COST-BENEFIT OF INCORPORATING THE DETECTION OF CIRCULATING PROSTATE CELLS IN A SCREENING PROGRAMME FOR PROSTATE CANCER

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Summary.- OBJECTIVES: Prostate cancer is the second most common cancer in men after skin cancer. Screening is used to detect early stage cancer using serum prostate specific antigen (PSA). A level of PSA > 4.0 ng/mL as a cutoff point or abnormal digital rectal examination (DRE) are used to indicate a prostate biopsy. Nevertheless, non-malignant pathologies can increase serum PSA level so that 70% of biopsies are negative for cancer, and thus potentially unnecessary, causing anxiety, costly clinical tests and prolonged follow-up. Thus the search for new biomarkers is important. Circulating primary prostate cells (CPCs) may be such a marker. We analyze a cohort of patients using CPCs to detect prostate cancer in men with a serum PSA > 4.0 ng/mL or abnormal DRE in terms of cost-benefit.

METHODS: A cohort of 263 patients with a PSA > 4.0 ng/mL and a test to detect CPCs who underwent prostate biopsy were analyzed. The results of both tests were compared with biopsy results; sensibility, specificity, and predictive values were calculated. Costs of each test, process, drug costs and complications were determined as well as indirect costs.

RESULTS: Of the 263 patients, 77 (28.6%) had prostate cancer detected, for the test using CPCs there was a sensibility of 85.7%, specificity of 90.3% and negative predictive value of 93.9%. Thus men CPC negative may not need a prostate biopsy. Potential savings for the 263 patients were between €32,068 in a public health service and €69,253 for inpatient private health insurance patients. Follow up cost were higher in false-positive CPC patients but, as there were fewer false positive patients, total costs were lower.

CONCLUSIONS: The use of primary CPC detection as a complementary test in men with a serum PSA > 4.0 ng/mL to indicate prostate biopsy is a specific, cost effective test, eliminating approximately 70% of prostate biopsies. This results in a significant health care saving both in direct and indirect costs, in the costs of complications. Implementation costs were minimal as equipment and reagents are part of the routine clinical laboratory. The method deserves further investigation to confirm the results.
Resumen.- OBJETIVO: El cáncer de próstata es el tumor más frecuente en varones después del cáncer de piel. Para detectar el cáncer prostático en estadios tempranos se realiza despistaje con el antígeno prostático específico (PSA). Para evaluar la necesidad de una biopsia prostática se utilizan un valor de PSA de 4.0ng/ml como corte y/o tacto rectal anormal. Sin embargo patologías benignas pueden elevar este biomarcador, con un 70% de las biopsias negativas para cáncer, y por lo tanto potencialmente innecesarias, causando ansiedad, estudios de laboratorio costosos y seguimientos prolongados. La búsqueda de nuevos biomarcadores es importante. Las células prostáticas circulantes en sangre (CPCs) pueden ser un marcador útil. En el presente artículo analizamos una cohorte de pacientes utilizando CPCs para detectar cáncer de próstata en hombres con un PSA 4.0ng/ml o un TR alterado en términos de costo - beneficio.

MÉTODO: Se analizó una cohorte de 263 pacientes con un PSA 4.0ng/ml y un test de CPCs que fueron sometidos a una biopsia prostática. Los resultados de los 2 test fueron comparados con los resultados de la biopsia, la sensibilidad, especificidad y valores predictivos fueron comparados. Se determinaron los costos de cada test, del proceso, medicamentos y complicaciones.

RESULTADOS: De los 263 pacientes, a 77 (28,6%) se les detectó un cáncer de próstata. Las CPCs tuvieron una sensibilidad de 86,2%, especificidad de 90,8% y un valor predictivo negativo de 94,3%, por lo tanto, pacientes con un test de CPCs negativo posiblemente no necesitaran de una biopsia. Los ahorros potenciales utilizando las CPCs en estos 263 pacientes rondaron entre los 32.068€ en el sistema de salud publico y 69.253€ en el privado. Los costos de seguimiento de los pacientes falsos positivos para CPCs eran superiores, pero como hubo poco falsos positivos, los costos totales fueron menores.

CONCLUSIÓN: El uso de CPCs como prueba complementaria en pacientes con un PSA elevado es un estudio específico y coste-efectivo que tiene la capacidad de eliminar aproximadamente el 70% de las biopsias de próstata. Esto resulta en un importante ahorro para los sistemas de salud tanto en los costos directos como en los indirectos, en los costos de las complicaciones. Los costos de implementación son mínimos ya que el equipoamiento es parte del laboratorio clínico de rutina. Este método merece estudios a mayor escala para confirmar sus resultados.

Keywords: Prostate cancer. Screening. Circulating prostate cells. Cost-benefit.

INTRODUCTION

Prostate cancer is the most common non-skin cancer in men with an estimated 1 in 6 men receiving a diagnosis during their lifetime (1). The PSA test was approved by the FDA in 1986 for prostate cancer screening and its use has increased since the mid-1990s (2). Early detection as a result of screening may result in a decrease in prostate cancer mortality as shown in the European Randomised study of Screening for Prostate Cancer (ERSPC) trial (3). In this European trial, screening with prostate-specific antigen (PSA) reduced prostate cancer mortality by at least 20%.

However, PSA testing is not specific for prostate cancer, common conditions such as benign hyperplasia and prostatitis increase PSA levels, attempts to improve PSA sensitivity and specificity such as PSA density, PSA velocity, PSA doubling time and percentage of free PSA have not been conclusive (4-7). Furthermore the cut-off point of 4.0ng/ml has been questioned with regards to the detection of small but clinically significant tumors, in Europe a level of 3.0ng/ml is being used (7). Consequently, the majority of men with an increased serum PSA does not have prostate cancer and thus undergo unnecessary prostate biopsies. Although some individuals who incurred a false positive screening test result did not receive any follow-up, the majority do. This has consistently been shown to be anxiety producing and lead to uncomfortable and potentially costly clinical work-ups. The actual costs of such clinical workups rarely have been studied. The most frequently received tests for men with a false-positive prostate cancer screen are repeat prostate-specific antigen (66.7%) and prostate biopsy (38.9%) (8).

Data from the USA estimate that of the millions of prostate biopsies performed annually, only 235,000 cases of cancer are detected, or that more than 750,000 men underwent a biopsy based on an elevated PSA caused by benign disease (9,10). Published data from the Prostate Cancer prevention Trail showed that there is no cut-off point for serum PSA, for values up to 4ng/ml the sensibility of the test showed a variation of between 21% and 83%, the specificity of between 39% to 94% with a positive predictive value of between 7% and 27% (11).

The search for new biomarkers such as percent free PSA (12), serum intact PSA (13), serum pro-PSA (14) and kallikrein (15) have shown to be useful in the detection of prostate cancer. However, although a biomarker could improve the precision of screening it is possible that in clinical practice it is not viable, for the need of fresh samples or high costs (16).
In this context, the use of the detection of circulating prostate cells could be a useful screening test in selected individuals. In men with prostate cancer, there is, at least, one subpopulation of cancer cells that disseminate early, to the neurovascular structures and then to the circulation (17). The number of cells is very small, however these CPCs can be detected using immunocytochemistry, PSA is not specific for prostate cancer, for this reason double-immunocytochemistry is essential. The use of P504S together with PSA could be useful in identifying malignant prostate cells. The use of P504S (methylacyl-CoA racemase) in prostate biopsies has facilitated the differentiation between normal, dysplastic and malignant tissues. Normal and benign cells do not express P504S, whereas dysplastic and malignant cells do. As dysplastic cells do not disseminate, those prostate cells expressing P504S in the circulation are considered to be malignant. However, P504S is not specific to the prostate; it is expressed in normal and malignant tissues, including leukocytes. For this reason the use of double immunomarcaration is essential for the identification of malignant prostate cells. There is no cutoff point, the test being reported as positive or negative, and there is a significant association with the biopsy results (18, 19).

In this article we analyze a cohort of patients who participated in a study of prostate cancer detection, comparing the detection of circulating prostate cells, as a sequential test in men with suspicion of prostate cancer and the results of the prostate biopsy. We analyze in terms of cost-benefit of the use of CPC detection in men with a PSA level of ≥4.0ng/ml or abnormal DRE and considered for a prostate biopsy. The objective of the detection of CPCs is the reduction in the number of prostate biopsies, not to replace the use of serum PSA. It’s role in the detection of prostate cancer, being a sequential test in men identified by an increased serum PSA and/or abnormal rectal examination in order to determine the need for a prostate biopsy, it is not designed to be a screening test in the general population.

**PATIENTS AND METHODS**

All men older than 45 years, without a previous history of prostate cancer and fulfilling the international criteria for a prostate biopsy were invited to participate. Biopsy criteria were a serum PSA >4.0ng/ml, abnormal digital rectal examination or a serum PSA velocity of >0.75ng/ml/year. For each patient, age, serum PSA, DRE and biopsy results were recorded. Each patient was assigned a code number, blood samples were sent to the Instituto de Bio-Oncologia por CPC detection, at room temperature within 48 hours, the immunocitologist was blinded in terms of patient details.

After written informed consent, a 4ml venous blood sample was taken from the cubital vein with a 21G needle and collected in tube containing EDTA (Beckinson-Vacutainer®) before the prostate biopsy. Each patient was identified with a three digit code, permitting a blinded study with respect to clinical details.

Mononuclear cells were obtained by differential centrifugation using Histopaque 1,077® (Sigma-Aldrich), washed and resuspended in 100µl of autologous plasma. 25µl aliquots were used to make slides (sialianized, DAKO, USA), dried in air for 24 hours and fixed as previously described (18,19).

**Immunocytochemistry**

Circulating prostate cells (CPCs) were detected using a monoclonal antibody directed against PSA, clone 28A4 (Novocastro Laboratory, Table 1. Association between CPC detection and prostate cancer detection in men with a PSA >4.0ng/ml and/or abnormal rectal examination.

<table>
<thead>
<tr>
<th>Biopsy positive for cancer</th>
<th>Biopsy negative for cancer</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPC positive</td>
<td>66</td>
<td>18</td>
</tr>
<tr>
<td>CPC negative</td>
<td>11</td>
<td>168</td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
<td>186</td>
</tr>
</tbody>
</table>

p<0.000001
UK) and identified using an alkaline phosphatase-anti-
alkaline phosphatase based system (LSAB2, DAKO,
USA), with new-fushcin as the chromogen. Positive
samples underwent a second process with anti-P504S
clon 13H4 (DAKO, USA) and identified with a
peroxidase based system (LSAB2, DAKO, USA) with
DAB as the chromogen.

A CPC was defined according to the criteria of
ISHAGE (18) and the expression of P504S according
to the Consensus of the American Association of
Pathologists (19). A test was considered positive if 1
or more CPCs were detected.

Clinical data

The analysis was based on patient level data
obtained from the present study; no adverse effect
data were collected during the clinical study and
were obtained from a previous study carried out in
the same hospital, these outcomes supplemented the
trial data.

Cost-Analysis

In the present analysis the main outcome
measure was the incremental cost-utility ratio of using
the detection of CPCs as opposed to serum PSA and/or
abnormal digital rectal examination to indicate
the need for a prostate biopsy, which calculated the
saving or additional cost of implementing a screening
program based on CPC. The analysis included direct
medical costs of the biopsy, direct costs of adverse
events (calculated from data obtained from a study
conducted in the same hospital), an estimation of
indirect costs in terms of lost income, were calculated
as days of work lost/average Chilean wage per
day as a percentage of the patient group in active
employment.

Costs of pre-biopsy tests, biopsy costs
(including biopsy kit, ultrasound time, procedure
cost, pathology cost, drug cost, hospital bed cost)
were obtained from the Hospital Costs Unit Hospital
de Carabineros de Chile and Hospital DIPRECA and
based on Public Health Service (PHS) list prices in the
case of Public Health Patients (FONASA) and Private
Health Insurance (PHI) list prices in the case of Private
Patients (Isapres).

Costs for CPC detection were obtained from the
Instituto de Bio-Oncology Costs Unit

Costs for complications of the biopsy were
based on local estimates derived from the Hospital
Statistical Unit20. Patients with fever, defined as >38°C
were hospitalized and treated with ceftriaxone 1gm
iv c/12 for 7 days and metronidazol 500mg c/8 PO
for 7 days, hemorrhage was treated with tranexamic
acid 500mg c/8 PO por 7 days as an outpatient. Complication rates were 2.9% infection and 0.5%
severe hemorrhage. The total cost of the adverse
effects was estimated by multiplying the number of
biopsies by the frequency of adverse events.

In men with a false positive test for PSA, an
estimation of increased follow-up costs was made, this
comprised of blood tests for PSA and free PSA and
evaluation by the urologist every 4 months, and an
estimated 8% of these patients underwent a second
biopsy within one year of the first biopsy. In men with
a false positive CPC detection, the hospital protocol is
repetition of the CPC test with the PSA and free PSA
at 4 months and evaluation by the urologist, if the
PSA value increased <1.0ng/ml and remained CPC
positive a second biopsy was performed. 5 patients
had a repeat biopsy.

Non-medical patient costs were estimated
from National Institute of Statistics, Chile for average
wage and travel costs. We did not consider the
capital costs of initiating or administering a screening
program and thus assumed that screening would
be opportunistic in both strategies. The costs were
calculated in Chilean peso and converted to Euros
with an exchange rate of 1€ = 640 Chilean pesos.

Analysis of data

To estimate the costs, the total cost of the
263 biopsies was calculated on an outpatient and
inpatient basis, the cost of using the CPC detection
system was calculated on the cost of 263 CPC tests.

| Table II. Costs of a prostate biopsy PHS = public health service PHI=private health insurance. |
|-------|-------|
|        | PHS   | PHI   |
| Pre-biopsy blood tests | 37€    | 57€    |
| Drug cost | 15€    | 15€    |
| Biopsy Kit | 62€    | 62€    |
| Prostate biopsy | 64€    | 102€   |
| Inpatient 1 day | 16€    | 122€   |
| CPC cost | 27€    | 43€    |
and the number of biopsies for patients who were positive for CPCs.

Statistical Analysis

Descriptive statistics were used for demographic variables, Student T –test for differences in mean, Chi-squared and Fisher Test for differences in proportions. For non-parametric values, Krusal-Wallis and Poisson distribution were used. An alpha error of 0.05, beta error of 0.20 and p<0.05 as significant were used.

Ethical considerations

The study was conducted in complete agreement with the Declaration of Helsinki (as well as the modifications of Venice and Hong Kong) and the approbation of the Hospital Ethical Committee.

RESULTS

Between January 2009 and October 2011, two hundred and sixty three consecutive men participated in the study, with a mean age of 66.9±SD8.7 years and a mean serum PSA of 10.26 ng/ml (range 3.48-748ng/ml (first quartile 4.17ng/ml, third quartile 7.38ng/ml).

Of the 263 biopsies, 186 (70.2%) were benign and 77 (29.8%) adenocarcinoma. CPCs were detected in 77 (29.3%) of all patients.

Association of the detection of CPCs and prostate biopsy results

The association between the detection of CPCs and prostate biopsy results is shown in Table I, with a sensibility of 85.7% (95% CI 75.3-93.5%), specificity of 90.3% (95% CI 85.3-94.8%), a positive predictive value of 78.6% (95% CI 67.6-87.7%), a negative predictive value of 93.9% (95% CI 89.4-97.3%), a positive diagnostic likelihood ratio of 8.86 (95% CI 5.65-14.00) and a negative likelihood ratio of 0.16 (95% CI 0.09-0.28) and odds ratio of 61.39.

Costs

Table II shows the costs for public and private health care systems for a prostate biopsy and CPC test costs. Complication costs for hemorrhage and sepsis are shown in Table III and indirect costs of wage lost was estimated using an average Chilean wage of €$16/day. The costs for the total study population of 263 patients is shown in Table IV, giving an average cost of €$208 for an outpatient public health care biopsy, €$240 for an inpatient public health care biopsy, €$290 outpatient private health care biopsy and €$428 for an inpatient private health care biopsy.

Costs for study group using CPC detection and omitting biopsies in CPC negative patients

The total cost of 263 CPC detection tests was €$7,006 (PHS) and €$11,211 (PHI), with the additional cost of 77 biopsies to be carried out in CPC positive men, the total cost for each group is shown in Table 5. The total saving in the 263 patients to the health care system using CPC detection was €$32,068 for an outpatient public health care biopsy, €$38,158 inpatient public health care, €$43,250 outpatient private health care and €$69,253 inpatient private health care systems (Table V).

Costs of false positive tests: (in the year after prostate biopsy)

Standard follow up procedure in men with an elevated PSA and biopsy negative for cancer, is a three monthly medical control with serum PSA and free serum PSA and medical control. Control procedure using CPC detection was three monthly medical control, serum PSA and CPC test. The indications for a biopsy within one year were; increase in serum PSA >1ng/ml, number of CPCs/ml increasing.

- standard control: serum PSA con percent free PSA: three four monthly blood tests with 3 urology consultations PHS €108 PHI €143. The number of patients in control was 186 men. The number of repeat biopsies, 8%, was estimated from patient activity records of the hospital, the number of estimated repeat biopsy was 15.

<table>
<thead>
<tr>
<th>Complication</th>
<th>PHS</th>
<th>PHI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization 7 days</td>
<td>112€</td>
<td>855€</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>232€</td>
<td>233€</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tranexamic Acid</td>
<td>46€</td>
<td>46€</td>
</tr>
<tr>
<td>Medical Control</td>
<td>9€</td>
<td>17€</td>
</tr>
</tbody>
</table>
• **CPC detection**: serum PSA, CPC detection and urology consultation cost of three four monthly controls PHS €141 PHI €227. The number of patients in control was 18 and there 5 repeat biopsies.

Total cost of follow-up controls: assuming an indirect cost of half a day of work, €8/visit, for a total annual of €24.

• **Standard protocol for 186 men**: PHS €20,088, PHI €31,062

• **CPC protocol for 18 men**: PHS €2,970, PHI €4,200

**DISCUSSION**

There is consensus in that evidence surrounding new technologies should include cost-effectiveness information. These economic evaluations are part of the daily practice in many countries, such as the United Kingdom. In the case of Latinamerica, including Chile, Pichon-Riviere et al. (21) have shown that there is limited use of the information collected from the evaluations of health technologies, limited resources designated for their development and little government support for these initiatives. In spite of this, countries such as Brazil, Mexico, Chile and Argentina have an active policy of evaluating health technologies and it appears that this is the tendency in other countries in the region (22).

In the process of prioritization and selection of health interventions, included in different packets (public health, community health programs of low and intermediate complexity, special health programs and those of high complexity), the disease frequency and evaluations of cost-benefit play a fundamental role (23). Chile has a mixed public-private health

### Table IV. Cost total of 263 patients and per biopsy according to PHS, PHI in or outpatient.

<table>
<thead>
<tr>
<th></th>
<th>PHS outpatient</th>
<th>PHS inpatient</th>
<th>PHI outpatient</th>
<th>PHI inpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-biopsy tests</td>
<td>9,755€</td>
<td>9,755€</td>
<td>15,098€</td>
<td>15,098€</td>
</tr>
<tr>
<td>Drug cost</td>
<td>3,918€</td>
<td>3,918€</td>
<td>3,918€</td>
<td>3,918€</td>
</tr>
<tr>
<td>Biopsy Kit</td>
<td>16,480€</td>
<td>16,480€</td>
<td>16,480€</td>
<td>16,480€</td>
</tr>
<tr>
<td>Biopsy</td>
<td>16,891€</td>
<td>16,891€</td>
<td>27,113€</td>
<td>27,113€</td>
</tr>
<tr>
<td>Inpatient</td>
<td>0€</td>
<td>4,223€</td>
<td>0€</td>
<td>32,381€</td>
</tr>
<tr>
<td>Indirect costs</td>
<td>4,254€</td>
<td>8,508€</td>
<td>4,254€</td>
<td>8,508€</td>
</tr>
<tr>
<td>Complication costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis: (N=8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>908€</td>
<td>908€</td>
<td>6,959€</td>
<td>6,959€</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>1,884€</td>
<td>1,884€</td>
<td>1,884€</td>
<td>1,884€</td>
</tr>
<tr>
<td>Indirect costs</td>
<td>911€</td>
<td>911€</td>
<td>911€</td>
<td>911€</td>
</tr>
<tr>
<td>Hemorrhage (N=1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug cost</td>
<td>45€</td>
<td>45€</td>
<td>45€</td>
<td>45€</td>
</tr>
<tr>
<td>Medical control</td>
<td>9€</td>
<td>9€</td>
<td>17€</td>
<td>17€</td>
</tr>
<tr>
<td>Indirect costs</td>
<td>112€</td>
<td>112€</td>
<td>112€</td>
<td>112€</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>263 patients:</td>
<td>55,167€</td>
<td>63,644€</td>
<td>76,791€</td>
<td>113,420€</td>
</tr>
<tr>
<td>Per biopsy</td>
<td>208€</td>
<td>240€</td>
<td>290€</td>
<td>428€</td>
</tr>
</tbody>
</table>
COST-BENEFIT OF INCORPORATING THE DETECTION OF CIRCULATING PROSTATE CELLS...

system, in that the public health insurance FONASA is financed on the basis of the social security and fiscal support which covers 70% of the population and a private health insurance system, the ISAPRES which covers a further 16% of the Chilean population (24).

In this context, our study makes a contribution of the decision making process of incorporating new health technologies. The Chilean male population aged between 45 and 75 years, according the 2003 Census, is estimated to be in 2010 and 2015 approximately 2,296,000 and 2,618,300. Using the results of the First Health Survey of the Health Ministry in 2003, it estimates there will be 95,425 men in 2010 and 116,241 men in 2015 with a serum PSA >4.0ng/ml. However, there is no national record of the number of prostate biopsies performed on an annual basis. The number of patients diagnosed in the public health service between 2005 and 2010 with prostate cancer was 17,719, assuming a positive biopsy rate of 27%, this corresponds to approximately 14,100 biopsies/year in the public health service. This represents 14.8% of the potential population of men with a serum PSA >4.0ng/ml.

Our pilot study has shown that it is possible to eliminate 70% of first time prostate biopsies with the use of the CPC system, which translates into a saving of between €23,874 and €51,807 in the 263 patients who were studied. If the results are confirmed in a larger number of patients this would represent a saving of between €1,465,829 and €3,180,998 per year, assuming an average of 14,000 biopsies/year.

We used a simple standard manual method of CPC detection, in the market there is the FDA approved CellSearch® system for detecting CPCs. However, the costs of the test on the open market are between US$770 and US$1,000. It must be noted that using the CellSearch® system, Davis et al. (25) did not find an association between the detection of CPCs and clinical parameters prior to radical prostatectomy, nor between cases of localized prostate cancer and controls (26). The reduced or absent expression of EpCAM and/or cytokeratins is the principal cause of detection failure, EpCAM being expressed in the majority but not all cancers (27). There is down regulation of EpCAM expression with tumor progression and in metastasis, furthermore cytokeratins are heterogeneously expressed and tend to be down regulated during cancer progression and in poorly differentiated tumors. During the epithelial-mesenchyme transition both markers are down regulated (34), down regulation of EpCAM permits the separation of the tumor cells and that of cytokeratins facilitates the cellular plasticity and thus migration. We consider that with an experienced immunocytologist the manual method and based on our results the method is acceptable. Although manual and as a result there is a greater inter-operator variation, pilot studies have shown they are reproducible and have been validated in clinical terms with the results of the prostate biopsy (19). In the context of prostate cancer screening, the biopsy procedure and pathological interpretation of the samples are operator dependent, probably more so than the CPC test. Differing from the CellSearch® system, where there is a cutoff point, which varies between cancer type and if there is the presence of metastasis or not, the CPC test is designed to be positive or negative, thus facilitating the clinical decision as to proceed to biopsy or not. The method of immunocytochemistry is routine in pathology, training is minimal and the identification of positively staining cells is part of the routine work in cytology. This means that the cost of installing the CPC program in terms of equipment is of zero cost, as all elements are found in a routine laboratory. The cost per test is much less, €23.50 per test, including labor costs.

Consistent with the findings of others documenting relatively high false-positive rates, we found a substantial number (186/263) of those

<table>
<thead>
<tr>
<th></th>
<th>Normal System</th>
<th>CPC System</th>
<th>Saving</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHS outpatient</td>
<td>55,167€</td>
<td>23,099€</td>
<td>32,068€</td>
</tr>
<tr>
<td>PHS inpatient</td>
<td>63,644€</td>
<td>25,486€</td>
<td>38,158€</td>
</tr>
<tr>
<td>PHI outpatient</td>
<td>76,791€</td>
<td>33,541€</td>
<td>43,250€</td>
</tr>
<tr>
<td>PHI inpatient</td>
<td>113,420€</td>
<td>44,167€</td>
<td>69,253€</td>
</tr>
</tbody>
</table>

Table V. Total of normal system versus CPC based system and saving in 263 biopsies.
undergoing cancer screening to incur at least one false-positive result, in terms of a serum PSA >4.0ng/ml. The CPC detection test had a significantly lower false positive rate (18/77). The majority of individuals who incurred a false positive screen result received some type of follow-up care in the year following their screening. Despite some individuals not receiving any follow-up care, rates of medical utilization for specific follow-up tests were almost always higher in the false-positive group. This translated into significantly more medical care costs. We calculated that men with a serum PSA >4.0ng/ml and negative first prostate biopsy incurred an average cost of PHS €141 and PHI €227. The number of men with a false positive CPC detection test is much lower, and although the cost per patient was higher, the overall cost for the system was much less, in terms of costs and medical time.

We estimated the number of repeat biopsies taken in these patients from previous hospital data, which further increases costs. When false-positive findings and their consequences are explicitly considered in economic evaluations, model results are often sensitive to the assumed rate of false positive screens (29-31). These results have led some to argue that the cost-effectiveness of different screening programs are primarily driven by rates of false-positive screens among other undesirable outcomes (e.g., overdiagnosis) (32,33). The reality is that false-positive findings among those undergoing cancer screenings are relatively common, usually constituting the large majority of all positive findings and often leading to follow-up investigations that do not result in a cancer diagnosis (34). Given the potential economic and other implications of a false-positive cancer screen result, it is important that when patients are offered cancer screening it is within a context that allows informed decision-making.

However, despite the convincing evidence in our pilot study of 263 patients, the implementation of CPC detection might result in unanticipated losses or dis-economies in the short run. There are two prime reasons, firstly that the new cost-effective technology will probably co-exist with the inefficient alternative for a considerable time period. In our study the idea is a complementary process, leading to decreased biopsies, thus there is not an alternative test; only that CPC detection is not performed. Secondly there might be dis-economies of learning, during the implementation phase, old and new practices may co-exist, with most health professionals being less familiar with new technologies than with the old process. Economies of learning refer to decreasing average cost or increasing average effectiveness, as a result of accumulating experience and know-how. The transition from old to new processes may well cause the opposite effect; increasing average costs or decreasing effectiveness as experience is lacking. Thus patients may have CPC detection performed and regardless of the result proceed to prostate biopsy. The investment necessary to embed the technology in the health organization was not calculated, this would mean capacitating health professionals, information to the patient of the incorporation of new test. That this study was performed as part of a clinical trial, thus had an experimental design, the reality in the clinical situation may be different, and a focus on common practice to order to consider the impact of potentially cost-effective technology on the production processes and budgetary constraints in the health organization.

CONCLUSIONS

We consider that the CPC detection test has an important impact in terms of cost-benefit in the context of a prostate cancer screening program, decreasing the number of false-positive cases, and the over-diagnosis of small insignificant tumors. The results deserve to be confirmed with a larger number of patients in an environment of common screening practice.

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REFERENCES AND RECOMMENDED READINGS

(*of special interest, **of outstanding interest)