

Commentary on Dr Richard Ablin and Ronald Piana's book "The Great Prostate Hoax" [1]

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Prostate cancer awareness and detection – a burgeoning medical problem

Prostate cancer has now assumed a significance in men almost akin to that of breast cancer in women, with campaigns and organisations using celebrities and the media to drive home throughout the media the need for surveillance and early diagnosis. It is the most common form of cancer in men, which in the near future might have such prominence as to be a major burden to any healthcare system. This is because its incidence increases with age, and as medical advancement over the last two decades has led to significantly increased longevity, this ironically exacerbates the problem. Unless an even wider policy of "wait and see" (active surveillance) is pursued, every man who lives to a hundred will have or have had some prostatic dysplasia, precancerous or cancerous in most cases. Many may outlive prostate cancer, but there will also be many who will not. Early diagnosis is therefore central issue, especially as progression in prostate cancer is unpredictable and can be very rapid. Like breast cancer, prostate cancers can suddenly metastasise, and "active surveillance" may involve review intervals that are too far apart to catch cases of rapid dissemination. Our dilemma is that we know virtually nothing about how this change in invasiveness comes about [2], also discussed by Dr Ablin in the editorial to this issue.

Campaigns

Have the campaigns to build public awareness in men about prostate cancer and the possibility that they might be vulnerable been effective? If we consider another tumour, lung cancer, we have seen campaigns in the UK (e.g. one of them featuring Sir Alec Ferguson) that try to get the message

across. Some people may take notice; but the perennial question is whether those most vulnerable heed these warnings. Putting danger of death on cigarette packets might help, but it seems that hardened smokers are still prepared to run the risk. It is different with the prostate because there is no clearly associated habit or life-style that precipitates cancer, other than a genetic defect in the GST gene, which can in some cases indicate a hereditary basis. Do campaigns like those featuring Bob Monkhouse or Bill Bailey (his "Men United" promotion) in the UK get the message across - do they alarm rather than alert men, or do they largely go unnoticed because they have become too widespread? Even the franking of letters can include words about prostate campaigns.

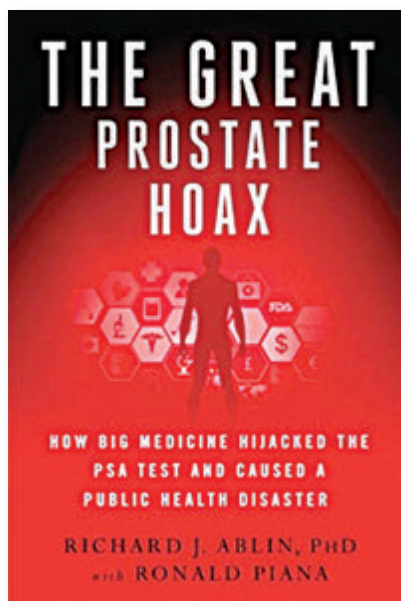
Many websites in the UK have charities doing their best to get men to understand the importance of knowing more about prostate problems and how might develop cancer, but has there been a significant increase in the number of hits on these sites? Are men in general better informed today, and will the more vulnerable men, often reluctant to visit their medical centres with problems that relate to urination and sexual dysfunction, take better notice?

PSA and prostate cancer

There is no doubt that the UK took a more sensible approach than the US in its attitude towards Prostate Specific Antigen, PSA [3], for which an assay was devised at the Rothwell Park Cancer Institute in Buffalo, NY State, USA, those responsible referring to it thereafter as a prostate cancer specific antigen. Thus a biomarker that ought to be a predictive test of the disease continued under the acronym PSA! PSA is a weak guide, one of the factors

that might be affected by prostate cancer, but it is by no means a directly correlated parameter when present at >4 ng/ml blood. Its presence in the blood simply means that some tissues, usually the prostate (but it possible others, especially inflamed tissues) release this enzyme, kallikrein 3 (KK3, a serine protease). In the early years of PSA testing, over 75% gave false-positives, which speaks for itself. Dr Richard Ablin, the discoverer of PSA, in "The Great Prostate Cancer Hoax" [1] takes to task in a comprehensive manner the people and organisations that misled men for over 40 years, with the situation only being corrected in the last few years apparently without apology or recompense, especially to men who unnecessarily had radical prostatectomy. This surgery often led to complications, which in some cases caused persistent problems, with considerable discomfort and loss of quality of life. The whole saga is spelled out in this book, especially the misleading aspect mentioned above, which refers to the whole business as a "hoax". This implies that, although it should have not involved in malice, there was intent.

Screening all men regularly to check their PSA level in some countries, including the US, is not cheap, and sending men with elevated PSAs for prostatectomy has lined the pockets of some medical practioners. The difficulty is to determine whether it was intentional rather than unintentional on their side, otherwise suggesting some ignorance or unwittingness for them to look deeper into the significance of PSA, with unfortunate consequences. The medical (licensing) authorities in the US allowed this misunderstanding to continue until very recently; they did not listen to the experts and therefore remain blameworthy – which amounts in the long-term more to a scandal than a hoax. Dr Ablin goes into detail about the scientific and medical aspects of prostate tumours following his discovery of PSA, but it is not an academic book. The research needed for it that has gone into it focuses on this inappropriate, if not irresponsible, behaviour of individuals and authorities. Ablin and co-author Ronald Piana have comprehensively compiled the evidence, which provides be the very documentation a lawyer would use in litigation (the hundreds of notes in the book's appendix would be invaluable to any prosecuting counsel). But will the



book reach the right readership and will any action follow? Only time will tell. Come what may, the truth is finally out, and the recent "sea-change" in the attitude and recommendations of the US authorities proves this point.

The future

Having drawn a line under the PSA debate, PSA will still be used as one small indicator if levels change significantly when there is suspicion of disease. The first signs of this otherwise asymptomatic cancer are that urination becomes slower and there is an increase in nocturnal of visits to the toilet. There can be undesirable changes in sexual function, but otherwise there is not much else to go on; this is why educating all men about these problems must continue, but how this is done in future needs careful thought. A visit to the doctor is warranted when these first signs are noted, and a digital rectal examination (DRE) carried out that takes usually no more than a minute, not just a PSA test on a blood sample. The prospect might seem daunting to many men, but it is necessary. It tells the doctor whether the prostate is enlarged, and is smooth or rough. Referral will be made if there is any suspicion, and sequential PSA readings over a short period of time might also be considered useful at this stage, should it rise quickly. At the urology clinic further examination will also measuring the rate of urine flow and perhaps a scan. This is followed by biopsies, at least 3 on each side of the prostate, which is

nothing more than mildly discomforting, but again many men would be reluctant to undergo the procedure.

Histopathology gives a relatively conclusive answer to the question of the stage of the disease, based on Gleason score, which determines in relation to age whether further intervention is needed rather than active surveillance. To reduce the burden of prostate cancer as far as medical intervention in the future is concerned, men do need to know about these procedures and not be alarmed by the measures that need to be taken, which can make the difference between a life and an early death.

There are other tests now being put forward that add some weight to the use of biomarkers as predictive of developing disease. Another antigen PCA3, known since 1999 [4], is only expressed in human prostate tissue, but once again we are back to DRE being used in which the prostate is massaged, following which a short time later a urine sample is examined for PCA3. Although the gene is over-expressed in many prostate cancer cells, its restricted expression profile means that it is its RNA that can be useful as a biomarker. But today it is advisable to use four criteria as indicative of the possibility of prostate cancer: (i) Free PSA, (ii) Total PSA, (iii) Intact PSA (a subfraction of Free PSA), and (iv) PCA3 (aka DD3, KLK2). To what extent these will now be used to improve diagnosis remains to be seen. The indicators of prostate cancer relate mostly to the functional disturbance that cancer can cause, and therefore greater attention to these changes remains the best guide to taking as early as possible the right course of action, the rapid spread in some cases being the most disturbing issue where action is delayed.

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