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Successes and Failures of Evidence  
Based Urology

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Thesis submitted for the degree of  
DSc in Medicine  
to the University of Glasgow in 2005

Volume I

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To my wife Helena Mary Boyle and my children Helen Boyle, Kathleen Boyle and Eileen Boyle whose love, patience and understanding have largely contributed to making this and all my life's work possible and meaningful.

*La grandeur d'un métier c'est d'unir les hommes*  
Antoine de Saint-Exupéry

*I belong to Glasgow*

Will Fyfe

## Abstract

I have conceived, undertaken and published a body of work in Urology which has applied an evidence-based approach to different aspects with widely varying success in modifying the impact on treatment choices and outcome.

On the positive side, the research work I have led has demonstrated that the era when death statistics could be used to the occurrence of benign prostatic hyperplasia was gone and that we had moved to an epoch where symptomatic disease and quality of life were the key issues [1-3]. I have worked on the creation of the questionnaire-based approach necessary for evaluating the presence of various urological conditions for use in different populations clearly identified [4-7] and quantified the extent and inter-relationships between the various benign urological conditions in communities [8-21]. This work has made it quite clear that such benign conditions as benign prostatic hyperplasia, erectile dysfunction, incontinence, prostatitis and cystitis are remarkably common conditions world-wide in ageing populations.

Since 1990, treatment options for men with symptomatic BPH have moved from an essentially surgical approach to an increasing introduction of pharmacologic options and less invasive approaches to disease management. The meta-analysis of the Phase III clinical trials of finasteride which I undertook, demonstrated that this drug was effective only in men with enlarged prostates [22] and justified the biological approach taken in the development of this drug which was an inhibitor of 5-alpha reductase, the enzyme which converts Testosterone (T) to Dihydrotestosterone (DHT) the metabolite which made the prostate hyperplastic. I then demonstrated that serum PSA was a good indicator of prostate volume [23] thus making identification of men who would most likely respond to this drug easily identifiable [23, 24]. Using this same dataset, I was able to demonstrate that finasteride reduced the risk of Acute Urinary Retention (AUR) [25-26] and that it was superior to alpha-blockers, the other major class of drugs used to treat

symptomatic BPH, in this regard [27]. I designed the phase III trials of dutasteride, a new five-alpha reductase inhibitor, and the findings lay on the regression line demonstrated in the meta-analysis of finasteride [28] and also had the identical effect on reducing the risk of AUR. Finasteride and Doxazosin, an alpha-blocker, act separately in reducing symptoms of benign prostatic hyperplasia [30] and also AUR. I was able to develop a method of predicting individual risk of AUR in men who were diagnosed with benign prostatic hyperplasia [31].

In addition, I was able to demonstrate that (the alpha-blocker) terasozin was effective in reducing the symptoms of BPH and also to increasing peak urinary flow rate and that it appeared equally effective at all doses tried [33]. Permixon, a drug comprising an extract of *seronoa repens*, has also been widely employed in the treatment of symptomatic men and I was able to demonstrate that this was effective [34] and subsequently that it also significantly reduced the symptoms scores [35]. More recently, I was able to demonstrate in a meta-analysis the efficacy of Trans Urethral Needle Ablation (TUNA) therapy in reducing symptoms in men with severe symptoms and that this treatment appears to be equally effective as those obtained by trans-urethral prostatectomy in similar groups of patients [36].

Overall, these findings have influenced clinical practice in benign prostatic hyperplasia in helping clarify what is the right treatment for a particular patient and this is reflected currently in international treatment guidelines [32].

I was able to demonstrate that in the Dialysis Registry of the *Regione Lombardia* in Italy that those patients who had been receiving renal replacement therapy, essentially renal dialysis, had an increased risk of certain specific types of cancer [38]. In a certain sense, I used this as a pilot study and we were able to undertake a pooled analysis of the world's three leading Dialysis Registries, involving over 900,000 patients, dialysed but not

transplanted, followed up for cancer. There is a clear association with an increased risk of certain types of cancer [38-39] and also specific associations with certain types of renal disease underlying the reason for dialysis [40]. These results, which involved such a large proportion of the world experience with renal dialysis, cannot be repeated for many years and clearly demonstrates the need for a re-think regarding the associations and mechanisms thought to be specific between recipients of renal grafts and risk of certain cancers.

Looking at all the incidence and mortality data available world-wide, the importance of urological cancers as a Public Health issue is clear: such cancers account for over a quarter of all cancer in men [41]. Testicular cancer was once almost uniformly fatal but a new and highly effective treatment schedule, evolved around cis-platin, was presented around the mid-1970's. Following that, the effect could be seen at a national level where, in Scotland, while the incidence continued to rise the mortality rate was clearly falling quickly by the mid-1980s [42]. Fortunately, this was the case in all countries where data were available with the notable exceptions of those countries of Central and Eastern Europe, which at the time were members of the COMECON [43-44]. However, when a specialist, well funded central treatment facility was established in Bratislava (Slovakia) in 1983, the subsequent impact on mortality was remarkable even although incidence continued to rise [45]. The most rapid economic change took place in the former German Democratic Republic (*East Germany*) and the fall in testicular cancer mortality was almost immediate [46]. It is now clear that mortality from testicular cancer is declining while incidence is rising [48] although the rate of decline is less in countries of central and eastern Europe [47]. Eradicating testicular cancer as a cause of death should prove possible within our current knowledge: it is not a matter requiring successful research merely an economic and logistic issue [49].

I published 20 years ago that there was little change taking place in time trends of prostate cancer world-wide [50] although a rising incidence rate was apparent by the early 1990s [51] and mortality was not increasing [52]. At the same time, little is known about the aetiology of prostate cancer [53-54] despite high-quality and quite innovative aetiological studies [55-66].

This is a very disappointing situation and has contributed to the desire and the rush to find effective ways of finding the disease earlier when outcome appears to be much improved [67]. I analysed data from the Tyrol Screening Study which clearly demonstrated that the mortality from prostate cancer declined following the introduction of a free-screening programme with PSA. This result was consistent with the hypothesis that a PSA screening programme, with a high uptake by the community and careful quality control, conducted in an area where all men had free access to high-quality diagnostics, urology and medical oncology could successfully reduce the mortality from prostate cancer [68-70]. Unfortunately, many men are being urged to have a PSA measured in areas where these circumstances do not apply. The overall net effect could well be a slight reduction in mortality offset by a large loss of quality-of-life in the community [71].

This evidence-based approach I have managed to create and undertake has resulted in major modifications to clinical practice in benign prostatic hyperplasia and this is represented in international treatment guidelines. Unfortunately, the decline in mortality from testicular cancer in Central and Eastern Europe is slower than I would have hoped and PSA screening for prostate cancer has become extremely prevalent among men without any secure data being available regarding its efficacy and in the absence of any widespread population-based evaluation of such screening strategy.

## Acknowledgements

What I describe below are a series of contributions to Urology in which I was the driving force. I persuaded several pharmaceutical companies, notably *Merck, Abbott, Pierre Fabre* and *Medtronic*, to release original data to me for the various meta-analyses described and also for the pooled analysis the long-term data regarding Acute Urinary Retention. *GlaxoWellcome* also released to me the data from the clinical trials of *dutasteride* for analysis and the development of the AUR Predictive model. I was responsible for the Urological Survey undertaken in France and the *UrEpiK* study which provided major insights into the epidemiology of benign urological diseases worldwide. I extracted the data from various databases for the analysis of incidence and mortality time trends. I was integrally involved in the design of the Australian Aetiological Study of Prostate Cancer and I am responsible for all epidemiological aspects of the Tyrol Screening Study.

Louis Denis, Fritz Schroeder, John McConnell and Pat Walsh have been outstanding role models to encourage my interest in Urology. It has been stimulating working with so many urologists and I must mention the considerable impact of the thinking of Claus Roehrborn (Dallas, United States), Paul Perrin (Lyon, France) but particularly Georg Bartsch (Innsbruck, Austria). Adolphe Steg has been a great friend and source of good counsel for many years. Chris Robertson has been an outstanding statistician to work with on many of these studies.

However, the idea to undertake the great majority of what is described below and the responsibility for the interpretation of the data and their publication, are my personal responsibility and contribution.

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## **1. Introduction**

1. Benign Urological conditions such as Benign Prostatic Hyperplasia, Urinary Incontinence and Erectile Dysfunction are very common and affect large numbers of the ageing population. Although they are benign in the sense that they do not pose an increased risk of death, these conditions can frequently be malignant in terms of their impact of quality of life. Urological Cancers are also very common and constitute a large proportion of the global cancer burden.
2. The past decade has seen enormous progress made in the quality of research in Urology. The introduction of an *evidence-based approach* has proved to be enormously successful in certain areas, notably in men with symptomatic Benign Prostatic Hyperplasia in identifying the right patient for the right treatment. However, there have been certain notable failures in other domains such as Testicular Cancer and Prostate Cancer, particularly Prostate Cancer Screening.
3. In this thesis, I will outline my contribution in several of these areas, some of which could be considered successful in terms of changing clinical practice and in other areas where the approach has identified a situation where no positive change has taken place.

## **2. Benign Prostatic Hyperplasia Epidemiology**

4. Urinary difficulties have presented problems to elderly men and their physicians dating back to antiquity. Despite its long history, BPH was not identified as a disease entity until the nineteenth century and it was only during the present century that effective treatment became available. Furthermore, only in the last decade has information regarding its epidemiology and natural history become available. This

information came originally from autopsy series and surgical series and it is only recently that better quality data have become available.

5. Benign Prostatic Hyperplasia (BPH) describes a proliferative process of both stromal and epithelial elements of the prostate which is characterised by progressive enlargement of the prostate gland which results in obstruction of the flow of urine from the bladder. The clinical manifestations commonly attributed to BPH include lower urinary tract symptoms, detrusor instability, incomplete bladder emptying, urinary retention and urinary tract infection.
6. Today it is common for men and women to live beyond 50 years but this is a common phenomenon only of this current century: research tells us that adaptation can take many centuries. With the twentieth century has come a wide range of diseases of affluence and aging, including appendicitis, myocardial infarction, osteoporosis and a range of urological disorders including cancers and a number of benign diseases notably Lower Urinary Tract Symptoms (LUTS) (frequently referred to as Benign Prostatic Hyperplasia (BPH)), Male Erectile Dysfunction (MED) and Urinary Incontinence (UI). Prior to age 40 these urological conditions are relatively uncommon but the prevalence rises such that the majority of men over 70 years of age may suffer from at least one of them and a large proportion of women. One hundred years ago this was of little consequence in Public Health terms, but today life expectancy approaches 80 years in the most developed countries. Urological cancers constitute over one-cancer in four in men and cause a large number of deaths world-wide each year. While most other urological conditions do not kill, they are major contributors to a reduced quality-of-life and the consequent psychological sequelae of many ageing people: although *benign* in nature, they are frequently *malignant* in terms of their impact on quality-of-life.

## 2.1 *BPH Epidemiology circa 1990*

7. A review I made of all the published epidemiological literature on Benign Prostatic Hyperplasia, published in 1991, came to some clear conclusions regarding the current situation and how to proceed [1]. The evidence base available was poor and fragmented and required strengthening. The estimates of occurrence were most frequently based on anecdote and, where quantified, based on autopsy series and death statistics. Virtually nothing was known about the aetiological determinants of BPH and all the available *evidence* was anecdotal. It was clear that both the Descriptive Epidemiology and the Analytical Epidemiology required to be strengthened since little was known to provide estimates of the prevalence of the condition in communities and prospects for prevention were exceedingly poor in the absence of knowledge of risk determinants.
8. Determination of disease frequency, the first step towards geographical and temporal comparisons, relies on a definition (or at least on a working epidemiological definition whose sensitivity and specificity are known) of the disease or condition under investigation. This has been a major problem with the common benign urological conditions (LUTS, MED and UI). Male erectile dysfunction shares with the other common urological condition of benign prostatic hyperplasia (BPH) the absence of a unifying definition, whose sensitivity and specificity can be determined.

## 2.2 *Trends in Mortality from Benign Prostatic Hyperplasia*

9. Benign Prostatic Hyperplasia has been a uniquely identified item in classifications of cause of death since early in the 20<sup>th</sup> century. Mortality data by cause are routinely available for many countries since 1950 in the World Health Organisation Mortality Database and this was used to examine BPH. The mortality rate from BPH has been declining

appreciably in most developed countries [2]. In the period 1950-1954, the highest mortality rate from BPH was 22.9 per 100,000 in Denmark, and 17 of 24 countries had a mortality rate greater than 10 per 100,000. In 1985-89, data available from 61 countries showed that only one (Saint Vincent and the Grenadines) had a mortality rate greater than 10 per 100,000. The decline is most notable in developed western countries such as the United States, Canada, Australia, New Zealand and the countries of western Europe. The death rate has been decreasing more slowly in countries of central and eastern Europe and has stabilized recently. Rates in the former USSR, Byelorussian SSR and Ukrainian SSR, are still very high, but the only data available are for recent time periods, which exclude the examination of secular trends. High death rates are still observed in countries of South America and in a cluster of countries around the Caribbean with high mortality rates. Although the numbers of cases in many of these countries are small, the rates appear to have stabilized over time. For example, the death rates are still high in Trinidad at 6.8 per 100,000 based on an average of 29 deaths per annum.

10. In the United States, the age-adjusted mortality rate fell from 7.5 per 100,000 in 1950-54 to 0.3 per 100,000 in 1985-89. The age-adjusted relative risk of death in 1987 was only 6% of that in 1957. The largest declines have taken place in the older age groups. In absolute terms, this represents a decline from an average of 6,261 deaths per annum in the period 1950-54 to 470 deaths per annum in 1985-89, a saving of at least 5,791 lives each year. In the United Kingdom, the age-adjusted mortality rate fell from 16.5 to 1.2 per 100,000 during these time periods. The age-adjusted relative risk of death in 1987 was only 9% that in 1957. The largest declines have taken place in the older age groups. In absolute terms, this represents a decline from an average of 5,027 deaths to 591 deaths per annum, a saving of at least 4,436 lives each year.

11. These estimates make no allowance for the increased number of men in these oldest age groups in 1990, which would further increase the magnitude of the decline. A better estimate of the number of deaths prevented can be obtained by applying age-specific rates from the 1950s to 1990 populations. The expected age-specific rates for each country were calculated using the earliest five years of data available, generally 1950 to 1954, which were applied to the population of 1990. The expected number of deaths for each country was then compared to the number of deaths observed. In the U.S., 449 deaths were observed in 1990. This compares to 14,130 expected deaths had the mortality rates of 1950-1954 been applied and means 13,681 deaths were prevented in that single year. Similar high numbers of prevented deaths were found for the Federal Republic of Germany, United Kingdom, and Italy.
12. During the period 1957 to 1987, the age-adjusted mortality rate did not increase in any country. In Japan, the age-adjusted rate prior to 1969 was 1.2 per 100,000 per annum, increasing to 1.9 in 1965-69 before falling to 0.4 per 100,000 in 1985-89. In absolute terms, this represents a slight increase from 260 to 269 deaths per annum in this time period. In central and eastern Europe, rates have changed slowly but remain high, as do mortality rates in South America. However, countries in North America, western and northern Europe, and the Caucasian populations of Australasia have experienced falls in the mortality rate from BPH greater than an order of magnitude over this 30-year period.
13. Today BPH can no longer be considered as a potentially fatal disease and focus has passed on to thinking about symptom alleviation and quality-of-life. The invention of the Hopkin's lens and the development of the resectoscope has made Trans-Urethral Prostatectomy (TURP) a safe and widely used surgical intervention.

Other invasive treatment modalities exist ranging from open surgery through balloon dilatation through a variety of heat and laser treatments. In the past 10-15 years there have been major developments in a pharmacological approach to the treatment of BPH symptoms. Although this has not been without controversy, this has become by far the most popular initial choice for truly bothered patients either in the form of alpha adrenergic receptor blocking agents such as doxazosin, tamsulosin or terazosin, or the 5-alpha reductase inhibitors, finasteride and dutasteride.

14. These trends have been confirmed by an up-dated analysis [3] and confirm that this decline in mortality is real and reflects a true triumph for many aspects of modern medicine notably in that modern anaesthesia means that more men can be operated safely and that there is better control of infection in the post-op period. Further progress in deriving better estimates of the impact of BPH in a population will require to come from the development of Symptom Scores to allow the disease to be identified in an individual and information about a population subsequently derived. Benign Prostatic Hyperplasia is no longer a fatal condition.

### 2.3 *Symptom Score Use in Different Populations*

15. The majority of progress in understanding the epidemiology of benign urological conditions has resulted from the development of symptom scores which can estimate the burden of symptoms of a condition. The *International Prostatic Symptom Score (I-PSS)* is the accepted international gold-standard for BPH symptoms: this is based strongly on the *American Urological Association Symptom Index* derived by Michael Barry. This gold standard was able to be established consequent to the development of a methodology for conducting linguistic and cultural translations of the I-PSS into different languages

[4]. This methodology has been applied to the I-PSS in several countries [5] and has also been employed in the translation of other questionnaires [6].

16. The I-PSS was translated into French and then followed a linguistic and cultural validation. The resultant questionnaire was then employed in a large survey of Urinary Tract Symptoms in a representative sample of the French population. The findings from that survey provided the first information about BPH and Lower Urinary Tract Symptoms (LUTS) in France [7-10].

#### 2.4 *Distribution and Prevalence of LUTS worldwide*

17. Using the process established, linguistic and cultural translations of the I-PSS emerged in many languages and enabled comparisons to be made between the prevalence of symptoms in many countries simultaneously, secure that the questions were deriving similar information in each community [11-13].
18. The Fifth report of the *International Consultation on Benign Prostatic Hyperplasia (BPH)* noted *with considerable satisfaction* the improvement in the extent and quality of the knowledge base in the *Epidemiology and Natural History of Benign Prostatic Hyperplasia* [14]. However, with increasingly available data some issues take on a different focus. For example, it is clear that there is a very wide range of reported prevalence data, even within age groups, from international studies of LUTS-BPH prevalence. Before when there were relatively few data, this variation was not so obvious: the delight of the Committee was having some real data. However, this situation is now beginning to be a cause for some concern and there is an overwhelming need to re-evaluate the published information and to begin the process of setting standards for epidemiological studies in this area.

19. With the standardisation of the instruments to collect data, it is easier to make international comparisons and understand the geographical patterns of BPH prevalence. Cultural differences across countries may, in fact, still produce a different impact on the lifestyle, but the use of culturally and linguistically validated questionnaires increased the homogeneity of data. Although hospital-based surveys are very interesting to understand and analyse changes in treatment- and diagnostic-trends, population health surveys are required to estimate the frequency of BPH in the community.
20. Over the five years 1995-1999, studies of urinary symptoms and benign prostatic hyperplasia have been undertaken in a number of countries. Some of the surveys have involved probability samples of entire countries (Canada, France). Some have represented age-stratified random or attempted total enrolment of male residents of communities meeting certain age and eligibility criteria (Olmsted County, Minnesota; a small fishing village in Japan; several communities in the Forth Valley Scotland; Madrid, Spain; Porirua, New Zealand; Kiryat Hayovel, Israel; North West Thames Health Region, England; Copenhagen, Denmark; Rotterdam, Holland; Trondheim, Norway). Some have enrolled samples of men from one or more general practices (Maastricht, Holland; Leicestershire, England). Some have involved hospital clinic populations (Seoul, Korea) or respondents to an advertisement for a prostate screening program (Singapore). Some have involved a number of different sampling methods in several different countries.
21. However, while many of the surveys used linguistically validated versions of the I-PSS, some involved self-administration, some used mail-administration, some used in-person interviews and some used telephone interviews. It is worth noting that scores on the AUA Symptom Index have been shown to be slightly lower when obtained

by in-person or telephone interview, as compared to self-administration.

22. Some investigators have noted difficulties in translating concepts from the English version of the IPSS into certain languages. For example, Pakistani investigators have noted difficulties in translating concepts into Urdu. In some countries it is customary to conduct medical examinations of men waiting together in large groups for the examination. When questionnaires are completed in such settings it is possible that answers could be different from what may be obtained in mail-based or home-based administration. In some cultures it is less common to discuss one's health problems openly than in others. Even in English-speaking populations there seem to be differences in how symptoms are perceived and reported in questionnaires. Finally, as many authors have observed, lower urinary tract symptoms are highly non-specific and can be elevated by factors having nothing to do with prostatic conditions. Such factors include diet, fluid intake, alcohol intake, and anticholinergic effects of commonly used non-prescription medications. For all these reasons it is difficult to draw etiologic conclusions from cross-cultural comparisons of symptoms. Nonetheless, symptom comparisons are useful in describing the patient-perceived problems in this medical area and within-country analyses may help refine methods for the study of urological conditions [14].
23. In considering all the available evidence regarding the Epidemiology and Natural History of Benign Prostatic Hyperplasia, the Committee of the Fifth International Consultation on BPH were able to formulate a number of Recommendations as priority for future research directions. The background and the rationale for these recommendations is explained in the main text of the report [14] These recommendations include (1) *Community-based distributions of LUTS, prostate size and peak uroflow rates by age on each continent should continue to be*

*determined; (2) Community-based occurrence on the concomitance of benign urological conditions such as LUTS, Male Erectile Dysfunction and Urinary Incontinence should be established with priority; (3) Community-based occurrence on the concomitance of benign urological conditions and other chronic conditions such as hypertension and vascular disease should be established; and (4) The epidemiology of doctor-seeking behaviour in men with LUTS should be a matter of priority.*

## 2.5 The UrEpiK Study

24. While great progress has been made on the epidemiology of Benign Prostatic Hyperplasia, the situation with regard to other common, benign urological conditions remains very poor. In order to make advances, a population-based, multi centre study was undertaken and completed in four countries, The Netherlands, France, United Kingdom and Korea, to study the epidemiology of these conditions. This study was a cross-sectional *Survey of Benign Prostatic Hyperplasia, Urinary Incontinence, Prostatitis, Cystitis and Male Erectile Dysfunction in the United Kingdom, France, the Netherlands and Korea* (The **UrEpiK** Study)[15].
  
25. The **UrEpiK** study is a descriptive epidemiological study which involved the recruitment of a random sample of men and their partners, if they had one. The recruitment was carried out in a defined geographical region in one of four international populations. These centres were Boxmeer (the Netherlands), Auxerre (France), West Midlands (United Kingdom) and Seoul (Korea). The main aim of the survey was to obtain population prevalence of Benign Prostatic Hyperplasia (Lower Urinary Tract Symptoms), Urinary Incontinence, Interstitial Cystitis, Prostatitis and Male Erectile Dysfunction in each of the four participating study centres.

26. Once the man had agreed to participate in the study and had given informed consent according to local requirements, a baseline questionnaire was administered. A common questionnaire was employed in each centre. Standard questionnaires, supplemented with extra questions, were employed in this study as far as possible. Furthermore, a series of questions were added to investigate the knowledge and attitudes of the population groups to these urological conditions. In particular, probes were developed to investigate what drives individuals to seek medical advice regarding urinary symptoms and how their behaviour, including social life, is effected by their symptoms.
27. The majority of progress in understanding the epidemiology of benign urological conditions has resulted from the development of symptom scores which can estimate the burden of symptoms of a condition. The International Prostatic Symptom Score (I-PSS) is the accepted international gold-standard for BPH symptoms; O'Leary and colleagues have developed a Sexual Function questionnaire which assesses erectile function; questions from the questionnaire of Nickel and Sorensen for Prostatitis and the Interstitial Cystitis questionnaire of O'Leary were also employed. Urinary Incontinence was assessed using the Questionnaire of Vierhout. Quality of Life was assessed using the SFI 12. These methodological issues were published in more detail just as the study was about to start [15].
28. Two levels of data collection were employed in each centre. The first level was for the collection of basic data through questionnaires and did not require any invasive testing. At the second level a small number of tests were performed on a sub sample of the responders to the first level. This sub-sample of men had a urological examination including a digital rectal examination, trans-abdominal or trans rectal ultrasound and uroflow measurements. They also completed the

urological part of the level 1 questionnaire again. This Level 2 sample permits the validation of some of the information collected by the questionnaire in Level 1. In particular, the sensitivity and specificity of the I-PSS questionnaire, and the sub-scores of irritative and obstructive symptoms, to the diagnosis of (true) benign prostatic hyperplasia could be investigated.

29. This study employed culturally, and linguistically validated versions of standard questionnaires to address the prevalence of the symptoms and the impact on quality of life of the men and their partners. The samples were selected randomly from population registers of men aged 40-79. This provided representative samples in each community [15]. The first level of data collected used postal questionnaires in the European centres and an interviewer in Korea. The second level involved a repetition of part of the questionnaire and a urological examination to a 10% sub sample of the respondents to the first level.

### 2.5.1 BPH/LUTS

30. It is important to start with an analysis of Lower Urinary Tract Symptoms (LUTS) to give some indication of how well the findings from **UrEpiK** correspond with those of other similar surveys. In addition, the epidemiology of lower urinary tract symptoms among men and women has significant unanswered questions concerning prevalence and impact in different populations [16]. One particular issues relates to the impact of such symptoms on quality-of-life.
31. 4969 index men and 3790 women were recruited with response rates among men of 77% in Boxmeer, 21% in Auxerre, 49% in Birmingham and 65% in Seoul. The percentages of men and women with scores on the IPSS of 8-35, indicating the presence of moderate to severe symptoms were, men first, 20.6, 17.9 (Boxmeer); 17.5, 12.5 (Auxerre); 26.5, 22.4 (Birmingham); 16.7, 19.9 (Seoul). Among

women the relationship between symptoms and age is not as steep as compared to men. The percentages of men and women with moderate to severe symptoms were, men first, 11.8, 15.8 (40-49); 20.3, 17.7 (50-59); 31.2, 24.3 (60-69); 41.8, 31.3 (70-79). Among 40-49 year olds the main differences between men and women come from the questions about the frequency of urination during the day and holding back urine. Among the older age groups men reported more symptoms on all questions apart from urination at night and difficulty in holding back urine, both of which were equally prevalent among men and women [17].

32. The overall prevalence of LUTS was significant and showed no marked cultural variation. Prevalence increases with age with severe LUTS commoner in older men. Women report similar levels of the symptoms traditionally associated with LUTS in men further demonstrating the non-specificity of the IPSS. In each age group the frequency of LUTS is similar to men and there are no major cultural differences. There are age differences between men and women: younger men have a lower prevalence than younger women but older men a much higher prevalence than older women. These findings emphasise that the IPSS be confined to within-patient comparisons and not as a diagnostic tool. The IPSS performs very similarly regardless of sex and a more sensitive instrument for use in BPH is required [17].

#### 2.5.2 Lower Urinary Tract Symptoms (LUTS) and Quality of Life

33. It has been hypothesised that as the severity of lower urinary tract symptoms (LUTS) increased, the impact as measured by the BPH Impact Index (BII) would also increase. The UREPIK survey was designed to collect this information from men in four countries: The Netherlands, Korea, France and the United Kingdom. The purpose of

this study was to test this hypothesis and describe to what extent the impact can be explained by LUTS.

34. This is the first study to employ culturally, and linguistically validated versions of standard questionnaires, the BPH Impact Index (BII), the SF-12 and the International Prostate Symptom Score (IPSS), to address the distribution of symptoms and the impact on quality of life of LUTS in men and their partners. A random selection mechanism with the aim of providing representative samples of the male population aged 40-79 in each community was used for recruitment. Regression analyses were undertaken on SF-12, the total BII and IPSS scores.
35. A total of 4800 index men and 3674 women responded to all the questions discussed. BII increased with increasing IPSS score. The correlation coefficients were: Boxmeer 0.65, Auxerre 0.66, Birmingham 0.60, and Seoul 0.66. Among men with an IPSS score of 0-7, the mean (standard deviation) BII score was 0.25 (0.90), 1.8 (2.2) for IPSS 8-19 and 4.5 (2.3) for IPSS 20-35. For women, the correlations were slightly lower except in Birmingham: 0.59 (Boxmeer), 0.48 (Auxerre), 0.71 (Birmingham), 0.57 (Korea). The impact of the symptoms is higher in women than in men with the same level of symptom severity. The mean (SD) BII among women with an IPSS score of 0-7, was 0.48 (1.30), 1.6 (2.7) for IPSS 8-19 and 5.4 (3.4) for IPSS 20-35. Adjusting for symptom severity there is no association between age and bother. Younger men and women with severe to moderate symptoms do not experience more bother with this level of symptoms than older men and women.
36. There was an association between the score on the quality of life question in the IPSS (question 8 in the IPSS) and BII. For men the correlation was 0.63 and for women it was 0.60. The BII scores range

from 0-13 and among men who are delighted or pleased with their urinary condition (scores 1 and 2 on IPSS question 8) the mean (SD) BII score is 0.1 (0.6), for those who are mostly pleased or mixed the score is 1.0 (1.4) while for those who are dissatisfied /unhappy/ terrible the score is 4.5 (2.6). Among their partners the scores are 0.3 (0.9), 1.5 (2.1), 4.5 (3.3), respectively. Men and women with the same level of satisfaction (IPSS question 8) report the same bother. Among those with an IPSS score of 20-35 women express significantly more bother ( $p<0.001$ ). The SF-12 scores decreased as the IPSS and the BII increased in men and women. Furthermore, the SDF-12 mental score decreased with increasing symptom scores in the partner [18].

37. The pattern of the relationship between severity of LUTS and BII is very similar between three European centres and the Far Eastern centre. More evidence is needed to better explain the relationship between symptoms and disease impact in men with LUTS although there is a clear association between the BII and the IPSS Quality of Life question in men and women. The BII discriminates between people who are unhappy about their urinary condition compared to those who are not. Greater attention should be paid to the use of this index in studying the impact of urinary conditions since it appears to be disease specific. Although designed for use in BPH the index also appears to be a useful measure of bother among women. The severity of symptoms of LUTS has an adverse effect on the individual and his/her partner [17].

### 2.5.3 Urinary Incontinence

38. There is little information on the prevalence and quality of life associated with male urinary incontinence (UI). A population-based, multicentre study has been completed in four countries, The Netherlands, France, United Kingdom and Korea, to study the

epidemiology of this condition. This study employs culturally, and linguistically validated versions of standard questionnaires to address the prevalence of the symptoms and the impact on quality of life of the men and their partners. The samples were selected randomly from population registers of men aged 40-79. This provided representative samples in each community.

39. A total of 4969 men and 3790 women responded to these questions. As measured by an incontinence symptom score 11.1% of men aged 40-79 reported mild to severe incontinence. There were no differences over the four centres. Typically the reported incontinence was leaking drops of urine a few times a week. Only in 1.7% of men was there severe and frequent incontinence. By comparison, on a self reported question, 14.3% of men in the UK and Netherlands thought that they had urinary leakage, compared to 7.1% of men in France and Korea. Of men with urinary leakage in the three European centres, 24.3% visited the doctor with this problem, compared to only 9.1% of Korean men. Very few men received treatment for urinary leakage and less than 1% were taking medication. 7.6% of men in the European centres used protective pads at least occasionally compared to only 2% on men in Korea. Incontinence is age related and the reporting of it is also culturally related. 14.7% of men in UK and 13.6% of men in the Netherlands aged 40-49 report some symptoms compared to 5% of men in France and 2% of men in Korea. Among men aged 60-69 the corresponding percentages are 15.6% in the UK, 23.4% in the Netherlands, 10.1% in France and 8.5% in Korea [19].

40. It is clear that urinary incontinence is commoner in older men and is relatively uncommon among younger men. Some men reported no problems on the symptom questionnaire but replied positively to a direct question. A surprisingly high number of men wear protective pads at least occasionally as a result of their incontinence. Urinary

incontinence appears to be a reasonably sized problem in men which remains largely untreated [19].

#### 2.5.4 Association between LUTS and Erectile Dysfunction (ED)

41. Recent small-scale epidemiological studies have suggested an association between benign prostatic hyperplasia (BPH) and sexual dysfunction. Both conditions are strongly associated with age and no study has been able to exclude age as a confounding factor to this relationship. We reported a large-scale multi-national investigation of lower urinary tract symptoms (LUTS) and sexual function that was designed to investigate the independent association between these conditions. The findings have considerable implications for the management of the BPH patient.
42. Culturally, and linguistically validated versions of standard questionnaires were used to estimate the prevalence of LUTS (using the IPSS) and Erectile Dysfunction (using O'Leary's Sexual Function Inventory (SFI)) in regions of the United Kingdom (Birmingham), the Netherlands (Boxmeer), France (Auxerre) and Korea (Seoul). In each centre, stratified random samples were selected from population registers to provide representative samples of the population of men aged 40-79 in each community. Face to face interviews were held in Seoul and postal questionnaires in the three European centres. The samples were selected randomly from population registers of men aged 40-79, providing representative samples in each community.
43. A total of 4800 men and 3674 women responded to these questions. The response rates among men were 77% in Boxmeer, 21% in Auxerre, 42% in Birmingham and 65% in Seoul. The overall prevalence of erectile dysfunction, for men aged 40 to 79, estimated from an ED score of 0 to 4, was 21.1%. There was evidence of a linear

increase with age ( $p < 0.001$ ) and the pattern was very similar in the four centres. From the weighted logistic model, there was evidence of an association between sexual dysfunction, other self-reported diseases and lifestyle. On the basis of the ED score, after adjusting for age and country, men with diabetes were more likely to get a score of 0-4 (OR=1.57, 95%CI=[1.09; 2.25]), so were those with High Blood Pressure (OR=1.38, 95%CI=[1.09; 1.75]) and with an IPSS score of 8-35 (OR=1.39, 95%CI=[1.10; 1.74]). For lifestyle, smokers were more likely to get a score of 0-4 (OR=1.54, 95%CI=[1.23; 1.92]), while physical activity during leisure time was slightly associated with a reduction in the odds of having a score of 0-4 (OR=0.87, 95%CI=[0.77; 0.99]). The analysis was repeated using self-reported ED instead of the dichotomised score and the same results were obtained [20].

44. Erectile dysfunction is clearly age related and a problem for a large proportion of men in the community. It can have a profound impact on the quality of life of the man and on his partner. Were all men with this problem to seek medical help there would be a large burden on the health care systems. There are cultural and age effects on the assessment of this problem [20].
45. To help confirm this finding, a large-scale, community-based, multi-national investigation of lower urinary tract symptoms (LUTS) and sexual function, designed specifically to investigate the independent association between these conditions, has been analysed and is reported [21]. The findings have considerable implications for the management of the BPH patient.
46. Detailed questionnaires were sent by mail to men aged 50-80 years in 7 countries (France, Germany, Italy, Netherlands, Spain, United Kingdom and USA). The sample in each country was representative of

the target population in terms of age and social characteristics. LUTS and sexual function were assessed by validated symptoms scales including the International Prostate Symptom Score (IPSS), the Danish Prostate Symptom Score (Dan-PSS), and the International Index of Erectile Function (IIEF). Subjects also completed a Health and Demographic Questionnaire, including presence of co-morbid medical conditions, medication use, smoking and alcohol consumption.

47. 12,815 questionnaires (a response rate of 36.7%) were evaluable and included in the analysis. 90% of men had LUTS (6% as severe, 25% as moderate, and 59% as mild) and only 11% were treated medically. Sexual activity was reported by 83% of the sample, with 71% reporting at least one episode of sexual intercourse in the previous 4 weeks. Frequency of sexual activity decreased with age, but was strongly associated with the presence and severity of LUTS. Erectile function and sexual activity were both independently associated with the presence of LUTS, independent of age and significant co-morbidities (diabetes, hypertension, hyperlipidaemia, heart disease and tobacco consumption). There was also a striking (independent) association between abnormal ejaculation and its bothersomeness with severity of LUTS. Men reporting mild LUTS (IPSS<8) had an odds ratio of 0.26 (95% confidence interval (0.21, 0.33)) compared to men reporting severe LUTS. The results were consistent from one country to another and there was every indication that this association was a general male problem and not one limited to a selected number of different cultures.
48. In this large-scale, multi-national study of LUTS and sexual function, as anticipated, a high prevalence of both LUTS and sexual problems was observed particularly in older men. These ejaculatory and erectile dysfunctions were strongly related to the severity of LUTS and were independent of age and other co-morbidities. There are two

conclusions from this study that have great clinical significance. Firstly, there is a need to investigate the joint aetiology of LUTS and sexual problems, especially ejaculation abnormalities [21]. Secondly, it is important that clinicians pay more attention to baseline sexual function and/or dysfunction in the initial evaluation, the choice of treatment and follow-up of men with LUTS.

#### 2.5.5 Urinary diseases in households

49. In the **UrEpiK** study, obtaining information on the symptoms of several different benign urological conditions allows for the first time estimates to be obtained regarding the overall burden of such conditions on the general population.
50. A total of 4800 men and 3674 women responded, providing information on 3474 couples. Among men aged 40-79, 20.3% report moderate to severe symptoms of LUTS, 10.2% report some urinary leakage and 21.1% report severe problems with ED. In their partners, 18.6% report moderate to severe symptoms of LUTS, 33.6% report some urinary leakage and 20.0% report some problems with Cystitis.
51. The percentage of men with no urinary problems decrease with age. 80% of men aged 40-49 report no problems compared to 20% of men aged 70-79. The decrease in women with age is much less: 60% of women partners aged <49 report no problems compared to 45% of women aged 70-79.
52. The prevalence of these symptoms increase with age. Among households where the man is 40-49, 51.9% report no symptoms, while both partners report at least one symptom in 10.6% of households. Among households where the man is 60-69 only 25.4% do not have any problems and in 27.7% both partners have at least one problem.

Among households where the man is 70-79, only 12.5% do not have any problems and in 38.5% both partners have at least one problem [16].

53. The **UrEpiK** study has clearly demonstrated the magnitude of the problem and the impact of benign urological diseases in the general population. The burden of benign urological diseases on couples is clearly demonstrated. Where the man is aged 70-79, seven out of eight couples report the symptoms of at least one benign urological condition [16]. As it is well accepted that these diseases interfere with the quality of life of the couple, the impact may be considerable.

### **3 Benign Prostatic Hyperplasia Treatments**

#### *3.1 Meta-Analysis of BPH Treatments*

54. There is little doubt that true Benign Prostatic Hyperplasia (BPH) in men is androgen dependent. Dihydrotestosterone (DHT) is the active metabolite of Testosterone (T) which is responsible for prostate growth: 5 $\alpha$ -reductase is the enzyme which converts testosterone to the active dihydrotestosterone. Furthermore, stromal 5 $\alpha$ -reductase activity is elevated in the hyperplastic human prostate. For reasons such as these *finasteride* was developed and introduced in the treatment of symptomatic benign prostatic hyperplasia in men.
55. In clinical studies, finasteride has been shown to reduce the volume of the prostate and to reduce the urinary symptoms in men labeled with this condition. The safety and efficacy profile of finasteride has been demonstrated in men with symptomatic BPH in one six-month, two twelve-month and one 24 month double-blind, placebo controlled trials. In all four studies finasteride produced significant improvements

in symptoms, maximum urinary flow rate and prostate volume compared to the placebo treated patients.

56. *Finasteride* is a 4-azosteroidal inhibitor of human  $5\alpha$ -reductase. Inhibition of  $5\alpha$ -reductase results in a decrease in plasma and prostatic dihydrotestosterone (DHT) levels. Men with an inherited deficiency in the  $5\alpha$ -reductase enzyme provide a human model for studying the effects of inhibiting this enzyme. Men with the disorder are born with ambiguous genitalia; otherwise their early growth and development are normal. Of particular interest was the observation that although these subjects virilize substantially at puberty, they have scant facial hair, no temporal hair loss, no acne and an undeveloped prostate gland. Women with the  $5\alpha$ -reductase deficiency are completely normal which suggested that this enzyme is necessary only for the normal development of the male external genitalia and primary and secondary sexual characteristics and does not have any more general biologic function.

57. Testosterone (T) is secreted by the testes and adrenal glands and is metabolized peripherally primarily in the liver, skin and prostate by the enzyme  $5\alpha$ -reductase to the potent androgen DHT. Finasteride has been demonstrated *in vitro* to be a pure  $5\alpha$ -reductase inhibitor which does not compete with DHT for the androgen receptor. DHT is strongly bound to the androgen receptor. In rat and human prostatic tissue, inhibition of  $5\alpha$ -reductase by finasteride was demonstrated while binding of DHT to the androgen receptor is not affected. Studies in the rat treated with finasteride demonstrated no progestational, gonadotropin inhibitory, androgenic estrogenic or anti-estrogenic effects. In intact rats and dogs, the only important effect produced by finasteride was a reduction in prostate size.

58. Not all men respond to finasteride and there are apparent discrepancies in the responses found in the available randomised trials involving finasteride use. It was not clear whether any baseline characteristics of the disease in individual men could indicate the outcome of finasteride therapy. With data available from six, placebo-controlled clinical trials involving two thousand six hundred men with BPH treated with finasteride (at 5 mg for one year) or placebo it seemed appropriate to examine whether there are any variables which could predict the outcome of finasteride treatment and to indicate which men should be candidates for finasteride therapy and which men are unlikely to respond to finasteride and who may be better suited to another therapeutic approach from the outset.

### 3.1.1 Meta-Analysis of Finasteride

59. Six randomized clinical trials were available comparing one year of 5mg finasteride and placebo for treating clinical benign prostatic hyperplasia (BPH). Findings had been published from four studies and data from the remaining two incomplete and unpublished studies were given to the author thereby avoiding the potential phenomenon of publication bias. The findings for the 2601 men in these trials provide an opportunity to investigate the heterogeneity of the effects seen in the individual studies and to identify pre-treatment predictors of outcome as expressed by prostate volume, symptoms, or peak urinary flow rates. Identifying these predictors is important and meta-analysis is useful because of the increased range of baseline values: for example, the mean prostate volume ranged from 32 cc to 60 cc in the six studies.

60. A formal meta-analysis using an Empirical Bayes approach, employed data from all finasteride Phase III trials in North America and Internationally, the Canadian, Early Intervention, and SCARP trials, and

the VA cooperative study comparing terazosin and finasteride in combination. A pooled analysis was also undertaken on the combined dataset. The statistical analysis is based on Empirical Bayes principles. Full details are included in the publication [22].

61. There were consistent effects across all six trials for finasteride and improvements in peak urinary flow rate, prostate volume and total symptom score among men with similar prostate volumes at baseline. Flow rate and symptom score change differed little between finasteride and placebo among men without enlarged prostates at baseline: symptom and flow rate improvement became more pronounced with increasing initial prostate volume. Baseline prostate volume is a key predictor of treatment outcome: approximately eighty per cent of the variation in the treatment effect could be attributed to differences in mean prostate volume between studies. Variations in entry criteria, associated with the lack of any uniform definition of BPH, resulted in large differences in baseline prostate volume and, consequently, apparent inconsistencies in the overall outcome of the trials [22].
  
62. It can be concluded based on this analysis [22], that there is a material effect of one year of finasteride therapy on reducing prostate size, on increasing maximum urinary flow rate, on reducing total symptom score and on reducing the quasi-AUA symptom index which is consistent across the six randomized trials. Men who received finasteride for one year in these trials had smaller prostates after one year's treatment than controls, had increased flow rates compared to controls and had lower symptom scores than controls. Not much difference in maximum urinary flow rate change between finasteride and placebo can be expected in men without enlarged prostates but that improvement in maximum urinary flow rate on finasteride becomes more pronounced with increasing prostate volume. A similar

situation was found with other treatment outcome measures such as total symptom score and quasi-AUA index [22].

63. Much of the apparent discrepancies observed between the outcome in the different trials can be ascribed to the role of chance given the major differences in the distribution of prostate volume between the trials conducted [22]. It seems reasonable on physiological grounds that larger prostates respond in a stronger manner to finasteride therapy than do the smaller prostates since these are the glands which are most likely to have true histological hyperplasia. In all these trials the diagnosis of BPH is made on clinical grounds and there have been no biological specimens removed for confirmatory histological confirmation.
64. In the light of these findings it appears to be important and timely to reconsider the terminology employed in the study of Benign Prostate Hyperplasia in order to seek better definitions of specific diseases and conditions. The overall umbrella condition is Lower Urinary Tract Dysfunction (LUTD) which leads through some or other mechanism to the development of a wide range of urinary symptoms, detrusor dysfunction, incomplete emptying of the bladder, pressure flow disturbances, urinary tract infections, urinary obstruction, urinary retention and haematuria. It is increasingly evident that true Benign Prostatic Hyperplasia is only one of the conditions included in this overall category and that a better, and more precise, definition of this condition, paying attention to the importance of prostate enlargement, could provide a clearer basis for indications for therapy for men with urinary problems.
65. This meta-analysis and pooled analysis of all available randomised trials of finasteride has subsequently changed treatment practices world-wide (the manufacturers (Merck) changed their label to exclude

small prostates) and has led to revisions in the terminology used to classify lower urinary tract symptoms in men. It has become one of the most cited publications in Benign Prostatic Hyperplasia [22].

### 3.1.2 Relationship between prostate volume and serum prostate specific antigen (PSA) in men without evidence for prostate cancer

66. Having demonstrated that prostate volume is a necessary indicator when choosing the correct treatment for a man with lower urinary tract symptoms (LUTS), practical considerations need to be addressed. From the trials available, the prostate volume had been measured by MRI which is expensive, time consuming and may lead to lack of patient compliance. The alternative, the transrectal ultrasound, is quite unpleasant to a lot of men and the results can be sometimes misleading (depending on the shape and orientation of the prostate). An accurate, acceptable and simple method to estimate prostate volume would be a great advantage.
67. It is well established that prostate size increases with advancing age. Cross-sectional data are available from autopsy studies, population based studies and clinical studies in men with benign prostatic hyperplasia (BPH) to demonstrate this relationship. In addition, longitudinal studies of prostate growth in population based studies have demonstrated a yearly growth of 0.7 to 1.5 ml/year over four years.
68. A relationship between age and serum prostate specific antigen (PSA) has also been established. This relationship forms the scientific basis for the development of the age specific reference ranges for serum PSA recommended in screening men for prostate cancer. In a detailed analysis of the baseline information on men with no evidence for prostate cancer by DRE enrolled into either studies of BPH (age 40

and above) or alopecia (age 20-60) a strong log-log linear relationship between serum PSA and prostate volume was identified [23]. This relationship allows physician to estimate with sufficient accuracy prostate volume without having to resort to TRUS measurement prior to initiating therapies for BPH for which the ultimate outcome is dependent on baseline prostate volume as is the case for finasteride.

### 3.1.3 Serum prostate-specific antigen and long-term changes in symptoms and flow rate

69. Having demonstrated a relationship between prostate volume and response to therapy in men with BPH [22] and between prostate volume and serum levels of Prostate Specific Antigen (PSA) [23], it became obvious to investigate the association between serum PSA and response to treatment. This was done in the four-year PLESS trial [24] and the aim was to determine whether baseline prostate-specific antigen (PSA), in addition to prostate volume, is associated with long-term changes in symptoms and urinary flow rate.
70. Three thousand and forty men with benign prostatic hyperplasia enrolled in the PLESS trial were randomly assigned to finasteride 5 mg or placebo for 4 years. Symptoms and flow rate were assessed every 4 months, and data were analyzed by dividing the patients into three groups by baseline PSA tertiles (0 to 1.3, 1.4 to 3.2, and 3.3 ng/mL or greater) and baseline prostate volume tertiles (14 to 41, 42 to 57, and 58 to 150 mL).
71. After the initial placebo effect, a slow deterioration in symptoms over time was observed in the placebo-treated men with a baseline PSA 1.4 ng/mL or greater. However, placebo-treated men in the lowest PSA tertile (less than 1.4 ng/mL) had sustained symptomatic improvement that was not seen in placebo-treated men in the higher tertiles ( $P < 0.001$ ). In all finasteride-treated groups, there was initial

improvement followed by maintenance or continued symptom improvement over time (approximately 3 to 3.5 points by the end of 4 years). The differences in symptom score improvement between placebo and finasteride were marginal for men with baseline PSA levels less than 1.4 ng/mL ( $P = 0.128$ ) but were highly significant for men with PSA levels 1.4 ng/mL or greater ( $P < 0.001$ ). Urinary flow rate results were similar to those observed for symptoms. Analysis of symptom and flow rate data by prostate volume tertiles in a 10% subset of men yielded similar results, namely a deterioration of symptoms and flow rate in the two higher tertiles treated with placebo (greater than 41 mL) and a sustained improvement in all three groups of finasteride-treated patients.

72. Baseline PSA and prostate volume are good predictors of long-term symptomatic and flow rate changes. Baseline PSA levels of 1.4 ng/mL or greater and enlarged prostate glands predict the best long-term response to finasteride compared with placebo [24]. The use of PSA in determining men with LUTS suitable for finasteride therapy is apparent.

#### 3.1.4 Acute Urinary Retention

73. Acute urinary retention is an unpleasant, painful experience which requires immediate medical, and frequently surgical intervention. Population studies reveal that acute urinary retention is a common event: a 60 year-old man who survives a further 20 years has a 23 per cent probability of experiencing an acute episode of urinary retention. About half of acute retention episodes appear to be linked to general anaesthesia and a further large proportion due to the natural history of benign prostatic hyperplasia.

### 3.1.5 Acute Urinary Retention –Epidemiology

74. The risk of acute urinary retention increases with increasing age. There are a number of other risk factors with risk increased in men with moderate and severe urinary symptoms, low peak urinary flow rates (less than 12 ml/sec) and among men with large prostates [25]. When simultaneous correction was made using logistic regression, baseline age, AUA Symptom Index. (I-PSS), initial peak flow rate and were independent predictors of outcome. Prostate volume could not be entered into the model due to the small numbers of subjects, but in an unadjusted analysis, the relative risk of acute urinary retention among men with prostates greater than 30 ml (on ultrasound) was 3.0 compared to the referent group (less than 30 ml). This probably covers all enlarged prostates as determined by the digital rectal examination, and over half of all patients being treated from BPH [25].
75. Thus, given that finasteride has a positive effect on three of the four risk factors for acute urinary retention (reduces symptoms, increases flow rate, reduces prostate volume) it could be expected that long-term finasteride use would lead to a reduction in AUR.

#### 3.1.5.1 Long-term Outcomes of Finasteride therapy in men with BPH

76. Reduction of urinary symptoms and improvement in urinary flow rate are the immediate short-term goals of therapy for benign prostatic hyperplasia. However, it is widely accepted that BPH is a progressive disease and it has frequently been of interest as to whether treatment for symptoms could lead to a reduction in prostate surgery and acute urinary retention, the more serious end-points of BPH.
77. Occurrences of acute urinary retention were investigated in a pooled analysis of three placebo-controlled, randomised clinical trials of

two years of finasteride therapy (5 mg daily) in men with benign prostatic hyperplasia [26]. These men had been recruited to three different randomised trials which utilized an identical protocol (further details in [26]). These studies involved a total of 4,222 men with moderately symptomatic BPH: a total of 2,113 men received finasteride and 2109 placebo.

78. In the primary analysis, occurrence of AUR were analysed by the Kaplan-Meier method and the hazard ratio, and corresponding 95% confidence intervals calculated. The primary analysis was intention-to-treat. A total of 57 men (out of 2109) on the placebo experienced on acute urinary retention (2.7 per cent). This compares to 24 (out of 2113) on finasteride (1.19%) and the corresponding hazard ratio was 0.43 (0.28, 0.67) [26].
79. Identical findings have emerged from two other sources. In a four-year randomised trial (PLESS), 3016 men were included (1513 on finasteride and 1503 on placebo). A blinded Data Monitoring Committee evaluated all cases of acute urinary retention reported. 98 men in the placebo group (6.5%), compared to 42 men (2.8%) on finasteride, experienced on acute urinary retention. The hazard ratio was 0.43 which is identical to that found in [24]. Similarly, the recently completed Phase III studies of dutasteride (another five alpha reductase inhibitor) demonstrated the exact same hazard ratio in a two-year study.
80. The proportion of the placebo group going into acute urinary is substantial and there is good agreement in a 57 per cent reduction in the risk of acute urinary retention associated with use of five-alpha reductase inhibitors (*finasteride* and *dutasteride*).

### 3.1.5.2 Comparison of 5ARIs and Alpha-blockers in Prevention of AUR

81. It has been clearly demonstrated (above) that five-alpha reductase inhibitors can reduce the risk of Acute Urinary Retention (AUR). Although an effect of alpha-blockers on the risk of acute urinary retention has been proposed. It has not been so clearly demonstrated. This analysis examines the relative effectiveness of current medical therapies for BPH in preventing AUR, AUR-related catheterisation and surgery in real-life clinical practice, using a large prescription database [27].
82. This is a retrospective analysis of observational data from the General Practice Research Database (UK) (GPRD). The cohort contains 4500 patients experiencing BPH or lower urinary tract symptoms strongly suggestive of BPH, aged over 50 years, who were prescribed a 5ARI (finasteride) or an alpha-blocker (alfuzosin, doxazosin, indoramin, prazosin, tamsulosin, terazosin) as their first BPH treatment between 1996 and 1999 inclusive. Cox regression and competing risks analyses, adjusted for age and year of first treatment, followed patients from the start of their first BPH treatment to AUR, catheterisation or surgery, or censoring [27].
83. Patients prescribed an alpha-blocker were significantly more likely to experience AUR (hazard ratio 2.32, 95%CI 1.37, 3.94) or surgery (hazard ratio 1.78, 95%CI 1.30, 2.44) than patients prescribed a 5-ARI. These differences were sustained with sensitivity analyses.
84. Real-life clinical practice shows that significantly fewer BPH patients prescribed a 5ARI experienced Acute Urinary Retention and other serious complications associated with the progression of BPH compared with those prescribed an alpha-blocker [27].

### 3.1.6 Designing Trials of a new 5ARI (Dutasteride)

85. In the light of the relationship between outcome of treatment with finasteride, the association of PSA with response and the reduction in Acute Urinary Retention after two years, the randomised PHASE III trial of a new five-alpha reductase inhibitor *dutasteride* was designed from the methodological viewpoint by myself.
86. To study the efficacy and safety of dutasteride, a novel, potent dual inhibitor of the 5 alpha reductase (5AR) isoenzymes type 1 and 2, in men with lower urinary tract symptoms (LUTS), prostatic enlargement and likely bladder outlet obstruction due to benign prostatic hyperplasia (BPH). A total of 4325 men with clinical BPH, moderate to severe symptoms, a peak flow rate of  $\leq 15$  ml/sec, a TRUS-measured prostate volume of  $\geq 30$  cc and a serum PSA 1.5–10.0 ng/mL (inclusive) were enrolled into three identical clinical trials and randomized to 0.5 mg dutasteride daily or placebo. After a 1-month, single-blind, placebo lead-in, patients were followed for 24 months with multiple interval assessments.
87. At 24 months, serum DHT was reduced from baseline by 90.2% and total prostate / transition zone volume was reduced by a mean of 25.7 and 20.4% respectively. AUA-SI was improved as early as 3 months with pooled significance from 6 months onwards and a reduction of 4.5 points at Month 24. Maximum flow rate improved significantly from 1 month, with an increase of 2.2 mL/sec reported at Month 24. Risk reduction of acute urinary retention was 57% and risk reduction of BPH-related surgical intervention was 48% compared with placebo. The drug was generally well tolerated [28].
88. Dutasteride, a potent inhibitor of DHT, is safe and effective in terms of reduction of prostate volume, symptoms, flow rate improvement and

the risk of AUR and surgery. The results fit directly onto the regression line established by the finasteride meta-analysis [22].

89. Detailed examination of the impact of dutasteride treatment on quality of life was undertaken within this clinical trial. The effect of dutasteride on benign prostatic hyperplasia (BPH)-specific health status, as measured by the BPH Impact Index (BII), and the identification of baseline and treatment risk factors for those most bothered by their BPH symptoms at the end of the protocol, was undertaken [29].
90. Data were derived from three randomized, double-blind, placebo-controlled, 2-year studies conducted in 4325 men with lower urinary tract symptoms caused by benign prostatic enlargement. Each study comprised a 1-month single-blind placebo run-in period, followed by randomization to oral dutasteride 0.5 mg once daily or placebo for 2 years. Patients eligible for inclusion were consenting men aged  $\geq 50$  years with moderate to severe symptoms (American Urological Symptom Index, AUA-SI, score  $\geq 12$ ), a prostate volume of  $\geq 30$  mL, a serum prostate-specific antigen (PSA) level of  $\geq 1.5$  or  $< 10$  ng/mL, and a maximum urinary flow rate (Q<sub>max</sub>) of  $\leq 15$  mL/s [29].
91. BII scores were recorded at baseline and each study visit. Clinically and statistically significant changes in BII scores from baseline were investigated for each study visit. Logistical regression analysis was used to assess the significance of baseline prostate volume, symptoms, BII item 3, baseline Q<sub>max</sub>, serum dihydrotestosterone, testosterone, PSA, age and weight in predicting the BII score at two years.
92. Dutasteride, but not placebo, resulted in clinically and statistically significant improvements in mean BII score from 6 months. Of patients with a baseline BII score of  $\geq 5$  (greatest symptomatic burden)

treatment with dutasteride improved the scores by 2.41, while the scores in placebo-treated patients only improved by 1.64. Dutasteride-treated patients with a baseline BII score of < 5 (least symptom burden) had a clinically significant improvement in health status, while placebo-treated patients deteriorated. Regression analysis showed that men with a combination of a baseline BII item-3 score of 3 (bothered a lot) and a high symptom score (AUA-SI  $\geq$  20) were more likely to be bothered by their symptoms at the end of the study. Men receiving placebo were also more likely to be bothered at the end of the study than were those receiving dutasteride [29].

93. Dutasteride treatment is associated with clinically significant improvements in BII score, reflecting improvements in the quality of life of men with BPH. Taken together with previously reported improvements in prostate volume, lower urinary tract symptoms and urinary flow, and diminution of the risk of acute urinary retention and the need for BPH-related surgery, dutasteride offers demonstrable efficacy in the management of BPH.

### 3.1.7 Comparison of 5ARIs and Alpha-blockers in treatment of LUTS

94. With both alpha-blockers and five-alpha reductase inhibitors demonstrating efficacy in reducing lower urinary tract symptoms it was a logical development to evaluate the joint efficacy of agents from both drug classes in symptomatic men. I was a member of the Working Group which designed a study to evaluate the efficacy and tolerability of the selective alpha(1)-adrenergic antagonist *doxazosin* and the 5-alpha-reductase inhibitor *finasteride*, alone and in combination, for the symptomatic treatment of benign prostatic hyperplasia [30].

95. In a prospective, double-blind, placebo-controlled trial, 1095 men aged 50 to 80 years were randomized to treatment for 52 weeks with

doxazosin, finasteride, the combination of doxazosin and finasteride, or placebo. The dose of finasteride (or its matched placebo) was 5 mg/day. Doxazosin (or its matched placebo) was initiated at 1 mg/day, and titrated up to a maximum of 8 mg/day over approximately 10 weeks according to the response of the maximal urinary flow rate (Q<sub>max</sub>) and International Prostate Symptom Score (IPSS). The IPSS and Q<sub>max</sub> were assessed at baseline and at weeks 10, 14, 26, 39, and 52 or at the endpoint.

96. An intent-to-treat analysis of 1007 men showed doxazosin and doxazosin plus finasteride combination therapy produced statistically significant improvements in total IPSS and Q<sub>max</sub> compared with placebo and finasteride alone (P <0.05). Finasteride alone was not significantly different statistically from placebo with respect to total IPSS and Q<sub>max</sub>. All treatments were generally well tolerated [30].
97. Doxazosin was effective in improving urinary symptoms and urinary flow rate in men with benign prostatic hyperplasia, and was more effective than finasteride alone or placebo. The addition of finasteride did not provide further benefit to that achieved with doxazosin alone.

### 3.1.8 Predictive Model for Acute Urinary Retention

98. The (very) similar nature of the findings of protection of Acute Urinary Retention in the three main randomised trial (described earlier) indicate the potential importance of being able to identify men at an elevated risk of developing Acute Urinary Retention.
99. Benign Prostatic Hyperplasia (BPH) is a progressive condition that is characterised by an increased risk of acute urinary retention (AUR) and BPH-related surgery. AUR presents a high-risk in older men although

there has been no attempt to predict individual men at high risk of this condition.

100. Three 2-year multi-centre, double-blind, placebo-controlled studies were conducted (n = 4325); dutasteride was administered at a dose of 0.5 mg/day. AUR was defined as inability to urinate requiring catheter. The three independent studies were designed for a pooled analysis and this report is restricted to the placebo control group(s).
101. There were 90 episodes of AUR determined among the 2,158 men in the control group in this study: the crude incidence of AUR was 4.2%. The risk of AUR was independently associated with Qmax, Prostate Volume and baseline PSA. Compared to the highest Qmax (13-33 ml/sec)(Hazard Ratio (HR)=1), the risk of AUR in the group with the lowest Qmax (<7 ml/s) was 4.5 (p for trend p<0.0006). For prostate volume, the risk in the group with the largest volume (69cc or more) was 6.3 (95% CI (5.9,23))(P trend (p<0.0001). For PSA, the risk in the five categories was 1 (PSA <2), 1.2 (2.1-2.9), 2.5 (2.9,4), 3.9 (4.1, 5.8) and 6.3 (PSA of greater than 5.9)(P trend (p<0001). After adjustment there was no association between risk of AUR and AUASI or age. A multidimensional model has been developed to predict individual risk and validated in the treatment group with good results [31].
102. AUR is an important hazard for ageing men and one which can profoundly affect quality of life. Risk factors for AUR have been identified and a multidimensional model has been developed. Identifying men at high risk of AUR should increase prospects for prevention since it has been convincingly demonstrated that pharmaceutical intervention can significantly reduce the risk of AUR.

### 3.1.9 Impact of Treatment of Lower Urinary Tract Symptoms / Benign Prostatic Hyperplasia

103. The most recent published guidelines on the Treatment of Lower Urinary Tract Symptoms/Benign Prostatic Hyperplasia are based on many of the findings which emerged from the work described above. Prostate volume is widely employed as the determinant for deciding on whether to treat a man with symptomatic Benign Prostatic Hyperplasia [32].

### 3.2 *Meta-analysis of Other Treatments for Benign Prostatic Hyperplasia*

104. The leading types of pharmaceutical treatments for BPH are five alpha-reductase inhibitors (such as finasteride and dutasteride) and alpha-blocker (such as terazosin, doxazosin). In many countries Permixon, a drug made from plant extracts, is widely employed. Apart from pharmaceutical treatment, surgery and trans-urethral needle ablation are common forms of treatment.

#### 3.2.1 Meta-analysis of Terazosin

105. Alpha<sub>1</sub>-adrenergic antagonists have been widely used in the treatment of men with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH). A high density of alpha receptors has been demonstrated in the areas of the bladder neck, the prostatic capsule and the prostate tissue itself. Furthermore, it has been demonstrated that while in young men the ration between stromal and glandular-epithelial tissue in the prostate is about 2:1, it changes with advancing age and the development of BPH and associated symptoms in favour of the stromal component to a ratio of approximately 5:1. Blockade of  $\alpha_1$ -receptors inhibits smooth muscle contraction and decreases muscle tone in the prostate. Consequently urethral pressure and resistance are decreased thereby reducing bladder outlet

obstruction. Thus, the use of  $\alpha_1$ -receptors antagonists such as terazosin would be expected to be effective in men with a high density of prostatic smooth muscle.

106. On the available alpha-blockers, terazosin has most extensively been studied in men with LUTS and clinical BPH. In large, double-blind placebo-controlled trials and long-term open studies, it has been found to significantly improve the symptoms of BPH and to increase peak urinary flow rate ( $Q_{max}$ ) compared with baseline and placebo, in a semi-quantitative overview, noted that symptom improvement with terazosin appeared to be dose dependent and the (higher) dose of 10 mg ameliorated obstructive, irritative and total symptom scores to a significantly greater extent than placebo.  $Q_{max}$  increased by between 1.5 to 4 ml/sec. in men treated with terazosin, representing a 20-40 percent increase which was generally 2-fold higher than the change seen with placebo.
107. Terazosin appears to be effective for LUTS within a few weeks and it has been speculated that men with low  $Q_{max}$ , moderate to severe symptoms, a predominance of obstructive symptoms or a high density of prostatic smooth muscle may predict a positive response to terazosin.
108. A meta-analysis of all clinical trials was undertaken to determine the effectiveness of the long-acting alpha-1 adrenergic receptor blocking agent terazosin compared to placebo therapy on lower urinary tract symptoms and peak urinary flow rate in men with clinical benign prostatic hyperplasia. The aims of the study included to determine whether or not the results reported in the literature are heterogeneous, and to determine whether baseline prostate volume influences the outcomes.

109. Original data on all patients from nine placebo-controlled randomized trials of varying duration comparing terazosin and placebo were obtained. A formal meta-analysis using an Empirical Bayes' [33] approach and a further employing a fully Bayesian approach were conducted. The primary endpoints of these studies were changes in peak urinary flow rate and urinary symptom scores from baseline to end of study. A further pooled analysis was conducted on those studies in which patients had a baseline assessment of prostate volume by transrectal ultrasonography [33].
110. There was no evidence of heterogeneity in the estimated effects of terazosin on the change in peak flow rates over the studies [33]. Terazosin treatment is associated with an increase of peak flow rate of 1.4 ml/sec (95% Confidence Interval (C.I.) (1.0, 1.7)) greater than the change in the placebo group. In terms of the change in the common symptom score (ranging from 0 to 35 points), terazosin resulted in an average reduction of 2.2 points over and above the placebo effect (95% C.I. (1.6, 3.0)). There is some evidence that there is mild heterogeneity across the studies, with regard to changes from baseline in the common symptom score associated with the duration of treatment, the decrease in symptom being slightly greater on longer treatment duration. There is a tendency for a greater effect to be seen at higher doses although this is difficult to interpret unambiguously. There was no evidence that the effect of Terazosin was influenced by baseline prostate volume [33].
111. Terazosin is effective in reducing lower urinary tract symptoms and increasing peak urinary flow rate in men with clinical BPH. The effect of terazosin appears to be greater in studies of longer duration (up to 1 year) although the effect on peak urinary flow rate is apparent in studies as short as eight weeks. Most importantly, the effect of terazosin on symptoms and peak urinary flow rate is independent of

baseline prostate size over the range of prostate volumes reported in the nine studies [33].

### 3.2.2 Meta-analysis of Permixon

112. Permixon® is a standardised lipido-sterolic extract of *Serenoa repens*. Its major mechanism of action is still uncertain; however several activities have been demonstrated. It repeatedly exerts anti-androgenic activity in the form of a non-competitive inhibition of 5 alpha-reductase type I and type II, resulting in a decrease in prostatic dihydrotestosterone content in BPH patients treated with this compound. Permixon® also appears to inhibit in vitro b-FGF and EGF-induced prostate epithelial cell proliferation and decreases EGF concentration in human prostate. It also exerts an anti-inflammatory effect through the inhibition of the enzymes responsible for prostaglandin, and leukotriene, synthesis.

113. Permixon® is extracted from the fruit of the American dwarf palm tree, *Serenoa repens*, which is widely used in the treatment of men with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH). There is significant controversy regarding the use of phytotherapeutic agents in such men. The purpose of this meta-analysis is to analyze all available clinical trial data of the Permixon® preparation to determine its clinical efficacy in comparison versus placebo.

114. All clinical trial data published on Permixon® were made available and utilized in the analysis [34]. Eleven randomized clinical trials and two open label trials comprised the database. These trials were disparate in size (from 22 to 592 patients) and duration (from 21 to 180 days). There were thirteen studies involving 2859 patients: 1961 on Permixon®, 278 on placebo, 545 on finasteride, 31 on alfuzosin, 22

on prazosin and 20 on an extract of pygeum africanum (Tadenum). Eleven studies had information on peak urinary flow and although widely different symptom scores were used in the trials, each had information on nocturia. The statistical analysis was based upon a random effects meta-analysis [34].

115. A random effects meta-analysis model was used where the studies were treated as the random effects [34]. For the majority of studies there were two observations: the response on placebo and the response on Permixon®. Some studies had three groups and in other the placebo was replaced by a comparator drug. The basic statistical model contained a term for the average response in each study, corresponding to effect of placebo, and terms comparing the other compounds to placebo, the treatment effects.
116. There was evidence of significant variation over the studies in the average response but no extra variation in the treatment effects. As the treatment effects represent deviations from the placebo effect if there is random variation in the placebo effect then there will be the same random variation in the treatment effects also. An attempt to try to investigate the between study heterogeneity was carried out using fixed effects known to differ over the studies. These included study type (randomized versus open label), dose of Permixon® and duration of study, but none was found to be important.
117. Over all the trials, the average placebo effect upon peak urinary flow rate was an increase of 0.94 (s. e. 0.49) ml/sec [31]. The estimated effect of Permixon® is a further increase of 1.87 (s. e. 0.55) ml/sec ( $p < 0.001$ ). There is no evidence of significant heterogeneity over studies in this effect, and study length (treatment duration) does not appear to impact on this effect. Placebo was associated with a reduction in the mean number of nocturnal urinations of 0.66 (s. e.

0.24). There is a further reduction attributable to Permixon® of 0.55 (s.e. 0.10) episodes of urination ( $p < 0.001$ ). There is some heterogeneity present which cannot be explained by differences in treatment duration.

118. Despite limitations in the information provided by some clinical trials and the need for caution in interpreting their findings, there does appear to be strong evidence that the use of Permixon® increases peak urinary flow rate in a consistent manner across studies and this is confirmed as a highly significant effect over placebo in the meta-analysis [34]. This meta-analysis of all available published trials of Permixon® in the treatment of men with BPH reveals a significant improvement in peak flow rate and reduction in nocturia above placebo [35]. This of considerable interest but one conclusion which could be drawn from this meta-analysis was the clear need for more studies with BPH Symptom Score endpoints.

### 3.2.3 Update meta-analysis of Permixon

119. Following publication of several large studies, including two randomised trial with a complete Symptom Score available, an updated meta-analysis of Permixon was undertaken [35].

120. All clinical trial data published on Permixon® comprising 14 randomized clinical trials and 3 open label trials, involving 4280 patients, were utilized. These trials were disparate in size (from 22 to 1100 patients) and duration (from 21 to 720 days). Peak urinary flow and nocturia were the two common endpoints. The statistical analysis was based upon a random effects meta-analysis [35].

121. Permixon® is associated with a reduction in IPSS of 4.78 (s.e. 0.41). The average placebo effect upon peak urinary flow rate was an

increase of 1.20 (s. e. 0.49) ml/sec. The estimated effect of Permixon® is a further increase of 1.02 (s. e. 0.50) ml/sec ( $p = 0.042$ ). Placebo was associated with a reduction in the mean number of nocturnal urinations of 0.63 (s. e. 0.14). There is a further reduction attributable to Permixon® of 0.38 (s. e. 0.07) episodes of urination ( $p < 0.001$ ). There is some heterogeneity over studies for nocturia. One study over 2 years involving 396 patients and showing no difference between placebo and Permixon® has a large impact on the results [35].

122. This meta-analysis of all available published trials of Permixon® in the treatment of men with BPH reveals a significant improvement in peak flow rate and reduction in nocturia above placebo and a five-point reduction in IPSS [35].

#### 3.2.4 Meta-analysis of Trans-Urethral Needle Ablation (TUNA)

123. Clinical Benign Prostatic Hyperplasia (BPH) is a progressive condition which affects a large proportion of men in the community. If left untreated it can lead to potentially serious complications including acute urinary retention, recurrent urinary tract infections and bladder calculi. Therapeutic interventions include medical management and intervention either surgically or with minimally invasive treatments. Transurethral Needle Ablation (TUNA) utilizes radio-frequency energy to heat prostate tissue. In order to investigate short- and long-term effectiveness, a meta-analysis of all clinical studies conducted on TUNA has been performed [36].

124. Data were abstracted from two randomised trials, two non-randomised observational protocols and seven single arm studies conducted on TUNA according to a determined protocol. As we have used before, the meta-analysis was based on the change in the mean score from baseline to the end of study. The estimation of the effects

from the meta-analysis used a multilevel model including random effects for the studies [36].

125. In all studies the patients recruited had severe LUTS with a mean IPSS score around 20 or more prior to treatment. The effect of TUNA was to halve the mean IPSS score one year after treatment (mean change 12.1 points) and although there was a slight tendency for IPSS to increase in all arms from year 1 to year 5, this 50% decrease was maintained at five years. Qmax also increased by around 70% from baseline to year 1 (mean improvement 5.1 ml/s) and in virtually all studies the mean Qmax approached or exceeded 15ml/s. Although there was a tendency for Qmax to slightly decline with time since treatment, mean Qmax five years after treatment was still over 50% higher than at baseline [36].

126. This meta-analysis has demonstrated that Transurethral Needle Ablation of the prostate is an effective and minimally invasive treatment for men with clinical BPH, even when symptoms are severe. There is a large improvement in symptoms and flow rate after one year, which persists until five years, and is only slightly less than that achieved by TURP. TUNA therapy would appear to be an alternative to surgery and also an attractive option for men who do not wish long-term medical therapy, or who are poor candidates for surgery or concerned about the side effects of TURP [36].

### 3.3 *Summary and Conclusions: Evidence-based Approach to Treatment Evaluation in BPH*

127. The initial meta-analysis of finasteride [22] has had a significant impact on how patients with lower urinary tract symptoms are treated as well as in the wider context of how the urological community considers BPH and LUTS. Patients with large prostates are generally directed towards a five-alpha reductase inhibitor (such as finasteride)

and those with small prostates are targets for alpha-blocker therapy (such as doxazosin).

128. The importance of prostate volume as a predictor of outcome of therapy [22] and the demonstration that serum PSA could predict outcome as well as the invasive Trans Rectal Ultrasound and MRI estimation [23, 24], has been a further aid to determining treatment choices [32]. The demonstration that finasteride therapy, and subsequently dutasteride therapy, could lead to a reduction in the risk of acute urinary retention [28] is a further addition to improvement in the quality of life of ageing men as is the ability to make a probability assessment of which men are at high risk of AUR [31].
129. The effect of the alpha-blocker, terazosin, on prostates of all sizes is of considerable interest [33] although more long-term data are required from all alpha-blockers. The demonstration of the efficacy of Permixon, particularly the magnitude of the improvement in flow rates, is another addition to the treatment options for men with urinary symptoms [35, 36].
130. The meta-analysis of TUNA has demonstrated the effectiveness of this therapy among men with severe symptoms and having the same effect as surgery in men with similar symptoms [32].
131. Thus, these meta-analyses have contributed significantly to helping improve the outcome of therapy of men with LUTS or BPH by helping select the right patients for the right treatment. Their importance is reflected by their impact in the available treatment guidelines from associations around the world [32].

#### **4 Renal Dialysis and Cancer Risk**

132. Although kidney transplantation is an effective treatment for end-stage renal disease (ESRD), dialysis is still the commonest treatment for such patients. Patients maintained on dialysis are potentially at increased risk of cancer for several reasons, including: the presence of chronic infection, especially in the urinary tract; a weakened immune system; previous treatment with immunosuppressive or cytotoxic drugs; nutritional deficiencies; and altered DNA repair. In addition, the underlying disease leading to renal failure, the persistent metabolic changes associated with it, and the development of certain complications, such as acquired renal cystic disease, may predispose to cancer.

133. Certain types of genitourinary disease are known to predispose to renal or urothelial tumours. For example, the risk of renal cancer is known to be increased in patients with inherited or acquired cystic disease of the kidney. Patients with Balkan nephropathy and analgesic nephropathy have a high risk of tumours of the renal pelvis and ureters. Although the increased risk of cancer after renal transplantation is well documented, there is less certainty about the risk of cancer in patients treated only with dialysis. Most of the reported studies are too small to detect potentially important findings on less common types of tumours or small increases in risk, or to study the relation between cancer and the various causes of renal failure or the method of dialysis treatment. By studying several hundred thousand patients with ESRD, we hoped to overcome some of these deficiencies.

##### **4.1 Cancer In Renal Dialysis in Lombardy Region, Italy**

134. The risks of primary cancers among patients who have been the recipients of a renal graft are known; there has been relatively little

investigation of patients who received long-term renal dialysis. There appears to be excess of renal-cell cancer characterised by being a more aggressive form of the disease. Reports of excesses of non-Hodgkin lymphoma have not always been confirmed. We obtained data from the Lombardy Regional Dialysis and Renal Transplant Registry. All patients on file during 1982-93 had complete demographic information and medical history. Patients with a history of cancer or who developed cancer during the first year of dialysis were excluded and only the first cancer was considered. 44,023 patient years were available for the study, 25,684 in men and 18,339 in women [37].

135. 479 cases of cancer at all sites was recorded. The average age at diagnosis was 59.5 years and the cases were on dialysis for an average of 6.37 years. There were statistically significantly raised risks of primary liver cancer, kidney cancer, thyroid cancer, lymphoma, and multiple myeloma. There were significantly decreased risks of cancers of the oral cavity and larynx, and a non-significant decrease in cancer of the oesophagus [37]. The excess of non-Hodgkin's lymphoma is similar to that found in recipients of renal transplants. The excess of liver cancer might be linked to materials used during dialysis.
136. Longer and better survival of patients with end stage renal disease undergoing renal replacement therapy means that there are many elderly patients receiving therapy. Our results highlight the need for careful follow-up and for early detection of cancers in these patients [37]. In addition, these findings were used in the context of a pilot study to demonstrate what would be the issues in putting together similar datasets on the same topic.

#### 4.2 Cancer in patients on dialysis for end-stage renal disease: an international collaborative study

137. The study described above [37], limited to one geographic region and a resultant limitation of cases of different forms of cancer, served as a pilot for a major study designed to give a clearer insight into the potential association between renal dialysis and the subsequent risk of developing cancer. We obtained previously stored data from dialysis registries in three continents: the *US Renal Data System*, the *European Dialysis and Transplant Association* and the *Australia and New Zealand Dialysis and Transplant Registry*. The Australia and New Zealand registry, although much smaller than the other two, was the only one with a uniform mechanism of reporting to the central registry for the diagnosis of cancer, and with complete, population-based information on dialysis. In view of possible variations in population coverage of dialysis and the completeness of coverage of cancer follow-up between the three registries, findings are presented separately for the three registries. This approach also allows the similarity of the findings in the three registries to be taken into account in interpretation of the data.

138. The data from Australia and New Zealand are the most complete in terms of both coverage and follow-up, although it is the smallest dataset. The US dataset is the largest and is also largely complete for coverage of patients on dialysis, although not necessarily for cancer follow-up. The European registry is of intermediate size; it has the lowest coverage and is likely to have the least complete cancer follow-up. We emphasise that these factors must be borne in mind in interpretation of the findings from this study and that the real strength of the approach taken to data analysis lies in the replication of findings between the registries [38].

139. The cohort consisted of patients in the three registries who underwent dialysis during the period 1980–94. We retrieved the

following information from the computerised databases: demography (country, region or state, date of birth, sex, and ethnic group); the cause of renal failure; treatment (date started, date of death or transplantation, type of dialysis); and diagnosis of cancer (date and type). We excluded patients with missing data on date of birth or follow-up; those treated in regions for which suitable background cancer rates were not available; those in whom the diagnosis of cancer preceded dialysis or in whom cancer treatment was the cause of renal failure; all those who received dialysis after transplantation; and those with AIDS. We excluded from the cancer analysis benign tumours, non-melanoma skin cancers, and metastatic cancers. All cancers were coded according to the ninth edition of the International Classification of Diseases (ICD9).

140. Because the classification of primary renal diseases in the three registries shows some differences, we reclassified the primary renal diseases into ten major groups: arteriopathic diseases; glomerulonephritis; diabetes; infective and obstructive nephropathy; congenital diseases; familial and hereditary diseases; toxic nephropathy; neoplasms; miscellaneous disorders; and uncertain cause.
141. For the USA, we calculated background cancer rates from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. Cancer incidence rates specific for age, sex, and race were calculated for all the Surveillance, Epidemiology, and End Results registries for each year from 1980 until 1994. In Europe, and in Australia and New Zealand, we used published rates for two periods around 1985 and 1990, respectively. We used country-specific cancer data if they were available. If national data were not available, we substituted data from regional registries. For countries without cancer incidence data, we substituted data from neighbouring countries.

142. For the Australia and New Zealand dataset, we identified ESRD patients with cancer directly from previously coded cancer data in each patient's computerised file. We verified the diagnosis of cancer through record linkage for patients treated in New South Wales, the Australian state with the highest population; 33.5% of the patients in this dataset were drawn from New South Wales, which has had a population-based cancer registry in operation since 1971. In this group, the Australia and New Zealand registry had recorded 228 cancers, whereas 221 cancers were recorded with the New South Wales Central Cancer Registry. For 200 (88%) of the 228 tumours, there was a close match on date of birth, date of diagnosis, and tumour type. For the US ESRD patients, the diagnosis of cancer depended on submission of reimbursement forms for hospital admission, which contained information about cancer diagnosis or treatment. For Europe, individual treatment centres submitted data on the presence or absence of cancer, but there was no standard cancer-reporting mechanism.

143. For patients who were alive at the end of the study period, we calculated the number of person-years at risk from the date of first dialysis until the end of the study period. Patients who had undergone transplantation were censored at the time of the operation. For patients who died during the study period we counted person-years from the start of dialysis until death. We calculated expected numbers of cancers by multiplying the number of person-years accumulated in each stratum of age, sex, race, country, and calendar time by the corresponding background specific rate. The standardised incidence ratio (SIR; the ratio of observed to expected cancers) was used to estimate the relative risk. 95% CI for these ratios were calculated with the assumption that the observed number of cancer cases followed a Poisson distribution.

144. The original datasets contained information on 963 250 patients. We excluded 131 446 patients in total: 24 014 with no available background cancer rates; 40 830 who started dialysis before 1980; 16 024 with missing data on date of birth or follow-up; 47 866 who had previously had cancer or whose primary renal disease was caused by cancer or amyloidosis; 1963 with AIDS; and 749 with renal failure that occurred after transplantation. The final cohort therefore consisted of 831 804 patients undergoing treatment for ESRD followed up for a mean of 2.5 years until last visit, transplantation, or death. The mean duration of follow-up ranged from 2.2 years in the USA to 2.9 years in the European registries, resulting in more than 2 million person-years of follow-up data. 110 110 patients were followed up for 5 years or longer and 15 825 for 10 years or longer. The mean age at start of dialysis differed in the three registries: patients treated in Australia and New Zealand were on average 9 years younger than those treated in the USA; patients in Europe were intermediate in age. In each of the registries there were more male (55.2%) than female patients [38].
145. The frequency of known underlying causes of renal failure during the study period differed between registries [38]. In Australia and New Zealand, glomerulonephritis was the commonest cause of renal failure (35.5%), followed by diabetes and toxic nephropathies. In Europe, infective and obstructive nephropathies were the most frequently defined diagnosis (16.2%); in the USA, diabetes was the commonest underlying disease (32.8%), followed by arteriopathic diseases (including hypertension) and glomerulonephritis. The distribution of underlying renal disease differed substantially between younger and older patients. In particular, glomerulonephritis (31%), infective obstructive nephropathy (12%), and congenital disorders (3%) were over-represented in the younger patients. The cause of the primary renal disease was missing or uncertain for more of the European patients than for the other cohorts [38].

146. During the study period, 25 044 primary cancers (non-melanoma skin tumours excluded), were recorded compared with 21 185 expected (SIR 1.18 [95% CI 1.17–1.20]). The excess of cancer was greatest in Australia and New Zealand (1.8 [1.7–2.0]) and lower in Europe (1.1 [1.0–1.1]) and in the USA (1.2 [1.2–1.2]). The proportion of patients with recorded cancers was 2.3% in Europe, 3.4% in the USA, and 3.7% in Australia and New Zealand. The risk of cancer was particularly high in the youngest age-groups (3.68 [3.39–3.99]); rates in the elderly were only slightly, if at all, increased [38].

147. To see whether the results were due to increased detection of cancer at the time of initial dialysis treatment (ascertainment bias), we analysed the findings in relation to the number of years since start of dialysis. Although the risk of cancer was slightly higher when cancer was diagnosed during the first year of dialysis (except in the USA), exclusion of the first year of follow-up from the analysis did not change the overall results. We also looked at risk of cancer in relation to the type of dialysis treatment: haemodialysis, peritoneal dialysis, or both types. We found no differences in the risk of cancer associated with these categories. In analyses of the relation between cancer and the underlying renal disease, the highest risk ratios were seen in patients with toxic or infective and obstructive nephropathies, and in the small group of patients with congenital kidney diseases.

148. We observed high cancer risks in several subsites. The number of tongue cancers reported was almost twice that expected. The risk of liver cancer was raised in several types of primary renal disease, but particularly in patients with diabetes. There were more cancers of the cervix, but not the body of the uterus, than expected. Vulvovaginal (n=112) and penile cancers (n=55), although rare, were about 1.8 times more common than in the background population. Thyroid and other endocrine tumours were more than twice as common in the

ESRD population as in the background population (2.28 [2.03–2.54]). There was an increased risk of various types of haemopoietic tumours, especially multiple myeloma. An increase in cancer was observed at some sites that are commonly involved in metastatic cancer, such as peritoneum (ICD9 158), other respiratory sites (ICD9 164–165), and bone (ICD9 170) [38].

149. High risks were observed for cancer of the bladder (1.50 [1.42–1.57]) and kidney (3.60 [3.45–3.76]). For both sites, rates were higher in younger than in older patients, and in those with toxic or infective and obstructive nephropathies than in those with other types of renal disease. There was little variation in the relative risk of bladder cancer with increasing time on dialysis [38], although duration of dialysis seemed to influence the relative risk of kidney cancer [38].

150. In agreement with several previous reports, our study shows an overall increased risk of cancer in ESRD patients; the risk was highest in Australia and New Zealand, and lower in Europe and in the USA. On the basis of the method used for ascertainment of cancer and the validation study carried out in the ESRD patients in New South Wales, we believe that the higher cancer rates observed in Australia and New Zealand reflect more accurate reporting of cancer in these patients. Because ascertainment of cancer in the other two registries was less rigorous, our report almost certainly underestimates the risk of cancer in European and US ESRD patients. In Europe, when we restricted the analysis to countries known to have high-quality cancer data (ie, the Scandinavian and Benelux countries), the observed cancer risks were similar to those in Australia and New Zealand.

151. Significantly increased cancer risks were seen in younger ESRD patients, and for several sites of cancer, such as the kidney and bladder, as well as the tongue, liver, lower genital tract in women,

external genitalia in men, the thyroid, lymphomas, and multiple myeloma. The high risk of cancer in younger ESRD patients, detected in all three registries, is an unexpected finding, which was not included in the list of prior study hypotheses. In comparison with the background population, the excess cancer risk was highest in the 0–34 year age-group, gradually declined with increasing age, and almost disappeared in patients in the oldest age-groups.

152. This age-related pattern has not been reported in previous studies, perhaps because most have been too small to include sufficient numbers of patients in younger and older age-groups. We do not believe that data entry errors explain the findings because in the USA we verified the age at diagnosis of cancer in patients younger than 35 years from original records, and in New South Wales patients, we found no errors in recorded year of birth. The excess risk in these younger patients was especially prominent for cancers of the kidney and bladder, and in patients with renal failure of infective, obstructive, congenital, or miscellaneous cause, but it occurred at many sites and with most primary renal diseases.
153. Between 13% (USA) and 25% (Australia and New Zealand) of the cancers occurred in the kidney or bladder, sites at which the nature of the primary kidney disease or associated urological abnormality, or the development of acquired renal cystic disease, may be the underlying cause. These increased risks are related to age and to primary renal disease. Cancer of the kidney but not that of the bladder was associated with duration of dialysis.
154. Certain tumours developing in ESRD patients before and after transplantation may share common risk factors. Viruses have been suggested as causative agents for some of the tumours in those sites. Viral infections occur in about 10% of patients after transplantation;

further studies are needed to assess the frequency of viral infection and the relation between viruses and cancer at these sites in ESRD patients.

155. The fact that ESRD patients have greater than normal exposure to hepatitis B and C viruses probably accounts for the observed excess of liver cancer. We found an excess of liver cancer in the diabetic ESRD group, as has been reported in diabetic patients with normal kidney function; however, overall, diabetes was the primary renal disease with the least increased risk of cancer in this study. The human papillomavirus has been linked to cancers of the tongue, cervix (but not the body of the uterus), vagina, vulva, and penis. Activation of dormant Epstein-Barr virus, which is associated with some lymphomas, is likely to explain the increased risks for these tumours in renal-dialysis patients and transplant recipients [38].
156. There is no explanation for the increased risk of thyroid and other endocrine tumours (ICD9 193–194) which was observed in all three registry populations. Ascertainment bias, through the repeated examination and imaging of the neck in relation to the diagnosis and management of secondary hyperparathyroidism, may have contributed, because the frequency of thyroid tumours rose with duration of dialysis.
157. Since the risk of cancer was not related to the type of dialysis, we deduce that the uraemic state, rather than any treatment-related phenomenon, is likely to be the cause of the increased risk.
158. There are several potential sources of bias in this study, all of which serve to produce conservative estimates of the relative risks. Closer surveillance of ESRD patients than of the general population could explain some of the excess cancer risk. We may not have excluded all

patients with prevalent cancers from the cohort. This possibility is one potential explanation of the large excess of multiple myeloma, which may have been the cause of the ESRD, soon after the start of dialysis. Unrecognised urothelial cancer as the cause of obstructive ESRD is unlikely to account for more than a fraction of the increased risk of bladder cancer. Because of the large size of the dataset, small differences in outcome will be significant; and with multiple endpoints, some positive results are likely to be chance findings. However, many of the associations identified in this study have been reported previously.

159. The findings of this study raise the question of the correct approach to cancer screening in ESRD patients. One previous study suggested that cancer screening may be an inefficient allocation of resources, adding little to life expectancy in these patients. Although we agree with this observation as it applies to the generality of ESRD patients on dialysis, our findings of substantially increased risks in younger patients, and in relation to specific organs, suggest that a selective approach to cancer screening and detection may be an appropriate research priority. It is difficult to attribute the large increased relative risks of cancer in younger patients, seen consistently in all three cohorts, to the effects of bias. There is no active screening of such patients for cancer, which could explain any of the observations. In future studies of younger patients, particularly those with bladder or kidney cancers, information on stage of disease at diagnosis and death would be very useful, although it might be very difficult to interpret [38].

160. Differences in the classification of the primary renal disease (PRD) used in different renal dialysis and transplant registries worldwide is noteworthy [40]. The heterogeneity of coding systems complicates the comparative analysis of end-stage renal disease from different regions.

Using data collected over two decades in the United States, Europe, and Australia/New Zealand, we present a method for reorganization of the classes of PRD that allows a straightforward comparison of retrospective data from these registries [39].

161. Using this classification enables use to be made of the large resource to investigate specific associations between underlying kidney disease and risk of specific forms of cancer. Patients on maintenance dialysis have increased risk for cancer, especially in the kidney and urinary tract. In this retrospective cohort of 831,804 patients starting dialysis during 1980 to 1994 in the United States, Europe, or Australia and New Zealand, standardized incidence ratios (SIR) with 95% confidence intervals (CI) were calculated for kidney and bladder cancers [40].
  
162. Risks for cancers of the kidney (SIR 3.6; CI 3.5 to 3.8) and bladder (SIR 1.5; CI 1.4 to 1.6) were increased, relatively more in younger than older patients and more in female patients (kidney: SIR 4.6, CI 4.3 to 4.9; bladder: SIR 2.7, CI 2.4 to 2.9) than male patients (kidney: SIR 3.2, CI 3.0 to 3.4; bladder: SIR 1.3, CI 1.2 to 1.3). SIR for kidney cancer were raised in all categories of primary renal disease, and for bladder cancer in all but diabetes and familial, hereditary diseases. Notably high SIR occurred in toxic nephropathies (chiefly analgesic nephropathy) and miscellaneous conditions (a category that includes Balkan nephropathy), the excess of kidney cancer in these conditions being urothelial in origin. SIR for kidney cancer rose significantly, and those for bladder cancer fell (not reaching significance) with time on dialysis. There was no association with type of dialysis [40].
  
163. The pattern of increased risk for renal parenchymal cancer in dialysis patients is consistent with causation through acquired renal

cystic disease and of urothelial cancers of the kidney and bladder with the carcinogenic effects of certain primary renal diseases [40].

## 5 Urological Cancers

164. Urological cancers represent a substantial proportion of cancers in men and women. Currently there are over 160 population-based cancer registries providing cancer incidence data of recognisably high-quality: the most recent data available cover the period around the mid-1980s. Out of a total of 3,618,375 cancer cases (non-melanoma skin cancers are excluded from virtually all registries) registered in men in these three registries, during the years covered by this volume, there were 221,033 bladder tumours (6.1% of all cancer in men); 92,064 kidney cancers (2.5%); 445,134 prostate cancers (12.3%); 38,462 testicular cancers (1.1%); and 9,036 cancers of the penis (0.26%) . In other words, 22.3% of all incident cancers in men world-wide occur at urological sites [41].

165. In women, there were a total of 3,351,605 incident cases of cancer in the same populations. Of these 77,220 were bladder cancers (2.24% of all cancers in women) and 59,655 were kidney cancers (1.7%). A total of 4% of all cancers in women were of urologic origin.

166. Some urologic cancers are relatively more frequent than others in different population groups. In men, bladder cancer represents 58.3% of all urologic cancers in Shanghai, China but only 10.2% of such cancers in Afro-Americans in the United States SEER (Surveillance, Epidemiology and End Results) Programme registries. In Afro-American men, prostate cancer represents nearly 80% of urologic cancers while only 14.7% of urological cancers in Shanghai. Kidney cancer represents less than 10% of all urologic cancers in North America and the United

Kingdom but one-quarter of all urologic cancers in Warsaw, Poland. Testicular cancer is more homogeneous except for a relatively low proportion among Afro-American men. Despite being relatively rare in most western populations, cancer of the penis still accounts for over 2 per cent of urologic cancers in Chinese populations [41].

167. In women, urologic cancers range between 3 and 5 per cent of all cancers world-wide and kidney cancer is between 1 and 2 per cent. There is little variation, although it is interesting to note that over 5 per cent of all cancers in Danish women are urologic in origin with both bladder and kidney cancer relatively high. However, it is difficult to ignore that urological cancers compromise a large proportion of the total cancer burden worldwide [41].

### 5.1 *Testicular Cancer Outcome*

168. Chemotherapy has been long used in the treatment of testicular cancer. Li and colleagues, in 1960, employed chlorambucil, actinomycin D and methotrexate to obtain seven responses out of 23 patients: three patients remained well for periods of between 9 and 18 months. MacKenzie, in 1966, reported that among 154 patients with advanced testicular cancer, that actinomycin D was the most active single agent for the treatment of teratomas. Other studies from the same era demonstrated that other agents were also useful: vinblastine sulphate, mithramycin, bleomycin, imidazole carboxamide, and adriamycin.

169. In 1976, Tim McElwain, writing in Symington's seminal book *Scientific Foundations of Oncology*, summarised the current state of knowledge of the treatment of testicular cancer. He concluded that chemotherapy had little place in the management of seminoma, a tumour so radiosensitive that it can be usually controlled by Radiotherapy. However, chemotherapy was more important in the

treatment of teratomas since over half of patients present with (or later develop) widespread metastases and such tumours are much less radiosensitive than seminomas. He did acknowledge that **"responses to chemotherapy are often transitory and it is doubtful if life is always prolonged in responders"**.

170. Remarkable progress has been made since then with survival rates increasing from around 10% in the 1970s to 90% in the 1990s with much of the improvement attributable to the development of chemotherapy schedules based on cisplatin, (first established by Larry Einhorn and John Donohue in 1977) and a realisation of the importance of combined management of such patients.
171. Using incidence and mortality data until 1983, Boyle et al in 1987 [42] showed a decline in mortality in Scotland from testicular cancer following the demonstration of effective therapy (in 1977) even against a background of increasing incidence. Since then incidence has continued to increase in Scotland while mortality has continued to decline. Similar patterns have been recorded in a number of countries including Denmark, Poland and England and Wales.
172. The decline in mortality rates from testicular cancer was evident in nearly all countries between 1975 (*pre-platinum*) and 1985 (*post-platinum*) with large decreases in the relative risk of death apparent almost everywhere. In 1990, Kaye and Boyle [43] were able to conclude that "it is widely appreciated that the application of chemotherapy in the treatment of germ cell tumours exemplifies the best results to be expected from this approach to solid tumours, since the majority of patients treated are now cured." 80-90% of patients with testicular cancer could expect to be cured of their disease and in most countries this seemed to be so, but not in Central and Eastern Europe where about 1 in 2 cases may die of their disease. Any

fundamental difference in biological behaviour is unlikely and a more likely explanation is that the differences in mortality relate to delivery of curative chemotherapy, including cisplatin, or to deficiencies in patterns of referral [42]. In the West of Scotland, a clinical audit was conducted on 440 (97%) of 454 men diagnosed with non-seminomatous germ cell tumours (NSGCT) between 1975 and 1989. Independent prognostic factors identified were extent of tumour at diagnosis ( $p < 0.001$ ), five-year time period of diagnosis ( $p < 0.001$ ) and treatment unit (the largest treatment unit compared to the four others) ( $p < 0.001$ ). This unit treated the majority of patients (53%), including the majority in the worst prognosis group (70% were poor-prognosis metastatic disease). In this unit, 97% of men received treatment according to the national protocol compared to 61% elsewhere ( $p < 0.0001$ ). When analysis was restricted to those men who protocol treatment, after adjustment for other prognostic factors, those men treated in other units had a Relative Risk of death of 2.8 (95% C.I. 1.53, 5.19) compared to the largest unit. This unit is characterised by having men assessed at a joint multidisciplinary clinic. These findings contain the clear message that specialisation and centralisation of treatment for non-seminomatous germ cell tumours improves outcome, the benefit being over and above the advantage resulting from protocol treatment.

174. Boyle, Maisonneuve and Kaye [44] speculated that the poor outcome from testicular cancer could be related to the lack of financial resources to purchase the expensive drugs necessary to treat disseminated testicular cancer. The economic situation in many of these countries has been changing rapidly including in Slovakia, where there has been an effective population-based Cancer Registry for many years making comparison of trends in incidence and mortality from testicular cancer possible. Another interesting aspect of testicular cancer treatment in Slovakia has been the establishment in 1982 of a specialist treatment centre for non-seminoma testicular cancer in the

Department of Urology in the School of Medicine of Bratislava. This centre initially treated approximately 50 new patients per annum with this disease employing a multidisciplinary approach. Following this, there has been the establishment of similar specialist units in the largest hospitals in central and eastern Slovakia.

175. Plesko et al [45], using data available until 1990, demonstrated that whereas the incidence rate of testis cancer has gradually increased between 1968 and 1990, the mortality rate has declined slightly since the early 1980s following an initial increase between 1968 and 1980. The gap between incidence and mortality is increasing indicating increasingly efficacious therapy of patients with testicular cancer in Slovakia. The authors concluded that this gap is likely to grow as more recent data become available and this has been the case.
  
176. The economical development taking place in Slovakia and the coincident establishment of specialist treatment centres have appeared to contribute to the improved outcome of testicular cancer in Slovakia. In no country of central and eastern Europe was the economic change as rapid as in the former German Democratic Republic (DDR, commonly called *East Germany*). Mortality data from the former German Democratic Republic (GDR) has become available since 1980. In the former Federal Republic of Germany (FRG), the mortality rate of testicular cancer peaked around the mid-1970s and by 1995 the mortality rate (0.4 per 100,000) was less than one-third the mortality rate in 1977 (1.4 per 100,000), when details of treatment advances were published. In the former German Democratic Republic, the mortality rate remained essentially unchanged until the opening of the border in 1989 (1.5 per 100,000) and has subsequently declined by over fifty percent in the following years [46]. The most recent mortality rate (0.7 per 100,000) remains a little higher in the territories of former GDR than that in former FRG (0.4 per 100,000).

177. The decline in mortality from testicular cancer in the former German Democratic Republic has paralleled the economic changes following German re-unification and provides further support to the hypothesis that economic considerations had previously limited the implementation of new treatment for this curable cancer. Unfortunately, this has caused at least 1000 deaths to occur since 1977 in this population which were avoidable [46].

**178.** In 2002, Levi et al [47] systematically considered trends in mortality from testicular cancer in Europe, the United States and Japan and, within Europe, in separate geographic areas and countries. In the European Union (EU), the peak rate (0.9/100,000 at all ages, 1.6/100,000 at age 20 to 44) was reached in the early 1970's, and mortality has decreased thereafter by 63% at all ages and 67% at age 20 to 44. In the six countries of central and eastern Europe providing data [to the World Health Organisation Mortality Database] the peak rate (0.9/100,000 at all ages, 1.9/100,000 at age 20 to 44) was reached in the late 1970's, but the declines have been much smaller thereafter (16% and 22%, respectively). In the United States, the peak (0.8 and 1.5) was even earlier, i.e., in the late 1960's, and testicular cancer rates have declined thereafter by over 70% both at all ages and at age 20 to 44, levelling around rates of 0.2/100,000 at all ages and 0.4/100,000 at age 20 to 44 in 1995-97. In Japan, testicular cancer mortality rates have systematically been much lower than in other areas. Appreciable declines were however observed during the late 1970's, to reach rates of 0.1/100,000 at all ages and 0.3/100,000 at age 20 to 44.

179. In 1975-79, the highest all age rates were in Denmark (1.7/100,000), Switzerland (1.5), Norway (1.3), Austria and the Czech Republic (1.2). The falls in rates were between 55 and 70% in most western European countries – with the major exception of Spain and

Greece – but comparatively smaller (25 to 30%) in the Czech Republic, Hungary and Poland. Mortality rates were upwards in Bulgaria and Romania. Consequently, in the late 1990's, the highest testicular cancer rates were in Bulgaria (1.0/100,000), the Czech Republic (0.9), Hungary (0.8) and Poland (0.7). The overall decline was 75% (from 0.8 to 0.2/100,000) in the whole European Union. The fall was 53% in the USA, and 58% in Japan, which reached rates of 0.1-0.2/100,000 in the late 1990's. The pattern of trends was similar at age 20 to 44, when approximately half of the deaths from testicular cancer were reported, although absolute values were higher [47].

180. The incidence rates of testicular cancer are increasing almost everywhere for reasons that are not entirely clear: for example, over a 60 year period incidence rose ten-fold in young men in Connecticut [48]. Hypotheses to be studied are complicated and exposure assessment is difficult. For a form of cancer which is increasing so much, there is some degree of complacency in undertaking aetiological studies. One principal contributory reason is the potential complacency induced by the low and declining mortality rate.

181. From examination of observations on the outcome of testicular cancer at population level, there are at least four main messages which emerge [49]:

- although platinum-based chemotherapy schemes have been available since the 1970's, the fall in testicular cancer mortality has not been the same in various areas of the world.
- there is some suggestion of a levelling off in the decline over the last few years, both in the European Union and the United States of America.

- within the European Union, the decline was proportionally smaller in Mediterranean countries, although absolute rates in the late 1990's were comparable to other European areas.
- the delay in the fall in testicular cancer mortality has been substantial in central and eastern Europe, although a 20 to 30% fall was observed during the 1990's. In any case, many avoidable deaths per year are still registered in eastern Europe for a largely curable disease in young men.

182. Although national mortality data cannot directly address issues of equity, they indicate that in central and eastern Europe the persisting inadequacies in adopting adequate treatments remain widespread and substantial, and require urgent action. One of the major challenges today in Cancer Control is to implement the knowledge which is currently available regarding effective ways of preventing cancer deaths. The causes of the anomalous situation of testicular cancer mortality rates in central and eastern Europe should be identified with a high priority otherwise there shall continue to be several hundred preventable deaths occurring every year.

183. When the (United States) National Cancer Act was signed into law on 23<sup>rd</sup> December 1971, what became widely known as the **War Against Cancer** was launched. At the time of this signing, testicular cancer was almost invariable fatal whereas today, in most developed countries, testicular cancer is almost always curable. This has been a major achievement for Cancer Control in the United States and similar countries.

184. Testicular cancer could become a very rare cause of death around the world if the knowledge currently available could be implemented world-wide. It is clear that when the economic situation makes the

necessary drugs available, large reductions in mortality can occur quite rapidly. It is clear also that when treatment can be centralised, outcome also improves.

185. Testicular cancer could be almost eliminated as a cause of death world-wide. All that is required is the political will, adequate finance and the necessary training and logistics to deliver the most appropriate treatment. The package to eliminate testicular cancer death is resource-based rather than depending on the outcome of further research [49].

186. Eradication of testicular cancer death will not make a large impact on overall cancer mortality although it will have a large impact at ages up until 45, where testicular cancer is the most common cancer in men. However, it will provide an example of what can be done when an achievable target is identified and all necessary resources, both financial and logistical, are brought to bear in an organised manner. The aim of all cancer research should be to do something for the benefit of the patient with cancer or those who are at risk of developing the disease. Implementation of research findings to bring about Testicular Cancer Control would mark the finest illustration of this entire process so far [49].

## 5.2 *Prostate Cancer*

187. Prostate cancer continues to present perplexing problems from the epidemiological perspective. Continual examination of temporal trends has proven difficult from changes in the basis of diagnosis (which have strongly perturbed incidence statistics) to changes in coding the underlying cause of death.

### 5.2.1 Prostate Cancer Trends until 1980

188. Prostate cancer has been poorly researched and understood from the epidemiological perspective. In the early 1980s, we undertook a systematic review of all existing incidence and mortality data [50].
189. These data demonstrated a 120-fold difference between the lowest and highest incidence rates of prostatic cancer, the disease being very common in North America, particularly among Blacks, and in Scandinavia, while it is rare in Japan and other oriental countries. The highest mortality for prostatic cancer is reported from St. Vincent and Grenadines, Martinique and Bermuda, from countries where the morbidity statistics are not available; the mortality rates reported from the United States and Canada are considerably lower. The incidence of and mortality from prostatic cancer have increased in most countries, in particular in areas with an initially low frequency of this disease. The ratio of mortality to incidence for prostatic cancer varies rather widely, being low in North America, Hawaii and Scandinavia.
190. We suggested that the observed variation in the mortality to incidence ratio for prostatic cancer could be due to differences in diagnostic practices between countries. This could explain, at least in part, the fact that the increasing trends of prostatic cancer incidence in North America are not accompanied by an increase in mortality from this tumour. This notion, however, does not exclude advances in treatment as possible determinants of the improved survival rate from prostatic cancer in this part of the world [50].
191. The available statistics on prostatic cancer are based on the sum of clinically diagnosed carcinomas and those latent tumours found unexpectedly at prostatectomy and autopsy. The proportion of latent carcinomas among all prostatic cancer cases depends on the detection

rate and varies from country to country, thus casting uncertainty on the comparability of prostatic cancer statistics from different areas. To avoid confusion in the statistics of prostatic cancer, it would be useful to consider introducing latent prostatic cancer as a separate entity in the next revision of the International Classification of Diseases (ICD) [50].

### 5.2.2 Prostate Cancer trends: an update

192. By 1990, in many countries of the world, prostate cancer is the second most common form of cancer in men, and in the United States it is now in first rank. It is an important public health problem, with more than 0.25 million new cases diagnosed worldwide in the year 1985. Whereas earlier large increases in the incidence of prostate cancer were apparent throughout the world, the mortality rate has remained constant in generations of men born since the early years of this century. Most importantly, given that in several countries the increased number of children born after World War II will be in their mid-50s in the early part of the 21st century (at an age when cancer risk is becoming an important consideration), and coupled with the trends in increasing life expectancy, the consequence will be an increase in absolute terms in the number of cases of prostate cancer diagnosed. In the absence of treatment improvements and with prospects for prevention by modification of lifestyle remote within current knowledge, there will also be an increase in the number of deaths from prostate cancer worldwide. The situation would be further augmented by the presence of a temporal trend in risk that is widely reported from many countries and unlikely to be entirely artefact [51].

193. To help clarify the situation regarding the evolution of temporal trends, all national time series of prostate cancer mortality data available in the World Health Organisation (WHO) mortality database

which fulfilled a series of conditions established *a priori* were analysed in a systematic manner to investigate whether prostate cancer mortality was increasing and whether there were any striking similarities in the nature of any changes between countries. Age-Period-Cohort modelling was employed to establish and estimate the nature of any changes taking place [52].

194. In all datasets there is evidence of the presence of a cohort effect. Risk of prostate cancer increased among those born from the mid-1880s onwards until the cohort born around 1910. Subsequently in many countries the cohort-risk has remained constant although there were several notable exceptions such as Finland, Denmark and Czechoslovakia where the risk continues to increase. It is notable that the cohort relative risks for any cohort in any country are small and never exceed 1.5. While in many countries the all-ages mortality rate of prostate cancer appears to be continuing to increase, this is being driven by increasing rates among the oldest age groups which could be subject to the potential influences of improvements in diagnosis and death certification [52].

195. Thus, based on an analysis of mortality data available until around 1990, it could be expected that overall mortality rates from prostate cancer will soon begin to decline in many countries. The small changes in mortality rates in more recent cohorts of men (born since 1910 onwards) contrast with the large increases seen in the incidence of prostate cancer and support the concept of an artificial inflation of incidence rates and a changing stage distribution brought about by aggressive histopathological examination of prostatectomy specimens (removed at TURP for benign prostatic hyperplasia) and the increasing use of prostate specific antigen (PSA) testing [52].

196. Mortality from prostate cancer has increased throughout Europe until the early 1990s. Trends in 24 European countries, the European Union (EU), six selected Central and Eastern European countries, and the Russian Federation have been updated to 1999 using cancer death certification data for Prostate Cancer abstracted from the World Health Organization database [53].
197. In the European Union, the peak rate (15.7/100,000) was reached in 1993, followed by a levelling off and a decline to 14.1/100,000 in 1999. Age-standardized analysis for each subsequent age group of men aged 50 or over showed larger absolute falls in the elderly. Prostate Cancer rates were lower in Central and Eastern European countries providing data, but showed a rise from 9.7/100,000 in 1980 to 11.3 in 1996, and levelled off thereafter. Rates were originally lower, but the rises larger in the Russian Federation (from 5.1/100,000 in 1980 to 8.1/100,000 in 1999). In the late 1990s, there was a threefold difference between the highest rates of 22/100,000 in Norway and those of 7.7 in Russia or 7.3 in Ukraine. Such a difference was, however, restricted to the elderly, since at age 35-64 the Russian rate (6.7/100,000) was the same as that of Norway, and only Greece and Italy had appreciably lower rates.
198. The pattern of trends in Prostate Cancer rates observed across Europe is as previously predicted and is consistent with a favourable role of improved diagnosis, but mainly of advancements of therapy (including more widespread adoption of radical prostatectomy and androgen blockage) on Prostate Cancer mortality in Western Europe [53].

### 5.2.3 Aetiology of Prostate Cancer

199. In a review of all the available epidemiological evidence [54] it was apparent that there was nothing known with certainty about the environmental causes of prostate cancer. Prospects for prevention of prostate cancer were exceedingly poor. Two decades later, an updated review concluded that little progress had been made in the interim [55] despite several intriguing glimpses from epidemiological studies [56-57].

200. In collaboration with colleagues in Australia, notably Graham Giles and John Hopper, a major case-control study was undertaken in various centres in Australia incorporating collection of interview and biological data. This is the most sophisticated aetiological study of prostate cancer undertaken to date and could provide the most reliable information regarding the causes of prostate cancer.

#### 5.2.3.1 Smoking and Prostate Cancer Risk

201. To examine the risk of smoking on histopathologically-confirmed moderate- and high-grade prostate cancer, a population-based case-control study was conducted in Melbourne, Sydney and Perth between 1994 and 1998 in men aged below 70 years. Cases were recruited from cancer registries and controls were selected from electoral registers. 1498 cases and 1434 controls were interviewed and a detailed smoking history obtained. Data were analyzed by unconditional logistic regression, adjusting for age, study centre, year of recruitment, family history and country of birth [58].

202. The odds ratios (OR) were 1.02 (0.85-1.22) for former smoking and 0.82 (0.65-1.05) for current smoking. The respective ORs were 0.95 (0.78-1.15) and 0.76 (0.59-0.99) for moderate grade tumours, and

1.28 (0.96-1.70) and 1.00 (0.67-1.47) for high-grade tumours ( $P = 0.2$  for test that ORs of the two grades were identical). There was no evidence of a dose-response effect for duration of smoking, amount smoked daily, pack-years of smoking and years since quitting and most ORs for these variables were close to unity [58].

203. Smoking was not associated with the risk of prostate cancer. The widths and upper limits of the confidence intervals for the effects of current and former smoking were consistent with weak effects at most [58].

#### 5.2.3.2 Early growth, adult body size and prostate cancer risk

204. The role of growth from birth through puberty and through adult life has been the subject of epidemiologic investigation in regard to the risk of prostate cancer but the evidence remains weak and inconsistent. We investigated associations between prostate cancer risk and a number of markers of body growth, size and changes to size in a population-based, case-control study in Australia from 1994 to 1998.

205. We analyzed data obtained in face-to-face interviews from 1,476 cases and 1,409 controls. The main outcomes of interest were the timing of the growth spurt in adolescence, the experience of acne and interviewer observation of facial acne scarring, body size at age 21, body size in reference year, maximum body weight and rate of body size change since age 21 years. Analysis was performed on all cases and also by tumour grade [59].

206. We found no associations with measures of body size including body mass index and lean body mass at age 21 or later in adult life. Having a growth spurt later than friends reduced risk (odds ratio [OR] 0.79 [0.63-0.97]) and some measures of acne also gave odds ratios

less than 1, for example, having facial acne scarring gave an OR of 0.67 (0.45-1.00) [59].

207. We conclude that markers of delayed androgen action, such as delayed growth spurt in puberty, and markers of other androgen-dependent activity in puberty, such as facial acne scarring, are associated with prostate cancer risk but we could detect no associations with markers of adult body size and growth including lean body mass.

#### 5.2.3.3 Risk Factors for Androgenic Alopecia Risk

208. The epidemiology of androgenetic alopecia (AGA) is not fully understood. Although a strong genetic basis has long been identified, little is known of its non-genetic causes. To estimate the prevalence of and to determine risk factors for AGA in men aged 40-69 years in Australia, men (n = 1390) were recruited at random from the electoral rolls to serve as controls in a population-based case-control study of prostate cancer. All were interviewed in person and direct observations of AGA were made. Men were grouped into the following categories; no AGA, frontal AGA, vertex AGA and full AGA (frontal and vertex AGA). Epidemiological data collected from these men were used for an analysis of risk factors for each AGA category using unconditional logistic regression with AGA category as the response variable adjusting for age, education and country of birth.

209. The prevalence of vertex and full AGA increased with age from 31% (age 40-55 years) to 53% (age 65-69 years). Conversely, the proportion of men with only frontal AGA was very similar across all age groups (31-33%). No associations were found between pubertal growth spurt or acne, reports of adult body size at time of interview,

urinary symptom score, marital status, or current smoking status or duration of smoking and the risk of any form of AGA [60].

210. The consumption of alcohol was associated with a significant increase in risk of frontal and vertex AGA but not full AGA. Men with vertex AGA had fewer female sexual partners but average ejaculatory frequency did not differ between men in different AGA categories. Reported weight and lean body mass at reaching maturity at about 21 years of age were negatively associated with vertex balding ( $P$  for trend  $< 0.05$ ) but not with frontal AGA or full AGA [60].

211. Evidence for environmental influences on AGA remains very slight. Our study failed to confirm previously reported or hypothesized associations with smoking and benign prostatic hypertrophy. The associations that we found with alcohol consumption and with lean body mass at age 21 years would be worthy of further research if they were able to be replicated in other studies [60].

#### 5.2.3.4 Androgenetic Alopecia and Prostate Cancer Risk

212. The purpose of this study was to examine the relationship between androgenetic alopecia (AA) and prostate cancer with particular emphasis on early age at diagnosis and higher grade tumors. We conducted an age-stratified, population-based case-control study in Australia of men who were diagnosed before 70 years of age during 1994-1997 with histopathology-confirmed adenocarcinoma of the prostate, excluding well-differentiated tumors. Controls were selected from the electoral rolls, and the frequency was matched on age. After excluding subjects with missing values, the analysis was based on 1446 cases and 1390 controls of whom direct observations were made of their pattern of AA during face-to-face interviews [61].

213. Our data suggest an association between prostate cancer and vertex baldness; compared with men who had no balding, the adjusted odds ratio (OR) was 1.54 (1.19-2.00). No associations were found between prostate cancer and frontal baldness or when frontal baldness was present concurrently with vertex baldness. The ORs were 0.98 (0.79-1.23) and 1.14 (0.90-1.45), respectively. The highest ORs were for high-grade disease in men 60-69 years of age: 1.80 (1.02-3.16) for frontal baldness; 2.91 (1.59-5.32) for vertex baldness; and 1.95 (1.10-3.45) for frontal and vertex baldness [61].

214. This association between the pattern of AA and prostate cancer points to shared androgen pathways that are worthy of additional investigation.

#### 5.2.3.5 Foods, Nutrients and Prostate Cancer

215. A major hypothesis of this study was to examine the risk of prostate cancer associated with foods and nutrients, including individual fatty acids and carotenoids.

216. Population-based case-control study of 858 men aged <70 years at diagnosis with histologically confirmed prostate cancer of Gleason Grade 5 or greater, and 905 age-frequency-matched men, selected at random from the electoral rolls. Dietary intakes were assessed with a 121-item food frequency questionnaire.

217. Inverse associations with prostate cancer were observed for (Odds ratio, OR, 95% confidence intervals, 95% CI for tertile III compared with tertile I) allium vegetables 0.7, 0.5-0.9; p trend 0.01, tomato-based foods 0.8, 0.6-1.0; p trend 0.03 and total vegetables 0.7, 0.5-1.0; p trend 0.04. Margarine intake was positively associated with prostate cancer 1.3, 1.0-1.7; p trend 0.04. The only statistically

significant associations observed with nutrients were weak inverse associations for palmitoleic acid (  $p$  trend 0.04), fatty acid 17:1 (  $p$  trend 0.04), and 20:5 n-6 (  $p$  trend 0.05); and a non-significant trend for oleic acid (  $p$  trend 0.09). Neither total, nor beverage-specific, intake of alcohol was associated with risk [62].

218. Based on these findings, diets rich in olive oil (a source of oleic acid), tomatoes and allium vegetables might reduce the risk of prostate cancer.

#### 5.2.3.6 Sexual factors and prostate cancer

219. To assess whether prostate cancer might be related to hormone levels and, by inference, to differences in sexual activity, a case-control study of men with prostate cancer aged < 70 years at diagnosis and age-matched control subjects, information was collected on two aspects of sexual activity; the number of sexual partners and the frequency of total ejaculations during the third to fifth decades of life [63].

220. There was no association of prostate cancer with the number of sexual partners or with the maximum number of ejaculations in 24 h. There was a negative trend ( $P < 0.01$ ) for the association between risk and number of ejaculations in the third decade, independent of those in the fourth or fifth. Men who averaged five or more ejaculations weekly in their 20s had an odds ratio (95% confidence interval) of 0.66 (0.49-0.87) compared with those who ejaculated less often [63].

221. The null association with the number of sexual partners argues against infection as a cause of prostate cancer in this population. Ejaculatory frequency, especially in early adult life, is negatively associated with the risk of prostate cancer, and thus the molecular

biological consequences of suppressed or diminished ejaculation are worthy of further research.

#### 5.2.3.7 Circulating steroid hormones and the risk of prostate cancer

222. Although it is established that sex steroid hormones, particularly androgens, are essential to the growth, development and maintenance of healthy prostate epithelium, and to the progression of prostate cancer, epidemiological studies have failed to support the hypothesis that circulating androgens are positively associated with prostate cancer risk ("the androgen hypothesis") and some recent studies have even suggested that high testosterone (T) levels might be protective, particularly against aggressive cancer. This hypothesis could be tested by measuring total T, androstenediol glucuronide, androstenedione (A), dehydroepiandrosterone sulfate (DHEAS), estradiol (E2) and sex hormone binding globulin (SHBG) in plasma collected at baseline in a prospective cohort study of 17,049 men.

223. We used a case-cohort design including 524 cases diagnosed during a mean 8.8 years follow-up and a randomly sampled sub-cohort of 1,859 men. The association between each hormone level and prostate cancer risk was tested using Cox and competing risk models adjusted for country of birth.

224. None of the hormones was associated with overall or non-aggressive prostate cancer (all P for trend  $\geq 0.2$ ). The hazard ratio (HR) (95% confidence interval) for aggressive cancer almost halved for a doubling of the concentration of T; HR 0.55 (0.32, 0.95) and A; HR 0.51 (0.31, 0.83), and was 37% lower for a doubling of the concentration of DHEAS; HR 0.63 (0.46, 0.87). The dose-response relationship for free T was virtually identical to that for T. Similar negative but non-significant linear trends in risk for aggressive cancer

were obtained for E2 and SHBG (P for trend = 0.2 and 0.1 respectively).

225. High levels of T and adrenal androgens are, thus, associated with reduced risk of aggressive prostate cancer but not with non-aggressive disease.

#### 5.2.3.8 ELAC2/HPC2 polymorphisms, prostate-specific antigen levels, and prostate cancer

226. This study, because of its advanced design, allowed detailed examination of genetic risk factors for prostate cancer. The ELAC2 gene has been proposed to be a prostate cancer susceptibility gene and is being referred to as HPC2, in part because three case-control studies suggested that two common polymorphisms (Ser217Leu and Ala541Thr) are associated with risk. However, four subsequent larger studies have not confirmed this association. In five of the seven total studies, subject selection was influenced by prostate-specific antigen (PSA) levels. We examined the association and possible effect of subject selection in a larger study and a meta-analysis.

227. In a population-based study in Australia, 825 case patients and 732 control subjects were genotyped for the Ser217Leu and Ala541Thr polymorphisms of ELAC2. Odds ratios (ORs) for prostate cancer were estimated by unconditional logistic and polytomous regression. A meta-analysis was conducted combining our data with those from seven published studies. The association of genotype with the logarithm of plasma PSA levels in control subjects was analyzed by linear regression [65].

228. The ORs for prostate cancer were 0.74 (95% confidence interval [CI] = 0.50 to 1.09) for Leu217 homozygotes and 1.01 (95% CI = 0.68 to 1.50) for Thr541 heterozygotes and homozygotes compared with

Ser217 and Ala541 homozygotes, respectively. ORs were not changed by excluding control subjects with elevated PSA levels. Among control subjects, there were no statistically significant associations between genotype frequencies and PSA level for either polymorphism (both  $P > .4$ ). The meta-analysis gave pooled OR estimates of 1.04 (95% CI = 0.85 to 1.26) for Leu217 homozygotes and 1.18 (OR = 0.98 to 1.42) for Thr541 homozygotes and heterozygotes [65].

229. There is no evidence that either ELAC2 polymorphism is associated with prostate cancer or PSA level.

#### 5.2.3.9 Polymorphisms in the prostate-specific antigen gene and prostate cancer risk and survival

230. The prostate-specific antigen (*PSA*) gene, also known as *KLK3*, is located on the long arm of chromosome 19 and encodes PSA that is widely used as diagnostic marker for prostate cancer. This gene contains several androgen responsive regions AREs. One of these AREs is located in the proximal promoter at -156 to -170 bp from the transcriptional start site of the gene and contains a polymorphic locus (rs266882) at -158 (A to G substitution) that was found to be associated with prostate cancer or circulating PSA levels in some studies but not in others. A recent study further characterized the *PSA* gene for polymorphisms and identified a sequence variation farther upstream of the *PSA* promoter at position -4643 (rs925013). This variant, a G to A substitution, was found to be associated with serum PSA levels and affected the functional activity of PSA promoter constructs. The hypothesis that the two variants rs266882 and rs925013 in the *PSA* gene are associated with circulating levels of PSA, prostate cancer risk and the risk of dying of the disease was tested using blood samples collected during a large population-based case-control study of prostate cancer.

231. 821 prostate cancer cases and 734 controls were genotyped and in controls circulating levels of PSA were measured. Cases in the Melbourne arm of the study were followed-up to 31/12/2004 and deaths from prostate cancer ascertained. Linear regression of the log 10-transformed PSA levels, unconditional logistic regression, Cox regression and haplotype analysis were used to test hypotheses.
232. No association was found between rs266882 and overall prostate cancer risk, survival and circulating PSA levels (all  $P > 0.1$ ) but the risk of advanced-stage tumor was elevated in carriers of the G allele (OR 1.5, 95% CI 1.1 to 2.2,  $P = 0.02$ ). The G allele in rs925013 was associated with an increased risk of prostate cancer (OR 1.4, 95% CI 1.1 to 1.7,  $P = 0.001$ , dominant model). Men homozygous or heterozygous for the G/G haplotype (rs266882/rs925013) were at higher risk of prostate cancer than men homozygous for the A/A haplotype (OR 1.3, 95% CI 1.1 to 1.6,  $P = 0.008$  and OR 1.7, 95% CI 1.1 to 2.4,  $P = 0.008$  respectively, additive model). Although cases homozygous for the G allele in rs925013 were at higher risk of dying from the disease than cases homozygous for the A allele, the hazard ratio was not statistically significant (hazard ratio [HR] 2.3, 95% CI = 1.0 to 5.6,  $P = 0.06$ , codominant model) and the overall tests for association between genotypes and survival were not significant (all  $P \geq 0.1$ ). Adjusted geometric means of circulating PSA levels in controls were 1.2, 1.1 and 1.3 ng/ml for men with respectively zero, one and two copies of the G allele in rs266882 and 1.1, 1.2, and 1.5 ng/ml for men with respectively zero, one and two copies of the G allele in rs925013 (all  $P > 0.1$ ).
233. The G variant in rs925013 and the G/G haplotype (rs266882/rs925013) in the *PSA* gene were associated with increased prostate cancer risk. This study found only weak evidence that cases homozygous for the G allele in rs925013 had an increased risk of dying

of the disease and little evidence of association between circulating PSA levels in controls and the two genetic variants.

#### 5.2.4 Screening for Prostate Cancer

234. It is hard to imagine a single topic in cancer research at the present time which provokes so much polarisation of scientists and clinicians in the field as does prostate cancer. Particularly important questions revolve around the usefulness of early diagnosis and the treatment of early stage tumours. The *prostate world* is split between those who advocate that every man should be 'screened' and those who equally vehemently insist that no asymptomatic man should ever be screened and there is a need for evidence of effectiveness from scientific studies [67].

##### 5.2.4.1 Prostate cancer mortality after introduction of prostate-specific antigen mass screening in the Federal State of Tyrol, Austria

235. To monitor the impact of screening in a natural experiment by comparing prostate cancer mortality in Tyrol, where prostate-specific antigen (PSA) testing was introduced at no charge, with the rest of Austria, where it was not introduced.

236. In 1993, PSA testing was made freely available to men aged 45 to 75 years in the Federal State of Tyrol, Austria. At least two thirds of all men in this age range have been tested at least once during the first 5 years of the study. Initially, only total PSA was measured, but free PSA measurement was added in 1995. The IMX assay was used. Digital rectal examination was not part of the screening examination [68].

237. Significant migration to lower stages has been observed since the introduction of this screening program. A reduction in mortality rates in the rest of Austria from 1993 onward has occurred, with the reduction

in Tyrol much greater; the mortality remained fairly constant between 1993 and 1995 and subsequently fell. The trends in prostate cancer mortality rates since 1993 differ significantly between Tyrol ( $P = 0.006$ ) and the rest of Austria. On the basis of the age-specific death rates averaged from 1986 to 1990, the difference between the number of expected and observed deaths from prostate cancer in Tyrol was 22 in the group aged 40 to 79 years in 1998 and 18 the following year [68].

238. These findings are consistent with the hypothesis that the policy of making PSA testing freely available, and the wide acceptance by men in the population, is associated with a reduction in prostate cancer mortality in an area in which urology services and radiotherapy are available freely to all patients. It is our opinion that most of this decline is likely to be due to aggressive downstaging and successful treatment and that any contribution from detecting and treating early cancers will only become apparent in the years to come.

239. The situation in Tyrol continues to be monitored [69-70]. We have been able to update outcome information using mortality data from Tyrol and Austria until 2003 [70]. Men with normal PSAs were invited to have a repeat test within a year while anyone with an elevated PSA was referred to their physician and then to a Urologist. The decision to perform biopsy was based on the age-specific PSA ranges, the percent free PSA and the transitional zone density. In all laboratories total PSA and percent free PSA concentration was assessed using the Abbott IMX assay. At the time of blood drawing no DRE was performed. In the first year alone, 32.3% of all men in this age group were tested and at least 85% of all men in this age range have been tested at least once in the first ten years of the study.

240. Significant migration to lower stages and an increase in the number of organ-confined, potentially curable prostate cancers have been observed since the introduction of this screening programme. Mortality from prostate cancer among Austrian men aged 40-79 increased slightly from 1970 until 1992. No difference was noted in this trend between Tyrol and the rest of Austria ( $p=0.23$ ). There has been a small but consistent reduction in prostate cancer mortality rates in the rest of Austria from 1993 onwards. The reduction in mortality rates in Tyrol has been much greater: mortality remained fairly constant between 1993 and 1995 and subsequently fell until 1999 and has subsequently achieved a plateau 20% lower than the rest of Austria. Trends in prostate cancer mortality rates since 1993 differ significantly between Tyrol ( $p = 0.0008$ ) and the rest of Austria [70].

241. Although this is not a randomised trial but a description of the findings of a unique, natural experiment. These findings are consistent with the hypothesis that the policy of making PSA testing freely available, and the wide acceptance by men in the population, is associated with a reduction in prostate cancer mortality. This reduction appears to be approximately 25% which is similar to that achieved by a high-quality breast cancer screening programme [70].

#### 5.2.4.2 Prostate Cancer Screening in Populations

242. Screening prostate cancer remains a highly controversial area between experts due to the lack of a clear evidence in the risk-benefit ratio: both screening and treatment of prostate cancer can be harmful making the trade off between benefits and risks, especially relevant. This deficiency in a proven clinical efficacy explains the varieties of contradictory recommendations from different organisations. In order to get a worldwide view of the different screening policies, a survey was conducted among the national delegates of the *Internationale*

*Société d'Urologie*, asking three very simple questions: (1) Is there a mass screening program for prostate cancer implemented in your country? (2) Is early detection for prostate cancer available in your country? (3) Is serum PSA test reimbursed in your country?

243. The survey revealed that no medical or health care organisation currently endorses mass screening for prostate cancer although Luxembourg is embarking on a national screening programme. This is due to the uncertainty regarding the efficacy of mass screening to decrease the specific mortality due to prostate cancer. However the lack of evidence does not prove there is no evidence to back up mass screening. To try to give a clear answer about the validity of mass screening several clinical studies have been undertaken.
244. The possible reduction in mortality due to screening, while uncertain, must be weighed against the substantial decrements in treatment-specific health outcomes among men treated for clinically localized tumours typically detected by screening. Concurrent with the successful life-saving efforts in terms of prostate cancer diagnosis and treatment, some men who do not need treatment are receiving it. These are men destined to die of causes other than prostate cancer.
245. Unfortunately, at diagnosis, men needing treatment for prostate cancer cannot be differentiated from men who do not. Unless the date of death from prostate cancer and the date of death from non-prostate cancer causes can be precisely determined for each patient, some men will always be over-treated or under-treated. Conservative strategies result in the under-treatment of some patients who would benefit from treatment while sparing other patients unneeded treatment. Aggressive strategies result in the over-treatment of patients who do not need therapy while curing other men of prostate cancer. Both strategies are correct, but only some of the time. Dramatic shifts in the incidence,

grade, stage, and age of men with prostate cancer have been observed with the advent of widespread PSA-based cancer detection in the United States. Grade and stage trends suggest that more biologically relevant (the shift from well-differentiated to moderately differentiated tumours) and yet therapeutically amenable (earlier stage) tumours have been identified in large numbers of patients during the PSA era. Many men have been diagnosed and treated who will not benefit from such treatment. Given the long delay between treatment and mortality that is inherent in prostate cancer, the full effects of treatment on prostate cancer mortality are probably not yet seen in prostate cancer mortality data [71].

246. Population data and ongoing screening trials in the United States and Europe will be complementary in the final determination of the relative contribution of the impact of screening versus other causes on recent mortality trends. Unfortunately, it is not feasible for a physician to advise the patient requesting advice about PSA testing to return in 4-6 years when the results of randomised trials will (probably) be available.
247. So what should be done and what should be recommended at the present time? Just imagine what the outcome of the much awaited randomised trials would be. If findings from both trials are positive in favour of PSA testing reducing prostate cancer mortality, then there would be an acceleration in the use of PSA testing and coverage of the population tested would grow.
248. But what would happen if both trials were to report null findings i.e. no reduction in prostate cancer mortality with PSA screening? It is highly likely that even if both trials are null, widespread PSA testing will continue to take place. There are several reasons for believing this. Trial results, pro and con, have been contentious issues among

supporters and opponents of screening every since they were first undertaken. Specifically, we have recently witnessed the situation where the utility of mammographic screening for breast cancer has come under strong attack [69]. Even with data available from nine randomised trials of reasonable methodology, claims were made strongly that there was no evidence to support mammographic screening. With fewer trials available for evaluating prostate cancer screening, and with contamination rates in the control group likely to be very high, questions will be posed about the reliability of the findings.

249. Secondly, and importantly, the PSA test is straightforward, cheap, readily available and easily acceptable by the majority of men. PSA testing has already achieved a high penetration among men and their physicians. In 2000, in the United States it was estimated that 12,514,000 PSA tests were provided to the male population (135,000,000). Furthermore, PSA use among black and white Medicare beneficiaries older than 65 years during the calendar period from January 1991 through December 1998 was determined. PSA use stabilized among white men, reaching an annual rate of 38% by 1995 and remaining at this level through 1998. The annual rate of use among black men reached 31% by 1998, but was still increasing at that time. By 1996, at least 80% of tests in both blacks and whites were second or later tests. By the end of 1996, 35% of white men and 25% of black men were undergoing testing at least biannually or more frequently. In 1996, 83% of diagnoses in whites and 77% in blacks were preceded by a PSA test. In both race groups, an overwhelming majority of diagnoses are associated with a PSA test, whether for screening or diagnostic purposes [71].

250. An age-stratified population-based random digit dial (RDD) telephone survey determined prevalence of prostate-specific antigen

(PSA) testing among Alberta men aged 40-74 years. The percentage of men who had ever had PSA testing was 4.5% at age 40-49, 13.1% at age 50-59, and 22.2% at age 60-74 years of age [72].

251. The extent of PSA testing outwith the North America is more surprising. For example, more than 2.2 million PSA tests were done on more than 1.1 million Australians between 1989 and 1996. The annual number of males tested increased fivefold in this period and peaked in 1995. Twenty-seven per cent of Australian men aged 50 years or over had at least one PSA test in 1995 or 1996; 33% of men aged 60-69 years had a test in this period [38]. To document the extent of prostate-specific antigen (PSA)-testing in the general population at Getafe (Spain) a total of 5371 PSA-test records (1997-1999) were reviewed and testing rates estimated per 1000 person-years [40]. PSA-testing rate in the general population was 21.6/1000 person-years. In the age-group 55-69 years, this rate was 86.8/1000 and increased to 152.6/1000 in men >70 years)[39]. In Milan, Italy where there is no campaign publicizing or encouraging prostate cancer screening, it has been estimated that 26.9% of men aged 40 and older and without a history of prostate cancer, received a PSA test in the two -year period 1999-2000. In men aged 50 and greater, this rate rose to 34% [71].

#### 5.2.4.3 Failure of Evidence-Based Urology

252. The degree of enthusiasm for prostate cancer screening seems high even given the limitations of the evidence of benefit and several reasons for this have been presented recently [71]. Given the current situation, there are several different strategies which could be introduced. For example, the (English) NHS Prostate Cancer Risk Management Plan recognises that an increasing number of men are sufficiently anxious about prostate cancer to seek help by asking for a PSA test. Under this plan any man considering a PSA test will be given

detailed information to enable him to make an informed choice about whether to proceed with the test. Properly managed access to the PSA test has a significant part to play in empowering people to make decisions about their own lives. If, having had access to this information, any man who still wishes to have his PSA tested can have this provided for him by the NHS.

253. Multiple sources of data show that prostate cancer incidence rates rose following the introduction of PSA testing. The average age at diagnosis has fallen, the proportion of advanced stage tumours has declined, the proportion of moderately differentiated tumours has increased, and patterns of care have changed accordingly. A decline in mortality began in the United States and other countries in 1991. The decline in mortality is well established but this recent trend may only retrace an increase in mortality that immediately preceded this phenomenon. The descriptive epidemiology of prostate cancer reveals many effects of the introduction of prostate cancer screening. Although the evidence suggests increased prostate cancer testing has yielded public health benefit, this has not yet been shown conclusively [71].

254. The key centres around the adverse effects associated with radical treatment: could a moderate reduction in mortality be offset by a decreased quality-of-life in men treated? Say, for arguments sake, one third of men diagnosed with prostate cancer die from the disease and, hence, in an unscreened population there are 1,000 prostate cancer deaths and 3,000 cases. If screening is introduced, decreases mortality by thirty per cent, then there should be 700 deaths. However, the incidence would double and there would be 6,000 prostate cancer cases, the majority of which would be early stage and suitable candidates for radical therapy. As mentioned above, in a random sample of Medicare patients the serious adverse effect rate was 28.6% in those treated radically. If 4,000 (out of 6,000) patients were treated

radically, then it could be expected that there would be 1,114 serious adverse events. Preventing one death could result in serious adverse events in 2-3 men. The importance of having outstanding therapy in place for all men in any community screened is paramount [68, 71].

255. It is very unlikely that there will be any brakes put on the continually increasing use of PSA in the detection of Prostate Cancer in the years to come. It is quite possible to believe that it will become as widespread among men as cholesterol measurement and will share with that mode of *screening* the notorious distinction of never having had its value (*mortality reduction*) demonstrated in a randomized trial. It is, however, an imperative *duty*, first of all, to ensure that the results of this *natural experiment* can be evaluated, and, secondly to seek ways to improve the outcome of therapy for prostate cancer. The adverse effects of radical therapy currently present the major hurdle in recommending mass screening for prostate cancer among populations. Systems should be in place right now to ensure that men and physicians participating in PSA testing should be participating in a programme in which the effect of the intervention can be evaluated. We owe this much to men in the community [71].

256. Whatever the arguments, the high penetrance of PSA testing in the male population around the world represents a colossal failure of the evidence-based approach to Policy formulation in Urology. The physician faced with a man asking about the advisability of having his PSA measured is now in a very difficult position. If he advises having the test performed the man runs the risk of having an adverse quality of life for no demonstrable gain in life expectancy. On the other hand if the physician advises against the test being performed, he (the physician) runs the risk of being confronted in five years time with the same man presenting with advanced (and fatal) prostate cancer. In large part, this dilemma has come about by the failure to respect the

need for an evidence-based approach and the failure to impose the necessity of having such an evidence based approach.