ProtecT Study Publications
Associations of aspirin, non-steroidal anti-inflammatory drug and paracetamol use with PSA detected prostate cancer: findings from a large, population-based, case-control study (the ProtecT study)

International Journal of Cancer

Authors:
Murad A
Down L
Davey Smith G
Hamdy F
Neal D
Donovan J
Martin R

Abstract:
Evidence from laboratory studies suggests that chronic inflammation plays an important role in prostate cancer aetiology. This has resulted in speculation that nonsteroidal anti-inflammatory drugs may protect against prostate cancer development. We analysed data from a cross-sectional case-control study (n cases= 1,016; n controls= 5,043), nested within a UK-wide population-based study that used PSA-testing for identification of asymptomatic prostate cancers, to investigate the relationship of aspirin, non-steroidal anti-inflammatory drug (NSAID) and paracetamol use with prostate cancer. In conditional-logistic regression models accounting for stratum matching on age (5-year age-bands) and recruitment centre, use of non-aspirin NSAIDs (odds ratio, OR = 1.32, 95% CI: 1.04 to 1.67) or all NSAIDs (OR = 1.25; 1.07 to 1.47) were positively associated with prostate cancer. There were weaker, not conventionally statistically significant, positive associations of aspirin (OR = 1.13; 0.94 to 1.36) and paracetamol (OR = 1.20; 0.90 to 1.60) with prostate cancer. Mutual adjustment for aspirin, non-aspirin NSAIDs or paracetamol made little difference to these results. There was no evidence of confounding by age, family history of prostate cancer, body mass index or self-reported diabetes. Aspirin, NSAID and paracetamol use were associated with reduced serum PSA concentrations amongst controls. Our findings do not support the hypothesis that NSAIDs reduce the risk of PSA-detected prostate cancer. Our conclusions are unlikely to be influenced by PSA detection bias because the inverse associations of aspirin, NSAID and paracetamol use with serum PSA would have attenuated (not generated) the observed positive associations.
Circulating folate, vitamin B12, homocysteine, and vitamin B12 transport proteins in relation to prostate cancer risk: a case-control study, systematic review and meta-analysis

Cancer Epidemiology Biomarkers and Prevention

Authors:
Collin S

Abstract:
PSA-detected prostate cancer and the potential of dedifferentiation - estimating the proportion capable of progression

International Journal of Cancer

Authors:
- Pashayan N
- Pharoah P
- Neal DE
- Hamdy F
- Donovan J
- Martin RM
- Greenberg D
- Duffy SW

Abstract:
Impact of prostate cancer testing: an evaluation of the emotional consequences of a negative biopsy result

British Journal of Cancer
2010, 102: 1335-1340

Authors:
Vedhara K
Avery K
Metcalfe C
Lane A
Down L
Donovan J
Neal D
Hamdy F

Abstract:

BACKGROUND: When testing for prostate cancer, as many as 75% of men with a raised prostate-specific antigen (PSA) have a benign biopsy result. Little is known about the psychological effect of this result for these men.

METHODS: In all, 330 men participating in the prostate testing for cancer and treatment (ProtecT) study were studied; aged 50–69 years with a PSA level of >3 ng/ml-1 and a negative biopsy result. Distress and negative mood were measured at four time-points: two during diagnostic testing and two after a negative biopsy result.

RESULTS: The majority of men were not greatly affected by testing or a negative biopsy result. The impact on psychological health was highest at the time of the biopsy, with around 20% reporting high distress (33 out of 171) and tense/anxious moods (35 out of 180). Longitudinal analysis on 195 men showed a significant increase in distress at the time of the biopsy compared with levels at the PSA test (difference in Impact of Events Scale (IES) score: 9.47; 95% confidence interval (CI) (6.97, 12.12); P<0.001). These levels remained elevated immediately after the negative biopsy result (difference in score: 7.32; 95% CI (5.51, 9.52); P<0.001) and 12 weeks later (difference in score: 2.42; 95% CI (0.50, 1.15); P<0.009). Psychological mood at the time of PSA testing predicted high levels of distress and anxiety at subsequent time-points.

CONCLUSIONS: Most men coped well with the testing process, although a minority experienced elevated distress at the time of biopsy and after a negative result. Men should be informed of the risk of distress relating to diagnostic uncertainty before they consent to PSA testing.
A polymorphism in the glucokinase gene that raises plasma fasting glucose, rs1799884, is associated with diabetes mellitus and prostate cancer

International Journal of Molecular Epidemiology and Genetics

2010, 1: 175-183

Authors:
Murad AS
Davey Smith G
Lewis S
Cox A
Hamdy FC
Neal DE
Donovan J
Martin RM

Abstract:
Epidemiological studies have identified an inverse association between type 2 diabetes mellitus and prostate cancer. The mechanisms underlying this association are not clear. A single nucleotide polymorphism in the glucokinase gene, rs1799884, is associated with higher circulating plasma fasting glucose and with an increased risk of type 2 diabetes mellitus. Using data from a large, population-based case-control study we replicate the association of rs1799884 with type 2 diabetes (ORGG v AA= 2.70, 95% CI= 1.25 to 5.85) and find suggestive evidence for a novel association of rs1799884 with prostate cancer (ORGG v AA= 1.40, 95% CI= 0.95 to 2.07). Our results provide further evidence for a link between type 2 diabetes mellitus and prostate cancer and we hypothesise that alterations in insulin concentration may be important in mediating this relationship.
Association of diabetes mellitus with prostate cancer: nested case-control study (ProtecT: Prostate testing for cancer and Treatment)

International Journal of Cancer

2010

Authors:
Turner EL
Lane JA
Donovan JL
Davis MJ
Metcalfe C
Neal DE
Hamdy FC
Martin RM

Abstract:
Observational studies suggest that diabetes is associated with a decreased risk of prostate cancer, but few are population based or have investigated associations with cancer stage or duration of diabetes. We report a case–control study nested within the population-based Prostate testing for cancer and Treatment (ProtecT) study ISRCTN20141297. Men aged 50–69 years based around 9 UK cities were invited for a prostate-specific antigen (PSA) test between June 2002 and November 2006. Amongst 55,215 PSA-tested men, 1,966 had histologically confirmed prostate cancer; of these, 1,422 (72.3%) completed the questionnaire and 1,291 (65.7%) had complete data for analysis. We randomly selected 6,479 age- (within 5 years) and general practice-matched controls. The prevalence of diabetes was 89/1,291 (6.9%) in cases and 555/6,479 (8.6%) in controls. Diabetes was associated with a reduced risk of prostate cancer (odds ratio 5 0.78; 95% confidence interval: 0.61–0.99). There was weak evidence that the inverse association was greater for well- versus poorly differentiated cancers (p 5 0.07). The magnitude of the inverse association did not change with increasing duration of diabetes (p for trend 5 0.95). Diabetes is associated with a decreased risk of PSA-detected prostate cancer. These data add to the evidence of the association of diabetes with prostate cancer in the PSA era.
The Potential Value of Microseminoprotein-beta as a Prostate Cancer Biomarker and Therapeutic Target

Prostate
2010, 70: 333-340

Authors:
Whitaker HC
Warren AY
Eeles R
Kote-Jarai Z
Neal DE

Abstract:

BACKGROUND. Recent genome-wide association studies have shown an association of a SNP two base pairs upstream of the 5' UTR of the microseminoprotein-b (MSMB) gene with an increased risk of developing the prostate cancer, re-igniting interest in its protein product, MSMB.

METHODS. As one of the most abundant prostatic proteins, MSMB can be reliably detected in tissue and serum.

RESULTS. It has been consistently shown that MSMB expression is high in normal and benign prostate tissue and lowered or lost in prostate cancer suggesting that it might be a useful tissue biomarker for prostate cancer diagnosis and its levels in serum may be useful as a marker for prognosis. Members of the cysteine-rich secretory protein family and laminin receptors have been shown to bind MSMB at the cell surface and in serum thereby regulating apoptosis. Thus, in the benign prostate, MSMB regulates cell growth, but when MSMB is lost during tumourigenesis, cells are able to grow in a more uncontrolled manner. Both full length MSMB and a short peptide comprised of amino acids 31-45 have been tested for potential therapeutic benefit in mouse models and humans.

CONCLUSIONS. MSMB has potential as a biomarker of prostate cancer development, progression and recurrence and potentially as a target for therapeutic intervention.
Factors distinguishing general practitioners who more readily participated in a large randomized trial were identified

Journal of Clinical Epidemiology
2009, 62: 67-73

Authors:
Down L
Metcalfe C
Avery K
Noble S
Lane JA
Neal DE
Hamdy FC
Donovan JL

Abstract:

Objective
To investigate factors associated with the successful recruitment of general practices to a randomized controlled trial.

Study Design and Setting
Analysis of accrual of primary care centers to a randomized controlled trial in the UK.

Results
Those practices promptly agreeing to take part had better target achievement and a higher proportion of white British residents locally. Participating practices had a mean Quality and Outcomes Framework attainment of 92% of the points available, whereas nonparticipating practices achieved 88% (P = 0.009). Participating practices were located in areas with a higher proportion of white British residents (mean 89%), in comparison to nonparticipating practices (mean 84%, P = 0.004). Reasons given by practices to explain nonparticipation were primarily related to internal factors, with 38% of practices approached saying that they could not participate for such reasons.

Conclusion
There are some small differences between participating practices and nonparticipants in achievement of government targets and in the local ethnic mix. The primary reason given by practices for nonparticipation was workload or time pressures, with over a third of practices reporting being prevented by issues relating to practice organization. It may be that practices with workload or organizational difficulties require additional support to participate in research.
Development of a complex intervention improved randomisation and informed consent in a randomised controlled trial

Journal of Clinical Epidemiology
2009, 62: 29-36

Authors:
Donovan JL
Lane JA
Peters JT
Brindle LA
Salter L
Gillatt D
Powell PH
Bolliina P
Neal DE
Hamdy FC

Abstract:
Objective:
Multicenter randomized trials are required for pragmatic evaluations of health care interventions, but recruitment is difficult. Systematic reviews failed to identify robust strategies to improve recruitment. We developed and evaluated a complex intervention to increase levels of randomization and informed consent.

Study Design and Setting:
The ProtecT (Prostate testing for cancer and Treatment) trial compares radical surgery, radical conformal radiotherapy, and active monitoring for men aged 50e69 years with localized prostate cancer. The intervention was developed using qualitative research methods (content, thematic and conversation analysis). Rates of randomization and immediate acceptance of allocation were measured every 6 months to evaluate the impact of the intervention.

Results:
The complex intervention comprised reviews of centers falling below study targets, training programmes, documents and individually tailored feedback. Over 65% of eligible participants consented to randomization. Trial participants became increasingly well informed as immediate acceptance of allocation rose from 65% to 81% between 2001 and 2005.

Conclusion:
This complex intervention resulted in high levels of randomization and informed consent in a difficult trial. The generic aspects of the intervention could be applied to other trials to maximize randomization and informed consent, and allow the mounting of trials previously considered too difficult.
It’s not just what you say, it’s also how you say it: Opening the ‘black box’ of informed consent appointments in randomised controlled trials

Social Science & Medicine
2009, 68: 2018-2028

Authors:
Wade J
Donovan JL
Lane JA
Neal DE
Hamdy FC

Abstract:

Randomised controlled trials (RCTs) represent the gold standard methodology for determining the effectiveness of health-care interventions. Poor recruitment to RCTs can threaten external validity and waste resources. There is an inherent tension in recruitment between maximising the number enrolled while ensuring informed decision-making by participants. This study aimed to identify aspects of the recruitment process that provided evidence that potential participants were making an informed decision as to whether to participate in an ongoing multi-centre RCT. Analysis of tape-recorded recruitment appointments led to a greater understanding of the process of recruitment and explored optimum methods for ensuring high levels of informed consent and participation in an ongoing multi-centre RCT.

A purposive sample of 23 recruitment appointments from three study centres and including several recruitment staff was analysed using qualitative conversation and thematic analysis techniques. Findings revealed variation in the content and structure of appointments that affected the interaction between recruiters and potential participants and available evidence about levels of informed consent. Techniques leading to high levels of informed consent included the use of open questions, pauses, and avoiding long passages of information, interruptions and confusing terminology. These techniques allowed recruitment staff to elicit then address participant concerns.

The current focus on written information for RCT participants and the conduct of recruiters needs to broaden to encompass consideration of how information is best conveyed to and received by participants in recruitment consultations. A model of tailored information provision centred on eliciting and addressing participants’ concerns within a participant-led framework is proposed. Use of these techniques should improve levels of informed consent and rates of recruitment to RCTs.
Life course sun exposure and risk of prostate cancer: population-based nested case-control study (ProtecT)

International Journal of Cancer

2009, 125: 1414-1423

Authors:
Gilbert R
Metcalfe C
Oliver S
Whiteman D
Bain C
Ness A
Donovan J
Hamdy F
Neal D
Lane JA
Martin R

Abstract:
There is currently no means of primary prevention for prostate cancer. Increased exposure to ultraviolet-radiation may be protective, but the literature is inconclusive. We investigated associations of life course exposure to sunlight with prostate cancer. The study design was a UK-wide nested case-control study, based on 1,020 prostate specific antigen-detected cases and 5,044 matched population controls and a systematic review with meta-analysis. Men with olive/brown skin (OR 5 1.47; 95% CI: 1.00 to 2.17), men who burnt rarely/never (OR 5 1.11; 0.95 to 1.29) and men with the lowest levels of intense sun exposure in the 2 years prior to diagnosis (OR 5 1.24; 1.03 to 1.50) had an increased prostate cancer risk. However, amongst men with prostate cancer, spending less time outside was associated with a reduced risk of advanced cancer (OR 5 0.49; 0.27 to 0.89) and high Gleason grade (OR 5 0.62; 0.43 to 0.91), and men who burnt rarely/never had a reduced risk of advanced cancer (OR 5 0.71; 0.47 to 1.08). The meta-analysis provided weak evidence that men with the lowest (versus highest) sunlight exposure had an increased prostate cancer risk (4 studies, random-effects pooled relative risk 5 1.13; 0.98 to 1.29) and higher advanced or fatal prostate cancer risk (6 studies, randomeffects pooled relative risk 5 1.14; 0.98 to 1.33). Our data and meta-analyses provide limited support for the hypothesis that increased exposure to sunlight may reduce prostate cancer risk. The findings warrant further investigation because of their implications for vitamin D chemoprevention trials.
Genetic Variants in the Vitamin D Receptor Are Associated with Advanced Prostate Cancer at Diagnosis: Findings from the Prostate Testing for Cancer and Treatment Study and a Systematic Review

Cancer Epidemiology Biomarkers and Prevention

2009, 18: 2874-2881

Authors:
Chen L
Davey Smith G
Evans DM
Cox A
Lawlor DA
Donovan J
Yuan W
Day INM
Martin RM
Lane A
Rodriguez S
Davis M
Zuccolo L
Collin S
Hamdy F
Neal D
Lewis SJ

Abstract:
Low levels of plasma vitamin D have been implicated as a possible risk factor for both prostate cancer incidence and advanced disease, and recent phase II trials suggest that vitamin D supplementation might delay progression of prostate cancer. Common polymorphisms in the vitamin D receptor (VDR) are associated with VDR activity and are therefore potentially useful proxies for assessing whether vitamin D is causally related to advanced prostate cancer. We genotyped five well-known VDR polymorphisms in 1,604 men with prostate cancer from the Prostate Testing for Cancer and Treatment study. Our aim was to examine the association between VDR polymorphisms and cancer stage (localized versus advanced) as well as cancer grade (Gleason score <7 versus ≥7). Moreover, we also carried out a systematic review and meta-analysis of 13 similar studies. As a result of our meta-analysis, we revealed three polymorphisms, BsmI, ApaI, and TaqI, associated with high Gleason score with an overall summary odds ratios (95% confidence intervals) of 1.12 (1.00-1.25; bb versus BB + Bb), 1.25 (1.02-1.53; aa versus AA + Aa), and 0.82 (0.69-0.98; Tt + tt versus TT), respectively. The haplotype analysis revealed that the BsmI (B)-ApaI (A)-TaqI (t) participants compared with BsmI (b)-ApaI (a)-TaqI (T) individuals were less likely to have high
Gleason scores (odds ratio, 0.84; 95% confidence interval, 0.71-1.00; Punadjusted = 0.050; Padjusted = 0.014). Our finding provides some support for the hypothesis that low levels of vitamin D may increase the risk of prostate cancer progression.
Do the risk factors of age, family history of prostate cancer or a higher prostate specific antigen level raise anxiety at prostate biopsy?

European Journal of Cancer
2009, 45: 2569-2573

Authors:
Macefield R
Lane JA
Metcalfe C
Down L
Hamdy FC
Neal DE
Donovan JL

Abstract:
To date, little is known of the impact knowledge of personal risk factors has on anxiety in men undergoing biopsy tests for prostate cancer. This analysis explores anxiety scores of men at higher risk due to age, family history of prostate cancer and a higher prostate specific antigen (PSA) level when proceeding from PSA test to prostate biopsy. A prospective cohort of 4198 men aged 50–69 years with a PSA result of >3 ng/ml was studied, recruited for the Prostate testing for cancer and Treatment study (ProtecT). Anxiety scores at the time of biopsy were lower in older men (p < 0.001). No age group showed an increase in anxiety as the men proceeded from PSA testing to biopsy, although older men did not show the same level of decrease in anxiety as younger men (p = 0.035). There was no difference in anxiety scores at biopsy between men with or without a family history of prostate cancer (p = 0.68), or between those with a raised PSA of 10–<20 ng/ml compared to a PSA result of 3–<10 ng/ml (p = 0.46). Change in scores since the initial PSA test appeared unaffected by family history (p = 0.995) or by PSA result (p = 0.76). Within the context of a research study, the increased risk of prostate cancer through older age, having a family history of prostate cancer, or having a significantly elevated PSA level appears to have no detrimental effect on men’s anxiety level when proceeding to biopsy.
Feasibility and cost of obtaining informed consent for essential review of medical records in large-scale public health research

Journal of Health Services Research & Policy

2009, 14: 77-81

Authors:
Noble S
Donovan J
Turner EL
Metcalfe C
Lane JA
Rowlands M
Neal D
Hamdy F
Ben-Shlomo Y
Martin RM

Abstract:

Objective: To evaluate the effectiveness and cost of obtaining consent for review of medical records within the passively observed non-intervention arm of a cluster randomized controlled trial, 'Comparison Arm for ProtecT'.

Methods: Two hundred and thirty men, who had been notified to the trial by cancer registries as having prostate cancer, were sent a consent form from their general practitioner or secondary care clinician. The consent rate of participants to the review of their medical records and the estimated costs of the process were evaluated.

Results: One hundred and seventy-nine men (84%: 95% CI = 78%, 89%) consented to have their medical notes reviewed at an estimated cost of £123 (172, $248) per person.

Conclusions: A high consent rate for review of medical notes is achievable but at a cost. There needs to be renewed debate about the automatic need for consent to review medical records where the chance of personal harm is negligible and the purpose of the review is to provide robust evidence to save lives, prevent needless suffering, and improve the effectiveness and efficiency of health care delivery.
Circulating insulin-like growth factor peptides and prostate cancer risk: a systematic review & meta-analysis

International Journal of Cancer

2009, 124: 2416-2429

Authors:
Rowlands M-A
Gunnell D
Harris R
Vatten LJ
Holly JMP
Martin RM

Abstract:
Insulin-like growth factors (IGF-I, IGF-II) and their binding proteins (IGFBP-1-6) play a key role in cell proliferation, differentiation and apoptosis, suggesting possible involvement in carcinogenesis. Several epidemiological studies show associations of IGFs with prostate cancer. We searched the published literature for all studies relating levels of IGFs or IGFBPs with prostate cancer. We performed random effects meta-analysis to calculate summary odds ratios. The number of studies (prostate cancer cases) included in each meta-analysis were 42 (7,481) IGF-I; 10 (923) IGF-II; 3 (485) IGFBP-1; 5 (577) IGFBP-2; 29 (6,541) IGFBP-3 and 11 (3,545) IGF-1:IGFBP-3 ratio. The pooled odds ratios (95% confidence intervals) per standard deviation increase in peptide were: IGF-I, OR = 1.21 (1.07, 1.36); IGF-II, OR = 1.17 (0.93, 1.47); IGFBP-1, OR = 1.21 (0.62, 2.33); IGFBP-2, OR = 1.18 (0.90, 1.54); IGFBP-3, OR = 0.88 (0.79, 0.98); IGF1:IGFBP-3 ratio, OR = 1.10 (0.97, 1.24). For all exposures, there was substantial heterogeneity (all I2 > 75%), partly explained by study design: the magnitude of associations was smaller in prospective vs. retrospective studies, and for IGFBP-3, the inverse association with prostate cancer risk was seen in retrospective but not prospective studies. There was weak evidence that associations of IGF-I and IGFBP-3 with prostate cancer were stronger for advanced disease. Our meta-analysis confirms that raised circulating IGF-I is positively associated with prostate cancer risk. Associations between IGFBP-3 and prostate cancer were inconsistent, and there was little evidence for a role of IGF-II, IGFBP-1 or IGFBP-2 in prostate cancer risk.
PTGS2 −899G>C and prostate cancer risk: population-based nested case-control study (ProtecT) and a systematic review with meta-analysis

Prostatic Cancer and Prostatic Diseases
2009, 12: 296-300

Authors:
Murad A
Martin R
Chen L
Donovan J
Hamdy F
Neal D
Davey Smith G
Lewis S

Abstract:
Prostaglandin endoperoxidase synthase 2 is a key regulator of inflammation and may play a role in prostate carcinogenesis. The polymorphism −899G>C (rs20417) alters a transcription factor binding site and is associated with a reduced risk of colorectal adenoma. We tested the hypothesis that rs20417 may influence prostate cancer risk using a large case-control study (n cases= 1,608, n controls= 3,058). We found no evidence that rs20417 alters prostate cancer risk (ORCC & GC v GG= 1.06, 95% CI= 0.93 to 1.21). A meta-analysis of three studies also found little evidence that rs20417 alters risk (pooled ORCC & GC v GG= 1.04, 95% CI= 0.93 to 1.17), making it unlikely that rs20417 contributes in any major way to prostate cancer aetiology.
Association of Folate-Pathway Gene Polymorphisms with the Risk of Prostate Cancer: a Population-Based Nested Case-Control Study, Systematic Review, and Meta-analysis

Cancer Epidemiology, Biomarkers and Prevention

2009, 18: 2528-2539

Authors:
Collin S
Martin R
Lewis S

Abstract:
Folate-pathway gene polymorphisms have been implicated in several cancers and investigated inconclusively in relation to prostate cancer. We conducted a systematic review, which identified nine case-control studies (eight included, one excluded). We also included data from four genome-wide association studies and from a case control study nested within the UK population-based Prostate Testing for Cancer and Treatment study. We investigated by meta-analysis the effects of eight polymorphisms: MTHFR C677T (rs1801133; 12 studies; 10,745 cases; 40,158 controls), MTHFR A1298C (rs1801131; 5 studies; 3,176 cases; 4,829 controls), MTR A2756G (rs1805087; 8 studies; 7,810 cases; 37,543 controls), MTRR A66G (rs1801394; 4 studies; 3,032 cases; 4,515 controls), MTHFD1 G1958A (rs2236225; 6 studies; 7,493 cases; 36,941 controls), SLC19A1/RFC1 G80A (rs1051266; 4 studies; 6,222 cases; 35,821 controls), SHMT1 C1420T (rs1979277; 2 studies; 2,689 cases; 4,110 controls), and FOLH1 T1561C (rs202676; 5 studies; 6,314 cases; 35,190 controls). The majority (10 of 13) of eligible studies had 100% Caucasian subjects; only one study had <90% Caucasian subjects. We found weak evidence of dominant effects of two alleles: MTR 2756A>G [random effects pooled odds ratio, 1.06 (1.00-1.12); P=0.06 (P = 0.59 for heterogeneity across studies)] and SHMT1 1420C>T [random effects pooled odds ratio, 1.11 (1.00-1.22); P = 0.05 (P = 0.38 for heterogeneity across studies)]. We found no effect of MTHFR 677C>T or any of the other alleles in dominant, recessive or additive models, or in comparing a/a versus A/A homozygous. Neither did we find any difference in effects on advanced or localized cancers. Our meta-analysis suggests that known common folate-pathways single nucleotide polymorphisms do not have significant effects on susceptibility to prostate cancer.
Associations of sexual dysfunction symptoms with PSA-detected localized and advanced prostate cancer: a case-control study nested within the UK population-based ProtecT (Prostate testing for cancer and Treatment) study

European Journal of Cancer
2009, 45: 3254-3261

Authors:
Collin S
Metcalfe C
Donovan J
Lane A
Neal D
Hamdy F
Davis M
Martin R

Abstract:
Background: Sexual dysfunction might be symptomatic of cancer spreading beyond the prostate by local invasion, a mechanism of tumour progression associated with prognosis. Conversely, among men with raised prostate-specific antigen (PSA) levels, a negative association might be expected if sexual dysfunction was symptomatic of benign, rather than malignant, prostatic disease.

Patients and methods: Cases and controls were selected from among men recruited to the UK population-based ProtecT (Prostate testing for cancer and Treatment) study. Men aged 50–69 years were invited for PSA testing and those with a PSA level >3.0 ng/ml were invited for biopsy. We investigated whether symptoms of sexual dysfunction, determined by self-completed questionnaire prior to biopsy, were associated with prostate cancer.

Results: Of the 8924 men who had a PSA level >3.0 ng/ml (11% of the men who had a PSA test), 6585 underwent biopsy of whom 2813 and 421, respectively, were subsequently diagnosed with localised and advanced prostate cancer and 3351 had a negative biopsy result. No individual symptom of sexual dysfunction was associated with risk of prostate cancer.

The symptom score was associated with advanced (odds ratio (OR) per one unit increase in score = 1.06; 1.00–1.12; P = 0.07) but not with localised (OR = 1.00; 0.97–1.02; P = 0.9) prostate cancer (P = 0.05 for heterogeneity).

Conclusions: Our study provides weak evidence that sexual dysfunction may be associated with PSA-detected advanced, but not localised, prostate cancer among men with raised PSA levels.
Mean sojourn time, overdiagnosis, and reduction in advanced stage prostate cancer due to screening with PSA: implications of sojourn time on screening

British Journal of Cancer
2009, 100: 1198-1204

Authors:
Pashyan N
Duffy SW
Pharoah P
Greenberg D
Donovan J
Martin RM
Hamdy F
Neal DE

Abstract:
Identification of new genetic risk factors for prostate cancer

Asian Journal of Andrology

2009, 11: 49-55

Authors:

Guy M

Abstract:

There is evidence that a substantial part of genetic predisposition to prostate cancer (PCa) may be due to lower penetrance genes which are found by genome-wide association studies. We have recently conducted such a study and seven new regions of the genome linked to PCa risk have been identified. Three of these loci contain candidate susceptibility genes: MSMB, LMTK2 and KLK2/3. The MSMB and KLK2/3 genes may be useful for PCa screening, and the LMTK2 gene might provide a potential therapeutic target. Together with results from other groups, there are now 23 germline genetic variants which have been reported. These results have the potential to be developed into a genetic test. However, we consider that marketing of tests to the public is premature, as PCa risk can not be evaluated fully at this stage and the appropriate screening protocols need to be developed. Follow-up validation studies, as well as studies to explore the psychological implications of genetic profile testing, will be vital prior to roll out into healthcare.
Development of a New Method for Monitoring Prostate-Specific Antigen Changes in Men with Localised Prostate Cancer: A Comparison of Observational Cohorts

European Urology
2009, 57: 446-452

Authors:
Tilling K
Garmo H
Metcalfe C

Abstract:

Background
Prostate-specific antigen (PSA) measurements are increasingly used to monitor men with localised prostate cancer (PCa), but there is little consensus about the method to use.

Objective
To apply age-specific predictions of PSA level (developed in men without cancer) to one cohort of men with clinically identified PCa and one cohort of men with PSA-detected PCa. We hypothesise that among men with clinically identified cancer, the annual increase in PSA level would be steeper than in men with PSA-detected cancer.

Design, setting, and participants
The Scandinavian Prostate Cancer Group 4 (SPCG-4) cohort consisted of 321 men assigned to the watchful waiting arm of the SPCG-4 trial. The UK cohort consisted of 320 men with PSA-detected PCa in the Prostate testing for cancer and Treatment (ProtecT) study who opted for monitoring. Multilevel models describing changes in PSA level were fitted to the two cohorts, and average PSA level at age 50, change in PSA level with age, and predicted PSA values were derived.

Measurements
PSA level.

Results and limitations
In the SPCG-4 cohort, mean PSA at age 50 was similar to the cancer-free cohort but with a steeper yearly increase in PSA level (16.4% vs 4.0%). In the UK cohort, mean PSA level was higher than that in the cancer-free cohort (due to a PSA biopsy threshold of 3.0 ng/ml) but with a similar yearly increase in PSA level (4.1%). Predictions were less accurate for the SPCG-4 cohort (median difference between observed and predicted PSA level: −2.0 ng/ml; interquartile range [IQR]: −7.6–0.7 ng/ml) than for the UK cohort (median difference between observed and predicted PSA level: −0.8 ng/ml; IQR: −2.1–0.1 ng/ml).

Conclusions
In PSA-detected men, yearly change in PSA was similar to that in cancer-free men, whereas in men with symptomatic PCa, the yearly change in PSA level was
considerably higher. Our method needs further evaluation but has promise for refining active monitoring protocols.

Take Home Message

In men with localised prostate cancer, yearly change in prostate-specific antigen (PSA) level was considerably higher in those whose cancer was detected through presentation of symptoms than in those whose cancer was detected through PSA screening. Our reference range method needs further evaluation but has promise for refining active monitoring protocols.
Population-based prostate-specific antigen testing in the UK leads to stage migration of prostate cancer

British Journal of Urology International

2009, 104: 1592-1598

Authors:

Moore AL
Dimitropoulou P
Lane A
Powell PH
Greenberg DC
Brown CH
Donovan JL
Hamdy FC
Martin RM
Members of the ProtecT Study Group
Neal DE

Abstract:

ABSTRACT
To determine, within the UK, the stage and grade of prostate cancers that would be found through population-based prostate specific antigen (PSA) testing and biopsy.

SUBJECTS AND METHODS
In the 'Prostate Testing for Cancer and Treatment' trial (ProtecT), men aged 50–69 years were recruited from nine cities in the UK and from randomly selected practices of general practitioners. Those with a PSA level of >3 ng/mL were offered a prostate biopsy. Age, PSA, stage and grade at diagnosis of ProtecT participants with cancer were compared with contemporaneous incident cases aged 50–69 years (age-restricted Cancer Registry cases) registered with the Eastern Cancer Registration and Information Centre (ECRIC).

RESULTS
Within ProtecT, 94 427 men agreed to be tested (50% of men contacted), 8807 (≈9%) had a raised PSA level and 2022 (23%) had prostate cancer; 229 (≈12%) had locally advanced (T3 or T4) or metastatic cancers, the rest having clinically localized (T1c or T2) disease. Within ECRIC, 12 661 cancers were recorded over the same period; 3714 were men aged 50–69 years at diagnosis. Men in ProtecT had a lower age distribution and PSA level, and the cancers were of lower stage and grade (P < 0.001 for all comparisons). If population-based PSA testing were introduced in the UK, ≈2660 men per 100 000 aged 50–69 years would be found to have prostate cancer, compared to current rates of ≈130 per 100 000. If half of men accepted PSA testing, ≈160 000 cancers would be found, compared to 30 000 diagnosed each year at present.

CONCLUSIONS
Population-based PSA testing resulted in a significant downward stage and grade migration, and most such cancers were of low stage and grade, which could lead to risks of over-treatment for some men.
Stage shift in PSA-detected prostate cancers – effect modification by Gleason score

Journal of Medical Screening

2009, 16: 98-101

Authors:
- Pashayan N
- Pharoah P
- Neal DE
- Hamdy F
- Donovan J
- Martin RM
- Greenberg D
- Duffy SW

Abstract:

Objective
This paper aims to investigate whether the stage shift (where more cancers are detected at an earlier stage) in prostate-specific antigen (PSA)-detected cancers differs by Gleason score.

Methods
Between 2002 and 2005, 1514 men aged 50–69 years were identified with prostate cancer following community-based PSA testing as part of the ProtecT study. In the same period, 2021 men aged 50–69 years with clinically diagnosed prostate cancer were registered at a population-based cancer registry in the East of England. Using logistic regression analysis and controlling for age, the odds ratio (OR) for advanced stage (TNM stage T3 and above) prostate cancer among the PSA-detected group was compared with the clinically diagnosed tumours. The evidence that stage shift differs by Gleason score was assessed using the likelihood ratio test for interaction.

Results
Advanced stage disease among the PSA-detected cancers was less common than among the clinically detected cancers (OR ¼ 0.47, 95% CI 0.39–0.56). PSA-detected tumours had a substantial shift to earlier-stage disease where the Gleason score was ,7 (OR ¼ 0.52; 95% CI 0.36–0.77, P , 0.001) but showed no such shift where the Gleason score was 7 or more (OR ¼ 0.84; 95% CI 0.66–1.07, P ¼ 0.1). There was evidence of interaction between detection mode and Gleason score (P ¼ 0.03).
Conclusion
The observed stage shift could be partially explained by length bias or overdiagnosis.
These findings may have implications on understanding pathways of prostate cancer progression and on identifying potential targets for screening, pending further investigation of complexities of associations between PSA testing, Gleason score, and stage.
Current strategies for monitoring men with localised prostate cancer lack a strong evidence base: observational longitudinal study

British Journal of Cancer

2009, 101: 390-394

Authors:

Metcalfe C
Tilling K
Davis M
Lane JA
Martin R
Kynaston H
Powell P
Neal DE
Hamdy F
Donovan J

Abstract:

BACKGROUND: The UK National Institute for Health and Clinical Excellence (NICE) guidance recommends conservative management of men with ‘low-risk’ localised prostate cancer, monitoring the disease using prostate-specific antigen (PSA) kinetics and re-biopsy.
However, there is little evidence of the changes in PSA level that should alert to the need for clinical re-assessment.

METHODS: This study compares the alerts resulting from PSA kinetics and a novel longitudinal reference range approach, which incorporates age-related changes, during the monitoring of 408 men with localised prostate cancer. Men were monitored by regular PSA tests over a mean of 2.9 years, recording when a man’s PSA doubling time fell below 2 years, PSA velocity exceeded 2 ng/ml–1 per year, or when his upper 10% reference range was exceeded.

RESULTS: Prostate-specific antigen doubling time and PSA velocity alerted a high proportion of men initially but became unresponsive to changes with successive tests. Calculating doubling time using recent PSA measurements reduced the decline in response. The reference range method maintained responsiveness to changes in PSA level throughout the monitoring.

CONCLUSION: The increasing unresponsiveness of PSA kinetics is a consequence of the underlying regression model. Novel methods are needed for evaluation in cohorts currently being managed by monitoring. Meanwhile, the NICE guidance should be cautious.
Multiple loci on 8q24 associated with prostate cancer susceptibility

Nature Genetics
2009, 41: 1058-1060

Authors:
Al Olama AA
Kote-Jarai Z
Giles GG
Guy M
Morrison J
Severi G
Leogamornlert DA
Tymrakiewicz M
Jhavar S
Saunders E
Et al

Abstract:
Psychological distress and prostate specific antigen levels in men with and without prostate cancer

Brain, Behavior and Immunity

2009, 23: 1073-1078

Authors:
Turner E
Lane JA
Metcalfe C
Down L
Donovan J
Hamdy F
Neal D
Vedhara K

Abstract:
The role of psychological distress in the onset and progression of prostate cancer is an under-researched area. We report results from a cohort study in which we have examined the relationship between indices of psychological distress and prostate specific antigen (PSA) levels (a glycoprotein associated with prostatic diseases including cancer) in men with and without prostate cancer and also the relationship between distress and the likelihood of receiving a diagnosis of prostate cancer. Data were obtained from 4886 men who attended PSA testing and biopsy as part of the ProtecT (Prostate testing for cancer and treatment) study (mean age 62 years; 98.9% White). Men completed questionnaires measuring anxiety, depression and urinary symptoms at initial PSA testing and again at biopsy when PSA was re-measured. Regardless of the subsequent diagnosis, there was no association between psychological distress scores at initial PSA testing and again at biopsy when PSA was re-measured. However, analyses pertaining to the relationship between distress and cancer diagnosis showed that men with ‘possible’ clinical depression at initial PSA testing (n = 519/4886) were 23% more likely to have a diagnosis of prostate cancer. These analyses highlight the need for further investigations into the possible role of depressed mood in the onset of prostate cancer and, in particular, research examining the biological basis for these relationships.
Mutation analysis of the MSMB gene in familial prostate cancer

British Journal of Cancer
2009, 102: 414-418

Authors:
Kote-Jarai Z
Leogamornlert DA
Tymrakiewicz M
Field H
Guy M
Al Olama AA
Morrison J
O’Brien L
Wilkinson R
Hall A
Sawyer E
Muir K
Hamdy F
Donovan J
Neal D
Easton D
Eeles R

Abstract:
BACKGROUND: MSMB, a gene coding for b-microseminoprotein, has been identified as a candidate susceptibility gene for prostate cancer (PrCa) in two genome-wide association studies (GWAS). SNP rs10993994 is 2 bp upstream of the transcription initiation site of MSMB and was identified as an associated PrCa risk variant. The MSMB protein is underexpressed in PrCa and it was previously proposed to be an independent marker for the recurrence of cancer after radical prostatectomy.

METHODS: In this study, the coding region of this gene and 1500 bp upstream of the 50UTR has been sequenced in germline DNA in 192 PrCa patients with family history. To evaluate the possible effects of these variants we used in silico analysis.

RESULTS: No deleterious mutations were identified, however, nine new sequence variants were found, most of these in the promoter and 50UTR region. In silico analysis suggests that four of these SNPs are likely to have some effect on gene expression either by affecting ubiquitous or prostate-specific transcription factor (TF)-binding sites or modifying splicing efficiency.

INTERPRETATION: We conclude that MSMB is unlikely to be a familial PrCa gene and propose that the high-risk alleles of the SNPs in
the 50UTR effect PrCa risk by modifying MSMB gene expression in response to hormones in a tissue-specific manner.
Screening for prostate cancer remains controversial

The Lancet
2009, 374: 1482-1483

Authors:
Neal DE
Donovan J
Martin RM
Hamdy FC

Abstract:
Identification of seven new prostate cancer susceptibility loci through a genome-wide association study

Nature Genetics
2009, 41: 1116-1121

Authors:
Eeles R
Kote-Jarai Z
Al Olama AA
Giles GG
Guy M
Severi G
Muir K
Hopper JL
Henderson BE
Haiman CA
Schleutker J
Hamdy FC
Neal DE
Donovan J
Et al

Abstract:
A recurrent truncating germline mutation in the BRIP1/FANCJ gene and susceptibility to prostate cancer

British Journal of Cancer
2009, 100: 426-430

Authors:
Kote-Jarai Z
Jugurnauth S
Mulholland S
Leogamornlert DA
Guy M
Edwards S
Tymrakiewicz M
O’Brien L
Hall A
Wilkinson R
Al Olama AA
Morrison J
Muir K
Neal D
Donovan J
Hamdy F
Easton DF
The UKGPCS Collaborators
The British Association of Urological Surgeons Section of
Eeles R

Abstract:
Prostate cancer (PrCa) aggregates in families, in a consistent manner with an important inherited component (reviewed in Edwards and Eeles, 2004). The genetic components underlying this familial risk have, however, proved difficult to identify. Genetic studies using linkage analysis in high-risk families have identified several possible susceptibility loci (Tavtigian et al, 2001; Carpten et al, 2002), but none of them have been definitively established (Easton et al, 2003). It seems likely now that susceptibility to PrCa is mediated, at least partially, through a combination of multiple low-penetrance loci (Haiman et al, 2007; Eeles et al, 2008; Thomas et al, 2008). Genome-wide association studies (GWAS) have identified common variants in several regions that are associated with PrCa risk (Eeles et al, 2008; Gudmundsson et al, 2008; Thomas et al, 2008). In addition, resequencing of candidate genes, notably those involved in DNA double-strand break repair, has identified rarer variants associated with a more substantial risk. The most important of these is BRCA2 mutations, which confer a risk of approximately five-fold, but there is evidence that truncating mutations in NBS1 and CHEK2 also...
confer susceptibility to PrCa (Dong et al, 2003; Edwards et al, 2003; Cybulski et al, 2004; Agalliu et al, 2007). The BRIP1/FANCJ gene encodes a helicase in which the C-terminal domain is reported to interact with BRCA1 (Cantor et al, 2001). The BRIP1 gene spans 180 kb, comprises 20 exons and encodes a protein of 1249 amino acids. It is located on chromosome 17q22, distal to BRCA1, which is at 17q21. BRIP1/FANCJ has an important role in BRCA-associated DNA damage repair functions, works as a DNA-dependent ATPase and a DNA helicase, and is essential for DNA repair and genomic stability. It forms a complex with the BRCT domain of BRCA1, and this is important for the role of BRCA1 in its DNA double-strand break repair function (Levitus et al, 2006). Germline mutations in BRIP1/FANCJ are associated with Fanconi anaemia, a chromosomal instability syndrome characterised by developmental abnormalities and predisposition to cancer (Levitus et al, 2005). Truncating mutations in the BRIP1/FANCJ gene have recently been shown to be associated with a moderate risk of breast cancer (Seal et al, 2006). Given the observed associations of PrCa with other DNA repair genes, we considered BRIP1/FANCJ as an attractive candidate for PrCapredisposition gene.
Low risk research using routinely collected identifiable health information without informed consent.

Medical Ethics
2008, 34: 37-40

Authors:
Metcalfe C
Martin RM
Noble S
Lane JA
Donovan J

Abstract:
Current UK legislation is impacting upon the feasibility and cost-effectiveness of medical record-based research aimed at benefiting the NHS and the public health. Whereas previous commentators have focused on the Data Protection Act 1998, the Health and Social Care Act 2001 is the key legislation for public health researchers wishing to access medical records without written consent. The Act requires researchers to apply to the Patient Information Advisory Group (PIAG) for permission to access medical records without written permission. We present a case study of the work required to obtain the necessary permissions from PIAG in order to conduct a large scale public health research project. In our experience it took eight months to receive permission to access basic identifying information on individuals registered at general practices, and a decision on whether we could access clinical information in medical records without consent took 18 months. Such delays pose near insurmountable difficulties to grant funded research, and in our case £560 000 of public and charitable money was spent on research staff while a large part of their work was prohibited until the third year of a three year grant. We conclude by arguing that many of the current problems could be avoided by returning PIAG's responsibilities to research ethics committees, and by allowing "opt-out" consent for many public health research projects.
**Decision-Making about PSA Testing and Prostate Biopsies: A Qualitative Study Embedded in a Primary Care Randomised Trial**

European Urology

2008, 53: 1186-1193

Authors:

Avery KNL  
Blazeby JN  
Lane JA  
Neal DE  
Hamdy FC  
Donovan JL

Abstract:

Objectives: The overall aim was to increase understanding of men’s decision-making about prostate-specific antigen (PSA) testing and subsequent biopsy.

Methods: This qualitative interview study was nested within the primary care-based Prostate Testing for Cancer and Treatment (ProtecT) trial in nine United Kingdom areas (ISRCTN number: 20141297). Fifty-eight men aged 50–69 yr (mean: 62 yr), accepting (n = 14) or not responding (n = 7) to invitations for PSA testing and accepting (n = 24) or refusing (n = 13) prostate biopsy were interviewed.

Results: In this study, men accepting PSA testing and biopsy reported positively on their experiences, regardless of the final outcome. PSA testing was considered routine and biopsy acceptable to most men. Men both responding and not responding to PSA testing often perceived themselves to be at low risk for prostate cancer. Men refusing biopsy also tended to perceive themselves to be at low risk and many were anxious about the test itself. Misunderstandings about the relationship between urinary symptoms and risk of prostate cancer were identified.

Conclusions: Most men found PSA testing and biopsy acceptable, but perceptions of risk were not always accurate and the provision of more tailored information may help facilitate informed decision-making.
Multiple newly identified loci associated with prostate cancer susceptibility

Nature Genetics
2008, 40: 316-321

Authors:
Eeles RA
Kote-Jarail Z
Giles GG
Al Olama AA
Guy M
Jugurnauth SK
Mulholland S
Daniel A
Leogamornlert DA
Edwards SM
Morrison J
Field HI
Southey MC
Severi G
Donovan JL
Hamdy FC
Dearnaley DP
Muir KM
Smith C
Bagnato M
Arden-Jones AT
Hall AM
O’Brien LT
Gehr-Swain BN
Wilkinson RA
Cox A
Lewis S
Brown PM
Jhavar SG
Tymrakiewicz M
Lophatananon A
Bryant SL
The UK Genetic Prostate Cancer Study Collaborators
Abstract:
Prostate cancer is the most common cancer affecting males in developed countries. It shows consistent evidence of familial aggregation, but the causes of this aggregation are mostly unknown. To identify common alleles associated with prostate cancer risk, we conducted a genome-wide association study (GWAS) using blood DNA samples from 1,854 individuals with clinically detected prostate cancer diagnosed at age 60 years or with a family history of disease, and 1,894 population screened controls with a low prostate-specific antigen (PSA) concentration (≤0.5 ng/ml). We analyzed these samples for 541,129 SNPs using the Illumina Infinium platform. Initial putative associations were confirmed using a further 3,268 cases and 3,366 controls. We identified seven loci associated with prostate cancer on chromosomes 3, 6, 7, 10, 11, 19 and X (P ≥ 2.7 × 10^{-8} to P ≥ 8.7 × 10^{-29}). We confirmed previous reports of common loci associated with prostate cancer at 8q24 and 17q. Moreover, we found that three of the newly identified loci contain candidate susceptibility genes: MSMB, LMTK2 and KLK3.

British Journal of Urology International

2008, 101: 547-555

Authors:

Hussain S
Gunnell D
Donovan J
McPhail S
Hamdy F
Neal D
Albertsen P
Verne J
Stephens P
Trotter C
Martin RM

Abstract:

OBJECTIVE

METHODS
Join-point regression was used to assess secular trends in mortality and incidence (source: Office of National Statistics), radical prostatectomy and orchidectomy (source: Hospital Episode Statistics database) and androgen-suppression drugs (source: Intercontinental Medical Statistics).

RESULTS
Prostate cancer mortality declined from 1992 (95% confidence interval, CI, 1990–94). The relative decline in mortality to 2004 was greater and more sustained amongst men aged 55–74 years (annual percentage mortality reduction 2.75%; 95% CI 2.33–3.18%) than amongst those aged ≥75 years (0.71%, 0.26–1.15%). The use of radical prostatectomy increased between 1991 (89 operations) and 2004 (2788) amongst men aged 55–74 years. The prescribing of androgen suppression increased between 1987 (33 000 prescriptions) and 2004 (470 000).

CONCLUSIONS
The decrease in prostate cancer mortality was greater amongst men aged 55–74 years than in those aged ≥75 years, but pre-dated the substantial use of prostate-specific antigen screening and radical prostatectomy in the UK. An increase in radical therapy amongst younger groups with localized cancers and screen-detected low-volume locally advanced disease as a result of stage migration, as well as prolonged survival from increased medical androgen suppression therapy,
might partly explain recent trends.
Endogenous Sex Hormones and Prostate Cancer: A Collaborative Analysis of 18 Prospective Studies

Journal of the National Cancer Institute

2008, 100: 170-183

Authors:
Roddam AW
Allen NE
Appleby P
Key TJ

Abstract:
Background: Sex hormones in serum have been hypothesized to influence the risk of prostate cancer. We performed a collaborative analysis of the existing worldwide epidemiologic data to examine these associations in a uniform manner and to provide more precise estimates of risks.

Methods: Data on serum concentrations of sex hormones from 18 prospective studies that included 3886 men with incident prostate cancer and 6438 control subjects were pooled by the Endogenous Hormones and Prostate Cancer Collaborative Group. Relative risks (RRs) of prostate cancer by fifths of serum hormone concentration were estimated by use of conditional logistic regression with stratification by study, age at recruitment, and year of recruitment. All statistical tests were two-sided.

Results: No associations were found between the risk of prostate cancer and serum concentrations of testosterone, calculated free testosterone, dihydrotestosterone, dehydroepiandrosterone sulfate, androstenedione, androstanediol glucuronide, estradiol, or calculated free estradiol. The serum concentration of sex hormone–binding globulin was modestly inversely associated with prostate cancer risk (RR in the highest vs lowest fifth = 0.86, 95% confidence interval = 0.75 to 0.98; Ptrend = .01). There was no statistical evidence of heterogeneity among studies, and adjustment for potential confounders made little difference to the risk estimates.

Conclusions: In this collaborative analysis of the worldwide data on endogenous hormones and prostate cancer risk, serum concentrations of sex hormones were not associated with the risk of prostate cancer.
Prostate cancer mortality in the USA and UK 1975 - 2004: an ecological study

Lancet Oncology
2008, 9: 445-452

Authors:
Collin SM
Martin RM
Metcalfe C
Gunnell D
Albertsen P
Neal D
Hamdy F
Stephens P
Lane JA
Moore R
Donovan J

Abstract:

Background: There is no conclusive evidence that screening based on prostate-specific antigen (PSA) tests decreases prostate-cancer mortality. In the USA, uptake of PSA testing has been rapid, but uptake is much less common in the UK. Our aim was to study trends over time in prostate-cancer mortality and incidence in the USA and UK in 1975–2004, and compare these patterns with trends in screening and treatment.

Methods: Joinpoint regression analysis of cancer-mortality statistics from Cancer Research UK (London, UK) and the USA National Cancer Institute Surveillance Epidemiology and End Results (SEER) programme from 1975 to 2004 were used to estimate the annual percentage change in prostate-cancer mortality in both countries and the points in time when trends changed. The ratio of USA to UK age-adjusted prostate-cancer incidence was also assessed.

Findings: Age-specific and age-adjusted prostate-cancer mortality peaked in the early 1990s at almost identical rates in both countries, but age-adjusted mortality in the USA subsequently declined after 1994 by 4·17% (95% CI 4·0–4·3) each year, four-times the rate of decline in the UK after 1992 (1·14% [0·8–1·4]). The mortality decline in the USA was greatest and most sustained in patients aged 75 years or older, whereas death rates had plateaued in this age group in the UK by 2000. The average ratio of USA to UK age-adjusted prostate-cancer incidence rates in 1975–2003 was 2·5, with a pronounced peak around the time that PSA testing was introduced in the USA. Numbers needed to treat to prevent one death from prostate cancer were 33 000 in the 55–64-year age group.

Interpretation: The striking decline in prostate-cancer mortality in the USA compared with the UK in 1994–2004 coincided with much higher uptake of PSA screening in the USA. Explanations for the different trends in mortality include the...
possibility of an early effect of initial screening rounds on men with more aggressive asymptomatic disease in the USA, different approaches to treatment in the two countries, and bias related to the misattribution of cause of death. Speculation over the role of screening will continue until evidence from randomised controlled trials is published.

61 Height and prostate cancer risk: a large nested case-control study (ProtecT) and meta-analysis

Cancer Epidemiology, Biomarkers & Prevention

2008, 17: 2325-2336

Authors:
Zuccolo L
Harris R
Gunnell D
Oliver S
Lane JA
Davis M
Donovan J
Neal D
Hamdy F
Beynon R
Savovic J
Martin RM

Abstract:

Background
Height, a marker of childhood environmental exposures, is positively associated with prostate cancer risk, perhaps through the insulin-like growth factor system. We investigated the relationship of prostate cancer with height in a dose-response meta-analysis, and with height and its components (leg and trunk length) in a nested case-control study.

Methods
We nested a case-control study within a population-based randomized controlled trial evaluating treatments for clinically localized prostate cancer in British men aged 50-69, including 1,357 cases detected through prostate-specific antigen (PSA) testing and 7,990 controls (matched on age, general practice, assessment date). Nine bibliographic databases were searched systematically for studies on the height-prostate cancer association that were pooled in a metaanalysis.

Results
Based on the nested case-control study, the odds ratio [OR] of PSA-detected prostate cancer per 10 cm increase in height was 1.06 (95% confidence interval [CI]: 0.97-1.16). Stronger evidence and stronger effect were found for high-grade prostate cancer (OR: 1.23, 95%CI: 1.06-
1.43), mainly due to the leg component, but not for low-grade disease (OR: 0.99, 95%CI: 0.90-1.10). In general, associations with leg length or trunk length were similar. A meta-analysis of 58 studies found evidence that height is positively associated with prostate cancer (random-effects OR: 1.06, 95%CI: 1.03-1.09), with a stronger effect for prospective studies of more advanced/aggressive cancers (random-effects OR: 1.12, 95%CI: 1.05-1.19).

Conclusion
These data indicate at most a limited role for childhood environmental exposures – as indexed by adult height – on prostate cancer incidence, whilst suggesting a greater role for progression, through mechanisms that need further investigation.
Associations of lower urinary tract symptoms with prostate-specific antigen levels, and screen-detected localized and advanced prostate cancer

British Journal of Urology International
2008, 102: 1400-1406

Authors:
Collin SM
Metcalfe C
Donovan J
Lane JA
Davis M
Neal D
Hamdy F
Martin RM

Abstract:

OBJECTIVE
To determine associations of lower urinary tract symptoms (LUTS) with prostate-specific antigen (PSA) levels and screen-detected localized and advanced prostate cancer.

SUBJECTS AND METHODS
A case-control study nested within the UK population-based ProtecT (Prostate testing for cancer and Treatment) study. Men aged 50–69 years were invited for PSA testing and those with a PSA level of ≥ 3.0 ng/mL were invited for biopsy. We determined whether LUTS were associated with a PSA level of ≥ 3.0 ng/mL and prostate cancer using logistic regression models adjusted for age, family history of prostate cancer and PSA level as appropriate. Areas under receiver operating characteristic curves (AUC) were compared between models with and without symptoms.

RESULTS
In all, 65,871 men had a PSA test: 7,251 had a PSA level of ≥ 3.0 ng/mL including 2,467 subsequently diagnosed with prostate cancer (2,119 localized, 348 advanced).

LUTS were positively associated with a PSA level of ≥ 3.0 ng/mL: odds ratios (Ors) were 1.18 (95% confidence interval, CI 1.01–1.38), 1.69 (95% CI 1.32–2.16), and 1.60 (95% CI 1.33–1.93) for daytime urination frequency (hourly vs less frequent), urgency and hesitancy (most/all the time vs never), respectively. LUTS among men with a PSA level of ≥ 3 ng/mL were negatively associated with prostate cancer: Ors were 0.44 (95% CI 0.22–0.83), 0.74 (95% CI 0.63–0.87), and 0.83 (95% CI 0.73–0.94) for nocturia (4+ vs 0), leakage and hesitancy (occasionally/ sometimes vs never), respectively. LUTS improved the prediction of a PSA level of ≥ 3.0 ng/mL (AUC 0.635 vs 0.606, P < 0.001) and prostate cancer (AUC 0.661 vs 0.638; P < 0.001).

CONCLUSIONS
A history of LUTS before PSA testing marginally improves the prediction of an individual’s risk for prostate cancer; men with a PSA level of ≥ 3 ng/mL and LUTS were more likely to be diagnosed with benign disease than prostate cancer.
Insulin-like Growth Factors, their Binding Proteins and Prostate Cancer Risk: A Collaborative Analysis of Individual Data from Twelve Prospective Studies

Annals Internal Medicine
2008, 149: 461-471

Authors:
Roddam AW
Allen NE
Appleby P
Key TJ

Abstract:
Background
Some, but not all, published results have shown an association between circulating blood levels of some insulin-like growth factors (IGFs) and their binding proteins (IGFBPs) and the subsequent risk of prostate cancer.

Purpose
To assess the association between IGFs, IGFBPs and the subsequent risk of prostate cancer.

Data Sources
PubMed, Web of Science, and CancerLit were searched to identify studies.

Study Selection
All studies which had published data on circulating concentrations of sex steroids, IGF or IGFBP and prostate cancer risk using prospectively collected blood samples were invited to be part of the collaboration.

Data Extraction
Investigators provided individual participant data on circulating concentrations of IGF-I, IGF-II, IGFBP-2, and IGFBP-3 and participant characteristics to a central dataset housed in Oxford.

Data Synthesis
The study included data on 3700 men with prostate cancer and 5200 controls. On average, cases were aged 61.5 years at blood collection and were diagnosed with prostate cancer 5 years after blood collection. The greater the serum IGF-I concentration the greater the subsequent risk of prostate cancer, the odds ratio (OR) in the highest versus lowest quintile being 1.38 (95% CI 1.19-1.60, Ptrend<0.001). Neither IGF-II nor IGFBP-2 concentrations were associated with prostate cancer risk, but statistical power was limited. IGF-I and IGFBP-3 were correlated (r=0.58) and although IGFBP-3 concentration appeared to be associated with prostate cancer risk, this was secondary to its association with IGF-I levels. IGF-I concentrations appeared to be more positively associated with low grade rather than high grade disease, otherwise there was no significant heterogeneity in the association between the IGFs and IGFBPs and prostate cancer risk by stage or grade of disease, time between blood collection and
diagnosis, age and year of diagnosis, prostate specific antigen level at recruitment, body mass index, smoking or alcohol intake.

Limitations
IGF concentrations were measured in only one sample for each participant and different laboratory methods were used in different studies to measure serum IGF concentrations. Not all patients had stage/grade information and there may be differences in the diagnosis of prostate cancer between the studies.

Conclusions
High circulating IGF-I concentrations are associated with a moderately increased risk of prostate cancer.
Multiple Loci with Different Cancer Specificities Within the 8q24 Gene Desert

Journal of the National Cancer Institute

2008, 100: 962-966

Authors:
Ghoussaini M
Song H
Koessler T
Amin Al Olama A
Kote-Jarai Z
Driver KE
Pooley KA
Ramus SJ
Kruger Kjaer S
Hogdall E
DiCioccio RA
Whittemore AS
Gayther SA
Giles GG
Guy M
Edwards SM
Morrison J
Donovan JL
Hamdy FC

Abstract:

Recent studies based on genome-wide association, linkage, and admixture scan analysis have reported associations of various genetic variants in 8q24 with susceptibility to breast, prostate, and colorectal cancer. This locus lies within a 1.18-Mb region that contains no known genes but is bounded at its centromeric end by FAM84B and at its telomeric end by c-MYC, two candidate cancer susceptibility genes. To investigate the associations of specific loci within 8q24 with specific cancers, we genotyped the nine previously reported cancer-associated single-nucleotide polymorphisms across the region in four case-control sets of prostate (1854 case subjects and 1894 control subjects), breast (2270 case subjects and 2280 control subjects), colorectal (2299 case subjects and 2284 control subjects), and ovarian (1975 case subjects and 3411 control subjects) cancer. Five different haplotype blocks within this gene desert were specifically associated with risks of different cancers. One block was solely associated with risk of breast cancer, three others were associated solely with the risk of prostate cancer, and a fifth was associated with the risk of prostate, colorectal, and ovarian cancer, but not breast cancer. We conclude that there are at least five separate functional variants in this region.
The decision-related psychosocial concerns of men with localised prostate cancer: targets for intervention and research

World Journal of Urology
2008, 26: 469-474

Authors:
Steginga SK
Turner E
Donovan J

Abstract:

Abstract
Purpose To describe decision-related psychosocial issues relevant for men with clinically localised prostate cancer.
Methods Searches were conducted across three electronic databases to search the health and psychological literature for articles examining decision-related psychosocial issues for men with localised prostate cancer and their partners. Medline, PsycINFO and CINAHL databases were examined for the period from 1990 to December 2007.
Results Most men with localised prostate cancer want active involvement in decision-making. Difficulty in making the decision is common and decision-related distress may persist over time. Cancer-specific psychological distress (such as fear of recurrence but not overall anxiety) appears to be related to changes in PSA levels; and this distress influences treatment pathways. Decision support interventions are acceptable to men, improve knowledge and might reduce decision and cancer-related distress. However, the quality of intervention studies to date is low.
Conclusion Clinicians should seek to involve men and their partners in treatment decision making concurrent with decision and psychological support. There is a need for high quality randomised control trials to identify the optimal approach to decision support for men with clinically localised prostate cancer.
Prostate-specific antigen testing and prostate biopsy: are self-reported lower urinary tract symptoms and health-related quality of life associated with the decision to undergo these investigations?

British Journal of Urology International

2008, 102: 1629-1633

Authors:
Avery KNL
Metcalfe C
Blazeby JM
Lane JA
Neal DE
Hamdy FC
Donovan JL

Abstract:

OBJECTIVE
To investigate whether men’s self-reported health-related quality of life and lower urinary tract symptoms (LUTS) are associated with acceptance of prostate-specific antigen (PSA) testing and subsequent prostate biopsy.

PATIENTS AND METHODS
In a prospective questionnaire study of men aged 50–69 years, nested within the primary-care-based Prostate testing for cancer and Treatment study in nine UK areas, the Hospital Anxiety and Depression Scale (HADS), 12-item Short Form Health Survey (SF-12) and a self-reported LUTS measure (ICS male SF) were completed immediately before having a PSA test or prostate biopsy, or after not responding to an invitation for a PSA test or refusing a biopsy. Analyses compared 348 men accepting or 232 not responding to invitations for PSA testing and 318 accepting or 48 refusing a prostate biopsy.

RESULTS
Men accepting or not responding to the invitation for a PSA test had similar HADS, SF-12 and LUTS scores. Men accepting a biopsy had similar HADS and SF-12 scores to those refusing biopsy, but significantly more LUTS (P<0.01 for hesitancy, reduced stream, intermittency, incomplete emptying, frequency during the day).

CONCLUSION
Depressed or anxious mood, comorbidity and LUTS were not associated with the decision to respond to invitations for a PSA test. Men agreeing to a biopsy were more likely to have LUTS than those refusing, suggesting that men believe that LUTS are a symptom of prostate cancer. Men needing a prostate biopsy require more information about LUTS so that they can make informed choices about testing for prostate cancer.
Multiple Novel Prostate Cancer Predisposition Loci Confirmed by an International Study: The PRACTICAL Consortium

Cancer Epidemiology Biomarkers and Prevention

2008, 17: 2052-2061

Authors:
Kote-Jarai Z
Easton DF
Stanford JL
Ostrander EA
Schleutker J
Ingles SA
Et al

Abstract:
A recent genome-wide association study found that genetic variants on chromosomes 3, 6, 7, 10, 11, 19 and X were associated with prostate cancer risk. We evaluated the most significant single-nucleotide polymorphisms (SNP) in these loci using a worldwide consortium of 13 groups (PRACTICAL). Blood DNA from 7,370 prostate cancer cases and 5,742 male controls was analyzed by genotyping assays. Odds ratios (OR) associated with each genotype were estimated using unconditional logistic regression. Six of the seven SNPs showed clear evidence of association with prostate cancer (P = 0.0007-P = 10^{-17}). For each of these six SNPs, the estimated per-allele OR was similar to those previously reported and ranged from 1.12 to 1.29. One SNP on 3p12 (rs2660753) showed a weaker association than previously reported [per-allele OR, 1.08 (95% confidence interval, 1.00-1.16; P = 0.06) versus 1.18 (95% confidence interval, 1.06-1.31)]. The combined risks associated with each pair of SNPs were consistent with a multiplicative risk model. Under this model, and in combination with previously reported SNPs on 8q and 17q, these loci explain 16% of the familial risk of the disease, and men in the top 10% of the risk distribution have a 2.1-fold increased risk relative to general population rates. This study provides strong confirmation of these susceptibility loci in multiple populations and shows that they make an important contribution to prostate cancer risk prediction.
Contribution of a single repeat PSA test to prostate cancer risk assessment - experience from the ProtecT Study.

European Urology
2007, 53: 777-784

Authors:
Rosario DJ
Lane JA
Metcalfe C
Catto JW
Dedman D
Donovan JL
Neal DE
Hamdy FC

Abstract:
Objective: To examine whether a single repeat prostate-specific antigen (PSA) helps discriminate cancer from non–cancer-related PSA elevation.

Methods: Men aged 50–70 yr (n = 54,087) in a multicentre randomised controlled trial comparing treatments for localised prostate cancer were tested. A total of 4102 (7.6%) with an initial PSA in the range of 3–19.9 ng/ml had repeat measurement (median interval: 50 d) followed by prostate biopsy. The decision to biopsy was based on the first PSA level. The outcome was whether prostate cancer was present on biopsy.

Results: Men with a 20% drop in PSA had a lower risk of cancer (odds ratio [OR] = 0.43; 95% confidence interval [CI], 0.35–0.52; p < 0.001) and high-grade cancer (OR = 0.29; 95%CI, 0.19–0.44; p < 0.001) compared to the rest of the cohort. The effect of percentage reduction was greater in men aged <60 yr than in those ≥60 yr. (OR for any cancer = 1.6; 95%CI, 1.0–2.4; p = 0.05; OR for high-grade cancer = 2.9; 95%CI, 1.2–6.7; p = 0.014). This equated to a risk reduction of high-grade cancer from 4% to 0.5%, 6% to 2%, and 15% to 2% in men <60 yr with an initial PSA of 3.0–3.99, 4.0–5.99, and ≥6 ng/ml, respectively. No level of repeat PSA confidently predicted absence of cancer.

Conclusion: Following an initial PSA of 3.0–19.99 ng/ml in men aged 50–70 yr, repeat PSA within 7 wk allows more accurate risk prediction that may assist in the decision-making as to whether or not to proceed with prostate biopsy.
Detection of prostate cancer in unselected young men: prospective cohort nested within a randomised controlled trial.

British Medical Journal
2007, 335: 1139-1143

Authors:
Lane JA
Howson J
Donovan JL
Goepel JR
Dedman DJ
Down L
Turner EL
Neal DE
Hamdy FC

Abstract:
ABSTRACT

Objective: To investigate the feasibility of testing for prostate cancer and the prevalence and characteristics of the disease in unselected young men.

Design: Prospective cohort nested within a randomised controlled trial, with two years of follow-up.

Setting: Eight general practices in a UK city.

Participants: 1299 unselected men aged 45-49.

Intervention: Prostate biopsies for participants with a prostate specific antigen level of 1.5 ng/ml or more and the possibility of randomisation to three treatments for those with localised prostate cancer.

Main outcome measures: Uptake of testing for prostate specific antigen; positive predictive value of prostate specific antigen; and prevalence of prostate cancer, TNM disease stage, and histological grade (Gleason score).

Results: 442 of 1299 men agreed to be tested for prostate specific antigen (34%) and 54 (12%) had a raised level. The positive predictive value for prostate specific antigen was 21.3%. Ten cases of prostate cancer were detected (2.3%) with eight having at least two positive results in biopsy cores and three showing perineural invasion. One tumour was of high volume (cT2c), Gleason score 7, with a positive result on digital rectal examination; nine tumours were cT1c, Gleason score 6, and eight had a negative result on digital rectal examination. Five of the nine eligible participants (55%) agreed to be randomised. No biochemical disease progression in the form of a rising prostate specific antigen level occurred in two years of follow-up.
Conclusions: Men younger than 50 will accept testing for prostate cancer but at a much lower rate than older men. Using an age based threshold of 1.5 ng/ml, the prevalence of prostate cancer was similar to that in older men (3.0 ng/ml threshold) and some cancers of potential clinical significance were found.

Trial registration: Current Controlled Trials
Establishing normal reference ranges for prostate volume change with age in the population-based Krimpen-study: prediction of future prostate volume in individual men

The Prostate
2007, 67: 1816-1824

Authors:
Bosch JLHR
Tilling K
Bohnen AM
Bangma C
Donovan J

Abstract:

Background: We aim to establish the normal pattern of prostate volume change with age to provide a baseline from which accelerated prostate growth might be identified in patients with lower urinary tract symptoms / benign prostatic hyperplasia (LUTS/BPH).

Methods: In a community-based study, prostate volume was determined at baseline and after 2.1 and 4.2 years in men without prostate cancer. A bivariate multilevel growth curve model was used to estimate the pattern of change of prostate volume with age.

Results: The average percentage increase of total prostate volume and transition zone volume per year of follow-up was 2.2% and 3.5%, respectively. The final model showed that prostate volume was related to age only. The future prostate volume of an individual can be predicted based on his age and known history of prostate volume. The model was also used to calculate time needed for the prostate volume to increase with a certain percentage, for men with different baseline prostate volume values at different ages.

Conclusions: This method establishes normal prostate volume values by age using prostate volume history in men without prostate cancer. The model provides baseline data from which disease progression might be detected.
How ProtecT aims to improve treatment for men with prostate cancer

Oncology Times

2007, 4: 6

Authors:
Salter L

Abstract:
Prostate cancer presents a significant public health issue in the UK with 30,000 new cases and 10,000 deaths reported in 2004. There are still major concerns regarding the lack of evidence about the effectiveness of treatments and the potential for diagnosis and over treatment of cancers that might never become clinically significant. No survival advantage has been identified for any of the recognised treatments used today, as all treatments can carry serious risks and treatment specific complications. The Protect Study (Prostate testing for cancer and Treatment), is now the largest worldwide study comparing treatments for localised prostate cancer that aims to answer some of these questions.
Prostate cancer is omnipresent, but should we screen for it?

International Journal of Epidemiology
2007, 36: 278-281

Authors:

Martin RM

Abstract:
27 **Screening for prostate cancer.**

(Book chapter)


2006, 3: 102-110

Authors:
- Hamdy FC
- Donovan JL
- Neal DE

Abstract:
- Abstract not available.
Establishing Normal Reference Ranges for PSA Change With Age in a Population-Based Study: The Krimpen-Study

The Prostate
2006, 66: 335-343

Authors:
Bosch JLHR
Tilling K
Bohnen AM
Donovan JL

Abstract:
BACKGROUND
We aim to establish the normal pattern of prostate specific antigen (PSA) change with age to provide a baseline from which disease progression might be identified in prostate cancer patients included in active surveillance programs.

METHODS
In a community-based study, PSA values were determined at baseline and after 2.1 and 4.2 years in men without prostate cancer. A bivariate multilevel growth curve model was used to estimate the pattern of change of PSA with age.

RESULTS
The final model showed that PSA was related to age only. The future PSA of an individual can be predicted based on his age and known history of PSA. The model was also used to calculate PSA doubling time for men with different PSA values at different ages.

CONCLUSIONS
This method establishes normal PSA levels by age using PSA history in men without prostate cancer. The model provides baseline data from which disease progression might be detected.
Continuing controversy over monitoring men with localized prostate cancer: a systematic review of programs in the Prostate Specific Antigen Era.

Journal of Urology
2006, 176: 439-449

Authors:
Martin RM
Gunnell D
Hamdy F
Neal D
Lane JA
Donovan JL

Abstract:

PURPOSE: There is continuing controversy over the most appropriate treatment for screen detected and clinically localized prostate cancer, and increasing interest in monitoring such men initially with radical treatment targeted at cancers showing signs of progressive potential but while they are still curable. Current evidence on monitoring protocols and biomarkers used to predict disease progression was systematically reviewed. MATERIALS AND METHODS: The MEDLINE and Excerpta Medica (EMBASE) bibliographic databases were searched from 1988 to October 2004, supplemented by manual searches of reference lists, focusing on studies reporting monitoring of men with localized prostate cancer. RESULTS: A total of 48 potentially eligible articles were found but only 5 studies, in which there was a total of 451 participants, restricted entry criteria to men with clinically localized (T1-T2) prostate cancer. Monitoring protocols varied with little consensus, although the majority used prostate specific antigen and digital rectal examination, while some added re-biopsy to assess progression. Actuarial probabilities of freedom from disease progression at 4 to 5 years of followup were 67% to 72%. However, up to 50% of men abandoned monitoring within 2 years, largely because of anxiety related to increasing prostate specific antigen rather than objective evidence of disease progression. There was no robust evidence to support prostate specific antigen doubling times or velocity to identify men in whom disease may progress. Studies were characterized by small sample size, short-term followup, observer bias and uncertain validity around variable definitions of progression. CONCLUSIONS: Current evidence suggests that some form of monitoring would be a suitable treatment option in men with localized prostate cancer but there is little consensus over what markers should be used in such a program or how progression should be properly defined. The search for a method that safely identifies men with prostate cancer who could avoid radical intervention must continue.
Screening for prostate cancer.

Trends in Urology Gynaecology and Sexual Health

2006, 11: 20-25

Authors:

Martin RM
Donovan JL
Verne J

Abstract:

The ongoing debate around prostate cancer screening has generated intense controversy, fuelled by advocacy in the absence of robust evidence. The aim of screening for prostate cancer should be to find potentially life-threatening tumours efficiently and safely among asymptomatic men, at a stage when lesions can be cured by effective treatment, leading to improvements in the quantity and quality of men’s lives. As screening requires intervention in healthy populations, the balance of evidence should convince that the prospect of benefit outweighs harm.
A comparison of socio-demographic and psychological factors between patients consenting to randomisation and those selecting treatment (the ProtecT) study.

Contemporary Clinical Trials

2006, 27: 413-419

Authors:

Mills N
Metcalfe C
Ronsmans C
Davis M
Lane JA
Sterne JAC
Peters TJ
Hamdy FC
Neal DE
Donovan JL

Abstract:

Background: Patient preferences for treatment can pose problems for the conduct of randomised trials: patients with a preference may refuse participation and thereby potentially compromise external validity. Moreover, randomising patients with a preference may affect treatment efficacy and threaten internal validity.

Aims: This study compared baseline characteristics and short-term psychological outcomes of patients who selected their treatment and those who agreed to random allocation.

Methods: Men participating in the prostate testing for cancer and treatment (ProtecT) study and who were randomised to active monitoring (n = 138) were compared with those who had refused randomisation and selected this management (n = 180). Socio-demographic data were collected at baseline, and anxiety and depression data were collected at baseline and six month follow-up. Socio-demographic characteristics were compared across these two groups in univariable analysis, and then linear regression was used to compare levels of anxiety and depression at follow-up with adjustments for confounders.

Results: Participants who selected active monitoring were more affluent (based on occupation details) and had less anxiety at baseline than those who were randomised. There were no differences with respect to age and marital status. Levels of anxiety and depression at six months follow-up were similar across the two groups of men.

Conclusions: This study found some differences at baseline between the socio-demographic and psychological status of those randomised and self-selecting treatment, but no psychological differences at short-term follow-up. Further empirical evidence is required to assess whether preferences impact upon the process and outcome of randomised controlled trials.
A model of the natural history of screen-detected prostate cancer.

British Journal of Cancer

2006, 95: 1122-1123

Authors:

Metcalfe C
Lane JA
Hamdy F
Neal D
Donovan JL

Abstract:

Extract from letter: Sir, In their recent British Journal of Cancer paper, Parker et al (2006) were careful not to overplay the conclusions that can be drawn from their model of the natural history of screen-detected prostate cancer. They alerted the reader to the dangers of trying to learn about the effects of treatment on localised prostate cancer detected through prostate-specific antigen (PSA) testing when the results of randomised controlled trials are not available and data from observational studies are only available on men whose cancers were detected at a later stage of the disease. Parker et al also emphasised the importance of ongoing randomised trials, such as ProtecT (Donovan et al, 2003), which will provide direct and robust evidence of the effectiveness of different treatment approaches in men with PSA-detected disease. Regrettably, these notes of caution were absent from the ensuing coverage of the study in the UK media (Press Association, 2006).
Measuring the psychosocial impact of population-based prostate-specific antigen testing for prostate cancer in the UK.

British Journal of Urology International

2006, 98: 777-782

Authors:
Brindle L
Oliver SE
Dedman D
Donovan JL
Neal DE
Hamdy FC
Lane JA
Peters TJ

Abstract:

Objective: To evaluate the psychosocial impact of participation in a population-based prostate-specific antigen (PSA) testing programme, akin to screening, and to explore the relationship between urinary symptoms reported before PSA testing and the response to the subsequent PSA result.

Patients and Methods: This prospective questionnaire study was nested within the case-finding component of the ProtecT (prostate testing for cancer and treatment) feasibility study (ISCRN20141297). Men aged 50-69 years from 18 general practices in three cities in the UK completed the Hospital Anxiety and Depression Scale (HADS), the Short Form-12 (SF-12) Health Survey, and the International Continence Society 'male' (ICSmale) questionnaires before giving consent for a PSA test in a community clinic (baseline). Men with an 'abnormal' PSA result returned for further investigation (including biopsy) and repeated these questionnaires before biopsy.

Results: At baseline, study participants had similar levels of anxiety and depression to the general male population. There was no increase in the HADS scores, or reduction in the SF-12 mental health component summary score, on attendance at the biopsy clinic after receiving an 'abnormal' PSA result. Urinary symptoms were associated with levels of anxiety and depression before receiving a PSA result (baseline), but were not associated with anxiety and depression at biopsy, independently of baseline scores. Therefore changes in anxiety or depression at biopsy did not appear to differ between those with and with no urinary symptoms.

Conclusions: This study confirms the findings of other studies that the deleterious effects of receiving an abnormal PSA result during population screening are not identified by generic health-status questionnaires. Comparisons with outcomes of studies measuring cancer-specific distress and using qualitative research methods raise the question of whether a prostate cancer screening-specific instrument is required. However, a standardized measure of anxiety identified differences at baseline between those who did and did not report urinary symptoms. These
findings suggest that it might be advisable to better inform men undergoing PSA testing about the uncertain relationship between urinary symptoms and prostate cancer, to minimize the baseline levels of psychological distress.
Statins and risk of cancer: A systematic review and meta-analysis

International Journal of Cancer

2006, 120: 833-843

Authors:

Browning DRL
Martin RM

Abstract:

We conducted a systematic review of the association between HMG-CoA reductase inhibitor (statin) use and cancer risk. We searched MEDLINE, EMBASE, Web of Science, ISI Proceedings and BIOSIS Previews bibliographic databases, electronic trials registers and reference lists for potentially eligible randomized trials and observational studies. Thirty-eight individual studies (26 randomized trials involving 103,573 participants and 12 observational studies with 826,854 participants) were included. Median follow-up was 3.6 and 6.2 years for trials and observational studies, respectively. In metaanalyses of randomized trials, there was no evidence that statin therapy was associated with incidence of all-cancers (26 trials; pooled risk ratio = 1.00; 95% CI 0.95-1.05; I² = 0%) or the following site-specific cancers: breast (7 trials; risk ratio = 1.01; 0.79-1.30; I² = 43%), prostate (4 trials; risk ratio = 1.00; 0.85-1.17; I² = 0%), colorectum (9 trials; risk ratio = 1.02; 0.89-1.16; I² = 0%), lung (9 trials; risk ratio = 0.96; 0.84-1.09; I² = 0%), genito-urinary (5 trials; risk ratio = 0.95; 0.83-1.09; I² = 0%), melanoma (4 trials; risk ratio = 0.86; 0.62-1.20; I² = 17%) or gastric (1 trial; risk ratio = 1.00; 0.35-2.85). There was no evidence of differential effects by length of follow-up, statin type (lipophilic vs. lipophobic) or potency. Trial results were generally consistent with observational studies. We conclude that statin use is not associated with short-term cancer risk, but longer-latency effects remain possible.
Screening for prostate cancer - the case against.

Annals of the Royal College of Surgeons
2005, 87: 90-91

Authors:
Donovan JL
Hamdy FC
Neal DE

Abstract:
Across the world, the suitability of prostate cancer for population screening continues to be highly controversial, fuelled by advocacy in the absence of robust evidence. The aim of screening for prostate cancer would be to find potentially life-threatening tumours efficiently and safely among asymptomatic men, at a stage when lesions could be cured by effective treatment, leading to improvements in the quantity and quality of men’s lives. As screening requires intervention in healthy populations, the balance of evidence should convince that the prospect of benefit outweighs harm.

There is no doubt that prostate cancer is a serious problem. It is rapidly becoming the most common cancer in men, with over 500,000 new cases estimated across the world in 2000, and it is a major cause of death in older men, second only to lung cancer among cancer deaths. Autopsy/post mortem studies have shown that prostate cancer is very common, with very many small tumours found in men dying of other causes. The life-time risk of having microscopic evidence of prostate cancer for a man of 50 years is 42%, while his risk of dying of it is only about 3%.
Screening for prostate cancer - from the Year in Urology.

The Year in Urology

2005, 2: 152-166

Authors:

Donovan JL

Abstract:

Abstract not available.
Reviewing negative prostatic core biopsies for the multidisciplinary team meeting.

Histopathology
2005, 47: 643-644

Authors:
Oxley J

Abstract:
Extract: Sir: Histopathologists are a key part of the multidisciplinary team (MDT) approach to treating cancer. Historically, the urology MDT meeting at Southmead Hospital, Bristol reviewed only prostatic cores that had been diagnosed as containing a tumour, but from January 2002 we started reviewing all prostatic cores taken.
25 Does current evidence justify prostate cancer screening in Europe?

Nature Clinical Practice Oncology Review

2005, 2: 538-539

Authors:
Martin RM
Davey Smith G
Donovan JL

Abstract:
The evidence for prostate cancer screening using prostate-specific antigen with reference to UK criteria is presented. Such screening might result in considerable over-diagnosis and over-treatment of clinically insignificant prostate cancer. Morbidity associated with treatment of suspected prostate cancer is substantial, so the likelihood of harm may outweigh the prospect of benefit.
Prostate cancer: Screening approaches.

British Journal of Hospital Medicine
2005, 66: 623-626

Authors:
Donovan JL
Martin RM
Neal DE
Hamdy FC

Abstract:
Introducing screening for prostate cancer requires evidence that this would do more good than harm. Current evidence about the impact and natural history of prostate cancer, screening and diagnostic tests, and the effectiveness of treatments is reviewed below.
Serum insulin-like growth factor-I is positively associated with serum prostate-specific antigen in middle-aged men without evidence of prostate cancer.

Cancer Epidemiology Biomarkers and Prevention 2004, 13: 163-165

Authors:
Oliver SE
Barass B
Gunnell DJ
Donovan JL
Peters TJ
Persad RA
Gillatt D
Neal DE
Hamdy FC
Holly JMP

Abstract:
We have examined the relationship between serum insulin-like growth factor-I (IGF-I) and prostate-specific antigen in 367 healthy men without evidence of prostate cancer and found a positive association (P = 0.05). In men without prostate cancer, serum prostate-specific antigen is closely related to prostate size, and our findings, therefore, suggest that IGF-I may induce prostatic epithelial proliferation. Higher circulating levels of IGF-I have been associated with increased risk of both prostate cancer and possible benign prostatic hyperplasia. Greater rates of cell proliferation induced by IGF-I may be a key biological pathway underlying these disorders.
Screen-detected prostate cancer and the insulin-like growth factor axis: results of a population-based case-control study.

International Journal of Cancer
2004, 108: 887-892

Authors:
Oliver SE
Gunnell D
Donovan J
Peters TJ
Persad R
Gillatt D
Pearce A
Neal DE
Hamdy FC
Holly JMP

Abstract:
Higher circulating levels of IGF-I have been associated with increased risk of prostate and some other cancers. Most research on prostate cancer has been based on men with symptoms or identified following treatment of benign disease. However, increasing numbers of cancer cases are now detected in asymptomatic men following prostate-specific antigen (PSA) tests. We therefore used a population-based case-finding exercise using the PSA test to examine whether associations between the IGF axis and cancer risk were apparent in this population. A matched case-control study was conducted among 7,383 men (50 - 70 years) receiving a PSA test as part of a case-finding exercise. Assays of IGF-I, IGF-II, IGFBP-2 and IGFB-3 were performed on cases and 2 controls matched on age, recruitment center and calendar time. Analyses were based on 176 cases and 324 matched controls. The risk of prostate cancer increased across quartiles of IGF-I (highest vs. lowest quartile, OR = 2.34; 95% CI = 1.26 - 4.34; p trend = 0.02) and IGF-II (OR = 1.78; 95% CI = 0.94 - 3.15; p trend = 0.09). Controlling for smoking history and IGFBP-3 strengthened associations with cancer for both IGF-I (OR = 3.00; 95% CI = 1.50 - 6.01; p trend 0.005) and IGF-II (OR = 2.02; 95% CI = 1.07 - 3.84; p trend = 0.04) Associations between the IGFs and cancer risk were stronger for advanced cases. Our findings suggest that both IGF-I and IGF-II are associated with an increased risk of screen-detected prostate cancer.
Do height-related variations in insulin-like growth factors underlie the associations of stature with adult chronic disease?

Journal of Clinical Endocrinology and Metabolism
2004, 89: 213-218

Authors:
Gunnell D
Oliver SE
Hamdy FC
Neal DE
Holly JMP

Abstract:
Tall people, particularly those with long legs, have an increased risk of developing cancer but a reduced risk of cardiovascular disease and type II diabetes. We examined associations of stature and body mass index with IGF-I, IGF-II, and IGF binding protein (IGFBP)-2 and IGFBP-3 in 274 men aged 50 - 70 yr to investigate whether variants in growth factor levels underlie associations of anthropometry with a number of adult diseases. Height and leg trunk length were not strongly associated with circulating levels of IGF-I, IGF-II, or IGFBP-3. The molar ratio of IGF-I/IGFBP-3 increased with increases in the leg/trunk length ratio (P = 0.06). IGFBP-2 was positively associated with leg length and inversely associated with trunk length. Mean levels of IGFBP-2 (in nanograms per milliliter) across quartiles of increasing leg length were 504.4, 493.6, 528.7, and 578.8 (P trend = 0.06), and for trunk length were 615.2, 507.2, 498.6, 488.5 (P trend = <0.01), suggesting that variations in IGFBP-2, or a factor influencing its levels in the circulation may, may contribute to biological mechanisms underlying height-disease associations. We conclude that whereas growth-influencing exposures during childhood, which may operate through effects on IGF-I levels, have a long-term influence on disease risk, they do not necessarily program IGF-I levels throughout life. The associations of anthropometry with IGFBP-2 merit additional investigation.
Measurement of insulin-like growth factor axis does not enhance specificity of PSA-based prostate cancer screening.

Urology
2004, 64: 317-322

Authors:
Oliver SE
Holly J
Peters TJ
Donovan J
Persad R
Gillatt D
Pearce A
Hamdy FC
Neal DE
Gunnell D

Abstract:

Objectives
To examine whether measurement of insulin-like growth factor (IGF)-I, IGF-II, IGF binding protein (IGFBP)-2 or IGFBP-3, alone or in combination, enhanced the specificity of prostate cancer detection among men with a prostate-specific antigen (PSA) level of 3 ng/mL or greater beyond that achieved by the free/total PSA index.

Methods
Cross-sectional analysis was performed on blood samples taken from 597 asymptomatic men (79% of those biopsied) participating in a community case-finding exercise. All men had a total PSA level of 3 ng/mL or greater and had undergone prostate biopsy. Assays of IGF-I, IGF-II, IGFBP-2, IGFBP-3, and free and total PSA were performed. The predictive performance of a range of measures was assessed using receiver operating characteristic analyses and compared with the free/total PSA index, for all biopsies and for men with a PSA level of 3 to 10 ng/mL. The overall test performance was summarized using the area under the receiver operating characteristic curve (AUC).

Results
Of the 597 men, 185 (31.0%) had prostate cancer identified at biopsy. When all biopsies were included, the performance of the free/total PSA index (AUC 0.73) was significantly greater than for IGF-I (AUC 0.59; P <0.0001), IGF-I/PSA ratio (AUC 0.65; P = 0.002), IGF-I + IGFBP-3 (AUC 0.59; P <0.0001), IGF-II (AUC 0.66; P = 0.002), and IGF-II + IGFBP-3 (AUC 0.67; P = 0.05). The combined measurement of free/total PSA, IGF-II, and IGFBP-3 resulted in a slight improvement in performance (AUC 0.76; P = 0.01). The results were similar when the analyses were restricted to men with an initial PSA level of 3 to 10 ng/mL.

Conclusions
We found no evidence that measurement of the IGF axis enhances the specificity of prostate cancer detection in clinical practice beyond that achievable using the free/total PSA index.
1 Perceptions of equipoise are crucial to trial participation: a qualitative study of men in the ProtecT study

Controlled Clinical Trials

2003, 24: 272-282

Authors:

Mills N
Donovan J
Smith M
Jacoby A
Neal D
Hamdy F

Abstract:

Recruitment to trials is known to be difficult. Previous research suggests that a crucial factor may be participants’ difficulty with the concept of randomization. This study explored patients’ perceptions of randomization and reasons for consent or refusal to participate in the ProtecT study (a randomized trial of surgery, radiotherapy, and monitoring for localized prostate cancer). In-depth interviews were conducted with 21 men diagnosed with localized prostate cancer who were invited to participate in the ProtecT treatment trial. Interviewees were selected purposefully from three U.K. clinical centers to ensure the inclusion of similar proportions of those agreeing or refusing random treatment allocation in each of the treatment groups. Interviews explored men’s recall and understanding of chance, comparison, and equipoise, and reasons for consent/refusal of randomization and acceptance/rejection of treatment allocation. Data were analyzed methodically using the techniques of constant comparison. Checking of coding and interpretation was assured by four experienced qualitative researchers. Recall and understanding of the major principles of the randomized design were good and were similar for “chance” and “comparison” between those who consented to and refused randomization. Clinical equipoise, however, caused difficulty. Almost all recalled and understood it, but those who found it acceptable tended to consent to randomization and those who could not accept it tended to refuse to participate. Belief in clinical equipoise was key to participants’ consent to randomization. Ensuring patients understand and accept equipoise may thus increase their readiness to consent to participate in trials. A priority for future research is to focus on the provision and presentation of suitable and effective trial information, concentrating in particular on the neglected concept of clinical equipoise.
Who can best recruit to randomized trials? Randomized trial comparing surgeons and nurses recruiting patients to a trial of treatments for localized prostate cancer (the ProtecT study)

Journal of Clinical Epidemiology
2003, 56: 605-609

Authors:
Donovan JL
Peters T
Noble S
Powell P
Gillatt D
Oliver S
Lane A
Neal D
Hamdy F

Abstract:

Background and Objective: Recruitment to randomized trials is often difficult, but few studies have investigated interventions to improve recruitment. In a randomized trial nested within a trial of treatments for localized prostate cancer, we investigated the comparative effectiveness and cost-effectiveness of nurses and surgeons in recruiting patients.

Methods: Men with localized prostate cancer were randomized to see a nurse or urologic surgeon for an “information appointment” in which they were asked to consent to the ProtecT treatment trial comparing surgery, radiotherapy, and active monitoring. Analysis was conducted by intention to treat using chi-square with 95% confidence intervals for proportions and differences between groups. An economic evaluation was performed using the duration of appointments and grade of recruitment staff.

Results: Case-finding identified 167 men with localized prostate cancer. One hundred fifty (90%) took part in the recruitment trial. There was a 4.0% difference between nurses and surgeons in recruitment rates (67% nurses, 71% urologists, 95% CI 10.8% to 18.8%, P .60). Cost-minimization analysis showed that nurses spent longer times with patients but surgeon costs were higher and nurses often supported surgeon-led clinics.

Conclusion: Nurses were as effective and more cost-effective recruiters than urologic surgeons. This suggests an increased role for nurses in recruiting patients to randomized trials.
Recent trends in the use of radical prostatectomy in England: the epidemiology of diffusion.

British Journal of Urology International
2003, 91: 331-336

Authors:
Oliver SE
Donovan JL
Peters TJ
Frankel S
Hamdy FC
Neal DE

Abstract:
Objective: To describe recent trends in the use of radical prostatectomy (RP) in England, as there is currently no consensus on the most effective treatment for localized prostate cancer, although RP is the treatment of choice among urological surgeons for men aged <70 years. Methods: Routine data were assessed to establish the number of RPs performed in England in 1991-99. Age-standardized operation rates were compared by region and socio-economic group, and the geographical spread of use mapped. Results: The number of RPs performed annually increased nearly 20-fold between 1991 and 1999. Rates of surgery were greatest in the London National Health Service (NHS) regions and lowest in the Trent region. Outside London, the risk of surgery in a NHS hospital was significantly greater for men living in the least deprived areas; in London this trend was reversed. Conclusion: Rapid increases in the use of RP showed marked regional variations, most likely related to access to prostate-specific antigen testing and the location of surgeons able to carry out radical surgery. By 1999, a third of procedures were still being undertaken in 'low-volume' hospitals, with implications for the quality of care and outcomes. Crucially, these developments occurred in the absence of robust information about the effectiveness of RP. Recent funding of a randomized trial of treatment options in this area is welcome, but wider questions remain about the timing of the evaluation of surgical technologies.

British Journal of Cancer
2003, 88: 1682-1686

Authors:
Gunnell D
Oliver SE
Peters TJ
Donovan JL
Persad R
Maynard M
Gillatt D
Pearce A
Hamdy FC
Neal DE
Holly JMP

Abstract:
We examined the association of diet with insulin-like growth factors (IGF) in 344 disease-free men. Raised levels of IGF-I and/or its molar ratio with IGFBP-3 were associated with higher intakes of milk, dairy products, calcium, carbohydrate and polyunsaturated fat; lower levels with high vegetable consumption, particularly tomatoes. These patterns support the possibility that IGFs may mediate some diet-cancer associations.
Ethics of clinical trials from bayesian perspective: Randomisation to clinical trials may solve dilemma of treatment choice in prostate cancer.

British Medical Journal

2003, 326: 1456-1456

Authors:
Hamdy FC
Donovan JL
Lane JA
Neal DE

Abstract:
Extract from letter: EDITOR - Lilford uses the example of the ProtecT study to raise concerns about recruitment to clinical trials, taking quotations out of context from Donovan et al. Lilford asserts that in this study men are simply told that the best treatment for localised prostate cancer is "uncertain"; that they are not given enough information or time to question the recruiter about essential details about treatments and side effects; and that they are not given sufficient clinical information about their disease. None of these assertions are true, as we argue on bmj.com.
Prostate Testing for Cancer and Treatment (ProtecT) feasibility study.

Health Technology Assessment
2003, 7

Authors:
Donovan JL
Hamdy F
Neal D
Peters T
Oliver SE
Brindle L
Jewell D
Powell PH
Gillatt D
Dedman D
Mills N
Smith M
Noble S
Lane JA

Abstract:

From the Executive Summary:
Background: There is currently insufficient evidence to introduce population screening for prostate cancer. While it is accepted that prostate cancer is an important public health problem, there is paucity of evidence on the natural history of the disease, the accuracy of the diagnostic tests (e.g. prostate-specific antigen (PSA) testing) and the effectiveness of treatments.
Objectives: The overall aim was to evaluate the feasibility of a randomised controlled trial (RCT) of treatments for localised prostate cancer, including: feasibility of 'case-finding' in the community (including the reliability and psychosocial impact of PSA testing); determining the most efficient and effective design for a major trial of treatments; randomised trial of recruitment strategies; piloting outcome measures and procedures for the main trial of treatments.
Screening for prostate cancer.

The Lancet
2003, 361: 1122-1128

Authors:
Frankel S
Davey-Smith G
Donovan J
Neal D

Abstract:
Epidemiologically, screening is justified by the importance of the disease and the lack of prospects for primary prevention, but evidence from natural history is unhelpful since men are more likely to die with, rather than from, prostate cancer. The available screening tests do not always detect men whose lesions could result in future morbidity or mortality. Evidence is limited for the benefits of treatments for localised cancers detected through screening, whereas the evidence for harm is clear. Observational evidence for the effect of population screening programmes is mixed, with no clear association between intensity of screening and reduced prostate cancer mortality. Screening for prostate cancer cannot be justified in low-risk populations, but the balance of benefit and harm will be more favourable after risk stratification. Prostate cancer screening can be justified only research programmes designed to assess its effectiveness and help identify the groups who may benefit.
Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT study.

British Medical Journal

2002, 325: 766-770

Authors:

Donovan JL
Mills N
Smith M
Brindle L
Jacoby A
Peters T
Frankel S
Neal D
Hamdy F
Little P

Abstract:

Problem: Recruitment to randomised trials is often difficult, and many important trials are not mounted because recruitment is thought to be "impossible". Design: Controversial ProtecT (prostate testing for cancer and treatment) trial embedded within qualitative research. Background and setting: Screening for prostate cancer is hotly debated, and evidence from trials about the effectiveness of treatments (surgery, radiotherapy, and monitoring) is lacking. Mounting a treatment trial is controversial because of past failures and concerns that differences in complications of treatment but not survival make randomisation unacceptable to patients and clinicians, particularly for a trial including monitoring. Strategy for change: In-depth interviews explored interpretation of study information. Audiotape recordings of recruitment appointments enabled scrutiny of content and presentation of study information by recruiters. Initial qualitative findings showed that recruiters had difficulty discussing equipoise and presenting treatments equally. Findings were used to determine changes to content and presentation of information. Effects of change: Changes to the order of presenting treatments encouraged emphasis on equivalence, misinterpreted terms were avoided, and the non-radical arm was redefined, and randomisation and clinical equipoise were presented more convincingly. The randomisation rate increased from 40% to 70%, all treatments became acceptable, and the three arm trial became the preferred design. Lessons learnt: Changes to information and presentation resulted in efficient recruitment acceptable to patients and clinicians. Embedding this controversial trial within qualitative research improved recruitment. Such methods probably have wider applicability and may enable even the most difficult evaluative questions to be tackled.
Clinical oncologists favour radical radiotherapy for localised prostate cancer: a questionnaire survey.

British Journal of Urology International

2002, 90: 558-560

Authors:
Hanna CL
Mason MD
Donovan JL
Barber JP

Abstract:
Objective: To explore the treatment preferences of clinical oncologists for managing early prostate cancer and to compare the results with the preferences of urologists. Methods: A postal questionnaire survey was conducted of consultant clinical oncologists in the UK. Results: Consultant clinical oncologists favour radical radiotherapy in most men aged <70 years, whereas a previous study showed that consultant urologists had a greater preference for radical surgery. Conclusion: There is little consensus about which treatment should be used for managing early prostate cancer. There is an urgent need for results from randomized clinical trials to determine the optimum treatment.

European Journal of Public Health
2000, 10: 289-295

Authors:
Faulkner A
Brookes ST
Donovan J
Selley S
Gillatt D
Hamdy FC

Abstract:
The prostate-specific antigen (PSA) test and its interpretation plays a crucial role in the detection of early localized prostate cancer. However, inaccuracy of the test, inability to predict the aggressiveness of the disease and the lack of evidence about the comparative effectiveness of treatments have led to major dilemmas in considering whether to employ the PSA test and which cut-off points to use in interpreting its results. The aim of this study was to evaluate current urological practice in the UK regarding the use of PSA testing. Methods: A postal questionnaire survey of all consultant urologist members of the British Association of Urological Surgeons was conducted. Statistical analysis included proportional odds regression models to examine factors associated with urologist's preferences for different definitions of 'norma' PSA cut-off levels. Results: The survey response rate was 60%. The majority of consultant urologists applied the PSA test routinely. There was a high level of agreement amongst UK urologists on normal PSA cut-off points (<4.0ng/ml) for asymptomatic men under 60 years of age. There was very wide variation in the definition of normal PSA cut-offs for older (>/=60 years) asymptomatic men. A preference for lower cut-off points, leading to investigation with ultrasound and biopsy, was significantly associated with larger urology department size, the presence of a prostate cancer subspecialist in the department and relatively short length of specialization in urology. Conclusions: Prostate cancer screening and early detection practices and reported incidence rates of the disease are likely to be influenced by variation in urologists' interpretations of PSA. Despite increasing evidence in favour of lower PSA cut-off levels, particularly for younger men (<60 years), urologists in the UK are divided over their interpretation. Men, particularly over age 60 years, have varying chances of further investigation following PSA testing. Any trial of prostate cancer screening or treatment should take this potential variation into account. Standard protocols for PSA interpretation should be implemented.
Comparison of trends in prostate-cancer mortality in England, Wales and the USA.

The Lancet
2000, 355: 1788-1789

Authors:
Oliver SE
Gunnell D
Donovan JL

Abstract:
Although trends in prostate-cancer screening and disease incidence differ substantially between the USA and England and Wales, trends in mortality are very similar.
Unanswered questions in screening for prostate cancer.

European Journal of Cancer

2000, 36: 1316-1321

Authors:

Neal DE
Leung HY
Powell PH
Hamdy FC
Donovan JL

Abstract:

Prostate cancer fulfils some of the conditions required of a disease that might be managed by population screening. In a cohort of 50- to 60-year-old men, carrying out a rectal examination and prostate specific antigen (PSA) test will detect clinically suspicious areas within the prostate in approximately 5%, and approximately 10% will have a raised PSA. We are however unsure which of the prostate cancers that are known to be present in approximately 30-40% of men aged over 60 years will be detected. Eventually after such screening, around 4% of men with an otherwise normal prostate will be found to have prostate cancers. The use of rectal examination may increase the number of tumours found, but will reduce compliance. The use of free/total PSA ratios will reduce the number of unnecessary biopsies at the expense of missing some tumours. Of more concern, we remain uncertain how effective aggressive local treatment is in altering the natural history of the disease. The risk of a 50-year-old-man with a 25 year life expectancy of having microscopic cancer is 42%, of having clinically evident cancer is 9.5%, and of dying of prostate cancer 2.9%. Only a small proportion of cancers known to be present become clinically evident: more men die with prostate cancer than of it. Screening will identify some men with cancer who will not benefit from treatment. It is unclear whether screening would be followed by a reduction in morbidity and mortality. Recent data suggest a screening effect has been observed in the USA with: an increase in incidence, a decrease in men with distant metases. The small decrease in mortality recently observed (many times smaller than the increase in incidence) may be confounded by inappropriate 'attribution' of cause of death, the detection of men with better prognosis distal metastatic disease responsive to hormonal ablation and changes in social factors such as diet. Future changes may incorporate molecular markers that might aid identification of men best treated aggressively because of a risk of progression. Tests to identify genetic pre-disposition may also allow targeted screening. New treatments and early chemoprevention or dietary strategies will again shift the ground on which these arguments are being rehearsed. The most urgent evidence required concerns the effectiveness of treatment strategies.
9 Prostate cancer: to screen or not to screen?

The Lancet Oncology
2000, 1: 17-24

Authors:
Neal DE
Donovan JL

Abstract:
The aim of screening is to identify cancers that are potentially curable; before a programme can be introduced, it must satisfy the requirement that it does more good than harm, particularly in terms of survival and quality of life. Prostate cancer is a common disease in older men and presents a significant burden to health services. Prostatic tumours range from small slow-growing lesions to aggressive tumours that metastasise rapidly, but because the natural history of prostate cancer is poorly understood, there is controversy about which screen-detected lesions will become clinically significant. Current methods of screening involve measurement of serum prostate specific antigen, followed by transrectal ultrasound scanning and biopsy, but these lack adequate specificity and sensitivity. There are three major treatment options for localised disease: radical prostatectomy, radical radiotherapy, and monitoring with treatment if required. There is no randomised controlled trial evidence to suggest a survival advantage of any of these treatments, and each has risks. There is intense speculation about future developments in diagnostic testing, molecular markers of progression, and early chemoprevention, but the central question that remains is whether radical treatments can improve survival and quality of life.
Screening for prostate cancer in the UK: Seems to be creeping in by the back door.

British Medical Journal
2000, 323: 763-764

Authors:
Donovan JL
Frankel SJ
Neal DE
Hamdy FC

Abstract:
Screening for prostate cancer is controversial. Findings from systematic and other reviews consistently conclude that there is insufficient evidence to recommend its introduction because of concerns that it may not improve survival or quality of life and may thus cause more harm than good.
Capturing users' experiences of participating in cancer trials.

European Journal of Cancer
2000, 11: 210-214

Authors:
Donovan JL
Brindle L
Mills N

Abstract:
Randomized controlled trials are accepted to be the research design of choice to evaluate the effectiveness of health care interventions and are commonly used to evaluate cancer treatments. There are concerns, however, that levels of recruitment are often much lower than anticipated, particularly in cancer trials. Several research methods have been used to collect aspects of users' experiences of participating in cancer trials. Perhaps the most common method has been through measures of outcome and the impact of treatments on quality of life (QoL), using standardized schedules to capture physical, social and psychological health. In some areas of cancer, individual patient testimonies illuminate particular issues or narratives. We searched MED-LINE and the Cochrane Trials Library from 1995 to 2001 for relevant publications. In this article, we review the literature in these areas and examine whether users' experiences of participating in cancer trials can be used to assist in the design or conduct of trials.
Dilemmas in treating early prostate cancer: the evidence and a questionnaire survey of consultant urologists in the United Kingdom.

British Medical Journal
1999, 318: 299-300

Authors:
Donovan JL
Frankel SJ
Faulkner A
Selley S
Gillatt D
Hamdy FC

Abstract:
Evidence based medicine suggests that evidence of effectiveness should accumulate, preferably from randomised controlled trials, before treatments for any condition become widely used. The case of localised prostate cancer shows how difficult this can be in practice. The suitability of population screening for localised prostate cancer has been debated, with particular concerns about the comparative effectiveness of the main treatments for the disease: radical prostatectomy, radical radiotherapy, and conservative management (also know as watchful waiting or surveillance).
4 Screening for prostate cancer.

Annals of Oncology
1998, 9: 1289-1292

Authors:
Neal DE
Donovan J

Abstract:
Taken from Introduction: There is considerable controversy concerning the suitability of prostate cancer for population or targeted screening, with weight of opinion suggesting that currently, there is insufficient evidence to recommend such screening. A number of criteria based on existing evidence concerning a range of epidemiological and health service factors are commonly used to determine the suitability of a condition for population screening for the disease. Some of these factors are considered below, drawing particularly upon evidence from a recent systematic review which concluded clearly that there is no evidence currently to justify the implementation of a screening programme for prostate cancer.
Diagnosis, management and screening of early localised prostate cancer: a review

Health Technology Assessment

1997, 1: 156-156

Authors:
Selley S
Donovan JL
Faulkner A
Coast J
Gillatt D

Abstract:
Extracted from Chapter 1 - Summary: The incidence of prostate cancer is rising worldwide, caused mainly by demographic factors, particularly the increasingly elderly population and, more importantly, the increasing number of cases identified following prostate specific antigen (PSA) testing. Unfortunately, clinical staging is unreliable, with approximately one half of all tumours upstaged following surgery. Although radical treatment rates are rising, good quality evidence concerning their comparative effectiveness and cost-effectiveness is lacking. In the past, investigations of prostate cancer were reserved largely for patients exhibiting symptoms, but the introduction of the PSA test has opened up the possibility of screening healthy men for the disease. Major questions remain concerning the natural history of prostate cancer, potential costs (financial, social and psychological) of a screening programme, and the effectiveness and cost-effectiveness of treatments for localised disease. The lack of good quality data and the strength of these concerns means that population screening for prostate cancer cannot be recommended.