

*Ministry of Defence*

## **Synopsis of Causation**

### **Cancer of the Bladder**

**Author: Mr Keith Baxby, Ninewells Hospital, Dundee**  
**Validator: Professor Alan Horwich, Royal Marsden Hospital, London**

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## **Disclaimer**

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This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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# 1. Definition

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- 1.1. Bladder cancer is a malignant tumour of the lining of the bladder (urothelium).
- 1.2. Over 90% of bladder cancers are transitional cell carcinomas (TCC). They are derived from the specialised cells which line the normal bladder.
- 1.3. Five percent of bladder cancers are squamous cell carcinomas (SCC). In these cases the cells have undergone changes as a result of long standing irritation.
- 1.4. Bladder cancer is the 4<sup>th</sup> most common malignancy in Caucasian men, and the 7<sup>th</sup> in Caucasian women. The annual incidence in the UK is 35 cases per 100,000 per year for men, and 10 for women. White men have a 3% lifetime risk of developing the disease. The risk for white women and for Afro-Caribbean men is 1%.

## 2. Clinical features

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- 2.1. Bladder cancer most commonly comes to medical attention in the 6<sup>th</sup> and 7<sup>th</sup> decades of life.
- 2.2. The usually quoted sex ratio is 3:1 male:female. Following the decline in smoking (see 3.3.) by men, but not by women, the overall sex ratio in the UK is now 2.5:1 (but as age increases the male: female ratio increases, up to 4:1 in old age). Despite the reduction in smoking, the age-standardised incidence of bladder cancer in England and Wales rose by 16% in men and by 37% in women in the 27 years to 1998. In the 1970s some of this apparent rise would have been due to a change from classifying low grade bladder cancers as “papillomas” but by 1980 this erroneous practice had virtually ceased and the increase over the past 20 years is a true one. There is a suggestion that the rate of rise is lessening.
- 2.3. The most typical presenting feature is haematuria (blood in the urine). This may be visible to the patient (“frank haematuria”), or may be detected only by “dipstick” chemical analysis of urine. The latter is still generally called “microscopic haematuria”.
- 2.4. Occasionally bladder cancer presents as repeated cystitis or as urinary symptoms such as a frequent and urgent need to pass urine.
- 2.5. Rarely bladder cancer presents as renal (kidney) failure due to obstruction of the ureters, or as anaemia due to continued blood loss in the urine which the patient has ignored or has not seen. Very rarely, the first sign of the disease is due to symptoms from a metastasis.
- 2.6. When bladder cancer spreads it does so by direct extension to the muscle layer of the bladder then surrounding pelvic organs and by metastasis first to lymph nodes, which often causes no symptoms, and later to the lungs, bones and liver.
- 2.7. Bladder cancers vary widely in stage and grade. Many tumours are superficial and well differentiated and have a good prognosis if managed appropriately. Some are invasive and/or poorly differentiated and may spread with fatal results, despite radical treatment.

### 3. Aetiology

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#### Transitional cell carcinoma (TCC)

- 3.1. Increasing age (2.1.) and male sex (2.2.) are obvious risk factors. Racial differences in incidence (1.4.) are at least partly genetic in origin. A clear inherited tendency is apparent in only a very small number of patients. As with other cancers, it is probable that many individuals with bladder cancer have an increased susceptibility to environmental carcinogens which is inherited in a complex way and which requires the coincidence of several factors to produce a clinically obvious tumour. Schistosomiasis is common in Africa and the Middle East and chronic infection in those regions is associated with the high incidence of both TCC and SSC (see below).
- 3.2. In about one third of cases nothing is detected in the patient's history to account for the tumour. In at least one third there is a history of smoking. In about one third there is a history of exposure to substances proven or suspected to be carcinogens for the bladder. The interval between exposure to such substances and presentation with the tumour is most commonly 15 to 20 years, with a wide range from 1 year to 40 years.
- 3.3. **Smoking.** The relationship between cigarette smoking and bladder cancer has been established for 50 years<sup>1</sup> and has been confirmed by multiple studies.<sup>2</sup> In up to 40% of cases in the western world, cigarette smoking is involved in the causation of bladder cancer.
  - Smoking increases the overall risk of bladder cancer between two- and three-fold in men and women<sup>3</sup>
  - The risk is "dose-related"; that is, the greater the number of cigarettes smoked, the greater the risk<sup>4</sup>
  - An increased risk persists for 20 years after stopping smoking.<sup>4</sup> Many urologists believe that continued smoking after first diagnosis worsens the prognosis, but there is no good evidence for this<sup>5</sup>
  - Smoking probably increases the risks posed by other factors<sup>6</sup>
- 3.4. **Recognised occupational/industrial carcinogens.** Some substances have long been recognised as causing TCC.<sup>7</sup> The Industrial Injuries Disablement Benefit Scheme provides compensation, without the need individually to prove causation, to those who have worked with specified substances, in most cases for more than a specified period.
  - 3.4.1. Such substances include benzidine, aniline dyes and aromatic amines.
  - 3.4.2. Some of these substances (but not the last two groups) have been out of use for 40 years. Exposed workers are subject to surveillance for bladder cancer to enable early detection and treatment.
  - 3.4.3. Published material contains no references to these well recognised carcinogens in a specific military context. Although military personnel are involved in a wide range of functions, many of which overlap with occupations in civilian life, the substances listed in the Industrial

Injuries Disablement Benefit Scheme are used in very specific industrial processes (mostly the production of dyes and the smelting of aluminium by one specific process). The risks of these substances are so well established and widely known that it seems unlikely that service in the armed forces would involve unrecognised exposure to these substances for the required period. However, a 1992 review of over 200 published occupational studies<sup>8</sup> concluded that there was “clear evidence” of increased bladder cancer risk for these occupational groups: dye workers, rubber workers, leather workers, aluminium workers, painters and truck drivers. The last 2 occupations may be relevant in a military context but do not fall within the Industrial Injuries Disablement Benefit Scheme.

- 3.5. **Possible occupational carcinogens.** There are many studies showing an increased risk of TCC associated with a wide range of occupations, for example,<sup>9,10</sup> machinist, textile worker, automobile mechanic, clerk, teacher, plumber, butler and even “homemaker” as well as dozens of others. None of these occupations is medically recognised as associated with a high risk of bladder cancer (although the odds ratios in some studies were of the order of 2 to 5). By selective quotation from published work, an association could be suggested between almost any occupation (including staying at home) and an increased risk of having this disease. However, these studies have significant flaws. Some are restricted to one workplace, or to one city or region, with the general population as “controls”. Others depend on retrospective analysis of medical and occupational records. The latter are notoriously inaccurate: they may skew the results by inclusion or exclusion of those who have spent only a short time in the suspect occupation; workers who have similar job titles in the same institution may have differing exposure to the suspect agent; and, especially, the time interval between exposure and presentation with the disease (see 3.2.) makes accurate assessment of occupational exposure very difficult. In any event, association is not proof of causation. Smoking status is often not taken into account and some of these reports state that smoking could be a confounding factor.
- 3.6. **Environmental carcinogens.** Published material shows many environmental agents apparently associated with an increased risk of TCC. These range from arsenic<sup>6</sup> to a diet high in fat (but not a diet high in red meat<sup>11</sup>) with a huge range of foodstuffs, cosmetics and building materials in between. Many of these are single observational studies and many have corresponding, equally compromised studies which find no effect or a negative effect of the claimed suspect substance. A recent review<sup>12</sup> of over 100 papers on environmental risk factors confirmed the importance of cigarette smoking status, “dose” and duration but found no role, or a clinically insignificant role, for alcohol, fruit, tea and coffee ( the last having been suggested as a risk factor in some studies). For suspected environmental and “lifestyle” factors, the results of this review were very similar to those of the earlier review<sup>8</sup> of over 200 papers, which also provided no support for the much publicised view that the use of artificial sweeteners increased the risk of bladder cancer.
- 3.7. **Therapeutic ionising radiation.** There is a clinically recognised increased risk of bladder cancer following radiotherapy to other organs in the pelvis. Case reports refer to this after treatment of cervical cancer, which is by far the most common reason for pelvic radiotherapy. There is probably an increased risk of bladder cancer after any exposure to abnormally high levels of ionising radiation as part of the well-recognised increased risk of malignancy in general

after such exposure. Published work does not suggest a specific risk for bladder cancer from such exposure.

- 3.8. **Bladder cancer caused by therapeutic drugs.** Cyclophosphamide, an antineoplastic drug used to treat leukaemia, lymphomas, breast and other solid cancers has metabolites which are excreted in the urine and can cause a severe chemical irritation of the bladder followed years later by bladder cancer. Phenacetin (which used to be a component of “over the counter” analgesics) is well recognised as causing transitional cell carcinoma when used in large quantities over many years.

### **Squamous cell carcinoma (SCC)**

- 3.9. **Mechanical irritation.** The presence of a foreign body in the bladder for several years (probably at least 5 to 10) causes irritation which can lead to SCC. The commonest example of such a foreign body in the Western world is a urinary catheter. Such catheters are used in some patients whose bladders are paralysed due to spinal (or occasionally pelvic) injury.
- 3.10. **Chronic infection.** The most relevant cause is urinary schistosomiasis. SCC develops at a late stage of the disease. In a situation where there is access to medical care, treatment would be given because of severe symptoms at a stage when the disease would be cured, long before the development of SCC.

## 4. Prognosis

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### Transitional cell carcinoma

- 4.1. Without treatment, all bladder cancers will sooner or later spread locally and then by metastasis, with a fatal outcome.
- 4.2. The prognosis of transitional cell carcinoma (TCC) is closely related to the stage and grade of the tumour. There is a wide spectrum of combinations of stage and grade, with clustering at each end of the spectrum. Superficial, generally well differentiated tumours form a large group and may behave in a relatively benign manner. A smaller group of invasive, generally poorly differentiated, highly malignant tumours occupy the other end of the spectrum. It is therefore impossible to give a prognosis for “the average case”.
- 4.3. At first presentation 70% of patients have superficial disease, that is, disease which shows little or no invasion. Such tumours are treated by endoscopic transurethral resection. All patients are followed by bladder examinations at increasing intervals for at least 7 years.
- 4.4. Most patients with superficial disease will develop further tumours in the bladder. The risk of this is generally given as about 70%, but varies from 50% to 88% in the published work.<sup>13-15</sup> The risk of further tumours is reduced by instilling chemotherapeutic agents into the bladder at, or shortly after, tumour resection.<sup>16</sup>
- 4.5. Patients with initial superficial disease who later develop further tumours fall into one of 2 groups.<sup>15</sup> Some patients develop occasional, single recurrent tumours. They have a 50% chance of being free of tumour at 3 years. Others develop multiple recurrences. Their prognosis is less good, and about 15% will progress to develop invasive disease.<sup>17</sup> Patients who develop invasive disease after presenting with superficial disease have only 37% 3 year survival (much less than those who initially present with invasive disease).<sup>18</sup>
- 4.6. Among the 70% of patients who have superficial disease at presentation, survival rates depend on the grade of the tumour. Patients with very superficial, well differentiated disease do not die from it over 6 years of follow-up. Those with poorly differentiated, but still superficial disease, have a reduced 6 year survival of 62%.<sup>14</sup>
- 4.7. At first presentation 30% of patients have invasive disease, that is, disease which has spread through the mucosa into the muscle of the bladder wall. Fifty percent of patients with invasive disease at first presentation already have distant spread which may be undetectable at that time. They are rarely cured.
- 4.8. Invasive disease is usually treated by radical surgery. This involves removal of the entire bladder (cystectomy<sup>19</sup>) and a procedure to divert urine into an external collecting device attached to the skin, or into an internal replacement bladder constructed from bowel. In unfit patients radiotherapy is used.
- 4.9. When invasive disease is confined to the bladder at the time of surgery, the 5-year survival after radical surgery is between 55% and 65%.<sup>19,20</sup> When the disease has extended beyond the bladder, 5 year survival is as low as 18%.<sup>21</sup>



Chemotherapy is being used increasingly as an adjuvant to local treatment, as there is evidence that it improves survival rates.<sup>22</sup>

- 4.10. A special case is carcinoma-in-situ (CIS) of the bladder. In this condition malignant cells are confined to the innermost layer of the bladder lining. Carcinoma-in-situ in some areas of the body is a relatively benign disease which progresses only slowly to true cancer, or may never do so. In the bladder, CIS is more dangerous and can progress to deeply invasive “aggressive” disease in a matter of months. The definitive treatment is cystectomy, but some patients are managed by instilling BCG (as used to inoculate against tuberculosis) into the bladder to stimulate an immune response which kills the malignant cells.
- 4.11. When the patient cannot be cured by surgery (or radiotherapy), systemic chemotherapy can produce temporary remission, but cannot cure.

### **Squamous cell carcinoma**

- 4.1. The prognosis of these rare tumours is generally worse than that of TCC, as many tumours are at an advanced stage at presentation.

### **General comments**

- 4.2. Prognosis after first tumour treatment may be improved by the use of photodynamic agents to better delineate tumours, and by increased use of chemotherapeutic agents instilled into the bladder at the time of first resection.
- 4.3. The use of systemic chemotherapeutic agents at the time of radical surgery may improve survival in invasive disease.
- 4.4. Treatment of advanced disease not curable by surgery may be improved by better systemic chemotherapy.
- 4.5. None of these strategies is likely to have a marked effect on prognosis in the near future.

## 5. Summary

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- 5.1. Cancer of the bladder is chiefly a disease of the 6<sup>th</sup> and 7<sup>th</sup> decades of life.
- 5.2. Most, perhaps virtually all, bladder cancers are caused by exposure to environmental carcinogens. The most important of these is cigarette smoke. Others include known and suspected occupational carcinogens. The latency period between exposure and presentation with a tumour is usually 15 to 20 years.
- 5.3. There is no recognised link between military service *per se* and bladder cancer.
- 5.4. The prognosis is closely related to the stage and grade of the tumour.
- 5.5. Most patients (70%) present with superficial disease which generally has a good prognosis, despite a tendency to recurrence.
- 5.6. Patients who present with invasive disease, or those who develop it during follow up of superficial disease, have a 5-year survival rate of around 60% at best and in some cases as low as 18%, despite radical surgery.
- 5.7. When surgery fails to cure, chemotherapy is only palliative.

## **6. Related Synopses**

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Cancer of the Kidney  
Cancer of the Prostate

## 7. Glossary

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carcinogen(s)	A substance known to cause cancer.
endoscopic transurethral resection	An operation carried out by passing an instrument through the urinary passage into the bladder and removing tissue under vision.
invasive	In this context, a tumour which has spread beyond the mucosa into the muscle of the bladder wall.
metastasis	A secondary tumour developing at a distance from the primary one, usually having spread by the blood stream or lymphatic system.
mucosa	The inner part of the bladder lining, as opposed to the muscular layer. It consists of the urothelium and underlying tissue, which separates the urothelium from the muscular layer of the bladder wall.
palliative	Treatment that can relieve symptoms but does not provide a cure.
poorly differentiated	Composed of cells which bear little or no resemblance to the normal cells of the parent tissue.
schistosomiasis	A parasitic disease acquired by transmission through the skin from infected water. The urinary form is widespread in the Middle East and in Sub-Saharan Africa.
stage and grade	Tumours are staged and graded according to an international system (the TNM system. <sup>23</sup> ). Stage relates to the degree of spread of a tumour; grade to the appearance of the cells.
superficial	In this context, a tumour which has not spread beyond the mucosa of the bladder.
ureters	The two tubes, one from each kidney, which drain urine from the kidneys into the bladder.
urinary catheter	A hollow tube of latex or silicone rubber, which is inserted into the bladder through the urinary passage, to keep the bladder empty of urine. It is retained in the bladder by a small balloon, which is inflated after insertion.

urothelium

The innermost layer of cells of the bladder lining.

well differentiated

Composed of cells which are similar to those of the parent tissue.

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