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Special article

Analysis of recommendations against prostate cancer screening with prostate specific antigen☆

Análisis de las recomendaciones en contra del cribado con antígeno prostático específico en cáncer de próstata

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Introduction

Prostate cancer (PCa) is the most commonly diagnosed male tumour in the Western world. It is the leading cause of cancer death in countries like Sweden, the second in the USA and the third in Spain (after lung and colorectal cancer).[1]

Prostate-specific antigen (PSA) is a specific organ marker but not of tumour pathology, as it can be found elevated in benign conditions such as benign prostatic hyperplasia, inflammatory (prostatitis) and after manipulations (digital rectal examination, cystoscopy, prostate biopsy). It represents, along with the digital rectal examination, the main PCa diagnostic tool, requiring confirmation by histological prostate biopsy.[1]

The clinical stage of the disease has changed radically since the introduction of PSA for PCa diagnosis. In the USA, it is estimated that since the 90s, coinciding with the introduction of PSA, prostate cancer mortality has decreased by 40% and the diagnosis of advanced disease has dropped by 75%.[2] Localized prostate tumour is the most common diagnosis scenario (80–90%) as per data from the National Prostate Cancer Registry (2010) in Spain. Metastatic tumours accounted for approximately 4%[3] in this same study.

There are 2 large population studies, published in 2009, which analyzed the role of PSA in PCa screening. On the one hand, the European study (European Aleatorized Study of Screening for Prostate Cancer [ERSPC]) and, secondly, the American (Prostate, Lung, Colon and Ovarian Cancer Screening Trial [PLCO]). While the ERSPC puts in objective terms a decrease of 21% in cancer-specific mortality due to screening in men between 55 and 69 years (RR 0.79, 95% CI, 0.69–0.92), the PLCO does not prove significant differences in this regard (RR 1.15, 95% CI, 0.86–1.54).[4,5]

Where both studies do agree, like others discussed later in this article, it is at the point where patients undergoing screening are diagnosed at earlier stages. Stage III-IV tumours as per PLCO represent 2.5% in the screening group (SCG) compared with 4.8% in the control group (CG); tumours with Gleason 8–10 are 6.5 and 11.5%, respectively. In the ERSPC, T3-T4 tumours encompass 9.6% (SCG) and 21% (CG), and tumours with Gleason 8–10 represent 7.4 and 16.4%, respectively. That means that the incidence of locally advanced and histologically more aggressive tumours doubles in the CG (Table 1).[4,5]

Recently, the ERSPC has published new data on the development of metastatic disease in the screening group and in the control arm, showing a lower risk of metastatic prostate cancer in the screening group; i.e. in the control arm there are more patients diagnosed with advanced/metastatic disease and are more likely to develop metastatic disease during follow-up than those in the screening group (between 30 and 42% increased risk at 12 years' follow-up).[6]

Subsequently, we analyzed the impact of this on the cancer-specific mortality. Although there are more factors to consider, these authors have observed a decrease in the risk of metastasis in the screening group of around 40% compared to CG, which would result in a 3-year decrease in cancer-specific mortality.[7]

Therefore, today, with updated data from the largest screening study in PCa (ERSPC) published to date, it seems that the reduction of cancer-specific mortality has, as one of its main factors, a reduced percentage of patients with metastatic tumours in the screening group.

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Table 1
Staging and histological grade of patients in the PLCO and ERSPC studies.

	PLCO[4]		ERSPC[5]	
	Screening group	Control group	Screening group	Control group
Stage I-III/T1-T2	1460 (97.3%)	2805 (94.3%)	5414 (90.4%)	3402 (79%)
Stage III-IV/T3-T4	37 (2.5%)	135 (4.8%)	576 (9.6%)	905 (21%)
Gleason ≤7	1375 (91.7%)	2572 (86.5%)	4510 (92.6%)	2317 (73.6%)
Gleason ≥8	98 (6.5%)	341 (11.5%)	363 (7.4%)	455 (16.4%)

Today, PCa screening with PSA is still a controversial issue and has even generated conflicting recommendations from different areas of medicine and from national and international urology. Our aim in this article is to summarize and update the main rationale behind the recommendations against PCa screening with PSA and assess its clinical impact.

Recommendations from the Spanish Society of Family and Community Medicine (SEMFYC)

In 2014, the SEMFYC working group for the Recommendations project published a 15-point guide. In paragraph No. 12, the non-use of PSA as a screening method in PCa is recommended in asymptomatic individuals.[8]

This recommendation is based on 3 references: (1) meta-analysis published in the Cochrane Library (2013)[9]; (2) recommendations of the group of experts in cancer prevention of the preventive activities and health promotion in primary care programme (2012), and (3) updated recommendations of the US Preventive Services Task Force (USPSTF, 2012).[10] First, we will analyze the first reference; the second is based, in turn, in a previous Cochrane meta-analysis by the same authors (2011), the PLCO study, with 13 years of follow-up (2012), and the recommendations of the USPSTF, which will be discussed in the next section.

The review published in Cochrane analyses five randomized studies after rejecting approximately 150 articles that did not meet the methodological requirements outlined by Cochrane itself (cohort, descriptive, preliminary results). The following studies were included: the European (ERSPC),[5] the American (PLCO),[4] one Canadian (Quebec)[11] and 2 from Sweden (Stockholm and Norrkoping).[12,13] The first thing that stands out is the significant variation in the number of patients included in the 5 studies and the asymmetry between screening and control groups, especially in smaller studies. In addition, in the same review it is highlighted that at least 3 of the studies had a high risk of bias due to their low methodological quality. This coincided with the fact that they were the studies which included fewer patients (Table 2).

In the overall analysis of 5 randomized studies in PCa screening, PCa mortality was not significantly decreased (RR 1.00, 95% CI, 0.86–1.17). Only ERSPC showed a significant decrease in cancer-specific mortality of 21% (RR 0.79, 95% CI, 0.69–0.92) in men between 55 and 69 years. PLCO observed a significant benefit (RR 1.15, 95% CI, 0.86–1.54). A sub-analysis was performed, discarding the 3 studies of fewer patients and increased risk of bias, and comparing the data between the ERSPC and PLCO, without showing significant difference (RR 0.96, 95% CI, 0.70–1.30).[9]

Moreover, PCa was diagnosed significantly more frequently in screening groups than in controls (RR 1.30, 95% CI, 1.02–1.65), being the number of localized tumours (T1-T2/N0M0) significantly higher in screening groups (RR 1.79, 95% CI, 1.19–2.70), while the number of advanced tumours (T3-T4/N1M1) was also significantly lower in the screening groups (RR 0.80, 95% CI, 0.73–0.87).[9]

Recommendations from the United States Preventive Services Task Force (May 2012)[10]

The USPSTF represents, together with the Canadian Task Force (CTF), one of the leading institutions in the development of recommendations in the context of primary care and prevention.

The USPSTF has published recommendations regarding PCa screening since 1989. In its latest update (2012) it advises against the use of PSA as a measure of *screening* in PCa with a 'D' as grade of recommendation (D: against the proposed measure. There is a moderate or high certainty that the proposed measure does not have a net benefit or that the disadvantages outweigh the benefits). In its previous version (2008), the USPSTF also recommended against screening in patients older than 75 years (grade of recommendation "D") but, in contrast, it concluded that in patients under 75 years of age there was not enough evidence to recommend or not recommend screening with PSA in PCa, grade of recommendation "I".[10]

The basis of these recommendations is, again, the ERSPC[5] and PLCO[4] studies. The main arguments are that, as we have seen, that cancer-specific mortality in the screening group does not diminish in the PLCO; moreover, although the ERSPC itself demonstrates a statistically significant cancer-specific mortality decrease of 21%, they consider that the number of patients to whom screening and then treatment should be provided is too high to compensate for the reduction in mortality.[10]

Regarding the PLCO, we want to highlight some aspects that somehow would question the consistency of their results. First, it is noteworthy that a PSA test was performed in 40% of patients before randomization; also in the CG, after a year of follow-up, between 40 and 52% of patients had a PSA test performed. Moreover, at the

Table 2
Summary of main variables of the 5 randomized studies reviewed in the meta-analysis of the Cochrane Library.

	ERPSC[5]	PLCO[4]	NORRKOPING[13]	QUEBEC[11]	STOCKHOLM[12]
Study population (years)	50–74	55–74	50–69	45–80	55–70
Screening tests	PSA + DRE 2–7 years	PSA and DRE yearly 6 and 4 years	DRE ± PSA Every 3 years	PSA and DRE (only first). After annual PSA	PSA and DRE
Follow-up time (years)	11	13	20 YEARS	11	15
PSA level	2.5–4	4	PSA > 4	>3	>7
Risk of bias (methodological quality)	Low	Low	High	High	High
Number of patients included	SCG 72,891 CG 89,352	SCG 38,340 CG 38,345	SCG 1459 CG 7532	SCG 31,133 CG 15,353	SCG 2374 CG 24,772

CG, control group; SCG, screening group; PSA, prostate specific antigen; DRE, digital rectal examination.
Dahm et al. taken from.[9]