Smoking and occupational exposure to certain aromatic amines are the most clearly established causative factors in the development of bladder cancer. According to experts, 50% of deaths due to bladder cancer in men and 25% in women – a total of approximately 2,700 cases per year – are avoidable (e1). Estimates for the year 2002 set the age-standardized incidence figures for bladder cancer in Germany at 38.5/100 000 for men and 10.5/100 000 for women (e2). Following rising incidence figures up until the early 1990s, the trend began to reverse from the mid-90s, and is still continuing. It is notable, however, that the figures were also influenced by an alteration to the histopathological criteria for malignancy (e2). This article presents current thinking on the etiology and prevention of bladder cancer. Special attention has been given to occupational causes with insurance implications.

Smoking is the most important risk factor

In the population at large, smoking is by far the most important risk factor in the development of bladder cancer (e3,1). This probably also applies to cigar and pipe smokers, though the effect for these is less pronounced (e4) (box 1). Black, air-dried tobaccos appear to carry a higher bladder cancer risk than blond, smoke-dried varieties (e5).

Although the size of risks of bladder cancer quoted in the literature varies, there is clear agreement that heavy smokers are at a higher risk of developing bladder cancer than lighter smokers (2, 3). Correspondingly, an analysis of 11 case-control studies in men showed a risk increase from 1.2 fold (1 to 4 years of smoking) to 6.1 fold (more than 60 years of smoking). Giving up smoking results in an immediate reduction in cancer risk. In most studies the risk for ex-smokers approaches that of non-smokers by around 20 years after smoking cessation (e4, 2, 3, e6, e7). An analysis of 11 case-control studies in women pointed in the same direction. A recent study suggests that women with comparable tobacco consumption with men have a higher disease risk (e6).

Cigarette smoke contains many substances (1); for some of these, a carcinogenic effect has been documented, including combustion products and aromatic amines such as β-naphthylamine, 4-aminobiphenyl and o-toluidine. In smokers, who are carriers of a particular isoenzyme, aromatic amines are more frequently converted to metabolites with carcinogenic properties (4).
Occupational causes

Two essential studies on the causation of cancer estimate the proportion of occupationally triggered bladder cancer in men to be 10% and in women, 5% (5, 6). Thus, the over 1,200 cases of bladder cancer that were recognized as occupationally related between 1978 and 2003 (7) represent only a fraction of the occupationally related cases. As well as unknown occupational risks, this is also attributable to insufficient exploration of the case histories. Occupational case histories should be recorded thoroughly, particularly as the latent periods for occupationally triggered bladder cancer can be very long (up to 40 years or more). Every physician in Germany is duty bound to report any founded suspicion of the presence of an occupational disease to the competent authorities. But since damages can only be paid for occupational illnesses that are reported while the person is still alive, any failure to report can quite possibly result in claims against the treating physician.

The most important occupational risk factor for the development of bladder cancer is exposure to carcinogenic aromatic amines. The carcinogenic potential of individual representatives of this substance group is extremely varied. Five aromatic amines are proven to trigger bladder cancer in humans. These are: \( \beta \)-naphthylamine (2-naphthylamine), benzidine, 4-aminobiphenyl, 4-chloro-o-toluidine und o-toluidine. Of these agents, the first two are of greatest significance.

In past decades, \( \beta \)-naphthylamine was used primarily as an antioxidant in the rubber industry. The ban on this substance, however, did not eliminate the higher risk for employees in this industry entirely (8). A study with over 11,000 workers in the German rubber industry (9) found that employees in the departments “Storage and Shipping” and “General Activities” showed higher bladder cancer mortality than the general population. It must also be

### BOX 1

Non-occupational risk factors for bladder cancer

- Significant risk increase: cigarette smoking
- Minimal risk increase: cigar smoking, pipe smoking
- Possible risk: coffee consumption
- Slightly reduced risk: frequent fruit consumption
- No or unclear association: alcohol and tea consumption, vegetable consumption, vitamin A and C intake

---

**DIAGRAM**

**benzidine-derived azo dyes**

reductive cleavage

\[ \text{H}_2\text{N} - \text{N} - \text{R} \]

\[ \text{H}_2\text{N} - \text{NH}_2 \]

Biological cleaving of an azo dye
remembered that mortality studies clearly underestimate risk in this disease, due to its favorable prognosis.

Benzidine was used primarily in the manufacture of numerous azo dyes and has the highest significance because of the high production volumes. In humans, this aromatic amine is a potent carcinogen. Accordingly, 92 out of 331 workers of a German company, who had been employed at a benzidine production plant that had already been shut down by the company in the 60s, presented with bladder cancer in the early 90s (10, e8). This example demonstrates that it is never too early to implement preventive steps, and that these steps cannot be comprehensive enough.

For practical purposes, it is essential to understand that carcinogenic amines, used as a coupling component in dye manufacturing, can be rereleased from soluble, i.e. bioavailable dyes, into the human body (diagram). Insoluble azo dyes (pigments), in contrast, do not constitute a disease risk (11).

Jobs with considerable dermal and/or inhalational exposure to carcinogenic azo dyes, such as, for example, dyeing in the textile and leather industries, are also associated with an elevated bladder cancer risk (e9, e10). All four case-control studies conducted in Germany to date have also observed an increased risk for housepainters and varnishers (e11, e12, e13, 12), albeit mostly only in individuals exposed before 1960.

Two studies published by a US research group (13, 14) that suggested a higher bladder cancer risk in hairdressers due to exposure to permanent hair dyes attracted a great deal of attention. Two studies carried out in Germany also pointed to an elevated risk for people in this profession (e11, e13). But currently available products should not be compared to products that were on the market decades ago. p-Phenylenediamine, a common component in modern dark-shade hair dyes, does not appear carcinogenic, based on the detected metabolites (e14, e15).

Exposure to carcinogenic aromatic amines and/or azo dyes can, however, also occur in workplaces where any handling of these substances is only occasional. The gathering of workplace specific case histories must therefore target these substances specifically in their inquiries. High exposure to combustion products as, for example in coking plants (e16, 15) or in connection with Söderberg type aluminum electrolysis (16), are also in part to blame for the development of bladder cancer. Considerably lower concentrations of combustion products occur with the exposure to tar and/or tar products. Nevertheless, two studies found that American roofers are at increased risk of bladder cancer (17, e17). The risks ensuing from exposure to tar in road construction (e18) is the subject of current controversy. A study of 568 workers in Europe’s largest tar processing factory identified 13 cases of bladder cancer (18). The carcinogenic potential of tar and/or tar products can therefore be viewed as confirmed in principle.

Among other occupational exposures described in association with increased bladder cancer risk are long-term underground mining activity in hard coal mines (e19, 19, 20, e20), chimney sweeping (e21, e22), high exposure to the explosive dinitrotoluene, which was used, in particular, in the former German Democratic Republic (e23, e24), and high exposure to tetrachloroethene that is used in chemical dry cleaning establishments (e25, e26, e27, e28) (table). In addition, there is evidence that cigarette smoking increases the occupational bladder cancer risk (e11, 19).

Environmental risks

The general public is also exposed to the above substances – even if for the most part at much reduced intensity. Urban populations seem to be affected to a higher degree, and show a higher bladder cancer risk than rural populations (e12, e29, e30, e31). Other environmental factors may also have an etiological role in bladder cancer, in particular substances ingested with drinking water (21). Secondary products involved in the chlorination (e32, e33, e34, e35, e36, e37) and ozone treatment (e38, e39) of drinking water are also implicated. A meta-analysis published in 2003 establishes that the bladder cancer risk increases 1.2 fold in men and women who consume chlorinated drinking water compared with the mean risk in the general population (e40).

Geologically determined high levels of arsenic in drinking water may also increase bladder cancer risk. Studies in Taiwan demonstrated an increased bladder cancer risk as a function of the arsenic level and the length of time such drinking water was consumed (22,
Based on this and other studies, the International Agency for Research on Cancer classified arsenic in drinking water in 2004 as a group 1 carcinogen. Specifically, arsenic in drinking water may cause bladder, lung and skin cancer in humans. In the meantime, water utilities in many regions with high concentrations of arsenic have implemented steps to reduce arsenic pollution.

Nitrate in drinking water is assumed to have carcinogenic potential, because nitrate is reduced to nitrite in the body, and in the presence of amines may be converted to carcinogenic N-nitroso compounds. However, studies to date have failed to establish a definite association between nitrate exposure and bladder cancer.

Nutritional factors
Excessive or insufficient fluid intake is currently under discussion as a possible risk factor, as is excessive coffee consumption. Newer studies find no evidence of a link between the use of artificial sweeteners, alcohol and tea consumption and any significant increase in bladder cancer risk. Carotinoids, vitamins A and C, and vegetable consumption appear to have no measurable influence on the bladder cancer risk. Frequent fruit consumption must be viewed as the commonest protective factor.

Therapeutic risks
Chemotherapeutic agents, such as cyclophosphamide, cause an increase in the number of bladder cancers. Thus, of 148 cyclophosphamide-induced secondary tumors 21% presented as bladder carcinomas which developed after a mean latent period of 52 months. There are indications that the outlook for treatment of this type of bladder cancer is less favorable.

### Nutritional factors

<table>
<thead>
<tr>
<th>Strongly increased risk</th>
<th>Clearly increased risk</th>
<th>Increased risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>benzidine</td>
<td>benzidine dyes</td>
<td>exposure to tar</td>
</tr>
<tr>
<td>β-naphthylamine</td>
<td>rubber industry</td>
<td>hairdresser</td>
</tr>
<tr>
<td>4-aminobiphenyl</td>
<td>worker in coking plants</td>
<td>underground hard coal mining</td>
</tr>
<tr>
<td>4-chloro-o-toluidine</td>
<td>painter (before 1960)</td>
<td>chemical dry cleaning</td>
</tr>
<tr>
<td>Siöderberg type</td>
<td>aluminum electrolysis</td>
<td>dinitrotoluene-containing explosives</td>
</tr>
<tr>
<td></td>
<td>massive exposure to combustion products</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o-toluidine</td>
<td></td>
</tr>
</tbody>
</table>

**Box 2**

**Treatments associated with increased bladder cancer risk**

- Cyclophosphamide
- Pelvic radiotherapy, especially in cervical cancer patients
- Chloronaphazine (historically)
- Phencetin (historically)
- Urinary drainage via indwelling catheter in paraplegic patients
1980 with cyclophosphamide showed an increased risk from 2.4 fold (total dosage < 20 g) to 14.5 fold (> 50 g) (23). Historical examples of bladder cancers caused by medication are seen in tumors arising following the use of chloronaphazine (in use until 1963) or phenacetine (available until 1986) (box 2).

In patients receiving radiotherapy for pelvic tumors, secondary malignancies may form in the bladder. This is most frequently described in curatively treated patients with cervical cancer. Hence, a study of 182 040 women treated for cervical cancer, showed 196 cases of bladder cancer in the radiotherapy arm, where only 74 cases would be expected in the general population. The increased risk was especially noticeable 10 years or more after radiotherapy (24). Other large studies documented comparable (e60, e61) or even higher risks (e62).

An increased bladder cancer risk is recognized, at least in paraplegic patients, due to urinary drainage over several years by way of a catheter (25, e63). This tallies with the observation that urinary tract infections and/or stones increase the risk of bladder cancer (e64).

**Prevention**

Few, but promising preventive strategies emerge from the available data on bladder cancer risk. The most notable is abstinence from smoking. When treating with alkylating agents, the coadministration of mesna (sodium 2-mercaptoethane sulphonate) is recommended to reduce bladder cancer risk; mesna lowers the risk of acute hemorrhagic cystitis, at least in animal studies, and exhibits anti-tumor efficacy (e65). Any exposure to known hazardous materials in the workplace must be minimized. Risks arising in insufficiently researched or new substances must be investigated and clarified as soon as possible. In terms of secondary prevention, the recording of smoking habits and taking of thorough occupational histories are essential, and the possibility of iatrogenic bladder cancer risks must be considered.

**Conflict of Interest Statement**

The author declares that no conflict of interest exists according to the Guidelines of the International Committee of Medical Journal Editors.

Manuscript received on 17 January 2006; revised version accepted on 28 August 2006.

Translated from the original German by R. Bittorf/H. Crossley and Dr Sandra Goldbeck-Wood.

**REFERENCES**

For e-references please refer to the additional references listed below.


Corresponding author
Prof. Dr. med. Klaus Golka
Institut für Arbeitsphysiologie an der Universität Dortmund
Arbeystr. 67
44139 Dortmund, Germany
golka@ifado.de