may lower their lifetime exposure to estrogen, decreasing the risk of breast cancer.

## Pathophysiology of obesity and cancer

The pathophysiology by which cancer is associated with obesity is multi-faceted and complex and hence poorly understood at present. The two main mechanisms postulated to explain these associations are:

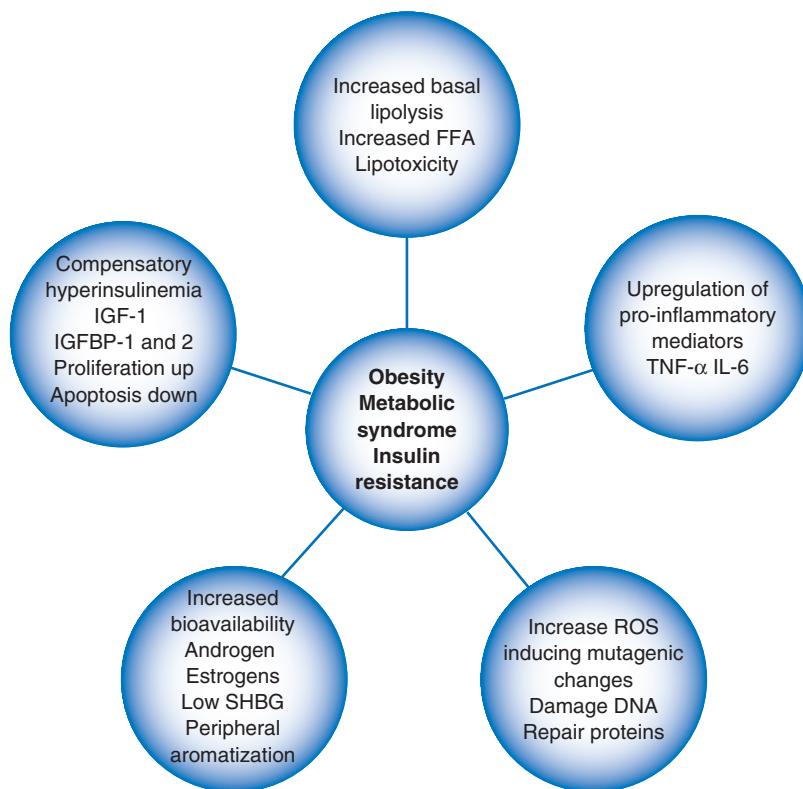
- biological changes leading to endocrine changes such as insulin resistance
- obesity-related metabolic syndrome (Figure 4.1).

## Can anything be done about it?

### Dietary factors

Since dietary factors are estimated to account for approximately 40% of all cancers in Western countries (estimated by the World Health Organization), and even higher, up to 60%, of the cancers of women in the countries with a high incidence of breast cancer, it is suggested that dietary strategies involving specific functional foods containing estrogen action modulators (steroid action modulators, e.g. phytoestrogens) can offer a feasible tool for prevention of cancers mediated by endocrine mechanisms.

Along with five cohort studies, there are two ongoing randomized trials – the Women's Intervention Nutrition Study (WINS) and the Women's Healthy Eating and Living Study – of breast cancer survivors that have diet as a main



**Figure 4.1** Proposed mechanisms of the association between obesity and cancer.  
 FFA, free fatty acid; IGF-1, insulin-like growth factor-1; IGFBP, insulin-like growth factor binding protein; SHBG, sex hormone-binding globulin; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; IL-6, interleukin 6; ROS, reactive oxygen species.

focus. These studies are aimed at examining whether differences in diet may result in differences in recurrence and mortality rates. They promise to provide novel objective information regarding diet and breast cancer prognosis and serve as models for studies of diet and prognosis of other cancers.

### Physical activity

Optimal physical activity is shown to be relevant in primary and secondary prevention of breast and colorectal cancers.

The Nurse's Health Study and Women Healthy Eating and Living Study have both shown a 50% relative risk reduction in physically active patients who were treated for breast or colorectal cancer in the past. This beneficial effect of physical activity was dose-dependent and seen in all stages of cancer. Patients with steroid receptor-positive tumors were most likely to benefit.

There are other cohort studies and randomized trials looking at the prognostic effect of physical activity. Their data should become available in the next 5 years.

## Conclusion

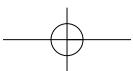
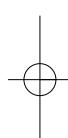
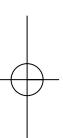
A consistent, independent, and positive association has been found between obesity and development of breast cancer risk in postmenopausal women, colorectal cancer, and renal cell carcinoma. There is also a preponderance of the literature linking obesity to poor prognosis of cancer. This raises fears that current epidemic of increasing obesity will not only add to the incidence of cancer but will also impact negatively on the efficiency of the national screening programs aimed at decreasing cancer mortality by early detection.

As obesity can be modified throughout life, it is suggested that increasing physical activity and maintaining a healthy body weight are appealing interventions for cancer prevention and prognosis.

Therefore, public health policies, planning, and health education campaigns are urgently required to curb the twin epidemics of obesity and cancer. These ambitious goals demand positive choices in diet and lifestyle at the level of the individual and a strong political will to provide a social climate where such lifestyle choices can be turned into reality.

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# Hormones

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## Introduction

Sex hormones are thought to be involved in the genesis of several frequently occurring malignant tumors in humans: breast and endometrial cancer in women and prostate cancer in men.

Initially, such a relation was based on observations – by Beatson in 1896 for breast cancer and by Huggins in 1941 for prostate cancer – that existing cancers regressed after removal of the gonads.

The additional basic pathophysiological argument was that hormones and related growth factors, which stimulate the growth of the epithelial cells in these tissues and have mitogenic properties, can increase the cancer risk:

- Without previous hormonal stimulation of these organs, cancer does not occur as demonstrated by the absence of prostate cancer in eunuchs.
- Sex hormones are required for the growth and maintenance of the hormone-sensitive organs. Their direct contribution in malignant transformation is debatable. There is evidence that hormones do not cause malignant degeneration of tissues but that their role in the process is more in line with stimulation of the growth of (pre)-malignant lesions.

## Breast cancer

### Breast cancer epidemiology in relation to hormones

Age-specific incidence rates for breast cancer show very large international variations: women living in Western countries have a much higher risk than women from non-Western societies. The incidence of breast cancer is rising, especially in countries where it used to be low, probably as a result of economic prosperity and changes in lifestyle.

Epidemiology has identified a number of reproduction-related events as risk factors for breast cancer.

- The increased risk of women with an early age at menarche, late first birth, low parity, and late menopause can be interpreted as related to exposure to sex hormones, in particular to estrogens.
- The lower risk for breast cancer in women with surgically induced menopause.
- Furthermore, high levels of endogenous estrogens (and androgens) and the administration of exogenous estrogens to postmenopausal women are correlated with increases in risk for breast cancer. Current thinking is that the use of hormone replacement therapy (HRT) leads to a slight increase in breast cancer, but that the majority of these tumors are estrogen receptor (ER)-positive and react favorably to therapy. The age of women at the start of HRT may be an additional factor, as HRT in women of (on average) 65 years of age, with estrogens alone did not show an increase in breast cancer incidence but HRT with estrogens plus progestin resulted in a higher incidence of cancers.

Altogether, these hormonal factors can explain only part of the geographical differences in incidence.

In addition to sex hormones, height and weight play a significant role in the marked international variation in incidence. In particular, the differences in risk related to height point to factors in the prepubertal and adolescent period of life, to factors playing a role in the early developmental phase of the breast, around its proliferation.

Studies in women after migration from non-Western to Western countries have shown that the geographical variation in breast cancer risk is almost exclusively due to non-genetic factors:

- Second and third generations of migrants into the United States show increases in incidence rates to levels comparable to those in women in Western countries. At least part of this increased risk must be attributed to changes in lifestyle before and during adolescence, as related to Western-type nutrition, lack of exercise, and Western-type women's emancipation with a late first pregnancy.
- Epidemiological findings by MacMahon on the effects of age at first full-term pregnancy, supported by the biological mechanism suggested by Russo, demonstrate the importance of an early pregnancy that induces the full differentiation of the human breast. Extension of the period between proliferation and this terminal differentiation of breast epithelium leads to elongation of the vulnerable period of the breast. This leads to the concept that risk of breast cancer is related to extension of the time period between proliferation of breast epithelium during early adulthood and the full

differentiation induced by pregnancy. Since it is unlikely that emancipated women in affluent societies will return to the original lifestyle of getting pregnant as soon as it is biologically possible, a novel way of protection has to be considered. One such way could be the induction of breast differentiation by (hormonal?) manipulation. However, at this moment, it is impossible to give clear guidelines on how this differentiation could be achieved, since knowledge is lacking.

### Breast cancer prevention

The hormone dependency of breast cancer in a large percentage of patients has led to the concept of preventive measures based on antagonising the action of estrogens and/or on inhibition of the synthesis of estrogens.

- Understanding of the mechanism of action of estrogen has stimulated the design of antiestrogenic agents such as tamoxifen and more recently of selective estrogen receptor modulators (SERMs), with raloxifene as the best studied example. Several large clinical trials have been conducted that show substantial reductions in the incidence of ER-positive cases of breast cancer in women at high risk by the prophylactic use of either of the mentioned antiestrogenic agents. In addition, clinical trials have also shown that estrogen deprivation by the use of aromatase inhibitors results in a reduction of the incidence of breast cancer. At this moment, the main issues under discussion are the criteria to select women for use of chemoprevention and the number of side effects induced by the different pharmacological agents in relation to the number of women that benefit from their use.
- There is, as yet, no experience in women of the possibility of inducing full differentiation of the breast with pregnancy-associated hormones. Animal experiments favor the use of the placental hormone human chorionic gonadotropin (hCG). However, probably, the issue is more complicated because only a full-term pregnancy gives protection against breast cancer, spontaneous or induced abortions do not affect incidence, whereas the very high levels of hCG exist mainly during the first months of pregnancy.
- So far, all interventions based on changes in nutritional habits have failed to demonstrate changes in breast cancer risk. It may be that, in the future, research will enable the identification of subgroups of the population that are especially vulnerable to deficiencies or that will benefit from specific dietary interventions.

### Endometrial cancer

Endometrial cancer is the commonest gynecological cancer mostly affecting women at postmenopausal age. Incidence rates vary worldwide and are highest in Caucasian women in Western populations.

Some risk factors are related to reproduction, such as early age at menarche, late age at menopause, and nulliparity, whereas other risk factors are more directly estrogen-related, such as obesity and polycystic ovary syndrome.

- Women with a body mass index (BMI) of >30 have a relative risk of 3 compared with those with a BMI of <25.
- A weight gain of >20 kg during adulthood is associated with a substantial increase in risk.
- Diabetes and hypertension increase the risk, whereas smoking, a low-fat diet, and physical exercise decrease the risk, possibly by their more indirect effects on estrogen levels.
- The risk may be associated with functionally relevant genotypes that are involved in the metabolism of steroid hormones.

It has been hypothesized that obesity is mostly related to a subtype of this tumor (type I) described as estrogen-dependent, constituting about 80% of tumors.

Recent evidence suggests that type II tumors, less-differentiated tumors with more DNA damage, represent a subgroup of cancers that show a higher local, intratumoral activity of aromatase, the enzyme responsible for the synthesis of estrogens. Type II patients are usually not obese.

Long-term use of unopposed estrogen replacement therapy after menopause clearly results in an elevated risk, whereas combined HRT of estrogens plus a progestin does not. Progestins protect the endometrium and in order to minimize the potential negative effects on the breast, the administration of progestins by using the vaginal or direct endometrial route is becoming popular. Intrauterine devices that are capable of delivering progestins for several years look promising as a preventive measure.

## Prostate cancer

### Prostate cancer epidemiology in relation to hormones

The epidemiology of prostate cancer strongly suggests that environmental factors, particularly diet and nutrition, but also lifestyle and genetic factors, are major determinants of risk. The incidence and the rate of death increase exponentially with age. Inherited prostate cancer susceptibility genes discovered thus far encode participants in host responses to inflammation, suggesting that infection and inflammation contribute to the early development of the tumor.

There are large geographical differences in the age-adjusted death rates from prostate cancer. In Japan, a country with a very low death rate from prostate cancer, the prevalence of prostate cancer detected at autopsy is almost 3000 times that of lethal prostate cancer, whereas the prevalence at autopsy in the United States is about 500 times that of death from prostate cancer. This illustrates the fact that the growth rate of tumors is not identical in these countries. There is a lack of ability to accurately differentiate clinically important prostate cancer from latent disease; no reliable biomarker exists that can act as a surrogate endpoint.

Plasma levels of testosterone and other androgens are only slightly different between the men living in both countries, and thus the relation between the androgen axis and prostate cancer development is debatable.

Also, clinical data on effects of exogenous androgen substitution in regard to prostate safety are non-conclusive.

Still, growth of the prostate is androgen-dependent but there may be discrepancies between androgen levels measured in blood and the levels of dihydrotestosterone (DHT), the major tissue androgen in the prostate.

### **Prostate cancer prevention**

Clinical trials aiming at chemoprevention of prostate cancer have been conducted with finasteride, an inhibitor of the enzyme 5 $\alpha$ -reductase, which is responsible for the conversion of androgens to DHT. It was concluded that finasteride prevents or delays the appearance of prostate cancer in men with a prostate-specific antigen (PSA) level of <3 ng/ml. However, the possible benefit and a reduced risk of urinary problems must be weighed against sexual side effects and the increased risk of high-grade tumors.

### **Conclusion**

Prevention of tumors by hormonal manipulations remains an interesting topic. In the breast cancer area, some positive results in high-risk populations have been obtained by application of drugs that interfere with the biosynthesis or the mechanism of action of estrogens.

For endometrial and prostate cancers, similar positive experiences are lacking.

Less specific hormonal manipulations and dietary interventions have not yet proven to be of value, and they remain subjects of research.

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# Environment-related factors

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## Introduction

Environmental exposures in cancer risk include natural and man-made agents present in air, water, soil, and food. Although the burden of cancer from these environmental exposures is relatively modest in comparison to lifestyle factors, there is a strong public perception of risk of cancer from environmental pollutants.

## Outdoor air pollution

Multiple components of air pollution are suspected to have deleterious effects on health, in particular inhalation of particulate matter (PM). In 2000, the mean  $PM_{10}$  concentration in the European region was  $24 \mu\text{g}/\text{m}^3$ .

Analyses of the risks of lung cancer from pollution have estimated relative risks (RRs) of 1.3–1.5 for residency in a high-pollution area in comparison to a low-pollution area. One study reported an RR for lung cancer of 1.14 (95% confidence interval [CI] 1.04–1.23) for exposure to fine particulate matter ( $PM_{2.5}$ ); other studies have additionally found increased risks.

The population attributable risk for lung cancer from air pollution in Europe is estimated at 5–7%. Other components of air pollution include nitrogen dioxide, polycyclic aromatic hydrocarbons (PAHs), formaldehyde, 1,3-butadiene, and benzene, several of which are classified by the International Agency for Research on Cancer (IARC) as class 1 human carcinogens based on risk in occupational settings. Although there is evidence of genotoxic effects in general population samples, data are limited linking exposure to these agents in ambient air to cancer incidence.

## Residential exposure to radon decay products

Radon is an established cause of lung cancer. It occurs through the decay of uranium-238 present in soil, and the gas is ubiquitous in the environment.

Air concentrations in residential settings are considerably lower than those incurred in occupational environments, but the duration of exposure may be considerably longer, and the gas may build up in areas of poor ventilation.

Pooled analyses of residential cohorts have estimated an 8–11% increased risk of lung cancer at radon exposure above 100 Bq/m<sup>3</sup>. Average residential radon concentrations in Europe are 59 Bq/m<sup>3</sup>, with wide variation according to uranium content in soil, ranging from 7 Bq/m<sup>3</sup> in Cyprus to 140 Bq/m<sup>3</sup> in the Czech Republic. It is estimated that radon is responsible for 9% of lung cancers in Europe.

## Second-hand smoke

Second-hand smoke consists of a number of carcinogenic compounds. Meta-analysis and pooled analyses estimate that exposure to a spouse's smoke increases the lung cancer risk by 10–20%, with similar increases in lung cancer risk seen with passive smoke in the workplace. Evidence for increased risks in childhood cancers from exposure to parental smoking has been mixed, with leukemia and brain cancers most often studied. At present, there is no strong evidence to support an association.

## Other sources of indoor air pollution

The other major sources of indoor air pollution are combustion by-products from heating and cooking, including smoke from burning coal, biomass, or cooking oil vapor. Solid fuel burning is a strong risk factor for lung cancer among women in China. There have been few studies of these exposures within European populations, and differences are likely to exist between Chinese and Europeans in the kinds of fuel or cooking oils, type of stove or central heating system, and in home ventilation. One study in Eastern Europe reported a 24% increased odds of lung cancer (95% CI 1.05–1.47) for use of solid fuels.

## Electromagnetic fields

Electromagnetic fields (EMFs) may be divided into extremely low frequency (ELF, 1 Hz to 1 kHz), radiofrequency (1 MHz to 1 GHz), and microwaves (1–300 GHz). These exposures come from power lines, industrial and medical sources, household electric appliances, radio and television broadcasts, and mobile telephones.

ELF fields have been classified as a possible human carcinogen by the IARC due to a potential association with childhood leukemia at exposures at or above 0.3–0.4 µT. In a pooled analysis, the RR of childhood leukemia for exposures above 0.4 µT was 1.9 (95% CI 1.1–3.4). However, only 1% of European children are exposed to EMF fields at that level, with exposure levels in the general population averaging 0.01–0.2 µT.

A number of recent studies have examined a possible association between mobile phone use and brain tumors, but the weight of the evidence does not support an association.

## Residential asbestos exposure

Exposure to asbestos may occur in the household, from air pollution in neighborhoods adjacent to mines and other sources. Exposures also occur during installation, removal, repair, or decomposition of asbestos products. Residential exposure levels are generally much lower and briefer in duration than those in occupational settings.

Asbestos is associated with the development of mesothelioma and lung cancer. A meta-analysis of studies of household exposures, most of which had high exposure levels, estimated the RR of mesothelioma to be 8.1 (95% CI 5.3–12) and the RR of lung cancer to be 1.1 (95% CI 0.9–1.5).

## Persistent organochlorines

Organochlorine compounds include polychlorinated biphenyls (PCBs), pesticides such as DDT, and chlorinated dioxins and furans. These compounds have been of particular interest due to their persistence in the environment and concentration up the food chain, and evidence of their potential endocrine-disrupting properties. Nonetheless, reviews of these compounds have not found persuasive evidence to link them with cancer.

Tetrachlorodibenzo-*p*-dioxin was classified by the IARC as carcinogenic in animal studies and, based on a shared mechanism in cancer development, was also classified as carcinogenic in humans. However, this classification did not identify an increased risk for a specific cancer site. Among groups highly exposed, increases in cancer mortality for lung cancer, non-Hodgkin's lymphoma, multiple myeloma, and digestive system cancers were sporadically seen, but dose-response effects were lacking. This suggests limited potential for increased cancer risks, particularly among groups exposed to lower levels of dioxin, as occurs in the general environment.

## Other pesticides

Several pesticides have been classified as carcinogenic in experimental animals by the IARC. Nevertheless, of the hundreds of commercial pesticides, none has been classified as human carcinogens other than arsenic, which is a component in some pesticide formulations. Potential associations between pesticides and cancer have been difficult to evaluate epidemiologically given that few records exist detailing exposures, most commercial pesticides include multiple agents, and farmers use varying pesticides over time.

In studies of occupational cohorts, which are likely to have the greatest specificity with regards to duration and type of pesticide exposures, consistent associations have generally not been seen with pesticide exposures and cancer. Phenoxy herbicides have been linked to prostate and hematolymphopoietic malignancies, although these findings are limited by a lack of specificity regarding the classes of chemicals.

## Inorganic arsenic in drinking water

Arsenic contamination in groundwater above the World Health Organization (WHO) recommended maximum standard of 10 µg/L is seen in several parts of Europe. In these areas, concentrations are generally low to intermediate (10–200 µg/L), although some counties in eastern Hungary have measured levels above 500 µg/L.

Inorganic arsenic in drinking water is an established cause of skin, lung, and bladder cancers, and is thought to have a synergistic effect with tobacco.

However, most research has occurred in groups exposed to very high concentrations of arsenic, and estimates of risk are sparse for persons exposed only sporadically or exposed to low or intermediate concentrations, as is typical in Europe.

Several studies have found elevated risks for bladder cancer among individuals exposed to intermediate levels of arsenic (>10 µg/L).

## Drinking water disinfection by-products

Chlorine, the most common water disinfection agent in use worldwide, reacts with organic materials in water to produce a number of by-products, including trihalomethanes (THMs, including chloroform, bromodichloromethane, dibromochloromethane, and bromoform).

The concentration of by-products depends on season, temperature, geographic area, amount of organic matter in the water, and water storage methods. A pooled analysis of six epidemiological studies linked THM exposure above 1 µg/L to bladder cancer (odds ratio [OR] = 1.18, 95% CI 1.06–1.32) in an analysis that accounted for smoking among subjects; however, the heterogeneity of results across groups suggests that these findings should be interpreted with caution.

## Susceptibility to environmental pollutants

Cancer susceptibility is modified by variation in genes associated with xenobiotic metabolism, DNA repair, and tumor suppression. In particular, polymorphisms for genes which encode the metabolic activation or detoxification of environmental agents are probably important factors in cancer risk.

For example, the glutathione *S*-transferase gene is involved in the metabolism of a number of chemicals such as pesticides and solvents. A recent pooled analysis identified a GSTT1 deletion as potentially protective in asbestos exposure. Further research in identifying polymorphisms active in chemical biotransformation may inform interventions to reduce cancer risk.

## Conclusion

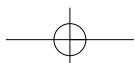
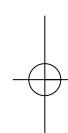
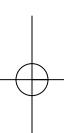
Epidemiological research has pointed to increases in cancer from certain environmental pollutants, in particular radon, indoor and outdoor air pollution, and the development of lung cancer. The potential effects from several other pollutants, such as pesticides, are difficult to quantify given the complexity of exposure assessment and the rarity of the cancers suspected to be associated. While increased risks are plausible for some pollutants, outside of areas of industrial contamination exposure is likely to be sporadic or at low concentrations, making quantification of risk difficult. However, given the ubiquity of several classes of pollutants, even modest relative risks may represent a considerable disease burden.

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# Viral agents: hepatitis B and hepatocellular carcinoma

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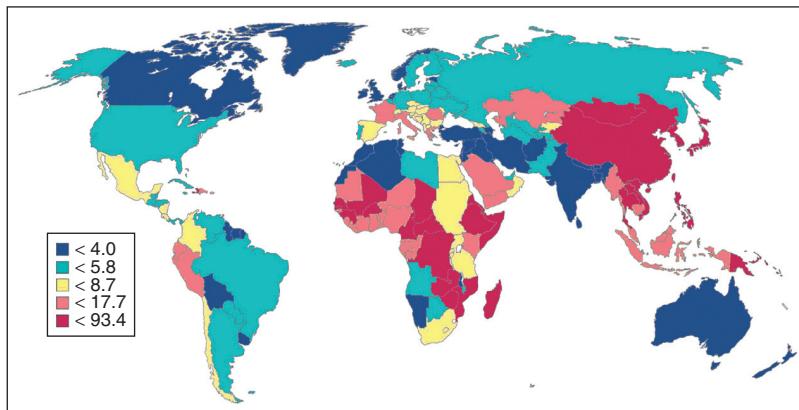
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## Introduction

Hepatocellular carcinoma (HCC) is one of the most common solid tumors worldwide and one of the most deadly diseases.

Although there are many patients affected by HCC scattered throughout the world (Figure 7.1), in some regions such as sub-Saharan Africa and Eastern Asia, a very high incidence of HCC is seen. In China alone, HCC accounts for more than 50% of the world's cases (age-standardized incidence rate: men, 35.2/100 000; women, 13.3/100 000). Other high-rate ( $> 20/100 000$ ) areas include Senegal (men, 28.47/100 000; women, 12.2/100 000), Gambia (men, 39.67/100 000; women, 14.6/100 000), and South Korea (men, 48.8/100 000; women, 11.6/100 000). In contrast, North and South America, Northern Europe, and Oceania are low-rate ( $< 5.0/100 000$ ) areas for liver cancer.

Among risk factors causing HCC (Table 7.1), hepatitis B virus (HBV) infection is the most common underlying cause of HCC. From data of the World Health Organization (WHO) in 2002, more than 2000 million people have been infected with HBV and approximately 350 million are chronic carriers. The annual incidence of HCC is only 0.1% in asymptomatic HBsAg (hepatitis



**Figure 7.1** Regional variation in the mortality rates of hepatocellular carcinoma categorized by age-adjusted mortality rates. The rates are reported per 100 000 persons. (Reprinted with permission from Paekin DM. Cancer incidence in five continents. IARC scientific publications volume VIII (No. 155). 2002: Lyon, IARC Press.)

B surface antigen) individuals, 1% in patients with chronic hepatitis B, but increases to 3–10% in patients with liver cirrhosis.

The mode of transmission of HBV differs throughout the world. Most common transmission is from mother to newborn (vertical transmission), particularly in endemic areas, and up to 90% of infected persons show a chronic course. In low-incidence areas of HCC, HBV transmission is mainly caused by sexual intercourse, intravenous drug abuse, or needlestick injuries in healthcare workers (horizontal transmission).

## Pathophysiology of infection and carcinogenesis

HBV is an enveloped virus and contains a circular partially double-stranded DNA genome only 3.2 kb in length that belongs to a group of hepatotropic DNA viruses (hepatnaviruses). When entering the body, HBV will replicate itself by using DNA polymerase-reverse transcriptase enzyme, encoded by the polymerase gene. Virus-specific T-cell responses activate other inflammatory cells and cytokines such as interferon and tumor necrosis factor are released, triggering several pathways that lead to inhibition of viral replication and destruction of infected cells. Inadequacy of HBV-specific T-cell

**Table 7.1** Risk factors for hepatocellular carcinoma

Infestation
Chronic hepatitis C
Chronic hepatitis B
Chronic delta hepatitis
Metabolic diseases
Diabetes mellitus
Hereditary hemochromatosis
$\alpha_1$ -antitrypsin deficiency
Porphyria cutanea tarda
Hereditary tyrosinemia
Toxins
Alcohol
Aflatoxin B <sub>1</sub>
Hormones
Anabolic steroids
Estrogens
Non-alcoholic steatohepatitis
Genetic polymorphisms
Other risk factors
Cirrhosis of any cause
Tobacco smoking
Obesity

response, persistence of the stable form of HBV, and replication of HBV in privileged sites are thought to be the causes of chronic HBV infection. Consequently, inflammatory responses to HBV persistence, namely chronic active hepatitis (CAH), cause hepatocyte necrosis, liver fibrosis, and may lead to liver cirrhosis. HBV-induced CAH and liver cirrhosis are major risk factors in hepatocellular carcinogenesis.

HBV-associated HCC may be induced by direct and indirect effects from integration of the HBV genome:

- Direct effect: HBV integrates its genome into the host chromosome and induces chromosomal deletions at the integration site. In addition, integration causes transpositions of viral sequences, together with nearby host cellular sequences. Thus, viral interference produces chromosomal instability and modification of cellular gene expression and protein encoding. Integrated HBV sequences frequently have a carboxy-terminal deleted X gene, resulting in translation of a truncated HBx protein, a 17-kDa protein, involved in HCC development. Overproduction of HBV envelope proteins (pre-S2/S), caused by truncated pre-S2/S sequence signaling, results in their intracellular accumulation and may predispose the cell to stress, which in turn may lead to the development of HCC.
- Indirect effect: the transcribed HBx protein takes a major role in hepatocarcinogenesis by acting at multiple cellular functions. The consequences of HBx protein transcription are antiapoptosis, induction of angiogenesis and cell cycle progression, and proto-oncogenes, including induction of HBV replication. The overall result of the HBx protein is tumor cell proliferation and metastasis.

## Prevention of hepatitis B infection and hepatocellular carcinoma development

With the strong correlation between HBV infection and development of HCC, prevention of HBV infection is an important factor to decrease the incidence and mortality of HCC. The most effective way to control hepatitis B is to prevent any susceptible person from virus infection, rather than treating those who are already infected.

Effective strategies to prevent HBV infection include:

- avoidance of high-risk behavior
- prevention of exposure to blood and body fluids
- screening of women in late pregnancy for the presence of HBV and prevention of perinatal transmission
- active immunization with hepatitis B vaccine
- passive immunization with hepatitis B immune globulin (HBIG) before or after exposure.

### Hepatitis B vaccination

HBV vaccine, first licensed in the United States in 1981, is now one of the most widely used vaccines in the world and is part of the routine vaccination schedule for many of the world's infants and children. It is the world's first

cancer prevention vaccine and the first vaccine to prevent a sexually transmitted disease. By the mid 1980s, several countries with very high prevalence of chronic HBV infection began the routine immunization of infants at birth. In 1992, the WHO recommended that hepatitis B vaccine should be integrated into national immunization services of all countries with a rate of chronic HBV infection of 8% or higher by 1995, and into the program of all countries by 1997.

In Taiwan, the vaccination program was implemented in July 1984. With the HBV vaccination program from 1989 to 1993, the prevalence of HBsAg in children aged 6 years fell from 10.5% to 1.7%. There was also a decreased rate of the HBsAg carrier among male and female university students, compared with the group born before and after the initiation of the HBV vaccination program, decreasing from 12.8% to 4.8% and 8.1% to 2.7%, respectively.

The average annual incidence of HCC in children 6–14 years, one of the endpoints of this intervention, declined significantly from 0.70 per 100 000 children between 1981 and 1986 to 0.57 between 1986 and 1990, and to 0.36 between 1990 and 1994. The decrease in incidence of HCC was more pronounced in boys than in girls.

It is anticipated that the implementation of global vaccination of all newborns will ultimately lead to a worldwide reduction in incidence of HBV-related HCC, although it may take a few decades for the impact to be observed among adults and in countries with low or intermediate carrier rates.

### **Hepatitis B immune globulin**

HBIG is used to prevent hepatitis B infection in persons without demonstrated immunity to HBV who have been exposed to the virus perinatally (i.e. infants born to HBsAg-positive mothers), by cutaneous or mucosal contact with HBsAg-positive blood or body fluids, or by sexual contact with a person who is positive for HBsAg. The reported efficacy of this approach is 85–95% for the prevention of newborn infections and approximately 75% for the prevention of infection after needlestick or sexual exposure. Recently, HIBG has been used in the prevention of intrauterine HBV infection. This use may be further explored to improve HBV prevention in newborns.

### **Prevention of liver fibrosis and cirrhosis**

Patients with chronic HBV infection have a risk of developing HCC, especially when liver cirrhosis occurs. One hypothesis to slow or stop the development of HCC is to inhibit the process that causes liver fibrosis and cirrhosis.

- HCC was not detected in any of 163 patients from Taiwan with chronic HBV infection who had a spontaneous HBsAg clearance after a mean follow-up of 5 years. However, data from China showed that there are no differences in the risk of development of HCC with longer follow-up about 10 years. These data show that the risk of HCC may substantially be reduced in patients with chronic HBV infection who are able to clear HBsAg.
- When chronic HBV infection occurs, the detection of HBeAg (hepatitis B envelope antigen) indicates the active replication of HBV and acts as a surrogate marker for the presence of HBV DNA. Concomitant with HBeAg positivity in patients who are positive for HBsAg, there is a six-fold increased risk of developing HCC compared with patients who are positive for HBsAg alone.
- Several studies from Japan and Taiwan indicate a higher incidence of HCC with a higher level of HBV DNA, especially when more than 10 000 copies/ml are present.
- Genotype C HBV infection is related to a higher HBV viral load compared with other genotypes (type A, B, or mixed types) and leads to poorer long-term outcomes.

Thus, to prevent HCC development, further studies may have to aim at decreasing the HBV DNA level to an undetectable level or at least a HBeAg seroconversion.

Based on this approach, many reports have focused on the effects of interferon therapy. All of these studies have failed to show an effect of interferon on the incidence of HCC. The negative results may be due to the small number of patients, mostly from non-randomized trials, the low rate of antiviral response, and the short duration of follow-up.

Recently, a randomized controlled trial performed by Lin et al in 466 patients who were HBeAg-positive with an active hepatitis showed that, after a median follow-up of 6.8 years, interferon therapy could significantly reduce HCC development, especially in patients with pre-existing liver cirrhosis. Further trials are needed to confirm the efficacy of interferon in the prevention of HCC.

## Conclusion

The prevention of HBV-related HCC is best accomplished by:

- preventing HBV infection via HBV vaccination and HBIG
- avoidance of high-risk behavior, especially intravenous drug abuse and sexual transmission.

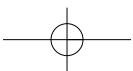
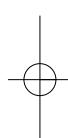
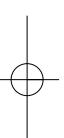
For persons who are already chronically infected, sustained suppression of HBV and reduction of liver damage by antiviral therapy may lead to reduction in incidence of HCC.

Further investigations are needed in terms of longer duration of follow-up and other new drugs that can produce a higher HBV antigen seroconversion rate, an undetectable level of HBV DNA, and more long-term response.

An effort is needed from the world population, including political, economic, and healthcare organizations, to join and eliminate HBV and HCC.

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# Viral agents: human papillomavirus

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## Introduction

In spite of the availability of effective preventive tools, cervical cancer still remains a significant public health problem in Europe. According to the most recent estimates for the first years of the 21st century, approximately 52 000 women on the European continent get cervical cancer and about 27 000 die from the disease each year.

## Risk factors

Persistent infection with one of 13 to 16 oncogenic human papillomavirus (HPV) types is necessary but not sufficient for the development of cervical cancer. Recent data from cohort studies have shown that HPV 16, in particular, has a high potential for malignant transformation of infected cervical cells. The main route of HPV transmission is sexual. Cervical cancer (CC) without HPV is extremely rare. Nevertheless, HPV infection is very common after onset of sexual activity and usually clears without any intervention. The factors that determine progression of HPV infection to high-grade cervical lesions and cancer are poorly understood. Co-factors for cervical cancer are: smoking, oral contraception, high parity, decreased immunity, including human immunodeficiency virus (HIV) infection and infection with *Chlamydia trachomatis*.

## Pathophysiology

Pathogenesis starts with penetration of HPV particles into the basal cells of the cervical epithelium of the transformation zone. Early expressed viral proteins

E1 and E2 assure viral replication at a low copy number. When infected epithelial cells migrate to the surface, further DNA synthesis continues contrary to non-infected cells which differentiate and are programmed to apoptosis. The viral oncogenes E6 and E7 interact with several cell-regulating processes and inactivate the tumor suppressor proteins such as p53 and retinoblastoma (RB) protein. Continued expression of these oncogenes eventually results in chromosomal instability and neoplastic transformation of cell clones. These molecular changes go along with morphological and cytological changes.

Most HPV infections clear as a consequence of a cell-mediated immune (CMI) response. This CMI is triggered by dendritic cells or Langerhans cells in the epithelium which recognize HPV infected cells and stimulate T-helper-1 (Th1) cells, eliciting the production of cytotoxic T lymphocytes. These cytotoxic effector cells attack infected cells, resulting in the resolution of infection and associated intraepithelial lesions.

When the CMI is inadequate, lesions can progress and evolve to invasive cancer.

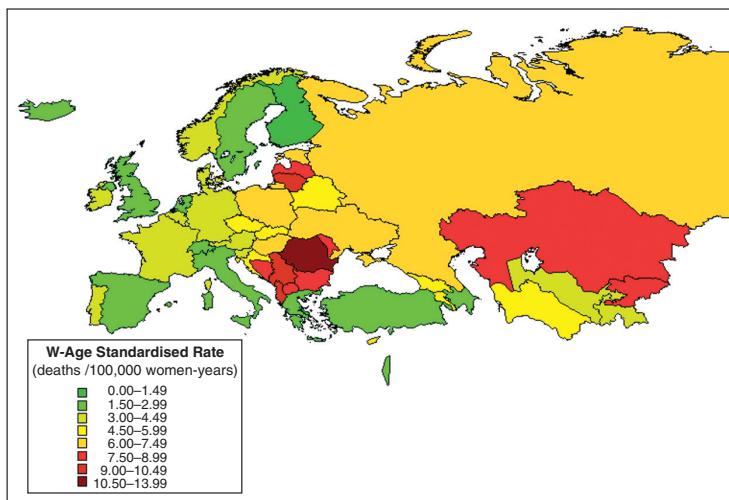
## Epidemiology

HPV infection is very common in young sexually active women. In Europe, the peak prevalence is highest in late teens and young twenties. Thereafter, prevalence drops significantly with aging. Nevertheless, often a secondary peak is observed in women of 50 years or older. The prevalence of HPV infection has increased over the last decades and is probably responsible for the increased risk of cervical cancer observed among women born after the 1940s in most industrialized countries. Substantial differences in incidence and mortality are observed throughout Europe. Mortality from CC is lowest in Finland and highest in Romania, with world-age standardized rates of respectively 1.1 and 13.7 per 100 000 women, for the year 2004. A remarkable west–east gradient in burden of disease can be discerned (see Figure 8.1). Differences in the burden of disease reflect variation in exposure to HPV and coverage and quality of screening.

## Overview of interventions

### Cytological screening

Recently, the International Agency for Research on Cancer (IARC), reconfirmed that the incidence of cervical cancer can be reduced up to 80% by well-organized cytological screening every 3–5 years. However, quality and coverage of cytological screening vary significantly, and successful screening



**Figure 8.1** Geographical distribution of the world age-standardized mortality rate (W-ASMR) from cervical cancer in the countries of Europe and West Asia belonging to the European WHO Region, estimates for 2002/2004, corrected for not otherwise specified uterine cancer (Source: Globocan 2002, IARC, Lyon (France); reproduced from Arbyn *et al* Ann Oncol 2007, with permission).

programs are currently being implemented only in North European countries and parts of Italy.

Liquid-based cytology (LBC) reduces the proportion of inadequate smears, requires less time for microscopic interpretation compared with conventional Pap smears, and allows ancillary molecular testing (for instance an HPV test if atypical cells of undetermined significance). However, LBC is more expensive and not more sensitive or specific for the detection of histologically confirmed high-grade cervical precancerous lesions.

### HPV testing

The recognition of the strong evidence linking HPV infection to CC has prompted the development of several test systems to detect its nucleic acids and to develop prophylactic and therapeutic vaccines.

HPV testing can be applied for:

- primary cervical screening
- triage of equivocal cytological lesions
- follow-up after treatment of high-grade cervical intraepithelial neoplasia (CIN) lesions.

For the second and third applications, sufficient evidence exists to recommend HPV testing in current practice.

European Union (EU) guidelines accept pilot testing of primary HPV screening in well-controlled settings but warn against general application. The EU policy will be reviewed as soon as the longitudinal results of the randomized trials comparing HPV and cytology screening are available.

Two elements are essential for a possible future switch to HPV-based screening:

- observing a significantly decreased cumulative incidence of CIN3 among screen test negatives in the HPV arm
- limitation of the proportion of screen-positive women requiring further follow-up and/or treatment.

### Prophylactic HPV vaccination

Prophylactic trials have demonstrated that a vaccine containing L1 VLPs (virus-like particles) is safe and triggers production of type-specific antibodies lasting for at least 5 years. The vaccine offers an excellent protection against persistent infection with the target HPV types and cervical precancerous lesions associated with those types, if administered to young women who are not infected with the HPV types included in the vaccine.

- One of the vaccines, manufactured by Merck, Sharp & Dohme (MSD), was licensed in 2006 in the United States and the EU.
- Licensure of a second vaccine, manufactured by GlaxoSmithKline (GSK), is expected for 2007.

Both vaccines contain VLPs of HPV 16 and 18, which cause about 70% of cervix cancers. The MSD vaccine contains also VLPs of HPV 6 and 11, which cause over 90% of genital warts. Partial protection against incident infection with genetically linked HPV types has been reported for the GSK vaccine.

The vaccines do not protect against an established HPV infection and, for this reason, the vaccine should be administered preferentially before onset of sexual activity, for instance to girls of 11–13 years. Screening policies should

not be modified for women who currently are 25 years or older. Since the vaccine does not protect against all oncogenic HPV types, screening cannot be obviated, but could start later and be offered less frequently. Nevertheless, currently, no observed data are available to define modified screening policies for vaccinated women.

## Conclusion

The highest level of protection against cervical cancer can be reached if prevention is well organized following an evidence-based, acceptable and economically affordable policy. Cost-ineffective opportunistic screening should be discouraged. Population coverage and quality should be maximized and actively monitored. New technologies should be introduced only after thorough evaluation of efficacy and cost-effectiveness. HPV vaccination offers new opportunities of primary prevention but will not obviate the need for screening for the next two decades.

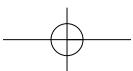
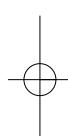
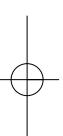
For the other HPV-related cancers, such as vaginal, vulvar, anal and oropharyngeal cancer, prevention of sexual transmission of the virus seems the best strategy. There are no data that vaccination against HPV protects for cancers other than cervical cancer.

## Acknowledgments

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# Cigarette smoking and smoking cessation

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## Epidemiology

There are nearly 1.1 billion users of nicotine and tobacco products worldwide. Tobacco use through cigarette smoking is the leading preventable cause of death in the world and kills nearly four million people annually. By 2020, this number is expected to more than double. It causes harm not only to users but also to second-hand smokers.

Smoking prevalence varies significantly by age, gender, ethnicity, socioeconomic status, and education level. In Europe, approximately 30% of the adult population are regular smokers. The prevalence among young people is around 27–30%, and individuals aged 65 or older have the lowest prevalence of smoking among adults. Nearly 38% of men smoke, whereas the rates among women are around 23%.

With the decline of tobacco use in many industrialized countries, the smoking epidemic is shifting from the developed to the developing world. To a large extent, this is due to the adoption of a very aggressive marketing strategy by the tobacco industry in these countries. The increase is particularly dramatic in China, where more than 60% of adult men are estimated to smoke, representing almost one-third of the total number of smokers worldwide. Current smoking prevalence is higher among adults living below the poverty level (29.1%) compared with those at or above the poverty level (20.6%). Education is inversely related to smoking status; college graduates are less likely to be current smokers and more likely to be never smokers compared with other adults.

**Table 9.1** Main cancer types linked to tobacco use, based on the evidences of causal association

**Cancer types convincingly associated with smoking**

Lung cancer  
Laryngeal cancer  
Esophageal cancer  
Oropharyngeal cancer  
Bladder cancer  
Pancreatic cancer  
Kidney (renal) cancer  
Stomach cancer

**Cancer types probably associated with smoking**

Acute myeloid leukemia  
Cervical cancer  
Colorectal cancer  
Liver cancer

Smoking is known to account for at least 30% of all cancer deaths. The causal link between tobacco use and cancer was first established in 1964, when smoking was implicated in the development of lung and laryngeal cancer. Since then, considerable evidence identified additional neoplasms caused by smoking, including cancers of the oral cavity, pharynx, bladder, esophagus, kidney, stomach, and pancreas. In addition, other cancer types seem to be related to smoking, including colorectal, liver, and cervical cancer, and acute leukemia. Table 9.1 summarizes the main cancer types linked to tobacco use, based on the evidences of causal association.

### The basis of smoking-related carcinogenesis

Tobacco is the most important human carcinogen. Mainstream smoke is an aerosol including approximately 4000 specific chemicals and containing  $10^{10}$  particles per ml. The particulate matter (tar) is made up of some 3500 compounds, the most abundant being nicotine (0.1–2.0 mg per cigarette) and also including most of the polycyclic aromatic hydrocarbons, which are products of combustion. Chemicals such as benzene, heavy metals, and aromatic amines are also present in tobacco smoke, and have been independently

established as carcinogenic for humans. Other smoking carcinogens are *N*-nitroso compounds, particularly nornicotine and the nitroso-derivatives of nicotine.

The risk of carcinogenesis is generally determined by the duration of administration and the intensity of exposure to carcinogens. Cancer development by tobacco smoke is attributable to an overall effect of the complex mixture of chemicals in smoke. Most of these chemical carcinogens require metabolic activation to exert a carcinogenic effect; consequently, there are individual risks affected by the levels and activity of key enzymes. Additionally, numerous studies suggest that there are many genes implicated in the carcinogenic outcome, including the mutated p53 gene. It is suggested that the binding of some polycyclic aromatic hydrocarbons to DNA could lead to mutations in smokers.

Epidemiological studies indicate that the components of tobacco smoke exert effects on both early and late steps of the carcinogenic process; there is a higher risk of cancer development with early age at starting smoking and with increasing time since beginning smoking, whereas the risk of most smoking-related cancers decreases within a few years of cessation. However, the risk for ex-smokers does not decrease to that for never smokers.

## Effectiveness of interventions to reduce the burden of smoking

- Numerous studies from both developed and emerging countries provide strong evidence that the smoking burden can be reduced by many interventions. Increased access to smoking cessation therapies, dissemination of information about health risks from smoking, restrictions on smoking in public and in workplaces, comprehensive bans on advertising, and tobacco tax increases are all effective in reducing tobacco use and its consequences. Laws and regulations that prevent young people from gaining access to tobacco products and reduce their exposure to tobacco smoke are effective general population approaches to preventing tobacco use in adolescents and young adults.
- The review of interventions aimed at the individual to promote smoking cessation compared with interventions directed to the workplace as a whole showed that the individual approach increased the likelihood of quitting smoking. These include the advice from a health professional, individual and group counseling, and pharmacological treatment to

overcome nicotine addiction. Although people taking up these interventions are more likely to stop, the absolute numbers who quit are low, limited to only 5%. Effective treatments can double or triple quit rates, but too few smokers try these interventions and too few physicians offer them. Across numerous studies, it has been identified that physicians lack skills and knowledge to promote smoking cessation and lack the time to discuss smoking behavior with their patients.

## Approaches for smoking cessation

The delivery of effective smoking cessation treatment involves several approaches, which include documenting tobacco use for every patient, strongly urging every tobacco user to quit, determining the willingness of the user to attempt quitting, using counseling and pharmacotherapy to aid in quitting, and scheduling follow-up contact, preferably within the first week after the quit date.

The pharmacological treatment should always be offered to assist with quitting, unless there is a medical contraindication. Various new pharmacological strategies have been developed in the last decade, since the standard medications such as nicotine replacement therapies and sustained-release bupropion are ineffective for many smokers.

Recent developments in understanding the neurobiology of nicotine dependency have identified several neurotransmitters that might contribute to smoking maintenance and relapse, including norepinephrine, dopamine, acetylcholine, 5-hydroxytryptamine, endogenous opioids, glutamate, endocannabinoids, and  $\gamma$ -aminobutyric acid (GABA). The main therapies and second-line treatments for smoking cessation are summarized in Table 9.2.

## Conclusion

Tobacco is the number one killer in the world. Efforts to ameliorate the current and projected harm caused by tobacco are urgently needed. Prevention, especially among youth, and cessation are the main strategies to reduce the smoking burden worldwide, requiring close attention from healthcare providers, healthcare organizations, and research support organizations. These efforts should be done in conjunction with firm and continuous anti-tobacco initiatives by governments and society as a whole, to neutralize the aggressive lobby and pro-tobacco strategies applied by the industry, especially in less-developed countries.

**Table 9.2** Current first- and second-line pharmacotherapies for the treatment of nicotine dependency

Medication	Clinical and pharmacological mechanisms
<b>First-line therapies</b>	
Nicotine patch	Nicotine replacement therapy: reduce nicotine craving and withdrawal
Nicotine gum	
Nicotine nasal spray	
Nicotine lozenge	
Nicotine vapor inhaler	
Bupropion hydrochloride	Blocks reuptake of NE and DA; functions as a neuronal nicotinic receptor antagonist, reducing withdrawal and craving
<b>Second-line therapies</b>	
Varenicline	Partial nicotine agonist and selective nicotinic receptor modulator; reduces withdrawal and decreases rewards by affecting the dopaminergic response to nicotine
Clonidine	$\alpha_2$ -Adrenoreceptor agonist; reduces nicotine withdrawal; side effects include hypotension and sedation
Nortriptyline	Blocks reuptake of NE and 5-HT; probably reduces withdrawal and depressive symptoms; side effects include anticholinergic toxicity and potential for lethal overdose
Moclobemide	Reversible MAO-A inhibitor; increases NE and 5-HT levels; potentially useful for smokers with comorbid mood disorders
Selegiline	Irreversible MAO-B inhibitor; increases DA levels; potentially reduces withdrawal and craving

(Continued)

**Table 9.2 (Continued)**

Medication	Clinical and pharmacological mechanisms
Buspirone	Partial agonist of 5-HT <sub>1A</sub> receptors; reduces 5-HT release; potentially useful for smokers with comorbid anxiety symptoms
Naltrexone	Endogenous opioid receptor antagonist; along with nicotine replacement, reduces withdrawal and craving; potentially reduces comorbid alcohol use
Mecamylamine	Nicotine receptor antagonist; along with nicotine replacement, reduces withdrawal and craving

DA, dopamine; 5-HT, 5-hydroxytryptamine; MAO, monoamine oxidase; NE, norepinephrine.

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# Alcohol

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## Introduction

The consumption of alcoholic beverages can be divided into recorded consumption (estimated from sales, production, and national taxation records) and unrecorded consumption (e.g. illegal production, smuggling, home production, and private importation).

Overall, recorded consumption has increased slightly over the past 20 years, but more substantial increases have occurred in China and some developing countries. In contrast, an overall decline in recorded consumption is observed in several developed countries.

In 2002, more than 1.9 billion adults (1.2 billion men and 750 million women) were estimated to consume alcoholic beverages, with an average daily consumption of 10–13 grams (g) of ethanol ( $= \pm 1$  drink), and 22% of the men and 3% of the women drank 40 g of alcohol ( $= \pm 3$  drinks) or more per day.

- In all regions of the world, men drink more often and in larger quantities than women; gender differences are largely culturally dependent:
  - smaller differences are observed in Europe
  - larger differences in developing countries.
- Consumption of alcohol is age-dependent: the frequency of drinking increases until middle age and the prevalence of heavy episodic drinking decreases over the adult life span.
- The lowest socioeconomic class tends to drink the cheapest beverage available in their respective countries.

## Cancer risk

The World Health Organization (WHO) identified the consumption of alcohol as one of the top 10 risks contributing to the worldwide burden of disease.

**Table 10.1** Relative risk for cancer, by gender and average drinking category

Cancer site	Drinking category					
	Women			Men		
	I	II	III	I	II	III
Mouth and oropharynx	1.45	1.85	5.39	1.45	1.85	5.39
Esophagus	1.80	2.38	4.36	1.80	2.38	4.36
Liver	1.45	3.03	3.60	1.45	3.03	3.60
Breast	1.14	1.41	1.59			
Breast: < 45 years old	1.15	1.41	1.46			
Breast: ≥ 45 years old	1.14	1.38	1.62			
Other neoplasms	1.10	1.30	1.70	1.10	1.30	1.70

#### *Definition of drinking categories*

category I: for women, 0–19.99 g of pure alcohol daily; for men, 0–39.99 g of pure alcohol daily

category II: for women, 20–39.99 g of pure alcohol daily; for men, 40–59.99 g of pure alcohol daily

category III: for women, ≥ 40 g pure alcohol daily, for men, ≥ 60 g of pure alcohol daily

The Working Group of the International Agency for Research on Cancer (IARC) stated that cancers of the oral cavity, pharynx, larynx, esophagus, liver, breast, and colorectum are causally related to the consumption of alcoholic beverages. Table 10.1 gives the relative risk of specific cancers in relation to gender and alcohol consumption.

### Cancer of the upper digestive tract

Regular alcohol consumption is associated with an increased risk for cancers of the oral cavity, pharynx, larynx, and the esophagus. Daily consumption of around 50 g of ethanol increases the risk for these cancers two to three times compared with the risk in non-drinkers. In addition, for these cancers the effects of drinking and smoking seem to be multiplicative.

### Liver cancer

Consumption of alcohol is an independent risk factor for primary liver cancer. Cirrhosis and other liver diseases often occur before cancer is diagnosed and patients with these disorders generally reduce their alcohol intake. Therefore,

the effect of alcohol consumption on the risk for liver cancer is difficult to quantify.

### Breast cancer

There is an increased risk of breast cancer with increasing alcohol intake. The daily consumption of about 50 g of alcohol is associated with a relative risk of about 1.5 (95% confidence interval [CI] 1.3–11.6), compared with non-drinkers. Even for a regular consumption of about 18 g of alcohol per day, there is an increase in relative risk.

### Colorectal cancer

The consumption of alcohol leads to an increased relative risk of about 1.4 for colorectal cancer with regular consumption of about 50 g of alcohol per day compared with non-drinkers. This association seems to be similar for colon cancer and for rectal cancer.

### Renal cell cancer

There is no increased risk for renal cell cancer with increasing alcohol consumption. Alcohol intake is associated with a significantly lower risk for renal cell cancer. This inverse trend is seen in both men and women.

### Non-Hodgkin's lymphoma

There is an inverse association or no association between alcohol consumption and non-Hodgkin's lymphoma and drinkers seem to have a lower risk than non-drinkers.

### Lung cancer

There is a strong correlation between the use of tobacco and the consumption of alcohol. Therefore, the observed increased risk for lung cancer associated with alcohol drinking might be confounded by smoking, the most important cause of lung cancer. In non-smokers, there are no clear data indicating a higher risk for lung cancer.

### Stomach cancer

The association between stomach cancer and the consumption of alcoholic beverages is not clear, with significantly increased risks in some studies but not in others. Potential confounding factors are *Helicobacter pylori* infection, dietary deficiencies, and other unfavorable lifestyle factors.

## Genetic susceptibility

The major alcohol-metabolizing enzymes in humans are the alcohol dehydrogenase (ADH) enzymes that oxidize ethanol to acetaldehyde, and the aldehyde dehydrogenase (ALDH) enzymes that detoxify acetaldehyde to acetate.

The variant allele *ALDH2*\*2, which encodes an inactive subunit of the enzyme ALDH2, is dominant and highly prevalent in certain East Asian populations (28–45%), but rare in other ethnic groups.

- Homozygous carriers of the allele (*ALDH2*\*2/\*2) are usually abstainers or infrequent drinkers, because the enzyme deficiency causes a strong facial flushing response, physical discomfort, and severe toxic reactions.
- Heterozygous carriers (*ALDH2*\*1/\*2, with about 10% residual ALDH2 activity) show less severe acute adverse effects, but alcohol consumption increases the risk for several alcohol-related aerodigestive cancers.

## Alcohol prevention

Factors contributing to alcohol use include established drinking cultures that feature drinking rituals and traditional celebrations, drinking after work and while on leave, drinking to cope or as a recreational activity, and the social and physical availability of alcohol.

Preventive measures of alcohol consumption should aim at reducing both long-term (e.g. liver toxicity, cancer) and acute risks (e.g. accidents, violence) associated with drinking.

Strategies to prevent alcohol misuse and related problems can be grouped as demand- or supply-oriented.

### Supply-oriented measures

Supply-oriented measures aim at limiting the access to alcohol. Since behavior is fairly resistant to attempts to change by education or information, supply-oriented measures are of particular importance.

#### Price policy

Increasing the price of alcoholic beverages is regarded as an important component of a policy to reduce consumption.

### *Outlet density*

Regions with a greater outlet density and higher ratios of outlets per person tend to have higher alcohol sales and probably also higher consumption.

### *Hours of sales*

Changes in hours of sale or opening days for shops selling alcohol have demonstrated that increased drinking is associated with increased number of hours, and decreased drinking with the elimination of some days of sale.

### *Age restrictions*

Most countries have regulations on the minimum age for purchase. Often, however, these regulations are not severely enforced.

## **Demand-oriented measures**

### *School-based education*

Education programs on alcohol at school are the most popular approach to prevention. Overall, education about alcohol that aims at influencing drinking behavior has methodological limitations and, overall, has little effect.

### *Family-based interventions*

There is no doubt that parents have much influence on the use of substances by their children, through both genetic and social factors, such as parental drinking and educational style. There is some evidence that family-based interventions may reduce alcohol abuse or risk factors for substance use.

### *Community action*

Community actions are purposeful efforts in a community setting to influence the way in which people drink or think about drinking. Most community-based programs combine means of reaching individuals in a catchment area and policy changes in the environment. Community-based programs to prevent alcohol consumption do not have a substantial impact on their targets, although some effect can be obtained. Community-based programs tend to reduce drunken driving and accidents in particular.

### *Mass media campaigns*

Mass media campaigns have no impact on self-reported drinking; however, limited effects on beliefs and attitudes have been reported. When the campaigns are

supplemented by interpersonal and policy-focused interventions (e.g. anti-drunken driving legislation; age limit for alcohol purchase), they may contribute to behavioral change.

#### *Brief interventions*

In most Western societies, a large proportion of persons drink more than the recommended limit of alcohol, which is 20 g of alcohol or two standard drinks per day for men and 10 g of alcohol or one standard drink per day for women. It is important to identify the persons who are 'at risk'. A number of instruments for screening 'at-risk' drinkers have been tested and validated in clinical settings and healthcare practices and been found to have high sensitivity and specificity (Table 10.2).

If the results of screening and assessment indicate that a patient is at risk, a brief intervention by the healthcare provider can significantly reduce alcohol use and associated problems. Various protocols for brief interventions exist, but all essentially consist of providing advice and counseling. Pharmacotherapy may be used to alleviate acute withdrawal symptoms and prevent reabuse of alcohol (Table 10.3).

#### *Warning labels on beverage containers*

The impact of labeling beverage containers with warnings about the effects of alcohol on health is low and induces no change in the perception of risk and no change in behavior, although pregnant women show some decrease in self-reported drinking after the introduction of warning labels.

#### *Restrictions on advertising*

The globalization of the media and markets is increasingly shaping people's perceptions, choices, and behavior. Many young people today have greater opportunities and more disposable income, but they are probably more vulnerable to selling and marketing techniques. Restrictions on advertising seem to have an influence on alcohol consumption.

## **Conclusion**

According to the current recommendations of the World Cancer Research Fund, consumption of alcohol is not recommended.

For people who do drink alcohol, there is a general consensus among the IARC, the WHO, the European Code Against Cancer, the World Cancer

**Table 10.2** Screening tests for unhealthy alcohol consumption. Reprinted with permission. Copyright © 2005 Massachusetts Medical Society. All rights reserved

Test or question	Score <sup>a</sup>
<b>CAGE questionnaire</b>	
Have you ever felt you should cut down on your drinking?	
Have people annoyed you by criticizing your drinking?	
Have you ever felt bad or guilty about your drinking?	
Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (eye opener)?	
<b>Alcohol Use Disorders Identification Test (AUDIT)</b>	
The following questions are about your use of alcoholic beverages in the past year. Questions refer to standard drinks. <sup>b</sup>	
How often do you have a drink containing alcohol?	
Never	0
Monthly or less	1
2–4 times a month	2
2–3 times a week	3
4 or more times a week	4
How many drinks containing alcohol do you have on a typical day when you are drinking?	
1 or 2	0
3 or 4	1
5 or 6	2
7 to 9	3
10 or more	4
How often do you have 6 or more drinks on one occasion?	
Never	0
Less than monthly	1
Monthly	2
Weekly	3
Daily or almost daily	4
How often during the past year have you found that you were not able to stop drinking once you had started?	
Never	0

(Continued)

**Table 10.2** (Continued)

Less than monthly	1
Monthly	2
Weekly	3
Daily or almost daily	4
How often during the past year have you failed to do what was normally expected from you because of drinking?	
Never	0
Less than monthly	1
Monthly	2
Weekly	3
Daily or almost daily	4
How often during the past year have you needed a drink in the morning to get yourself going after a heavy drinking session the previous night?	
Never	0
Less than monthly	1
Monthly	2
Weekly	3
Daily or almost daily	4
The following questions are about your use of alcoholic beverages in the past year. Questions refer to standard drinks. <sup>b</sup>	
How often during the past year have you had a feeling of guilt or remorse after drinking?	
Never	0
Less than monthly	1
Monthly	2
Weekly	3
Daily or almost daily	4
How often during the past year have you been unable to remember what happened the night before because you had been drinking?	
Never	0
Less than monthly	1
Monthly	2
Weekly	3
Daily or almost daily	4

(Continued)

**Table 10.2** (Continued)

Have you or someone else been injured as a result of your drinking?	
No	0
Yes, but not in the past year	2
Yes, during the past year	4
Has a relative, friend, or doctor or other health worker been concerned about your drinking or suggested you cut down?	
No	0
Yes, but not in the past year	2
Yes, during the past year	4
<b>Screening question about per-occasion consumption</b>	
For women: When was the last time you had more than 4 drinks in one day?	
For men: When was the last time you had more than 5 drinks in one day?	
<b>Screening questions about consumption</b>	
On average, how many days per week do you drink alcohol?	
On a typical day when you drink, how many drinks do you have?	
What is the maximum number of drinks you had on any given occasion during the past month?	

<sup>a</sup> Cutoff scores with reasonable sensitivity and specificity for unhealthy alcohol use are as follows: CAGE, one or two positive responses (sensitivity, 53–92%; specificity, 81–95%); AUDIT, score of 8 or more (sensitivity, 51–97%; specificity, 78–96%); AUDIT-C (first three questions, about consumption), score of 4 or more (sensitivity, 86%; specificity, 72%); AUDIT question 3 ('How often do you have 6 or more drinks on one occasion?'), score of 1 or more (sensitivity, 77%; specificity, 83%); screening question about per-occasion consumption, 'in the past 3 months' (sensitivity, 62–86%; specificity, 86–93%) (see Supplementary Appendix). The CAGE and consumption screening questions can be used in combination; this seven-question test is considered positive if the results exceed either the cutoffs for 'risky drinking' or there is an affirmative answer to any of the CAGE questions (sensitivity, 83%; specificity, 84%). Laboratory tests (e.g. levels of  $\gamma$ -glutamyltransferase [sensitivity, 65%] and carbohydrate-deficient transferrin [sensitivity,  $\leq 60\%$ ]) are not more sensitive than are validated screening questionnaires and need to be followed by questions about alcohol use. As such, the tests have unknown incremental value. Questions regarding consumption and an additional interview are required to assess patients whose results on the screening tests are positive to identify the amounts and consequences of risky drinking.

<sup>b</sup> A standard drink is approximately 12–14 g of ethanol, which corresponds to 12 oz of beer, 5 oz of wine, or 1.5 oz of 80 proof liquor.

**Table 10.3** Medical therapy for alcohol dependency

Medication	Presumed mechanism of action	Dose
<i>For detoxification or treatment of withdrawal</i>		
Benzodiazepines (diazepam, chlordiazepoxide, lorazepam)	Decrease hyperautonomic state by facilitating inhibitory $\gamma$ -aminobutyric acid receptor transmission, which is downregulated by long-term exposure to alcohol	Diazepam, 10–20 mg; chlordiazepoxide, 50–100 mg; lorazepam, 2–4 mg every 1–2 hours until symptoms subside for 24 hours
<i>For treatment of alcohol dependency to prevent relapse</i>		
Naltrexone	Acts as an opiate agonist; decreases heavy drinking by blocking endogenous opioids, a process that attenuates craving and the reinforcing effects of alcohol	Initial dose, 12.5 mg daily or 25 mg daily; therapeutic dose, 50 mg daily
Acamprosate	Increases abstinence by stabilizing activity in the glutamate system, which is affected by long-term heavy consumption	666 mg 3 times a day
Disulfiram	Blocks aldehyde dehydrogenase; blockade allows acetaldehyde to accumulate with alcohol consumption, causing unpleasant symptoms (e.g., flushing, headache, vomiting, dyspnea, confusion)	Initial dose, 250 mg daily; therapeutic dose, 500 mg daily

Research Fund, and many other organizations that intake should be limited to no more than two standard drinks per day for men and one standard drink per day for women. The measure of 'one unit' of alcohol varies by country, consisting of 8 g, 10 g, or 13 g. The strength (alcohol content by volume) of a

drink should be taken into account when estimating alcohol intake or the number of 10 g units.

Non-governmental organizations should inform and mobilize society about alcohol-related problems, lobby for implementation of effective policy at government level, and expose harmful actions of the industry. Great vigilance and effective monitoring of industry behavior are needed.

Current strategies to prevent alcohol problems should also institute and enforce policies that regulate alcohol availability and pricing, deglamorize alcohol use, and promote personal responsibility and good health. Legislation should prohibit selling alcohol to minors and drunken driving.

The healthcare giver should screen patients for alcohol abuse and dependency and refer to an adequate service for treatment and help.

## Further reading

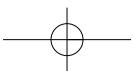
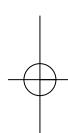
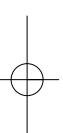
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# Nutrition

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## Introduction

It is estimated that poor nutrition, physical inactivity, and obesity may be responsible for 30% of all cancers. The relationship between nutrition and cancer has been known for centuries and, during the Song Dynasty (AD 960–1279), Yong-He Yan already described the relationship between malnutrition and esophageal cancer.

Food deficiencies are responsible for cancer in economically underdeveloped regions, whereas an imbalance between physical activity and energy supply, exposure to carcinogens, and an oversupply of sugars and fat are the main factors in the economically developed countries.

## Relationship between nutrition and cancer

It is difficult to show a firm evidence-based relationship between nutrition and cancer.

Epidemiological studies that have been published are mainly observational studies with some interventional studies. The results of these studies may be influenced by difficult-to-control biases and confounding factors that are less present in large prospective, randomized studies.

- Studies on cell lines evaluate genetic interactions and elucidate mechanisms, which can be confirmed by molecular biology.
- Animal studies show a relationship between nutrition and cancer but are not applicable to humans.

Difficulties to clearly show the relationship between nutrition and cancer are:

- Cancer is a chronic multifactorial disease that takes years to develop and to manifest itself.

- Most studies are performed in an adult population, but the influence of a change in diet may be more appropriate in children.
- The impact of exposure to a genotoxic carcinogen is highly variable among individuals:
  - Carcinogens are toxic by their electrophilic nature, which they have inherently or acquire after enzymatic conversion. The majority of carcinogens require an enzymatic conversion in order to damage the DNA.
  - There are detoxification enzymes which convert toxic lipophilic compounds into water-soluble metabolites that can be excreted into urine or bile.
  - Free radical intermediates can also be bound by antioxidants and thus become inactive.
  - Individual harm due to exposure of a procarcinogen is the result of a competition between activation and detoxification enzymatic pathways, which are influenced not only by genetic predisposition but also by environmental factors.
- Genomes evolve in response to many types of environmental influences, including nutrition. Dietary constituents can alter gene expression and gene structure. However, a nutrient contains hundreds of chemical constituents and the genetic information that is expressed or regulated by nutrients, micronutrients, or phytochemicals is very complex.

It is not only important who is eating what but also what food is combined in a meal and how it is prepared. This makes it difficult to give general advice on healthy food.

## Nutritional aspects in cancer development

### Physical activity

There is convincing evidence that physical activity is not only protective against colorectal cancer but also improves disease outcome of patients after chemotherapy.

Physical activity is probably also protective against breast, lung, and prostate cancer. Physical activity requires between 18 and 27 metabolic equivalent task (MET) hours a week.

- An hour jogging, bicycling, playing tennis, or swimming is good for 7 MET points.

- Mowing the lawn or aerobic exercise for an hour is good for 6 MET points.
- Walking for an hour during 6 days a week accounts for 18 MET points.

The causal relationship between energy balance and cancer risk is not well established but physical activity might lower the level of circulating insulin-like growth factor (IGF). Prospective studies show a higher risk of breast, prostate, and possibly colon and lung cancer in individuals with high levels of IGF-1.

Physical activity also improves insulin sensitivity, and type 2 diabetes mellitus is associated with increased risk of endometrial, colon, kidney, pancreas, and postmenopausal breast cancer.

## Obesity

There is convincing evidence that obesity increases the risk for endometrial cancer. The body mass index (BMI) should be between 18.5 and 25. A small, sedentary woman only needs 1450 kcal a day for sufficient energy supply. Weight changes during adulthood should be restricted to 5 kg.

A BMI above 28 increases the incidence of breast cancer in postmenopausal women. It probably also raises the risk for renal cancer.

## Nutrition

There is convincing evidence that vegetables and fruit are protective against oral, esophageal, lung, and stomach cancer and that vegetables are protective against colon cancer. This is probably also true for laryngeal, pancreatic, breast, and bladder cancer. Vegetables and fruit are sources of fiber, vitamins, and phytochemicals.

The daily recommended dose of vegetables and fruit for an adult is 400–800 g of vegetables and at least two pieces of fruit.

The carcinogenesis process involves a recurrent and accumulative alteration of DNA in genes that control tissue growth; therefore, one should consume a variety of vegetables and fruit all year round.

- Eating vegetables and fruit at the time when they are naturally harvested makes it cheaper and renders the vegetables and fruit highest in micronutrients and phytochemicals.
- Fruits with the highest level of natural antioxidants are small red fruit like blueberry, cranberry, blackberry, raspberry, or strawberry.
- Other natural antioxidants are vitamins C, E, A, coenzyme Q<sub>10</sub>, lycopene, melatonin, quercetin, selenium, and zinc.

- Vitamin C is present in products such as blackberry, red capsicum, parsley, broccoli, and green cabbage. It is sensitive to heating (all vitamins are sensitive to light and should therefore be stored in dark places).
  - Vitamin A can be found as β-carotene in apricots, spinach, green cabbage, parsley, and watercress. It cures oral leukoplakia. Heavy smokers (more than 1 pack/day) should not take vitamin A supplements because this vitamin increases their risk for lung cancer.
  - Vitamin E is present in polyunsaturated fat, eggs, meat, fish but also in cereals, seed, nuts, and soya beans. Case-control studies suggest a protective effect against prostate cancer.
  - Lycopenes are found in tomatoes when these are slowly heated for a longer period of time.
  - Selenium is an essential trace element occurring in organic and inorganic forms. The organic form is found predominantly in unrefined grains, meat, poultry, fish, eggs, and dairy products, with a marked variability geographically due to a difference in soil content. Higher selenium levels seem to lower the risk for prostate cancer, and reduce total cancer mortality and cancer incidence.
- Vegetables such as endive, celery, lettuce, fennel, spinach, purslane, and turnip tops have a high level of nitrates, especially being stored longer than 2 days and in winter periods. Heating and combining them with proteins results in nitrosamines, which are potentially carcinogenic.
  - Forty-five to sixty percent of the total energy required should be provided by protein-rich food of plant origin. It should be unrefined to have the desired amount of vitamins, minerals, and fibers.
  - Polysaccharides are found in cereals, legumes, and starch, as well as in vegetables and fruit. Ingestion of refined mono- and disaccharides gives a rapid rise of glucose levels and a subsequent fall, leading to an early feeling of hunger and resulting in an oversupply of energy. They are poor in micronutrients. A diet containing high amounts of refined sugar possibly increases the risk for colon and rectal cancer.
  - A diet containing substantial amounts of fibers possibly decreases the risk for breast, colon, rectal, and pancreatic cancer: 600–800 g a day is the recommended but substantial amount.

A diet containing red meat probably increases the risk of cancer of the colon and rectum, and possibly increases the risk for breast, pancreatic, kidney, and prostate cancers. Therefore it is advisable to limit the intake of beef, lamb, and pork, and of derived products. Grilled, barbecued, or fried meat gives heterocyclic amines and possibly raises the incidence of colon and rectal cancer.

Alternative vegetable sources of proteins are dried legumes, soy, wheat gluten, nuts and seeds, and quorn.

It is possible that a diet high in fat increases the risk of cancer of the lung, colon and rectum, breast, and prostate. It certainly increases the risk of obesity and therefore increases the risk for endometrial cancer and probably also the risk for kidney and postmenopausal breast cancer.

Saturated fat should be avoided. Saturated fat is derived from animal sources, but also from coconut oil and palm oil. Polyunsaturated fats derived from linoleic and linolenic acids are preferred. In contemporary diets, there is an unwanted preponderance of *n*-6 fatty acids. Natural sources of *n*-3 fatty acids are fat fish, walnuts, linseed, and nut oil.

### **Preparation of food**

Low-temperature cooking by steaming, boiling, poaching, stewing, and braising are preferred methods of food preparation.

It is possible that heavily cooked or grilled meat and fish increases the risk of stomach cancer. Diets high in grilled, barbecued, or fried meat possibly increase colon and rectal cancer, as do diets high in processed meat.

Heterocyclic aromatic amines produced by grilling or broiling food have been found to be carcinogenic in animal studies, which have also shown a similar effect for *N*-nitrosamines originating in food treated with nitrites. Smoking food produces polycyclic aromatic hydrocarbons that also appear to be carcinogenic in animal experiments.

Thiamine and vitamin C are sensitive to heat. Vitamin C protects vitamins A, E, and B complexes and enhances the uptake of iron and folic acid. Balancing the consumption of raw and lightly cooked vegetables is to be preferred.

### **Food storage**

To preserve micronutrients, vegetables should be stored in dark, cold places. The period between harvest and consumption should be as short as possible. These measures limit the nitrate levels in certain vegetables.

Using salt to preserve food should be restricted. Diets high in salted food probably increase the risk of stomach cancer. Refrigerating instead not only decreases the risk for stomach cancer but also makes fresh food and vegetables obtainable year-round and preservatives superfluous.

Storing food in ambient temperatures may cause the growth of mycotoxins, of which the aflatoxins probably increase the risk for liver cancer.

There is no proof that additives and residues in the amounts found in food are harmful. Much remains to be learnt about cumulative doses, synergism, and possible metabolic differences to understand their influence on individuals.

## Nutritional recommendations in cancer prevention

- Maintain physical activity: obtain 18–27 MET a week.
- Maintain body weight: BMI should be between 18.5 and 25; fluctuations should be restricted to 5 kg.
- Eat 400–800 g of a variety of raw and lightly cooked vegetables and two pieces of fruit every day. Eat seasonable and fresh vegetables and fruit.
- Eat 600–800 g/day of minimally processed grains, legumes, nuts and seeds, roots, tubers, and plantains.
- Avoid refined sugar.
- Avoid red meat.
- Limit fat to 15% of energy supply. Use polyunsaturated fats well-balanced between *n*-3 and *n*-6 fatty acids.
- Use herbs and spices instead of salt.

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# Work-related risk factors

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## Introduction

Occupational exposure to carcinogens is a well-established cause of cancer.

Whereas many cancers have an unknown source, cancers due to occupational exposures have known sources. This means that they are preventable if proper safety guidelines and equipment are used all the time. If they are correctly applied, the number of occupational cancers should be reduced.

Workplace exposures may affect only a relatively small number of people but the level of exposure and risk for that group can be high.

The most common cancers associated with occupational exposure are:

- lung and pleura
- bladder
- skin
- laryngeal
- nasal cavity
- leukemia
- throat
- lymphoma
- soft tissue sarcoma
- liver.

## Causes of work-related cancers

### Tobacco

Smoking is considered the greatest risk factor for lung cancer. Employees in environments such as bars, restaurants, and offices are at greatest risk from second-hand smoke. Second-hand smoke is highly dangerous. Non-smokers who live with a smoker are at 30% greater risk of developing lung cancer than if they lived with a non-smoker.

### Asbestos

Asbestos is a known carcinogen. In more than 75–85% of patients with mesothelioma, there is a history of exposure to asbestos.

Asbestos is a broad term which refers to different minerals known as asbestos-form minerals. It is a small mineral comprised of tiny fibers. These fibers exist in two forms: amphibole or serpentine (chrysotile). Several studies suggest that the amphibole form of asbestos is more dangerous than the chrysotile form, especially for mesothelioma.

These small particles float in the air, and may be inhaled or swallowed. Asbestos fibers breathed into the lungs cannot be expelled; they become embedded in the thin lining of the lungs, the mesothelium. Over a period of many years, cells in the mesothelium can become cancerous.

Asbestos is used in many products that need to withstand high heat such as home insulation and construction, brake pads, electrical equipment, hot water piping, boilers, ship engines, and welding supplies. When the asbestos is contained within finished products such as walls and tiles, it poses no health problem. However, damage or inadvertent destruction can release dangerous fibers into the air. When asbestos fibers are free, they can be inhaled, and exposed individuals are at risk of developing an asbestos-related disease.

Although smoking has not been found to cause mesothelioma, it has been linked to an increased incidence of mesothelioma in asbestos-exposed workers.

Asbestos in the past has been extensively used in industrial products, including cement, brake linings, roof shingles, flooring products, textiles, and insulation, as well as in shipbuilding and other forms of construction. The risk of developing mesothelioma increases according to the length and level of exposure to asbestos.

Asbestos is still contained in schools, offices, factory buildings, and homes in the form of insulation. Workers who remove asbestos from buildings need to take special precautionary measures to avoid inhalation of asbestos fibers

and wear special clothing so that they do not take home the dust on their clothes.

Asbestos can also affect automotive mechanics, boilermakers, carpenters, dry wallers, electricians, iron workers, machinists, metal lathers, millwrights, pipefitters, power plant workers, railroad workers, and shipbuilders.

Unfortunately, asbestos legislation remains insufficient in some countries and this does not contribute to the world control of this strong carcinogen.

## Radon

Radon is a radioactive gas that can cause lung cancer. Houses or commercial properties that are built on soil containing radon may contain radon in gas form. The risk of lung cancer increases with radon concentration.

## Formaldehyde

Formaldehyde is an organic compound with a characteristic and unmistakable smell that has several commercial and industrial applications:

- in laboratories of pathological anatomy and histology, for the fixation and the inclusion of tissues and cells
- for sterilizing equipment, environments, and healthcare material in hemodialysis and in surgery
- in mortuary rooms and by embalmers for tanning of the skin.

Formaldehyde is a ubiquitous microcontaminant to which the population is exposed through the atmospheric air, particularly in urbanized areas. Nevertheless, the most remarkable exposures to formaldehyde are verified in confined working and domestic environments. The active or passive exposure to tobacco smoke significantly contributes to the exposure to formaldehyde: a heavy smoker (20 cigarettes/day) is exposed to 1 mg/day of formaldehyde.

Formaldehyde is mainly absorbed by the respiratory system and causes an increased risk of nasal and nasopharyngeal cancer. Cohort studies of embalmers and other professionals that use formaldehyde have shown some excess risk for brain cancer.

## Silica

Employees exposed to fine silica particles have an increased risk for lung cancer. Silica appears in sand, rock, and mineral ores, and is used in sandblasting,

masonry work, tunnel construction, ceramics, laying railroad track, soap manufacturing, glass manufacturing, shipbuilding, and agriculture.

## Dyes

Bladder cancer from occupational exposure is most common in individuals working with dyes that contain aromatic amines such as benzidine and  $\beta$ -naphthylamine. Factory workers involved in the production of these dyes, as well as those who use these substances, such as hair colorists, and possibly even people who apply their own permanent hair dye at least once a month, may be at increased risk for bladder cancer.

## Herbicides and pesticides

Farmers and others who have long-term exposure to herbicides and pesticides are at increased risk of leukemia. Herbicides and pesticides are both associated with the development of lymphomas, so workers involved in their production as well as their application are at increased risk. Children exposed to pesticides on a regular basis are significantly more likely to develop non-Hodgkin's lymphoma than children not exposed.

Pancreatic cancer appears to be associated with significant exposure to pesticides, certain dyes, and chemicals found in gasoline.

## Dioxin

Dioxin is a known carcinogen, and may be a causative factor in a variety of cancers. It is a product in industrial processing that deals with chlorine and hydrocarbons, such as found in incinerators and paper and pulp factories.

Epidemiological studies have reported an increase in overall cancer mortality. A dose-response relation was observed. A significant increased combined risk was found for all cancers combined, lung cancer, and non-Hodgkin's lymphoma.

## Infected blood

Healthcare professionals, both human and veterinary, may be exposed to infected body fluid that can increase the risk of hepatitis B and hepatitis C. This can cause liver failure and increase the risk of liver cancer. Human immunodeficiency virus (HIV) can cause an acquired immunodeficiency syndrome (AIDS) and increase the risk of a variety of malignant tumors.

## Electric and magnetic fields

Electric and magnetic fields surround electric tools and machinery. Studies have been done to investigate whether these fields are harmful to humans. Research findings continue to be controversial: some show an increased incidence of cancers, whereas others find no association.

## Work-related protection measurements

National regulations should be in place to improve employee safety.

Regulation of exposure to occupational carcinogens can be an effective strategy and achieved by:

- replacing carcinogens with other materials and processes
- mandating protective equipment
- biological monitoring of workers.

Regulations need to be supported by education of employers and workers because the regulations are ineffective if the employees do not utilize the protective clothing, mask, and other safety measures at their disposal.

Studies of occupationally exposed cohorts are useful in identifying environmental factors linked to cancer risk because effects are easier to detect among workers who have higher levels of exposure than in the general population.

The International Agency for Research on Cancer (IARC) evaluates the potential exposure to the agent or mixture by providing data on chemical and physical properties and methods of analysis and by providing a carcinogen classification that is periodically updated.

This classification summarizes a complete list of agents:

- Group 1: substances and mixtures that were recently evaluated as carcinogens to humans (101).
- Group 2A: probably carcinogenic to humans (69).
- Group 2B: possibly carcinogenic to humans (245).
- Group 3: not classifiable as to carcinogenicity to humans (516).
- Group 4: probably not carcinogenic to humans (1).

In certain situations it may be difficult to prove that the work environment was the causal factor in the development of cancer. This can make it harder to

obtain benefits that would be attributed to work-related diseases. Consequently, financial concerns may be a great problem. Also, certain cancers (e.g. mesothelioma) may develop from the inhalation of substances that were brought home on the worker's clothing. The cancers of these patients are not recognized as work-related and there is no financial compensation for them.

## Conclusion

Work-related cancers should be prevented by adequate protection measures and education of the employers and employees.

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# Drug-related cancers

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## Introduction

Some drugs have been linked to the development of hematological and solid tumors.

The assessment of carcinogenicity of drugs during their development is by in-vitro (genotoxicity) and in-vivo tests. The hazard and risk may vary during the development as more persons are exposed for longer periods of time.

According to the International Conference on Harmonization (ICH) Guideline S1A, carcinogenicity studies should be performed for any pharmaceutical where the expected clinical use is continuous for at least 6 months or repeatedly intermittent for chronic conditions.

In the development of a new drug, it is also important to consider:

- previous evidence of carcinogenic potential in the product class relevant to humans
- a structure-activity relationship that suggests a carcinogenic risk
- evidence of precancerous lesions in repeated-dose toxicity studies
- long-term tissue retention of the parent compound or metabolite(s), resulting in local tissue reactions or other pathophysiological responses.

Herbal and nutritional supplements or treatments are not submitted to these control mechanisms and their carcinogenic effect is often unknown.

Carcinogenic effects of drugs may manifest themselves in humans after many years of use. For some products for which a risk is perceived, data should be collected prospectively. It is known that immunosuppressive compounds and alkylating agents may cause cancer in humans after less

**Table 13.1** Known human carcinogens

Antineoplastic agents	Busulfan Chlorambucil Lomustine Cyclophosphamide Melphalan Mustin and combinations Thiotepa Treosulfan
Dermatologicals	Arsenic salts Coal tars Methoxypsoralen + UVA
Hormonal drugs	Diethylstilbestrol Estrogen replacement therapy Sequential oral contraceptives Combined oral contraceptives Tamoxifen
Immunosuppressants	Azathioprine Cyclosporin A
Miscellaneous	Phenacetin in analgesic mixtures

than 10 years, whereas for most products it may take 20 years before cancer occurs. It is very difficult to attribute cancer to a particular drug unless a specific cancer occurs in a high percentage of persons using the drug, the drug–cancer relationship is studied extensively, or the drug induces a rare form of cancer.

## Carcinogenic risk of prescription drugs

The carcinogenicity of some prescription drugs has been demonstrated (Table 13.1). These drugs are mainly hormones, immunosuppressive or chemotherapeutic agents. Nevertheless some other classes of drugs are also linked to the development of cancer (e.g. phenacetin-containing medication).

**Table 13.2** Drugs anticipated to be human carcinogens

Analgesics	Phenacetin Phenazopyridine hydrochloride
Antiepileptics	Phenytoin
Antibiotics	Chloramphenicol Metronidazole
Antineoplastic agents	Azacitidine 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea bis(Chloroethyl) nitrosourea Chlorozotocin Cisplatin Dacarbazine Doxorubicin hydrochloride Nitrogen mustard hydrochloride Procarbazine hydrochloride Propylthiouracil Streptozotocin
Hormones	Progesterone Oxymetholone
Miscellaneous	Chloroform Danthron (1,8-dihydroxyanthraquinone) Iron dextran complex Lindane and other hexachlorocyclohexane isomers Phenoxybenzamine hydrochloride Reserpine

Besides these drugs, there are many drugs that are suspected of causing cancer (Table 13.2).

For these suspected drugs there is one of the following:

- Limited evidence of carcinogenicity from studies in humans indicating that a causal relationship is possible but that other reasons (e.g. chance, bias, or confounding factors) cannot adequately be excluded.

- Sufficient evidence of carcinogenicity from studies in experimental animals indicating that there is an increased incidence of malignant and/or a combination of malignant and benign tumors:
  - in multiple species or at multiple tissue sites
  - by multiple routes of exposure
  - to an unusual degree of incidence, site, or type of tumor, or age at onset.
- Less than sufficient evidence of carcinogenicity in humans or laboratory animals; but the drug belongs to a well-defined, structurally related class of substances whose members are listed as carcinogenic.

There are regular updates of the carcinogenicity of (medicinal) agents (e.g. <http://ntp.niehs.nih.gov>; <http://monographs.iarc.fr/ENG/Classification/crthgr01.php>).

The risk of developing a cancer by using these drugs is relatively small and is outweighed by the benefit of the treatment. However, patients should be informed about this risk to make an informed decision in relation to treatment.

- Most carcinogenic alkylating agents can cause a second hematological cancer such as leukemia.
- Hormone use may lead to an increased risk of breast cancer (oral contraceptives, hormone replacement therapy) and endometrial cancer (estrogen, tamoxifen).
- Immunosuppressive drugs have been linked with lymphoma and skin cancer (cyclosporin) or non-Hodgkin's lymphoma, squamous cell carcinoma of the skin, hepatobiliary carcinoma, and mesenchymal tumors (azathioprine).
- A carcinogenic effect has also been demonstrated with diethylstilbestrol (vaginal cancer), coal tar (skin cancer), arsenic salts (skin, lung, digestive tract, liver, bladder, kidney, lymphatic and hematopoietic system), methoxypсорalen in combination with ultraviolet A (squamous cell cancer of the skin), and phenacetin-containing combinations (urothelial tumors).

## Carcinogenic risk of non-prescription drugs and food supplements

The use of non-prescription drugs and food supplements is high in the overall population and in specific patient populations (e.g. cancer patients).

### Herbal medicines

There are general and herb-specific concerns in the use of herbal medications and their ability to induce carcinogenic effects.

Toxicity due to herbal medication can occur due to:

- a lack of pharmaceutical quality control in harvesting and preparation, with contamination by herbicides
- confusing nomenclature
- the actual dose of active compounds is often variable, unpredictable, or simply unknown
- lack of quality control
- lack of accurate identification of plants.

There are no governmental regulations on the manufacture, purity, concentration, or labeling claims of herbal remedies.

A carcinogenic effect has been observed with the use of Chinese herbs contaminated by *Aristolochia fangchi*, causing a progressive nephropathy and urothelial cancer.

### Vitamin supplements

Several vitamins have been tested in chemoprevention studies. In some of these studies (e.g. lung cancer prevention studies), the incidence of cancer was higher in the groups taking vitamins or nutritional supplements ( $\beta$ -carotene, retinoic acid, isotretinoin, fenretinide, retinyl palmitate) compared to the placebo group.

Vitamin supplements should be used carefully in chemoprevention.

## Prevention of cancer development due to carcinogenic drugs

Several strategies have been developed to limit the exposure to carcinogenous drugs:

- Production regulation to avoid exposure of workers to active components.
- Regulations for packaging and handling of drugs to prevent accidental intake.
- Prevention of contamination of ((para-)medical) personnel who handle drugs by strict regulation of cytotoxic drug handling.
- Information and education about the risks of (potentially) carcinogenic drugs.
- Indication and prescription regulations to protect the patients. The carcinogenic risk depends on the intensity, route, and duration of exposure to a carcinogen. Patients may respond differently to similar exposures, depending

on their age, gender, nutritional status, overall health, genetics, and many other factors.

- Guidelines for treatment duration and follow-up to evaluate secondary cancers after anticancer therapy.
- Use of alternative prescription drugs.

## Conclusion

The carcinogenicity of some prescription drugs has been demonstrated but the effect is relatively small and does not outweigh the benefit of the treatment. However, patients should be informed about the risk, and measures to decrease the carcinogenic effect of these drugs should be adapted.

It has also been shown that herbal medications and vitamins or nutritional supplements may increase the risk of certain cancers in specific populations. Patients should be warned about the possible consequences of their use.

Limiting human exposure during the production process by strict regulation is of utmost importance. For patients, treatment and follow-up guidelines should include the long-term carcinogenic effects of drugs.

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# Radiation

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## Introduction

Cancer and radiation are, both negatively and positively, indissolubly associated. The carcinogenic potential of ionizing radiation was recognized soon after Roentgen's discovery of X-rays in 1895. In 1902 the first radiation-induced cancer was reported arising in the skin. Since the atomic bombing of Hiroshima and Nagasaki in 1945 there has been interest and concern about risks arising from this and other nuclear incidents, such as the Chernobyl accident in 1986. In the last few decades there is also concern about a possible link between cancer and transmission masts, electricity pylons, and, more recently, cell phones.

In 1907, Dubreuilh published the first report of skin cancer caused by sun exposure. Ultraviolet radiation (UVR) is now recognized as the major environmental risk factor for skin cancer.

Recent studies, however, have provided strong evidence that sunlight reduces the risk of other types of cancer, such as colon, breast, and prostate cancer.

## Ionizing radiation

### Nuclear accidents

- The long-term follow-up of the atom bomb survivors of Hiroshima and Nagasaki has shown that ionizing radiation is a 'universal carcinogen', in that it will induce cancer in most tissues of most species.
- The Chernobyl nuclear power plant was the scene of the most severe accident that has ever occurred in the nuclear industry. From a radiological point of view, iodine-131 and cesium-137 were the most important

radionuclides. Among cleanup workers in Chernobyl, a measurable increased incidence of leukemia was found. The evidence with regard to thyroid cancer among cleanup workers is more equivocal.

- In the residents of contaminated areas (Belarus, Ukraine, and parts of Russia) an excess of thyroid cancers was observed. It has been clearly shown that the risk of developing thyroid cancer increases with decreasing age at exposure. The small size of the gland, the radiosensitivity of the thyroid gland of children, their high intake of milk and, possibly, a diet deficient in iodine increases the risk of relatively low doses of radioactivity.
- The available evidence does not indicate an effect of Chernobyl fallout on leukemia (with exception of the cleanup workers) and solid cancer (other than thyroid) risk. There is a suggestion of an increased risk of leukemia for persons exposed in utero and of a premenopausal breast cancer in women in some of the contaminated areas.
- Various reports have been published on cancer risk in groups exposed to fallout from nuclear-weapons testing on the Marshall Islands, in French Polynesia, and in Nevada. There were some indications of higher risk of thyroid cancer and leukemia.
- In persons living near nuclear plants and workers at these plants where incidents have occurred, such as the Three Mile Island plant in the United States and the Windscale reactor in the UK, no consistent evidence was found of an association between cancer rates around these plants and radiation releases. People who lived in Russia near the River Techa, where large amounts of radioactive materials were discharged, and who also were exposed following the explosion of a high-level waste container at the Mayak nuclear plant, show increased leukemia risk with increasing dose.
- Analyses of more than 400 000 nuclear industry workers show a significant association between radiation dose and all-cancer mortality. Among 31 specific types of malignancy, a significant association was found for lung cancer and a borderline significant association for multiple myeloma and ill-defined and secondary cancers.

### **Diagnostic and therapeutic radiation**

Radiation is an integral part of cancer management. All cancer patients undergo X-ray examinations and many receive radiotherapy. In both cases the benefits are generally believed to far outweigh the risks.

#### ***Radiotherapy***

Concern for risk of radiation-induced cancer, however, is growing with the increasing number of long-term cancer survivors. A recent analysis of second cancers in 14 series of radiation-treated patients demonstrates increased risks over a wide

variety of dose ranges. Certain sites, such as thyroid, breast, and bone marrow, appeared to be more radiosensitive than others. Consequently, patients treated for lymphomas, leukemias, neoplasms of breast, and male and female reproductive organs had higher chances of developing secondary malignancies. Radiotherapy is assumed to increase the risk of developing a secondary cancer by about 10%.

#### *Diagnostic radiation*

The radiation risk of X-ray imaging is very small, but over the last several years increasing attention has been focused on the risk of inducing secondary cancers by using computed tomography (CT), particularly in children, who are more radiosensitive. The available evidence is not consistent, but suggests a potentially increased cancer risk associated with CT exposure.

Consequently, it is advised to use CT only when indicated and to keep patients' doses as low as reasonably achievable (ALARA).

### **Non-ionizing radiation**

#### **Radiofrequency emissions**

The advent of mobile telephones (cell phones), now used by billions of people worldwide, was accompanied by an upsurge in public and media concern about the possible dangers of radiofrequency emissions.

The International Commission for Non-ionizing Radiation Protection (ICNIRP) concluded from the available data that there was no consistent evidence that occupational or environmental exposure to radiofrequency fields (cell phone base stations and radio and television transmitters) and cell phones conferred an increased risk of cancer. The (methodological) limitations of the available studies, however, leave unresolved the possibility of an association between radiofrequency and cancer.

Some, but by no means all, studies that have been carried out in relation to exposures to electromagnetic fields of electricity pylons and cancer risk report a doubling of risk of childhood leukemia. The International Agency for Research on Cancer (IARC) has therefore assigned these magnetic fields as 'possibly carcinogenic'.

#### **Sunlight and ultraviolet radiation**

Until recently, the interest in the effects of sunlight and UVR on human health was mainly focused on the negative aspects. During the last few decades, there have been steady rises in the incidence of skin cancer.

Many skin cancers are detected early, at a stage in which they can be easily and effectively treated and, consequently, the mortality due to these tumors is limited. The majority of these cancers, the non-melanoma skin cancers (basal cell and squamous cell carcinomas) have a low malignant potential, which also reduces their fatality. The relatively rare melanomas have a high malignant potential and a relative mortality between 15% and 20%.

- There is a linear relationship between the degree of sun exposure and squamous cell carcinoma of the skin. However, the relationship between melanoma, the most aggressive type of skin cancer, and sunlight, is more complicated. Intermittent sun exposure at a young age causing severe sunburn is the most important exogenous risk factor, whereas a certain degree of chronic exposure may have a preventive effect. Moreover, sun exposure might be associated with increased survival from melanoma. In addition to sun exposure, endogenous factors such as skin type, hair color, and the number of both normal and atypical nevi play a role in the genesis and the prevention of skin cancer.
- The rise in skin cancer incidence, largely caused by increased sun exposure, has in most Western countries led to public health recommendations that sun exposure should be avoided.
- In a recent systematic review, all published studies concerning sun exposure and cancers, excluding skin cancer, were evaluated. For many types of cancer only ecological studies were available. For prostate, breast, and ovary cancer, in addition to ecological studies, several case-control and prospective studies were available, all showing a significantly inverse correlation between sunlight and mortality and/or incidence. Also for colon carcinoma and more recently for non-small-cell lung carcinoma, the available evidence is quite convincing for a risk-reducing effect of sun exposure. Ecological studies on non-Hodgkin's lymphoma (NHL) mortality and sunlight gave conflicting results: early studies showing mostly positive and later studies mostly negative correlations. All case-control and prospective studies found a significant inverse association between the incidence of NHL and sunlight. Of interest is the finding in several studies that the season of diagnosis and treatment was a prognostic factor for patients with prostate, breast, colon, and lung cancer, and NHL. Patients diagnosed during summer had a 10–70% (depending on type of tumor, duration of follow-up, and age of the patient) lower case fatality compared with those diagnosed in winter. The quantitative relationship between sunlight and the incidence and/or mortality from these cancers seems to follow a dose-response curve: the more sunlight received, the higher the preventive effect. This is suggested by the north-south gradients in the ecological

studies and by the finding that increased chronic exposure gives increased protection. Moreover, features of acute exposure, such as childhood sunburn, regular foreign holidays, and a high adult sunbathing score, were demonstrated to have a reducing effect on risk.

#### *Mechanism of cancer prevention by sunlight*

As an explanation for the preventive effect of sunlight on cancer, the role of ultraviolet B (UVB) in vitamin D synthesis is usually given. Most humans obtain 80–90% of their requirement for vitamin D from sunlight.

Vitamin D<sub>3</sub> is synthesized from its precursor 7-dehydrocholesterol in the skin by the direct action of sunlight. The steroid hormone 1,25(OH)<sub>2</sub>D<sub>3</sub> is much more active than its precursors and is produced by the 25-hydroxylation of vitamin D<sub>3</sub> in the liver, followed by 1 $\alpha$ -hydroxylation in the kidney.

Only recently it was discovered that in addition to the kidney-localized main production of the active steroid hormone, a variety of cell types (both normal and malignant) in different organs, such as prostate, colon, and breast, have the capacity to synthesize 1,25(OH)<sub>2</sub>D<sub>3</sub> from 25(OH)D<sub>3</sub>. Vitamin D is a well-known regulator of cell proliferation and differentiation, apoptosis, tumor invasion, and angiogenesis and, consequently, is a potential candidate for cancer regulation.

Higher rates of cancer mortality have been found among African-Americans and obese and overweight people, each associated with lower circulating vitamin D levels. The evidence that the genesis of colorectal, prostate, and breast cancer is inhibited by vitamin D is substantial. Many authors assume that the vitamin D levels necessary for cancer prevention are considerably higher than the levels recommended to prevent osteoporosis.

#### *Sun protection*

There is now increasing evidence that (at least moderate) sun exposure may have a preventive effect on several forms of cancer, possibly even on melanoma, the most aggressive type of skin cancer. However, intensive exposure to the sun can also cause all types of skin cancer by a direct mutational effect on epidermal cells. In countries with a moderate climate, such as the Netherlands, the absolute mortality of prostate, breast, colon, and lung cancer is almost 40 times higher than that of skin cancer (Table 14.1). Thus, the benefits of solar UV irradiation seem to outweigh the risks of solar UV if sunburn and excess tanning are avoided.

The question that remains is how to apply these findings to (public) health recommendations. Until recently, recommendations relating to sun exposure

**Table 14.1** Number of new cancer cases and cancer deaths in 2003 in the Netherlands

Cancer	Incidence (number of new cases)	Mortality (number of deaths)
Prostate	7902	2349
Breast	11758	3391
Colorectal	9898	4429
Lung	9014	8862
Melanoma	2869	548
Squamous cell carcinoma of skin	3883	68
Basal cell carcinoma <sup>a</sup>	14853	—

<sup>a</sup> Only first primary basal cell carcinomas, based on estimations from the Eindhoven Cancer Registry.

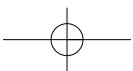
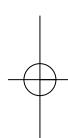
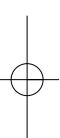
Source: Netherlands Cancer Registry ([www.kankerregistratie.nl](http://www.kankerregistratie.nl)).

were only given from the viewpoint of its deleterious effects. The challenge is to provide a public health message that ensures that (mortality of) skin cancer risk is limited while taking a precautionary approach to the possible harms of insufficient circulating levels of vitamin D; therefore, promotion of moderate sun exposure should be considered, besides warning against intensive (over)-exposure to sunlight. This would particularly apply to people living in countries with a moderate climate and those running the risk of vitamin D deficiencies (elderly and heavily pigmented people, veiled women) and also to individuals without known risks for skin cancer. More definite data are needed to decide definitively whether the advantages of sun exposure exceed the disadvantages to the extent that an even further adaptation in health recommendations becomes advisable.

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# Breast cancer: chemoprevention and screening

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## Chemoprevention of breast cancer

The antiestrogenic properties of tamoxifen have been known since the 1960s. The ability of the compound to prevent the development of the hormonally responsive 7,12-dimethylbenz[a]-anthracene (DMBA)-induced tumor in rodents was recognized in the 1970s. Its clinical value in inducing remissions in metastatic and locally advanced breast cancer led to the establishment of trials seeking to demonstrate the efficacy of tamoxifen in the adjuvant setting. When the results of these studies displayed a convincing reduction in breast cancer in the opposite breast, it became a logical step to propose that the drug might be beneficial in the primary prevention of breast cancer.

### Tamoxifen

In 1998 the results of three randomized chemoprevention trials (Italian, English, and US) comparing tamoxifen (20 mg/day) with placebo were reported: the two European trials showed no protective effect, whereas the third (US) trial demonstrated a large benefit of tamoxifen in reducing the incidence of both invasive and non-invasive breast cancer by 49% and 50%, respectively.

- The Italian investigation recruited only women of low to normal risk of developing breast cancer. All the women had undergone hysterectomy, 48% of whom had also undergone oophorectomy and many (14%) were taking hormone replacement therapy (HRT). The dropout rate was over 26%.
- The English trial involved women who were considered to be at increased risk because of a family history of breast cancer. About 26% received HRT during the study and 35% stopped the trial treatment prematurely.

- HRT was not permitted in the National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 trial (the US trial) and the study population was defined as being at increased risk because of (1) age over 60 years old, (2) history of lobular carcinoma in situ or a predicted 5-year risk ratio for breast cancer of at least 1.66 based on the Gail model. The NSABP-P1 trial involved 13 388 women, whereas much smaller numbers participated in the Italian and the English studies.

Vigorous and often highly speculative controversy and argument followed the conflicting results of these trials, a debate fundamentally not winnable due to the differences in trial design and the numerous confounding variables involved in the investigations. However, a recent 20-year follow-up of the English trial reported a statistically significant 39% reduction in estrogen receptor positive (ER+) tumors with tamoxifen, a finding that was not apparent in the 1998 report.

The International Breast Cancer Intervention Study (IBIS-1) involved 7152 women with a family history of breast cancer, randomized to tamoxifen or placebo for 5 years. It confirmed the NSABP-P1 findings, showing a 32% reduction in the incidence of ER+, but not estrogen receptor-negative (ER-) breast cancer. However, the incidence of venous thromboembolism was 2.5 times higher and gynecological and vasomotor symptoms were 21% higher in the tamoxifen group.

A 96-month follow-up report in 2007 reinforced the findings of the initial observation and demonstrated that the tamoxifen-induced reduction of ER+ tumors was maintained for at least 10 years. Of importance also was the observation that the excess of thromboembolic, vasomotor, and gynecological symptoms did not persist after the 5-year treatment phase of the study. Thus, the benefit to risk ratio increased with the passage of time and implies a truly preventive effect of tamoxifen rather than a temporary reduction in risk of breast cancer.

Tamoxifen appears to reduce the risk of contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers. As primary chemoprevention, evidence exists that it reduces breast cancer incidence by 62% in *BRCA2* carriers but does not appear to confer risk reduction in healthy women who carry mutations in the *BRCA1* gene.

### Raloxifene

Meanwhile, the second-generation selective estrogen receptor modifier (SERM) raloxifene was undergoing evaluation in a randomized placebo-controlled study

primarily designed to investigate whether the use of this agent would reduce the incidence of bone fracture in 6828 postmenopausal women with osteoporosis. While showing a 30% reduction in the incidence of vertebral fracture, the trial also demonstrated a 72% reduction in ER+ breast cancer during 4 years of raloxifene treatment. The effect of an additional 4 years of raloxifene was assessed in women who agreed to continue the medication, and it was found that the incidence of invasive breast cancer was reduced by 66%. Although the risk of thromboembolism was increased (relative risk = 3.1) in the raloxifene group, the increased risk of endometrial cancer noted in a small number of women after prolonged tamoxifen use was not observed.

### Comparison of tamoxifen and raloxifene in chemoprevention

A direct comparison of raloxifene and tamoxifen was needed and was conducted by the NSABP (Study of Tamoxifen and Raloxifene [STAR] trial), the results being published in 2006. The STAR trial recorded the incidence of invasive and non-invasive breast cancer, thromboembolism, bone fractures, and uterine cancer in women aged  $\geq 35$  years old considered to have an increased risk of breast cancer with a 5-year predicted risk of  $\geq 1.66$  using the Gail risk model. A total of 19 747 women were randomized to either raloxifene (60 mg/day) or tamoxifen (20 mg/day) for 5 years. There were no statistically significant differences between the two groups in the incidence of invasive breast cancer or in uterine or other cancers. Likewise, the incidence of ischemic heart disease and bone fractures was similar in both groups of women. The incidence of uterine hyperplasia, with or without atypia, was significantly lower in the raloxifene group, as was the incidence of deep venous thrombosis, pulmonary embolism, and cataracts. Non-invasive cancers were identified less frequently in the tamoxifen group, the rate being 1.51 per 1000 women compared with 2.11 per 1000 in the raloxifene group, but this difference did not reach statistical significance.

### Ongoing studies

The adjuvant ATAC (Anastrazole, Tamoxifen, Alone or in Combination) study comparing a tamoxifen with an aromatase inhibitor (AI) provided clear information of the value of both of these agents in preventing contralateral breast cancer. The low rate of undesirable side effects with aromatase inhibitors makes them attractive for primary chemoprevention. Trials are underway comparing raloxifene with an AI and AI with placebo in high-risk women.

Observational studies have suggested that non-steroidal anti-inflammatory drugs (NSAIDs) and statins may be associated with a reduction in breast

cancer incidence, but data from rigorous randomized studies to evaluate their place in breast cancer chemoprevention are not available at present.

As the long-term, enduring efficacy of SERMs becomes consolidated and the adverse effects become lessened (possibly by reduction in dosage of tamoxifen and raloxifene or by prophylaxis of thromboembolism with low-dose aspirin) or more easily managed, it is likely that the chemoprevention of breast cancer will become more acceptable to women, to primary care physicians, and to those who specialize in oncology.

## Mammography screening for breast cancer

Whereas recommendations concerning the primary prevention of breast cancer are being defined continually and have not yet been applied routinely in clinical practice, the place of mammographic screening for early detection has been accepted in general for many years (Table 15.1) although questions and concerns remain.

The purpose of screening is to reduce premature mortality from the disease, and results in screening trials obviously take many years to mature. During the past 25 years, increased public awareness and improvements in diagnosis and treatment have reduced mortality from breast cancer in both screened and non-screened populations. Therefore, it is difficult to assess the impact of screening on survival in isolation. In the context of population screening, no evidence exists that breast self-examination reduces mortality from breast cancer.

For a screening program to be successful in its goal, a high level of compliance (over 70%) must be achieved, high quality must be obtained in radiographic imaging, and radiological interpretation and precision in image-guided biopsy must be obtained. Obviously, the diagnostic act per se of identifying breast cancer cannot influence mortality; good treatment is obviously also needed. Hence, some screening programs have as their endpoint, not the diagnosis but the completion of primary treatment.

### Randomized trials of screening by mammography

Seven well-publicized and influential trials concluded that formal periodic population-based screening by mammography was followed by a significant reduction in mortality from breast cancer (Tables 15.2 and 15.3).

The information derived from these investigations prompted the initiation of many regional and national breast screening programs.

**Table 15.1** Guidelines for breast cancer screening according to the American Cancer Society and the European Union

Population	Test or procedure	Frequency
American Cancer Society Women aged 20 years	Breast self-examination (BSE)	Beginning in their early 20s, women should be told about the benefits and limitations of BSE. The importance of prompt reporting of any new breast symptoms to a health professional should be emphasized. Women who choose to do BSE should receive instruction and have their technique reviewed on the occasion of a periodic health examination. It is acceptable for women to choose not to do BSE or to do BSE irregularly
	Clinical breast examination (CBE)	For women in their 20s and 30s, it is recommended that CBE be part of a periodic health examination, preferably at least every 3 years. Asymptomatic women aged 40 years should continue to receive a clinical breast examination as part of a periodic health examination, preferably annually
European Union Women aged 50–69	Mammography	Begin annual mammography at age 40 years Screening intervals 2–3 years

**Table 15.2** Results of randomized trials showing reduction in deaths from breast cancer after 7 and 13 years in screened groups of women with a relative risk of < 1 in 8 of 9 studies. Canada (1980) (a) = women aged 40–49 years old; Canada (1980) (b) = women aged 50–59 years old

Trial	Number enrolled	Breast cancer death rate per 1000 women at 7 years		Breast cancer death rate per 1000 women at 13 years		
		Screened	Not screened	RR + 95% CI	Screened	
New York (1963)	62,000	2.61	4.00	0.65 (0.49, 0.86)	7.03	8.45
Malmö (1976)	42,283	2.99	3.11	0.96 (0.68, 1.35)	4.20	5.20
Kopparberg (1977)	57,897	1.82	2.76	0.66 (0.46, 1.24)	3.27	5.60
Ostergotland (1978)	76,970	1.36	1.77	0.77 (0.54, 1.10)	3.51	4.63
Edinburgh (1978)	45,130	2.93	3.47	0.84 (0.61, 1.17)	6.15	7.19
Canada (1980) (a)	50,430	1.51	1.11	1.36 (0.83, 2.21)	4.16	4.28
Canada (1980) (b)	39,405	1.93	1.98	0.97 (0.62, 1.52)	5.43	5.33
Stockholm (1981)	59,176	1.38	1.94	0.71 (0.47, 1.07)	1.64	2.56
Gothenburg (1982)	51,611	2.91	3.74	0.79 (0.58, 1.08)	4.06	5.41

**RR**, relative risk; **CI**, confidence interval.

**Table 15.3** Results from randomized trials indicating no significant differences in overall death rates between screened and non-screened groups at 13 years. Canada (1980)  
 (a) = women aged 40–49 years old; Canada (1980) (b) = women aged 50–59 years old.

Trial	Overall death rate per 1000 women at 13 years		
	Screened	Not screened	RR + 95% CI
New York (1963)	68.19	68.78	0.99 (0.94, 1.05)
Malmo (1976)	121.31	122.34	1.00 (0.96, 1.04)
Kopparberg (1977)	156.45	151.31	1.03 (0.99, 1.08)
Ostergotland (1978)	124.0	124.38	1.00 (0.96, 1.04)
Canada (1980) (a)	16.38	16.38	1.00 (0.87, 1.14)
Canada (1980) (b)	37.24	35.04	1.06 (0.96, 1.18)
Gothenburg (1982)	69.10	76.75	0.89 (0.83, 0.95)

**RR**, relative risk; **CI**, confidence interval.

A Cochrane review in 2002, reassessed in 2006, made significant criticisms of the trials, including:

- suboptimal methodology in randomization
- unreliability of cause of death in many cases, with a bias in favor of screening
- a putative increased risk of cardiovascular death related to radiotherapy in the screened group, for whom radiation therapy was more frequently administered.

The review concluded that the trials that were ‘adequately randomised’ did not show a survival advantage in the screened group and those trials that found that screening did bring about a survival advantage of 25% after 13 years had suboptimal randomization. Nevertheless, the review reaffirmed that breast cancer mortality was reduced by 15% in the screened group. However, the review concluded that screening (1) is associated with an increase in ‘unnecessary’ diagnostic procedures, (2) identifies many ‘slow-growing’ tumors that may never be biologically dangerous, and (3) leads to the diagnosis of many cases of ductal carcinoma in situ (DCIS) that may never become invasive cancers. The 2002 review led to huge controversy in the scientific and medical community and even within the Cochrane groupings.

From another meta-analysis reviewing long-term results of population-based mammography screening programs, a reduction in breast cancer mortality of 22% was confirmed in women >50 years of age. In general, the value of screening in reducing breast cancer mortality has been accepted. Uncertainty exists about the upper age at which women are invited for screening and the ideal, cost-effective interval between screenings in population-based programs. The incidence of breast cancer increases with age, and compliance with invitations for screening is also likely to increase with age.

### **Screening by mammography in women aged 40–50 years old**

The efficacy of population-based screening of women between 40 and 50 years old has for many years been disputed because of the radiological ‘density’ of the breast in younger women, but the meta-analysis demonstrated a 15% reduction in mortality in this group of women. Other studies, while confirming a breast cancer mortality reduction in the 40–49-year-old age group, point to high rates of false-positive mammograms (20–50%), leading to many invasive procedures and inducing much anxiety among women who are subsequently shown to be free of breast cancer. For women in this age range, the risks of population-based screening may outweigh the advantages.

There can be no doubt that, by drawing attention to the need for teamwork and high quality at every stage, mammography screening programs have helped raise the standards of care for women with breast disease both within and outside of the screening process.

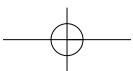
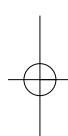
### **Magnetic resonance imaging in breast cancer screening**

Magnetic resonance imaging (MRI) screening is under evaluation in women who have a high risk of developing breast cancer. It appears to have a specificity of about 95%. In *BRCA* carriers, more than twice as many cancers were detected by MRI as by mammography, although some cancers, identifiable by mammography, were not found on MRI. At present, MRI and mammography are considered as complementary screening investigations for women who carry the *BRCA1* mutation and for the subgroup of *BRCA2* carriers who have radiologically dense breasts.

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# Cervical cancer

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## Epidemiology

In the year 2002, the incidence of cervical cancer accounted for almost 500 000 new cases. It varies widely depending on geographical, socio-economic, and lifestyle factors. The incidence is higher in developing nations (three-quarters of the patients), but even in developing nations there is an urban–rural difference.

- Data from the Surveillance, Epidemiology, and End Results (SEER) program from 17 geographic areas during the years 2000–2004 shows an age-adjusted incidence of 8.7 per 100 000 women per year. There is a racial difference in the incidence rates, with the Hispanics and African-Americans showing a higher incidence at 13.8 per 100 000 women and 11.4 per 100 000 women, respectively. The Caucasians, on the other hand, have an incidence of 8.5 per 100 000 women.
- An Indian hospital-based National Cancer Registry Program (Indian Council of Medical Research [ICMR]) showed cervical cancer as the leading female cancer in Bangalore, Chennai, and Dibrugarh, with the highest incidence in Chennai, where it constitutes 38.5% of all cancers. The other centers, Thiruvananthapuram and Mumbai, have cervical cancer as the second most common female malignancy. The population-based National Cancer Registry Program reports under the ICMR and shows the highest incidence of cervical cancer in Pondicherry 39.2/100 000 women and similar high rates in other parts of Tamil Nadu. On the other hand the states of districts in West Bengal and Karnataka show a much lower incidence at 13–13.9/100 000 women, again confirming the wide variability of this disease in different population groups. Overall, India sees 100 000 new patients with cervical cancer every year (one-fifth of the world's burden). A total of 83% of deaths due to cervical cancer occur in developing countries (282 000 deaths in the year 2002).

## Risk factors

Traditional risk factors include early age at first intercourse, multiple sexual partners, promiscuous behavior, early childbearing, and high-risk behavior of the male partner. With the availability of better methods of detection of human papillomavirus (HPV) infection in patients with cervical cancer, it is now clear that the traditional risk factors and associations only serve as a surrogate marker for genital HPV infection.

## Pathophysiology

More than 35 different HPV strains tropic to the genital tract have been identified, of which HPV types 16, 18, 31, 33, 42, and 45 are associated with high-grade cervical intraepithelial neoplasia (CIN) or invasive cervical cancer. Most HPV infections remain asymptomatic and are cleared from the genital tract within 1–2 years. Persistence of the virus in the keratinocytes is required for a neoplastic transformation.

With more sensitive tests now available, it is evident that more than 95% of cervical cancer is associated with HPV infection, of which HPV16 and HPV18 account for approximately 68% of squamous cell cancers and 83% of adenocarcinomas. All histological subtypes of cervical cancer are associated with HPV infection.

Infection with multiple subtypes of HPV does not confer additional risk. However, persistent HPV infection and a high viral load increases the risk of development of cervical cancer.

The HPV genome can be divided into two distinct regions:

- an ‘early’ region, E1–E7, which encodes the viral proteins involved in viral DNA replication, transcriptional regulation, and cellular transformation
- a ‘late’ region, L1 and L2, which encodes the viral capsid proteins.

Studies conducted in the related bovine papillomavirus show two transforming genes, the E5 gene and the E6 and E7 genes.

- E5 seems to act through the platelet-derived growth factor β. The HPV E5 gene is incorporated into the cell genome and is postulated to decrease the growth factor requirements of the infected keratinocytes.
- E6 and E7 genes play an important role in immortalization of keratinocytes:
  - The E6 protein combines with cellular ubiquitin protein ligase E6AP and the resulting complex, E6/E6AP, acts as a p53-specific ubiquitin ligase and mediates degradation of p53. The half-life of the p53 protein

is reduced from several hours to 20 minutes *in vitro* in E6-immortalized cells.

- The E7 protein acts through the retinoblastoma (Rb) tumor suppressor gene. In the normal state, the hypophosphorylated Rb, which is the active form, prevents the entry of the cell into the S phase. The E7 protein binds to the hypophosphorylated form and inactivates it, allowing cell entry into the S phase and oncogenesis.

## Screening in cervical cancer

The role of early detection and appropriate treatment is well established in cervical cancer. The incidence of cervical cancer-related mortality has come down by 70% in the last 50 years in countries with effective screening programs.

The cervical cancer screening program consists of a routine cytological examination with a Papanicolaou smear (Pap smear). The American College of Obstetricians and Gynecologists (ACOG), the American Cancer Society (ACS), and the US Preventive Services Task Force (USPSTF) recommendations are that screening should start approximately 3 years after the onset of sexual activity or by 21 years of age and recommend a follow-up examination once every 3 years or earlier if indicated based on previous cytology. The upper age limit for screening is not clearly defined. The cytological findings are classified according to the Bethesda, dysplasia/CIN, or Papanicolaou system (Table 16.1).

The lower grade lesions are observed and followed up with periodical Pap smear for progression. The high-risk lesions are treated with locoregional ablative/excisional procedures.

In many developing countries, routine Pap smear screening has not been feasible for various logistic reasons. The World Health Organization (WHO) has suggested alternative approaches such as visual inspection (VI), visual inspection with acetic acid (VIA), visual inspection with Lugol's iodine (VILI), and visual inspection with acetic acid plus magnification (VIAM).

VI is considered inadequate as it does not identify microscopic cancer, but these strategies may help in downstaging the disease.

## Prevention, including human papillomavirus vaccination

HPV infection is essentially a sexually transmitted disease, and hence safe sexual practices and barrier contraception can play a major role in prevention.

**Table 16.1** Comparison of Bethesda, CIN, and Papanicolaou systems

Bethesda system	Dysplasia/CIN system	Papanicolaou system
Within normal limits	Normal	Class I
Infection (specify organism)	Inflammatory atypia (organism)	Class II
Reactive and reparative changes		
Squamous cell abnormalities		
Atypical squamous cells of undetermined significance	Squamous atypia	Class IIR
Low-grade squamous intraepithelial lesion	Human papillomavirus atypia	Class IIR
	Mild dysplasia	CIN 1 Class III
High-grade squamous intraepithelial lesion	Moderate dysplasia	CIN 2 Class III
	Severe dysplasia	CIN 3 Class III
	Carcinoma in situ	CIN 3 Class IV
Invasive squamous carcinoma	Invasive squamous carcinoma	Class V

CIN, cervical intraepithelial neoplasia.

The etiological link between HPV and cervical cancer has led to the development of several HPV vaccines.

Three different vaccines have been developed:

- a monovalent vaccine for HPV16
- a bivalent vaccine for HPV types 16 and 18
- a quadrivalent vaccine for HPV types 6, 11, 16, and 18.

The protection offered by the vaccine is type-specific, and hence vaccination against more than one high-risk type offers more protection. HPV vaccination studies show that HPV16 L1 vaccination prevents persistent cervical HPV16 infection, which is taken as a surrogate marker for vaccine efficiency given the strong correlation between persistent HPV infection and cervical cancer.

A large randomized trial of quadrivalent vaccine, comprising 12 167 women who were followed for a period of 3 years, showed that when administered to subjects who had not been previously exposed to either HPV16 or HPV18, the prophylactic HPV vaccine was highly effective (98%) in preventing HPV16- and HPV18-related CIN grade 2 or 3 and adenocarcinoma in situ. Efficacy was 44% in the whole randomized group, which included women who were serologically positive for HPV16 or HPV18 prior to the first injection.

The vaccine appears to be more effective when administered prior to exposure to the putative virus type. The benefit of vaccination after exposure to a particular HPV type is not significant, but there may be protection against the other HPV types in the quadrivalent vaccine to which the patient has not been exposed.

The vaccine licensed for use consists of type-specific L1 capsid protein of HPV types 6, 11, 16, and 18, which forms a non-infectious virus-like particle (VLP) that induces immune response. Using recombinant DNA technology, the L1 protein is expressed in the yeast *Saccharomyces cerevisiae* and the proteins self-assemble into conformationally intact, non-infectious VLPs. Each 0.5 ml dose contains 20 µg of HPV6 L1 protein, 40 µg of HPV11 L1 protein, 40 µg of HPV16 L1 protein, and 20 µg of HPV18 L1 protein.

The administration schedule consists of a dose of 0.5 ml at 0, 2, and 6 months, administered intramuscularly in the deltoid muscle.

The Advisory Committee on Immunization Practices (ACIP) recommends the administration of the vaccine at 11–12 years of age. Vaccination can be started as young as 9 years of age. The vaccine is currently licensed for use between 9 and 26 years of age. Ideally, vaccination should be prior to onset of sexual activity but the vaccine can be used in older subjects who are serologically negative for the HPV types in the vaccine.

The adverse reactions to vaccine administration are:

- Minor:
  - local area pain, swelling, and erythema
  - fever on the day of vaccination.
- Major:
  - anaphylaxis in subjects sensitive to yeast – *S. cerevisiae*.

Other adverse effects, such as bronchospasm, gastroenteritis, and vaginal bleeding, have been reported in isolated patients; their association with the vaccine is unclear. No vaccine-related deaths have been reported. The vaccine may be administered during lactation but is contraindicated during pregnancy.

HPV vaccination clearly provides an alternative strategy for cervical cancer prevention in addition to regular screening. The impact will be even higher in countries where effective screening programs do not exist.

## Conclusion

Vaccination, screening, and safe sexual practices can reduce the cervical cancer morbidity and mortality significantly. However, this goal requires widespread health education and motivation of the target population to adopt these measures.

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# Colorectal cancer

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## Epidemiology

Colorectal cancer (CRC) is a common disease associated with considerable morbidity and mortality, with more than 1 000 000 new patients and 500 000 deaths annually. CRC has a natural history of transition from precursor to malignant lesion that spans, on average, 10–15 years, providing a window of opportunity for effective interventions and prevention. CRC might be preventable in up to 90% of patients with:

- Lifestyle modifications (balanced diet; avoidance of smoking and alcohol; and moderate physical activity). These can prevent up to 50% of the CRC cases.
- Compliance with screening methods: this remains a major barrier to the achievement of optimal results since a large part of the average-risk population are not being screened by any method.
- Chemoprevention that may, in future, constitute an alternative approach to reduce mortality from CRC.

## Colorectal cancer prevention

Several primary prevention strategies have been tested to prevent colorectal cancer. At the moment, besides the use of a healthy balanced diet and moderate physical activity, no prevention interventions have been shown to have a significant benefit in lowering the CRC risk.

## Dietary factors

### *Dietary fat and meat intake*

CRC rates are higher in populations with a high total fat intake compared to those consuming less fat.

- In animal studies, a high-fat intake increases the incidence of induced colon tumors.
- A number of prospective cohort studies have been conducted showing an increased risk of CRC with a higher meat, processed meat, or red meat consumption (beef, pork, lamb), and also with the intake of saturated and monounsaturated fat, predominantly derived from animals. There also seems to be a relationship with heterocyclic amines (HCAs) that are formed when meat and fish are cooked at high temperatures. Other studies could not show such a relationship.
- A randomized controlled study of dietary modification with reduction of the total fat intake by 20%, while increasing daily intake of vegetables, fruit, and grains, showed no evidence of reduction of invasive CRC.

These differences might be explained by:

- the validity of dietary questionnaires used
- differences in the average age of the population studied
- variations in methods of meat preparation (in some instances, mutagenic and carcinogenic HCAs could have been released at high temperatures)
- variability in the consumption of other foods such as vegetables.

### *Dietary fibers, vegetables, and fruit*

Dietary fibers, vegetables, and fruit might also have a protective effect against CRC.

- Fiber is a complex mixture of compounds, including insoluble fibers such as wheat bran and cellulose and soluble fibers such as dried beans. Ingestion of fiber could modify carcinogenesis in the large bowel by a number of mechanisms:
  - binding to bile acids
  - increasing fecal water and possibly diluting carcinogens
  - decreasing transit time
  - being a substrate for bacterial fermentation, with an increase in bacterial mass and the production of short-chain fatty acids, typified by butyrate, which has an anticancer effect in vitro.

- Most animal studies show a protective effect of dietary fiber on colon carcinogenesis.
- A meta-analysis of 13 case-control studies concluded that intake of fiber-rich foods is inversely related to CRC.
- The large prospective Nurses' Health Study found no difference in risk of CRC between women in the highest compared with the lowest quintile group with respect to dietary fiber.
- In two large prospective studies (Nurses' Health Study; Health Professional Follow-up Study) there was no relationship between fruit and vegetable consumption and CRC risk, whereas in a Swedish population-based prospective cohort study in 61 463 women the consumption of very low amounts of fruit and vegetables (<1.5 servings of fruit and vegetables/day) resulted in a higher risk ratio for developing CRC of 1.65 (95% confidence interval [CI] 1.23–2.2;  $p = 0.001$ ) compared to the consumption of more than 2.5 servings.

### *Calcium*

Calcium might lower the risk of CRC by binding bile acids and fatty acids, thereby reducing exposure to toxic intraluminal compounds or by an indirect effect on bile acid metabolism and a direct effect on colonic epithelial cells.

- Experimental studies in rodents showed a decrease in colonic epithelial cell proliferation after the administration of calcium citrate.
- Several epidemiological studies have observed an inverse relationship between calcium intake and cancer risk, but the interpretation of these studies is quite complex.
- A randomized placebo-controlled trial showed that calcium supplementation – 3 g of calcium carbonate daily (1200 mg of elemental calcium) – in patients with a recent diagnosis of adenoma reduced the risk of a recurrent adenoma (adjusted risk ratio [ARR] = 0.81; 95% CI 0.67–0.99) and the average number of adenomas (ARR = 0.76; 95% CI 0.60–0.96). The usual daily doses in trials ranged from 1250 to 2000 mg of calcium.

### *Vitamins*

In some studies, vitamins showed a protective effect of CRC, whereas this was not the case in others.

- In a prospective cohort study, there was an inverse association between the risk of CRC and vitamin E intake. However, the Women's Health Study showed no relationship between CRC in women and the use of 600 IU of vitamin E every other day.

- In a meta-analysis of supplemental antioxidant vitamins, no evidence of prevention of colorectal adenomas or cancer or other gastrointestinal tumors was found.
- A daily intake of 1000 IU of vitamin D and a concentration of serum 25-hydroxyvitamin D of 33 ng/ml are each associated with a 50% lower risk of CRC.

### Physical activity

A sedentary lifestyle has been associated with an increased risk of CRC. The average relative-risk reduction in CRC is between 40% and 50%. It is not known, however, whether the observed association is due to confounding variables such as diet or genetic predisposition to CRC. Obesity is associated with a two-fold increase in the risk of CRC in premenopausal women.

### Alcohol consumption

There is an association of CRC with alcoholic beverage consumption. This higher risk is mainly in men, particularly in regard to beer consumption and rectal cancer. Alcohol may stimulate mucosal cell proliferation, activate intestinal procarcinogens, and possibly may provide a source of unabsorbed carcinogens that can reach the distal large bowel.

### Cigarette smoking

Twelve percent of the CRC deaths are due to smoking.

- The Health Professionals Follow-up Study showed an association with the history of smoking with both small and large adenomas and with a long induction period of at least 35 years for colorectal cancer.
- In the Cancer Prevention Study II (CPS-II), a large multivariate-adjusted cohort study, CRC mortality rates were highest among current smokers, intermediate among former smokers, and lowest in never smokers, with increased risk observed after 20 or more years of smoking in men and women combined. It was estimated that 12% of colorectal cancer deaths in the US population in 1997 were attributable to smoking.
- A large population-based cohort study of Swedish twins found that heavy smoking of 35 or more years' duration was associated with a nearly three-fold increased risk of developing CRC, although subsite analysis found a statistically significant effect only for rectal but not colon cancer.

## Colorectal screening

Potential screening options for CRC include home fecal occult blood test (FOBT), flexible sigmoidoscopy, the combination of home FOBT and flexible sigmoidoscopy, colonoscopy, and double-contrast barium enema.

Each option has advantages and disadvantages that may vary for individual patients and practice settings. The choice of specific screening strategy should be based on patient preferences, medical contraindications, patient adherence, and available resources for testing and follow-up. Clinicians should inform their patients about the benefits and potential harms associated with each option before selecting a screening strategy.

### Starting screening

The start of CRC screening depends on the risk of the person:

- In persons without risk factors, CRC screening should start at 50 years of age.
- In persons at higher than an average risk, defined as individuals with a history of adenomatous polyps, with a personal history of curative-intent resection of colorectal cancer, or individuals with a family history of either colorectal cancer or colorectal adenomas diagnosed in a first-degree relative before 60 years, initiating screening at an earlier age and higher frequency is reasonable.
- In very high-risk patients, including those with a history suggestive of familial polyposis or hereditary non-polyposis CRC, or those with a personal history of inflammatory bowel disease, early screening with colonoscopy may be appropriate, and genetic counseling or testing is indicated for patients with genetic syndromes.

### Screening tests and intervals

Several screening tests are available and the screening interval depends on the test:

- Digital rectal examination and single office FOBT is of limited benefit as a screening method:
  - fewer than 10% of CRC arise within reach of the examining finger
  - the sensitivity of a single office FOBT is likely to be substantially lower than that of screening protocols involving multiple test cards.
- Annual FOBT offers greater reductions in mortality rates than biennial screening but produces more false-positive results. FOBT reduces CRC mortality by 16%.

- The recommended take-home multiple sample method should be used and consists of three test cards impregnated with guaiac that, when treated with a developer containing hydrogen peroxidase, give a color-coded result based on the presence of peroxidase-like activity of the heme in the stool. False-positive results are seen if certain foods, vitamins, or drugs (including meat, some raw fruit and vegetables, vitamin C tablets or high levels of foods containing vitamin C, or aspirin) are ingested in the days before taking the test.
  - Immunochemical tests employ labeled monoclonal and/or polyclonal antibodies that detect the intact globin protein portion of human hemoglobin. These antibodies do not react with non-human hemoglobin or with uncooked fruit and vegetables that may contain peroxidase activity. Immunochemical tests have performed well in clinical studies but their use in clinical practice is not frequent, due to technical and commercial reasons.
  - Specific DNA mutations are associated with the process of carcinogenesis and can be detected in the stool by polymerase chain reaction. Preliminary results show that this kind of testing is possible with a high sensitivity for cancer and large adenomas.
  - All positive tests should be followed up with colonoscopy.
- Flexible sigmoidoscopy is recommended every 5 years. Flexible sigmoidoscopy together with FOBT is preferred compared with FOBT or flexible sigmoidoscopy alone. All positive tests should be followed up with colonoscopy.
  - Colonoscopy every 10-year interval has been recommended regarding the natural history of adenomatous polyps.
  - Double-contrast barium enemas are recommended every 5 years because of their lower sensitivity. All positive tests should be followed up with colonoscopy.
  - Computed tomography (CT) colonography is an emerging technology that shows considerable promise, but it has not yet been studied in a typical screening population. It is not yet known if it has a comparable or superior performance compared with conventional tests.

The European Union (EU) stated in 1999 that if screening programs are implemented they should use the fecal occult blood test, and colonoscopy should be used for the follow-up of positive cases. Other screening methods – such as immunological tests, flexible sigmoidoscopy, and colonoscopy – can not be recommended for population screening at present.

### Screening duration

The appropriate age at which colorectal cancer screening should be discontinued is not known. Screening studies have generally been restricted to

patients younger than 80 years old, with colorectal cancer mortality rates beginning to decrease within 5 years of initiating screening. Yield of screening should increase in older persons (because of the higher incidence of colorectal cancer), but benefits may be limited as a result of competing causes of death. Discontinuing screening is therefore reasonable in patients whose age or comorbid conditions limit life expectancy.

The EU stated in 1999 that screening should be offered to men and women aged 50 to about 74 years old. The screening interval should be 1–2 years.

### Potential harms of screening

FOBT has few potential harms but false-positive tests can lead to invasive procedures such as colonoscopy. Sigmoidoscopy can lead to bowel perforation (1–2 in 10 000 examinations) or result in side effects such as pain (14%), anxiety, bleeding (3%), gas or flatus (25%). Barium enema results in important complications of any type in 1 in 10 000 examinations, perforation in 1 in 25 000 examinations, and death in 1 in 55 000 examinations.

Screening colonoscopy leads in 0.2–0.3% of procedures to major complications during or immediately after the procedures, the most common being bleeding that requires hospitalization or emergency care. Rates of perforation for diagnostic procedures ranged from 0.03% to 0.61%. Risks are higher in therapeutic (e.g. polypectomy) than in diagnostic or screening procedures and perforation rates of 0.07–0.72% and bleeding rates of 0.2–2.67% have been reported. Death is rare (1 in 16 000 to 1 in 27 000) and more likely in symptomatic patients with acute problems or those with comorbid conditions.

## Chemoprevention

At the moment, there is not enough evidence to advise the use of non-steroidal anti-inflammatory drugs (NSAIDs) or estrogens as chemopreventive treatments for CRC.

### Non-steroidal anti-inflammatory drugs

NSAIDs inhibit the activity of cyclooxygenase (COX), which metabolizes arachidonic acid into prostanoids, prostaglandins, and thromboxane A<sub>2</sub>. NSAIDs include aspirin, first-generation non-selective inhibitors of COX-1 and COX-2 (e.g. indometacin, sulindac, piroxicam, ibuprofen, naproxen), and second-generation drugs that inhibit COX-2 (e.g. celecoxib).

## Aspirin

- Several epidemiological studies have reported a reduction of 30–40% in CRC incidence associated with the use of aspirin. The benefit appears to be dose-related. A similar dose–response relationship was observed for non-aspirin NSAIDs. However, the incidence of major gastrointestinal bleeding events also appears to be dose-related.
- In the Physicians' Health Study, 22 000 men aged 40–84 years old were randomly assigned to receive placebo or aspirin (325 mg every other day) for 5 years. There was no reduction in invasive cancers or adenomas at a median follow-up of 4.5 years.
- In a randomized study of 635 patients with prior colorectal cancer (T1T2N0M0) who had undergone curative resection, aspirin intake at 325 mg/day was associated with a decrease in the ARR of any recurrent adenoma as compared with the placebo group (0.65; 95% CI 0.46–0.91) after a median duration of treatment of 31 months.

## Sulindac

- Several studies have demonstrated the effectiveness of sulindac in reducing the size and number of adenomas in familial polyposis.

## Celecoxib

- In a randomized double-blind placebo-controlled study of 77 patients with familial adenomatous polyposis, patients receiving 400 mg of celecoxib twice a day had a 28.0% reduction in the mean number of colorectal adenomas ( $p = 0.003$  for the comparison with placebo) and a 30.7% reduction in the polyp burden (sum of polyp diameters;  $p = 0.001$ ) as compared with reductions of 4.5% and 4.9%, respectively, in the placebo group. The reductions in the group receiving 100 mg of celecoxib twice a day were 11.9% ( $p = 0.33$  for the comparison with placebo) and 14.6% ( $p = 0.09$ ), respectively.

The potential use of NSAIDs as a primary prevention measure is being studied. There are several unresolved issues, making general recommendations for their use at this moment questionable, such as:

- a paucity of knowledge about the proper dose and duration
- concerns about whether the potential preventive benefits such as a reduction in the frequency or intensity of screening or surveillance could counterbalance long-term risks such as gastrointestinal ulceration and hemorrhagic stroke for the average-risk individual.

## Postmenopausal female hormone supplements

Several epidemiological studies have suggested a decreased risk of colon cancer among users of postmenopausal hormone replacement therapy (HRT). For rectal cancer, most studies have observed no association or a slightly elevated risk.

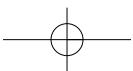
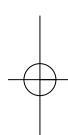
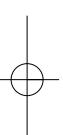
- In the Women's Health Initiative Trial, 16 608 postmenopausal women aged 50–79 years old were randomly assigned to a combination of conjugated equine estrogens (0.625 mg/day) + medroxyprogesterone (2.5 mg/day) or placebo. There was a risk reduction of CRC by 44% in the HRT group compared with placebo (hazard ratio [HR] 0.56; 95% CI 0.38–0.81,  $p = 0.003$ ).

## Conclusion

Preventive strategies may decrease the incidence and mortality of CRC. The introduction of CRC screening should be encouraged, as in many European countries this screening measure is not routinely used. The study of chemopreventive strategies is ongoing and results will be available in years to come.

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# Prostate cancer prevention

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## Introduction

Prostate cancer is the most frequently occurring cancer in men in most Western countries, and in the United States it is the second leading cause of cancer-related deaths after lung carcinoma. In Europe, an estimated 2.6 million new cases of cancer are diagnosed each year. Prostate cancer constitutes about 11% of all male cancers in Europe, and accounts for 9% of all cancer deaths among men within the European Union (EU).

Among factors that determine the risk of developing clinical prostate cancer, age (70% of all cases occur in men older than 65 years old) and heredity have been recognized as important risk factors.

## Hereditary factors

- If one first-line relative has the disease, the risk is at least doubled. If two or more first-line relatives are affected, the risk increases 5- to 11-fold.
- A small subpopulation of individuals with prostate cancer (about 9%) have true hereditary prostate cancer, defined as three or more relatives affected or at least two who have developed early-onset disease, i.e. before 55 years.
- Sub-Saharan African ancestry has been recognized as an important risk factor for prostate cancer.

## Age

- Autopsy studies show that a third of men in their fourth decade of life harbor microscopic prostate cancer cells. By 60 years old, this number reaches over 50%.

## Regional differences

The prevalence of microscopic prostate cancer seems to be the same across the globe. This finding is in sharp contrast with the incidence of clinical prostate cancer, which varies widely between different geographical areas and ethnic groups, being high in the United States and Northern Europe and low in South-East Asia. The lifetime risk of being diagnosed with prostate cancer now approaches 1 in 7 and may hit 25% in the next decade in North America. The risk of dying from the disease is, however, much lower, around 4%.

There is a large discrepancy between histological incidence and death and potentially for overdiagnosis and overtreatment of clinically insignificant disease. This is even more relevant as treatment-related morbidities associated with prostate cancer treatment can impact urinary and sexual functions as well as quality of life.

Prostate cancer represents an ideal target for chemoprevention because of its long latency, its high incidence, tumor marker availability (prostate-specific antigen [PSA]), and identifiable preneoplastic lesions (high-grade prostatic intraepithelial neoplasia [PIN]) and high-risk groups.

## Genetic factors in prostate cancer

In the last 20 years, evidence that prostate cancer may be caused by multiple genes, possibly interacting with endocrine and environmental factors, has continued to grow. Linkage studies have identified susceptibility loci for prostate cancer on several chromosomes, including *HPC1* on chromosome 1q23-25, *HPC2* on chromosome 17p, *HPC20* on chromosome 20q13, *HPCX* on chromosome Xq27-28, linkage to chromosome 8p22-23, *PCAP* on chromosome 1q42-43, and *CAPB* on chromosome 1p36, while several strong candidate genes have been mapped, including *RNASEL*, *ELAC2*, and *MSR1*. Recently, translocations fusing the strong androgen-responsive gene, *TMPRSS2*, with ERG or other oncogenic E26 transformation-specific (ETS) factors may facilitate prostate cancer development.

## Roles of dietary and environmental/lifestyle factors

Although several genetic predisposition factors for prostate cancer have been discovered during the previous years, an environmental trigger is probably necessary for the disease to become manifest, even for carriers of strong cancer susceptibility genes, because only a minority of these men will develop the disease.

- A study of 44 788 pairs of twins listed in the Swedish, Danish, and Finnish twin registries found that inherited genetic factors make a minor contribution to susceptibility to most types of neoplasms, including prostate cancer, and indicated that environment played the principal role in causing sporadic cancers. Among these environmental factors, nutrition has been suspected to play a major role. Most of the available clinical evidence on the influence of diet on prostate cancer comes from observational rather than interventional studies and should be analyzed with caution.

Evidence supporting a role of dietary and/or environmental/lifestyle factors in the pathogenesis of prostate cancer includes the strikingly different incidence and mortality rates evident in different geographic areas, e.g. Japan and China, where incidence and mortality rates are low, versus the United States and Caribbean nations, where they are high, and the fact that migrants from low- to high-incidence areas adopt a higher risk of the disease.

- A number of epidemiological studies implicate a high intake of saturated fat, red meat, and dairy products, in the pathogenesis of prostate cancer.
- Recent findings suggest that obesity may be associated with progression of latent to clinically significant prostate cancer.
- The association between dietary factors and prostate cancer has now been investigated in epidemiological studies of 30–40 populations. The results of these studies are mostly conflicting but some dietary components are consistently associated with prostate cancer, such as high intakes of  $\alpha$ -linolenic acid (a polyunsaturated fatty acid in vegetables and dairy products) and calcium.

One explanation for the low incidence of prostate cancer in Asia might be high consumption of dietary phytoestrogens. Soybeans (generally processed into soymilk or tofu) have one of the highest contents of phytoestrogens, especially flavonoids, which have a prophylactic effect on prostate cancer. Several mechanisms might explain how these natural estrogens affect prostate cancer cells:

- an antiestrogenic effect via the estrogen receptor
- reduction of circulating concentrations of androgens by increasing the concentration of the sex hormone-binding globulin
- increase of apoptosis
- regulation of angiogenesis.

Frequent intake of tomato-based products, particularly tomato sauce, is associated with a reduced risk of prostate cancer. Tomatoes contain lycopene, a carotenoid and potent antioxidant. The effects have been proven in a transgenic mouse model. In a study of 2481 men with prostate cancer, men who consumed large amounts of lycopene had a 16% lower risk than men who consumed small amounts of lycopene. Lycopene is a promising compound for chemoprevention.

Of the micronutrients that have been investigated in prostate cancer, selenium and vitamin E are the most promising. After 4–5 years of follow-up of 1312 patients with a history of skin cancer, incidence of this disease did not differ between those given selenium and those given placebo; however, prostate cancer was 66% lower in the selenium group than in the placebo group.

Vitamin E ( $\alpha$ -tocopherol) is a fat-soluble vitamin that has antioxidant effects, with particular activity in oxidative-induced DNA damage. Results from the Finnish randomized prevention trial, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) trial, showed a 40% decrease in incidence and mortality in prostate cancer in men taking  $\alpha$ -tocopherol compared with those taking placebo.

### Hormones and other risk factors

Androgens play an important part in the development of the healthy prostate and in the treatment of prostate cancer. The prostate converts testosterone to dihydrotestosterone, a key substrate for downstream hormone metabolism, through the  $\alpha$ -reductase enzymatic pathway. Finasteride inhibits the type 2  $\alpha$ -reductase whereas dutasteride inhibits both type 1 and type 2 subtypes.

### Prostate cancer chemoprevention: clinical trials

Currently, several National Cancer Institute (NCI)-sponsored prostate cancer clinical trials are in progress at various institutions in the United States (Table 18.1).

**Table 18.1** Prostate cancer clinical trials

Agent	Institute
Exisulind	Mayo Clinic
Celecoxib	Johns Hopkins
Soy isoflavones (genistein)	Wayne State University
l-Selenomethionine	Roswell Park Cancer Institute/SWOG
Selenium yeast	University of Arizona
Difluoromethylornithine (DFMO)	University of California – Irvine
Toremifene	University of Pittsburgh
DFMO and bicalutamide	University of Alabama
Vitamin D analogue (Hectorol; doxercalciferol)	University of Wisconsin
Vitamins E, C and multivitamin	Brigham and Women's Hospital
Soy isoflavones (genistein)	Northwestern University
Selenium	Southwest Oncology Group
Calcitriol	Robert Wood Johnson Medical School
Fish oil	Oregon Health and Science University
Aspirin	University of Washington
Lycopene	University of Illinois

Source: <http://www.cancer.gov/prevention/pucrg/prostataftrials.html>.

### Phase III trials

- The Selenium and Vitamin E Cancer Prevention Trial (SELECT) sponsored by the NCI is a randomized, prospective, double-blind study designed to determine whether a 7- to 12-year regimen of daily selenium, vitamin E supplements, or both, or placebo in a four-arm intervention design will decrease the risk of prostate cancer in healthy men. Study supplements include 200 g l-selenomethionine, 400 IU/day racemic  $\alpha$ -tocopherol and an optional multivitamin that does not contain either selenium or vitamin E. The target accrual is 32 400 individuals, and the results are expected to be announced in 2013. The true safety and effectiveness of selenium and vitamin E should become clearer when the results of the SELECT study

become available (SELECT details available at <http://www.crab.org/select/>).

- In 1993, the Prostate Cancer Prevention Trial (PCPT) was initiated and funded by NCI to investigate chemoprevention of prostate cancer with the 5 $\alpha$ -reductase inhibitor finasteride: 18 882 men who had normal digital rectal examination (DRE) and a PSA level of <3.0 ng/ml were randomized to either finasteride 5 mg/day or placebo for 7 years. Prostate biopsy was advised if the PSA rose to >4.0 ng/ml or the DRE became abnormal. Prostate cancer was detected in 18.4% of men in the finasteride group and 24.4% in the placebo group. The finasteride reduced the period of prevalence of prostate cancer by 24.8% ( $p < 0.001$ ), compared with placebo. However, tumors were of Gleason score 7–10 in 6.4% of the finasteride-treated men, compared with 5.1% of the placebo group ( $p = 0.005$ ), and sexual side effects were more common in the finasteride arm. The explanation for more aggressive tumors in the men treated with finasteride has been attributed to a ‘volume-artifact’ effect (<http://www.cancer.gov/pcpt>).
- Another phase III clinical trial using 5 $\alpha$ -reductase inhibitor is the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial which will evaluate dutasteride, a dual inhibitor of both 5 $\alpha$ -reductase types 1 and 2. The difference from PCPT is that all men will have pretreatment biopsies and PSA in the intermediate range (2.5–10 ng/ml). Dutasteride suppresses levels of dihydrotestosterone by >90%, compared with a suppression of  $\pm 70\%$  with finasteride. So far, 8000 men have been recruited to receive either 0.5 mg of dutasteride or placebo for 4 years. The results of this study will not be available for some time yet, but may shed new light on the subject of the effectiveness of dutasteride in preventing prostate cancer.

### Prostate cancer chemopreventive agents in phase I and II clinical trials

- Selective estrogen receptor modulators (SERMs) are generally considered to be ‘weak estrogens’ because they possess both agonist and antagonist activities, depending on the specific tissue type and on the relative estrogen receptor (ER) subtype interactions. Toremifene has been evaluated in a phase IIa exploratory trial in men with high-grade PIN. After 4 months of treatment with a daily oral dose of toremifene, 18 men with high-grade PIN underwent a repeat prostate biopsy. The prostate biopsy specimens showed significantly less high-grade PIN than historical controls. This trial provided the proof-of-concept support behind a currently open 485 patient placebo-controlled, randomized dose finding phase IIb/III clinical trial. This trial is investigating the efficacy of toremifene in reducing prostate cancer incidence in men with high-grade PIN. Men with high-grade PIN

are treated for 12 months with placebo or toremifene and will undergo a repeat prostate biopsy at 6 and 12 months (<http://www.gtxinc.com/tech/clinical.htm>).

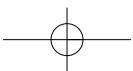
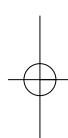
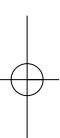
- Difluoromethylornithine, vitamin D, soy isoflavones, and lycopene are all currently being evaluated in several ongoing trials. The trial details are available at <http://www.cancer.gov/search/ViewClinicalTrials>.
- Green tea catechins are also potential candidates for chemoprevention.
- Statins might also be investigated in the near future.

## Conclusion

Prostate cancer prevention has grown from a virtually unknown field 15 years ago into a major area of scientific and clinical investigations. Prostate cancer is basically an ideal candidate for exogenous preventive measures, such as dietary and pharmacological prevention, due to some specific features: high prevalence, long latency, endocrine dependency, availability of serum markers (prostate-specific antigen), and histological precursor lesions (PIN). From a public health standpoint there is tremendous potential for benefit from large-scale cancer prevention trials. Prospective randomized chemoprevention trials for prostate cancer are expensive and require long periods of time to conduct, yet they are worth embarking on.

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# Lung cancer screening

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## Epidemiology

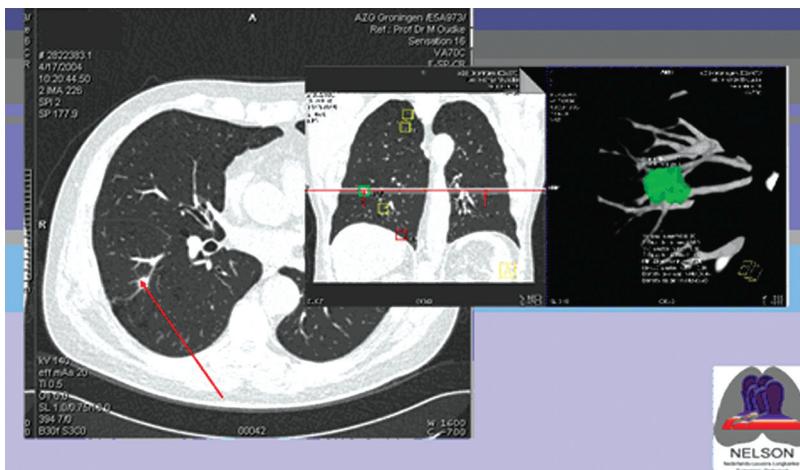
Lung cancer is today the most frequently occurring cancer in the world. It currently accounts for approximately 5% of all deaths in most developed countries and, as such, constitutes a major public health problem. Despite the fact that prostate cancer is more common in men than lung cancer, and breast cancer more common in women than lung cancer, mortality from lung cancer exceeds these two cancers plus colorectal cancer combined. Lung cancers are estimated to account for about 15% of all cancers and represent the leading cause of death from cancer.

At the beginning of the 20th century lung cancer was a very rare disease, but rates have increased so dramatically that lung cancer can be considered a major epidemic of the 20th century. Theoretically, primary prevention, quitting smoking, or, more importantly, measures to reduce starting smoking may almost totally eliminate the disease, but although several such measures have been successful, the number of lung cancer deaths each year is still unacceptably high. At the same time, the risk for lung cancer is increasing rapidly in women, and increasing rapidly in many other countries in Europe and worldwide, and smoking in adolescents is also unfortunately increasing. It is further estimated that the risk for the population remains very high for a long time after quitting smoking: in the United States, more ex-smokers now develop lung cancer than current smokers.

More than two-thirds of these people are diagnosed with locally advanced or metastatic disease, and their poor prognosis is due to late diagnosis and lack of effective treatment of metastatic disease. Less than 15% of the patients are surviving 5 years, and in several European countries the 5-year survival is far less.

## Lung cancer screening

With the advent of a new screening technique, the low-dose multislice computer tomography (CT) scan, screening for lung cancer has received renewed



**Figure 19.1** Example of a low-dose multislice CT scan with volumetric software.

Workstation: Syngo Lungcare, Leonardo. (Courtesy of Siemens Sensation – 16, Siemens Medical Solutions, Forchheim, Germany.)

interest after the negative results of large randomized trials with chest X-rays in the 1970s (Figure 19.1).

The technique is well suited to high throughput screening programs: no contrast is needed; the lungs can be completely scanned within one breath hold; and radiation exposure is comparable to a chest X-ray in two directions.

As in other cancer screening programs, lung cancer screening is subject to participation grade, lead time, length time, overdiagnosis, and sticking diagnosis biases. Due to these biases, the most appropriate way to determine the effectiveness of lung cancer screening is a prospective randomized controlled trial comparing lung cancer mortality in the screen arm with the control arm.

### Observational vs low-dose CT (LDCT) screening trials

Currently, a large number of non-randomized cohort studies on lung cancer multislice CT screening trials are running or have been completed. In a review, Mulshine et al performed a pooled analysis of five large observational studies including the Anti-Lung Cancer Association (ALCA) and the Hitachi Health Center study from Japan, the Early Lung Cancer Action Project (ELCAP) and

the Mayo Clinic Study from the United States, and the Lung Cancer Screening Study from Milan in Italy. In total, 13 122 baseline and 10 245 annual follow-up scans have been evaluated: 55–85% of the lung cancers detected at baseline and 60–100% of the cancers detected at annual repeat screening were stage I tumors. This is markedly better than in the current clinical practice, where only 15–20% of all newly diagnosed lung cancer patients have stage I disease. The lung cancer detection rate varied between 0.4–2.7% in these trials at baseline and 0.07–1.1% at annual repeat. Invasive procedures for benign lesions have been performed in 4–22% at baseline and in 14–55% at annual repeat screening and the proportion of interval cancers ranged between 0 and 22%.

Since the introduction of spiral CT screening in the 1990s in Japan, the 5-year survival rate of all stages of lung cancer has improved to 76.2%. Henschke et al even reported 10-year survival rates of 88% of the subgroup of 412 stage I lung cancer patients detected at baseline or annual repeat screening. In a different study, Henschke et al found a clear relationship between tumor size and lymph node status. The percentages of patients without lymph node metastases were 91%, 83%, 68%, and 55% for tumor size categories of <15 mm, 16–25 mm, 26–35 mm, and >35 mm, respectively.

The percentages of N0M0 cases in screen-diagnosed lung cancers are much higher than previously reported in the Surveillance, Epidemiology, and End Results (SEER) registry, which may support the hypothesis that the smaller the cancer detected, the better the prognosis is, but again all earlier mentioned biases from cohort studies do apply. The only study published so far with five consecutive annual screening rounds and a very high attendance rate is the Mayo Clinic study. Of the 68 lung cancers detected over the 5-year period, only three interval cancers were detected, two of them by sputum cytology. This means that the sensitivity of the spiral CT scan in detecting lung cancer is 93% (63/68), the specificity 99%, and the positive predictive value 84%.

### Randomized LDCT screening trials

At present, there are basically only two large randomized clinical trials: the Dutch–Belgian NELSON trial in conjunction with a Danish center and a German screening center in Heidelberg, and the National Lung Screening Trial (NLST) in the United States.

- The NLST was launched in 2002, and randomized 53 476 smokers (>30 pack-years) or ex-smokers (<15 years) between annual CT screening or

chest X-ray for three screening rounds in 46 sites. Participants were recruited from the media. All participants have completed the three screening rounds and the participation rate was more than 90% in both arms of the trial. Final analysis is intended to take place in 2009.

- The NELSON trial has randomized 16 000 subjects between 50 and 75 years of age between a multislice CT scan in years 1, 2, and 4 versus no screening. The second screening interval is 2 years. Current or former smokers have been selected with a history of at least 11 cigarettes per day for at least 30 years or 16 cigarettes per day for at least 26 years. Former smokers may not have quit more than 10 years ago. Baseline and the first incidence screening round have been completed. Mortality data will become available in 2015. In contrast to the other randomized trials (except for the ITALUNG-CT trial) participants of the NELSON trial have been selected by taking a random sample from the population to avoid selection bias.
- The Danish randomized screening trial ( $n = 4000$ ) is conducted according to the NELSON design, with similar selection criteria and radiological and work-up protocols. The difference with the Dutch part of the NELSON trial is that participants have been recruited through the media and that there are five annual screening rounds. Baseline screening and half of the first incidence round have been completed.
- The randomized trial in Heidelberg, Germany, has recently been launched ( $n = 4000$ ), completely in accordance with the NELSON design, including random sampling from the population of participants.

## Overdiagnosis

Overdiagnosis or the detection of lung cancer that would otherwise not have been diagnosed during lifetime, because of slow growth rate or competing age-related risks for death, remains an important concern as CT resolution continues to find much smaller lung cancers.

Whether overdiagnosis is really an issue in lung cancer screening is yet unknown.

- Assuming that overdiagnosed cancers have a volume doubling time (VDT) of more than 400 days, in the Mayo Clinic CT screening trial, 27% of all cancers detected were overdiagnosed cases. Eighty-five percent of the tumors with a VDT of >400 days were women and only 15% men. The nodules with ground glass or part-solid attenuation constituted only a slight majority of the tumors with a VDT of >400 days.
- Overdiagnosis rates of around 40% have been reported in Japan.

## Stage shift and mortality reduction

While awaiting the lung cancer mortality data from randomized trials, several groups have attempted to estimate the mortality reduction by CT screening.

- Swensen et al used data from 1520 patients screened with CT for 5 years and found lung cancer incidence and mortality rates that were similar to those of persons screened with chest radiographs in the previous Mayo Lung Project (MLP) (2.8 vs 2.0 per 1000 person-years).
- In a recent paper, Bach et al reported their analysis of CT screening based on a combined cohort of three single-arm studies of 3246 participants, and compared the observed numbers of lung cancer outcomes with the expected numbers from a validated lung cancer prediction model. They observed a three-fold increase in the number of new lung cancer cases detected and a 10-fold increase in the number of lung cancer patients resected, but no decrease in advanced-stage disease (42 observed vs 38.8 expected) or in lung cancer deaths (38 observed vs 38.8 expected). The investigators acknowledge that within a median 3.7 years follow-up period only a 30% mortality reduction could have been observed, and that prolonged follow-up or more screening rounds could have led to a mortality difference. Also, the accuracy of the Bach model is of concern because it might have underestimated the expected number of lung cancer patients in the screen cohort, which biases against CT screening, while the population of Bach's study had probably a higher cancer risk because of a stronger smoking history and prevalence of chronic obstructive pulmonary disease (COPD), although adjustments for the increased cancer risk by COPD have been made.

## Current position statements

Based on the results of several completed and ongoing lung cancer screening studies, several new position statements from professional organizations have been released recently. In fact, all stress that available data now show that spiral CT screening can diagnose lung cancer at a significantly earlier stage.

However, it remains still unclear whether this will lead to a reduction in advanced-stage disease and lead to a health benefit and reduction in lung cancer mortality.

Therefore, the International Association for the Study of Lung Cancer (IASLC) recently recommended against the widespread adoption of costly CT screening interventions and await the results of large randomized controlled screening trials such as the US National Lung Screening Trial and the Dutch–Belgian NELSON trial.

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# Hereditary cancer syndromes: general principles on the role of prevention and screening

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## Introduction

Growing understanding of cancer genetics has led to better identification of carriers of mutations that confer a high risk of developing particular types of cancer. Once identified, these mutation carriers can be offered tailored preventive options. Many dozens of hereditary cancer syndromes have already been reported and most types of cancer can be part of one or more of these syndromes.

## Prevention in hereditary cancer

Prevention of hereditary cancer has four different approaches:

- Surveillance aimed at detecting early-stage cancers or their precursors (e.g. colorectal adenomas). This is offered to proven mutation carriers or, in case the causative mutation has not yet been identified in a family, to affected relatives, because of their risk of developing additional primary tumors, as well as to their close asymptomatic relatives. Surveillance protocols have been developed for a large number of syndromes. As most of these syndromes are (very) rare, the screening guidelines are usually based on expert opinion rather than on the outcome of prospective (randomized) studies on screening efficacy. The guidelines may show large differences between countries, and even between regional clinics.

- Risk-reducing surgery is usually only offered to proven gene carriers. Best-known examples are prophylactic colectomy in familial adenomatous polyposis (FAP), thyroidectomy in multiple endocrine neoplasia type 2 (MEN2), mastectomy and salpingo-oophorectomy in hereditary breast–ovarian cancer, and gastrectomy in hereditary diffuse type gastric cancer.
- Chemoprevention is still in its infancy with respect to its use in hereditary cancer. Very few examples exist. A range of non-steroidal anti-inflammatory drugs (NSAIDs), including sulindac, have been shown to reduce polyp size and numbers in FAP, which can be helpful in the clinical management of FAP but cannot replace the role for prophylactic colectomy.
- Modifying the clinical manifestation, i.e. ‘penetration’ of inherited gene defects, by changing lifestyle or reducing exogenous risk factors can be part of cancer prevention as well, but very little of its effect on tumor risk in hereditary cancer syndromes is known.

Guidelines for preventive options for hereditary cancer syndromes can be found on the GeneClinics website ([www.geneclinics.org](http://www.geneclinics.org), GeneReviews section). It should, however, be remembered that the largest group of patients screened for familial cancer is that of those identified by a positive family history of cancer, and/or early age at diagnosis, without known underlying gene defect and without meeting clinical criteria for the known hereditary cancer syndromes. Familial clustering of colorectal cancer, and of breast cancer, are the most important subgroups. They are discussed in detail in the next chapter.

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# Hereditary cancer syndromes: role of prevention and screening

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## Introduction

Cancer results from complex interactions between multiple genes and environmental factors. In families with hereditary cancer, one single altered susceptibility gene is largely responsible for cancer risk. Most hereditary cancer syndromes are inherited in an autosomal dominant fashion. Individuals who inherit cancer susceptibility genes inherit a predisposition to cancer rather than the cancer itself. Some mutation carriers do not develop cancer, indicating that these altered genes are ‘incompletely penetrant’, and a mutation in the second allele is required for cancer to develop.

This chapter gives a review of the main surveillance, surgery, and screening measures used in the most frequent hereditary cancer syndromes.

## Hereditary breast and ovarian cancer syndrome

The most common defined predispositions of the hereditary breast and ovarian cancer syndrome (HBOC) are highly penetrant mutations in the breast cancer-associated genes, *BRCA1* and *BRCA2*. The overall risk over a lifetime of breast cancer associated with the *BRCA* genes ranges from 40% to 85%.

*BRCA1* or *BRCA2* mutation carriers may be advised to follow general health guidelines, thought to reduce cancer risk, although the benefits have not been demonstrated in this group.

They include the following:

- a low fat diet
- a high fiber diet, rich in fresh fruit and vegetables
- regular exercising
- avoiding cigarettes and excessive alcohol use.

Two studies have been published suggesting that obesity at an early age could be a risk factor in mutation carriers. Physical activity, a normal weight at menarche, a low weight at the age of 21 years, or weight loss between the ages of 21 and 31 years, have been associated with a later age of onset of breast cancer in mutation carriers.

The strategies of screening or reducing the risk of cancer in women with hereditary cancer susceptibility genes can be classified in three groups:

- prophylactic surgery (mastectomy and/or oophorectomy)
- chemoprevention
- surveillance.

### Prophylactic surgery

In women with *BRCA* mutations, the risk of breast cancer may be reduced by both prophylactic mastectomy and oophorectomy.

Prophylactic mastectomy reduces the incidence of breast cancer in mutation carriers, with a risk reduction of about 85–95%, depending on the type of surgery:

- A total (simple) mastectomy is recommended for prophylaxis because subcutaneous mastectomy leaves behind more glandular tissue that remains at risk for future cancers.
- Skin-sparing mastectomy with or without preservation of the nipple–areolar complex appears to provide superior cosmetic results.

Prophylactic bilateral salpingo-oophorectomy (BSO) decreases the incidence of subsequent breast and ovarian cancer (55–70% and 85–95% risk reduction, respectively), and sometimes leads to the diagnosis of occult early-stage ovarian cancer. In view of the lack of efficacy of increased surveillance for ovarian cancer, it is recommended that *BRCA1* and *BRCA2* carriers undergo prophylactic BSO after age 35 years or once childbearing is completed. Removal of both tubes should be performed because of the risk of fallopian tube carcinoma. Despite the reduction in ovarian and fallopian tube cancer, women who undergo prophylactic BSO have a small residual risk for primary peritoneal cancers.

The acute symptoms derived from the precocious menopause, the increase of the cardiovascular risk, and osteoporosis should be considered in relation to the risk/benefit of oophorectomy.

Hormone replacement therapy (HRT) for the symptoms associated with menopause is a controversial subject. Tamoxifen and raloxifene, selective estrogen receptor modulators (SERMs), are an alternative to HRT, protecting the bone mass and reducing the risk of developing cancer in high-risk women.

### Chemoprevention

Chemoprevention (i.e. pharmacological risk reduction) is another strategy for reducing cancer development in high-risk patients.

- *Tamoxifen.* In *BRCA* genes mutation carriers diagnosed with breast cancer, adjuvant treatment with tamoxifen has been demonstrated to reduce the risk of contralateral breast cancer, but there are no studies demonstrating a benefit in prevention in healthy *BRCA* gene mutation carriers. There are four chemoprevention randomized studies published comparing tamoxifen with placebo in healthy women. None of them specifically evaluated the role of chemoprevention in *BRCA* gene mutation carriers. A subset analysis performed in the NSABP-P1 study demonstrated a non-significant risk reduction with tamoxifen in *BRCA2* mutation carriers (odds ratio [OR] = 0.38, 95% confidence interval [CI] 0.06–1.56) and no risk reduction in *BRCA1* mutation carriers (OR = 1.67, 95% CI 0.32–10.7). Tamoxifen was approved by the US Food and Drug Administration (FDA) for breast cancer prevention, but is not yet recommended in Europe as a chemopreventive agent.
- *Raloxifene and aromatase inhibitors.* There are no data regarding the benefit of these drugs in *BRCA* mutation carriers.

In conclusion, there are no data to recommend chemoprevention with tamoxifen, raloxifene, or aromatase inhibitors to reduce the risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers. Chemoprevention must be considered in the context of clinical trials and randomized trials should be performed in order to show any benefit.

- *Oral contraceptives.* Oral contraceptives decrease the risk of ovarian cancer in the general population, but they may increase the risk of breast cancer in mutation carriers, particularly with *BRCA1*. Thus, it is possible that oral contraceptives have a dual impact on cancer risk in carriers of *BRCA1/2* mutations, providing protection against ovarian cancer, but increasing the risk of breast cancer.

- **Selenium.** *BRCA1* and *BRCA2* are implied in DNA mismatch repair routes, and heterozygote carriers have greater rates of chromosomal aberrations. Selenium is being investigated as a potential chemopreventive agent, because preliminary data have shown that oral supplementation could reduce the rate of chromosomal breakage present in normal tissues of *BRCA1* mutation carriers.

### Surveillance

Randomized clinical trials of breast and ovarian cancer screening have not yet been completed in women with HBOC. Mammography and clinical breast examination have been the most important tools for screening in women with HBOC; however, during the last few years, evidence is emerging that magnetic resonance imaging (MRI) offers additional benefits, with a sensitivity and specificity of 77% and 95.4%, respectively. These results indicate that MRI is more sensitive for detecting breast cancer compared with other modalities. Unfortunately, MRI has more false positives. Table 21.1 summarizes the current surveillance recommended for HBOC. Table 21.2 compares sensitivity and specificity of different diagnostic tools.

In conclusion, for women who have a genetic mutation that predisposes them to breast and ovarian cancer, the available options of prophylactic surgery, intensified surveillance, and chemoprevention should be explained in detail. The comparative benefits of each of these strategies should be discussed individually with each woman and her family. Although the strategy of bilateral oophorectomy and mastectomy may provide the greatest degree of risk reduction, the impact on quality of life cannot be trivialized, and residual risks for malignancies remain.

## Hereditary colon cancer syndrome: familial adenomatous polyposis and hereditary non-polyposis colorectal cancer

A number of environmental and genetic risk factors for colorectal cancer (CRC) have been identified. The most important factors are aging, personal history of CRC or adenomas, dietary patterns, inflammatory bowel disease, familial history of CRC, and hereditary colon cancer syndromes. Approximately 10% of people who develop colorectal cancer have an inherited genetic susceptibility to the disease. Between 3% and 5% of colorectal cancers are linked to hereditary non-polyposis colorectal cancer (HNPCC), and an additional 1% of patients are associated with familial adenomatous polyposis (FAP).

**Table 21.1** Surveillance recommendations in hereditary breast and ovarian cancer syndrome

Primary site	Screening	Age to begin (years)
Breast	Monthly self-examination	18
	Clinical examination every 6 months	25
	Annual mammography	25
	Annual MRI	25
Ovarian <sup>a</sup>	Semiannual TVUS	25
	Semiannual CA-125	25
Prostate	Annual DRE	50
	Annual PSA	50

MRI, magnetic resonance imaging; TVUS, transvaginal ultrasound; CA-125, cancer antigen-125; DRE, digital rectal examination; PSA, prostate-specific antigen.

<sup>a</sup> If preservation of fertility desired.

**Table 21.2** Comparative sensitivity and specificity of MRI, mammography, ultrasound, and clinical examination in hereditary breast and ovarian cancer syndrome

Test	Sensitivity (%)	Specificity (%)
MRI	77	95.4
Mammography	36	99.8
Ultrasound	33	96
Clinical breast examination	9.1	99.3

MRI, magnetic resonance imaging.

### Familial adenomatous polyposis

FAP can be classified into two groups according to the number of colonic adenomatous polyps and age of onset: the classic and the attenuated form.

#### Classic familial adenomatous polyposis

In the classic form, penetrance is very high (nearly complete) by the age of 35 years. Children with classic FAP can present with hundreds to thousands of adenomatous polyps at a young age and risk of colorectal cancer is approximately 100%.

In classic FAP, *APC* gene testing should be offered at approximately age 10–12 years, which is just before the age at which clinical surveillance should be initiated.

When the *APC* mutation has been identified, it is essential that an annual colonic examination be performed.

Colectomy is recommended in patients with multiple large adenomas or adenomas with villous histology and/or high-grade dysplasia. In general, it is recommended to perform colectomy after puberty. Only if large-size polyps or high-grade dysplasia occurs, surgery might be performed earlier before the patient reaches the age of 18 years.

#### *Attenuated familial adenomatous polyposis*

In attenuated FAP, the number of colonic adenomas is less than in classic FAP, and there is a delayed onset of CRC at about the age of 50 years.

In the case of attenuated FAP, in which adenomas may not occur until the 20s or 30s, the age at which genetic testing and clinical surveillance begin may be delayed, and colonoscopy should be used instead of flexible sigmoidoscopy, because there is a predominance of right-sided tumors.

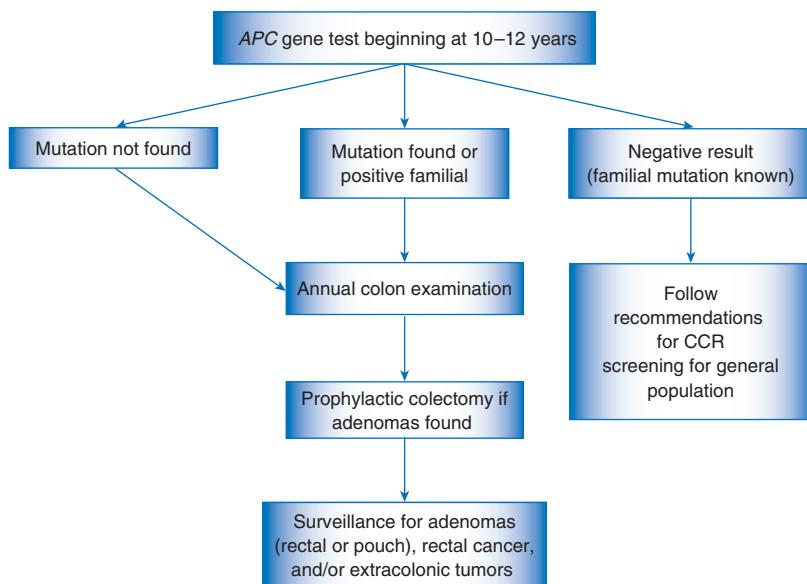
#### *Screening*

Screening of the upper gastrointestinal tract with upper endoscopy for gastric and duodenal polyps is recommended by some physicians to start close to the time of colectomy. The ileal pouch, if restorative proctocolectomy was performed, has to be followed because these patients can develop pouch adenomas. A flow diagram for *APC* suspected individuals is depicted in Figure 21.1.

#### *Chemoprevention*

Suppression of polyposis by chemoprevention with non-steroidal anti-inflammatory drugs (NSAIDs) is possible.

- Sulindac can cause regression of colorectal adenomas in patients with FAP, but regression of polyps is incomplete, and the degree of protection from the development of colorectal cancer is unknown. It is unlikely that sulindac will replace colectomy as primary therapy for FAP, but it is being used to slow the development of adenomas prior to colectomy and to delay new polyps formation in the rectum after subtotal colectomy.
- Cyclooxygenase-2 inhibitors also appear to be effective in this setting. In a randomized placebo-controlled trial of 77 patients with FAP who received



**Figure 21.1** Approach to management of a suspected APC: *adenomaus polyposis coli*; CCR: colorectal cancer

either placebo or celecoxib (400 mg orally twice daily) for 6 months, celecoxib reduced the mean number of polyps by 28% compared with placebo. The possibility of delaying colectomy while patients are treated pharmacologically is still under study.

### Hereditary non-polyposis colorectal cancer

HNPCC-associated cancers are predominantly of the colon and endometrium. Additional tumor sites also have been reported, including cancers of the stomach, ovary, small intestine, ureter, and kidney. The risk of developing colon cancer varies from 54% to 82%, with a median age of 45 years; the risk for developing endometrial cancers varies from 30% to 60%. Several organizations have published surveillance recommendations for families affected with HNPCC, but none has been validated prospectively. These recommendations are based on experts' opinions and observational data.

Screening colonoscopy every 1–2 years, beginning between 20 or 25 years, or 10 years earlier than the youngest age of colon cancer diagnosis in the family (whichever comes first), is recommended. The importance of surveillance in

**Table 21.3** Surveillance recommendations for hereditary non-polyposis colorectal cancer

Primary site	Screening	Age to begin
Colon	Colonoscopy every 1–2 years	25–30
Endometrial – ovarian	Semiannual TVUS ± annual endometrial aspirate	25–35
Gastric	Annual EGD	30–35 <sup>a</sup>
Urinary tract	Ultrasound and cytology every 1–2 years	30–35 <sup>b</sup>
Skin	Annual	Unknown

TVUS, transvaginal ultrasound; EGD, esophagogastroduodenoscopy.

<sup>a</sup> If gastric cancer in family

<sup>b</sup> If genitourinary cancer in family

people with HNPCC is based on a non-randomized trial that demonstrated a relative risk of 0.377 (95% CI 0.171–0.829) in the group of surveillance with colonoscopy.

Total or subtotal colectomy with continued surveillance of the rectum is recommended for patients with HNPCC who are found to have colorectal cancer or an advanced adenoma during surveillance. The rationale for this advice is the high incidence of metachronous cancer (25–40%) in patients who have undergone segmental colectomy. There are no data regarding the potential role of offering primary prophylactic surgery to patients who have not developed an advanced lesion.

Women with HNPCC should be screened between ages 25 and 35 years with pelvic examination as well as transvaginal ultrasound, with visualization of the ovaries and endometrium. Endometrial aspirate should begin between the ages of 25 and 35 years. For women, prophylactic hysterectomy and bilateral salpingo-oophorectomy is a viable option after childbearing years, because of the limited sensitivity of surveillance measures for these tumors. If there is genitourinary cancer in the family, annual analysis and cytological examination, and urinary tract ultrasound should be considered starting at age 30–35 years.

Annual skin surveillance for sebaceous gland adenoma, sebaceous carcinoma, and/or keratoacanthomas (HNPCC Muir–Torre variant) should be performed.

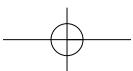
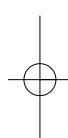
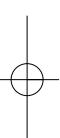
The use of periodic upper endoscopy is controversial. Table 21.3 summarizes the current surveillance recommendations for HNPCC.

## Conclusion

Hereditary cancer syndromes are sometimes associated with known mutations, but it is often not possible to identify the mutation responsible for the syndrome. The role of prevention is less determinant than in non-hereditary tumors, because an inherited mutation is mainly responsible for the cancer. Surveillance in some patients and prophylactic surgery in others have diminished cancer mortality in some hereditary predisposition syndromes.

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# Recommendations

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Prevention is an essential part of cancer control and should be integrated in every (national) cancer control plan. Several players are involved and should take up their respective responsibilities.

## Governmental organizations

Governmental organizations have the obligation to support cancer prevention by legislature. They can promote healthy living and avoidance of carcinogenic risks by:

- Developing a national cancer control program with the integration of prevention.
- Developing screening programs for cervical, breast, and colorectal cancer, if the infrastructure and manpower are available for their implementation and subsequent diagnosis and treatment of the patient.
- Legislature to protect the environment from carcinogenic agents.
- Legislature to protect the workers from carcinogenic agents.
- Restricting the exposure to carcinogens in public and work places.
- Regulation on handling and use of carcinogenic substances and drugs.
- Creating price measures to promote healthy living (e.g. subsidies for fruit and vegetables) and discourage cancer-related behavior (e.g. tobacco consumption).
- Increasing consumer awareness by information.
- Dissemination of research findings.
- Warning labels in relation to carcinogenic risk.
- Counter-advertising.
- A comprehensive ban on advertising and promotion of unhealthy living (e.g. cigarette smoking).

## Scientific organizations

Scientific organizations should be involved in creating a knowledge base for carcinogenic risk factors and evaluation of preventive measures. They should advise the governmental bodies on the cost–benefit of preventive strategies. They also should promote prevention among their members.

## Professional healthcare providers

Professional healthcare providers should know all the benefits and risks of prevention. They should integrate prevention in their daily clinical practice and patient care.

Professional health providers play an important role in the information and promotion of preventive strategies to their patients.

They should screen for risk factors and behavior, inform the patients, and motivate and help them to participate in prevention programs (e.g. smoking cessation program).

They should be aware of the importance they play as role models.

Healthcare providers should not only be familiar with primary and secondary prevention but also tertiary prevention, and the reintegration of the patient into society should also be part of patient care. Revalidation programs should be developed and offered to every cancer survivor in order to improve the quality of life and the possibility for reintegration into society.

## Public

The individual person should feel responsible to prevent avoidable cancers. To this aim, Europe against Cancer developed a ‘Code against Cancer’ that stated:

- Many aspects of general health can be improved, and certain cancers avoided, if one adopts a healthier lifestyle:
  - Do not smoke; if you smoke, stop doing so. If you fail to stop, do not smoke in the presence of non-smokers.
  - Avoid obesity.
  - Undertake some brisk, physical activity every day.
  - Increase the daily intake and variety of vegetables and fruit: eat at least five servings daily. Limit your intake of foods containing fats from animal sources.

- If you drink alcohol, whether beer, wine, or spirits, moderate your consumption to two drinks per day if you are a man and one drink per day if you are a woman.
  - Care must be taken to avoid excessive sun exposure. It is specifically important to protect children and adolescents. For individuals who have a tendency to burn in the sun, active protective measures must be taken throughout life.
  - Apply strict regulations aimed at preventing any exposure to known cancer-causing substances. Follow all health and safety instructions on substances that may cause cancer. Follow advice of the national radiation protection office.
- There are public health programs that could prevent cancers of developing or increase the probability that a cancer may be cured:
- Women from 25 years of age should participate in cervical screening. This should be within programs with quality control procedures in compliance with European Guidelines for Quality Assurance in Cervical Screening.
  - Women from 50 years of age should participate in breast screening. This should be within programs with quality control procedures in compliance with European Guidelines for Quality Assurance in Mammography Screening.
  - Men and women from 50 years of age should participate in colorectal screening. This should be within programs with built-in quality assurance procedures.
  - Participate in vaccination programs against hepatitis B virus infection.

Some symptoms may lead to the early detection of cancer. These signs include lumps, sores that fail to heal, abnormal bleeding, persistent indigestion, and chronic hoarseness. Patients should contact their physician in case of such symptoms.

## Conclusion

Cancer prevention plays an integral and important part in cancer control. Several institutional bodies and the broad public should be aware of its importance and promote the development of scientifically based prevention programs.

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