

Review

Epidemiological Models of Carcinogenesis: The Example of Bladder Cancer

Paolo Vineis

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Abstract

Epidemiological studies have clearly shown that smokers have an increased risk of bladder cancer. Chemical, biochemical, and molecular investigations indicate that such risk might be due to aromatic amines which are present in tobacco smoke. In particular, collaborative studies have shown that smokers have increased levels of hemoglobin-4-aminobiphenyl adducts in their blood and that these levels show a dose-response relationship and an association with the most carcinogenic variety of tobacco, air-cured or black tobacco. Adduct concentrations were also modulated by the genetically based slow acetylator phenotype. In addition, investigations in dogs and humans have described a DNA adduct in bladder biopsies and in exfoliated bladder cells that is a derivative of 4-aminobiphenyl. This paper summarizes the epidemiological, biochemical, and molecular evidence concerning the possible mechanisms of bladder cancer induction in smokers and in occupationally exposed workers. The case of bladder cancer is an example of integration between epidemiological studies, mathematical modeling, and laboratory investigations aiming at the elucidation of mechanisms of carcinogenesis.

Introduction

Through experimental examples, Cohen and Ellwein (1) have suggested that cell proliferation may be a crucial step in bladder carcinogenesis, in addition to events that induce mutation. This suggestion is not new, being included also in the epidemiological model of carcinogenesis proposed by Moolgavkar (2). The latter model is based on two mutational events, with an intermediate step of increased cell proliferation. Exposures can act by increasing the rate of the first (initiation) or second (progression) mutation, or through the balance between cell death and cell division. The model has been successful in at least three, qualitatively different, instances.

1. Partially based on a lecture given at the 82nd Annual Meeting of the American Association for Cancer Research, Houston, TX, May 15-18, 1991.
2. To whom requests for reprints should be addressed.

Received 6/12/91.

Human Retinoblastoma. The need for two mutations has been clearly shown, although there is no evidence of any chemical exposure which might be a risk factor for this cancer (3).

Lung Cancer and Cigarette Smoking. The most recent analyses of epidemiological data sets clearly suggest that the effect of timing of smoking habits (age at start, age at cessation) fits better with Moolgavkar’s model than with others. In this case the relevant chemical exposure has been identified, although it is a complex mixture rather than a single chemical.

Animal Experiments Based on Skin Painting. Several experiments have shown that two mutations are necessary, one at the “initiation” stage, leading to benign papillomas, and one at the “conversion” stage, leading to carcinomas. The role of promoters is proposed to be exerted in between the two mutations, and mainly consists of a proliferative stimulus.

The problem with mathematical models is that most of the available data sets are usually compatible with different models, and the choice between two or more of these is based on statistical aspects (i.e., “goodness of fit”), which have nothing to do with the available biological knowledge.

To make more credible inferences to be used in “risk assessment” procedures, the integration of both epidemiological and biological data is absolutely needed. In particular, the following types of information should become available, if possible, for at least one risk factor and the corresponding cancer site: (a) shape of the dose-response relationship; (b) effects of timing of exposure (age at start, age at cessation, pattern of risk after exposure); (c) internal dosimetry (adducts); (d) experimental data on the putative mechanism of action (genotoxic/epigenetic); (e) other relevant data on important effect modifiers, like genetically based metabolic polymorphism.

The relationship between lung cancer and cigarette smoking is probably the best-known demonstration of epidemiological patterns such as the dose-response relationship and effect of timing of exposure. However, there is no evidence available suggesting that one particular component of tobacco is responsible for the lung carcinogenicity of smoking. The state of knowledge thus far has been too incomplete to use an individual chemical (or a chemical class) as a “marker” to study the biological mechanisms of lung carcinogenesis. However, there is increasing evidence of a possible mechanism of induction of bladder cancer by amines, which is at the moment the most comprehensive example of this type.
Role of Arylamines in Bladder Carcinogenesis: Epidemiological Evidence

It is well known that occupational exposure in dye-producing industries to high levels of arylamines, such as benzidine, 2-naphthylamine, and 4-aminobiphenyl, was followed by enormously increased risks of bladder cancer, on the order of 50- to 60-fold or more (4). Tobacco smoking is also a risk factor, being responsible for about 50% of bladder cancers in males living in Western countries (5). It can be reasonably hypothesized that what makes tobacco smoke carcinogenic to the bladder is its arylamine content. Table 1 shows the concentration of several arylamines in smoke from air-cured and flue-cured tobaccos (6). Doll et al. (7) estimated in 1972 that the risk of a light smoker of flue-cured tobacco was grossly comparable to the risk of a gasworker exposed to arylamines, at a concentration much lower than that found in dye-producing industries. In both cases (smokers and gasworkers) the estimated exposure to 2-naphthylamine was around 100 μg in the course of 20 years, and the relative risk was around 2.

Table 1

<table>
<thead>
<tr>
<th>Arylamine</th>
<th>United States</th>
<th>France</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-Toluidine</td>
<td>32.2</td>
<td>16.2</td>
</tr>
<tr>
<td>N-Toluidine</td>
<td>15.3</td>
<td>30.4</td>
</tr>
<tr>
<td>P-Toluidine</td>
<td>13.5</td>
<td>33.8</td>
</tr>
<tr>
<td>2-Ethylaniline + 2.6-dimethylaniline</td>
<td>14.9</td>
<td>54.2</td>
</tr>
<tr>
<td>2.5-Dimethylaniline</td>
<td>19.1</td>
<td>87.2</td>
</tr>
<tr>
<td>3-Ethylaniline + 2.4-dimethylaniline</td>
<td>14.0</td>
<td>56.7</td>
</tr>
<tr>
<td>4-Ethylaniline + 2.3-dimethylaniline</td>
<td>7.8</td>
<td>27.3</td>
</tr>
<tr>
<td>1-Naphthylamine</td>
<td>4.3</td>
<td>2.5</td>
</tr>
<tr>
<td>2-Naphthylamine</td>
<td>1.0</td>
<td>1.7</td>
</tr>
<tr>
<td>2-Aminobiphenyl</td>
<td>1.8</td>
<td>3.0</td>
</tr>
<tr>
<td>3-Aminobiphenyl</td>
<td>2.7</td>
<td>5.0</td>
</tr>
<tr>
<td>4-Aminobiphenyl</td>
<td>2.4</td>
<td>4.6</td>
</tr>
<tr>
<td>2-Methyl-1-naphthylamine</td>
<td>5.8</td>
<td>3.6</td>
</tr>
</tbody>
</table>

*Ref. 6.

Evidence for Metabolic Polymorphism as an Effect Modifier

N-Acetyltransferase is an enzyme involved in the deactivation of some arylamines, the urinary excretion of which is increased after acetylation. Human populations show a characteristic genetically based polymorphism for the activity of this enzyme, with about 50% of subjects being “slow” acetylators and 50% “fast” acetylators.

In their classic report, Cartwright et al. (15) described a hospital-based case-control study of 111 bladder cancer cases and 207 controls (one group of healthy subjects recruited in London and one group of urological patients in Huddersfield). The N-acetylation phenotype was assessed by the measurement of the monoacetyldapsone:dapsone ratio, and 0.3 was used as the cut point between the phenotypes. The proportion of “slow acetylators” was 57% among the controls and 67% among the cases. However, this proportion was strikingly increased in a group of 23 occupationally exposed cases of bladder cancer. It suggests that smoking may be responsible for the increased proportion of slow acetylators. However, the proportion of slow acetylators was 57% among the controls and 67% among the cases. This result strongly supports the hypothesis that smoking is responsible for the increased proportion of slow acetylators.

Role of Arylamines in Bladder Carcinogenesis: Evidence from "Molecular Epidemiology"

There are at least four sources of information that indicate 4-aminobiphenyl is relevant to bladder carcinogenesis in smokers: studies on hemoglobin adducts; studies on DNA adducts in exfoliated bladder cells; studies on bladder biopsies in humans; and studies on bladder biopsies in dogs. Talaska et al. (11) have shown that the administration of 4-ABP to dogs resulted in the formation of a main DNA adduct, N-(deoxyguanosin-8-yl)-4-aminobiphenyl, in bladder cells. Subsequently, they studied DNA adducts in the biopsies of 42 subjects with bladder cancer and again found that N-(deoxyguanosin-8-yl)-4-aminobiphenyl was one of the main adducts in smokers (12).

In the light of the above evidence, it can be hypothesized that smoking is responsible for the increased proportion of slow acetylators. However, the proportion of slow acetylators was 57% among the controls and 67% among the cases. This result strongly supports the hypothesis that smoking is responsible for the increased proportion of slow acetylators.

1 The abbreviation used is: 4-ABP, 4-aminobiphenyl.

Table 2  Proportion (%) of slow acetylators among bladder cancer cases and controls in different studies *

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>65</td>
<td>51</td>
</tr>
<tr>
<td>Huddersfield</td>
<td>67</td>
<td>57</td>
</tr>
<tr>
<td>Sweden</td>
<td>70</td>
<td>67</td>
</tr>
<tr>
<td>Germany</td>
<td>62</td>
<td>43</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>59</td>
<td>49</td>
</tr>
<tr>
<td>New York state</td>
<td>46</td>
<td>69</td>
</tr>
<tr>
<td>Newcastle</td>
<td>70</td>
<td>59</td>
</tr>
<tr>
<td>Liverpool</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>Rural Denmark</td>
<td>64</td>
<td>54</td>
</tr>
<tr>
<td>Spain</td>
<td>64</td>
<td>57</td>
</tr>
<tr>
<td>Spain (exposed to arylamines)</td>
<td>73</td>
<td></td>
</tr>
</tbody>
</table>

* Ref. 16, modified.

Table 3  Means and SEs of 4-aminobiphenyl hemoglobin adducts in the blood of black and blond tobacco smokers and nonsmokers (pg/g Hb), by acetylation phenotype *

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Acetylation phenotype</th>
<th>Slow</th>
<th>Fast</th>
<th>Slow:fast ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsmokers</td>
<td>Slow</td>
<td>31.7 (3.8)</td>
<td>19.4 (4.9)</td>
<td>1.6</td>
</tr>
<tr>
<td>Blond tobacco</td>
<td>Slow</td>
<td>111.8 (13.0)</td>
<td>86.4 (14.5)</td>
<td>1.3</td>
</tr>
<tr>
<td>Black tobacco</td>
<td>Slow</td>
<td>175.0 (11.0)</td>
<td>117.5 (13.7)</td>
<td>1.5</td>
</tr>
</tbody>
</table>

* Ref. 14.

(With probable exposure to benzidine). In fact, 22 of 23 (P = 0.0005) were slow acetylators; in addition, the only fast metabolizer had an adenocarcinoma, i.e., a histological type different from the other 22 (transition cell carcinomas). The proportion of virtually 100% slow acetylators among occupationally exposed bladder cancer cases is the highest reported in the literature; all the procedures were blind, and the method used for phenotyping is simple and accurate.

Other hospital-based case-control investigations on bladder cancer have been reported, in which controls are usually patients with urological conditions or healthy volunteers. Methods used for phenotyping were based on sulfaazinidine or sulfaazmethzenine (for a review see Ref. 16). Table 2 reports the proportions of slow acetylators in cases and controls. Overall, these data are an argument for a small (30–50%) increase in the proportion of slow acetylators in bladder cancer patients, particularly among arylamine-exposed workers. However, the slight elevation of risk is also compatible with bias.

In addition to these data concerning bladder cancer, information from “molecular epidemiology” is also available. In the study on 97 volunteers mentioned above, the concentration of 4-ABP-hemoglobin adducts was clearly higher in slow acetylators, as Table 3 shows. When smoking habits (dose, type of tobacco) and the metabolic phenotype were included in a multivariate model, an independent and statistically significant contribution by the latter was found. In addition to this direct evidence of a role played by the phenotype for N-acetylation in the concentration of adducts, there is also indirect, but quite suggestive evidence of polymorphism. We have analyzed the hemoglobin adducts formed by 14 different arylamines which were the object of a first pilot study among smokers. After controlling strictly for smoking habits, we analyzed the residual individual variability for the adduct concentration, by the means of factor analysis; the aim was to identify potential sources of variability not explained by smoking. The result was surprising, since the adduct concentration varied considerably according to the type of arylamine (mono- or binuclear). In fact, adducts from binuclear arylamines (2-naphthylamine, 4-aminobiphenyl, 3-aminobiphenyl) were highly correlated reciprocally, and so were adducts from mononuclear arylamines (all the others). This is strongly suggestive of a metabolic polymorphism in the study population that is responsible for interindividual variability not explained by smoking habits (17).

### Dose-Response Relationship

The shape of dose-response relationships in cancer epidemiology has been interpreted in at least two different ways: (a) to infer the number of stages, within the frame of multistage carcinogenesis; (b) to make inferences about saturation or induction of enzymes involved in the metabolism of carcinogens. An example of the first inference is the observation of a quadratic dose-response relationship between the number of cigarettes smoked and the risk of lung cancer, and the ensuing inference that tobacco smoke acts on two stages of the carcinogenic process in the lung (18). An example of the second type is the observation of a convex dose-response relationship after experimental administration of some carcinogens to animals, which was interpreted as an expression of enzyme saturation. It is clear that both types of inference are rather arbitrary, if based on the simple observation of the shape of the relationship. At least a third possibility exists, i.e., that the dose-response relationship is an expression of polymorphism within the study population, indicating the presence of subgroups with different susceptibilities to the action of carcinogens.

Cohen and Ellwein (1) have inferred from the observation of bladder cancers experimentally induced with an arylamine (2-acetyaminofluorene) that this chemical would act on two mutational stages and stimulate cell proliferation at high doses. In practice, the increase of tumor prevalence was very slow and about linear at low doses, while at high doses the dose-response curve became much steeper. The authors conclude that, in addition to the two mutations induced at all doses, 2-acetyaminofluorene at high doses would also have an effect on urothelial hyperplasia.

As far as epidemiological studies of bladder cancer are concerned, rather than an exponential shape, a convex dose-response relationship between the amount of cigarettes smoked and the relative risk has been repeatedly observed. In other words, the relative risk increases quickly and then seems to reach a plateau. For example, in the largest case-control study the relative risks by

---


One subject only.

found: a Danish investigation, the following relative risks were 20-39, 2.6 (1 102 cases); and 40+, 2.6 (392 cases) (19). In
ence category) were: <20, 1 .8 (based on 658 cases); number of cigarettes smoked (nonsmokers were the nef-
response relationship has also been observed when cor-
investigations, however, the demonstration of a plateau 193)

priori would include two subgroups, one metabolizing rapidly
emerged. It is

tobacco and bladder cancer, as far as time-related van-

made in animals treated with 2-acetylaminofluorene; i.e., it is unlikely that tobacco smoke acts on two mutational
stages and induces urothelial hyperplasia, as hypothe-
sized by Cohen and Ellwein.

Table 4
Levels of 4-aminobiphenyl-hemoglobin adducts according to
levels of nicotine plus cotinine in the urine: smokers only

<table>
<thead>
<tr>
<th>Cotinine + nicotine (μmol/mmol)</th>
<th>ABP adds (pg/g)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Slow acetylators only</td>
<td></td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>153</td>
</tr>
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<td>0.5-1.4</td>
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<td>148</td>
</tr>
<tr>
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<td>92</td>
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<tr>
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</tr>
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* One subject only.

Table 5
Effect of switching from black to blond tobacco

<table>
<thead>
<tr>
<th></th>
<th>Black tobacco throughout life</th>
<th>Black tobacco switching to blond</th>
</tr>
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<tr>
<td></td>
<td>Current</td>
<td>Former</td>
</tr>
<tr>
<td></td>
<td>OR*</td>
<td>95% CI</td>
</tr>
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* OR, odds ratio; CI, confidence interval.

Timing of Exposure and Risk of Bladder Cancer:
Smoking and Occupational Exposure

In the case of cigarette smoking, increasing age at start

made animals treated with 2-acetylaminofluorene; i.e., it is unlikely that tobacco smoke acts on two mutational
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</tr>
<tr>
<td></td>
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stages and induces urothelial hyperplasia, as hypothe-
sized by Cohen and Ellwein.
Using the nonexposed as reference category, the relative risks were
confounding effect of occupational exposure on the
followed in the cohort study (however, there was no
cancer which occurred among the dye workers
coming from a case-control study, also includes 10 bad-
graphic area, the province of Tomino. The first data set,
occupational exposure to highly carcinogenic arybamines.
10, 40, 19.5, 15.
-1035
-844
-994
-954
-975
-914
-872
Conclusions and Perspectives
I have made a series of inferences which need further
support from the data: (a) that the bladder carcinogenic-
ity of smoking is mainly due to arylamines, which
undergo genetically based metabolic polymorphism; (b)
that the role played by arylamines and the metabolic
polymorphism for N-acetylation might explain the similar
dose-response relationship which has been found for
both the risk of bladder cancer and the concentration of
4-ABP-hemoglobin adducts in the blood of smokers; (c)
that, again, the role played by arylamines in cigarette
smoke might explain the similarities between smokers
and occupationally exposed workers in the effects of
exposure timing (age at start, age at cessation). A further
inference might be that arylamines (which include potent
mutagens, like 2-naphthylamine and 4-aminobiphenyl)
act on two mutational stages in the carcinogenic process,
i.e., inducing mutations of the ras or p53 genes. Although
this is only a model, I believe it has the advantage of
being based on both mathematical treatment of epide-
miological data and the use of the biomarkers of internal
dose and susceptibility. Any model is a temporary pic-
torial representation of reality, and its success is revealed
by its ability to make predictions and by the confirmation
of such predictions.

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phenotypes in the urinary bladder carcinogenesis of a low-risk popula-
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J. Bladder cancer mortality of workers exposed to aromatic amines: an

<table>
<thead>
<tr>
<th>Age at start</th>
<th>Time since cessation</th>
</tr>
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<tbody>
<tr>
<td>&lt;17</td>
<td>17-20</td>
</tr>
<tr>
<td>Air-cured tobacco</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 6 Relative risks by age at start and years since cessation, among air-cured tobacco smokers and a cohort of occupationally exposed workers*

- Air-cured tobacco:
- Age at start: <17, 17-20, 21-24, 25+.
- Time since cessation: <3, 3-9, 10+.
- Occupational exposure: 1.0, 0.4, 0.4, 0.3, 1.0, 0.45, 0.27.

* Refs. 8 and 22.

** Estimates adjusted for age and number of cigarettes smoked.

† Using the nonexposed as reference category, the relative risks were 101, 40, 19.5, 15.
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