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Overview of smoking and all cancers

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Article Outline

The magnitude of adverse health effects associated with the use of tobacco products has been well demonstrated over the past several decades. In the United States, approximately 46.3 million people are current smokers, and nearly 440,000 people die prematurely each year from tobacco-related diseases [1]. Tobacco smoking is the greatest single cause of premature death, killing approximately half of all people who continue to smoke for most of their lives. Half of these deaths occur before the age of 69 [2]. In the United States, smoking-related illnesses have been responsible for approximately $157 billion in annual health-related economic loss annually, in the latest data for 2001 [3].

The World Health Organization reports that almost 1 billion men and 250 million women worldwide are daily smokers. The rate of increase of global cigarette consumption is decreasing, yet overall consumption is still growing, with approximately 5.5 trillion cigarettes consumed in 2000 [4]. It is estimated that, of everyone alive today, 500 million people will eventually be killed by tobacco use, with cancer being one of the main causes of death [5], [6]. Cigarette smoking is directly responsible for approximately 90% of lung cancer cases, and is the leading cause of cancer-related death in the world, representing nearly 1.2 million deaths annually [7]. The attributable risk for oral, pharyngeal, and esophageal cancers is significant, although less than that for lung cancer [8], [9], [10]. The International Agency for Research on Cancer published an authoritative series on the evaluation of carcinogenic risks to humans, and came to the following conclusions on the basis of an extensive evaluation of the international literature. First, cigarette smoking increases the risk of all histologic types of lung cancer. Smoking is causally associated with cancer of the oral cavity, including the lip and tongue, and these risks are greatly increased by the use of smokeless tobacco or by alcohol consumption in combination with smoking. Second, cigarette smoking is causally associated with laryngeal, oropharyngeal, and hypopharyngeal cancer, and increases the risk of leukemia, sinonasal cancer, nasopharyngeal cancer, and esophageal cancer. Furthermore, cigarette smoking has been proved as a risk factor for developing cancer of the stomach and pancreas; transitional cell carcinoma of the bladder, ureter, and renal pelvis; and cancer of the uterine cervix and kidney [7].

Tobacco smoke consists of more than 4000 chemical compounds, and more than 60 of these are known carcinogens [11]. In 1992, the US Environmental Protection Agency classified environmental tobacco smoke, so-called “passive” or “second-hand smoke,” as one of the most dangerous cancer-causing agents in humans [12]. It is labeled a group A carcinogen. The irrefutable link between tobacco products and human cancers results from the combination of two key factors: nicotine content and the presence of carcinogens. Without either of these factors, tobacco would not be responsible for its deadly legacy. Instead, it is the single greatest preventable cause of death from cancer worldwide. Nicotine, the second most abundant constituent in tobacco smoke, is addictive and toxic, but it is not carcinogenic. Addiction to nicotine results in continual use of tobacco products, leading to repeated and prolonged exposure to the many carcinogens contained within tobacco smoke [13].

The first part of this article reviews the carcinogens found in tobacco products and the mechanisms by which exposure to these compounds causes cancer. The second part focuses on specific cancer types and their association with tobacco use. Unless noted, studies that examined tobacco smoke were limited to cigarette smoke, and not to cigar or pipe smoke. Studies of smokeless tobacco usually differentiate chewing tobacco from snuff.

Carcinogens in tobacco products

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Tobacco likely acts on multiple stages of carcinogenesis; it not only delivers a host of carcinogens but also causes irritation and inflammation and interferes with the body's natural protective barriers [14]. Both tobacco smoke and smokeless tobacco products contain a diverse array of compounds that can initiate tumors, promote the development of previously initiated tumors, or act as cocarcinogens [11]. For risk assessment, tobacco smoke is classified as either mainstream or sidestream. Mainstream smoke is that which is inhaled through the column of the cigarette and filter tip during puffing, whereas sidestream smoke is emitted from the burning cone between puffs, and is inhaled by smokers and nonsmokers. Sidestream smoke is often referred to as “second-hand smoke” exposure. Most of the same carcinogens are present in both mainstream and sidestream smoke, and although the chemicals released are similar, the concentration of many of the carcinogens is actually higher in sidestream smoke [13].

There is a broad range of potencies and concentrations among the various carcinogens in tobacco smoke, but in general, strong carcinogens, such as polycyclic aromatic hydrocarbons, nitrosamines, and aromatic amines, occur in lesser amounts than weaker carcinogens, such as acetaldehyde. The first carcinogen to be discovered in cigarette smoke was benzo[*a*]pyrene [15]. Recent studies have implicated its metabolite as the cause of mutations in the TP53 tumor suppressor gene [16], [17]. Benzo[*a*]pyrene is only one of more than 60 carcinogens in cigarette smoke and although considerable evidence implicates benzo[*a*]pyrene and other polycyclic aromatic hydrocarbons as important causative agents of smoking-related cancers, particularly lung cancer, their role is clearly not

exclusive. First, levels of benzo[*a*]pyrene in cigarette smoke are relatively low [18]. Moreover, initial studies on tobacco carcinogenesis clearly show that its tumorigenic activity cannot solely be accounted for by polycyclic aromatic hydrocarbons or benzo[*a*]pyrene alone, and that other cocarcinogens (eg, catechols and methylcatechols) and tumor promoters are critical for full tumor development and activation [19].

Unburned tobacco contains fewer carcinogens than cigarette smoke because most carcinogens are formed during combustion [20]. Levels of polycyclic aromatic hydrocarbons in unburned tobacco are low. Nitrosamine and its metabolites are by far the most prevalent strong carcinogens in unburned tobacco products, which include oral snuff, chewing tobacco, and other smokeless tobacco products. The levels of these chemicals in smokeless tobacco products are several-fold higher than those of carcinogenic nitrosamines in any other tobacco consumer product [21]. Although the cancer risk from smokeless tobacco products is considerably less than that of cigarettes, these products still contain high levels of certain potent carcinogens. Smokeless tobacco products are known to cause oral cavity cancer, and there is some evidence that they may also elevate the risk of pancreatic cancer [21], [22].

Mechanisms of carcinogenesis

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Carcinogens form the central link between tobacco use and cancer, and DNA adducts, as described here, are critical in this process [23]. Most carcinogens in tobacco products require metabolic activation before they are able to react with DNA, although some are capable of reacting with DNA directly. This metabolic activation is generally initiated by cytochrome P-450 enzymes, which are part of the normal mechanisms of metabolism and detoxification of foreign compounds. Most of the metabolites processed by this system are excreted in the urine or undergo further detoxification reactions. Some of these compounds are electrophilic and react with DNA, however, forming DNA adducts. There is convincing evidence for the presence of adducts in the DNA of human lung cancer cells and there is accumulating knowledge regarding the metabolic activation pathways that lead to DNA adduct formation. Cellular repair systems remove DNA adducts, with the goal of maintaining DNA structure in its native state, but if the adducts persist and escape repair, mutations may result. DNA adducts derived from cigarette smoke carcinogens lead to miscoding, most frequently resulting in point mutations from G T (guanine to thymidine) and G A (adenine) mutations [24], [25], [26]. If these mutations occur in critical regions of oncogenes, such as *ras* and *myc*, or in tumor suppressor genes, such as TP53, the result can be loss of normal cellular growth control mechanisms and development of malignancies. Clearly, there are many pathways involved in this process, which are much more complex than is described here. Nevertheless, there is no question that tobacco smoke carcinogens and their metabolically activated forms induce mutations through the formation of DNA adducts, and there is little doubt that these mutations are associated with disruption of cell-cycle check points, with resultant chromosomal instability [13].

There are other known mechanisms of tobacco's carcinogenesis. Nitrosamine bioproducts in tobacco smoke have recently been identified as stimulants for some cell surface receptors [27]. These chemicals act as ligands for the nicotinic-acetylcholine receptors, leading to activation of specific protein kinases. This leads to downstream effects, including impaired apoptotic mechanisms, increased formation of arachidonic acid inflammatory metabolites, and increased cellular proliferation [28].

Additional mechanisms of carcinogenesis, such as hypermethylation of tumor suppressor genes, are active areas of investigation, and further understanding of this complex process will perhaps serve as a foundation for new approaches for cancer prevention.

Cancer types associated with tobacco

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Lung cancer

Before the twentieth century, tobacco usually was chewed or inhaled in the form of snuff. With the introduction of blended cigarettes in the early part of the twentieth century, the practice of inhaling tobacco smoke became popular. The first studies that showed a strong association between cigarette smoking and lung cancer were published in the early 1950s [29], [30]. Since that time, many studies have further implicated cigarette smoking as a major risk factor for lung cancer. In 1964, the US Surgeon General's report on the health effects of smoking concluded that cigarette smoking was the major cause of lung cancer in American men [24]. Even though this report suggested a causal relationship between smoking and lung cancer in women, it was not until 16 years later

that the Surgeon General issued the first report on women's health and smoking, which affirmed a similar strong causal relationship between cigarette smoking and lung cancer in women [31], [32].

Today, lung cancer is the leading cause of cancer death in the United States, and of cancer deaths worldwide. Lung cancer was rare in the nineteenth century, but its incidence increased dramatically throughout the twentieth century. It is now the leading cause of cancer mortality in both men and women, accounting for 31% of cancer deaths in men and 25% of cancer deaths in women [33]. Lung cancer is extraordinarily lethal, with more than 90% of affected patients dying of their disease [34]. Cigarette smoking is the primary cause of lung cancer, and the incidence of the disease in a given population largely reflects the prevalence of smoking that took place decades earlier. Populations with the highest incidence of lung cancer are those whose tobacco consumption had been highest during the previous three or four decades, and lower in countries where tobacco consumption has declined or increased only recently [35]. Smoking rates vary widely between regions and between countries within the same region. The prevalence of smoking in men is currently highest in countries of the Western Pacific region, such as South Korea (68%); China (61%); and Japan (59%). In Europe, where almost one half of adult men are regular smokers, the prevalence ranges from 63% of men in the former Soviet Bloc, to only 17% in Sweden. Among women, the regional pattern of smoking is quite different, with a dramatic contrast seen between the developed and developing world. For example, one third of women in Norway and Denmark smoke, compared with fewer than 5% of those in the Indian subcontinent. In many countries, the number of young people who smoke is increasing, as it is in the United States. Although 17% of high school students smoked in 1992, alarmingly the prevalence of smoking increased to 22% of this population by 1995. As tobacco consumption rises, there is a resulting increase in smoking-related mortality [36]. The American Cancer Society estimates that in 2003, there will be over 170,000 new cases of lung cancer diagnosed and over 157,000 deaths from lung cancer in the United States. For women, lung cancer deaths surpassed deaths from breast cancer in 1987 and are expected to account for 25% of all female cancer deaths. In 2004, it is estimated that there will be 41,000 deaths from breast cancer in women and close to 69,000 deaths from lung cancer [37].

Tobacco use increases the risk of all types of lung cancer; however, the strongest associations are with squamous cell carcinoma and small cell carcinoma. Interestingly, the frequency of different histologic types of lung cancer has changed over the past two decades, making squamous cell carcinoma less common and adenocarcinoma more frequent [38]. The proposed reasons for this change are discussed later.

Multiple prospective cohort studies involving millions of people throughout the world have shown significantly higher lung cancer mortality rates among smokers than nonsmokers. In current male smokers, the relative risk for death from lung cancer compared with nonsmokers averages approximately 10-fold [33]. There is a strong dose-response relation between cumulative consumption of cigarettes and the risk for death from lung cancer. In the Cancer Prevention Study II, which included more than 1 million participants in the United States, followed for more than 6 years, men who smoked 20 cigarettes per day had 22 times the risk for dying from lung cancer when compared with lifetime nonsmokers. Those who consumed more than 41 cigarettes per day experienced a 45-fold increased risk of lung cancer. Other smoking-related factors contributing to a higher risk include earlier age of smoking initiation, deeper inhalation of tobacco smoke, higher tar and nicotine content of cigarettes, and the use of unfiltered cigarettes [31], [39], [40], [41].

There is considerable evidence that the polycyclic aromatic hydrocarbons and nitrosamines enriched in cigarette smoke are strongly implicated in the causation of lung cancer. Polycyclic aromatic hydrocarbon DNA adducts and mutations in the tumor suppressor gene TP53 have been isolated in human lung cancer samples [2], [17], [18]. Nitrosamines have also been proved to induce lung tumors by DNA adducts [42], [43], [44]. Nitrosamine concentrations have increased in mainstream smoke from the 1950s to current times, resulting from changes in tobacco blends, and this may be responsible for the changing histology of lung cancer [45]. Adenocarcinoma has surpassed squamous cell carcinoma in lung cancer incidence. Publications have shown that nitrosamines and derivative metabolites primarily induce adenocarcinoma rather than squamous cell carcinoma in rat models [13].

There are several important additional factors regarding lung cancer carcinogenesis that require notation. Risk reduction for the development of lung cancer has clearly been demonstrated by smoking cessation. As compared with continuous smokers, the excess risk of lung cancer sharply decreases in ex-smokers after approximately 5 years of cessation. Some risk probably persists throughout life; however, there are some reports demonstrating that the excess risk drops to baseline after 20 years [46]. Another important risk factor is age at which regular tobacco use began; smokers who started smoking before age 15 have a fourfold to fivefold higher risk of lung cancer than smokers who started at age 25 or later [46]. Also, the carcinogen content varies depending on the type of tobacco used. For example, black (air-cured) tobacco has a higher content of nitrosamines than blond (flue-cured) tobacco, and hand-rolled cigarettes have a higher tar content than filtered cigarettes.

Cigarettes have changed dramatically from the 1950s to the 1980s. Filter use has increased and the average tar and nicotine concentrations per cigarette have fallen [35]. Until recently, however, nearly all previous epidemiologic

studies of risk of lung cancer in relation to the type of cigarette smoke had compared smokers of high-tar nonfilter cigarettes with those of medium-tar filter cigarettes. No large, long-term prospective epidemiologic study had specifically compared the risk of lung cancer in smokers of medium-tar filter brands with the risk in smokers of low-tar and very-low-tar filter brands. The Cancer Prevention Study II recently showed that the risk of lung cancer was no different in people who smoked medium-tar cigarettes, low-tar cigarettes, or very-low-tar cigarettes. In addition, men and women who smoked nonfiltered cigarettes with high-tar contents had an even higher risk of lung cancer. Finally, this study concluded that all current smokers, regardless of the tar level, had a substantially greater risk of lung cancer than those people who had never smoker or who had quit smoking [41]. This is consistent with the evidence of compensatory smoking. Addicted smokers who switch from high-tar to lower-tar cigarettes can maintain their nicotine intake by increasing puff volume, increasing time the smoke is retained in the lungs, and smoking more cigarettes. As a result, the actual dose of toxicants to the smoker may be much higher than is predicted by machine-measured yields [47].

The first reports of passive or second-hand smoke exposure and lung cancer risk came to light in the 1980s when scientific committees and national organizations concluded from available data that exposure to environmental tobacco smoke, also called “passive smoking,” is a cause of lung cancer [48], [49], [50], [51], [52]. Although the evidence for other smoking-related cancers is not as consistent, substantial additional evidence has since been published from large case-control studies confirming an excess risk of lung cancer of 24% in nonsmokers who lived with a smoker ($P < .001$) [53]. Furthermore, these studies showed that there is a dose-response relationship between a nonsmoker's risk of lung cancer and the number of cigarettes and years of exposure to a smoker. Additionally, tobacco-specific carcinogens are found in the blood and urine of nonsmokers exposed to environmental tobacco smoke [53], [54], [55], [56]. Although most studies have shown an increased risk mainly in the spouses of smokers, a case-control study of 191 patients with lung cancer showed the highest risk to be present in those exposed to household smoke during their childhood and adolescence years. Household exposure to 25 or more smoker-years during childhood and adolescence doubled the risk for lung cancer [56]. The epidemiologic and biochemical evidence on the exposure to environmental tobacco smoke, with the supporting evidence of tobacco-specific carcinogens in the blood and urine of nonsmokers exposed to environmental tobacco smoke, provides compelling confirmation that environmental tobacco smoke is a cause of lung cancer [55].

Oral and pharyngeal cancer

Cancers of the oral cavity and pharynx are a heterogeneous group of cancers, with an estimated 30,000 cases diagnosed in the United States annually. Most cancers diagnosed in the oral cavity are squamous cell carcinomas, and smokers are at a dramatically increased risk for oral cancer, especially of the lip, tongue, floor of the mouth, and pharynx. The relative risk associated with smoking ranges from 2- to 10-fold in various studies. The risk decreases on cessation of smoking, and it approximates the risk for never-smokers after 10 years of cessation [35].

Several case-control studies have explored the relationship between smokeless tobacco and carcinomas of the oral cavity and pharynx. A landmark study was published in the 1970s demonstrating a strong association for smokeless tobacco use and oral and pharyngeal cancers [57]. With snuff dipping, an odds ratio of 4.2 was noted in women for cancers of the gum and buccal mucosa. In addition, a dose-response relationship was observed, with those women who used snuff for more than 50 years having a greater risk of cancer in these locations. This study remains the strongest evidence for an association of smokeless tobacco use with oral cancers in the United States, although it is limited to women, and was published many years ago. Recent American studies have failed to demonstrate an increased risk between smokeless tobacco and oral and pharyngeal cancers. There is some speculation in the literature that current tobacco products may have reduced levels of carcinogens in smokeless products. In most studies, however, the number of smokeless tobacco users is small, resulting in insufficient statistical power to demonstrate an effect unless the risk is markedly elevated [58], [59], [60], [61], [62].

Laryngeal cancer

Laryngeal cancer is the second most common respiratory cancer after lung cancer. It is estimated that there will be 10,270 new cases of laryngeal cancer diagnosed in the United States in 2004, and three quarters of these occurred in men [37]. The incidence of laryngeal cancer is increasing in much of the world, often in parallel with changes in tobacco use and alcohol consumption. There are a few encouraging examples worldwide of declining trends of laryngeal cancer that may be attributable to decreasing use of either tobacco or alcohol. There are additive effects of tobacco and alcohol exposure in the development of laryngeal cancer; however, alcohol alone does not seem to be a risk factor [63].

Globally, the incidence of laryngeal cancer is highest in Southern and Central Europe, South America, and among African Americans in the United States. Low rates of incidence are noted in Southeast Asia and Central Africa. Over 90% of the laryngeal cancers are squamous cell carcinomas, and most laryngeal cancer in Western countries is attributable to smoking, alcohol drinking, and the interaction between these factors [64]. Indeed, the increased

risk from tobacco is substantial, with a 10-fold increase compared with nonsmokers and more than 15-fold increase for heavy smokers. These risks tend to be higher for glottic than for supraglottic neoplasms [65]. Several studies in various populations have proved a dose-response relationship in relation to the intensity and duration of smoking [66], [67], [68]. The risk decreases after cessation of smoking, and it approaches that of a nonsmoker after approximately 15 years [69]. Smoking black tobacco has a higher risk than that of blond tobacco cigarettes, and the use of a filter does seem to provide some protection [35].

Esophageal cancer

Esophageal cancer is diagnosed in more than 300,000 people worldwide each year, and is expected to account for over 14,000 new cases in the United States in 2004 [37]. Esophageal cancer is the seventh leading cause of death from cancer among American men. African American men have a higher incidence of this disease compared with men in other racial or ethnic groups. More than 90% of esophageal cancers are either squamous cell carcinomas or adenocarcinomas, and both are associated with tobacco consumption. Direct contact of tobacco carcinogens, particularly nitrosamines, with esophageal mucosa increases the risk of esophageal carcinoma [70]. The risk of esophageal cancer correlates directly with the quantity of cigarettes smoked per day and the duration of smoking [71].

The overall incidence of esophageal cancer in the United States and the associated mortality rate reveal increases of 15% to 20% over the past decades, during which time the histologic patterns have changed significantly. As with lung cancer, in which adenocarcinomas are now more common than squamous cell carcinomas, esophageal carcinomas have followed a similar pattern of histology. As recently as 1975, about three quarters of cases of esophageal cancer were squamous cell carcinomas, with the remaining one quarter represented by adenocarcinomas. Over the past 20 years, the incidence of squamous cell carcinoma has decreased in both the black population and white population, whereas the incidence of adenocarcinoma has increased by 450% among white men and 50% among black men [72], [73], [74]. It is estimated that in the United States in 2003, more than 50% of the new cases of esophageal cancer were adenocarcinoma [75]. This may be associated with increases in the nitrosamine content in tobacco products over the past 30 years.

Smoking cessation is an important step in reducing the risk of squamous cell carcinoma of the esophagus. The risk of this cancer decreases substantially one decade after smoking cessation. The risk of adenocarcinoma of the esophagus is not altered after smoking cessation, however, with similar incidence at 30 years after discontinuation of tobacco use [35]. There have been conflicting data regarding smokeless tobacco use as a risk factor for esophageal cancer. One study found an elevated odds ratio for chewing tobacco in association with esophageal cancer [76]. This study also found a significant dose-response relationship between the frequency of daily consumption, the duration of use in years, and the age when chewing was initiated. The odds ratio associated with chewing tobacco in excess of 20 years was 10.6 in men, compared with 1.8 who had practiced this habit for less than 10 years. Two additional studies, however, both reported from India, failed to demonstrate a statistically significant association between chewing tobacco and esophageal cancer [59].

Pancreatic cancer

Pancreatic cancer, usually adenocarcinoma, has been rising in incidence over the past 40 years, with 30,700 new cases and 30,000 deaths anticipated in 2003 [33]. Pancreatic cancer is approximately equally frequent in men and women, and most cases occur in high-income countries [33]. Treatment of this disease has limited efficacy, with 5-year survival rates less of than 5%. Overall, smoking is associated with an approximate twofold to fourfold increased risk of developing pancreatic cancer. One study has estimated that 25% of pancreatic cancers are attributable to cigarette smoking, and other studies have confirmed a significant dose-response increased risk with increasing pack-years of smoking [77], [78]. Compared with people who continue to smoke, ex-smokers halved their risk of pancreatic cancer within 2 years [79].

Perhaps the most convincing data demonstrating the link between smoking and pancreatic cancer came from the National Cancer Institute in 1994, where researchers performed a case-control study based on direct interviews with patients [80]. The previous case-control studies were based largely on interviews with proxy respondents, who are historically less accurate. The results of 526 cases and over 2000 control subjects were impressive, with a 70% increased risk of pancreas cancer among smokers compared with nonsmokers. Contrary to other studies, 10 years or less of abstinence showed no reduction of risk; however, after 10 years the risk was reduced. Cigarette smokers who switched from nonfiltered to filtered cigarettes did not show any benefit in reducing their risk. The authors estimated that elimination of cigarette smoking could prevent approximately 27% of pancreatic cancer, saving nearly 7000 lives in the United States annually [80].

Bladder cancer

More than 57,000 people in the United States were diagnosed with bladder cancer in 2003, with over 12,000 deaths from this malignancy [32]. It is estimated that close to 13,000 Americans will die in 2004 from bladder cancer [37]. The incidence is higher in men than in women, and is transitional cell carcinoma in most cases. *Schistosoma mansoni* is the main cause of bladder cancer in Northern Africa, but in North America and Europe cigarette smoking is estimated to be responsible for nearly half (47%) of male bladder cancer deaths and 37% of female bladder cancer deaths [35]. The aromatic amines found in tobacco products are implicated as the main carcinogens [81]. Many reports based on case-control and cohort studies have concluded that there is a strong association between cigarette smoking and bladder cancer [80], [82], [83], [84], [85], [86], [87], [88]. Cigarette smoking is implicated in the occurrence of a greater proportion of bladder cancer than any other known factor. A systematic review of 43 epidemiologic studies, base on case-control data, concluded that current cigarette smokers have an approximate threefold risk of bladder cancer compared with lifelong nonsmokers [89]. In a combined analysis of 11 case-control studies from six European countries, the risk of bladder cancer increased with both duration and intensity of tobacco use [90]. Even though the relative risk of bladder cancer declines rapidly after smoking cessation, it never decreases to that of nonsmokers. The relative risk decreases by more than 30% after 1 to 4 years, and by 60% after 25 years [90], [91].

Kidney and renal pelvis cancer

Approximately 32,000 Americans were diagnosed with kidney or renal pelvis carcinoma in 2003 [32] and over 12,000 will die of this malignancy in 2004 [37]. Adenocarcinomas of the renal parenchyma arise from tubular epithelial cells, accounting for approximately 85% of malignant tumors of the kidney. Transitional cell carcinoma of the renal pelvis accounts for most of the remainder of the cases [32]. Many studies have indicated an increased risk among smokers in comparison with nonsmokers [92], [93], [94]. In an international, population-based, case-control study, the risk of cancer increased with the duration of smoking and the number of cigarettes smoked per day. In this same study, there was no noted effect of cigar or smokeless tobacco use in the causation of these tumors. It is not clear if the cessation of smoking decreases the risk of renal cancer. One study reports that long-term quitters (>15 years) experienced a 15% to 25% reduced risk compared with current tobacco users [95], yet other studies have not confirmed these results [35]. Smoking has been shown to significantly increase the risk of cancer of the renal pelvis and this risk was particularly high among heavy smokers, and declined with time after smoking cessation [35].

Gastric cancer

Despite the marked decline in the incidence of gastric carcinoma in many industrialized nations, cancer of the stomach remains the second most common cause of cancer deaths in the world. An estimated 22,700 new cases of gastric carcinoma will be diagnosed in the United States in 2004, and 11,780 will succumb to this disease [37]. The highest incidence occurs in populations from Eastern Asia, Eastern Europe, and South America. This is currently believed to be a result of a higher prevalence of *Helicobacter pylori* infection in these areas. More than 90% of stomach cancers are adenocarcinomas. Several publications, including cohort studies, case-control studies, and meta-analyses, have assessed the risk of smoking and gastric cancer. The cohort and case-control studies have shown a 1.5- to 3-fold increase in the risk of gastric cancer among smokers, although most of these studies have failed to demonstrate a clear dose-response relationship [96]. A meta-analysis demonstrated a similar increased risk of gastric cancer in smokers, and also confirmed an increased risk of gastric carcinoma with increased intensity and duration of smoking [97].

Cervical cancer

Cervical cancer is the third most common cancer in women globally, and is particularly frequent in low-income countries, where more than three quarters of the cases occur. In 2004, it is estimated that 10,520 new cases of cervical cancer will be diagnosed in the United States, and close to 4000 women will die of this disease [37]. Approximately 80% to 95% of the cervical cancers are squamous cell carcinoma, and a minority is adenocarcinomas [32]. The most important factor in the development of cervical cancer is exposure to oncogenic serotypes of human papillomavirus. There have been many studies investigating the association between smoking and cervical cancer; however, these published reports have been criticized extensively, because they overlook the confounding factors of sexual practice, which have been strongly linked to tobacco use [35].

In support of tobacco-related causation of cervical cancer, a recent case-control study from the United Kingdom found evidence for an association between the duration of smoking and the risk of squamous cell carcinoma, but not adenocarcinoma [98]. Furthermore, this study found that a duration of smoking in excess of 20 years was associated with a twofold increase in the risk of squamous cell carcinoma. This is consistent with the results of prior studies, which demonstrated a similar relationship between squamous cell carcinomas of the cervix and

smoking. Many studies have consistently failed to establish a significant association between smoking and adenocarcinoma of the cervix. One study examined women aged 20 to 44 years old, and smoking was associated with an increased risk of squamous cell carcinoma, yet a decreased risk of adenocarcinoma was noted (odds ratio of 0.6). Multiple lines of evidence support that smoking is a risk factor for squamous cell carcinoma, and not for adenocarcinoma [98].

Leukemia

Cigarette smoking has not classically been considered an etiologic factor in leukemia; however, an association was first noted in 1978 [99]. Since this time, several epidemiologic studies have reported an increased risk of leukemia among cigarette smokers [100], [101], [102]. A meta-analysis published in 1993 assessed seven prospective cohort studies and eight case-control studies. A statistically significant increased risk of leukemia was noted in tobacco users, and subsequent studies have confirmed this finding [103]. Two prospective studies showed an approximate 50% increase in leukemia risk with tobacco use [104]. Some of these studies have also provided evidence for a dose-response relationship and suggested an association that is most pronounced for acute myeloid leukemia. The most recent study, a retrospective evaluation of 643 patients with newly diagnosed acute myeloid leukemia, examined the role of tobacco on the initial characteristics at the time of presentation and on the course of disease [105]. Cigarette smoking seems to have a deleterious effect on survival in acute myeloid leukemia, with shortening of complete remission duration. Smoking was also associated with more severe infections during the aplastic period following chemotherapy [105].

Endometrial cancer

Endometrial cancer is diagnosed in over 140,000 women each year worldwide, and accounts for over 42,000 deaths annually. In the United States, over 40,000 women will be diagnosed and close to 4000 women will die of endometrial cancer in 2004 [37]. Most endometrial cancers are adenocarcinomas and they are the most commonly occurring gynecologic malignancy in developed countries. Unlike the other cancers discussed in this article, endometrial cancer is unique in that there is an inverse relationship between tobacco use and endometrial cancer [35]. The relative risk of endometrial cancer among smokers is about one half that of never smokers. This protective effect of smoking seems to be stronger among postmenopausal women, and women with higher levels of estrogen [106]. This relationship suggests that smoking may reduce the risk of endometrial cancer through an antiestrogenic effect [107]. In fact, there is epidemiologic evidence to indicate that women who smoke cigarettes are relatively estrogen-deficient [107], [108], [109]. Smokers have an earlier natural menopause and an increased risk of osteoporotic fractures. Moreover, women who smoke may have a reduced risk of uterine fibroids, endometriosis, and benign breast disease. Several possible mechanisms for these effects have been identified; however, none have been conclusively proved. There is no clear effect of duration or intensity of smoking, but there are similar risks of developing endometrial carcinoma in former smokers when compared with never smokers. This suggests a detrimental effect of smoking cessation for this particular tumor type [106], [108], [109], [110], [111], [112], [113].

Tumor types generally not associated with tobacco consumption

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Clearly not all cancers have shown a direct causal relationship with tobacco use. Tables 1 summarizes those cancers in which tobacco may have some minimal effect on risk, whereas Table 2 shows the cancer types that seem unlikely to be associated with smoking.

Table 1. Cancers for which tobacco may increase risk

Cancer type	Relative risk
Liver [114], [115], [116]	2
Colorectal [39], [117], [118]	2
Gallbladder [119], [120], [121]	1.3
Adrenal gland [122], [123]	2–5

Small intestine [124], [125]	0.5–4
Sinonasal [126], [127], [128]	2–3
Testicular cancer [129], [130], [131], [132]	2

Table 2. Cancers unlikely to be related to tobacco

Cancer type	Number of known studies
Skin cancer	
Melanoma [133], [134], [135], [136], [137], [138], [139]	5 Case-control studies
Nonmelanoma [134], [137], [140], [141], [142], [143], [144]	1 Prospective, 3 case-control, and 3 cohort studies
Breast cancer [145], [146], [147]	14 Case-control and 5 cohort studies
Prostate cancer [148]	22 Prospective cohort studies and 30 case-control studies
Lymphoma	
Non-Hodgkin's lymphoma [149]	6 Cohort, 1 prospective, and 2 case-control studies
Hodgkin's lymphoma [73], [149], [150]	5 Case-control, 1 large cohort studies
Multiple myeloma [151], [152], [153], [154]	4 Cohort, 3 case-control studies
Ovarian cancer [155], [156], [157], [158], [159]	7 Retrospective studies
Soft tissue sarcoma	1 Cohort study
Central nervous system cancer [160], [161], [162], [163], [164], [165], [166]	2 Population-based retrospective, 4 case-control, and 2 prospective studies
Thyroid cancer [167], [168], [169], [170], [171], [172], [173]	6 Case-control, 1 cohort study

Summary

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Tobacco consumption has been clearly implicated in the causation of many cancer types, with irrefutable evidence to support the association in multiple organ systems. More than 400,000 deaths per year and 30% of all cancers in the United States are attributable to smoking. Chief among these are cancers of the aerodigestive tract. Tobacco cessation leads to reduced cancer risk, and improved survival of those under treatment for their already established cancers. Prevention and cessation of tobacco use are currently the first line of defense against the epidemic of tobacco-related cancers. Avoidance of initiation of smoking by younger generations should have a profound impact on cancer rates and mortality. As the understanding of the mechanisms by which tobacco products cause cancer increases, clinicians may be able to identify those at highest risk for tobacco-related malignancies and allow for more focused interventions toward risk reduction among current tobacco users.

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