Early Testing for Prostate Cancer – A Guide for General Practitioners

Dr Tom Dean

The Ongoing Controversy

Despite the death from prostate cancer of some 3000 men every year in Australia, many cancer experts claim that early testing is not worthwhile as it results in more harm than benefit, and that active treatment in any case achieves little. Conversely, there are many who are perplexed by the continuing debate. This is especially so for patients who have undergone curative treatment and in all likelihood owe their life to early testing.

There is general consensus that population based screening for prostate cancer is not appropriate because this will result in the over diagnosis and overtreatment of non-lethal cancers. This has led to some authorities actively discouraging PSA testing - patients with potentially lethal cancers will therefore only have the chance of being diagnosed and treated early if they request it or their doctor recommends it.

How is this dilemma resolved?

It is inappropriate to advise patients against having their PSA checked as every man with a 10-15 year life expectancy should have the opportunity to undergo early testing if he wishes. It is necessary to counsel each patient individually regarding the benefits and risks. In this complex situation, shared decision making between the doctor and patient is recommended as every patient has different cancer experiences, beliefs, goals and priorities. It is recognised that this can be very time consuming for the general practitioner.

The Argument for Testing

- Prevention is not possible so early detection and treatment is needed
- Early prostate cancer causes no symptoms
- Delayed diagnosis of significant cancers results in poorer outcomes
- The European Randomised Study of Screening for Prostate Cancer reveals a 21% reduction in prostate cancer deaths in men screened (29% reduction after adjustment for noncompliance)
- In the US where early detection is common, prostate cancer mortality has reduced over the last 10 years
- There is an ever increasing focus on avoiding unnecessary biopsies and avoiding treatment in patients with insignificant cancers
- Improvements in treatment are likely to reduce the risks of complications, particularly if cancers are diagnosed early

Risk Stratification

High risk
- A strong family history (first degree relative diagnosed before 70 years: the younger the age and the more relatives the higher the risk)
- A PSA higher than the median for age (see Table 1)
- An abnormal Digital Rectal Examination (DRE)

Table 1 Normal Ranges for PSA

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<tr>
<th>Age range</th>
<th>50th (median)</th>
<th>95th Percentile</th>
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<tr>
<td>40-49</td>
<td>0.65</td>
<td>2.0</td>
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<tr>
<td>50-59</td>
<td>0.85</td>
<td>3.0</td>
</tr>
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<td>60-69</td>
<td>1.30</td>
<td>4.0</td>
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<tr>
<td>70-79</td>
<td>1.64</td>
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- Men with a PSA above the median are at a higher long term risk for prostate cancer
- Men with a PSA above the 95th percentile may have prostate cancer

If testing is undertaken, it is necessary to act on a suspicious result to facilitate early diagnosis and treatment, if appropriate. Failure to do so may have medico-legal consequences. Table 2 serves as a guide to the need for referral based on median PSA levels in patients with a NORMAL DRE.

Table 2

<table>
<thead>
<tr>
<th>PSA (ng/mL)</th>
<th>0.5-1.0</th>
<th>1.0-1.5</th>
<th>1.5-2.0</th>
<th>2.0-3.0</th>
<th>3.0-4.0</th>
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<td>3</td>
<td>4</td>
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<tr>
<td>50-60 yrs</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>60-65 yrs</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
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<tr>
<td>65-75 yrs</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

0 No concern – testing or further testing not required
1 No concern – testing or further testing optional
2 Increased risk of developing cancer – at least annual checks
3 Suspicious – consider referral
4 Highly suspicious – referral appropriate

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Dr Dean is a consultant urological surgeon at the SAH and Hornsby Hospital. He has a particular interest in laser treatment for benign prostate hyperplasia and the early diagnosis of prostate cancer including the role of prostate MRI. Other interests include stone disease and incontinence. He is a member of the SAH Medical Advisory Committee.
MINIMALLY INVASIVE HIP REPLACEMENT
There has been a great deal of publicity about anterior approach to the hip for THR. This technique is associated with more rapid recovery. However, significantly higher early revision and complication rates have been recorded compared to lateral and posterior approaches. Patients undergoing this procedure need to be made aware of the increased risk.

OUTLOOK
Outcomes continue to improve in terms of safety, post op pain relief, recovery rate and implant longevity. Monitoring of these results is important. The Australian Joint Replacement Registry (now a decade old) will be of increasing value in assessing our progress and identifying problems.

Dr Lawrence Giutronich
MBBS, FRACS
Dr Giutronich is an orthopaedic surgeon specialising in hip and knee replacement surgery. He has rooms in the San Clinic and operates at the Sydney Adventist Hospital. He is currently Chairman of the Medical Advisory Committee and has been the Senior Examiner in Orthopaedics for the Royal Australian College of Surgeons. Phone 94738673
VASECTOMY AND VASECTOMY REVERSAL SURGERY

Dr. Phillip Katelaris

VASECTOMY TECHNIQUES

In the modern era, the traditional vasectomy technique first involved general anaesthesia and bilateral scrotal incisions to detach the vas. The skin was closed by suture. However, there was a significant incidence of post-operative sexual dysfunction, hematoma and pain. The LI technique

Four years ago, Dr. Li Shangping developed the intra-vitelline vasectomy (IVV) technique, which consists of two intravenous injections of local anaesthetic and an incision in the testis, followed by a needle puncture of the vas deferens. The injection is performed under ultrasound guidance. The incision is small and allows for quick healing. This technique reduces the risk of complications associated with general anaesthesia. The LI technique is currently the preferred method for vasectomy.

CHOICE OF ANAESTHESIA

Local anaesthesia is the preferred method for vasectomy as it is less invasive and allows for faster recovery. General anaesthesia may be preferred in cases where topical anaesthesia is not sufficient.

ADVICE TO THE PATIENTS

The decision to undergo vasectomy should be made between a man and his partner in a careful, well-informed manner. The procedure should be performed by a qualified urologist or surrogegrapher. It is important to note that the procedure is not reversible.

POSSIBLE COMPLICATIONS

Utilizing the LI technique, scrotal swelling, pain and haematoma are uncommon, occurring in 10% of cases. There is no demonstrable increased risk of developing testicular or prostate cancer following vasectomy.

Dr. Phillip Katelaris

Regional and national guidelines vary, and the vasectomy should be performed by a qualified urologist or surgeon. The procedure is not recommended for those under 25 years of age. Intra-vitelline vasectomy is the preferred method for sperm retrieval.

One of the San's vasectomy programmes involves a team of experts including Dr. Li Shangping, who is a urologist with extensive experience in vasectomy reversal. The programme involves a combination of techniques including microsurgical vasectomy reversal and laparoscopic vasectomy reversal. The success rate of vasectomy reversal surgery is around 80-90%, with a failure rate of less than 10%.

The LI technique is generally combined with the open-ended vasectomy technique. The open-ended technique involves division of the vas, the testicle end of the vas is left open and the cut end is covered with parietal fascia. The open-ended technique was introduced in an attempt to prevent post-vasectomy pain syndrome, which presents chronically in a very small number of men being vasectomised.

The advantage of the open-ended vasectomy is to allow the epididymis to drain, the fluid being reabsorbed by scrotal lymphatics.

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INTRODUCTION
An International Conference of scientists and clinicians was held at Leipzig University in March, focussing on B-vitamins. Convenors included world authorities such as Wolfgang Herman, Donald Jacobsen and Ebba Nexo. This paper summarises some of the key issues presented and discussed.

KEY PAPERS
Vitamin B12 deficiency issues
In 2008 the World Health Organisation commissioned an international study on the incidence of folate and vitamin B12 deficiencies worldwide (McLean 2008). Table 1a reveals some of the report findings (see over). Table 1b shows similar data for Australia.

The data reveals three significant findings:
• B12 deficiency is common and is an International problem;
• Notice the different ‘cut-off’ values used to define vitamin B12 deficiency. An Internationally agreed reference range based on clinical considerations to define vitamin B12 deficiency is required. There is a significant difference between reference ranges calculated from population means +/- 2SD, and reference ranges derived clinically. So what is the desirable ‘normal’ or ‘reference’ range for vitamin B12?
  - Population studies suggest >148 pmol/L as ‘normal’;
  - Herbert recommended >221pmol/L as acceptable;
  - Allen in 2009 suggests that 148-221 pmol/L is marginal with levels >221pmol/L satisfactory.
• However, neurological symptoms have been reported in patients with concentrations below 258 pmol/L, hence the call for a clinically based reference range.
• Food fortification works – as evidenced by the data from USA. Note that the only country in the world that has a high prevalence of (voluntary) food fortification with vitamin B12 has an exceptionally low incidence of vitamin B12 deficiency. An inadequate dietary intake of vitamin B12 is the prominent cause of vitamin B12 deficiency. This is rare in USA as their deficiency incidence is almost exclusively due to malabsorption.

The issue of a clinically based reference range did not gain traction due to the view that there “was so much interpersonal variation that a reliable range was difficult to determine – and that Transcobalamin II (also called Active B12) was the new and more reliable test.” Active B12 is the new and upcoming test of choice, but unfortunately, the reference range for this test has been based at least partially on a too-low serum vitamin B12 cut-off value.

Choline and the Brain
J. K. Blusztajn
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Choline is an essential nutrient for humans. Metabolically Choline is used for the synthesis of phospholipids, and as a precursor of the neurotransmitter acetylcholine. Following oxidation to betaine, choline functions as a methyl group donor, and thus its supply influences DNA and histone methylation – two central epigenomic processes that regulate gene expression. Studies in rodents have shown that high choline intake during gestation and the perinatal period improves cognitive function in aging humans. [Choline is found in the same foods as cholesterol!]

These actions of choline correlate with cerebral cortical changes in global- and gene-specific DNA cytosine methylation and with changes of the methylation pattern of lysine residues 4, 9 and 27 of histone H3. Moreover, gestational choline modulates the expression of DNA and histone methyltransferases. In addition to the central role of DNA and histone methylation in brain development, these processes are highly dynamic in adult brain, modulate the expression of genes critical for synaptic plasticity, and are involved in mechanisms of learning and memory. A recent study documented that in a cohort of normal elderly people, verbal and visual memory function correlated positively with the amount of dietary choline intake, further supporting the idea that adequate choline nutrition is essential for the maintenance of cognitive function in aging humans.

Riboflavin as a determinant of iron status
H. Powers
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Background: Riboflavin, in the form of derivatives flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) is essential for many redox reactions in intermediary metabolism. Additionally, experimental evidence suggests that the importance to oxidation/reduction reactions may extend to aspects of iron handling. The relevance of this to human populations is uncertain.

Aim: To investigate the effect on haematological status of improving riboflavin status in young women in the United Kingdom.

Methods: A randomised placebo controlled trial was conducted in women aged 19 to 25 years with biochemical evidence of poor riboflavin status. Women were randomised to receive 2mg or 4mg riboflavin, or a placebo, daily, for 8 weeks. Effects of the intervention on measures of iron status and iron bioavailability were determined.

Results: There was a dose-response improvement in riboflavin status in response to the supplement. Improvement in riboflavin status elicited an increase in haemoglobin and red blood cell number, being greatest in those women with poorer riboflavin status at the outset. Women in the lowest tertile for riboflavin status at baseline showed...
a significantly greater improvement in haemoglobin and red blood cell number than women in the highest tertile (P < 0.01) and those in the middle tertile (P < 0.05). There was no change in dietary iron or riboflavin during the study. Results could not be explained by an improved iron bioavailability but there was a suggestion that the supplement might have enhanced mobilisation of ferritin iron stores.

Discussion and Conclusion: Improving riboflavin status can have a beneficial effect of measures of iron status, independent of dietary iron.

Hyperhomocysteinaemia is associated with microvascular rarefaction in men, not in women. A population-based study

*J. Hornstra 1, T. Hoekstra 2, E. Serne 1, N. Wijnstok 2, H. Blom 3, J. Twisk 2, Y. Smulders 1

Background: Homocysteine (Hcy) is an independent predictor of cardiovascular risk. The pathophysiological mechanisms underlying this link are not fully elucidated. Whereas the association between Hcy and vascular dysfunction in conduit arteries is extensively studied, the potential role of the microcirculation is largely unknown.

Aim: To assess the relationship of Hcy levels and microvascular structure and function in a population-based study in healthy, young adults.

Methods: They cross-sectionally studied 260 participants (aged 42 years, 47% men) of the Amsterdam Growth and Health Longitudinal Study (AGAHLIS). Nailfold videocapillaroscopy (100x) was used to assess capillary density (number of perfused capillaries/mm²) at baseline, during venous congestion and during reactive hyperaemia (after 4 minutes of arterial occlusion). The relationship between fasting plasma Hcy and microvascular outcomes was evaluated using regression analyses with a dichotomous variable comparing the highest tertile with the two lowest tertiles of homocysteine with adjustment for BMI and blood pressure.

Results: Stratified analyses were performed for gender. In men, they observed an inverse, non-linear relationship between Hcy and capillary density at baseline as well as during reactive hyperaemia, showing lower microvascular counts in the highest two tertiles of Hcy [β of -7.3 (c.i. -13.6 to -1.1) and -9.1 (c.i. -17.5 to -0.8) capillaries/mm² respectively (P < 0.05)]. In women, no sucassociation was apparent.

Conclusions: In men, but not in women, elevated Hcy levels are associated with microvascular rarefaction, i.e. a decrease in the number of perfused capillaries at rest and during reactive hyperaemia.

CONCLUSIONS

Many research facilities around the world are undertaking important studies into B-vitamins and much is now known. This is not the “beginning of the end”, but perhaps we now better know what questions to ask.

References available on request

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<th>Reference range (Cut off used to define deficiency) pmol/L</th>
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<td>Germany</td>
<td>25</td>
<td>&lt;173</td>
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<tr>
<td></td>
<td>14.7</td>
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Table 1a

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Table 1b