Risk of prostate cancer associated with benign prostate disease

a primary care case-control study

Brian S Buckley, Marie Carmela M Lapitan, Colin R Simpson and Aziz Sheikh

Risk of prostate cancer associated with benign prostate disease:

a primary care case–control study

Abstract

Background
Benign diseases of the prostate are common in the general male population, and prostate cancer is the most common cancer in men. Uncertainty as to the nature of the association between benign and malignant disease is a source of concern for patients and clinicians.

Aim
To determine the likelihood of men with benign prostate disease developing prostate cancer compared with men without disease.

Design
Incident matched case–control study

Method
All incident cases of prostate cancer (n = 984) were identified in a nationally representative community-based population, and each was matched by age with two controls with no prostate cancer (n = 1968). Participants' records of the previous 5 years were searched for diagnoses of benign prostate disease. Analyses investigated an a priori hypothesis that clinicians may record disease as benign until proven to be malignant, causing misleading significant associations between benign and malignant diagnoses.

Results
There was a significant association between a diagnosis of prostate cancer and a benign diagnosis at any time in the previous 5 years: odds ratio (OR) 1.57 (95% confidence interval [CI] = 1.32 to 1.88). However, there was no significant association when benign diagnoses within 6 months and within 12 months of cancer diagnoses were excluded: OR 1.19 (95% CI = 0.97 to 1.46) and OR 1.00 (95% CI = 0.79 to 1.27) respectively.

Conclusion
Findings from this study suggest that unless prostate cancer is detected within 6 months, men diagnosed for the first time with benign disease are at no greater risk of prostate cancer than those with no recorded prostate disease.

Keywords
primary health care; prognosis; prostatic hyperplasia; prostatic neoplasms; prostate-specific antigen.

INTRODUCTION

Benign diseases of the prostate, and the urinary and pelvic symptoms associated with them, are common in the general male population. Even though many men will never experience bothersome symptoms and many will be undiagnosed, benign prostate diseases result in considerable demands on health services.[1,2] Despite this, knowledge of the natural history of benign prostatic diseases is far from complete, and uncertainty persists with regard to prognosis.[3]

In the community, men affected by benign prostate disease are often concerned about whether they have an increased risk of prostate cancer.[4] Men with lower urinary tract symptoms consistent with benign disease are more likely to expect to be tested for cancer than those without.[5] Prostate cancer is the most common cancer in men, accounting for some 24% of new cancer cases in men in the UK.[6]

The nature of the relationship between benign prostate disease and prostate cancer remains controversial.[7] Both benign and malignant prostate disease are hormone dependent, their incidence increases with age, and they are often found in the same patients.[8] Epidemiological relationships are well established: autopsy data suggest that most prostate cancers (83%) develop in men in whom benign prostatic hyperplasia (BPH) is also present, and a 67% prevalence of BPH has been reported in men whose prostate-specific antigen (PSA) levels indicate an increased prostate cancer risk.[9] There is also increasing evidence of genetic, anatomical, and pathological connections between the two conditions. Studies have identified a genetic overlap between symptomatic BPH and prostate cancer,[10,11] while 5-alpha-reductase inhibitors used to treat symptomatic benign prostatic disease appear to be effective in preventing prostate cancer.[12,13] Studies have also identified both fast-growing BPH and bacterial prostatitis as risk factors for clinical prostate cancer.[14–16]

That said, no causal link has been demonstrated. Observed epidemiological associations between prostate cancer and previous benign disease may not relate to any aetiological association, but rather to the increased interaction with health services among patients with benign disease, and greater expectation of PSA testing, resulting in a greater likelihood of cancer being detected.[7,17,18]

There is a need for research that helps to clarify whether the concerns of patients are well founded and whether men with benign

BS Buckley, PhD, clinical research fellow at NUI Galway, and visiting professor at UP Manila, Department of General Practice, National University of Ireland, Galway, Ireland and Department of Surgery, University of the Philippines, Manila, Philippines. **MCM Lapitan**, MD, clinical and research associate professor, Division of Urology, Department of Surgery, College of Medicine, Philippine General Hospital and National Institutes of Health, University of the Philippines-Manila, Manila, Philippines. **CR Simpson**, PhD, senior research fellow; **A Sheikh**, MD, professor of primary care research and development and director of Research Centre for Population Health Sciences, eHealth Research Group, Centre for Population Health Sciences, The University of Edinburgh, Edinburgh, Scotland.

Address for correspondence
Brian S Buckley, Department of Surgery, University of the Philippines Manila, Philippine General Hospital, Taft Avenue, Manila, Philippines.
E-mail: briansbuckley@gmail.com

Submitted: 26 February 2011; **Editor's response:** 21 March 2011; **final acceptance:** 6 April 2011.

This is the full-length article (published online 31 Oct 2011) of an abridged version published in print. Cite this article as: **Br J Gen Pract 2011; DOI: 10.3399/bjgp11X606573**

How this fits in

This study provides empirical information for men affected by benign prostate disease and their physicians. Some degree of uncertainty persists as to whether any link exists between benign and malignant prostate disease. Yet for men affected by benign disease, this is a considerable cause of concern and they are more likely than unaffected men to expect to be tested for cancer. This study suggests that among men diagnosed for the first time in primary care with prostate disease, unless a diagnosis of malignant disease is confirmed within 6 months, the incidence of subsequent diagnoses of prostate cancer is low and the risk of prostate cancer is not significantly higher than in men with no recorded prostate disease.

disease ought to consider being tested for cancer more readily than others. Considered in combination with other clinical indicators, the PSA test is increasingly used and it has led to prostate cancers being diagnosed earlier and an increase in recorded incidence.[19–21] However, the test also yields considerable numbers of false positives, which can, in turn, lead to unnecessary anxiety and potentially risky biopsies.[22] Furthermore, there remains considerable debate as to whether early detection is beneficial.[23,24]

Providing advice about PSA testing and test results presents a considerable challenge to primary care physicians,[22] and further evidence is desirable that clarifies the relationship, if any, between benign and malignant disease.[17,25] This study sought to assess, over 5 years, in an unselected and representative Scottish community-based population, whether there is an association between diagnoses of benign prostate disease and prostate cancer.

METHOD

The sampling frame for this study was all men registered with 40 GP surgeries located throughout Scotland. These clinics contribute data to the Primary Care Clinical Informatics Unit and participate in the quality-assured Practice Team Information project operated by the NHS Information Services Division.[26] The completeness of recording of consultations and the accuracy of data encoding in GP clinics, using the Read Code system, has been found to be above 91%.[27]

To create a primary–secondary care-linked research database, primary care patient data were linked in May 2007 with hospital-based specialist secondary care data held on the Scottish Morbidity Record (SMR01) databases hosted by the Information Services Division. Secondary care data have been found to be reliable from 1981, with completeness and accuracy rates exceeding 90%.[28]

The total patient population within the database (n = 238 064) is broadly representative of the Scottish population, with respect to age, sex, and social deprivation.[29] The postcode of each patient was used to assign a deprivation status on a 10-point scale, which was then converted to quintiles for analysis (1 = most affluent to 5 = most deprived). The assigned deprivation scores were derived from the Scottish Index of Multiple Deprivation, the Scottish Government's official tool for identifying and coding levels of deprivation nationally, which uses 37 indicators of poverty across seven domains (current income, employment, health, education, housing, access to services, and crime).[30,31]

An incident-matched case–control study was conducted to determine the likelihood of men with benign prostate disease developing prostate cancer, compared with men without recorded prostate disease. From the anonymised linked database, all men who were diagnosed with prostate cancer over a 4-year period (1 January 2003 to 31 December 2006) were identified (Read Codes B46, B834, and International Classification of Diseases version 10 codes 233.4 , 185, C61).

Electronic records of cases were checked backwards, for as long as records existed, for any previous recorded history of the condition prior to the date of the index episode. Individuals with a previous relevant record were excluded from the study. Those without a previous record were deemed to have experienced an incident (first-ever) diagnosis of prostate cancer on that date.

Age is the most significant risk factor for both benign and malignant prostate disease. Each incident prostate cancer case was therefore matched by age with two controls, men with no cancer diagnosis on the same date, selected randomly from the practice population. Diagnosis dates of the cases were considered the index dates for the controls.

Records of both cases and controls were then checked for the 5 years previous to the index date for a previous diagnoses of benign prostate disease (BPH or prostatitis; Read Codes K20, K21z). Data on body mass index (BMI), whether the man was known to be a smoker, and deprivation, which are all

potentially important confounders, were extracted from the records at the index date. Men were only regarded as current smokers when data were available, with missing-data cases regarded as non-smoking.

Statistical analysis

Descriptive statistics are presented for continuous and categorical variables. A conditional logistic regression model for two controls per case was fitted to determine odds ratios (ORs) for diagnoses of benign disease within the preceding 5 years associated with a prostate cancer diagnosis, compared with no such diagnosis. Regardless of physicians' suspicions, and until proven to be malignant, diagnoses of prostate disease may first be recorded as benign. To consider and to mitigate the influence of this recording behaviour, it was decided a priori that analyses should be performed in several steps: first including the whole cohort and subsequently excluding benign diagnoses within 6 and then within 12 months of the index date. Analyses were conducted using SPSS (version 16.0).

Sample size calculations

With definitions of benign prostate disease differing between studies, and few studies reporting the prevalence of both benign and malignant disease in the same population, estimating the required sample size presents difficulties. Prevalence estimates for BPH of 83% and 67% have been reported in men with prostate cancer and high risk of prostate cancer.[9]

A previous Scottish primary care study determined prevalence estimates for clinically symptomatic BPH in the general male population of 20.2% in men aged 40–64 years and 42.8% in men aged 65–79 years.[32] Other studies have reported up to 50% of all men over 80 years experiencing symptomatic BPH.[33–35] Taking the latter higher estimate for BPH prevalence of 50% in the general male population and lower estimate of 67% in high-cancer-risk patients, this might suggest the prevalence of prior BPH is some 35% greater in prostate cancer cases than in the general male population: an OR of approximately 2.00. To give an 80% power to detect a significant OR of 2.00 with 95% confidence intervals (CIs), with controls among whom prevalence is estimated at the lower 20% level, it was estimated that a sample of 126 cases and 252 controls would be necessary; to detect an OR of 1.50, a sample of 395 cases and 790 controls would be necessary.[36]

RESULTS

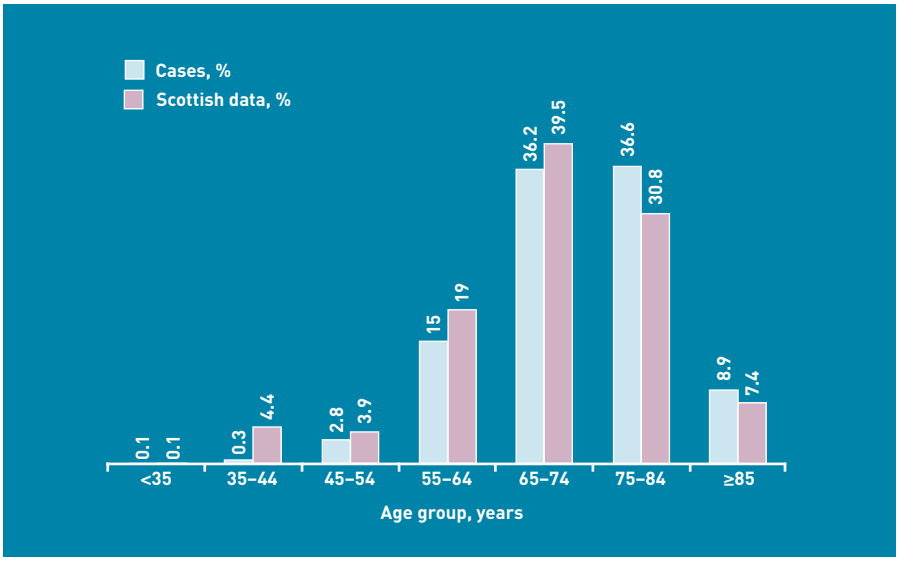
In the practice population, 984 men were identified with a first diagnosis of prostate cancer between 1 January 2003 and 31 December 2006; each case (n = 984) was matched with two controls (n = 1968). The characteristics of cases and controls are presented in Table 1. There was little difference between cases and controls in terms of BMI, smoking status, and socioeconomic status. Levels of missing data for BMI were similar between cases and controls. Figure 1 plots the cases by 10-year age group compared with national data for new cases of prostate cancer 2001–2005.[37] The identification of cases, controls, and previous benign prostate disease diagnoses in the two groups is

Table 1. Age, known smoking status, body mass index, and socioeconomic status of cases and controls at the index date

	Cases (n = 984)	Controls (n = 1968)
Mean (SD) age in years	72.8 (9.3)	72.8 (9.3)
% (n) recorded as smokers at index date	13.7 (135)	14.6 (287)
Mean (SD, n) body mass index	23.4 (6.3, n = 815)	23.8 (5.9, n = 1741)
% (n) socioeconomic status: SIMD		
1 (most affluent)	13.0	10.5
2	8.2	7.1
3	13.3	12.0
4	9.8	10.1
5	11.6	10.1
6	13.6	15.1
7	9.7	11.3
8	7.7	9.6
9	7.8	9.2
10 (most deprived)	5.3	5.0

Cases = men diagnosed with prostate cancer. Controls = men of same age with no cancer diagnosis (two controls per case) on date of case's diagnosis. SIMD = Scottish Index of Multiple Deprivation.

Figure 1. Prostate cancer (new cases) 2001-2005 by 10-year age group: study cases versus Scottish national data cases (Information Services Division).



illustrated schematically in the flow chart (Figure 2).

Results of conditional logistic regression used to consider the association between a diagnosis of prostate cancer and a prior diagnosis of benign prostate disease are presented in Table 2. Whereas there was a significant association between prostate cancer and a prior diagnosis of benign disease when all previous benign diagnoses

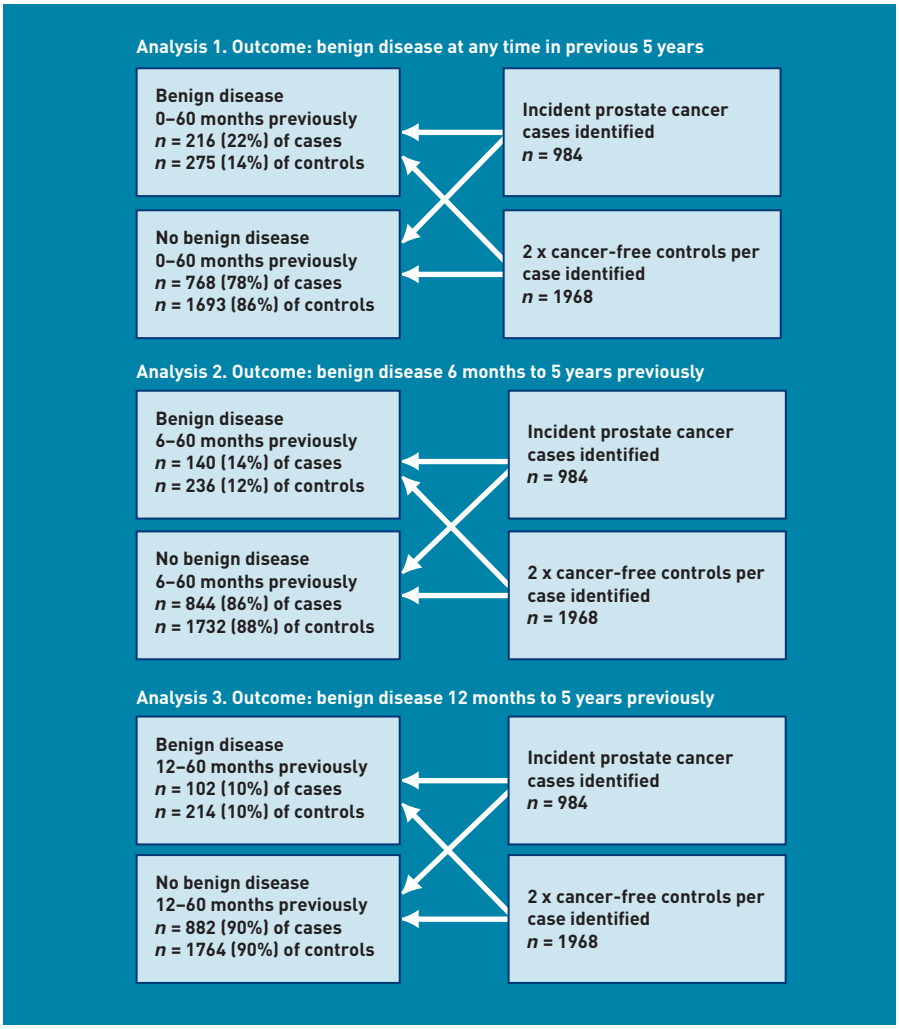


Figure 2. Steps in data analysis. Cases = men diagnosed with prostate cancer. Controls = men of same age with no cancer diagnosis (two controls per case) on date of case's diagnosis.

Table 2. Previous diagnosis of benign prostate disease for men with a diagnosis of prostate cancer (cases) compared with those without (controls), and time between diagnoses

	Cases (*n* = 984)	Controls (*n* = 1968)	Odds ratio (95% CI)
In prior 5 years			
Number (%) with no benign prostate disease	768 (78.0)	1693 (86.0)	Reference group
Number (%) with benign prostate disease	216 (22.0)	275 (14.0)	1.57 (1.32 to 1.88)
Mean (SD) time (months) between index data and benign diagnosis	16.9 (16.7)	25.4 (16.6)	
>6 months to 5 years previously			
Number (%) with no benign prostate disease	844 (85.8)	1732 (88.0)	Reference group
Number (%) with benign prostate disease	140 (14.2)	236 (12.0)	1.19 (0.97 to 1.46)
Mean (SD) time (months) between index data and benign diagnosis	24.7 (16.0)	29.1 (14.9)	
>12 months to 5 years previously			
Number (%) with no benign prostate disease	882 (89.6)	1764 (89.6)	Reference group
Number (%) with benign prostate disease	102 (10.4)	214 (10.4)	1.00 (0.79 to 1.27)
Mean (SD) time (months) between index data and benign diagnosis	30.1 (13.7)	31.7 (13.5)	

were included, when diagnoses within 6 months of cancer diagnoses were excluded, there was no longer a significant association. When benign diagnoses within 12 months of cancer diagnoses were excluded, the OR was 1.0 (95% CI = 0.79 to 1.27). Mean times from diagnosis of prostate cancer (or equivalent index date for controls) to a previous diagnosis of benign disease are also presented in Table 2.

DISCUSSION

Summary

This study determined a significant association between a diagnosis of prostate cancer and a previous diagnosis of benign disease at any time in the preceding 5 years. However, in an a priori planned exclusion of those whose recorded previous benign diagnoses were within the 6 months and the 12 months immediately preceding their first cancer diagnoses, no significant association was detected between diagnosis of prostate cancer and a prior diagnosis of benign prostate disease. A likely explanation is that for a proportion of those whose benign diagnosis is followed by a cancer diagnosis in the subsequent few months, the benign diagnosis may be a misdiagnosis or a 'working diagnosis' in those being clinically followed up. The data from this study indicate that if cancer is not detected within 6 months, most diagnoses of benign prostate disease in a representative, community-based population are not associated with an increased risk of subsequent prostate cancer.

Strengths and limitations

A major strength of the study was the use of a large incident case–control cohort of patients that included, insofar as is possible, every new case of prostate cancer in a whole population in a given time period. The risk of selection bias is therefore low. Other key strengths include the fact that cases and controls were selected from the same population and that it was possible to account for a range of relevant potential confounders. The use of a linked primary–secondary care dataset was also an important strength, as it thereby allowed a comprehensive assessment of patient and healthcare interaction. The study demonstrates that linked clinical datasets provide an important opportunity to study aetiology and prognosis quickly and cost-effectively.

The definition and diagnosis of BPH and prostatitis is challenging. These diseases are the subject of debates among urologists and other medical disciplines. A pragmatic approach was adopted to the definition of BPH and identification of cases that reflects routine practice in primary care: the BPH population included men who have presented with and have been diagnosed as having prostatic enlargement, with or

without lower urinary tract symptoms, as well as those whose BPH has been confirmed histologically. Continuing debate as to their optimal use has resulted in inconsistent use and recording of PSA testing, with patient self-selection and physician selection introducing an unknown confounding influence. Thus, this study has not attempted to analyse different BPH diagnostic subgroups.

Although 5 years of clinical data were available for use in searching for prior diagnoses of benign disease for each case or control, it is possible that this may not be fully sufficient to determine the risk of a disease like prostate cancer, which may be relatively indolent. However, this period of time does represent a timescale that is relatively rare in studies including community-based cohorts of all cases within primary care practice populations, and is equivalent to that used in other longitudinal studies.[38]

The effect of treatments after diagnosis was not considered because data were not available about contraindications, illness severity, patient preferences, or adherence to treatments, all of which contribute to both prescribing patterns and prognostic risk. Residual confounding due to treatment and indication bias, therefore, could explain some of the study findings. It is regrettable that no data were available about race/ethnicity or family history, although there is no reason to suspect difference between cases and controls in this respect. Finally, as with all observational research, some findings may have occurred as a result of residual confounding.

Comparison with existing literature

Epidemiological studies have suggested that benign prostatic disease and prostate cancer are often associated and share certain predisposing factors.[7] However, it has also been suggested that these associations may result from a higher likelihood of identifying prostate cancer in patients already being observed for benign disease and that there is no aetiological association.[17,18] The relationship between the two conditions remains uncertain and a cause for concern among patients and physicians alike, and there have been calls for studies that can assess the risk of subsequent prostate cancer in men with benign prostate disease.[17,25]

This case–control study is the first to use linked primary–secondary care datasets to consider the relationship. It sought to assess the association between the two diseases in a large and representative community-based population. The mean age in the cases identified for the study was 72.8 years, in keeping with the mean age of prostate cancer diagnosis in the UK, which is 70–74 years.[39] The age-group profile of the study cases also closely matched the age-group profile of newly identified prostate cancer cases in all of Scotland between 2001 and 2005 (Figure 1).[37] The risk of prostate cancer is strongly related to age: in the UK, the incidence rate is estimated to be 144/100 000 in men aged 55–59 years, 500/100 000 in men 65–69 years, and 789/100 000 in men over 85 years:[37,40–42] a trend confirmed by autopsy data.[43,44]

This study tested the hypothesis that some recorded diagnoses of benign disease may in reality indicate the early stages of a patient's interaction with health services and of the diagnostic process for prostate cancer, with presentations being recorded as benign that would subsequently be confirmed as malignant. Whether benign prostate disease is a 'working diagnosis' where a physician suspects malignancy but records a tentative diagnosis until confirmation, or whether an unwittingly inaccurate diagnosis, such records portray changes in diagnosis rather than disease progression, and could lead to erroneous associations in epidemiological research.

The study data indicate that, among men with prostate symptoms that are sufficiently bothersome to result in a primary care consultation, and a diagnosis of benign disease, those whose disease is in fact malignant are likely to be diagnosed within the first 6 months after presentation. If not diagnosed with cancer at 6 months after diagnosis of benign disease, the risk of a subsequent diagnosis of prostate cancer is no longer statistically significantly higher than it is for men with no previously recorded prostate disease, and at 1 year the risk appears to be even. The study confirms and extends previous work that has found no true association between the two diseases, and provides further reassurance to both patients and clinicians about the prognosis for men with benign prostate disease.

Implications for practice

Physicians treating patients with symptoms of prostate should be reassured that in men where a diagnosis of prostate cancer is not confirmed in the first 6 months, there is no significantly increased risk of prostate cancer when compared with patients without these symptoms.

The study data suggest that any higher

Funding

The study was not supported by any external funding source. The authors were supported by their respective institutions. Colin Simpson was supported by a health services and health of the public post-doctoral fellowship from the Chief Scientist Office of the Scottish Government (PDF/08/02).

Ethical committee

Use of the anonymised PCCIU/SMR/GROS linked database for this research was approved by the Privacy Advisory Committee for the Information Services Division of NHS National Services Scotland.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

Acknowledgements

The authors thank Professor James MO N'Dow of the Academic Urology Unit, University of Aberdeen, Scotland for his assistance with the application for ethical approval for the study; and Professor Andrew W Murphy, Professor Peter Cantillon, and Dr Liam Glynn of the Department of General Practice, National University of Ireland, Galway, for their assistance in reviewing the manuscript. No compensation was received for their contributions.

Discuss this article

Contribute and read comments about this article on the Discussion Forum:
http://www.rcgp.org.uk/bjgp-discuss

incidence of malignancy observed in those with a recent diagnosis of benign disease is likely to represent misdiagnosis or the possibility of rapidly evolving disease. Clinicians should therefore remain vigilant about the possibility of those who are first presenting or have recently presented with apparently benign prostate disease.

Among men diagnosed for the first time in primary care with prostate disease, unless a diagnosis of malignant disease is confirmed within 6 months, the incidence of subsequent diagnoses of prostate cancer is low and the risk of prostate cancer is not significantly higher than in men with no recorded prostate symptoms.

REFERENCES

1. Naslund MJ, Gilsenan AW, Midkiff KD, *et al.* Prevalence of lower urinary tract symptoms and prostate enlargement in the primary care setting. *Int J Clin Pract* 2007; **61(9):** 1437–1445.
2. Wei JT, Calhoun E, Jacobsen SJ. Urologic diseases in America project: benign prostatic hyperplasia. *J Urol* 2005; **173(4):** 1256–1261.
3. Jacobsen SJ, Girman CJ, Lieber MM. Natural history of benign prostatic hyperplasia. *Urology* 2001; **58(suppl 6a):** 5–16.
4. Bright E, Abrams P. Diseases of the prostate. *Rev Clin Gerontol* 2010; **20:** 10–19.
5. Young JM, Muscatello DJ, Ward JE. Are men with lower urinary tract symptoms at increased risk of prostate cancer? A systematic review and critique of the available evidence. *BJU Int* 2000; **85(9):** 1037–1048.
6. Thorpe A, Neal D. Benign prostatic hyperplasia. *Lancet* 2003; **361(9366):** 1359–1367.
7. Alcaraz A, Hammerer P, Tubaro A, *et al.* Is there evidence of a relationship between benign prostatic hyperplasia and prostate cancer? Findings of a literature review. *Eur Urol* 2009; **55(4):** 864–875.
8. Pienta KJ, Esper PS. Risk factors for prostate cancer. *Ann Intern Med* 1993; **118(10):** 793–803.
9. Andriole G, Brawley O, Tammela T, Rittmaster R. Baseline characteristics of patients in the REDUCE chemoprevention study. *Eur Urol* 2005; **4(suppl 3):** 184.
10. Habuchi T, Liqing Z, Suzuki T. Increased risk of prostate cancer and benign prostatic hyperplasia associated with a CYP17 gene polymorphism with a gene dosage effect. *Cancer Res* 2000; **60(20):** 5710–5713.
11. Prakash K Pirozzi G, Elashoff M, *et al.* Symptomatic and asymptomatic benign prostatic hyperplasia: molecular differentiation by using microarrays. *Proc Natl Acad Sci U S A* 2002; **99(11):** 7598–7603.
12. Andriole GL, Roehrborn C, Schulman C, *et al.* Effect of dutasteride on the detection of prostate cancer in men with benign prostatic hyperplasia. *Urology* 2004; **64(3):** 537–541.
13. Canby-Hagino E, Hernandez J, Brand TC, Thompson I. Looking back at PCPT: looking forward to new paradigms in prostate cancer screening and prevention. *Eur Urol* 2007; **51(1):** 27–33.
14. Haas GP, Sakr WA. Epidemiology of prostate cancer. *CA Cancer J Clin* 1997; **47(5):** 273–287.
15. Hammarsten J, Hogstedt B. Calculated fast-growing benign prostatic hyperplasia — a risk factor for developing clinical prostate cancer. *Scand J Urol Nephrol* 2002; **36(5):** 330–338.
16. Hammarsten J, Hogstedt B. Hyperinsulinaemia: a prospective risk factor for lethal clinical prostate cancer. *Eur J Cancer* 2005; **41(18):** 2887–2895.
17. Guess HA. Benign prostatic hyperplasia and prostate cancer. *Epidemiol Rev* 2001; **23(1):** 152–158.
18. Hamilton W, Sharp D. Symptomatic diagnosis of prostate cancer in primary care: a structured review. *Br J Gen Pract* 2004; **54(505):** 617–621.
19. Adolfsson J, Garmo H, Varenhorst E, *et al.* Clinical characteristics and primary treatment of prostate cancer in Sweden between 1996 and 2005. *Scand J Urol Nephrol* 2007; **41(6):** 456–477.
20. Farwell WR, Linder JA, Jha AK. Trends in prostate-specific antigen testing from 1995 through 2004. *Arch Intern Med* 2007; **167(22):** 2497–2502.
21. Thompson IM, Canby-Hagino E, Lucia MS. Stage migration and grade inflation in prostate cancer: Will Rogers meets Garrison Keillor. *J Natl Cancer Inst* 2005; **97(17):** 1236–1237.
22. Buckley BS. Conventional medicine is less than perfect. [commentary] *Br J Gen Pract* 2009; **59(564):** 519.
23. Barry MJ. Prostate specific antigen testing for early diagnosis of prostate cancer. *N Engl J Med* 2001; **344(18):** 1373–1377.
24. US Preventive Services Task Force. Screening for Prostate Cancer: US Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2008; **149(3):** 185–191.
25. Chokkalingam AP, Nyren O, Johansson J-E, *et al.* Prostate carcinoma risk subsequent to diagnosis of benign prostatic hyperplasia. A population-based cohort study in Sweden. *Cancer* 2003; **98(8):** 1727–1734.
26. ISD Scotland. *General practice – practice team information (PTI).* http://www.isdscotland.org/pti (accessed 5 May 2011).
27. Whitelaw FG, Nevin SL, Milne RM, *et al.* Completeness and accuracy of morbidity and repeat prescribing records held on general practice computer systems in Scotland. *Br J Gen Pract* 1996; **46(404):** 181–186.
28. Harley K, Jones C. Quality of Scottish Morbidity Record (SMR) data. *Health Bull* 1996; **54(5):** 410–417.
29. McAlister FA, Murphy NF, Simpson CR, *et al.* The influence of socioeconomic deprivation on the primary care burden and treatment of heart failure in Scotland. *BMJ* 2004; **328(7448):** 1110–1112.
30. The Scottish Government. *Scottish Index of Multiple Deprivation 2006: general report.* Edinburgh: The Scottish Government, 2006. http://www.scotland.gov.uk/Publications/2006/10/13142739/1 2006 (accessed 5 May 2011).
31. Donnelley R. *Scottish Index of Multiple Deprivation 2009: general report.* Edinburgh: The Scottish Government, 2009. http://www.scotland.gov.uk/Publications/2009/10/28104046/14 (accessed 5 May 2011).
32. Garraway WM, Russell EBAW, Lee RJ, *et al.* Impact of previously unrecognised benign prostatic hyperplasia on the daily activities of middle-aged and elderly men. *Br J Gen Pract* 1993; **43(373):** 318–321.
33. Alcaraz A, Hammerer P, Tubaro A, *et al.* Is there evidence of a relationship between benign prostatic hyperplasia and prostate cancer? Findings of a literature review. *Eur Urol* 2009; **55(4):** 864–875.
34. Lourenco T, Armstrong N, N'Dow J, *et al.* Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement. *Health Technol Assess* 2008; **12(35):** iii, ix–x, 1–146, 169–515.
35. Thorpe A, Neal D. Benign prostatic hyperplasia. *Lancet* 2003; **361(9366):** 1359–1367.
36. Glaziou P. *Sampsize home page.* http://sampsize.sourceforge.net (accessed 5 May 2011).
37. ISD. *Cancer Incidence (2005).* Edinburgh: ISD Online Information and Statistics Division, NHS Scotland, 2007. http://www.isdscotlandarchive.scot.nhs.uk/isd/183.html (accessed 21 Sep 2011).
38. Buckley BS, Simpson CR, McLernon DJ, *et al.* Five year prognosis in patients with angina identified in primary care: incident cohort study. *BMJ* 2009; **339(7718):** 438–441.
39. Burfor DC, Kirby M, Austoker J. *Prostate cancer risk management programme information for primary care; PSA testing in asymptomatic men — evidence document.* London: NHS Cancer Screening Programmes, 2009. http://www.cancerscreening.nhs.uk/prostate/pcrmp02.pdf (accessed 21 Sept 2011).
40. *Cancer incidence in Wales, 2002–2006.* Cardiff: Welsh Cancer Intelligence and Surveillance Unit, 2008.
41. *Cancer incidence and mortality.* Belfast: Northern Ireland Cancer Registry, Queen's University Belfast, 2008.
42. Office for National Statistics. *Cancer Statistics registrations: registrations of cancer diagnosed in 2005.* London: Office for National Statistics, 2008.
43. Nelson WG, De Marzo AM, Isaacs WB. Prostate cancer. *N Engl J Med* 2003; **349(4):** 366–381.
44. Sakr WA, Grignon DJ, Crissman JD, *et al.* High grade prostatic intraepithelial neoplasia (HGPIN) and prostatic adenocarcinoma between the ages of 20–69: an autopsy study of 249 cases. *In Vivo* 1994; **8(3):** 439–443.