Langenbecks Arch Surg (2006) 391:603–613
DOI 10.1007/s00423-006-0111-z

NEW SURGICAL HORIZONS

Cigarette smoking: cancer risks, carcinogens, and mechanisms

Stephen S. Hecht

Received: 26 July 2006 / Accepted: 30 August 2006 / Published online: 10 October 2006

Abstract
Background Cigarette smoking causes about 30% of all cancer mortality in developed countries. Although smoking is decreasing in developed countries, it is increasing in some developing countries.
Discussion Cigarette smoke contains over 60 well established carcinogens. There are strong links between some of these carcinogens and various types of smoking-induced cancers. Mechanisms by which cigarette smoke carcinogens cause cancer are well established and are discussed here.
Conclusions A great deal is known about cigarette smoke carcinogens and the mechanisms by which they cause cancer. It is hoped that this will provide new insights for the prevention and cure of tobacco-induced cancer.

Keywords Carcinogens · Cigarette smoke · Tobacco · Carcinogenesis mechanisms · DNA adducts

Introduction

Although cigarette smoking has decreased in some countries, there are still about 1,200 million smokers in the world [1, 2]. China alone has approximately 300 million male smokers, about the same as the population of the U.S. [1]. Table 1 summarizes smoking prevalence in the world [2]. Trends in cigarette consumption by development level are shown in Fig. 1 [2]. Globally, about 57% of men and 10% of women smoke tobacco products. Cigarettes are the main type of tobacco product worldwide. About 5.5 trillion cigarettes were consumed annually in 1990–2000, about 1,000 cigarettes for every person on Earth [1]. Over 15 billion cigarettes are smoked per day [1]. Manufactured cigarettes are available everywhere, but roll-your-own cigarettes are still popular in some areas of the world. Other smoked products include *kreteks*, which are clove-flavored cigarettes popular in Indonesia, and "sticks" which are smoked in Papua New Guinea. *Bidis*, which consist of a small amount of tobacco wrapped in *temburni* leaf and tied with a string, are popular in India and neighboring areas. Cigars and pipes are still used. Water pipes are increasing in popularity.

Cigarette smoking causes well over 1 million cancer deaths annually in the world [2] and about 30% of all cancer deaths in developed countries (Table 2). The corresponding figure for developing countries is 13%. Lung cancer is the dominant malignancy caused by smoking. The total number of cases is estimated to be 1.2 million annually, with about 90% attributed to smoking [3]. Lung cancer was rare at the beginning of the 20th century, but incidence and death rates increased as smoking became more popular. The lung cancer death rate in 1930 for men in the U.S. was only 4.9 per 100,000. By 1990, it had increased to 75.6 per 100,000, parallel to the curve for cigarette smoking prevalence (Fig. 2). The first U.S. Surgeon General's report on the health consequences of cigarette smoking was published in 1964. Subsequently, smoking prevalence began to decrease in the U.S., fairly sharply from 1964 to 1990, and gradually since 1990. There are presently 44.5 million adult smokers in the U.S. about 20.9% of the adult population [4].

Epidemiology of smoking and cancer

In 1950, Wynder and Graham in the U.S. and Doll and Hill in England published the first large-scale studies linking

S. S. Hecht (✉)
The Cancer Center, University of Minnesota,
Box 806 Mayo, 420 Delaware Street SE,
Minneapolis, MN, USA
e-mail: hecht002@umn.edu

Table 1 Prevalance of cigarette smoking in the world[a]

	Prevalance [percentage of the population ≥15 years of age (%)]			Number of tobacco users (≥15 years) (millions)		
	Men	Women	Total	Men	Women	Total
WHO region						
African Region	29.4	7.4	18.4	51.967	13.420	65.387
Region of the Americas	32.0	20.9	26.3	94.035	64.072	158.107
Eastern Mediterranean Region	35.3	6.1	21.0	52.543	8.670	61.213
European Region	44.9	18.7	31.2	150.628	68.545	219.173
South-East Asian Region	48.1	5.3	27.3	251.699	26.484	278.183
Western Pacific Region	61.2	5.7	33.8	390.632	35.784	426.416
Levels of development						
Developed	33.9	21.2	27.4	114.783	75.891	190.674
Developing	49.8	7.2	28.9	809.725	114.718	924.443
Transitional	54.1	13.9	32.7	82.837	24.153	106.990
World	57.4	10.3	28.9	1,005.927	217.755	1,223.682

[a] From: IARC volume 83, 2004 [2]

smoking and lung cancer [5, 6]. Numerous large international prospective epidemiologic studies and case-control studies involving millions of subjects repeatedly confirmed and extended these findings [3]. The relationship between cigarette smoking and cancer is probably the most researched subject in the history of cancer epidemiology. The 2004 U.S. Surgeon General's Report and Volume 83 of the International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans summarize the data [3, 7]. Some of the important conclusions are given here [3].

The strongest determinant of lung cancer in smokers is duration of smoking, and risk also increases with the number of cigarettes smoked [3]. Smoking increases the risk of all histologic types of lung cancer: squamous cell carcinoma, small cell carcinoma, adenocarcinoma (including bronchiolar–alveolar carcinoma) and large cell carcinoma. Adenocarcinoma has replaced squamous cell carcinoma as the most common type of lung cancer caused by smoking in the U.S. and elsewhere. Smoking causes lung cancer in both men and women. Cessation of smoking at any age avoids the further increase in risk of lung cancer caused by continued smoking. However, the risk of ex-smokers for lung cancer remains elevated for years after cessation, compared to the risk of never smokers (Table 3). Cigarette smoking is a major cause of transitional cell carcinomas of the bladder, ureter, and renal pelvis. Similar to lung cancer, risk increases with smoking duration and number of cigarettes smoked, and cessation avoids further increases in risk. Renal cell carcinoma is also associated with smoking [3]. Cigarette smoking is causally associated with cancer of the oral cavity including the lip and tongue in both men and women. Alcohol consumption in combination with smoking greatly increases the risk of oral cancer. Duration of smoking and number of cigarettes smoked are major determinants of risk, and cessation decreases risk [3].

Cigarette smoking increases the risk of sinonasal and nasopharyngeal cancer. It is a cause of oropharyngeal and

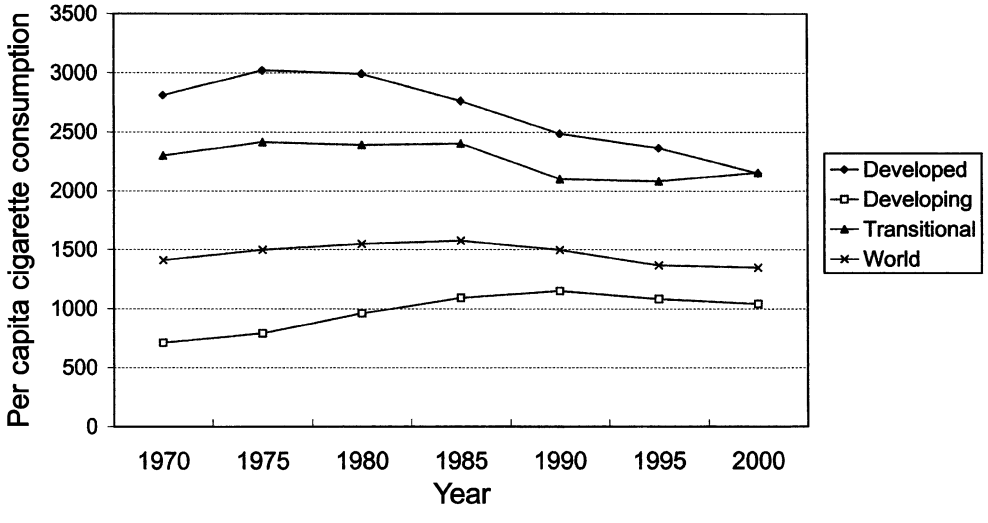

Fig. 1 Trends in cigarette consumption in developed and developing countries; From: IARC volume 83, 2004 [2]

Table 2 Estimated percentage of deaths caused by smoking in 1995, all developed countries, by sex, age, and major cause of death groupings[a]

Sex	Age	All causes	All cancer	Lung cancer	Upper aerodigestive cancer[b]	Other cancer	Chronic obstructive pulmonary diseases	Other respiratory diseases	Vascular diseases	Other causes
Men	35–69	36	50	94	70	18	82	29	35	35
	70+	21	36	91	59	13	73	11	12	12
	All ages	25	43	92	66	15	75	14	21	18
Women	35–69	13	13	71	34	2	55	16	12	15
	70+	8	13	74	38	2	54	7	5	6
	All ages	9	13	72	36	2	53	7	6	7
Both sexes	35–69	28	35	89	65	10	73	25	28	27
	70+	13	25	86	52	7	65	9	8	8
	All ages	17	30	87	60	8	66	10	13	12

[a] From: World Health Organization, 1997 [77]
[b] Cancers of the mouth, esophagus, pharynx, and larynx.

hypopharyngeal cancer and the risk increases with duration of smoking and daily cigarette consumption and decreases with time since quitting [3]. Cigarette smoking causes cancer of the esophagus, particularly squamous cell cancer. It is also a cause of adenocarcinoma of the esophagus, which has been increasing. The risk for esophageal cancer is related to duration of smoking and number of cigarettes smoked per day and remains elevated after cessation [3]. Laryngeal cancer is caused by cigarette smoking, and the risk increases with duration of smoking and number of cigarettes smoked. Risk is greatly enhanced by alcohol consumption and decreases upon cessation. Similarly, pancreatic cancer and stomach cancer are caused by cigarette smoking and are related to dose [3].

Cigarette smoking is a cause of liver cancer, independent of the effects of hepatitis B and C virus infection and alcohol consumption. Most studies show a relationship to dose and cessation. Similarly, cigarette smoking is a cause of cervical squamous cell carcinoma, controlling for infection with human papilloma virus, a known cause of cervical cancer. Myeloid leukemia in adults is also causally related to cigarette smoking [3]. Cigar and/or pipe smoking are strongly related to cancers of the oral cavity, oropharynx, hypopharynx, larynx, and esophagus, with the risk being similar to that of cigarette smoking. Dose response relationships have been documented. Cigar and/or pipe smoking are causally associated with lung cancer and possibly with cancers of the pancreas, stomach, and urinary bladder [3]. Recent evaluations by the U.S. Surgeon General and the International Agency for Research on Cancer summarize conclusive evidence that secondhand smoke is a cause of lung cancer [3, 8].

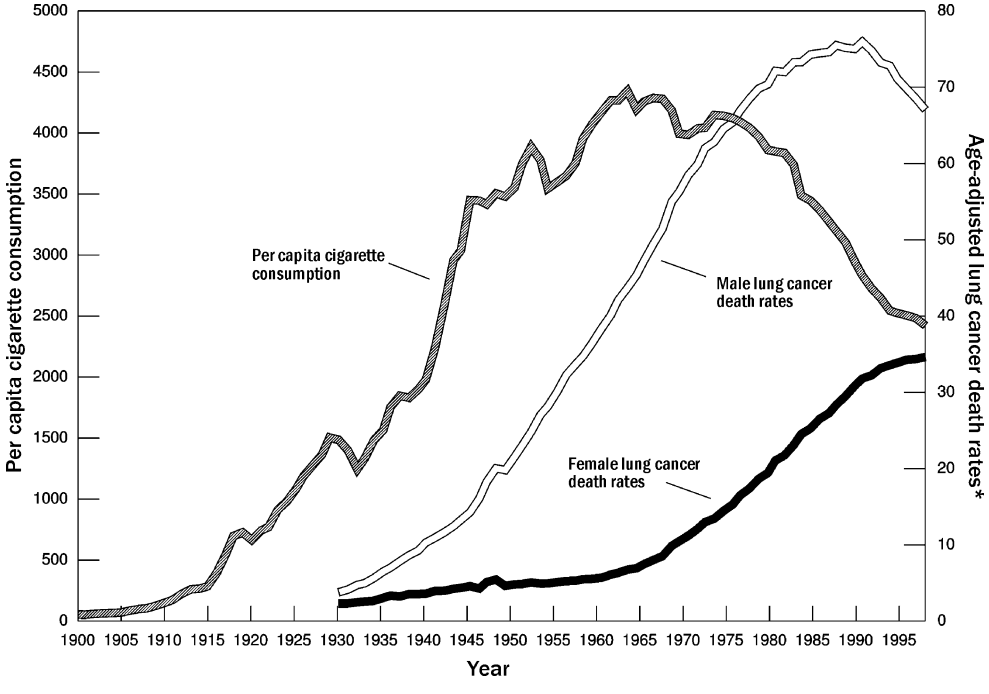

Fig. 2 Tobacco use and lung cancer mortality, U.S., 1900–1997. *Asterisk* (*) Per 100,000 and age-adjusted to 1970 US standard population. Source: Death rates: US mortality public use tapes, 1960–1997, US mortality volumes, 1930–1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 1999. Cigarette consumption: US Department of Agriculture, 1900–1987, 1988, 1989–1997. Figure from: *Cancer Prevention & Early Detection Facts & Figures, 2001, American Cancer Society* [79]

Table 3 Relative risk of developing lung cancer according to years since quitting smoking among males in three cohort studies of smokers[a]

Years since quitting smoking						
Cohort	0	1–4	5–9	10–14	15–19	20+
British physicians	15.8	16.0	5.9	5.3	2.0	2.0
U.S. veterans	11.3	18.8	7.5	5.0	5.0	2.1
American Cancer Society[b]	13.7	12.0	7.2	1.1	1.1	1.1

From: Blot and Fraumeni, 1996 [78]
[a] All risks relative to lifelong nonsmokers
[b] Excludes those who smoked less than one pack of cigarettes per day

Carcinogens in cigarette smoke

A carcinogen is any agent, chemical, physical, or viral that causes cancer or increases the incidence of cancer. The chemical carcinogens of cigarette smoke are the causes of cancer. A list of carcinogens in cigarette smoke is presented in Table 4 [2]. All 62 compounds are carcinogenic in laboratory animals, and 15 are carcinogenic in humans. Based on this list, the range of total carcinogen exposure in smokers is approximately 1.4–2.2 mg/cigarette, which can be compared to the current sales-weighted average nicotine delivery of about 0.8 mg/cigarette. However, it should be noted that some of the strongest carcinogens listed in Table 4 (such as polycyclic aromatic hydrocarbons (PAH), *N*-nitrosamines, and aromatic amines) occur in the lowest amounts while some of the weaker carcinogens (such as acetaldehyde and isoprene) occur in the highest amounts. Thus, simple addition of amounts of carcinogens could be misleading.

PAH are incomplete combustion products that were first identified as carcinogenic constituents of coal tar [9]. They occur as mixtures in tars, soots, broiled foods, automobile engine exhaust, and other materials generated by incomplete combustion [10]. PAH are usually locally acting carcinogens, and some, such as benzo[*a*]pyrene (BaP), have powerful carcinogenic activity. PAH carcinogenicity has typically been evaluated by application to mouse skin, but they also induce tumors of the lung, trachea, and mammary gland depending on the route of administration and animal model used [11]. BaP is considered carcinogenic to humans by IARC [12].

Heterocyclic compounds include nitrogen-containing analogues of PAH and simpler compounds such as furan, a liver carcinogen. *N*-Nitrosamines are a large class of carcinogens with demonstrated activity in at least 30 animal species [13]. *N*-Nitrosamines are potent systemic carcinogens that affect different tissues depending on their structures. Two of the most important *N*-nitrosamines in cigarette smoke are the tobacco-specific *N*-nitrosamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*′-nitrosonornicotine (NNN) [14]. NNK and NNN are found only in tobacco products. NNK causes lung tumors in all species tested and has particularly high activity in the rat. NNK can also induce tumors of the pancreas, nasal cavity, and liver. NNN produces esophageal and nasal tumors in rats and respiratory tract tumors in mice and hamsters [15]. NNK and NNN are considered as carcinogenic to humans by IARC [16].

Aromatic amines are combustion products and include the well-known human bladder carcinogens 2-naphthylamine and 4-aminobiphenyl, first characterized as human carcinogens due to industrial exposures in the dye industry [17]. Heterocyclic aromatic amines are also combustion products and are best known for their occurrence in broiled foods [18]. Aldehydes such as formaldehyde and acetaldehyde occur widely in the human environment and are also endogenous metabolites found in human blood [19, 20]. The phenolic compounds catechol and caffeic acid are common dietary constituents. Relatively high doses of catechol, administered in the diet, cause glandular stomach tumors. Catechol can also act as a co-carcinogen [20]. Dietary caffeic acid caused renal cell tumors in female mice [21]. The volatile hydrocarbons include 1,3-butadiene, a powerful multi-organ carcinogen in the mouse, with weaker activity in the rat, and benzene, a known human leukemogen [22, 23]. 1,3-Butadiene and benzene are arguably the two most prevalent strong carcinogens in cigarette smoke.

Among the other carcinogenic organic compounds in cigarette smoke are the human carcinogens vinyl chloride, in quite low amounts, and ethylene oxide, in substantial quantities [24, 25]. Ethylene oxide is associated with malignancies of the lymphatic and hematopoietic system in both humans and experimental animals [25]. Diverse metals and the radionuclide polonium-210 are also present in cigarette smoke. Cigarette smoke also contains oxidants such as nitric oxide (up to 600 μg per cigarette) and related species [26]. Free radicals have been detected by electron spin resonance and spin trapping [26]. The major free radical species are postulated to be a quinone–hydroquinone complex. In addition, several studies demonstrate the presence in cigarette smoke of an as yet uncharacterized ethylating agent, which ethylates both DNA and hemoglobin [27, 28]. In summary, there are diverse carcinogens in

Table 4 Carcinogens in cigarette smoke

Carcinogen	Amount in mainstream cigarette smoke	*IARC Monographs* evaluation of carcinogenicity			Monograph volume, year
		In animals	In humans	IARC Group	
Polycyclic aromatic hydrocarbons (PAH)					
Benz[*a*]anthracene	20–70 ng	Sufficient		2A	*32*, 1983a; *S7*, 1987
Benzo[*b*]fluoranthene	4–22 ng	Sufficient		2B	*32*, 1983a; *S7*, 1987
Benzo[*j*]fluoranthene	6–21 ng	Sufficient		2B	*32*, 1983a; *S7*, 1987
Benzo[*k*]fluoranthene	6–12 ng	Sufficient		2B	*32*, 1983a; *S7*, 1987
Benzo[*a*]pyrene	8.5–17.6 ng	Sufficient	Limited	1	*32*, 1983a; *S7*, 1987; *92*, 2005
Dibenz[*a,h*]anthracene	4 ng	Sufficient		2A	*32*, 1983a; *S7*, 1987
Dibenzo[*a,i*]pyrene	1.7–3.2 ng	Sufficient		2B	*32*, 1983a; *S7*, 1987
Dibenzo[*a,e*]pyrene	Present	Sufficient		2B	*32*, 1983a; *S7*, 1987
Indeno[*1,2,3-cd*]pyrene	4–20 ng	Sufficient		2B	*32*, 1983a; *S7*, 1987
5-Methylchrysene	ND-0.6 ng	Sufficient		2B	*32*, 1983a; *S7*, 1987
Heterocyclic compounds					
Furan	20–40 μg	Sufficient		2B	*63*, 1995b
Dibenz[*a,h*]acridine	ND-0.1 ng	Sufficient		2B	*32*, 1983a; *S7*, 1987
Dibenz[*a,j*]acridine	ND-10 ng	Sufficient		2B	*32*, 1983a; *S7*, 1987
Dibenzo[*c,g*]carbazole	ND-0.7 ng	Sufficient		2B	*32*, 1983a; *S7*, 1987
Benzo[*b*]furan	Present	Sufficient		2B	*63*, 1995b
N-Nitrosamines					
N-Nitrosodimethylamine	0. 1–180 ng	Sufficient		2A	*17*, 1978; *S7*, 1987
N-Nitrosoethylmethylamine	ND-13 ng	Sufficient		2B	*17*, 1978; *S7*, 1987
N-Nitrosodiethylamine	ND-25 ng	Sufficient		2A	*17*, 1978; *S7*, 1987
N-Nitrosopyrrolidine	1.5–110 ng	Sufficient		2B	*17*, 1978; *S7*, 1987
N-Nitrosopiperidine	ND-9 ng	Sufficient		2B	*17*, 1978; *S7*, 1987
N-Nitrosodiethanolamine	ND-36 ng	Sufficient		2B	*17*, 1978; *77*, 2000
N′-Nitrosonornicotine	154–196 ng	Sufficient	Limited	1	*37*, 1985; *S7*, 1987; *89*, 2004
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone	110–133 ng	Sufficient	Limited	1	*37*, 1985; *S7*, 1987; *89*, 2004
Aromatic amines					
2-Toluidine	30–200 ng	Sufficient	Limited	2A	*S7*, 1987; *77*, 2000
2,6-Dimethylaniline	4–50 ng	Sufficient		2B	*57*, 1993
2-Naphthylamine	1–22 ng	Sufficient	Sufficient	1	*4*, 1974; *S7*, 1987
4-Aminobiphenyl	2–5 ng	Sufficient	Sufficient	1	*1*, 1972; *S7*, 1987
Heterocyclic aromatic amines					
A-α-C	25–260 ng	Sufficient		2B	*40*, 1986b; *S7*, 1987
MeA-α-C	2–37 ng	Sufficient		2B	*40*, 1986b; *S7*, 1987
IQ	0.3 ng	Sufficient		2A	*S7*, 1987; *56*, 1993
Trp-P-1	0.3–0.5 ng	Sufficient		2B	*31*, 1983b; *S7*, 1987
Trp-P-2	0.8–1.1 ng	Sufficient		2B	*31*, 1983b; *S7*, 1987
Glu-P-1	0.37–0.89 ng	Sufficient		2B	*40*, 1986b; *S7*, 1987
Glu-P-2	0.25–0.88 ng	Sufficient		2B	*40*, 1986b; *S7*, 1987
PhIP	11–23 ng	Sufficient		2B	*56*, 1993b
Aldehydes					
Formaldehyde	10.3–25 μg	Sufficient	Sufficient	1	*S7*, 1987;*62*,1995a
Acetaldehyde	770–864 μg	Sufficient		2B	*S7*, 1987; *71*, 1999
Phenolic compounds					
Catechol	59–81 μg	Sufficient		2B	*S7*, 1987; *71*, 1999
Caffeic acid	<3 μg	Sufficient		2B	*56*, 1993b
Volatile hydrocarbons					
1,3-Butadiene	20–40 μg	Sufficient	Limited	2A	*S7*, 1987; *71*, 1999
Isoprene	450–1,000 μg	Sufficient		2B	*60*, 1994; *71*, 1999
Benzene	12–50 μg	Sufficient	Sufficient	1	*29*, 1982; *S7*, 1987
Nitrohydrocarbons					
Nitromethane	0.5–0.6 μg	Sufficient		2B	*77*, 2000
2-Nitropropane	0.7–1.2 ng	Sufficient		2B	*S7*, 1987; *71*, 1999

Table 4 (continued)

Carcinogen	Amount in mainstream cigarette smoke	*IARC Monographs* evaluation of carcinogenicity			Monograph volume, year
		In animals	In humans	IARC Group	
Nitrobenzene	25 μg	Sufficient		2B	*65*, 1996
Miscellaneous organic compounds					
Acetamide	38–56 μg	Sufficient		2B	*S7*, 1987; *71*, 1999
Acrylamide	Present	Sufficient		2A	*S7*, 1987; *60*, 1994
Acrylonitrile	3–15 μg	Sufficient		2B	*S7*, 1987; *71*, 1999
Vinyl chloride	11–15 ng	Sufficient	Sufficient	1	*19*, 1979; *S7*, 1987
1,1-Dimethylhydrazine	Present	Sufficient		2B	*4*, 1974; *71*, 1999
Ethylene oxide	7 μg	Sufficient	Limited	1	*60*, 1994; *S7*,1987
Propylene oxide	0–100 ng	Sufficient		2B	*60*, 1994; *S7*, 1987
Urethane	20–38 ng	Sufficient		2B	*7*, 1974; *S7*, 1987
Metals and inorganic compounds					
Arsenic	40–120 ng	Sufficient	Sufficient	1	*84*, 2004a
Beryllium	0.5 ng	Sufficient	Sufficient	1	*S7*, 1987; *58*, 1993a
Nickel	ND-600 ng	Sufficient	Sufficient	1	*S7*, 1987; *49*, 1990
Chromium (hexavalent)	4–70 ng	Sufficient	Sufficient	1	*S7*, 1987; *49*, 1990
Cadmium	41–62 ng	Sufficient	Sufficient	1	*S7*, 1987; *58*, 1993a
Cobalt	0.13–0.20 ng	Sufficient		2B	*52*, 1991
Lead (inorganic)	34–85 ng	Sufficient	Limited	2A	*23*, 1980; *S7*,1987; *87*, 2004b
Hydrazine	24–43 ng	Sufficient		2B	*S7*, 1987; *71*, 1999
Radio-isotope Polonium-210	0.03–1.0 pCi	Sufficient		1	*78*, 2001

This table (modified from Hoffmann et al., 2001 [40] and IARC volume 83 [2]) shows components of unfiltered mainstream cigarette smoke, with amounts given per cigarette. Virtually all these compounds are known carcinogens in experimental animals. In combination with data on cancer in humans and—in some cases—other relevant data, IARC Monographs classifications for these agents have been established as Group 2B (possibly carcinogenic to humans), Group 2A (probably carcinogenic to humans), or Group 1 (carcinogenic to humans). When IARC evaluations were made more than twice, only the two most recent Monographs are listed, with volume number and year of publication. No entry in the column 'humans' indicates inadequate evidence or no data.

S7 Supplement 7 of the *IARC Monographs*, *ND* not detected, *A-α-C* 2-amino-9*H*-pyrido[2,3-*b*]indole, *MeA-α-C* 2-amino-3-methyl-9*H*-pyrido [2,3-*b*]indole, *IQ* 2-amino-3-methylimidazo[4,5-*b*]quinoline, *Trp-P-1* 3-amino-l,4-dimethyl-5*H*-pyrido[4,3-*b*]indole, *Trp-P-2* 3-amino-l-methyl-5*H*-pyrido[4,3-*b*]indole, *GIu-P-1* 2-amino-6-methyl[1,2-*a*:3′,2″-*d*]imidazole, *GIu-P-2* 2-aminodipyrido[1,2-*a*:3′,2″-*d*]imidazole, *PhIP* 2-amino-l-methyl-6-phenylimidazo[4,5-*b*]pyridine, *pCi* picoCurie

cigarette smoke. Among the well characterized compounds in Table 4, the most important, based on their carcinogenic potency and levels in cigarette smoke are probably PAH, *N*-nitrosamines, aromatic amines, 1,3-butadiene, benzene, aldehydes, and ethylene oxide. The same carcinogens are also present in secondhand cigarette smoke, but human exposure is considerably less due to dilution with ambient air.

The role of carcinogens in specific cancers caused by cigarette smoke

Although difficult to prove, data from carcinogenicity studies, product analyses, and biochemical and molecular biological investigations do support a significant role for certain carcinogens in specific types of cancer (Table 5). Considerable evidence favors PAH and NNK as major etiological factors in lung cancer. PAH are strong locally acting carcinogens, and tobacco smoke fractions enriched in these compounds are carcinogenic [10, 29, 30]. PAH–DNA

Table 5 Carcinogens and tobacco-induced cancers

Cancer type	Likely carcinogen involvement[a]
Lung	PAH, NNK (major);1,3-butadiene, isoprene, ethylene oxide, ethyl carbamate, aldehydes, benzene, metals
Larynx	PAH
Nasal	NNK, NNN, other *N*-nitrosamines, aldehydes
Oral cavity	PAH, NNK, NNN
Esophagus	NNN, other *N*-nitrosamines
Liver	NNK, other *N*-nitrosamines, furan
Pancreas	NNK, NNAL
Cervix	PAH, NNK
Bladder	4-aminobiphenyl, other aromatic amines
Leukemia	Benzene

[a] Based on carcinogenicity studies in laboratory animals, biochemical evidence from human tissues and fluids, and epidemiological data, where available

NNAL 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, *NNK* 4-(methyl nitrosamino)-1-(3-pyridyl)-1-butanone, *NNN N′*-nitrosonornicotine, *PAH* polycyclic aromatic hydrocarbons

Adapted from Surgeon General's Report 2006, in preparation.

adducts have been detected in human lung, and the spectrum of mutations in the *TP53* tumor suppressor gene isolated from lung tumors is similar to the spectrum of DNA damage produced in vitro by PAH metabolites and in cell culture by BaP [31–34].

NNK is a strong systemic lung carcinogen in rodents, inducing lung tumors independently of its route of administration [15]. The strength of NNK is particularly great in the rat, in which total doses as low as 6 mg/kg (and 1.8 mg/kg when considered as part of a dose-response trend) induce a significant incidence of lung tumors [35]. This compares to an estimated 1.1 mg/kg dose of NNK in humans in 40 years of smoking [15]. DNA adducts derived from NNK or the related tobacco-specific nitrosamine NNN are present in lung tissue from smokers, and metabolites of NNK are present in smokers' urine [36]. Epidemiologic data indicate that a systemic carcinogen causes lung cancer in cigar smokers who do not inhale, consistent with the systemic tumorigenic properties of NNK [37, 38]. The changing histology of lung cancer, in which adenocarcinoma has now overtaken squamous cell carcinoma as the most common lung cancer type, is also consistent with the role of NNK, which produces primarily adenocarcinoma in rodents, although this has also been attributed to differing inhalation patterns of current cigarettes [15, 39]. NNK concentrations in mainstream smoke increased, while those of BaP decreased, as nitrate concentrations in tobacco increased over the period of 1959–1997 due to the use of tobacco blends containing higher levels of air-cured tobacco, use of reconstituted tobacco, and other factors [40]. Other compounds that could be involved in lung cancer include 1,3-butadiene, isoprene, ethylene oxide, ethyl carbamate, aldehydes, benzene, metals, and oxidants, but the collective evidence for each of these is not as strong as for PAH and NNK [26].

The particulate phase of cigarette smoke causes tumors of the larynx in hamsters—this could be attributed to PAH [41]. *TP53* gene mutations identified in tumors of the human larynx are consistent with a role for PAH [31]. *N*-Nitrosamines and acetaldehyde and formaldehyde, induce nasal tumors in rodents and are likely candidates as causes of smoking associated nasal tumors [13, 19, 22]. PAH, NNK, and NNN are the most likely causes of oral cancer in smokers based on animal studies [42]. *N*-Nitrosamines are the most effective esophageal carcinogens known, and NNN, which causes tumors of the esophagus in rats, is the most prevalent *N*-nitrosamine carcinogen in cigarette smoke [43, 44].

NNK and several other *N*-nitrosamines in cigarette smoke are effective hepatocarcinogens in rats, as is furan [13, 45]. NNK and its major metabolite NNAL are the only pancreatic carcinogens known to be present in tobacco products. Biochemical data from studies with human tissues provide some support for their role in smoking related pancreatic cancer, although DNA adducts were not detected [46–48]. Biochemical studies demonstrate that both NNK and PAH can reach the cervix in humans, and are metabolically activated there [49, 50]. DNA adducts derived from BaP and other hydrophobic compounds have been detected in cervical tissue from smokers [33, 50]. Therefore, these compounds might contribute to the etiology of cervical cancer in smokers, in combination with human papilloma virus [51]. 4-Aminobiphenyl and 2-naphthylamine are known human bladder carcinogens, and considerable data support the role of aromatic amines as major causes of bladder cancer in smokers [52–57]. The most probable cause of leukemia in smokers is benzene, which occurs in large quantities in cigarette smoke, and is a known cause of acute myelogenous leukemia in humans [23]. Cigarette smoke also causes oxidative damage, probably because it contains free radicals such as nitric oxide and mixtures of hydroquinones, semiquinones, and quinones [26, 58]. Smokers have lower levels of ascorbic acid and sometimes higher levels of oxidized DNA bases than non-smokers but the role of oxidative damage as a cause of specific tobacco-induced cancers remains unclear [26].

Overview of mechanisms of tumor induction by cigarette smoke

Figure 3 gives a schematic overview of the mechanisms by which cigarette smoke causes cancer [26]. The central track of Fig. 3, involving exposure to carcinogens, the formation of covalent bonds between the carcinogens and DNA producing DNA adducts, and the resulting permanent mutations in critical genes of somatic cells is the major established pathway of cancer causation by cigarette smoke. Somatic mutations occur in somatic cells, and therefore, affect only their descendants and are not inherited. The somatic mutation theory of cancer is well established, and the presence of multiple mutagenic carcinogens in cigarette smoke is completely consistent with this theory.

Most people start smoking as teenagers, generally due to peer pressure. Some become addicted to nicotine and then smoke habitually. While nicotine, the main known addictive agent in cigarette smoke, is not carcinogenic, each puff of each cigarette contains a mixture of well established carcinogens (Table 4), along with thousands of other compounds. Extensive data demonstrate the uptake of these carcinogens by smokers and confirm the expected higher levels of their metabolites than in nonsmokers.

Most cigarette smoke carcinogens require a metabolic activation process, generally catalyzed by cytochrome *P*450 enzymes (*P*450s), to convert them to electrophilic entities that can covalently bind to DNA, forming DNA adducts [59, 60]. P450s 1A1 and 1B1, which are inducible by

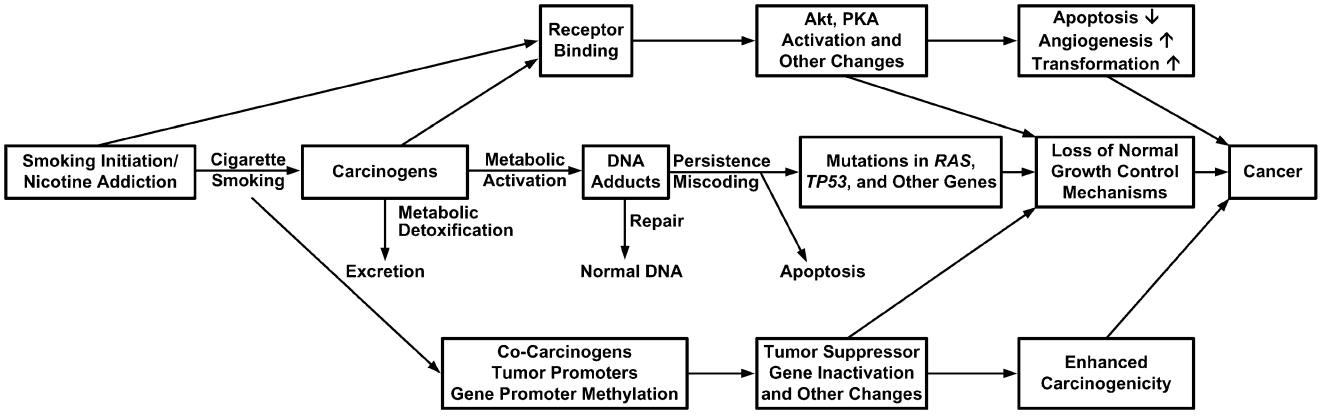

Fig. 3 Scheme linking nicotine addiction and cancer via tobacco smoke carcinogens

cigarette smoke via interactions with the aryl hydrocarbon receptor, are particularly important in the metabolic activation of PAH [61]. The inducibility of these P450s may be a critical aspect of cancer susceptibility in smokers. *P*450s 1A2, 2A13, 2E1, and 3A4 are also important in the activation of cigarette smoke carcinogens. Competing with the activation process is metabolic detoxification, which results in excretion of carcinogen metabolites in generally harmless forms, and is catalyzed by a variety of enzymes including glutathione-*S*-transferases and UDP-glucuronosyl transferases [62, 63]. The balance between carcinogen metabolic activation and detoxification varies among individuals and is likely to affect cancer susceptibility with those having higher activation and lower detoxification capacity being at highest risk. This is supported, in part, by evidence from molecular epidemiologic studies of polymorphisms or variants in these enzymes [64].

Continuing along the central track of Fig. 3, the metabolic activation of carcinogens results in the formation of DNA adducts, and these are absolutely central to the carcinogenic process. Starting in the mid-1980s, extensive studies examined the presence of DNA adducts in human tissues. There is massive evidence, particularly from studies which use relatively nonspecific adduct measurement methods, that adduct levels in the lung and other tissues are higher in smokers than in nonsmokers, and some epidemiologic data link higher adduct levels with a higher probability of cancer development [3].

Cellular repair systems can remove DNA adducts and return the structure of DNA to normal. These include direct base repair by alkyltransferases, excision of DNA damage by base and nucleotide excision repair, mismatch repair, and double strand repair. If these repair enzymes are overwhelmed by DNA damage or for other reasons cannot efficiently perform their function, then adducts may persist, leading to a higher probability of cancer development. There are polymorphisms in some DNA repair enzymes and the resulting deficient DNA repair can lead to a higher probability of cancer development, a subject of current interest in molecular epidemiology [65].

Persistent DNA adducts can cause miscoding during replication when DNA polymerase enzymes process them incorrectly. There is considerable specificity in the relationship between DNA adducts caused by cigarette smoke carcinogens and the types of mutations which they cause. G to T and G to A mutations are frequently observed [26]. Mutations have been seen frequently in the *KRAS* oncogene in lung cancer and in the *TP53* tumor suppressor gene in a variety of cigarette smoke-induced cancers [31, 66]. The cancer-causing role of these genes has been firmly established in animal studies [67, 68]. The *KRAS* and *TP53* mutations observed in lung cancer in smokers appear to reflect DNA damage by metabolically activated PAH, although other carcinogens are also likely to be involved. In addition, numerous cytogenetic changes have been observed in lung cancer, and chromosome damage throughout the aerodigestive tract is strongly linked with cigarette smoke exposure. Gene mutations can cause loss of normal cellular growth control functions, via a complex process of signal transduction pathways, ultimately resulting in genomic instability, cellular proliferation, and cancer [69, 70]. Apoptosis, or programmed cell death, is a protective process which can remove cells with DNA damage and serves as a counterbalance to these mutational events. The balance between mechanisms leading to apoptosis and those suppressing apoptosis has a major impact on tumor growth [70].

While the central track of Fig. 3 proceeding through genetic damage is clearly established as the major pathway by which cigarette smoke carcinogens cause cancer, epigenetic pathways also contribute, as indicated in the top and bottom tracks of Fig. 3 [71, 72]. Nicotine and tobacco-specific nitrosamines bind to nicotinic and other cellular receptors leading to activation of Akt (also known as protein kinase B), protein kinase A, and other changes, resulting in decreased apoptosis, increased angiogenesis, and increased transformation [73, 74]. Cigarette smoke

activates the epidermal growth factor receptor and cyclo-oxygenase-2 [75]. Furthermore, co-carcinogens and tumor promoters occur in cigarette smoke. Another important epigenetic pathway is enzymatic methylation of promoter regions of genes, which can result in gene silencing. If this occurs in tumor suppressor genes, the result can be unregulated proliferation [76].

Conclusion

The decrease in cigarette smoking in countries such as the U.S. results in a decrease in lung cancer and predicts a decrease in other tobacco-related cancers (Fig. 2). This is a very encouraging development, and the major successful methods of tobacco control—legislation to ban smoking in public places, increased taxation, and aggressive anti-tobacco advertising—must be continued. These policies have strongly influenced overall cancer mortality. The situation in developing countries is not as encouraging because tobacco use is increasing in many of these countries. Overall, cigarette smoking in the world continues to be pervasive and is unlikely to abate in the near future. Research on mechanisms of tobacco-induced cancer has provided a strong framework for understanding the actions of tobacco carcinogens (Fig. 3). We have an excellent understanding of the carcinogens in cigarette smoke, their metabolism to DNA adducts, and their competing detoxification pathways. We have also achieved an ever-increasing appreciation of the complex pathways that lead to genomic instability and ultimately to cancer due to the persistence of unrepaired DNA adducts in tissues of people who smoke cigarettes. These findings provide new insights for blocking key steps in the cancer induction process. It is hoped that these mechanistic insights will be translated into practical approaches for the prevention and cure of tobacco-induced cancer.

Acknowledgements The author's research on cigarette smoking and cancer is supported by grants CA-81301, CA-92025, CA-102502, DA-13333, and ES-11297 from the U.S. National Institutes of Health and RP-00-138 from the American Cancer Society.

References

1. Mackay J, Eriksen M (2002) The tobacco atlas. World Health Organization, Geneva, pp 24–27
2. International Agency for Research on Cancer (2004) Tobacco smoke and involuntary smoking. IARC monographs on the evaluation of carcinogenic risks to humans, vol 83. IARC, Lyon, FR, pp 53–119
3. International Agency for Research on Cancer (2004) Tobacco smoke and involuntary smoking. IARC monographs on the evaluation of carcinogenic risks to humans, vol 83. IARC, Lyon, FR, pp 1179–1187
4. Centers for Disease Control (2005) Cigarette smoking among adults—United States, 2004. MMWR 54:1121–1124
5. Wynder EL, Graham EA (1950) Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma. A study of six hundred and eighty-four proved cases. JAMA 143:329–336
6. Doll R, Hill AB (1950) Smoking and carcinoma of the lung. A preliminary report. Br Med J ii:739–748
7. U.S. Department of Health and Human Services (2004) The health consequences of smoking: a report of the surgeon general. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Health Promotion and Education, Office on Smoking and Health, Rockville, MD
8. U.S.Department of Health and Human Services (2006) The health consequences of involuntary exposure to tobacco smoke: a report of the surgeon general. U.S. Dept. of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Washington, DC, p 709
9. Phillips DH (1983) Fifty years of benzo[*a*]pyrene. Nature 303:468–472
10. International Agency for Research on Cancer (1983) Polynuclear aromatic compounds, part 1, chemical, environmental, and experimental data. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, vol 32. IARC, Lyon, FR, pp 33–91
11. Dipple A, Moschel RC, Bigger CAH (1984) Polynuclear aromatic hydrocarbons. In: Searle CE (ed) Chemical carcinogens, second edition, ACS monograph 182, vol 1. American Chemical Society, Washington, D.C., pp 41–163
12. Straif K, Baan R, Grosse Y, Secretan B, El Ghissassi F, Cogliano V (2005) Carcinogenicity of polycyclic aromatic hydrocarbons. Lancet Oncol 6:931–932
13. Preussmann R,Stewart BW (1984) *N*-Nitroso carcinogens. In: Searle CE (ed) Chemical carcinogens, second edition, ACS monograph 182, vol 2. American Chemical Society, Washington, DC, pp 643–828
14. Hecht SS, Hoffmann D (1988) Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. Carcinogenesis 9:875–884
15. Hecht SS (1998) Biochemistry, biology, and carcinogenicity of tobacco-specific *N*-nitrosamines. Chem Res Toxicol 11:559–603
16. International Agency for Research on Cancer (2006) Smokeless tobacco and tobacco-specific nitrosamines. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol 89. IARC, Lyon, FR (in press)
17. Luch A (2005) Nature and nurture—lessons from chemical carcinogenesis. Nat Rev Cancer 5:113–125
18. Sugimura T (1995) History, present and future, of heterocyclic amines, cooked food mutagens. Princess Takamatsu Symp 23:214–231
19. International Agency for Research on Cancer (1995) Wood dust and formaldehyde. IARC monographs on the evaluation of carcinogenic risks to humans, vol 62. IARC, Lyon, FR, pp 217–362
20. International Agency for Research on Cancer (1999) Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide (Part Two). IARC monographs on the evaluation of carcinogenic risks to humans, vol 71. IARC, Lyon, FR, pp 319–451
21. International Agency for Research on Cancer (1993) Some naturally occurring substances: food items and constituents, heterocyclic aromatic amines and mycotoxins. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, vol 56. IARC, Lyon, FR, pp 115–134
22. International Agency for Research on Cancer (1999) Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide (part one). IARC monographs on the evaluation of carcinogenic risks to humans, vol 71. IARC, Lyon, FR, pp 109–225

23. International Agency for Research on Cancer (1982) Some industrial chemicals and dyestuffs. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, vol 29. IARC, Lyon, FR, pp 93–148
24. International Agency for Research on Cancer (1979) Some monomers, plastics and synthetic elastomers, and acrolein. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, vol 19. IARC, Lyon, FR, pp 377–438
25. International Agency for Research on Cancer (1994) Some industrial chemicals. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, vol 60. IARC, Lyon, FR, pp 73–159
26. Hecht SS (1999) Tobacco smoke carcinogens and lung cancer. J Natl Cancer Inst 91:1194–1210
27. Carmella SG, Chen M, Villalta PW, Gurney JG, Hatsukami DK, Hecht SS (2002) Ethylation and methylation of hemoglobin in smokers and non-smokers. Carcinogenesis 23:1903–1910
28. Singh R, Kaur B, Farmer PB (2005) Detection of DNA damage derived from a direct acting ethylating agent present in cigarette smoke by use of liquid chromatography-tandem mass spectrometry. Chem Res Toxicol 18:249–256
29. Hoffmann D, Schmeltz I, Hecht SS, Wynder EL (1978) Tobacco carcinogenesis. In: Gelboin H, Ts'o POP (eds) Polycyclic hydrocarbons and cancer. Academic, New York, pp 85–117
30. Deutsch-Wenzel R, Brune H, Grimmer G (1983) Experimental studies in rat lungs on the carcinogenicity and dose–response relationships of eight frequently occurring environmental polycyclic aromatic hydrocarbons. J Natl Cancer Inst 71:539–544
31. Pfeifer GP, Denissenko MF, Olivier M, Tretyakova N, Hecht SS, Hainaut P (2002) Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. Oncogene 21:7435–7451
32. Boysen G, Hecht SS (2003) Analysis of DNA and protein adducts of benzo[*a*]pyrene in human tissues using structure-specific methods. Mutat Res 543:17–30
33. Phillips DH (2002) Smoking-related DNA and protein adducts in human tissues. Carcinogenesis 23:1979–2004
34. Liu Z, Muehlbauer KR, Schmeiser HH, Hergenhahn M, Belharazem D, Hollstein MC (2005) p53 mutations in benzo(a)pyrene-exposed human p53 knock-in murine fibroblasts correlate with p53 mutations in human lung tumors. Cancer Res 65:2583–2587
35. Belinsky SA, Foley JF, White CM, Anderson MW, Maronpot RR (1990) Dose–response relationship between O^6-methylguanine formation in Clara cells and induction of pulmonary neoplasia in the rat by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. Cancer Res 50:3772–3780
36. Hecht SS (2002) Human urinary carcinogen metabolites: biomarkers for investigating tobacco and cancer. Carcinogenesis 23:907–922
37. Shapiro JA, Jacobs EJ, Thun MJ (2000) Cigar smoking in men and risk of death from tobacco-related cancers. J Natl Cancer Inst 92:333–337
38. Boffetta P, Pershagen G, Jockel KH, Forastiere F, Gaborieau V, Heinrich J, Jahn I, Kreuzer M, Merletti F, Nyberg F, Rosch F, Simonato L (1999) Cigar and pipe smoking and lung cancer risk: a multicenter study from Europe. J Natl Cancer Inst 91:697–701
39. Travis WD, Travis LB, Devesa SS (1995) Lung cancer. Cancer 75:191–202
40. Hoffmann D, Hoffmann I, El Bayoumy K (2001) The less harmful cigarette: a controversial issue. A tribute to Ernst L. Wynder. Chem Res Toxicol 14:767–790
41. International Agency for Research on Cancer (1986) Tobacco smoking. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, vol 38. IARC, Lyon, FR, pp 37–385
42. Hoffmann D, Hecht SS (1990) Advances in tobacco carcinogenesis. In: Cooper CS, Grover PL (eds) Handbook of experimental pharmacology. Springer, Berlin Heidelberg New York, pp 63–102
43. Lijinsky W (1992) Chemistry and biology Of *N*-nitroso compounds. Cambridge University Press, Cambridge, England
44. Hecht SS, Hoffmann D (1989) The relevance of tobacco-specific nitrosamines to human cancer. Cancer Surv 8:273–294
45. International Agency for Research on Cancer (1995) Dry cleaning, some chlorinated solvents and other industrial chemicals. IARC monographs on the evaluation of carcinogenic risks to humans, vol 63. IARC, Lyon, France, pp 393–407
46. Prokopczyk B, Leder G, Trushin N, Cunningham AJ, Akerkar S, Pittman B, Ramadani M, Straeter J, Beger HG, Henne-Bruns D, El Bayoumy K (2005) 4-Hydroxy-1-(3-pyridyl)-1-butanone, an indicator for 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced DNA damage, is not detected in human pancreatic tissue. Cancer Epidemiol Biomarkers Prev 14:540–541
47. Rivenson A, Hoffmann D, Prokopczyk B, Amin S, Hecht SS (1988) Induction of lung and exocrine pancreas tumors in F344 rats by tobacco-specific and *Areca*-derived *N*-nitrosamines. Cancer Res 48:6912–6917
48. Prokopczyk B, Hoffmann D, Bologna M, Cunningham AJ, Trushin N, Akerkar S, Boyiri T, Amin S, Desai D, Colosimo S, Pittman B, Leder G, Ramadani M, Henne-Bruns D, Beger HG, El Bayoumy K (2002) Identification of tobacco-derived compounds in human pancreatic juice. Chem Res Toxicol 15:677–685
49. Prokopczyk B, Trushin N, Leszczynska J, Waggoner SE, El Bayoumy K (2001) Human cervical tissue metabolizes the tobacco-specific nitrosamine, 4- (methylnitrosamino)-1-(3-pyridyl)-1-butanone, via alpha-hydroxylation and carbonyl reduction pathways. Carcinogenesis 22:107–114
50. Melikian AA, Sun P, Prokopczyk B, El Bayoumy K, Hoffmann D, Wang X, Waggoner S (1999) Identification of benzo[a]pyrene metabolites in cervical mucus and DNA adducts in cervical tissues in humans by gas chromatography-mass spectrometry. Cancer Lett 146:127–134
51. International Agency for Research on Cancer (1995) Human papillomaviruses. IARC monographs on the evaluation of carcinogenic risks to humans, vol 64. IARC, Lyon, FR, pp 35–378
52. International Agency for Research on Cancer (1973) Some aromatic amines, hydrazine and related substances, *N*-nitroso compounds and miscellaneous alkylating agents. IARC monographs on the carcinogenic risk of chemicals to man, vol 4. IARC, Lyon, FR, pp 127–136
53. Skipper PL, Tannenbaum SR (1990) Protein adducts in the molecular dosimetry of chemical carcinogens. Carcinogenesis 11:507–518
54. Skipper PL, Peng X, SooHoo CK, Tannenbaum SR (1994) Protein adducts as biomarkers of human carcinogen exposure. Drug Metab Rev 26:111–124
55. Landi MT, Zocchetti C, Bernucci I, Kadlubar FF, Tannenbaum S, Skipper P, Bartsch H, Malaveille C, Shields P, Caporaso NE, Vineis P (1996) Cytochrome P450 1A2: enzyme induction and genetic control in determining 4-aminobiphenyl-hemoglobin adduct levels. Cancer Epidemiol Biomark Prev 5:693–698
56. Probst-Hensch NM, Bell DA, Watson MA, Skipper PL, Tannenbaum SR, Chan KK, Ross RK, Yu MC (2000) *N*-Acetyltransferase 2 phenotype but not NAT1*10 genotype affects aminobiphenyl–hemoglobin adduct levels. Cancer Epidemiol Biomark Prev 9:619–623
57. Castelao JE, Yuan JM, Skipper PL, Tannenbaum SR, Gago-Dominguez M, Crowder JS, Ross RK, Yu MC (2001) Gender- and smoking-related bladder cancer risk. J Natl Cancer Inst 93:538–545
58. Pryor WA, Stone K, Zang LY, Bermudez E (1998) Fractionation of aqueous cigarette tar extracts: fractions that contain the tar radical cause DNA damage. Chem Res Toxicol 11:441–448
59. Guengerich FP (2001) Common and uncommon cytochrome *P*450 reactions related to metabolism and chemical toxicity. Chem Res Toxicol 14:611–650

60. Jalas J, Hecht SS, Murphy SE (2005) Cytochrome *P*450 2A enzymes as catalysts of metabolism of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a tobacco-specific carcinogen. Chem Res Toxicol 18:95–110
61. Nebert DW, Dalton TP, Okey AB, Gonzalez FJ (2004) Role of aryl hydrocarbon receptor-mediated induction of the CYP1 enzymes in environmental toxicity and cancer. J Biol Chem 279:23847–23850
62. Armstrong RN (1997) Glutathione-*S*-transferases. In: Guengerich FP (ed) Comprehensive toxicology: biotransformation, vol 3. Elsevier Science, New York, pp 307–327
63. Burchell B, McGurk K, Brierley CH, Clarke DJ (1997) UDP-glucuronosyltransferases. In: Guengerich FP (ed) Comprehensive toxicology: biotransformation, vol 3. Elsevier Science, New York, pp 401–436
64. Vineis P, Veglia F, Benhamou S, Butkiewicz D, Cascorbi I, Clapper ML, Dolzan V, Haugen A, Hirvonen A, Ingelman-Sundberg M, Kihara M, Kiyohara C, Kremers P, Le Marchand L, Ohshima S, Pastorelli R, Rannug A, Romkes M, Schoket B, Shields P, Strange RC, Stucker I, Sugimura H, Garte S, Gaspari L, Taioli E (2003) CYP1A1 T3801 C polymorphism and lung cancer: a pooled analysis of 2451 cases and 3358 controls. Int J Cancer 104:650–657
65. Liu G, Zhou W, Christiani DC (2005) Molecular epidemiology of non-small cell lung cancer. Semin Respir Crit Care Med 26:265–272
66. Ahrendt SA, Decker PA, Alawi EA, Zhu Yr YR, Sanchez-Cespedes M, Yang SC, Haasler GB, Kajdacsy-Balla A, Demeure MJ, Sidransky D (2001) Cigarette smoking is strongly associated with mutation of the K-ras gene in patients with primary adenocarcinoma of the lung. Cancer 92:1525–1530
67. Johnson L, Mercer K, Greenbaum D, Bronson RT, Crowley D, Tuveson DA, Jacks T (2001) Somatic activation of the K-*ras* oncogene causes early onset lung cancer in mice. Nature 410:1111–1116
68. Lubet RA, Zhang Z, Wiseman RW, You M (2000) Use of p53 transgenic mice in the development of cancer models for multiple purposes. Exp Lung Res 26:581–593
69. Sekido Y, Fong KW, Minna JD (1998) Progress in understanding the molecular pathogenesis of human lung cancer. Biochim Biophys Acta 1378:F21–F59
70. Bode AM, Dong Z (2005) Signal transduction pathways in cancer development and as targets for cancer prevention. Prog Nucleic Acid Res Mol Biol 79:237–297
71. Hecht SS (2003) Tobacco carcinogens, their biomarkers, and tobacco-induced cancer. Nature Rev Cancer 3:733–744
72. Schuller HM (2002) Mechanisms of smoking-related lung and pancreatic adenocarcinoma development. Nat Rev Cancer 2:455–463
73. West KA, Brognard J, Clark AS, Linnoila IR, Yang X, Swain SM, Harris C, Belinsky S, Dennis PA (2003) Rapid Akt activation by nicotine and a tobacco carcinogen modulates the phenotype of normal human airway epithelial cells. J Clin Invest 111:81–90
74. Heeschen C, Jang JJ, Weis M, Pathak A, Kaji S, Hu RS, Tsao PS, Johnson FL, Cooke JP (2001) Nicotine stimulates angiogenesis and promotes tumor growth and atherosclerosis. Nat Med 7:833–839
75. Moraitis D, Du B, De Lorenzo MS, Boyle JO, Weksler BB, Cohen EG, Carew JF, Altorki NK, Kopelovich L, Subbaramaiah K, Dannenberg AJ (2005) Levels of cyclooxygenase-2 are increased in the oral mucosa of smokers: evidence for the role of epidermal growth factor receptor and its ligands. Cancer Res 65:664–670
76. Belinsky SA (2005) Silencing of genes by promoter hypermethylation: key event in rodent and human lung cancer. Carcinogenesis 26:1481–1487
77. World Health Organization (1997) Tobacco or health: a global status report. WHO, Geneva, pp 10–48
78. Blot WJ, Fraumeni JF Jr (1996) Cancers of the lung and pleura. In: Schottenfeld D, Fraumeni J (eds) Cancer epidemiology and prevention. Oxford University Press, New York, pp 637–665
79. American Cancer Society (2001) Cancer facts and figures 2001. American Cancer Society, Atlanta, GA, pp 29–32