Approaches to Chemoprevention of Lung Cancer Based on Carcinogens in Tobacco Smoke

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Chemoprevention may be one way to prevent lung cancer in smokers who are motivated to quit but cannot stop. The approach to chemoprevention of lung cancer described in this article is based on an understanding of the lung carcinogens present in tobacco smoke. The available data indicate that the compounds in cigarette smoke most likely involved in the induction of lung cancer in humans are the complex of polynuclear aromatic hydrocarbons typified by benzo[a]pyrene (B[a]P) and the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNK). A large number of compounds are now available that inhibit lung tumorigenesis by B[a]P or NNK in rodents. Inhibition of NNK-induced lung carcinogenesis by phenethyl isothiocyanate (PEITC) and inhibition of B[a]P-induced lung carcinogenesis by benzyl isothiocyanate (BITC) are discussed as examples. Studies with PEITC in rodents clearly demonstrate that it inhibits NNK-induced lung tumorigenesis by inhibiting the metabolic activation of NNK. Successful changes appear to occur in humans according to data generated in smokers who ate watercress, a source of PEITC. It is likely that mixtures of chemopreventive agents with activity against carcinogens in tobacco smoke, such as NNK and B[a]P, will be useful in chemoprevention of lung cancer in smokers. Furthermore, there is a need to develop suppressing agents for lung cancer that might be applicable in both smokers and ex-smokers. — Environ Health Perspect 105(Suppl 4):955-963 (1997)

Key words: chemoprevention, tobacco smoke, benzo[a]pyrene, B[a]P, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, NNK, phenethyl isothiocyanate, PEITC

Introduction

Lung cancer is the leading cause of cancer death in the United States, with over 160,000 deaths expected in 1997 (1). Smoking causes at least 80% of lung cancer (2). Therefore, smoking cessation is clearly the best way to decrease incidence and mortality from the great majority of lung cancer; however, smoking cessation has not been uniformly successful. Available data indicate that approximately 26% of the adult population in the United States still smokes, in spite of widespread knowledge of the associated hazards (3). Many of these people are addicted to nicotine and cannot stop smoking even after participation in smoking cessation programs. Considering the immense death toll from lung cancer, chemoprevention would make a significant impact even if it were successful in a relatively small percentage of smokers.

Our approach to chemoprevention of lung cancer is based on an understanding of the carcinogens in tobacco smoke. Tobacco smoke is a complex mixture of compounds and contains at least 40 known carcinogens. Carcinogens identified in cigarette smoke include polynuclear aromatic hydrocarbons (PAHs), aza-arenes, which are PAHs containing a nitrogen in the ring system; nitrosamines; aromatic amines; aldehydes; miscellaneous organic compounds such as benzene, acrylonitrile, vinyl chloride, 2-nitropropane, and ethyl carbonate; and inorganic compounds such as hydrazine and various metals (4). Among these, the PAHs and nitrosamines have in their families the strongest respiratory carcinogens, while certain aldehydes and metals are also known respiratory carcinogens. In contrast, some of the other carcinogens such as aromatic amines and benzene are associated with other cancers, such as bladder cancer and leukemia. The role of specific carcinogens of tobacco smoke in human cancers can be assessed by considering the amounts of the carcinogens in tobacco products, their target tissues and carcinogenic potency in laboratory animals, and biochemical evidence that humans and laboratory animals respond in similar ways. Likely causative agents for lung cancer are summarized in Table 1.

Table 1. Smoking and lung cancer: causative agents.a

| Carcinogens | Modifying agents |
|-------------|------------------|
| PAHs (B[a]P, benzo[b], and kfluoranthenes, 5-methylchrysene, dibenz[a,h]anthracene, indeno[1,2,3-cd]pyrene) | Co-carcinogens (catechols) |
| NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNAL-gluc, (4-methylthio-2H-benzopyran-5(4H)-one) | Tumor promoters (phenols and others) |
| Benzo[a]pyrene, benzyl isothiocyanate; PEITC, phenethyl isothiocyanate; PEITC—NAC, N-acetyl-S-(N-phenethylcarbamoyl)-L-cysteine | Toxic aldehydes (acrolein) |
| Weak evidence | Diet |

aCriteria: animal carcinogenicity, presence in cigarette smoke, biochemical studies—animal and human lung.
lung are generally induced by carcinogenic \textit{PAHs} such as B(\textit{a})P. Considering the amounts of these compounds in cigarette smoke and their carcinogenic potency, one can plausibly argue that they are important in lung cancer induction (4). This argument is bolstered by biochemical studies that have demonstrated that human lung tissue can metabolize \textit{PAHs} by pathways that lead to covalent modification of DNA and by the detection of the relevant DNA adducts in lung tissue of smokers.

4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNK), a nitrosamine formed from the major tobacco constituent nicotine during tobacco processing and smoking, is a powerful and organ-selective lung carcinogen in laboratory animals (8). NNK is one of a family of nicotine-derived nitrosamines that are collectively called tobacco-specific nitrosamines. Adenocarcinoma of the lung is the main type of lung cancer induced by NNK. The total amount of NNK required to produce lung cancer in rats is similar to the total amount of this compound to which a smoker would be exposed in a lifetime of smoking (9,10). These data support the role of NNK in the induction of lung cancer, particularly adenocarcinoma. Moreover, human lung tissue metabolically activates NNK, although not as efficiently as rodent lung tissue (11). DNA adducts specific to NNK and the related nitrosamine \textit{N}'-nitrosornornicotine (NNN) have been detected in smokers’ lungs, and metabolites of NNK are present in smokers’ urine (10,12).

Table 1 lists some other tobacco-smoke constituents that could be involved in lung cancer induction; the evidence suggesting a role for these compounds is weaker than that discussed above for \textit{PAHs} and NNK. Polonium-210 is present in cigarette mainstream smoke and is a strong pulmonary carcinogen, inducing tumors of the lung upon inhalation in rats or on intratracheal instillation in Syrian golden hamsters (4). The significance of polonium-210 in tobacco-induced lung cancer has been questioned based on comparisons of doses experienced by smokers versus miners. It has been estimated that about 1% of the lung cancer risk associated with cigarette smoking could be ascribed to polonium-210.

Chromium, cadmium, and nickel are all present in cigarette smoke (4). Calcium chromate is carcinogenic in rats, inducing lung tumors after instillation. Cadmium chloride aerosols produce adenocarcinoma and squamous cell carcinoma in rats. Nickel sulfide yields lung cancer in rats upon inhalation. Because levels of exposure to chromium, cadmium, and nickel compounds in cigarette smoke may be comparable to those of some \textit{PAHs}, these metal ions may play some role in lung cancer induction.

Inhalation studies of formaldehyde and acetaldehyde have demonstrated that they are respiratory carcinogens in the rat, inducing mainly nasal cavity tumors (4). There may be a direct effect of these compounds on the lung upon inhalation in tobacco smoke. Although they are weak respiratory carcinogens, the levels of formaldehyde and acetaldehyde in cigarette smoke are at least 1000 times greater than those of \textit{PAHs} and nitrosamines.

Cigarette smoke contains some stable free radicals and is known to induce oxidative damage (4,13). Products that result from oxidative damage to both lipids and DNA have been detected in smokers and their levels are higher than in nonsmokers (14,15). Although the direct role of such products in carcinogenesis is unclear, 8-oxoguanine, a DNA adduct detected at elevated levels in smokers, has miscoding properties associated with the cancer induction process.

Collectively, the available evidence favors \textit{PAHs} and NNK as important compounds responsible for lung cancer induction in smokers. Their role in lung cancer is consistent with results of analyses of mutations in the \textit{p53} and \textit{ras} genes from human lung tumors. These analyses have demonstrated the presence of a large number of \textit{G} \rightarrow \textit{T} transversions and \textit{G} \rightarrow \textit{A} transitions in these genes, which is consistent with mutational spectra expected from \textit{PAHs} and NNK (16–20).

With each cigarette, the smoker is exposed to \textit{PAHs} and NNK. As illustrated in Figure 1, these carcinogens undergo metabolic activation to DNA adducts. If these adducts persist unrepaired during DNA replication, miscoding can occur, leading to permanent mutations in critical genes such as \textit{p53} and \textit{ras}, which are likely to be important in the lung cancer induction process. Blocking any one of these steps would decrease the probability of lung cancer development. Our strategy has been to block the metabolic activation step. This approach will be discussed in this report, using phenethyl isothiocyanate (PEITC), a chemopreventive agent against NNK-induced lung tumorigenesis, as one example, and benzyl isothiocyanate (BITC), an inhibitor of B(\textit{a})P-induced lung tumorigenesis, as another. Other known inhibitors of NNK- and B(\textit{a})P-induced lung tumorigenesis will also be reviewed. We emphasize that the approach discussed here is only one example of strategies that can be employed for chemoprevention of lung cancer.

\textbf{Inhibition of NNK-induced Lung Tumorigenesis by PEITC}

A naturally occurring isothiocyanate, PEITC (\textit{PhCH2CH2N=C=S}), is found as its glucosinolate conjugate glucostaurtiun in several vegetables including watercress. PEITC is released from watercress upon chewing by the action of myrosinase, a thioglucosidase present in the plant (21,22). Consumption of approximately 50 g of watercress releases 10 to 15 mg of PEITC (22). When PEITC was added to NIH-07, an open formula rodent diet, at a concentration of 498 ppm (3 \textmu mol/g diet) before and during treatment of male F344 rats with NNK, it caused a significant and selective 50% reduction in the incidence of adenocarcinoma of the lung (23) (Table 2). There were no toxic effects of PEITC at this dose. A single dose of 5 \textmu mol of PEITC administered to A/J mice 2 hr prior to treatment with 10 \textmu mol of NNK resulted in a significant 62% reduction in lung tumor multiplicity (24). Other studies using multiple doses of PEITC have shown similar results in A/J mice (25,26). Thus PEITC has been firmly established as an effective inhibitor of lung tumorigenesis induced by NNK in both rats and mice.

An overview of the major metabolic activation and detoxification pathways of NNK is illustrated in Figure 2 (27). In laboratory animals and humans, NNK is rapidly converted to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL).

![Figure 1](image)

\textbf{Figure 1.} Relationship of tobacco-smoke carcinogen exposure, metabolic activation, DNA adduct formation, mutations, and lung cancer.
by carboxyl reductase enzymes. Also a potent pulmonary carcinogen, NNAL is partially converted to its diastereomeric glucuronides, [4-(methylamino)-1-(3-pyridyl)but-1-yl]-3-O-b-glucosiduronic acid (NNAL-\text{gluc}). These glucuronides are likely detoxification products of NNK. Pyridine N-oxidation of NNK and NNAL gives the corresponding N-oxides, which are detoxification products. Metabolic activation of NNK proceeds by \(\alpha\)-hydroxylation of the methylene and methyl carbons producing unstable intermediates 1 and 2. These spontaneously decompose with formation of aldehydes and the electrophilic diazohydroxides 4 and 5. Diazohydroxide 4 methylates DNA of NNK target tissues, producing permanent mutations, mainly of the \(G \rightarrow A\) type. Diazohydroxide 5 alkylates DNA producing both \(G \rightarrow A\) and \(G \rightarrow T\) mutations. It also reacts with hemoglobin to form ester adducts. Hydrolysis of DNA or hemoglobin obtained from animals treated with NNK or from smokers produces 4-hydroxy-1-(3-pyridyl)-1-butaneone (HPB) (6), which is a biomarker of the metabolic activation of NNK (28). Smokers’ urine contains quantifiable amounts of NNAL and NNAL-\text{gluc} as biomarkers.

The mechanism of NNK carcinogenesis inhibition by PEITC has been examined. Initial studies demonstrated that PEITC inhibited the metabolic activation of NNK to electrophiles, which methylate and pyridyloxobutylate pulmonary DNA in rats (23). Subsequently, detailed investigations of the effects of PEITC on NNK metabolism in mouse and rat liver and lung, as well as studies of other enzyme activities, have clearly demonstrated that the inhibitory effect of PEITC on NNK carcinogenesis is due mainly to inhibition of NNK metabolic activation to methylating and pyridyloxobutylating electrophiles (29,30). In rats treated with PEITC by gavage or by addition to the diet, a persistent inhibition of metabolic activation of NNK is observed in lung microsomes, which results from inhibition of cytochrome P450 enzymes. In contrast, a persistent inhibition in liver microsomes is not observed. Experiments in vitro have shown that PEITC is a competitive inhibitor of NNK metabolic activation in rat liver microsomes, with the concentration that inhibits 50% ranging from 150 to 210 nM, and in explants of rat lung (30,31).

The effects of PEITC on NNK metabolism have also been examined in vivo. In these experiments, the goal was to determine whether the observed inhibition of tumorigenesis was due to specific inhibition of metabolic activation of NNK, or
whether treatment with PEITC might have caused a change in distribution of NNK resulting in diminished amounts of the carcinogen reaching extrahepatic tissues. In experiments carried out using a protocol essentially identical to that employed in the carcinogenicity study described above, it was shown that the levels of NNK and its primary metabolite NNAL were not markedly different in tissues of PEITC treated and control rats. However, the data clearly indicate a decrease in the levels of NNK metabolic activation in the PEITC treated rats in almost all tissues examined (32).

The effects of chronic PEITC treatment on hemoglobin adducts and urinary metabolites of NNK have been examined in rats. Results of the urinary metabolite analyses are summarized in Table 3. Chronic PEITC treatment caused significant 4- to 6-fold increases in the levels of NNAL and NNAL-gluc in urine; this most likely results from a decrease in metabolic activation of NNK since hemoglobin adducts of NNK also decreased (data not shown). The ratio of NNAL-gluc to NNAL, a potential biomarker of NNK detoxification, increased upon PEITC treatment. Collectively, the results of these studies clearly show that PEITC exerts a specific inhibitory effect on the metabolic activation of NNK without causing any apparent toxic effects in rats.

### Inhibition of B[a]P-induced Lung Tumorigenesis by Benzyl Isothiocyanate

Whereas PEITC is an effective inhibitor of lung carcinogenesis by NNK, studies to date have not demonstrated efficacy with respect to B[a]P. In one study in A/J mice, PEITC was administered by gavage prior to ip injection of B[a]P. No inhibition of B[a]P-induced lung tumorigenesis was observed over a range of PEITC doses (33). In a second study, a single dose of 6.7-μmol PEITC was given by gavage to A/J mice 15 min prior to gavage of 7.9-μmol of B[a]P. No inhibition of lung tumorigenesis was observed, although PEITC did inhibit forestomach tumor induction by B[a]P. In contrast, a 7.9-μmol dose of BITC given by the same protocol did result in a statistically significant 50% reduction of B[a]P-induced lung tumor multiplicity in the A/J mouse model (Table 4) (34). These results are in agreement with previously reported data on inhibition of B[a]P-induced lung tumorigenesis by BITC (35). The contrasting effects of PEITC and BITC on lung tumorigenesis by B[a]P in A/J mice are consistent with mechanistic studies, which have shown that BITC but not PEITC significantly inhibited ethoxyresorufin O-dealkylase activity in A/J mouse lung microsomes, which is indicative of inhibition of P4501A. P4501A may be involved in the metabolic activation of B[a]P (36). In ongoing studies, we are examining the effects of BITC and PEITC on the metabolic activation and DNA binding of B[a]P in A/J mouse lung and liver (36).

### Inhibitors of Lung Tumorigenesis Induced by NNK or B[a]P

The studies described above indicate that two isothiocyanates, PEITC and BITC, inhibit metabolic activation and lung tumorigenesis of NNK and B[a]P, respectively. The data for PEITC are now particularly strong and recent studies indicate that PEITC will also inhibit the metabolic activation of NNK in smokers (below). Although few compounds other than PEITC have been investigated as extensively as chemopreventive agents against lung cancer induced by NNK or B[a]P, there exists nevertheless a rich selection of compounds that have shown inhibitory activity against NNK- or B[a]P-induced lung tumorigenesis in rodents. Compounds tested as inhibitors of NNK-induced lung tumorigenesis are summarized in Table 5. Although this table includes only defined compounds, certain mixtures such as green tea, black tea, snuff extract, orange oil, and NIH-07 diet also inhibit NNK-induced tumorigenesis; however, the responsible compounds have not been identified (43,49,52–54). More than 25 inhibitors of NNK-induced lung tumorigenesis are known (Table 5). Isothiocyanates appear to be the strongest inhibitors according to presently available data. Other inhibitors include natural products such as sinigrin, indole-3-carbinol, d-limonene, diallyl sulfide, epigallocatechin-3-gallate, and ellagic acid; antioxidants such as butylated hydroxyanisole; and drugs such as sulindac, ibuprofen, and piroxicam. Other compounds, such as the ipomeanol analogue 7-hydroxy-1-phenyl-1-octanone, the P450 suicide inhibitor 4-phenyl-1-butyne, and the organoselenium compound 1,4-phenylenebis(methylene)selenocyanate, have been developed based on mechanistic considerations and by analogy to other chemopreventive agents. All compounds tested to date have shown activity when administered before or concurrently with NNK. There are no reported suppressors of NNK-induced lung tumorigenesis, e.g., agents that are effective when administered only after NNK treatment.

Compounds tested as inhibitors of B[a]P-induced lung tumorigenesis are listed in Table 6. At least 20 inhibitors have been identified. Some of the inhibitory compounds are the same as those that inhibit NNK-induced lung tumorigenesis; these include butylated hydroxyanisole, ellagic acid, and diallyl sulfide. As in the case of NNK, the inhibitors include natural products, drugs, and antioxidants. Only three compounds—myo-inositol, dexmethasone, and butylated hydroxyanisole—have been shown to inhibit B[a]P-induced lung tumorigenesis when administered after B[a]P.

Neither β-carotene nor vitamin A has shown reproducible inhibitory effects on

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### Table 3. Effect of PEITC on excretion of NNAL and NNAL-gluc in rats treated with NNK

| Group          | Metabolites in urine, nmol/24 hr | Fold increase in total |
|---------------|---------------------------------|------------------------|
|               | NNAL   | NNAL-gluc | Total      |
| 68-week data  |        |           |            |
| NNK           | 4.1 ± 1.0 | 9.4 ± 3.8 | 13.5 ± 4.8 | –                     |
| NNK + PEITC   | 11.6 ± 2.5 | 44.8 ± 15.8 | 56.1 ± 17.9 | 4.2*                  |
| 79-week data  |        |           |            |
| NNK           | 3.1    | 8.8       | 11.9      | –                     |
| NNK + PEITC   | 14.3 ± 5.7 | 59.6 ± 36.8 | 73.9 ± 42.4 | 6.2*                  |

*NNK in drinking water (2 ppm); PEITC in diet (3 μmol/g) for 68 or 79 weeks. *Metabolites: mean ± SD, n = 3. *Mean of two rats (NNK group); mean ± SD, n = 3 (PEITC group). *p < 1 x 10^-4.

### Table 4. Effects of BITC and PEITC on B[a]P-induced lung and forestomach tumorigenesis in A/J mice

| Group          | Mice with tumors, % | Tumors per mouse |
|---------------|---------------------|------------------|
|               | Lung | Forestomach | Lung | Forestomach |
| B[a]P only    | 95   | 95         | 4.8  | 4.8        |
| BITC/B[a]P    | 80   | 95         | 2.6* | 4.9        |
| PEITC/B[a]P   | 90   | 90         | 4.0  | 2.5*       |

*Data from Lin et al. (34). Female mice given 6.7-μmol isothiocyanate ig 15 min prior to 7.9-μmol B[a]P 3 times at 2-week intervals and sacrificed 26 weeks after first dose. *p < 0.001.
lung cancer induction in rodents treated with either NNK or B[a]P. In view of this finding, it is perhaps not surprising that β-carotene was ineffective in a trial as a chemopreventive agent against lung cancer in smokers (87).

### Effects of Watercress Consumption on NNK Metabolism in Smokers

The studies described above demonstrate that PEITC inhibits NNK-induced lung tumorigenesis in rats and mice by inhibiting its metabolic activation. We wanted to determine whether similar effects would occur in smokers. The source of PEITC used in this study was watercress (*Nasturtium officinale*), which contains substantial amounts of glucosinat
turrin, the glucosinolate precursor of PEITC (22).

Eleven smokers maintained constant smoking habits and avoided cruciferous vegetables and other sources of isothiocyanates throughout the study (82). They donated 24-hr urine samples on 3 consecutive days (baseline period). After 1 to 3 days, they began the watercress consumption period, 3 days during which they consumed 2 oz (56.8 g) of watercress at each meal and donated 24-hr urine samples on each day. One and two weeks later they again donated 24-hr urine samples on 2 to 3 consecutive days (follow-up periods). The samples were analyzed for two metabolites of NNK; NNAL and NNAL-gluc, as well as N-acetyl-S-(N-phenethylthiocarbamoyl)-t-cysteine (PEITC–NAC), a metabolite of PEITC. Minimum exposure to PEITC during the watercress consumption period averaged 19 to 38 mg per day. Seven of the eleven subjects had increased levels of urinary NNAL plus NNAL-gluc on days 2 and 3 of the watercress consumption period, compared to the baseline period. Overall, the increase in urinary NNAL plus NNAL-gluc in this period was significant [mean ± SD, 0.924 ± 1.12 nmol/24 hr (33.5%), p < 0.01]. Urinary levels of NNAL plus NNAL-gluc returned to near baseline levels in the follow-up periods. The percent increase in urinary NNAL plus NNAL-gluc during days 2 and 3 of the watercress consumption period correlated with PEITC intake during this period as measured by total urinary PEITC–NAC (r = 0.62, p = 0.04). The results of this study support our hypothesis that PEITC inhibits the oxidative metabolism of NNK in humans, as seen in rodents, and support further development of PEITC and other compounds as chemopreventive agents against lung cancer.

### Summary

The research described in this paper conclusively demonstrates that a large number of compounds can inhibit the lung tumorigenicity of the important tobacco-smoke pulmonary carcinogens NNK and B[a]P in rodent models. Among these, isothiocyanates have been investigated extensively with respect to efficacy and mechanisms of inhibition. One of the most thoroughly studied isothiocyanates, PEITC, inhibits lung tumor induction by NNK in rodents, and apparently in smokers, by inhibiting the metabolic activation of NNK. Considering the large number of chemopreventive agents that are effective against lung tumorigenesis by either NNK or B[a]P, it seems likely that appropriately designed mixtures of agents should be effective against both NNK and B[a]P. An A/J mouse lung tumorigenesis model for testing the efficacy of chemopreventive agents against NNK and B[a]P is available (83). Development of chemopreventive agents against other carcinogens in tobacco smoke is also important, not only with respect to

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### Table 5. Inhibition of NNK-induced lung tumorigenesis.

| Compound                      | Strain and species | Protocol type | Result | Reference |
|-------------------------------|--------------------|---------------|--------|-----------|
| Isothiocyanates (R—N=C=S) R= |
| Phenyl                        | A/J mouse         | Pre           | No effect | (37)      |
| Benzyl                        | A/J mouse         | Pre/post      | No effect | (37,38)   |
| Phenethyl                     | A/J mouse         | Pre           | Inhibition | (24–26,37)| |
| (4-0xen4l-3-penyriyIbuyNAJ    | F344 rat           | Pre-con       | Inhibition | (23)      |
| 3-Phenyl(propyl)              | A/J mouse         | Pre           | Inhibition | (25,26)   |
| 4-Phenyl(butyl)              | A/J mouse         | Pre           | Inhibition | (25,26)   |
| 5-Phenyl(pentyl)              | A/J mouse         | Pre           | Inhibition | (26)      |
| 6-Phenylhexyl                 | A/J mouse         | Pre           | Inhibition | (24,26,39)| |
| 8-Phenyl(octyl)              | A/J mouse         | Pre           | Inhibition | (40)      |
| 10-Phenyl(decyl)              | A/J mouse         | Pre           | Inhibition | (40)      |
| 1,2-Diphenylethyl             | A/J mouse         | Pre           | Inhibition | (40)      |
| 2,2-Diphenylethyl             | A/J mouse         | Pre           | Inhibition | (40)      |
| Allyl                         | A/J mouse         | Pre           | No effect  | (40)      |
| Hexyl                         | A/J mouse         | Pre           | No effect  | (40)      |
| Allyloctyl                    | A/J mouse         | Pre           | No effect  | (40)      |
| 4-Oxo-4(3-pyridyl)butyl       | A/J mouse         | Pre           | No effect  | (25,26)   |
| Sinigrin                      | F344 rat           | Pre-con       | No effect  | (41)      |
| Indole-3-carbol               | A/J mouse         | Pre           | Inhibition | (42)      |
| o-Limonene                    | A/J mouse         | Pre           | Inhibition | (43)      |
| Ellagic acid                  | A/J mouse         | Pre-con       | Inhibition | (44,45)   |
| Butylated hydroxynisole       | A/J mouse         | Pre-con       | Inhibition | (44)      |
| Sulindac                      | A/J mouse         | Pre-con       | Inhibition | (44,46,47)|
| β-Carotene + retinol          | A/J mouse         | Pre-con       | No effect  | (44)      |
| Sodium selenite               | A/J mouse         | Pre           | No effect  | (44)      |
| Oltipraz                      | A/J mouse         | Pre           | No effect  | (46)      |
| Diallyl sulfide               | A/J mouse         | Pre           | No effect  | (48)      |
| Epigallocatechin-3-gallate    | A/J mouse         | Pre-con       | Inhibition | (49)      |
| Caffeine                      | A/J mouse         | Pre-con       | Inhibition | (49)      |
| Esculin                       | A/J mouse         | Pre-con       | No effect  | (45)      |
| Esceulin                      | A/J mouse         | Pre-con       | No effect  | (45)      |
| 4-Hydroxy-1-phenyl-1-pentanone| A/J mouse         | Pre           | Inhibition | (50)      |
| 7-Hydroxy-1-phenyl-1-octanone | A/J mouse         | Pre           | Inhibition | (50)      |
| 4-Hydroxy-1-(2-thienyl)-1-pentanone | A/J mouse   | Pre           | No effect  | (50)      |
| 4-Hydroxy-1(3-pyridyl)-1-pentanone | A/J mouse | Pre           | No effect  | (50)      |
| 4-pomeanol                    | A/J mouse         | Pre           | No effect  | (50)      |
| Ibuprofen                     | A/J mouse         | Pre-con       | Inhibition | (47)      |
| Piroxicam                     | A/J mouse         | Pre           | No effect  | (47)      |
| Naproxen                      | A/J mouse         | Pre           | No effect  | (47)      |
| 1,4-Phenylenesimethylene)selenocyanate | A/J mouse | Pre-con       | Inhibition | (51)      |
| 4-Phenyl-1-butyne             | A/J mouse         | Pre           | No effect  | (39)      |
| 5-Phenyl-1-pentyne            | A/J mouse         | Pre           | No effect  | (39)      |
| 2-Ethynylphthalic             | A/J mouse         | Pre           | No effect  | (39)      |

Abbreviations: pre, compound given before NNK treatment; pre-con, compound given before and during NNK treatment or before, during, and after NNK treatment; post, compound given after NNK treatment. Only defined compounds are considered.
Table 6. Inhibition of B(α)P-induced lung tumorigenesis.9

| Compound                  | Strain and species | Protocol type | Result       | Reference |
|---------------------------|--------------------|---------------|--------------|-----------|
| Vitamin A palmitate       | Syrian hamster     | Post          | Inhibition   | (55)      |
| Vitamin A acetate         | Syrian hamster     | Post          | Enhancement  | or (56,57) |
| Vitamin A acetate/palmitate | Syrian hamster  | Pre-con       | No effect    | (58)      |
| Sodium selenite           | Syrian hamster     | Pre-con       | No effect    | (59)      |
| β-Carotene                | Syrian hamster     | Pre-con       | No effect    | (60)      |
| Phenethyl isothiocyanate  | A/J mouse          | Pre-con       | No effect    | (33)      |
| Butyrylated hydroxyanisole| ICR/Ha mouse       | Pre           | No effect    | (34)      |
| Chloramphenicol           | A/J mouse          | Pre           | Inhibition   | (34,35)   |
| Dexamethasone             | A/J mouse          | Pre           | Inhibition   | (61)      |
| Anisole                   | A/J mouse          | Pre           | Inhibition   | (62)      |
| β-Naphthoflavone          | A/J mouse          | Pre           | Inhibition   | (63)      |
| Quercetin pentamethyl ether | A/J mouse       | Pre           | Inhibition   | (63)      |
| Rutin                     | A/J mouse          | Pre           | Inhibition   | (63)      |
| Butyrylated hydroxyanisole| A/J mouse          | Pre, pre-con  | Inhibition   | (64-66)   |
| Elagic acid               | A/J mouse          | Pre           | Pre-inhibition| (67)      |
| Newborn Ha (ICR)          | A/J mouse          | Pre           | Pre-inhibition| (68)      |
| Ferulic acid              | A/J mouse          | Pre-con       | Inhibition   | (69)      |
| Chlorogenic acid          | A/J mouse          | Pre-con       | Inhibition   | (69)      |
| Rosmarinic acid           | A/J mouse          | Pre-con       | Inhibition   | (69)      |
| Myricetin                 | Newborn Ha (ICR)   | Pre           | No effect    | (70)      |
| Quercetin                 | Newborn Ha (ICR)   | Pre           | No effect    | (70)      |
| Aspirin                   | A/J mouse          | Pre-con       | No effect    | (71)      |
| Glucotropaeolin           | ICR/Ha mouse       | Pre           | No effect    | (72)      |
| Glucosinibin              | ICR/Ha mouse       | Pre           | No effect    | (72)      |
| Glucobrassicin            | ICR/Ha mouse       | Pre           | Pre          | (72)      |
| Diallyl trisulfide        | A/J mouse          | Pre           | No effect    | (73)      |
| Diallyl sulfide           | A/J mouse          | Pre           | No effect    | (73)      |
| Dipropyl trisulfide       | A/J mouse          | Pre           | No effect    | (73)      |
| Dipropyl sulfide          | A/J mouse          | Pre           | No effect    | (73)      |
| Allylmethyl disulfide     | A/J mouse          | Pre           | Inhibition   | (73)      |
| Allylmethyl trisulfide    | A/J mouse          | Pre           | No effect    | (73,74,75)|
| Propylmethyl disulfide    | A/J mouse          | Pre           | No effect    | (73)      |
| Calcium t-glucurate       | A/J mouse          | Pre-con       | Inhibition   | (74)      |
| Methyl N-salicylate       | A/J mouse          | Post          | Inhibition   | (75)      |
| Dexamethasone             | A/J mouse          | Post          | Inhibition   | (76)      |
| Olitraz                   | ICR/Ha mouse       | Pre           | Inhibition   | (77)      |
| A/J mouse                 | Pre-con            | No effect     | (78)        |
| Trifurilin                | A/J mouse          | Pre-con       | Inhibition   | (79)      |
| Toxophene                 | A/J mouse          | Pre-con       | Inhibition   | (80)      |
| Carbaryl                  | A/J mouse          | Pre-con       | No effect/   | enhancement |

Abbreviations:SS: pre, compound given before B(α)P treatment; pre-con, compound given before and during B(α)P treatment or before, during, and after B(α)P treatment; post, compound given after B(α)P treatment. *Only defined compounds are considered.

A

Initiation (PAH/NNK) → Promotion (weak acids) → Progression (diet, alcohol, other cofactors)

B

DNA-damaging carcinogens (PAH/NNK) → Multiple genetic changes (p53, ras)

Other DNA-damaging agents (oxygen radicals, nitrogen oxides)

Toxic and cocarcinogenic agents (aldehydes, catechols)

Enhancing effects

Modifying factors (diet/others)

Figure 3. Two models of tobacco-induced lung cancer. (A) In the classical sequential model, exposure to a DNA-damaging initiating compound is followed by exposure to compounds that cause promotion and progression. (B) In the chronic exposure model, continual simultaneous exposure to all cigarette-smoke compounds leads to multiple genetic changes and other effects associated with carcinogenesis.

may be somewhat unrealistic. Smokers are simultaneously exposed to carcinogens, promoters, cocarcinogens, and toxic compounds with every cigarette. Therefore, the chronic exposure model may be more realistic and is consistent with the concept that multiple genetic changes are involved in the carcinogenic process. These changes will be decreased by favorable alteration of several steps involved in carcinogen-related gene changes (Figure 1). Protocols should be developed to identify agents that would be effective against all known steps in the lung-cancer induction process; typical animal data are summarized in Tables 5 and 6, and by Moon et al. (84).

There is a clear need for identification of suppressing agents (compounds active after carcinogen exposure) in future studies, in part because there are a large number of ex-smokers who would benefit from chemoprevention. Such compounds would inhibit nongenotoxic aspects of lung carcinogenesis. Only a few suppressing agents are known at present that are active against lung tumors induced by tobacco smoke carcinogens. The further development of such agents should be a major research priority.

lung cancer, but also for inhibition of other cancers caused by smoking.

Most of the inhibitors discussed in this paper must be present at the time of carcinogen administration to be effective, since in many cases they are inhibitors of metabolic activation or enhancers of carcinogen detoxification. This raises questions about their potential efficacy, depending on how tobacco carcinogenesis is viewed. Two models of tobacco carcinogenesis are outlined in Figure 3. In the classical sequential model, initiation by compounds such as NNK or B(α)P is followed by promotion and progression. Tobacco smoke contains tumor promoters, and the partial reversibility of lung cancer risk associated with smoking cessation is consistent with the reversibility of promotion. However, this model
and dexamethasone as suppressors of pulmonary tumorigenesis (85). The inhibitory effect of PEITC against rat lung tumorigenesis induced by NNK was demonstrated in two further studies: Chung et al. (86) and Hecht et al. (87).

REFERENCES

1. Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1997. CA Cancer J Clin 47:5-27 (1997).

2. Shipman DR, Eeye HJ, Pechacek TF. Smoking-attributable cancer mortality in 1991: is lung cancer now the leading cause of death among smokers in the United States? J Natl Cancer Inst 83:1142-1148 (1991).

3. Cigarette smoking among adults—United States, 1994. Morb Mortal Wkly Rep 45:588-590 (1996).

4. Hoffmann D, Hecht SS. Advances in tobacco carcinogenesis. In: Handbook of Experimental Pharmacology, Vol. 94/1 (Cooper CS, Grover PL, eds). Heidelberg:Springer-Verlag, 1990;63-102.

5. Wolterbeek APM, Schoevers EJ, Rutten AAJL, Feron VJ. A critical appraisal of intratracheal instillation of benzo[a]pyrene to Syrian golden hamsters as a model in respiratory tract carcinogenesis. Cancer Lett 89:107-116 (1995).

6. Stanton MF, Miller E, Wrench C, Blackwell R. Experimental induction of epidermoid carcinoma in the lungs of rats by cigarette smoke condensate. J Natl Cancer Inst 49:867-877 (1972).

7. Thysen J, Althoff J, Kimmerle G, Mohr U. Inhalation studies with benzo[a]pyrene in Syrian golden hamsters. J Natl Cancer Inst 66:575-577 (1981).

8. Hecht SS, Hoffmann D. Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. Carcinogenesis 9:875-884 (1988).

9. Hecht SS, Hoffmann D. 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone, a nicotine-derived tobacco-specific nitrosamine, and cancer of the lung and pancreas in humans. In: Origins of Human Cancer: A Comprehensive Review (Brugge J, Curran T, Harlow E, McCormick F, eds). Cold Spring Harbor, NY:Cold Spring Harbor Laboratory Press, 1991;745-755.

10. Carmella SG, Akkerk S, Hecht SS. Metabolites of the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in smokers' urine. Cancer Res 53:721-724 (1993).

11. Castonguay A, Stoner GD, Schut HAJ, Hecht SS. Metabolism of tobacco-specific N-nitrosamines by cultured human tissues. Proc Natl Acad Sci USA 80:6694-6697 (1983).

12. Foiles PG, Akkerk SA, Carmella SG, Kagan M, Stoner GD, Resau JH, Hecht SS. Mass spectrometric analysis of tobacco-specific nitrosamine-DNA adducts in smokers and nonsmokers. Chem Res Toxicol 4:364-368 (1991).

13. Church DF, Pryor WA. Free radical chemistry of cigarette smoke and its toxicological implications. Environ Health Perspect 64:111-126 (1985).

14. Morrow JD, Frei B, Longmire AW, Gazzano JM, Lynch SM, Shyr Y, Strauss WE, Oates JA, Roberts LJ II. Increase in circulating products of lipid peroxidation (F2-isoprostanes) in smokers. N Engl J Med 332:1198-1203 (1995).

15. Loft S, Vistisen K, Ewertz M, Tjonneland A, Overvad K, Poulsen HE. Oxidative DNA damage estimated by 8-hydroxydeoxyguanosine excretion in humans: influence of smoking, gender and body mass index. Carcinogenesis 13:2241-2247 (1992).

16. Rodenhuis S, Slebos RJC. Clinical significance of ras oncogene activation in human lung cancer. Cancer Res(Suppl) 52:2665s-2669s (1992).

17. Greenblatt MS, Bennett WP, Hollstein M, Harris CC. Mutations in the p53 tumor suppressor gene: clues to cancer etiology and molecular pathogenesis. Cancer Res 54:4855-4878 (1994).

18. Belinsky SA, Devereux TR, Maronpot RR, Stoner GD, Anderson MW. The relationship between the formation of mutagenic adducts and the activation of the K-ras protooncogene in lung tumors from A/J mice treated with nitrosamines. Cancer Res 49:5305-5311 (1989).

19. You M, Candrian U, Maronpot RR, Stoner GD, Anderson MW. Activation of the Ki-ras protooncogene in spontaneously occurring and chemically induced lung tumors of the strain A mouse. Proc Natl Acad Sci USA 86:3070-3074 (1989).

20. Ronal Z, Gradia S, Peterson LA, Hecht SS. G to T transversions in codon 12 of the Ki-ras oncogene isolated from mouse lung tumors induced by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and related DNA methylating and pyridylloxobutylating agents. Carcinogenesis 14:2419-2422 (1993).

21. Sones K, Heaney RK, Fenwick GR. An estimate of the mean daily intake of glucosinolates from cruciferous vegetables in the U.K. J Soc Food Agric Sci 27:12-20 (1984).

22. Chung F-L, Morse MA, Eklind KI, Lewis J. Quantitation of human uptake of the anticarcinogenic phenethyl isothiocyanate after a watercress meal. Cancer Epidemiol Biomarkers Prev 1:383-388 (1992).

23. Morse MA, Wang C-X, Stoner GD, Mandel S, Conran PB, Amin SG, Hecht SS, Chung F-L. Inhibition of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced DNA adduct formation and tumorigenesis in lung of F344 rats by dietary phenethyl isothiocyanate. Cancer Res 49:549-553 (1989).

24. Morse MA, Eklind KI, Amin SG, Chung F-L. Effect of frequency of isothiocyanate administration on inhibition of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced pulmonary adenoma formation in A/J mice. Cancer Lett 62:77-81 (1992).

25. Morse MA, Eklind KI, Amin SG, Hecht SS, Chung F-L. Effects of allyl chain length on the inhibition of NNK-induced lung neoplasia in A/J mice by arylalkyl isothiocyanates. Carcinogenesis 10:1757-1759 (1989).

26. Morse MA, Eklind KI, Hecht SS, Jordan KG, Choi C-I, Desai DH, Amin SG, Chung F-L. Structure-activity relationships for inhibition of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone lung tumorigenesis by arylalkyl isothiocyanates in A/J mice. Cancer Res 51:1846-1850 (1991).

27. Hecht SS. Metabolic activation and detoxification of tobacco-specific nitrosamines—a model for cancer prevention strategies. Drug Metab Rev 26:373-390 (1994).

28. Hecht SS, Carmella SG, Foiles PG, Murphy SE. Biomarkers for human uptake and metabolic activation of tobacco-specific nitrosamines. Cancer Res(Suppl) 54:1912s-1917a (1994).

29. Yang CS, Smith TJ, Hong J-Y. Cytochrome P-450 enzymes as targets for chemoprevention against chemical carcinogenesis and toxicity: opportunities and limitations. Cancer Res 54:1982s-1986s (1994).

30. Guo Z, Smith TJ, Wang E, Eklind KI, Chung F-L, Yang CS. Structure-activity relationships of arylalkyl isothiocyanates for the inhibition of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone metabolism and the modulation of xenobiotic-metabolizing enzymes in rats and mice. Carcinogenesis 14:1167-1173 (1993).

31. Doer-O'Rourke K, Trushin N, Hecht SS, Stoner GD. Effect of phenethyl isothiocyanate on the metabolism of the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone by cultured rat lung tissue. Carcinogenesis 12:1029-1034 (1991).

32. Staretz ME, Hecht SS. Effects of phenethyl isothiocyanate on the tissue distribution of 4-(methylnitrosamino)-1-(3-pyridyl)-
1-butane and metabolites in F344 rats. Cancer Res 55: 5580–5588 (1995).
33. Adam-Rodwell G, Morse MA, Stoner GD. The effects of phenethyl isothiocyanate on benzo[a]pyrene-induced tumors and DNA adducts in A/J mouse lung. Cancer Lett 71:35–42 (1993).
34. Lin J-M, Amin S, Trushin N, Hecht SS. Effects of isothiocyanates on tumorigenesis by benzo[a]pyrene in murine tumor models. Cancer Lett 74:151–159 (1993).
35. Wattenberg LW. Inhibitory effects of benzy1 isothiocyanate administered shortly before diethyl nitrosamine or benzo[a]pyrene on pulmonary and forestomach neoplasia in A/J mice. Carcinogenesis 8:1971–1973 (1987).
36. Staretz ME, Koenig LA, Hecht SS. Effects of isothiocyanates on benzo[a]pyrene metabolism by mouse lung and liver microsomes. Proc Am Assoc Cancer Res 36:593 (1995).
37. Morse MA, Amin SG, Hecht SS, Chung F-L. Effects of ar-omatic isothiocyanates on tumorigenicity, O2-methylguanine DNA-transmethylation activity, and metabolism of the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in A/J mouse lung. Cancer Res 49:2894–2897 (1989).
38. Morse MA, Reinhardt JC, Amin SG, Hecht SS, Stoner GD, Chung F-L. Effect of dietary aromatic isothiocyanates fed subsequent to the administration of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone on lung tumorigenicity in mice. Cancer Lett 49:225–230 (1990).
39. Alworth WL, Young-Sriage R, Hecht SS. Inhibition of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone mouse lung tumorigenesis by arylalkynes, mechanism-based inactivators of cytochrome P-450. Carcinogenesis 14:1711–1713 (1993).
40. Jiao D, Eklind KL, Choi CI, Desai DH, Amin SG, Chung FL. Structure–activity relationships of isothiocyanates as mechanism-based inhibitors of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis in A/J mice. Cancer Res 54:4327–4333 (1994).
41. Morse MA, Wang CX, Amin SG, Hecht SS, Chung F-L. Effects of dietary sinigrin or indole-3-carbonyl on O2-methylguanine-DNA-transmethylase activity and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced DNA methylation and tumorigenicity in F344 rats. Carcinogenesis 9:1891–1895 (1988).
42. Morse MA, LaGreeca SD, Amin SG, Chung F-L. Effects of indole-3-carbonyl on lung tumorigenesis and DNA methylation induced by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and on the metabolism and disposition of NNK in A/J mice. Cancer Res 50:2613–2617 (1990).
43. Wattenberg LW, Coccia JB. Inhibition of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone carcinogenesis in mice by D-limonene and citrus fruit oils. Carcinogenesis 12:115–117 (1991).
44. Castonguay A, Pepin P, Stoner GD. Lung tumorigenicity of NNK given orally to A/J mice: its application to chemopreventive efficacy studies. Exp Lung Res 17:485–499 (1991).
45. Boukharta M, Balbert G, Castonguay A. Biodistribution of epilagic acid and dose-related inhibition of lung tumorigenization in A/J mice. Nutr Cancer 18:181–189 (1992).
46. Pepin P, Bouchard L, Nicole P, Castonguay A. Effects of sulindac and oltipraz on the tumorigenicity of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in A/J mouse lung. Carcinogenesis 13:341–346 (1992).
47. Balbert G, Castonguay A. Effects of NSAIDs on NNK-induced pulmonary and gastric tumorigenesis in A/J mice. Cancer Lett 66:21–28 (1992).
48. Hong J-Y, Wang ZY, Smith TJ, Zhou S, Shi S, Pan J, Yang CS. Inhibitory effects of diallyl sulfide on the metabolism and tumorigenicity of the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in A/J mouse lung. Carcinogenesis 13:901–904 (1992).
49. Xu Y, Ho CT, Amin SG, Han C, Chung FL. Inhibition of tobacco-specific nitrosamine-induced lung tumorigenesis in A/J mice by green tea and its major polyphenol as antioxidants. Cancer Res 52:3875–3879 (1992).
50. Lin J-M, Desai DH, Morse MA, Amin S, Hecht SS. Inhibition of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone pulmonary metabolism and tumorigenicity in mice by analogues of the investigational chemotherapeutic drug 4-ipomeanol. Chem Res Toxicol 5:674–679 (1992).
51. El-Bayoumy K, Upadhyaya P, Desai DH, Amin S, Hecht SS. Inhibition of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone tumorigenicity in mouse lung by the synthetic organoselenium compound, 1,4-phenylenedis(methylene)selenocyanate. Carcinogenesis 14:1111–1113 (1993).
52. Shi ST, Wang Z-Y, Smith TJ, Hong J-Y, Chen W-F, Ho C-T, Yang CS. Effects of green tea and black tea on 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone bioactivation, DNA methylation, and lung tumorigenesis in A/J mice. Cancer Res 54:4641–4647 (1994).
53. Hecht SS, Rivenson A, Braley J, DiBello J, Adams JD, Hoffmann D. Induction of oral cavity tumors in F344 rats by tobacco-specific nitrosamines and snuff. Cancer Res 46:4162–4166 (1986).
54. Hecht SS, Morse MA, Amin S, Stoner GD, Jordan KG, Choi C-I, Chung F-L. Rapid single-dose model for lung tumor induction in A/J mice by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and the effect of diet. Carcinogenesis 10:1901–1904 (1989).
55. Saffiotti U, Montesano R, Sellakumar AR, Borg SA. Experimental cancer of the lung. Inhibition by vitamin A of the induction of tracheobronchial squamous metaplasia and squamous cell tumors. Cancer 20:857–864 (1967).
56. Smith DM, Rogers AE, Herndon BJ, Newberne PM. Vitamin A (retinyl acetate) and benzo[a]pyrene-induced respiratory tract carcinogenesis in hamsters fed a commercial diet. Cancer Res 35:11–16 (1975).
57. Smith DM, Rogers AE, Newberne PM. Vitamin A and benzo[a]pyrene carcinogenesis in the respiratory tract of hamsters fed a semisynthetic diet. Cancer Res 35:1548–1556 (1975).
58. Beems RB. Modifying effect of vitamin A on benzo[a]pyrene-induced respiratory tract tumors in hamsters. Carcinogenesis 5:1057–1060 (1984).
59. Beems RB. Dietary selenium- and benzo[a]pyrene-induced respiratory tract tumors in hamsters. Carcinogenesis 7:485–489 (1986).
60. Berg RB. The effect of β-carotene on BP-induced respiratory tract tumors in hamsters. Nutr Cancer 10:197–204 (1987).
61. Wattenberg LW. Inhibition of carcinogenic and toxic effects of polycyclic hydrocarbons by several sulfur-containing compounds. J Natl Cancer Inst 52:1583–1587 (1974).
62. Borchert P, Wattenberg LW. Inhibition of macromolecular binding of benzo[a]pyrene and inhibition of neoplasia by disulfiram in the mouse forestomach. J Natl Cancer Inst 57:173–179 (1976).
63. Wattenberg LW, Leong JL. Inhibition of the carcinogenic action of benzo[a]pyrene by flavones. Cancer Res 30:1922–1925 (1970).
64. Wattenberg LW. Inhibition of chemical carcinogen-induced pulmonary neoplasia by butylated hydroxyanisole. J Natl Cancer Inst 50:1541–1544 (1973).
65. Wattenberg LW, Borchert P, Destafney CM, Coccia JB. Effects of p-methoxyphenol and diet on carcinogen-induced neoplasia of the mouse forestomach. Cancer Res 43:4747–4751 (1983).
66. Speier JL, Lam LKT, L.Wattenberg LW. Effects of administration to mice of butylated hydroxyanisole by oral intubation on benzo[a]pyrene-induced pulmonary adenoma formation and metabolism of benzo[a]pyrene. J Natl Cancer Inst 60:605–609 (1978).
67. Witschi HP, Doherty DG. Butylated hydroxyanisole and lung tumor development in A/J mice. Fundam Appl Toxicol 2:829–831 (1984).
68. Wattenberg LW. Inhibition of polycyclic aromatic hydrocarbon-induced neoplasia by sodium cyanate. Cancer Res 40:232–234 (1980).
69. Lesca P. Protective effects of ellagic acid and other plant phenols on benzo[a]pyrene-induced neoplasia in mice. Carcinogenesis 4:1651–1653 (1983).
70. Chang RL, Huang MT, Wood AW, Wong CQ, Newmark HL, Yagi H, Sayer JM, Jerina DM, Conney AH. Effect of ellagic acid and hydroxylated flavonoids on the tumorigenicity of benzo[a]pyrene and (±)β,8a,9a-dihydroxy-9a,10α-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene on mouse skin and in the newborn mouse. Carcinogenesis 6:1127–1133 (1985).

71. Adriaenssens PI, Sivarajah K, Boorman GA, Eling TE, Anderson MW. Effect of aspirin and indomethacin on the formation of benzo[a]pyrene-induced pulmonary adenomas and DNA adducts in A/HeJ mice. Cancer Res 43:4762–4767 (1983).

72. Wattenberg LW, Hanley AB, Barany G, Sparnins VL, Lam LKT, Fenwick GR. Inhibition of carcinogenesis by some minor constituents. In: Diet, Nutrition and Cancer (Hayashi Y, ed). Tokyo: Japan Science Society Press, 1986:193–203.

73. Sparnins VL, Barany G, Wattenberg LW. Effects of organosulfur compounds from garlic and onions on benzo[a]pyrene induced neoplasia and glutathione S-transferase activity in the mouse. Carcinogenesis 9:131–134 (1988).

74. Walaszek Z, Hanausek-Walaszek M, Webb TE. Dietary glucarate-mediated reduction of sensitivity of murine strains to chemical carcinogenesis. Cancer Lett 33:25–32 (1986).

75. Sparnins VL, Mott AW, Barany G, Wattenberg LW. Effects of allyl methyl trisulfide on glutathione S-transferase activity and BP-induced neoplasia in the mouse. Nutr Cancer 8:211–215 (1986).

76. Estensen RD, Wattenberg LW. Studies of chemopreventive effects of myo-inositol on benzo[a]pyrene-induced neoplasia of the lung and forestomach of female A/J mice. Carcinogenesis 14:1975–1977 (1993).

77. Wattenberg LW, Bueding E. Inhibitory effects of 5-(2-pyrazinyl)-1-methyl-1,2-dithiol-3-thione (oltipraz) on carcinogenesis induced by benzo[a]pyrene, diethylnitrosamine and uracil mustard. Carcinogenesis 7:1379–1381 (1986).

78. Morse MA, Zu H, Kresty LA, Stoner GD. Failure of dietary oltipraz to inhibit benzo[a]pyrene-induced lung tumorigenesis in strain A mice. Cancer Lett 91:133–138 (1995).

79. Triano EA, Simpson JB, Kratky M, Lang WR, Triolo AJ. Protective effects of trifluralin on benzo[a]pyrene-induced tumors in A/J mice. Cancer Res 45:601–607 (1985).

80. Triolo AJ, Lang WR, Coon JM, Lindstrom D, Herr DL. Effect of the insecticides toxaphene and carbaryl on induction of lung tumors by benzo[a]pyrene in the mouse. J Toxicol Environ Health 9:637–649 (1982).

81. The alpha-tocopherol beta carotene cancer prevention study group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. New Engl J Med 330:1029 (1994).

82. Hecht SS, Chung F-L, Richie JP Jr, Akerkar SA, Borukhova A, Skowronski L, Carmella SG. Effects of watercress consumption on metabolism of a tobacco-specific lung carcinogen in smokers. Cancer Epidemiol Biomarkers Prev 4:877–884 (1995).

83. Hecht SS, Isaacs S, Trushin N. Lung tumor induction in A/J mice by the tobacco smoke carcinogens 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and benzo[a]pyrene: a potentially useful model for evaluation of chemopreventive agents. Carcinogenesis 15:2721–2725 (1994).

84. Moon RC, Rao KVN, Detrisac CJ, Kelloff GJ. Retinoid chemoprevention of lung cancer. In: Cancer Chemoprevention (Wattenburg L, Lipkin M, Boone CW, Kelloff GJ, eds). Boca Raton, FL: CRC Press, 1992:83–93.

85. Wattenberg LW, Estensen RD. Chemopreventive effects of myo-inositol and dexamethasone on benzo[a]pyrene and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced pulmonary carcinogenesis in female A/J mice. Cancer Res 56:5132–5135 (1996).

86. Chung FL, Kelloff G, Steele V, Pittman B, Zang E, Jiao D, Rigott J, Choi CI, Rivenson A. Chemopreventive efficacy of arylalkyl isothiocyanates and N-acetyl cysteine for lung tumorigenesis in Fischer rats. Cancer Res 56:772–778 (1996).

87. Hecht SS, Trushin N, Rigott J, Carmella SG, Borukhova A, Akerkar S, Rivenson A. Complete inhibition of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced rat lung tumorigenesis and favorable modification of biomarkers by phenethyl isothiocyanate. Cancer Epidemiol Biomarkers Prev 5:645–652 (1996).