


# Cancer and Tobacco: Its Effects on Individuals and Populations

---

Bernard W. Stewart,  
Patricia F. Cotter and  
James F. Bishop



## Abstract

Tobacco smoking as the major cause of cancer is unrivalled and as western countries come to terms with its toll and smoking rates decline, the burden of tobacco-caused disease is far from reaching its peak in developing countries. Tobacco smoking causes cancer of the lung, as well as cancer of the oral cavity, naso-, oro- and hypopharynx, nasal cavity and paranasal sinuses, larynx, oesophagus, stomach, pancreas, liver, kidney (body and pelvis), ureter, urinary bladder, uterine cervix and bone marrow (myeloid leukaemia).

For lung cancer, incidence is almost precisely correlated with mortality and the only option currently available to markedly reduce the burden of lung cancer in the community is to reduce tobacco consumption.

For the cancer patient, continued smoking carries an increased risk of treatment complications or a second malignancy at the same or another site and the increased risk of a new primary cancer for many years after the original diagnosis. There is substantial medical evidence that continued smoking may reduce the effectiveness of treatment or worsen side effects of treatment.

The risk of death from smoking is substantial: about half of all cigarette smokers are eventually killed by their habit. Physicians and health professionals are in a unique position to capitalise on the teachable moment presented by the diagnosis of a smoking-caused disease and advise all smokers to quit. Unless these and other effective measures are implemented to prevent people from smoking and to help current users quit, tobacco will kill one billion people in the 21st century.

**Keywords:** Tobacco, environmental tobacco smoke, teachable moment, treatment effects.

## 1. The Need to Eliminate Tobacco-Induced Cancer

Reference to tobacco occupies a singular position in any overview of cancer biology and clinical oncology. Theoretically, exogenous causative factors may be considered with reference to any tumour type and any such discussion has ramifications for prevention and the possibility of reducing the burden of incidence and mortality. Exogenous carcinogens include tobacco, alcoholic beverages, ultra-violet light and a range of occupational and environmental exposures.

In the classic appraisal made by Doll and Peto in 1981<sup>1</sup> regarding the causation of cancer in the USA, 30% of all cancer deaths were attributable to tobacco, with no other single agent of comparable standing with regards to cancer causation.<sup>2</sup> Lung cancer is the leading cause of cancer-related mortality worldwide, with almost 1.2 million deaths per year.<sup>3</sup> In delineating the role of tobacco smoking in lung cancer, many studies are directed to a heterologous grouping identified as non-small-cell lung cancer (NSCLC, comprising 80% of lung cancers), which includes adenocarcinoma, bronchioloalveolar, squamous, anaplastic and large-cell carcinomas.

### 1.1 Causation proven

The overwhelming body of epidemiological evidence indicates that the risk of lung and other cancers is determined by the duration of smoking, the amount of tobacco smoke inhaled (usually

expressed in 'pack years') and the intensity of exposure, as indicated by the depth of inhalation. The carcinogenicity of tobacco smoke is clear both from such epidemiological studies and also from a huge spectrum of experimental data. The vital contribution of experimental studies has come through detailed analyses of the processes whereby the multiple carcinogens in tobacco smoke cause malignant transformation of respiratory and other epithelial tissue.

The particulate phase of tobacco smoke contains nicotine, nitrosamines, *N*-nitrosonornicotine, metals (cadmium, nickel and polonium-210), polycyclic aromatic hydrocarbons and carcinogenic aromatic amines (4-aminophenyl). The vapour phase contains carbon monoxide, carbon dioxide, benzene, ammonia, formaldehyde, hydrogen cyanide, and nitrosamines. Approximately 60 recognised carcinogens are present, along with toxic agents likely to induce tissue injury and consequent proliferative activity in respiratory epithelium.<sup>4</sup> Nicotine may contribute directly to carcinogenesis by stimulating cell proliferation and inhibiting apoptosis, thereby mediating promotion and progression of lung cancer.<sup>5</sup>

In the face of such a carcinogenic insult, which may continue over several decades, the lung is remarkably resistant to tumourigenesis. Only a minority of heavy smokers — 16% of men and 9.5% of women — develop lung cancer.

## 1.2 *Multiple target organs*

The most authoritative statements on the carcinogenicity of particular agents are evaluations made in the context of *IARC Monographs on the Evaluations of the Carcinogenic Risks to Humans*, edited by the International Agency for Research on Cancer, an arm of the World Health Organization (WHO). *IARC Monographs on Tobacco Smoking and on Involuntary Smoking* were published in 2004 and are the definitive publications in relation to a range of matters.<sup>6</sup> Tobacco smoking causes cancer of the lung, as well as cancer of the oral cavity, naso-, oro- and hypopharynx, nasal cavity and paranasal sinuses, larynx, oesophagus, stomach, pancreas, liver, kidney (body and pelvis), ureter, urinary bladder, uterine cervix and bone marrow (myeloid leukaemia). Available data

indicate that tobacco smoking does not cause cancers of the female breast and endometrium.

The *IARC Monograph* on tobacco smoking provides comprehensive information in relation to each of the tumour types caused by smoking. Such details include the relationship of risk to exposure, the proportion of disease attributable to tobacco and the extent of reversibility of risk consequent upon smoking cessation. The causation of each of the tumour types known to be a consequence of tobacco smoking may be analysed with reference to the route of exposure to tobacco smoke or related metabolites, organic-specific metabolism of particular carcinogens and the cell biology of relevant tumours.

In respect of tobacco-induced lung cancer, the basics have been known for decades, though even in relation to lung cancer, new insights regarding tobacco continue to be revealed. The most important matter resolved in recent years concerns the carcinogenicity of so-called 'light' or 'mild' cigarettes. Cigarettes formulated to deliver less tar when subjected to 'smoking machine' analysis were marketed and advertised as presenting a lesser risk of ill-health than regular cigarettes. It is now established that smokers of light or mild cigarettes are essentially subject to the same risk of lung cancer as smokers of regular cigarettes.<sup>7</sup> The data indicate that smoking behaviour is dominated by the smoker's need to achieve a given intake of nicotine. Low or mild cigarettes provoke changes in smoking behaviour: more frequent inhalation, deeper inhalation and/or consumption of a greater number of cigarettes per day.<sup>8</sup> It is hypothesised that the usage of light or mild cigarettes accounts for an increasing proportion of adenocarcinoma by comparison with other histological types of non-small cell lung cancer.

Despite early implications, recent data suggest that women are no more susceptible than men to the carcinogenic effects of cigarette smoking to the lung.<sup>9</sup> Paradoxically, in the same study amongst those reporting having never smoked tobacco in any form, women had slightly higher rates of lung cancer than men. Lung cancer is a lethal disease and although some progress has been made in recent years, the five-year survival rate in developed countries remains less than 15%. For lung cancer, incidence is almost precisely correlated with mortality, which is not the situation for the other common cancers in developed countries: breast,

colon and prostate cancer. As a consequence, the only option currently available to markedly reduce the burden of lung cancer in the community is to reduce tobacco consumption.

## 2. The Genetics of Susceptibility

Knowledge of the genes mediating metabolism of tobacco smoke-derived carcinogens and those genes accounting for the repair of such damage was vigorously pursued. A specific stimulus for this research was the hypothesis that individual susceptibility to lung cancer may be revealed by genetic variation amongst such genes. Information concerning genetic determination of susceptibility to lung cancer independent of smoking behaviour and for susceptibility to nicotine addiction is available,<sup>10</sup> but will not be considered here. On the specific issue of genetic determination of susceptibility to tobacco smoke carcinogenesis, there has been no consistent association between specific SNPs in XRCC1 and risk of lung cancer.

### 2.1 *Lung cancer is a different disease in smokers*

The characteristics of lung cancer in smokers, as distinct from lung cancer in never smokers, are sufficiently marked as to justify characterising these as two different tumour types with reference to both aetiology and clinical course.<sup>11</sup> A difference between the putatively distinct tumour types is most clearly indicated by mutation in epidermal growth factor receptor (EGFR). EGFR mutations are much more common in lung cancers afflicting people who have never smoked (45%), by comparison with those with tobacco-associated disease (7%).<sup>12</sup> This scenario is correlated with markedly increased responsiveness to the corresponding low molecular weight kinase inhibitors erlotinib and gefitinib. Patients likely to respond to these kinase inhibitors are those who are non-smokers, women and those of Asian ancestry; smokers with lung cancer show little response.<sup>13</sup> Lung cancers in smokers exhibit distinct patterns of TP53 and KRAS mutations, with KRAS mutations almost unknown in never smoker lung cancers. Indeed, it appears that EGRF and KRAS mutations are mutually exclusive.<sup>14</sup> Histologically, adenocarcinomas are considered to be less commonly

attributable to tobacco smoking than squamous or large cell lung cancers. The distinction being drawn between apparently different lung tumour types affecting smokers and never smokers means that smoking status and history are not only relevant to public health, but to the clinical management of lung cancer. In a recent Japanese study, the 'never-smoking NSCLC' patient group exhibited significantly superior overall and cancer-specific survival than the 'smoking NSCLC' group.<sup>15</sup>

## **2.2 Evidence of reversibility**

Elucidation of the molecular processes resulting in cancer causation by tobacco smoke has contributed directly to proving that the epidemiological association between smoking and lung cancer is causal. A decreased risk of cancer amongst former smokers indicates the degree to which carcinogenesis is reversible, which is consistent with both cellular and molecular data.<sup>16,17</sup>

Once direct exposure to tobacco smoke ceases, the tissue and molecular injury, which may otherwise contribute to cancer development, tends toward normal.<sup>18</sup> Accordingly, the aetiology of tobacco-induced lung cancer strongly favours smoking cessation as the most immediate, and effective, preventive measure. Both public health policy and primary health care are properly based on smoking cessation as a central tenet of cancer control.

## **3. Prospects for Population-Based Screening**

In developed countries, risk factors for lung cancer are clear. As summarised by Spitz and her colleagues, for never smokers they include regular exposure to environmental tobacco smoke and a family history of cancer in two or more first-degree relatives. For former smokers, risk factors are emphysema, no prior hay fever, dust exposure, and family history of cancer in two or more first-degree relatives. For current smokers, additional risk factors include asbestos exposure, and the family history variable involves one or more first-degree relatives with a smoking-related cancer.<sup>19</sup>

With criteria which clearly establish persons at high risk of lung cancer being evident over decades, and the clinical prospect of extremely poor survival once diagnosis is made, the context

and benefits of population-based screening for lung cancer are immediately clear, and have been so for years.

In the 1950s autopsy studies showed that the lungs of heavy smokers were affected by multiple sites of preinvasive and early invasive cancer associated with the clinical disease leading to the patients' death. Protocols for lung cancer screening initially involved chest X-rays and sputum cytology and prior to 1980, evaluation of such procedures was undertaken in multiple studies. The results of these trials were uniformly negative, insofar as none showed any reduction in lung cancer mortality in the group subject to X-ray, with or without sputum cytology.<sup>20</sup> Chest X-ray was effective at identifying many additional small tumours in the lung that could be removed. However, that intervention did not reduce the likelihood that individuals would be diagnosed with new cases of advanced lung cancer or would die of lung cancer.

### **3.1 Current status of computed tomography (CT) screening**

Current approaches to lung cancer screening are totally focused on CT because this technology is demonstrably more sensitive for the detection of very small nodules. That said, the titles of recent editorials — referring to 'are we ready?', 'spiraling into confusion' and 'yet another problem'<sup>21–23</sup> — clearly indicate that no basis has been established for the widespread introduction of CT screening for lung cancer. A central consideration is that the available data do not reveal a consistent reduction in lung cancer mortality as a consequence of CT-based screening. As might be anticipated from the earlier X-ray studies, many more patients with stage one disease are identified amongst those at risk as subjected to CT than amongst controls. Some insight into the challenge posed by data currently available is posed by Black and Baron,<sup>21</sup> who asked "How is it possible that two large studies published within six months of each other could lead to such dramatically different conclusions about the effectiveness of CT screening?" The best explanation for the paradox is the difference in the primary outcome measurements. One study,<sup>24</sup> concluding that asymptomatic individuals should not be screened, relied on mortality. The other,<sup>25</sup> which focused on survival, suggested that CT screening of high-risk

individuals could prevent 80% of lung cancer deaths. Prolonged survival need not imply reduced mortality in the population.

There is direct evidence that, by comparison with chest X-ray and sputum cytology, spiral CT is a more effective screening methodology, and has the potential to detect disease more accurately. However, the potential for over diagnosis is also evident.<sup>26</sup> For lung cancer screening purposes, publications involving CT include 11 observational studies and six randomised trials.<sup>20</sup> Taking these data into account, Field and Duffy conclude that “we still do not have experimental evidence for or against the implementation of this screening modality”. It may be, however, that lung cancer screening predicated on the detection of early stage lesions is an inherently flawed approach. The notion that for a period before advanced disease, lung cancer is localised and treatable may be wrong. Perhaps the early stage lesions currently detected in trials are not the precursors of advanced disease, which otherwise develops via a different pathway<sup>27</sup> and attempts are being made to characterise subsets of early disease in order to clarify this matter. A significant fraction of patients (30–40%) with stage one disease who undergo surgery die of recurrent disease. Such patients appear to be characterised by methylation of the promoter regions of four particular genes.<sup>28</sup>

### **3.2 Genetic profiling of pre-malignant tissue**

Gene expression profiling has been extensively assessed in relation to clinical disease, specifically as a possible means to predict metastatic behaviour.<sup>29</sup> The same technology has been applied to bronchial epithelium at risk of tobacco smoke-induced malignant transformation. Spira and colleagues<sup>30</sup> analysed histologically normal large-airway cells obtained at bronchoscopy from smokers, to determine whether gene expression data might be used for biomarker purposes. They identified an 80-gene biomarker that distinguished smokers with and without lung cancer (80% sensitive, 84% specific). Combining cytopathology of lower airway cells with the biomarker suggested a means of assessing cancer-specific airway-wide responses to cigarette smoke, as a means of indicating individuals at highest risk. In a further study, the independence of the biomarker from other clinical risk factors was demonstrated,

suggesting that use of a 'clincogenomic' model may expedite more invasive testing and definitive therapy for smokers with lung cancer and reduce invasive diagnostic procedures for individuals without lung cancer.<sup>31</sup>

#### **4. Chemoprevention**

Granted the ready identification of persons at high risk for lung cancer (i.e. current and former smokers), chemoprevention has been, and continues to be, an immediately attractive and obvious consideration. Cancer chemoprevention is, in large part, predicated on epidemiological data indicating above average consumption of fresh fruit and vegetables as reducing cancer risk for multiple tumour types, and the efficacy of micronutrients in reducing, if not preventing, carcinogenesis in rodents.<sup>32</sup> However, attempts to prevent lung cancer by relatively short-term consumption of certain vitamins and antioxidants met with spectacular failures: a slightly increased incidence of lung cancer was recorded by comparison with relevant control groups in a trial context. In the case of a trial based in Finland,  $\beta$ -carotene-induced lung cancer elevation was most pronounced in men who smoked heaviest and drank the most.<sup>33</sup> In the US trial a similar effect was most pronounced in current (as opposed to former) smokers and in participants with the highest alcohol intake.<sup>34</sup> Better results might be obtained using different agents over a longer timeframe, and using biomarkers rather than cancer diagnosis as an end point.<sup>35</sup> For the moment, there appears to be few if any attempts to present chemoprevention as a credible response to the burden of tobacco-induced lung cancer.

#### **5. Passive Smoking**

No level of exposure to environmental tobacco smoke may be regarded as safe. Apart from cancer, passive smoking can cause heart disease in non-smoking adults and increase the risk of sudden infant death syndrome, acute respiratory infections, middle-ear disease and exacerbation of asthma in children. This discussion of the hazard is limited to cancer causation.

As established in active smokers, tobacco smoke is carcinogenic, with the polycyclic hydrocarbons and nitrosamines therein

exhibiting a genotoxic mechanism of action. On this basis, any level of exposure to such a biological toxin would be anticipated to present a carcinogenic risk. Accordingly, good public health practice would dictate that preventable exposure to any level of tobacco smoke should not occur. The present discussion of passive smoking (which is synonymous with exposure to environmental tobacco smoke, or to secondhand smoke) might therefore proceed directly to the implementation of practicable measures to prevent exposure. In practice, however, the social and economic considerations which surround tobacco smoking have dictated that specific research be conducted to establish that exposure to environmental tobacco smoke — investigated in its own right — does present a carcinogenic hazard to humans.

### **5.1. Chemical composition**

Environmental tobacco smoke consists of a mixture of exhaled mainstream smoke and smoke emitted from the burning tip of the cigarette (or its equivalent in relation to other smoking techniques), called sidestream smoke, all diluted with ambient air. Environmental tobacco smoke consists of a particulate and a gaseous phase, and the chemical composition of mainstream and sidestream smoke have been extensively documented.<sup>36</sup> Carcinogens that occur in environmental tobacco smoke include benzene, 1,3-butadiene, benzo[*a*]pyrene, 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone and many others. Such compounds may mediate specific mutations of genes encoding for cell cycle and growth control, thereby leading to tumourigenesis. Moreover, epigenetic mechanisms, which could result in gene silencing without any effect on the coding sequence of the gene in question, may also be involved in malignant transformation occurring as a result of passive smoking.<sup>37</sup>

Cotinine, and its parent compound nicotine, are highly specific for exposure to secondhand smoke; cotinine is currently the most suitable biomarker for assessing recent exposure to environmental tobacco smoke.<sup>38</sup> Several studies have shown that concentrations of smoke-derived carcinogen adducts, including haemoglobin adducts of aromatic amines, are higher in adult involuntary smokers and in the children of smoking mothers than in individuals not

exposed to secondhand smoke. Metabolites of the tobacco-specific carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, have been found to be consistently elevated in passive smokers.<sup>6,39</sup>

Exposure to secondhand smoke may occur in many contexts, but has been most extensively investigated in relation to smoking by spouses at home, and in the workplace. Before various smoking restrictions were adopted, particularly high levels of environmental tobacco smoke were encountered by flight attendants and hospitality workers.

## **5.2 ETS and cancer causation**

In its 2002 evaluation of 'Involuntary Smoking', the IARC noted more than 50 relevant studies concerning risk of lung cancer, concerning which there are a limited number of meta-analyses.<sup>6</sup> These show a statistically significant and consistent association between lung cancer risk in spouses of smokers and exposure to secondhand smoke from the smoking spouse. The excess risk is of the order of 20% for women and 30% for men, and the excess risk increases with increasing exposure. Lung cancer in never-smokers subject to passive smoking at work exhibits an increase in risk of 12–19%. The evidence is sufficient to conclude that involuntary smoking is a cause of lung cancer (IARC Group one carcinogen). Evidence in relation to other cancers, specifically including breast cancer and childhood cancer, is equivocal in relation to establishment of causation.

In the United States, exposure to secondhand smoke declined approximately 70% from the late 1980s through 2002.<sup>40</sup> Restrictions placed on smoking indoors in jurisdictions throughout the world have reduced exposure to environmental tobacco smoke. However, it is evident that not all options are equally effective in this regard. Within single buildings, the banning of smoking in particular areas or rooms is markedly ineffective so far as protecting non-smokers is concerned, with levels of smoke-related pollutants and particulates in such areas sometimes being comparable to those where smoking is allowed.<sup>41</sup> The US Surgeon General has concluded that protecting non-smokers from environmental tobacco smoke can only be accomplished by completely eliminating smoking in indoor places.

Measures to prevent involuntary exposure to secondhand smoke have been developed and adopted widely and recently, IARC assessed the evidence for effectiveness of such policies.<sup>42</sup> Where studied, smoke-free workplace policies consistently decrease exposure to secondhand smoke in high-exposure settings by 80–90%, and can lead to widespread decreases in exposure of up to 40%. Studies of workers affected by workplace smoking restrictions reveal individual decreased cigarette use of two to four cigarettes per day. The weight of evidence suggests that smoke-free work places do not result in increased smoking at home.

## **6. Cancer Patients Who Smoke**

### **6.1 *The effects of smoking on survival***

The diagnosis of cancer provides an incentive for many patients to make a serious attempt to quit smoking.<sup>43</sup> The diagnosis provides a ‘teachable moment’ for clinicians. Assisting smokers to quit may also have a favourable outcome on their long term prognosis.<sup>44</sup> In contrast, continued smoking carries an increased risk of treatment complications or a second malignancy at the same or another site and the increased risk of a new primary cancer for many years after the original diagnosis. There is substantial medical evidence that continued smoking may reduce the effectiveness of treatment or worsen side effects of treatment. This section focuses on the outcomes expected for those current and former smokers who have a cancer diagnosis and how their cancer prognosis is affected by their ability to quit.

Both current and former smokers may be expected to have an increased number and severity of tobacco-related co-morbid conditions that would adversely affect their general health status, symptom experience and quality of life.<sup>44</sup> The long term effects of smoking in cancer patients are uniformly negative, although risk will decline with time since cessation.<sup>44</sup> Independent of the aetiologic effects of tobacco carcinogens in relation to numerous tumour types, a growing literature also documents the direct and indirect adverse effects of smoking on oncologic treatment efficacy

(short and long term outcomes), treatment-related toxicity and consequent morbidity, quality of life, recurrence of primary disease, second primary tumours and survival time.<sup>43</sup>

Specifically for NSCLC patients, smoking is both the cause of lung cancer and, when it continues following diagnosis, is also a cause of worse prognosis.<sup>45,46</sup> Smoking is an important independent predictor of poor lung cancer prognosis, increasing the hazard of dying by approximately one third compared to former or never smokers.<sup>46,47</sup> With regards to overall survival, the outcome is significantly more positive for former smokers (RR = 0.543), recent quitters (RR = 0.340) and non-smokers (RR = 0.447), when compared to current smokers.<sup>46</sup> This adverse effect on patients with lung cancer occurs relatively late in the course of management and may in part be due to the ongoing smoking that occurs after diagnosis.<sup>47</sup> The effect of smoking on survival has also been studied among breast cancer patients. A history of smoking increased mortality following diagnosis from causes other than breast cancer, but not mortality from breast cancer.<sup>48,49</sup> However, one study found conflicting associations between hormone receptor status and smoking, where women with oestrogen receptor (ER) and progesterone receptor (PR) positive tumours who were current smokers had an increased risk of breast cancer death, compared with never smokers.<sup>49</sup> Another study has suggested that the lower survival rate of smokers with breast cancer may be the result of an impairment of immunity or that smoking may promote the development of more aggressive, oestrogen-receptor negative tumours. Further, exposure to HRT before diagnosis was associated with an improved prognosis among smokers.<sup>48</sup>

## **6.2 Smoking as a risk factor for increased cancer stage at diagnosis**

The effects of smoking on the spread of cancer have not been widely studied. However there is some evidence that smoking is associated with an increased stage at diagnosis and an adverse affect on metastatic behaviour.<sup>50</sup>

## 6.2.1 *Increased secondary primary tumours*

The information reported about second lung cancers in patients treated for NSCLC is quite different from that reported about patients treated for SCLC. Patients with NSCLC develop second primary cancers at a rate of approximately 1–2% per year. Patients successfully treated for SCLC develop second primary lung cancers at an average rate of approximately 6% per year, which increases from 2% to more than 10% per patient per year after ten years.<sup>51</sup> Cancer patients who smoke have a significantly increased risk of secondary primary tumours, with an elevated risk observed regardless of whether the initial malignancy is related to smoking or not.<sup>44</sup> For example, individuals treated with radiation therapy to the chest (e.g. for breast cancer) are at increased risk of secondary primary tumours of the lung if they smoke.<sup>44</sup> Smoking increases the risk of SCLC from six-fold to 15-fold in patients treated for Hodgkin disease and breast cancer. This suggests a multiplicative interaction between smoking and chest radiotherapy in patients treated for small-cell lung cancer, Hodgkin disease, and breast cancer.<sup>51</sup>

In patients with small-cell lung carcinoma who continue to smoke, the risk of a second lung cancer is approximately doubled overall.<sup>52</sup> In two studies of survivors of SCLC, the risk of a second cancer (mostly non-SCLC) was 3.5-fold to 4.4-fold higher than in the general population. In those who continued to smoke, the risk was far higher in those who also received chest irradiation (RR = 21.0) and alkylating agents (RR = 19.0).<sup>52–54</sup> This risk increased over time for SCLC survivors, with a cumulative incidence of 44% at 14 years.<sup>55</sup> In contrast, patients with a first primary tobacco-related cancer such as NSCLC also have a high risk of a second tobacco-related cancer, but their risk appears to remain more stable over time.<sup>55</sup>

## 6.3 *Treatment*

### 6.3.1 *Surgery and wound healing*

Smoking has major consequences for patients who undergo surgery and specifically in relation to the period immediately

following surgery. Smoking affects tissue oxygenation, heart rate, airways clearance, immune response, and circulation. In addition, smokers on average also require higher doses of analgesia for pain relief.<sup>56</sup>

Respiratory complications in the post-operative period, such as some combination of pulmonary infections, atelectasis, bronchospasm, and the need for prolonged ventilation, as well as a higher post-operative mortality rate, are more common in smokers.<sup>57</sup> In addition, reconstructive surgery may be compromised, as smoking substantially increases the risk of wound infection, flap necrosis, and fat necrosis, and these complications may also delay adjuvant chemotherapy and radiotherapy.<sup>58</sup> Smoking cessation for longer than three weeks before reconstructive head and neck surgery is beneficial for all smokers and reduces the incidence of impaired wound healing.<sup>59</sup>

The Faculty of Anaesthetists of the Royal Australian College of Surgeons advises that smokers be counselled to stop smoking completely, or failing that, to abstain for at least six to eight weeks before surgery. Abstinence for the 12 hours immediately prior to surgery is particularly important, in order to achieve maximum tissue oxygenation.<sup>60</sup> The timing of cessation is relevant, as a reduction in peri-operative complications is not seen until a period of abstinence of five to eight weeks' duration. In general, smokers have a nearly six-fold increase in risk of a post-operative pulmonary complication.<sup>61</sup> In addition, several early studies have documented that smokers who decrease consumption but do not quit entirely, or quit but have been abstinent for less than two months, may have a higher rate of complications post-operatively.<sup>62</sup> Recently the issue of smoking cessation and peri-operative complications has been studied specifically in patients undergoing thoracotomy for primary or secondary lung tumours. In this study there was no evidence of a paradoxical increase in pulmonary complications among those who quit smoking within two months of undergoing surgery. However the types of complications differed between the recent quitter and ongoing smoker subgroups. All the complications in the ongoing smoker group were pneumonias; in the recent quitter subgroup fewer pneumonias occurred.<sup>59,63</sup> There is a strong incentive to advise patients to quit smoking

immediately and capitalise on the 'teachable moment' that a cancer diagnosis provides.

### 6.3.2 Radiation therapy and chemotherapy

Smoking cigarettes during radiotherapy appears to prolong the period of reaction and may reduce the chance of cure.<sup>64</sup> Radiation therapy for head and neck cancer patients who continue to smoke has been associated with lower rates of complete response (45% in smokers vs. 74% in non-smokers) and a poorer two-year survival (39% in smokers vs. 66% in non-smokers).<sup>65</sup> In addition, among NSCLC patients diagnosed with early stage disease, current smokers have a poorer prognosis for survival after radiation therapy.<sup>66</sup> Similarly, in patients with advanced NSCLC, never smokers have an improved outcome over smokers when treated with chemotherapy.<sup>67</sup> This effect has also been demonstrated in lung cancer patients (both NSCLC and SCLC), where those with a cigarette burden of 40 or over pack years have a worse response to platinum-based chemotherapy, compared to those who have a cigarette burden of less than 40 pack years.<sup>68</sup>

Radiotherapy for breast cancer also significantly increases the risk of lung carcinoma more than ten years after exposure in women who smoked at the time of their breast cancer treatment. The increased risk is restricted to women who smoked at the time of radiotherapy and is not evident in non-smoking women. Squamous cell carcinoma of the lung appears to be the histopathologic subgroup most closely related to ionizing radiation.<sup>69</sup> Complications for patients receiving radiation therapy for cervical cancer are also more evident among patients who smoke, as they experience an increased incidence of gastro-intestinal complications.<sup>70</sup> Smokers present with higher risk grade prostate cancers<sup>71</sup> and smokers (both current and previous), treated with external beam radiotherapy for localised prostate cancer appear to be at a greater risk of developing metastatic disease.<sup>72</sup>

In addition, particular attention should be devoted to preventing patients from both smoking and taking antioxidant supplements during radiation therapy, as this combination appears to reduce the efficacy of radiation therapy.<sup>73</sup>

## 6.4 Drug interactions

Treatment-related weight loss and cachexia would be expected to be exacerbated by smoking, as smoking suppresses appetite and weight gain. In addition nicotine, via the induction of hepatic enzymes, increases metabolism of many pharmaceutical agents and potentially decreases their efficacy.<sup>44</sup> The effect of smoking on the pharmacology of many anti-cancer drugs is not well understood.

## 6.5 Inflammatory markers

Inflammation is associated with poor prognosis and decreased survival in many types of cancer, and higher levels of inflammatory markers have been seen in smokers.<sup>74</sup> These in turn may influence drug pharmacology and are implicated as prognostic markers.

## 6.6 Future directions/further research

Tobacco smoking is the largest single preventable cause of death and disease in Australia today. More than 50 years ago Doll and Bradford Hill in the UK and Wynder in the US reported that smoking and lung cancer appeared to be causally linked.<sup>56</sup> Since that time the health consequences of smoking have been widely studied and extensively reported, but in comparison the effects of smoking on cancer patients are relatively under-researched. Table 1 outlines some areas of potential future research.

**Table 1.** Recommendations for future research on smoking in cancer patients.

Area of research	Recommendation
Pharmacotherapy for nicotine dependence treatment	<ul style="list-style-type: none"><li>• Evaluate the efficacy of NRT (gum, patch, nasal spray, inhaler), non-nicotine medications (bupropion, clonidine, nortriptyline, and varenicline), and combination therapies (e.g. high-dose NRT, combined NRT and bupropion) in increasing tobacco abstinence rates in oncology patients.</li></ul>

*(Continued)*

**Table 1.** (Continued)

Area of research	Recommendation
Methodologic issues	<ul style="list-style-type: none"><li>• Assess the efficacy of nicotine and non-nicotine medications in managing symptoms of nicotine withdrawal, craving, stress, and depression among cancer patients.</li><li>• Assess the effect of nicotine in cigarettes and nicotine in NRT on cancer drugs/treatment.</li><li>• Obtain sample sizes needed to provide adequate statistical power for hypothesis testing.</li><li>• Collect and report demographic and medical data including disease site, type, stage, and treatment.</li><li>• Report on the timing of intervention relative to time of cancer diagnosis and treatment.</li><li>• Include at least six-month outcomes to assess stability of treatment effects.</li><li>• Assess tobacco use status using both seven-day point prevalence and continuous abstinence.</li></ul>
Prevention of disease recurrence	<ul style="list-style-type: none"><li>• Examine factors predictive of smoking relapse and relapse in cancer patients.</li><li>• Evaluate relapse prevention strategies within nicotine dependence treatment interventions: cognitive-behavioural strategies, long-term use of pharmacotherapy, support mechanisms, and extended follow-up may increase abstinence maintenance.</li></ul>
Cancer treatment and quality of life	<ul style="list-style-type: none"><li>• Studies to determine the extent of interaction of radiation and chemotherapy agents in smokers compared to non-smokers. Further determine the type and extent of physical and psychological benefits experienced by cancer patients who stop smoking. This research is needed across cancer sites, as benefits may differ.</li><li>• Clinical trials should routinely collect smoking status and include primary outcomes related to quality of life and oncology treatment.</li><li>• Quality of life assessment may include global measures and site-specific measures.</li></ul>

Source: Adapted from Ref. 86.

## 7. Cancer Prevention — Reversal of Risk Upon Quitting

### 7.1 *The individual*

For much of the 20th century, smoking was regarded as a socially learned habit and as a personal choice, but it is now recognised that cigarette smoking is primarily a manifestation of nicotine addiction and that smokers individualise their level of nicotine intake. Although by the age of 20, 80% of cigarette smokers regret that they ever started, as a result of their addiction to nicotine, many will continue to smoke for a substantial proportion of their adult life.<sup>75</sup>

The risk of death from smoking is substantial: about half of all cigarette smokers are eventually killed by their habit.<sup>76</sup> Many are killed while they are still only in middle age (35–69 years of age), and could have anticipated living for another ten, 20, 30 or more years.<sup>77</sup> Those who continue to smoke lose on average about ten years of life, compared to non-smokers. Individuals who stop smoking at around 60, 50, 40, or 30 years gain respectively about three, six, nine, or ten years of life compared with those who continue to smoke.<sup>76</sup> Hence, those who stop smoking in early middle age (around the age of 40) avoid most of their risk of being killed by tobacco smoking.

The risk of dying from lung cancer for people who never smoke, is less than 1% (Fig. 1). However the risk of lung cancer is high for people who smoke all their lives, but this risk can be substantially modified if quitting occurs at any age.<sup>77</sup>

Sixteen percent of smokers will die from lung cancer by age 75 if they don't die from something else first. Smoking causes even more deaths from other diseases than from lung cancer; overall, half of all persistent smokers are killed by tobacco. For people who stop at age 50, the risk of dying of lung cancer is only about 6%.<sup>77</sup>

The main findings of Sir Richard Doll's study on smoking and death in British doctors are that the chances of a 35-year-old surviving to age 70 and beyond are 81% for non-smokers, compared to only 58% for smokers. A quarter of all the smokers were



## Stopping smoking: avoiding lung cancer

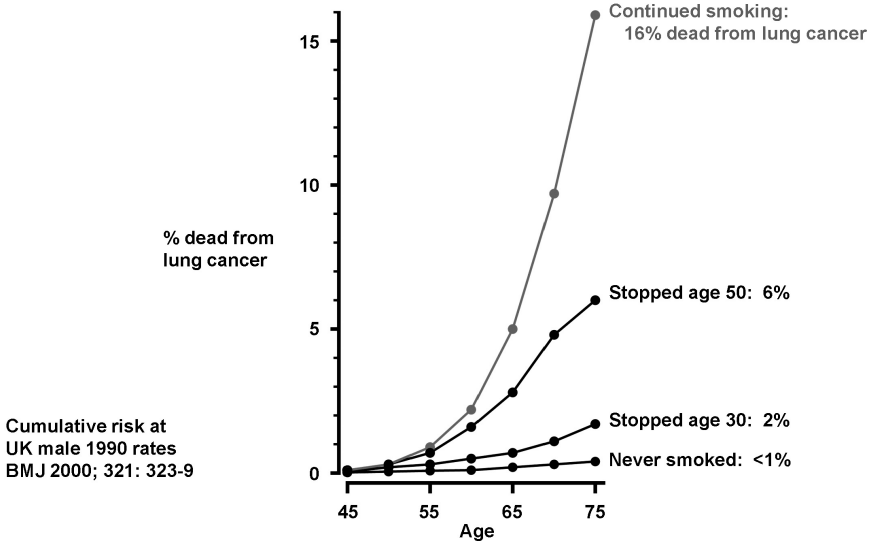


Figure 1. Risk of lung cancer with smoking cessation.<sup>87</sup>

killed by tobacco when they were aged 35 to 69 years, mainly from diseases such as lung cancer, coronary events and chronic lung disease. On average, the doctors who smoked died ten years earlier than non-smokers (Fig. 2). But it is not just a question of mortality: long-term smokers suffer more disease and disability before they die at younger ages. On average smokers suffer reduced quality of life for a greater number of years than non-smokers.<sup>78</sup>

The other main finding from Richard Doll's study was that stopping smoking was remarkably effective (Fig. 3). Even in early middle age (or at about age 40 years), those who stopped before they had incurable lung cancer or some other fatal disease avoided most of their risk of being killed by tobacco, and stopping before middle age was even more effective.

There are health benefits of quitting for all smokers, regardless of age, sex or length of time that they have been smoking.



## Survival to age 70 and beyond: effect of smoking in male British doctors

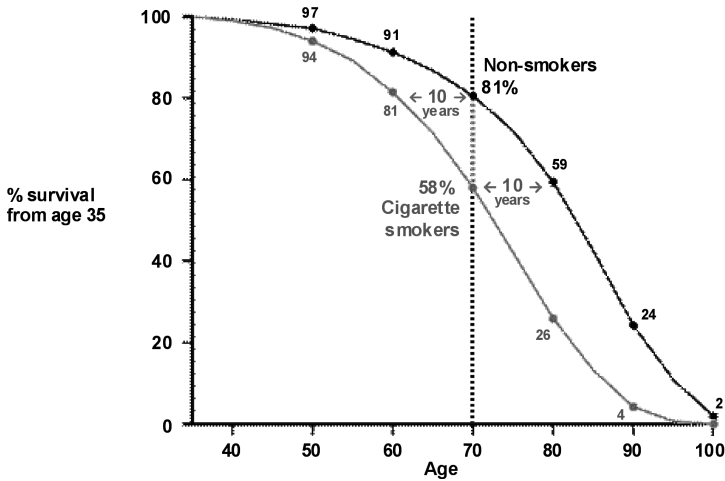


Figure 2. Survival from age 35 years in British doctors.<sup>88</sup>



## Effect of stopping smoking at about age 40

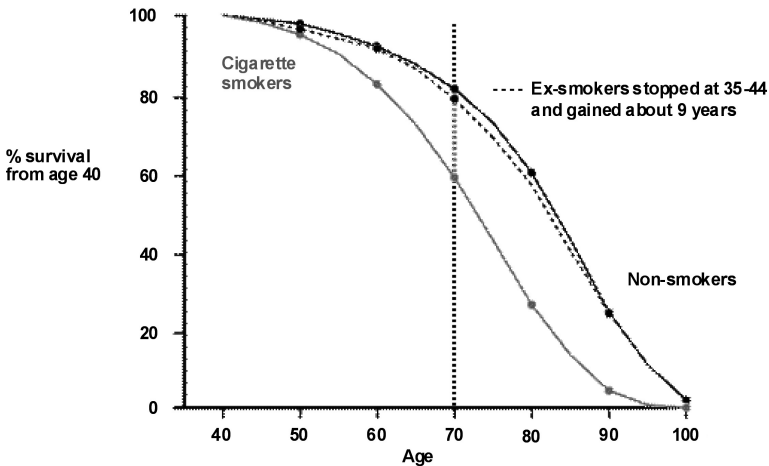


Figure 3. Effect of smoking cessation at age 40 years.

People who have already developed smoking-related health problems, like heart disease, can still benefit from quitting. For example, compared to continuing smokers, people who quit smoking after having a myocardial infarction reduce their chances of having another one by 50%. There are many benefits to quitting, with some even occurring within hours of stopping smoking.

## 7.2 Cancer patients

Some information about barriers to smoking cessation can be inferred from the characteristics of patients who continue to smoke following a cancer diagnosis (Table 2). Patients diagnosed with tobacco-related cancers typically report long histories of heavy tobacco use, indicating strong nicotine dependence.<sup>79</sup> Success in quitting smoking may also be challenged by the pressure for abrupt and immediate cessation following diagnosis. In addition, the cancer diagnosis is often confirmation of a smoker's worst fears and a reinforcement of their previous inability to quit leading to the fatalistic belief that it is too late to quit. The psychological distress of a cancer diagnosis is likely to lead heavily nicotine-dependent smokers to rely on smoking to regulate mood and cope with distress.<sup>79</sup>

**Table 2.** Benefits and barriers to quitting.

Benefits	Barriers
Improved survival rate	High psychological distress
Fewer treatment complications	High nicotine dependence
Improved treatment efficacy	Abrupt cessation vs. 'commitment to abstinence'
Reduced risk of disease recurrence and second primary tumour	Low quitting self-efficacy
Improved mastery and control	Knowledge deficits
	Negative social support

Source: Ref. 79.

### 7.3 *The population perspective*

Around 30% of male cancer deaths are smoking-related, compared to around 13% of female cancer deaths; two in five of all deaths caused by smoking are from cancer.<sup>80</sup> Unlike many other areas of public health, there is little debate about the best way to mitigate the tobacco problem. The seven components of a comprehensive strategy were originally laid out in the landmark 1962 Smoking and Health Report of the Royal College of Physicians.<sup>81</sup> These components — public education, restriction of sales to minors, restriction of tobacco promotion, restricting smoking in public places, increasing tobacco tax/price, consumer information and production regulation, and cessation support services — are required to act synergistically to reduce smoking rates in a population.

It has been estimated that \$2 has been saved on health care for each \$1 spent on tobacco control programs to date.<sup>82</sup> The total economic benefits of tobacco control programs are estimated to exceed health-related and other expenditure by at least fifty to one.<sup>83</sup>

### 7.4 *A global perspective*

Tobacco is the largest cause of preventable death in the world, causing one in ten deaths worldwide. If current trends continue, it is projected that by 2030 tobacco will result in ten million deaths annually, of which 70% will have occurred in developing countries.<sup>84</sup>

The total number of smokers is increasing mainly due to expansion of the world's population; by 2030 there will be at least another two billion people. Unless smoking prevalence rates decline dramatically, the absolute number of smokers will increase. The expected continuing decrease in male smoking prevalence also may be offset, in part, by a potentially dangerous increase in female smoking rates, especially in developing countries.<sup>85</sup>

One hundred million people died from tobacco use in the 20th century and unless effective measures are implemented to prevent people from smoking and to help current users quit, tobacco will kill one billion people in the 21st century.<sup>85</sup>

## Acknowledgements

The authors wish to thank Usha Salagame for assistance with retrieving references and with formatting the reference list for publication.

Figures 1 to 3 of this chapter are obtained from “Deaths from Smoking” © 2006 International Union Against Cancer (UICC), available online at [www.deathsfromsmoking.net](http://www.deathsfromsmoking.net). (Copyright waiver: Because this resource is intended to communicate the evidence that it summarises, any part of it may be reproduced for bona fide educational purposes without seeking copyright permission from the publisher or authors.)

## References

1. R. Doll and R. Peto, The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today, *J. Natl. Cancer Inst.* **66**: 1192–1308 (1981).
2. *World Cancer Report* (IARC Press, Lyon, 2003).
3. A. Jemal, R. Siegel, E. Ward, Y. Hao, J. Xu, T. Murray and M. J. Thun, Cancer statistics, 2008. *CA Cancer J. Clin.* **58**: 71–96 (2008).
4. S. S. Hecht, Cigarette smoking and lung cancer: Chemical mechanisms and approaches to prevention, *Lancet Oncol.* **3**: 461–469 (2002).
5. A. Catassi, D. Servent, L. Paleari, A. Cesario and P. Russo, Multiple roles of nicotine on cell proliferation and inhibition of apoptosis: Implications on lung carcinogenesis, *Mutat. Res.* **659**: 221–231 (2008).
6. IARC, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 83. Tobacco Smoke and Involuntary Smoking* (International Agency for Research on Cancer, Lyon, 2004).
7. J. E. Harris, M. J. Thun, A. M. Mondul and E. E. Calle, Cigarette tar yields in relation to mortality from lung cancer in the cancer prevention study II prospective cohort, 1982–8, *Br. Med. J.* **328**: 72 (2004).
8. N. L. Benowitz, P. Jacob, III, J. T. Bernert, M. Wilson, L. Wang, F. Allen and D. Dempsey, Carcinogen exposure during short-term switching from regular to “light” cigarettes, *Cancer Epidemiol. Biomarkers Prev.* **14**: 1376–1383 (2005).
9. N. D. Freedman, M. F. Leitzmann, A. R. Hollenbeck, A. Schatzkin and C. C. Abnet, Cigarette smoking and subsequent risk of lung cancer in

- men and women: Analysis of a prospective cohort study, *Lancet Oncol.* **9**: 649–656 (2008).
10. G. K. Alderton, Predisposing to behaviour?, *Nat. Rev. Cancer* **8**: 321 (2008).
  11. S. Sun, J. H. Schiller and A. F. Gazdar, Lung cancer in never smokers — A different disease, *Nat. Rev. Cancer* **7**: 778–790 (2007).
  12. J. Subramanian and R. Govindan, Molecular genetics of lung cancer in people who have never smoked, *Lancet Oncol.* **9**: 676–682 (2008).
  13. S. V. Sharma, D. W. Bell, J. Settleman and D. A. Haber, Epidermal growth factor receptor mutations in lung cancer, *Nat. Rev. Cancer* **7**: 169–181 (2007).
  14. I. Y. Tam, L. P. Chung, W. S. Suen, E. Wang, M. C. Wong, K. K. Ho, W. K. Lam, S. W. Chiu, L. Girard, J. D. Minna, A. F. Gazdar and M. P. Wong, Distinct epidermal growth factor receptor and KRAS mutation patterns in non-small cell lung cancer patients with different tobacco exposure and clinicopathologic features, *Clin. Cancer Res.* **12**: 1647–1653 (2006).
  15. T. Yano, N. Miura, T. Takenaka, A. Haro, H. Okazaki, T. Ohba, H. Kouso, T. Kometani, F. Shoji and Y. Maehara, Never-smoking non-small cell lung cancer as a separate entity: Clinicopathologic features and survival, *Cancer* **113**: 1012–1018 (2008).
  16. R. H. Breuer, A. Pasic, E. F. Smit, E. van Vliet, N. A. Vonk, E. J. Risse, P. E. Postmus and T. G. Sutedja, The natural course of preneoplastic lesions in bronchial epithelium, *Clin. Cancer Res.* **11**: 537–543 (2005).
  17. Y. E. Miller, P. Blatchford, D. S. Hyun, R. L. Keith, T. C. Kennedy, H. Wolf, T. Byers, P. A. Bunn, Jr., M. T. Lewis, W. A. Franklin, F. R. Hirsch and J. Kittelson, Bronchial epithelial Ki-67 index is related to histology, smoking and gender, but not lung cancer or chronic obstructive pulmonary disease, *Cancer Epidemiol. Biomarkers Prev.* **16**: 2425–2431 (2007).
  18. F. Veglia, S. Loft, G. Matullo, M. Peluso, A. Munnia, F. Perera, D. H. Phillips, D. Tang, H. Autrup, O. Raaschou-Nielsen, A. Tjønneland and P. Vineis, DNA adducts and cancer risk in prospective studies: A pooled analysis and a meta-analysis, *Carcinogenesis* **29**: 932–936 (2008).
  19. M. R. Spitz, W. K. Hong, C. I. Amos, X. Wu, M. B. Schabath, Q. Dong, S. Shete and C. J. Etzel, A risk model for prediction of lung cancer, *J. Natl. Cancer Inst.* **99**: 715–726 (2007).

20. J. K. Field and S. W. Duffy, Lung cancer screening: The way forward, *Br. J. Cancer* **99**: 557–562 (2008).
21. W. C. Black and J. A. Baron, CT screening for lung cancer: Spiraling into confusion?, *J. Am. Med. Assoc.* **297**: 995–997 (2007).
22. S. G. Spiro, Screening for lung cancer: Yet another problem, *Thorax* **62**: 105–106 (2007).
23. J. Aisner, CT screening for lung cancer: Are we ready for wide-scale application? *Clin. Cancer Res.* **13**: 4951–4953 (2007).
24. P. B. Bach, J. R. Jett, U. Pastorino, M. S. Tockman, S. J. Swensen and C. B. Begg, Computed tomography screening and lung cancer outcomes, *J. Am. Med. Assoc.* **297**: 953–961 (2007).
25. C. I. Henschke, D. F. Yankelevitz, D. M. Libby, M. W. Pasmantier, J. P. Smith and O. S. Miettinen, Survival of patients with stage I lung cancer detected on CT screening, *N. Engl. J. Med.* **355**: 1763–1771 (2006).
26. Y. Toyoda, T. Nakayama, Y. Kusunoki, H. Iso and T. Suzuki, Sensitivity and specificity of lung cancer screening using chest low-dose computed tomography, *Br. J. Cancer* **98**: 1602–1607 (2008).
27. P. B. Bach, Is our natural-history model of lung cancer wrong?, *Lancet Oncol.* **9**: 693–697 (2008).
28. M. V. Brock, C. M. Hooker, E. Ota-Machida, Y. Han, M. Guo, S. Ames, S. Glockner, S. Piantadosi, E. Gabrielson, G. Pridham, K. Pelosky, S. A. Belinsky, S. C. Yang, S. B. Baylin and J. G. Herman, DNA methylation markers and early recurrence in stage I lung cancer, *N. Engl. J. Med.* **358**: 1118–1128 (2008).
29. P. Workman and P. Johnston, Genomic profiling of cancer: What next?, *J. Clin. Oncol.* **23**: 7253–7256 (2005).
30. A. Spira, J. E. Beane, V. Shah, K. Steiling, G. Liu, F. Schembri, S. Gilman, Y. M. Dumas, P. Calner, P. Sebastiani, S. Sridhar, J. Beamis, C. Lamb, T. Anderson, N. Gerry, J. Keane, M. E. Lenburg and J. S. Brody, Airway epithelial gene expression in the diagnostic evaluation of smokers with suspect lung cancer, *Nat. Med.* **13**: 361–366 (2007).
31. J. Beane, P. Sebastiani, T. H. Whitfield, K. Steiling, Y. M. Dumas, M. E. Lenburg and A. Spira, A prediction model for lung cancer diagnosis that integrates genomic and clinical features, *Cancer Prev. Res.* **1**: 56–64 (2008).
32. B. W. Stewart, D. McGregor and P. Kleihues, *Principles of Chemoprevention* (IARC Scientific Publications, Lyon, 1996).
33. D. Albanes, O. P. Heinonen, P. R. Taylor, J. Virtamo, B. K. Edwards, M. Rautalahti, A. M. Hartman, J. Palmgren, L. S. Freedman,

- J. Haapakoski, M. J. Barrett, P. Pietinen, N. Malila, E. Tala, K. Liippo, E. R. Salomaa, J. A. Tangrea, L. Teppo, F. B. Askin, E. Taskinen, Y. Erozan, P. Greenwald and J. K. Huttunen, Alpha-tocopherol and beta-carotene supplements and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: Effects of base-line characteristics and study compliance, *J. Natl. Cancer Inst.* **88**: 1560–1570 (1996).
34. G. S. Omenn, G. E. Goodman, M. D. Thornquist, J. Balmes, M. R. Cullen, A. Glass, J. P. Keogh, F. L. Meyskens, Jr., B. Valanis, J. H. Williams, Jr., S. Barnhart, M. G. Cherniack, C. A. Brodtkin and S. Hammar, Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial, *J. Natl. Cancer Inst.* **88**: 1550–1559 (1996).
35. R. L. Keith and Y. E. Miller, Lung cancer: Genetics of risk and advances in chemoprevention, *Curr. Opin. Pulm. Med.* **11**: 265–271 (2005).
36. M. R. Law and A. K. Hackshaw, Environmental tobacco smoke, *Br. Med. Bull.* **52**: 22–34 (1996).
37. A. Besaratinia and G. P. Pfeifer, Second-hand smoke and human lung cancer, *Lancet Oncol.* **9**: 657–666 (2008).
38. S. Willers, G. Skarping, M. Dalene and S. Skerfving, Urinary cotinine in children and adults during and after semiexperimental exposure to environmental tobacco smoke, *Arch. Environ. Health* **50**: 130–137 (1995).
39. M. Neri, D. Ugolini, S. Bonassi, A. Fucic, N. Holland, L. E. Knudsen, R. J. Sram, M. Ceppi, V. Bocchini and D. F. Merlo, Children's exposure to environmental pollutants and biomarkers of genetic damage. II. Results of a comprehensive literature search and meta-analysis, *Mutat. Res.* **612**: 14–39 (2006).
40. J. L. Pirkle, J. T. Bernert, S. P. Caudill, C. S. Sosnoff and T. F. Pechacek, Trends in the exposure of nonsmokers in the U.S. population to secondhand smoke: 1988–2002, *Environ. Health Perspect.* **114**: 853–858 (2006).
41. T. Cains, S. Cannata, R. Poulos, M. J. Ferson and B. W. Stewart, Designated “no smoking” areas provide from partial to no protection from environmental tobacco smoke, *Tob. Control* **13**: 17–22 (2004).
42. J. P. Pierce and M. E. Leon, Effectiveness of smoke-free policies, *Lancet Oncol.* **9**: 614–615 (2008).

43. E. R. Gritz, D. J. Vidrine and M. C. Fingeret, Smoking cessation a critical component of medical management in chronic disease populations, *Am. J. Prev. Med.* **33**(6S), 414–422 (2007).
44. E. R. Gritz, C. Dresler and L. Sarna, Smoking, the missing drug interaction in clinical trials: Ignoring the obvious, *Cancer Epidemiol. Biomarkers Prev.* **14**(10): 2287–2293 (2005).
45. A. Bryant and R. J. Cerfolio, Differences in epidemiology, histology, and survival between cigarette smokers and never-smokers who develop non-small cell lung cancer, *Chest* **132**(1): 185–192 (2007).
46. P. S. Nia, J. Weyler, C. Colpaert *et al.*, Prognostic value of smoking status in operated non-small cell lung cancer, *Lung Cancer* **47**: 351–359 (2005).
47. C. M. Tammemagi, C. Neslund-Dudas, M. Simoff *et al.*, Smoking and lung cancer survival. The role of comorbidity and treatment, *Chest* **125**(1): 27–37 (2004).
48. J. Manjer, I. Andersson, G. R. Berglund *et al.*, Survival of women with breast cancer in relation to smoking, *Eur. J. Surg.* **166**: 852–858 (2000).
49. M. D. Holmes, S. Murin, W. Y. Chen *et al.*, Smoking and survival after breast cancer diagnosis, *Int. J. Cancer* **120**: 2672–2677 (2007).
50. N. L. Kobrinsky, M. G. Klug, P. J. Hokanson *et al.*, Impact of smoking on cancer stage at diagnosis, *J. Clin. Oncol.* **21**(5): 907–913 (2003).
51. B. E. Johnson, Second lung cancers in patients after treatment for an initial lung cancer, *J. Natl. Cancer Inst.* **90**(18): 1335–1345 (1998).
52. M. A. Tucker, N. Murray, E. G. Shaw *et al.*, Second primary cancers related to smoking and treatment of small-cell lung cancer, *J. Natl. Cancer Inst.* **89**(23): 1782–1788 (1997).
53. G. E. Richardson, M. A. Tucker, D. J. Venzon *et al.*, Smoking cessation after successful treatment of small-cell lung cancer is associated with fewer smoking-related second primary cancers, *Ann. Intern. Med.* **119**(5): 383–390 (1993).
54. T. Kawaguchi, A. Matsumura, K. I. S. Ishikawa *et al.*, Second primary cancers in patients with stage iii non-small cell lung cancer successfully treated with chemo-radiotherapy, *Japan J. Clin. Oncol.* **36**(1): 7–11 (2006).
55. B. S. Glisson and W. K. Hong, Survival after treatment of small-cell lung cancer: An endless uphill battle, *J. Natl. Cancer Inst.* **89**(23): 1745–1747 (1997).
56. M. Winstanley, S. Woodward and N. Walker, *Tobacco in Australia: Facts and Issues*, 2nd ed. (Victorian Smoking and Health Program, Melbourne, 1995), p. 2.

57. S. Murin, Smoking cessation before lung resection, *Chest* **127**(6): 1873–1875 (2005).
58. M. J. Peters and L. Glantz, Should smokers be refused surgery? *Br. Med. J.* **334**: 20–21 (2007).
59. M. Kuri, M. Nakagawa, H. Tanaka *et al.*, Determination of the duration of preoperative smoking cessation to improve wound healing after head and neck surgery, *Anesthesiology* **102**: 892–896 (2005).
60. M. Winstanley, S. Woodward and N. Walker, *Tobacco in Australia: Facts and Issues*, 2nd ed. (Victorian Smoking and Health Program, Melbourne, 1995), p. 369.
61. L. G. Bluman, L. Mosca, N. Newman *et al.*, Preoperative smoking habits and postoperative pulmonary complications, *Chest* **113**(4): 883–889 (1998).
62. A. A. Vaporciyan, K. W. Merriman, F. Ece *et al.*, Incidence of major pulmonary morbidity after pneumonectomy: Association with timing of smoking cessation, *Ann. Thorac. Surg.* **73**: 420–426 (2002).
63. R. Barrera, W. Shi, D. Amar *et al.*, Smoking and timing of cessation: Impact on pulmonary complications after thoracotomy, *Chest* **127**(6): 1977–1983 (2005).
64. C. D. Rochers, S. Dische and M. I. Saunders, The problem of cigarette smoking in radiotherapy for cancer in the head and neck, *Clin. Oncol.* **4**: 214–216 (1992).
65. G. P. Browman, G. Wong, I. Hodson *et al.*, Influence of cigarette smoking on the efficacy of radiation therapy in head and neck cancer, *N. Engl. J. Med.* **328**(3): 159–163 (1993).
66. J. L. Fox, K. E. Rosenzweig and J. S. Ostroff, The effect of smoking status on survival following radiation therapy for non-small cell lung cancer, *Lung Cancer* **44**: 287–293 (2004).
67. A. S. Tsao, D. Liu, J. J. Lee *et al.*, Smoking affects treatment outcome in patients with advanced nonsmall cell lung cancer, *Cancer* **106**(11): 2428–2436 (2006).
68. R. Duarte, R. Luiz and M. Paschoal, The cigarette burden (measured by the number of pack-years smoked) negatively impacts the response rate to platinum-based chemotherapy in lung cancer, *Lung Cancer* **61**(2): 244–254.
69. M. Prochazka, P. Hall, G. Gagliardi *et al.*, Ionizing radiation and tobacco use increases the risk of a subsequent lung carcinoma in women with breast cancer: Case-only design, *J. Clin. Oncol.* **23**(30): 7467–7474 (2005).

70. P. J. Eifel, A. Jhingran, D. C. Bodurka *et al.*, Correlation of smoking history and other patient characteristics with major complications of pelvic radiation therapy for cervical cancer, *J. Clin. Oncol.* **20**(17): 3651–3657 (2002).
71. T. Pickles, M. Liu, E. Berthelet *et al.*, The effect of smoking on outcome following external radiation for localized prostate cancer, *J. Urol.* **171**: 1543–1546 (2004).
72. J. Pantarotto, S. Malone, S. Dahrouge *et al.*, Smoking is associated with worse outcomes in patients with prostate cancer treated by radical radiotherapy, *Br. J. Urol. Int.* **99**: 564–569 (2006).
73. F. Meyer, I. Bairati, A. Fortin *et al.*, Interaction between antioxidant vitamin supplementation and cigarette smoking during radiation therapy in relation to long-term effects on recurrence and mortality: A randomized trial among head and neck cancer patients, *Int. J. Cancer* **122**: 1679–1683 (2008).
74. D. Il'yasova, L. H. Colbert, T. B. Harris *et al.*, Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort, *Cancer Epidemiol. Biomarkers Prev.* **14**(10): 2413–2418 (2005).
75. M. J. Jarvis, ABC of smoking cessation. Why people smoke, *Br. Med. J.* **328**: 277–279 (2004).
76. R. Doll, R. Peto, J. Boreham *et al.*, Mortality in relations to smoking: 50 years' observations on male British doctors, *Br. Med. J.* **328**: 1519 (2004).
77. International Union Against Cancer (UICC), Deaths from smoking, available at <http://www.deathsfromsmoking.net/> (accessed 30 October 2008), Switzerland, Geneva, 2008.
78. H. Bronnum-Hansen and K. Juel, Abstinence from smoking extends life and compresses morbidity: A population based study of health expectancy among smokers and never smokers in Denmark, *Tob. Control* **10**: 273–278 (2001).
79. C. M. McBride and J. S. Ostroff, Teachable moments for promoting smoking cessation: The context of cancer care and survivorship, *Cancer Control* **10**(4): 325–333 (2003).
80. B. Ridolfo and C. Stevenson, *The Quantification of Drug-Caused Mortality and Morbidity in Australia, 1998* (Australian Institute of Health and Welfare (AIHW), Canberra, 2001).
81. *Smoking and Health: A Report of the Royal College of Physicians on Smoking in Relation to Cancer of the Lung and Other Diseases* (Pitman Medical Publishing Co. Ltd, London, 1962).

82. D. J. Collins and H. M. Lapsley, *Counting the Cost: Estimates of the Social Costs of Drug Abuse in Australia in 1998–99. National Drug Strategy Monograph Series No. 49* (Commonwealth Department of Health and Ageing, Canberra, 2002).
83. Returns on investment in public health: An epidemiological and economic analysis (Department of Health and Ageing, 2003).
84. Curbing the epidemic: Governments and the economics of tobacco control, in *Development in Practice* (The World Bank, Washington D.C., 1999).
85. J. Mackay and M. Eriksen, *The Tobacco Atlas* (World Health Organization, Geneva, 2002).
86. L. Sanderson Cox, N. L. Africano, K. P. Tercyak *et al.*, Nicotine dependence treatment for patients with cancer, *Cancer* **98**(3): 632–644 (2003).
87. R. Peto, S. Darby, H. Deo, P. Silcocks, E. Whitley and R. Doll, Smoking, smoking cessation and lung cancer in the UK since 1950: Combination of national statistics with two case-control studies, *Br. Med. J.* **321**: 323–329 (2000).
88. The Clinical Trial Service Unit and Epidemiological Studies Unit at the University of Oxford, *Survival to Age 70 and Beyond: Effect of Smoking in Male British Doctors*, available at [www.deathsfromsmoking.net](http://www.deathsfromsmoking.net).