Acta Oncologica, 2010; 49: 298–304

informa
healthcare

ACTA ONCOLOGICA LECTURE

The prostate cancer pseudo-epidemic

HANS-OLOV ADAMI[1,2]

[1]*Department of Epidemiology, Harvard School of Public Health, and Dana Farber/Harvard Cancer Center, Boston, Massachusetts, USA and* [2]*Department of Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden*

Abstract
Screening for prostate cancer with prostate-specific antigen (PSA), a simple blood test, is complex, controversial, intellectually challenging and ethically concerning. Sweden has contributed actively to the knowledge base for PSA screening in the last couple of years and a more informed debate is now possible. I will in this article summarize what we currently know about PSA testing. I discuss the closely related issues of the natural history of early-stage disease and the risks and benefits of radical local treatment. I propose that the mortality reduction following PSA screening is probably modest, whilst substantial harms are well documented. Furthermore, there is growing evidence that the PSA test is profoundly limited for screening purposes. I therefore concur with the growing number of health and professional agencies – notably outside the US – that advise against population screening with PSA. Through PSA screening the medical community has generated a pseudo-epidemic of over-diagnosed non-lethal prostate cancer. Molecular tools to distinguish innocent, over-diagnosed prostate cancer from lethal tumors that deserving curative treatment are necessary to improve screening test performance. To date, extensive attempts to identify molecular predictors of outcome have remained unsuccessful, and no ideal screening test is within sight.

> "*I will prescribe regimens for the good of my patients according to my ability and my judgment and never do harm to anyone*".
>
> *Hippocratic Oath*

When the history of medicine is compiled, the current prostate cancer epidemic may appear enigmatic. Historians will know that wide-spread testing for prostate-specific antigen (PSA) among asymptomatic men caused the epidemic. But it will be difficult to comprehend its continuation over decades despite limited evidence of benefit and overwhelming evidence of harm. Historians will find meagre evidence of the necessary [1] open, public, and ethical discourse of this epidemic, caused by diagnostic intervention among healthy people. They may indeed consider the epidemic a disaster of contemporary medicine [2].

In 2009, two ongoing randomized trials of PSA screening – one in Europe [3] and one in USA [4] – provided the first quantitative estimates of the survival benefit due to early detection of prostate cancer. Based on 162 387 men from seven countries followed for an average of nine years, the European trial found a 20% reduction in prostate cancer mortality following PSA screening approximately every four years [relative risk=0.80; 95% CI 0.65–0.98]. The absolute risk difference was 0.71 cancer deaths/1 000 men screened, meaning that 1 410 men must be screened and 48 cases of prostate cancer treated to avert one death [3]. In contrast, the smaller US trial found no survival benefit from annual PSA screening combined with digital rectal examination. At 10 years, there were 92 prostate cancer deaths among 38 343 men randomized to screening but only 82 among 38 350 men randomized to no screening. The difference was not statistically significant [relative risk=1.11; 95% CI 0.83–1.50] [4].

Randomized trials are fundamental to prove screening efficacy. However, indirect evidence can also guide our understanding of the pros and cons of PSA testing. Incidence and mortality trends may be informative. Studies of the natural history and treatment impact are particularly important to justify

Correspondence: Hans-Olov Adami, Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, Massachusetts 02115, USA. Tel: +1 617 4326477. Fax: +1 617 5667805. E-mail: Adami@hsph.harvard.edu
*Presented at SOF-meeting in Uppsala, Sweden, March 18–20, 2009.

(Received 18 November 2009; accepted 29 December 2009)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.3109/02841860903584945

a screening intervention [5]. In this review, I will summarize such evidence with a focus on studies carried out in Sweden and other Nordic countries during the two last decades. But first, we need to acknowledge prostate cancer's vast range of malignant potential.

The iceberg phenomenon

In many cancer sites, the clone of malignant cells grows at a rate that varies enormously. One corollary of this phenomenon is that autopsy studies reveal tumors that never surfaced during the patient's lifetime and that represent a selection of slow-growing cancers. We do not know how many of the autopsy-detected cancers would ever have progressed to a clinical, symptomatic stage. This uncertainty drives the concern about over-diagnosis caused by cancer screening.

Prostate cancer is an extreme example of autopsy-detected tumors. The prevalence of such lesions is about 20% already among men aged 45 years and increases with age [6]. Variation in the prevalence of prostate cancer observed across studies is likely explained by differences in sampling of deceased individuals, in histopathologic criteria and in number of sections examined. With regard to natural history, we know one thing with certainty: these lesions first detected at autopsy neither caused symptoms that prompted clinical diagnosis nor contributed to death. As a corollary, any diagnostic tests sensitive enough to detect the lesions among living men would entail over-diagnosis.

A fundamental dilemma arises: we must assume that clinically evident cancers, some of which are lethal, pass through a subclinical stage where they are currently indistinguishable from malignant lesions that would never become symptomatic. The problem of distinguishing indolent, over-diagnosed prostate cancers from those predestined to progress became acute about 20 years ago, when the simple blood test for PSA was discovered and promoted as a screening tool [7]. But before discussing PSA screening, let us consider the natural history of localized prostate cancer and the benefit of radical surgical treatment.

The natural history of early prostate cancer

Palliation remained the only therapeutic option in the prostate cancer management until in the 1980s, when radical prostatectomy was introduced as a potential cure. Prior to that, watchful management with no initial therapeutic intervention was considered ethically acceptable, and indeed often preferable, in men with localized disease. Applied in many European countries, including Sweden, watchful management provided a unique opportunity to study the disease's natural history. Although the empirical evidence from this era applies only to early-stage patients, this subgroup is closely related to those now considered for curative local treatment. Six different cohorts of conservative management have been scientifically scrutinized, revealing surprisingly homogeneous low prostate-cancer-specific mortality [8].

The largest cohort of patients managed by watchful waiting, comprising 223 patients from Örebro County in Sweden, enrolled before the PSA era (1977–1984) and thus had symptomatic disease [9]. We have now continued follow-up beyond 20 years. As of 2001, when only 9% of the men were still alive, only 16% had died from prostate cancer, whereas 75% had died from other causes [10]. This low disease-specific mortality following expectant management of symptomatic disease implies that the survival benefit from radical treatment is limited among patients diagnosed with early-stage particularly asymptomatic disease. Even if the relative reduction in prostate-cancer-specific mortality were substantial, the absolute reduction in terms of lives saved would be small.

Survival benefit of radical local treatment

A benefit of treatment, documented through randomized controlled trials, is a prerequisite for effective cancer screening [5]. In prostate cancer, however, no such evidence existed until 2002 [11]. Then, results from the first, and so far only, randomized trial were published with extended follow-up reported in 2005 [12] and 2008 [13]. In this multi-center trial, 695 men newly diagnosed with a clinically localized (T1B and T2) prostate cancer, and with a PSA value less than 50 pg/nl and no evidence of metastases, were randomized to radical prostatectomy or watchful waiting. Because only 5.2% of the patients were diagnosed as a result of PSA screening, the results pertain primarily to symptomatic prostate cancer [13].

At 12 years of follow-up, 47 (12.5%) of the surgery group and 68 (17.9%) of the watchful waiting group had died of prostate cancer, yielding a relative risk of 0.65 [95% CI 0.45–0.94; $p=0.03$] comparing radical prostatectomy to watchful waiting. The absolute risk reduction at 12 years was 5.4% (95% CI 0.2–11.1), which translates into 19 patients needing to be treated with radical prostatectomy in order to avert one prostate cancer death. Although we expected the absolute benefit from curative treatment to increase over time, the cumulative incidence of distant metastases and of prostate cancer death instead remained stable after about 10 years of follow-up (Figure 1) [13].

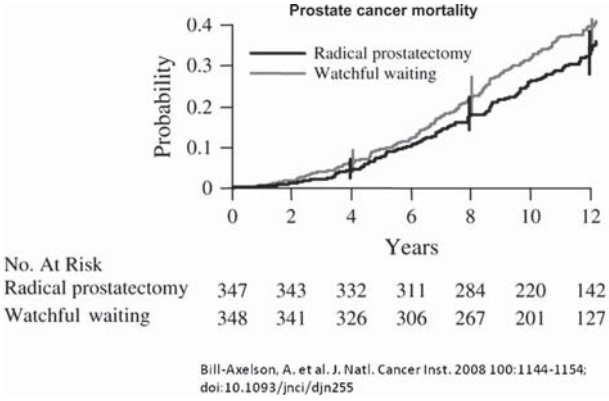

Figure 1. Cumulative incidence of prostate cancer mortality with 95% confidence intervals (CIs) at 4, 8, and 12 years of endpoints for all patients [13]. Reprinted from Bill-Axelson A et al. J Natl Cancer Inst 2008;100:1144–54 with permission from Oxford Journals.

Because after about 10 years prostate cancer mortality increased at a similar rate among men managed by watchful waiting and those with surgery, the relative benefit of treatment decreased over time. It went from a 50% reduction in cumulative mortality after five years [4] to only 35% after 12 years of follow-up [13]. Furthermore, after 12 years, when the absolute risk reduction due to radical prostatectomy was 5.4%, over 20% of the patients in both randomization groups had died from causes other than prostate cancer. Because cardiovascular disease, the predominant cause of mortality in western populations, is highly preventable [14], lifestyle intervention has the potential to provide an improvement in overall survival of at least the same magnitude as radical prostatectomy [15].

PSA screening

In the US National Cancer Act of 1971, President Nixon proclaimed that early diagnosis and improved treatment are the main armaments in the war on cancer – at least until effective prevention strategies are implemented [16]. Early diagnosis can improve survival through two main approaches. The first is advancement of treatment among patients who have already developed symptomatic disease. This outcome is typically achieved by increasing awareness in the general population and among health care providers, and by enabling access to medical care. The second is detection of asymptomatic cancer or its precursors, when the disease is curable, by screening. The former approach has been a major force behind increased survival rates from many cancer sites. In contrast, cancer screening has contributed only modestly to control of a few cancer sites, particularly cancer of the cervix and breast.

Although cancer screening is intuitively appealing, the logistic complexities, ethical dilemmas and potential harms of intervention in a healthy population are often underestimated [16]. There is no better example of this than screening for prostate cancer. PSA was approved by the US Food and Drug Administration in 1986 for monitoring of diagnosed prostate cancer, and also for screening purposes in 1994, and is widely used.

The performance of PSA as a screening test has been extensively investigated. It is now clear that detection of prostate cancer can be advanced in time considerably through the use of PSA testing [17]. Recent research indicates that PSA-detected cancers that would otherwise have been diagnosed during the patients' lifetime have a lead-time that is on average five to seven years [18]. In addition, PSA may also detect cancers that would never have surfaced clinically, a propensity described as the "iceberg phenomenon". If this problem of over-diagnosis were prominent, we would expect extensive PSA testing to increase the recorded population-wide incidence of prostate cancer that would not return to the pre-testing trajectory over time.

The pseudo-epidemic

Environmental factors can influence temporal trends in cancer incidence. Rarely, however, are such trends dramatic, except perhaps the rise and fall of lung cancer in several populations, occurring some decades following similar trends in the prevalence of smoking. Hence, the Tsunami in the numbers of newly diagnosed prostate cancer witnessed from the late 1980s in the US (Figure 2) [19], as well as several Nordic countries including Sweden (Figure 3) somewhat later [20], is unprecedented in cancer epidemiology.

In the US, the age-standardized incidence rate of prostate cancer increased by 16.5% per year from 1988 to 1992 and doubled from little over $100/10^5$ person-years in the mid 1980s to about $240/10^5$ in 1992. This was followed by a steep and then modest decline to $160/10^5$ in 2005 [19]. This decline probably reflects a relative depletion in the pool of indolent cancers (the iceberg), perhaps combined with some reduction in PSA screening. Welsh estimated that in the US alone, over one million men were over-diagnosed with prostate cancer between 1975 and 2000, chiefly as a consequence of PSA testing [16]. In stark contrast, age-standardized mortality rates were largely stable during the same 25-year period [19]. Given that the average lead-time of PSA-detected cancers is on average five to seven years, we would have expected to see a population-wide survival benefit reflected in lower mortality rates by now.

Trends of a magnitude similar to that in the US occurred also in nearly all Nordic countries (Figure 3).

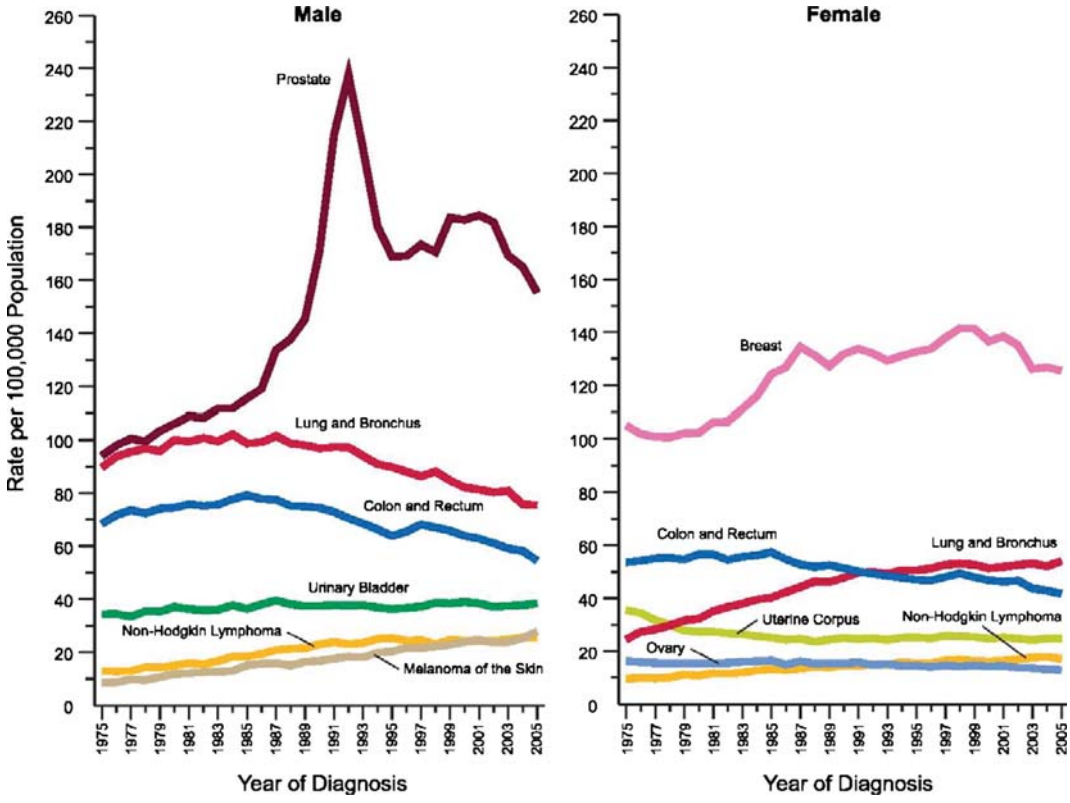

Figure 2. Age-adjusted incidence rates of selected cancers among males and females in the United States, 1975–2005 [19]. Reprinted from Jemal A et al. CA: Cancer Journal for Clinicians 2009;59:225–49 with permission from John Wiley and Sons.

For example, beginning in the mid 1990s, incidence rates approximately doubled within a decade in both Norway and Sweden; this increase coincided with a remarkable increase in PSA testing [20]. In Sweden, the annual number of newly diagnosed prostate cancers increased from 4 788 in 1990 to 8 870 in 2007, despite a stable population size.

In countries with high-quality health care and similar cure rates, temporal trends in cancer mortality usually mimic the incidence rates. In this context, prostate cancer is a profound outlier. Across the Nordic countries, the variation in incidence rates in 2001 was indeed ten times higher than the variation in mortality rates [20]. Despite the unprecedented differences in incidence, the cumulative risk of dying from prostate cancer at a given age remained virtually constant in all Nordic countries over the 40-year period from 1965 to 2005 [21]. Theoretically, this situation could arise if a true increase in the incidence of lethal cancer were balanced by better curative treatment. For a number of reasons, however, [22] this explanation is unlikely to apply to prostate cancer. Most importantly, curative treatment was not widely used in the Nordic countries until the mid or late 1990s. Furthermore, these treatments are considered only for early-stage disease, which accounts only for a small proportion of total prostate cancer mortality.

The emerging explanation for the apparent prostate cancer epidemic is sobering. Whilst the prostate cancer mortality rate has varied little over 40 years, the detection of clinically insignificant cancers through PSA testing – has entailed a drastic increase in the recorded incidence. The medical community has created a pseudo-epidemic of cancer with no clear evidence of a true increase in occurrence or any firmly established mortality benefit.

Benefits and harms of PSA screening

Pap smear screening for cervix cancer and colonoscopy screening for large bowel cancer may allow cancer prevention through minimal procedures to remove precursor lesions, namely, dysplasia or carcinoma *in situ* of the cervix and polyps in the colon. In contrast, due to its anatomic location, radical treatment of an early prostate cancer requires major surgery or radical radiotherapy. Following radical prostatectomy, approximately two thirds of all men lose their erectile function and up to one third has varying degrees of urinary incontinence [23]. Unfortunately, these adverse effects – as well as problems with defecation following radiation therapy – affect all men with similar probability, regardless of whether or not they benefit from the treatment.

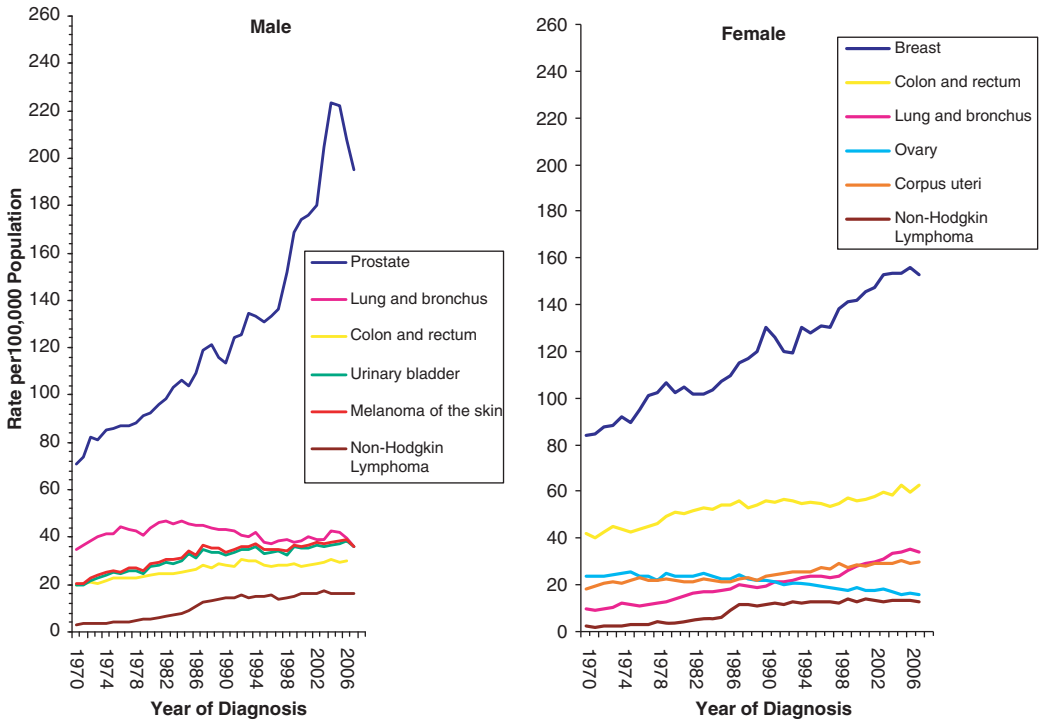

Figure 3. Age-adjusted incidence rates of selected cancers among males and females in Sweden, 1970–2007.

Healthy men who undergo PSA screening will belong to one of seven mutually exclusive categories, two of which benefit whilst five do not – and may likely be harmed. Quantifying the relative sizes of these groups is currently not possible (Table I). Men in group 1 are those for whom death from prostate cancer is averted due to screening. Reassurance following a normal PSA test (group 2) can clearly be beneficial but is time-limited. Moreover, the ability of a PSA level adequately to predict low future risk is a trade-off between sensitivity and specificity. Although somewhat arbitrary, I have made an attempt in Table I to grade harm in the remaining five groups from mild (+) to severe (+++). Few would disagree that men who are over-diagnosed (group 5) are the most disadvantaged. They are affected by all the negative effects of treatment and of being a cancer patient, as well as the financial cost of unnecessary medical procedures, with no survival benefit. Men with a false positive test (group 7) are also substantially burdened because multiple biopsies from the prostate may be required to rule out a malignancy with confidence.

Discussion

Without any compelling evidence of a true underlying increase in the occurrence of lethal prostate cancer the medical community has created a pseudo-epidemic in the recorded incidence of prostate cancer (Figures 2 and 3). The development of a simple and cheap blood test for PSA seems to be the sole cause of this epidemic. Certainly, doctors test PSA because they want to avert suffering and death from prostate cancer, the most common malignancy among men in many western countries. Unfortunately, however, a blood test is easier to perform than a Pap smear, mammogram, or

Table I. Groups that would and would not benefit from routine PSA screening. Estimated harm classified as none (−), some (+), moderate (++) or severe (+++).

Group	Groups that benefit	Estimated harm
1.	Men who would have died from prostate cancer butare cured owing to earlier detection	−
2.	Men with no prostate cancerand a normal PSA result (reassurance)	−
	Groups that do not benefit (and may be harmed)	
3.	Men who die from a PSA-detected prostatecancer and whose clinical course has not been improved by earlier treatment	+
4.	Menwith prostate cancer who would have survived even without screening	+
5.	Menwith a PSA-detected prostate cancer that would have not surfacedclinically during their lifetime (over-diagnosis)	+++
6.	Men with afalse negative result	+
7.	Men with a false positive result	++

colonoscopy, and the nuanced discussion required for true informed consent may be lacking.

Notwithstanding doctors' good intent, it is nevertheless surprising that PSA testing had already become wide-spread in the late 1980s, when most of the established World Health Organization criteria [5] for a screening intervention were unmet. The natural history of early disease was uncertain, little was known about the test's sensitivity and specificity, no curative treatments had been tested in clinical trials; and preliminary data from randomized screening trials would be unavailable for more than 15 years. A more informed and sobering view on PSA screening is now possible. As summarized above, we know more about the natural history and the effects of radical local treatment, and we have access to early results from two screening trials.

In addition, the driving force behind the pseudo-epidemic has now been sapped, as accumulated evidence shows that PSA is an inadequate screening test [24]. There are many problems. The ideal test should detect only potentially lethal cancers or as the second-best alternative, all those that would become symptomatic during a patient's life-time. Instead, the pseudo-epidemic itself documents the extensive over-diagnosis of clinically insignificant, non-lethal cancer.

As expected, lowering the cut-off value for PSA increases sensitivity but reduces specificity, and vice versa. Hence, there is no general agreement about an optimal cut-off – not even between centers participating in the same randomized trial [3]. Whilst a positive likelihood ratio higher than 10 is an accepted criterion for a screening test, no cut-off value for PSA generates a value higher than 5.5 (for a PSA of 4 ng/ml). To achieve the goal of a negative likelihood ratio not exceeding 0.1, the PSA cut-off has to be set at 1.0, a level that almost rules out a subsequent diagnosis of prostate cancer. However, with this low cut-off, the specificity of PSA is only 44%, implying a false positive test result in 56% of all men with no detectable cancer at biopsy [24].

Due to growing knowledge regarding PSA screening, international guidelines have become increasingly restrictive [25,26]. Routine testing is not recommended by the US Preventive Services Task Force [26], the European Urologic Association, the National Health Service in the UK, the Japanese Urological Association, the National Health Committee in New Zealand, or the Swedish Board of Health and Welfare. As an outlier, the American Urologic Association recommends that PSA testing should be offered to men aged 40 years or older. An intermediate position is taken by the American Cancer Society (ACS). While not supporting routine testing, the ACS recommends that physicians discuss the PSA test with patients and offer the test beginning at age 50 for average-risk men [25].

In the era of evidence-based medicine, it will be informative to follow the medical community's compliance with these recommendations. Ethical and scientific reasoning – reinforced by recommendations from respected authorities – clearly urge us to bring careless PSA testing to an end, notably among men who are poorly informed or even ignorant that PSA is analyzed in their blood sample. However, these recommendations will promote unavoidable frustration because no better performing screening test is in sight. Intense efforts to distinguish lethal from non-lethal prostate cancer with advanced molecular tools have so far remained unsuccessful. Meanwhile, the number of men dying from prostate cancer, often following substantial suffering, remains difficult to accept.

Acknowledgements

I would like to acknowledge Swen-Olof Andersson, Ellen Chang, Michelle Holmes and Jan-Erik Johansson for generously sharing with me their experience and providing important input.

Declaration of interest: The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

References

[1] Adami HO, Baron JA, Rothman KJ. Ethics of a prostate cancer screening trial. Lancet 1994;343:958–60.

[2] Le Fanu J. The rise and fall of modern medicine. New York: Carroll & Graf Publishers, Inc.; 1999.

[3] Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al; ERSPC Investigators. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320–8.

[4] Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, Church TR, et al; PLCO Project Team. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009;360:1310–9.

[5] Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: World Health Organization; 1968.

[6] Breslow N, Chan CW, Dhom G, Drury RA, Franks LM, Gellei B, et al. Latent carcinoma of prostate at autopsy in seven areas. The International Agency for Research on Cancer, Lyons, France. Int J Cancer 1977;20:680–8.

[7] Catalona WJ, Smith DS, Ratliff TL, Dodds KM, Coplen DE, Yuan JJ et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. N Engl J Med 1991;324:1156–61.

[8] Chodak GW, Thisted RA, Gerber GS, Johasson JE, Adolfsson J, Jones GW et al. Outcome following conservative management of patients with clinically localized prostate cancer. N Engl J Med 1994;330:242–8.

[9] Johansson JE, Adami HO, Andersson SO, Bergström R, Krusemo UB, Kraaz W. Natural history of localized prostatic cancer. A population-based study in 223 untreated patients. Lancet 1989;i:799–802.

[10] Johansson JE, Andrén O, Andersson SO, Holmberg L, Magnuson A, Adami HO. Natural history of early localized prostate cancer. JAMA 2004;291:2713–9.
[11] Holmberg L, Bill-Axelsson A, Helgesen F, Salo J, Folmerz P, Häggman M, et al; and the SPCG-4 Study Group. Radical prostatectomy versus watchful waiting for early prostatic cancer – results from the Scandinavian prostatic group randomised clinical trial [SPCG-4]. N Eng J Med 2002; 347:781–9.
[12] Bill-Axelson A, Holmberg L, Ruuti M, Häggman M, Andersson SO, Bratell S, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Eng J Med 2005;352:1977–84.
[13] Bill-Axelson A, Holmberg L, Filén F, Ruutu M, Garmo H, Busch C, et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: The Scandinavian Prostate Cancer Group-4 randomized trial. J Natl Cancer Inst 2008;100:1144–54.
[14] Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med 2000;343:16–22.
[15] Lajous M, Mozaffarian D, Mozaffarian R, Schrag D, Adami HO. Lifestyle prescriptions for cancer survivors and their communities. NEJM (submitted).
[16] Welsh HG. Should I be tested for cancer? Berkeley: University of California Press; 2004.
[17] Draisma G, Boer R, Otto SJ, van der Cruijsen IW, Damhus RA, Schröder FH et al. Lead times and over-detection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 2003;95:868–78.
[18] Draisma G, Etzioni R, Tsodikov A, Mariotto A, Wever E, Gulati R, et al. Lead time and overdiagnosis in prostate-specific antigen screening: Importance of methods and context. J Natl Cancer Inst 2009;101:374–83.
[19] Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225–49.
[20] Kvåle R, Auvinen A, Adami HO, Klint A, Hernes E, Möller B, et al. Interpreting trends in prostate cancer incidence and mortality in the five Nordic countries. J Natl Cancer Inst 2007;99:1881–7.
[21] Engholm G, Ferlay J, Christensen N, Bray F, Gjerstorff ML, Klint Å, et al. NORDCAN: Cancer incidence, mortality, prevalence and prediction in the Nordic Countries, Version 3.5. 2009. Association of the Nordic Cancer Registries. Danish Cancer Society (http://www.ancr.nu).
[22] Meyer M, Tretli S, Mucci L, Bray F, Adami HO. Stable prostate cancer mortality rates over 40 years in the Nordic countries. Submitted
[23] Steineck G, Helgesen F, Adolfsson J, Dickman PW, Johansson JE, Norlén BJ et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med 2002;347:790–6.
[24] Holmström B, Johansson M, Berg A, Stenman UH, Hallmans G, Stattin P. Prostate specific antigen for early detection of prostate cancer: Longitudinal study. BMJ 2009;339:b3572.
[25] Stark J, Mucci L, Rothman K, Adami HO. Prostate cancer screening: the controversy continues. BMJ 2009;339:b3601.
[26] U.S. Preventive Services Task Force. Screening for Prostate Cancer: U.S. Preventive Services Task Force. Recommendation Statement. Ann Intern Med 2008;149:185–91.