« Cost effectiveness analysis of strategies for screening prostatic cancer»

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INTRODUCTION

A screening programme is justified if it fulfils three criteria : the disease incidence is high, the natural course is known and effective treatment exists. If we confine ourselves to the first criterion, then screening for cancer of the prostate seems an absolute necessity. In 1982, 27% of the 282,660 male deaths recorded in France were due to cancer. Prostate cancer accounted for 1 in 10 cases. In others terms, 2.5% of deaths among the male population is caused by a malignant tumour of the prostate, which corresponds to a crude mortality rate in France of 27 per 100,000. On the international level, statistics show that the problem is at least as acute in the other Western countries. The rate of mortality standardized for the world population reaches 14.7 per 100,000 in the United States, vers us 15 per 100,000 in France. The crude rate of incidence for the Americans is three times greater than the crude rate of mortality in the country. According to Silverberg (1987), 1 American out of 11 (8.7%) born in 1985 risks developing cancer of the prostate during the course of his life. The risk is as great as for lung cancer. On the other hand, however, it should be noted that if 90% of lung cancer patients die from their disease, death from cancer of the prostate occurs in one case out of three.

These differences between the rates of incidence and of mortality can be explained in three ways. The first is the possibility of overdiagnosing cancer of the prostate. Several lesions which are described as cancers correspond, in fact, to normal aging of the cells. The second possibility is that cancer of the prostate is mainly encountered among the elderly, who die from other concomitant diseases. The third, and more optimistic, is that two thirds of all prostate cancers are cured. Unfortunately, nothing can be found in the literature to back up this point of view.
In order to explain these differences, we need to consider the natural course of the disease. The essential variable in cancer of the prostate, as Boccon-Gibod (1988) has emphasized, is "the tumour volume which grows slowly, regularly and progressively, and this governs its potential for malignancy. Three groups of patients can be distinguished in this respect :
The first group includes patients who present with well-differentiated localized tumours whose kinetics are weak. Patients in this group have every chance of dying from another intercurrent disease. This group is far more important than it would appear from the clinical series. On post-mortem, cancer cells are found in almost 40% of all 80-year old men who were never suspected on clinical examination of having cancer of the prostate.
The second group concerns poorly differentiated non-localized tumours with spread to the seminal capsule at the time of diagnosis. The possibility of metastases must be considered in such cases and early diagnosis is of little help.
The third group, whose number represents no more than 5 to 10% of the total, presents with a localized tumour for which early diagnosis and appropriate treatment may prove curative.
In view of these sub-populations, Whitmore's question (1988) "Is treatment necessary when it is possible, is it possible when it is necessary ?" is better understood.
The decision to screen is therefore controversial. We have not sought to demonstrate that screening has a satisfactory cost-effectiveness ratio, but to study the cost-effectiveness ratio of the different programmes that are possible, once the decision to screen has been taken.

The diagnostic methods which can be used are: digital rectal examination (DRE), prostate specific antigen (PSA) measurement, ultrasonography (US) and biopsy (8). We have used a decision theory model to compare and evaluate 6 different screening protocols. Sensitivity and specificity for the different examinations were assessed on the basis of the international literature and French series. The protocols were compared in terms of cost per person screened and the number of cancers

identified. Sensitivity was analyzed for the different rates of clinical and post-mortem prevalence. lastly, the different programmes were classified.

1. METHODS

1.1 Medical issues

1.1.1 Tumour classification

An ability to know the extent of the tumour and its malignant potential is essential for estimating what might be the consequences of the various screening programs. Numerous classification are in use to categorize prostatic carcinoma, but none has received general agreement. We chose to elect the ABCD and the World Health Organizations Systems. The reasons for such a choice are very pragmatic. First the clinical staging proposed by Whitmore and Jewett (1984) has received widespread use, especially in the US, even if the TNM classification (Hermanek 1988) will probably become more popular in the future. Second, the International Classification System (1980) for histological grading was applied in one of the few available studies on the natural history of the disease (Johansson, 1989), while none could be found on the Gleason system (1966).

According to the Whitmore-Jewett classification, cancer of the prostate is divided into four clinical stages depending on disease extension :

Stage A_1 non palpable, focal
Stage A_2 non palpable, diffused
Stage B_1 palpable, one lobe
Stage B_2 palpable, two lobes

Stage C local extension
Stage D metastases

These clinical parameters indicate how far the tumour has progressed along its course. Screening aims at diagnosing cancers amenable to curative therapy, i.e. stages A and B. Only palliative treatment is possible in stages C and D for the time being and it is doubtful whether palliation prolongs survival.

The WHO system is based upon pattern of glandular differenciation, and it reflects the tumour growth kinetics. Three categories are distinguished :

- Well-differentiated tumour ,
- Moderately differentiated tumour ,
- Poorly differentiated tumour.

Evidence available of the tumour growth demonstrates a more agressive behavior of the cancer with increased grade. Well-differentiated tumour grows slowly, poorly differentiated tumour grows rapidly.

1.1.2 Testing procedures

Prostate cancer is mainly detected by three examinations which may complement each other : digital rectal examination (DRE), trans-rectal ultrasonography (US) and prostate specific antigen (PSA).
For long, DRE was the only means of detecting the disease and it is still regarded by clinicians as an essential examination. The posterior face is palpated to seek abnormalities in shape and consistency which may be manifestations of adenocarcinoma. The information given by the examination is incomplete.

Certain anomalies are not carcinomas, whilst small tumours and lesions on the anterior surface cannot be felt. For Stamey and McNeal (1987), only cancers of the postero-lateral third can be palpated in this way. Only 45% of prostate tumours are located in this part of the gland. Another disadvantage of DRE is that only tumours that have reached a certain size are detected : in tact they have often spread beyond the capsule and curative therapy no longer possible. Thus, 95% of cancers that have reached 4mm in size have spread beyond the gland. Despite these limitations, DRE is considered as a useful test: it is inexpensive, non-iatrogenous and its sensitivity and specificity seems to be correct.

Historically, ultrasonography (US) is the second method of detecting cancer of the prostate. Abnormalities in the consistency of the gland or in the echo are looked for. The procedure proved to have poor specificity. Many studies have shown the limitations of ultrasound in displaying signs of disease of the prostate gland and its usefulness is now questionable.

Biological markers seem more promising. Of these, the prostate specific antigen (PSA) is undoubtedly the most effective. It is not specific against tumour tissue: benign hypertrophy of the prostate also produces PSA. However, whereas BHP prostate tissue causes a rise of 0.3 nanogrammes per millilitre of PSA serum levels, tumour tissue results in an increase which is ten times greater. This explains the number of false positives when the threshold value is low : benign hypertrophy of the prostate (adenoma of the prostate) may be accompanied by a rise in the marker in the absence of any malignancy.

The value of the information provided by the diagnostic procedures used is essential in order to assess their impact on the number of tumours detected and the cost of the programmes under study. The contribution made by each type of information is evaluated through its sensitivity, specificity, the positive predictive value and the negative predictive value of each procedure.

1.1.3 Possible protocols

Six strategies of medico-economic interest have been assessed, and the choice approved by the main clinical specialists in the field.

The first screening strategy begins with digital-rectal examination by general practitioners (DREg). If positive, the same examination is then performed bya specialist (DREs). Positive DRE patients become candidates for US. Of the patients who undergo US, those with a positive result are biopsied. Patients with negative US receive a PSA test. If the PSA is higher than five or ten nanograms. then a biopsy is done.

The second strategy differs from the first, in that all patients have US after examination by a specialist, whether their DREs findings *are* normal or not. If US is positive, the patients are biopsied : if US is negative, only patients with a positive DREs undergo biopsy .

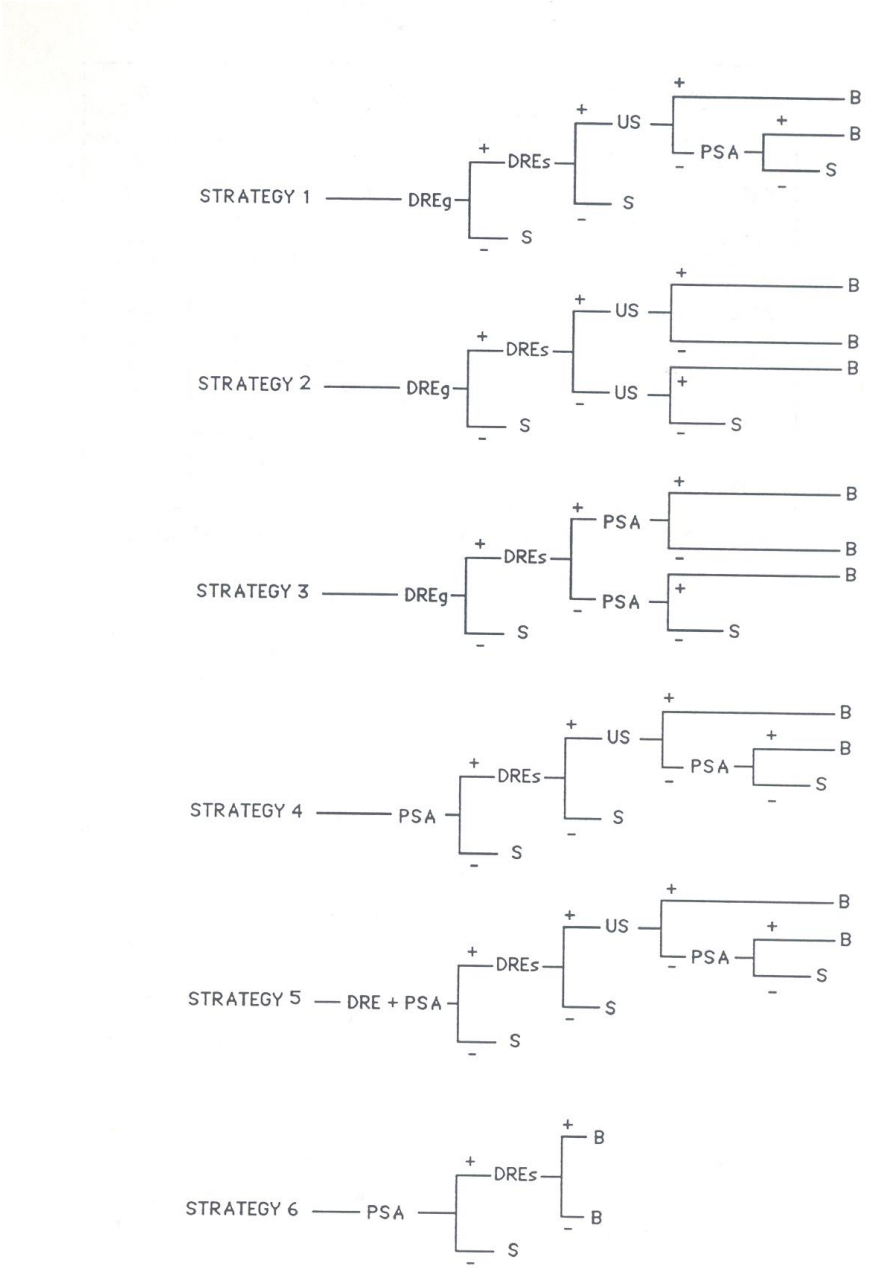
In the third strategy, PSA measurement replaces US after DREs. If PSA is elevated, a biopsy is systematically performed, whatever the results of the former tests. If PSA is normal, only patients with positive DREs undergo biopsy.

PSA is the starting point in the fourth strategy. Only patients with an elevated PSA are referred to the urologist. Patients with a positive clinical exam undergo US and if the result is positive, they are biopsied. Patients with a negative test have only biopsy if a second PSA measure is higher than 5 or 10 nanograms.

The fifth strategy is identical to the fourth, except that DREs and PSA are associated tests carried out simultaneously during the first visit.

In the sixth strategy, all patients have only a PSA test as initial test. All positive results are referred to a specialist, both positive and negative DREs undergo biopsy.

Fig 1 : Different screening programmes available



1.2 Analytical framework

1.2.1 Choice of end-points

The most difficult problem in any measurement of cost effectiveness is to define effectiveness in health care.

For our purpose, we define it in two ways :

1. The number of cancers found. This straightforward definition limits the gains of a screening program to the sole enumeration of detected tumours, without considering the more controversial point of treatment efficacy. But it leaves unanswered the fundamental question: should all cancers that exist be identified ?
2. The gain in life expectancy. In order to take into account several of the clinical variables that influence the management of the disease, we also defined the effectiveness in terms of the clinical outcome for patients undergoing the screening tests. The purpose was to calculate the effect of screening on the length of the patient's life according to the stage and grade of the cancer .

1.2.2. Design of the model

Evaluating the number of examinations necessary to a policy of screening presupposes that we know how to conceptualize, within the same schema, elements which are determined by the Doctor's decision and elements that depend on chance. The first step in designing a model of decision-making is to schematize events according to the choices made by doctors or dictated by the natural course of events. The decision tree is elaborated from left to right. The branching-out corresponds either to decision nodes when they express the choice of treatment or to chance nodes when events occur whose outcome depends on chance. When the branches only hold chance nodes the term probability tree is used.

If the decision-maker opts for a screening strategy, he has no control over concordance between his aim and reality : chance will take him to the branch "cancer" or "no cancer". The tree begins with two master branches "disease", "no disease" and the branches which grow from them, express the aleatory results of the examinations used. Three procedures (vi) (i = 0,..2) can be employed in a first round: clinical examination which includes DRE, measurement of PSA or association of the two. The rational course is to resort to one of these 3 techniques and only to propose further investigation if findings are suspect. The type of complementary examination (Ni)(i = 3...6) varies according to the programme chosen.

Once the different stages have been defined, each examination is attributed the probabilities which correspond to its diagnostic value; for each chance node, the sum of the probabilities for each eventuality, of course, equals 1. The probability or the frequency of an anomaly in a population with cancer is equal to the sensitivity of the procedure (ai) : that of its absence (1 - ai). The probability or frequency of the examination proving normal in a population without cancer is equal to specificity (bi) and that of a positive result within the same group of normal subjects is equal to (1 - bi).
If the distribution of probabilities p and 1 - p for the natural course is known, the joint probability of a positive or negative result at the end of a series of investigations can be calculated.

The frequency of positives (true or false, since the clinician limits himself to noting an anomaly without being able to distinguish between sick or non-sick subject) determines the proportion (ni) of individuals explored who must have complementary investigations. Applied to the population entered into the programme (NO), this frequency allows the number of complementary tests asked for, to be calculated : Ni = ni.NO

The symbols used are given in the Table below :

Table 1 : Symbols

Type of Exploration	Proportion of R+ in previous tests	N° Exams	Se	Sp
Initial Vis.				
DREg (i=0)	0	V0	a0	b0
PSA (i=1)	0	V1	a1	b1
DREg+PSA (i=2)	0	V2	a2	b2
Compl. Exams				
DREs (i=3)	n3	N3 = n3 N0	a3	b3
Echo (i=4)	n4	N4 = n4 N0	a4	b4
PSA (i=5)	n5	N5 = n5 N0	a5	b5
Biop (i=6)	n6	N6 = n6 N0	a6	b6
Biop+ (i=7)	n7	N7 = n7 N0	–	–
Number of Individuals sampled		N0		

DREg : DRE general practitioner, DREs : DRE specialist, R+ : positive result
Se : Sensitivity, Sp : Specificity

If the cost (c_t) of the first examinations and of the complementary investigations (P_k) are considered as known, the total cost (c_t) of a strategy depends exclusively on the number of initial examinations (v_i) and complementary (N_k) examinations used.

$$C_t = c_i v_i + \sum_{k=3}^{6} p_k N_k \qquad (i=0,..2)$$

The numbers vary for each programme (j) (j = 0,...6), depending on the investigations carried out previously and their classification. The above equation can then be rewritten as :

$$C_t{}^j = c_i v_i{}^j + \sum_{k=3}^{6} p_k n_k{}^i N_0 \qquad (i=0,...2)\ (j=0,...6)$$

The frequency of detection of cancer in the population that has accepted to take part in the screening programme (j) is equal to the proportion of biopsies that turn out to be positive. The number of tumours detected therefore amounts to :

$$C_\alpha j = n_7{}^j N_0 \qquad (j=0,...6)$$

1.2.. Decision rules

Establishing the cost and effectiveness of a screening programme is of little sense in absolute terms. What is more important is to define the cost and effect of one decision in relation to another. All positive and negative effects are studied in relation to a standard situation. Two approaches can be considered : either the cost and effectiveness of screening are assessed in relation to a policy of no screening or the additional cost and advantages of each screening programmes are evaluated differentially from the simplest ta the most elaborated. The second solution reflects better the choices available and is the one that has been selected. The programmes were first classified according to the number of tumours detected. When results were equal or inferior, the more costly programme in absolute terms was excluded from the analysis. The remaining programmes were analyzed solely in terms of their incremental cost-effectiveness. The additional cost of a programme that was more aggressive than another (incremental cost) was then divided by the additional advantage that it brought in terms of the number of additional tumours detected (incremental effectiveness). The programmes, whose cost-effectiveness ratio was dominated, were eliminated and the others classified according to the increase in cost that they required for each new tumour detected.

1.3 Available data

1.3.1 Characterization of the pretest likelihood

Estimates of the prostatic cancer prevalence is complicated because the adenocarcinoma may be identified in three different settings. First, it can be clinically diagnosed by physical exams or symptoms. Second, it can be discovered when the prostate is removed for other reasons th an prostatic cancer, for instance during a radical cystoprostatectomay for bladder cancer. In such a case, the term "incidental cancer" is used. Third, the tumour can be discovered at autopsy ; it is then called "latent cancer". Estimates of clinical prevalence are derived from american tumour registeries or from clinical series. They vary from 0.3 % in the Connecticut (Feldman, 1986) to 3 % reported by Teillac (1990) in a screening context. and 14 % in a French hospital setting (Vallancien, 1990). The clinical prevalence increases dramatically with age -0.9% of men 60-69 years'old, compared with 3.7% of men over 70.

Table 2 : Prevalence of clinical cancers

%

	30-49	50-59	60-69	> 70	Average
Feldman 1986	0.002	0.1	0.9	3.6	0.372

It has long been recognized that the clinical prevalence represents only the top of the iceberg, reported rates of incidental cancer by Kabalin (1989) or Montie (1989) reach respectively 38 % and 46 % (table 3) .

Table 3 : Prevalence of incidental cancers
%

Patients		40-49	50-59	60-69	70-79	80 +	Average
Sheldon 1981	Survey Stad A	6.3	10.4	18.5	28.7	37.1	10
Prichett 1988	195	11	14	36	28	50	27 (45/165)
Kabalin 1989	66						38 (25/66)
Montie 1989	84	< 60 26 (7/27)		60-75 61 (23/28)	> 75 43 (3/7)		46.0 (33/72)

Franck (1954) found a 30 % prevalence in 180 men over 50 year old examined at autopsy. The prevalence of latent cancer reaches even 40% for the 70-79 group (Table 4).

Table 4 : Prevalence of latent cancers
%

Patients		40-49	50-59	60-69	70-79	80 +	Average
Edwards 1953	173	3.4 (1/23)	9.7 (3/31)	18.5 (10/54)	25 (12/48)	17.6 (3/17)	16.7 (29/173)
Franks 1954	210	0 (0/18)	29.0 (11/38)	30.2 (16/53)	40.0 (28/70)	73.0 (14/19)	37.6 (69/210)
Hudson 1954	261	4.2 (2/48)	12.9 (17/133)	16.1 (17/99)	16.9 (3/17)	0	13.0 (39/300)
Scott 1969	158	-	-	-	41.0 (41/1)	57.0 (33/58)	46.0 (74/158)
Wynder 1971	Survey	4	5-14	8-30	20-40		
Holund 1980	223	12.5 (1/8)	8.6 (2/23)	12.5 (7/56)	25.8 (24/93)	40.0 (16/4)	22.4 (50/223)

The high prevalence of silent cancers poses a unique problem, some of them will never present clinically during the lifetime of men in whom they occur. If methods for early diagnoses are introduced, how do we know that only dangerous lesions are identified and treated ?

1.3.2 Characterization of screening tests

The series are infrequent and often biased. For example, with regard to DRE, only three investigators (Guinan, 1980 ; Vallancien, 1989 ; Perrin and Maquet, 1989) have applied the gold standard biopsy to the whole population included in the studies. Other authors contented themselves with exploring only patients whose DRE was positive.

The key parameters are then calculated either for the biopsied sub-population, which is not representative of the population in general, and the results suffer from a work-up bias[1]. (Devonnec, 1990 ; Perrin and Maquet, 1989 ; Teillac, 1990), or they are based on all the patients in the study at the cost of an unacceptable hypothesis ; negative DREs are assimifated to true negatives without any proof. Vihko's series (1985) is a typical example. He studied 771 patients and 66 biopsies were conducted. The number of true negatives reached 743. The 707 apparentLy normal DREs were obviously reintegrated into the final result along with the 36 negative DREs where biopsies had been pertormed. The statistical bias is obvious.

Table 5 : Results of DRE studies

Authors	Patients	Biopsies	False+	True+	False-	True-	Total	Se	Sp
Systematic Biopsy									
Guinan 1980	300	300	ND	63		ND	300	0.69	0.89
Perrin 1989	481	481	24	59	24	342	481	0.71	0.95
Vallancien 1989	167	167	12	32	7	116	167	0.82	0.90
Work-up Bias									
Devonec 1990	666	226	30	34	11	151	226	0.75	0.83
Perrin 1989	1,147	354	157	87	7	103	354	0.92	0.39
Teillac 1990	600	93	18	8	11	56	93	0.42	0.75
Statistical Bias DRE- = True negative									
Vicko 1985	771	66	21	6	3	741	771	0.66	0.97
Lee 1988	784	77	19	10	12	743	784	0.45	0.97

[1] There is a workup bias when the chances of the patient having the verification test is strongly related to the results of the test under study, in that the patient with a positive result is more likely to undergo the verification test (Ransohoff D, Feinstein A, 1978)

Table 6 : Results of US studies

Authors	Patients	Biopsies	False+	True+	False-	True-	Total	Se	Sp
Systematic Biopsy									
Perrin 1989	481	481	168	65	18	230	481	0.78	0.57
Vallancien 1989	167	167	21	27	12	107	167	0.69	0.83
Work-up Bias									
Teillac 1990	600	93	74	9	10	35	93	0.47	0.43
Statistical Bias									
Cooner 1989	1,035	275	221	54	760		1,035	0.10	0.76
Lee 1988	784	77	44	20	2	718	784	0.91	0.94

Table 7 : Results of PSA studies

Authors	Patients	Biopsies	False+	True+	False-	True-	Total	Se	Sp
Systematic Biopsy									
Lee 1989 (> 2.5 ng)	248	248	87	94	8	59	248	0.92	0.40
Work-up Bias									
Teillac 1990 (> 5 ng)	600	93	42	18	1	32	93	0.94	0.43
Statistical Bias									
Cooner 1989 (> 4 ng)	1,035	275	nd	nd	nd	nd	1,035	0.68	0.83

1.3.3 Survival assumptions

A key factor in estimating the benefit of screening is the distribution of survival by stages and grades. Our estimates were derived from a population-based study published by Johansson (1989). The following distribution was observed : stages A and B, 47 %, stages C and D 53%. If we combine all B_1, well-differentiated B_2 and A_2 into a low-risk group that we consider the most important target group for prostatic screening and radical prostatectomy, we found only 17.3 % of the detected patients. This subgroup was chosen as a treatable population. The survival rate of treated patients was derived from a retrospective survival analysis conducted by Lepor (1989) for patients with clinical stage B_1 who underwent radical prostatectomy at the Johns Hopkins hospital. In both cases, the survival has been ascertained, using a cause-specific survival curve. The corrected ten years survival for patients who were left untreated in the Swedish series until progression occurred was approximately equal to 89%. The ten-year corrected survival following radical prostatectomy for men with B_1 carcinoma was approximately 92.5%. For calculating the corresponding life expectancy, we used the DEALE method elaborated by Beck and al. (1982). The curative potential of the intervention has been expressed as the increment in life expectancy following treatment, compared with no treatment. We calculated the net expected gain per detected cancer to be 0.18 years for the 50 year-old, 0.09 years for the 65 year-old and 0.04 for the 75 year-old.

1.4 Qualitv of the data

1.4.1 An imperative : deciphering information

Some of the series published in France give consolidated results and the authors prefer to use straightforward parameters such as the positive predictive value and the detection rate rather than to reason in terms of sensitivity and specificity. This approach deprives the scientific community of data which could be very helpful and it impedes reasoning of a sequential type based on likefihood ratio. Perrin and Maquet's (1989) prospective study including 481 patients is exemplary. All patients who had a positive DRE or a positive ultrasound scan were biopsied. The authors' findings are presented in the following table :

Table 8 : DRE and US results

DRE	US	D+	D-	Total
-	-	16	215	231
-	+	8	127	135
+	-	2	15	17
+	+	57	41	98
		87	398	481

D+ : cancer present D- : cancer absent

It is possible, from the results for the association DRE + US, to determine the number of positive or negative results for DRE alone : all positive DRE results are added together (whatever the US result) and the same is done for all the negative results.

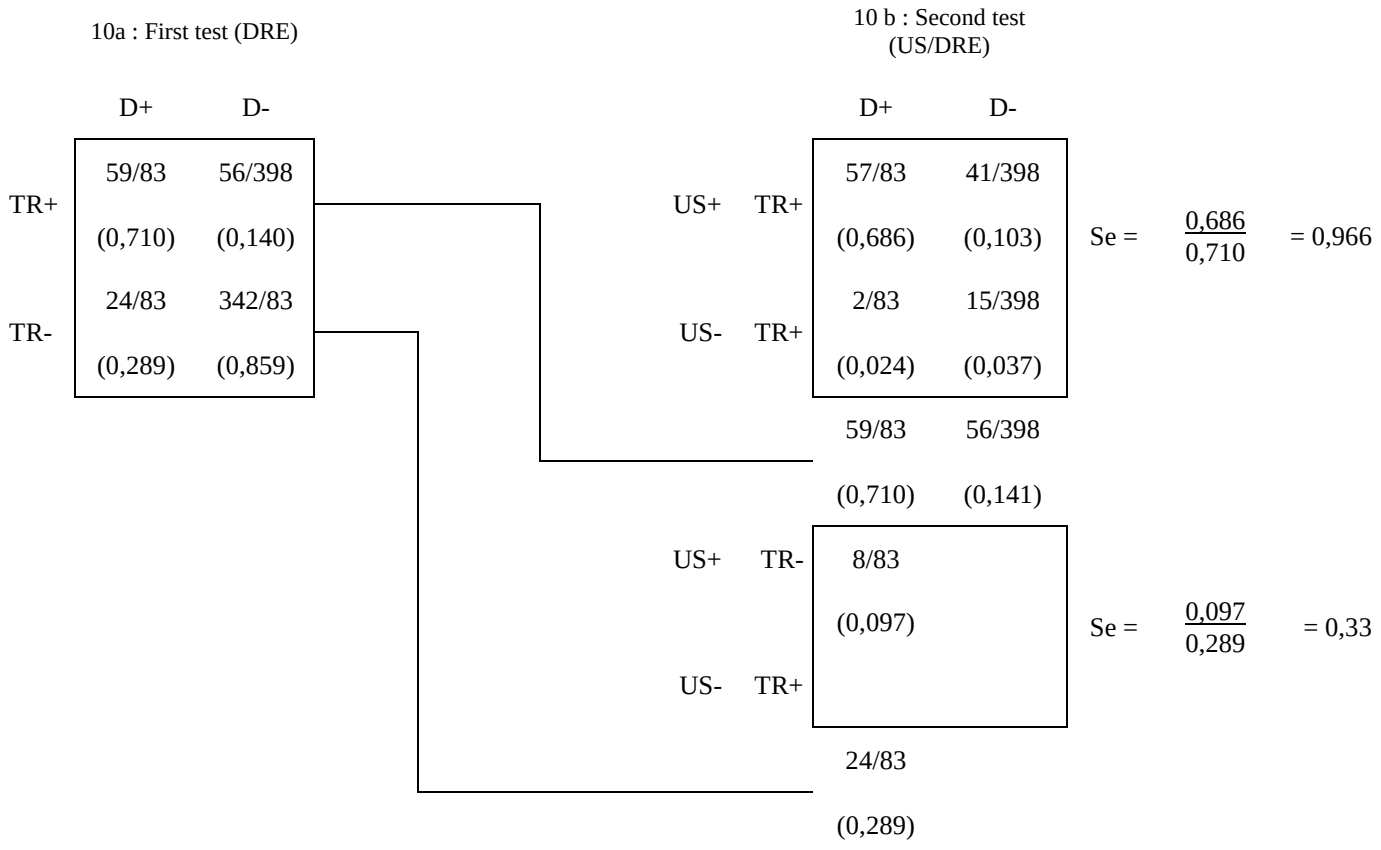
For DRE alone, the results are :

Table 9 : Results DRE alone

	D +	D -	Total
DRE +	59	56	115
DRE -	24	342	366
Total	83	398	481

If the disease can only be considered as present if both examinations are positive, then 57 tumours were detected. If DRE alone is positive, then 59 cancers were found. US has consequently ruled out 2 lesions, which become false positives.

Table 10 :Comparison of the results of US + DRE and DRE alone



It may legitimately be argued (Perrin and Maquet 1989), that a positive US scan and a positive DRE increase the predictive value from 11% (2/17) to 58% (57/98) in comparison with what would have been found in the event of an ab normal scan following a suspect DRE.
But the efficacy of combining the two positive tests could have been assessed by comparison with a positive DRE alone. The increase in information would then have been much smaller, 7 points only (58% versus 51%), since the positive predictive value of the DRE alone immediately reached this last value (59/115).
Moreover, to be really precise, the probability of a negative error and the probability of a positive finding cannot be reduced to a common dimension.

1.4.2 Conditional sensitivity and specificity

Table 8 not only allows calculation of overall sensitivity for DRE and US, but it also shows that the sensitivity of US differs according to whether DRE is positive or negative. The overall sensitivity of each examination taken separately can be calculated from the data it contains (Table 11a), as can that a conditional sensivity of an ultrasound scan which depends on the positive or negative findings of the prior DRE (Table 11 b).

Table 11 a : Overall sensitivity

	D+		
	US+	US-	
TR+			59
TR-			24
	65	18	83

Table 11b : Conditional sensitivity

	D+		
	US+	US-	
TR+	57	2	59
TR-	8	16	24
	65	18	83

Overall US sensitivity can be calculated from Table 11a : 65 of the 83 patients have an anomaly on scanning. Overall US sensitivity is 65/83, i.e. 0.783.

Table 11 b supplies the information needed to calculate the conditional sensitivity of US when its results depend on those obtained by ORE. In the sub-population of 59 patients with a positive ORE, scan findings were ab normal in 57 cases. Of all 83 patients, only 65 had a positive US scan. Only 8 patients, therefore, of the 24 with a negative ORE correspond to a positive scan.

If sensitivity for the whole of the patient population is 0.783 (65/83), it rises to 0.96 (57/59) in the group of positive DREs and drops to 0.33 (8/24) in the patients with a negative DRE.
Conditional sensitivity is rarely published in the literature, and it is to the credit of Perrin and of Vallancien that their work draws attention to it. The numbers in the 4 cells in the above fourfold tables can only be obtained by scrupulous clinical examination which demonstrates the non-independence of the examinations.

Specificity for the two examinations in the group of subjects without disease (D-) can be analysed in the same fashion.

Table 12a : Overall specificity

	D+		
	US+	US-	
TR+			56
TR-			342
	168	230	398

Table 12b : Conditional specificity

	D+		
	US+	US-	
TR+	41	15	56
TR-	127	215	342
	168	230	398

Sp Overall : 230/398 = 0.577
Sp US/DRE+ : 15/56 = 0.267
Sp US/DRE- : 215/342 = 0.628

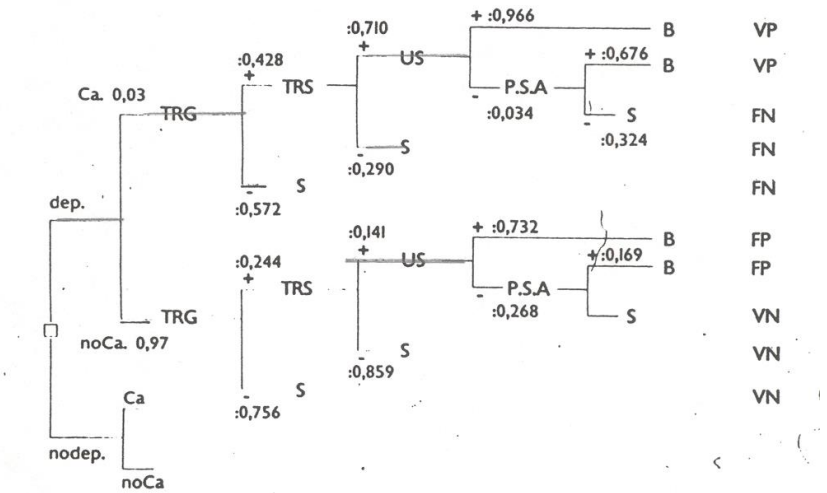
1.4.3 Queries about the gold standard

Last and by no means least, the gold standard chosen may be queried. Biopsy fails to detect tumours located beyond the area considered suspect on clinical examination. Three biopsies are now advocated for each lobe in order to prove the presence or absence of a cancer. This modification in diagnostic criteria means earlier series are out of date. But we have even doubts on the ability of this new procedure to discriminate between the presence or the absence of cancer. In the basic model. we assume that biopsy is a perfect test, but in the sensitivity analysis, we consider the possibility of errors, in particular confronting clinical series (Vallancien, 1990) and autopsy data (Franks, 1954), we assume that a procedure fails to identify the disease 30% of the time, but we keep the perfect specificity assumption.

1.5. An example of costing

The model is elaborated to assess the effects of a more or less intensive screening policy when the clinical prevalence is equal to 3%, the latest data available for France (Teillac 1990) (cf. Decision tree, Fig 2).

Fig 2 : Decision tree



The tree begins with the decision node with which the decision-maker is immediately confronted : Which screening programme (Prj) (j = 0...6) does he intends to apply ? Whatever his decision, a tumour mayor may not be present. The prevalence of the disease defines the first random choice node of each branch. If screening is decided on, a DRE is performed by a general practitioner (GP) : the results may be positive or negative. In the first instance. referral to a specialist is mandatory; in the second. follow-up (S) is recommended. DRE by a specialist (SP) can confirm or refute the first findings of the first examination. If the opinion of the two physicians concords, then a US scan is obtained and if this is positive a biopsy is performed. If the scan is negative, then biological examination is requested. When the PSA value exceeds the normal upper limit, a biopsy is carried out. If the PSA value is normal, the patient is followed-up regularly. If the opinions of the GP and the specialist do not concord, then it is the absence of an anomaly noted by the specialist that prevails and he prescribes simple surveillance.

When the main branches of the chart have been identified, the tree is completed by adding above each branch the frequency of positive and negative results observed in the French series after each examination :

Table 13 : FreQuencv of positive and neaative results in French series

		TP rates α_i	FN rates $1 - \alpha_i$	FP rates $1 - B_1$	TN rates B_1
DREg	Teillac 1689	0,428	0,572	0,244	0,756
PSA 1st round	Teillac 1689	0,947	0,053	0,568	0,432
DREg + PSA	Teillac 1689	0,971	0,029	0,673	0,327
DREs	Perrin 1989	0,710	0,290	0,141	0,859
US/DRE +	Perrin 1989	0,966	0,034	0,733	0,267
US/DRE -	Perrin 1989	0,335	0,665	0,372	0,628
PSA 2nd round	Cooner 1989	0,685	0,315	0,169	0,831
PSA 2nd round	Teillac corrected	0,676	0,324	0,111	0,889

By definition, $n_0 = n_1 = n_2 = 1$ since each person screened had at least one of the three examinations. The frequency with which the other examinations are applied has been established as follows :

Consultation with a specialist : n_3

$= p\ \alpha_0 = (1 - p)(1 - \beta_0)$
$= 0,03 \times 0,428 + 0,097 \times 0,244$
$= 0,2495$

Ultrasound scans : n_4

$= p\ \alpha_0\ \alpha_3 + (1 - p)(1 - \beta_0)(1 - \beta_3)$
$= 0,03 \times 0,428 \times 0,710 + 0,97 \times 0,244 \times 0,141$
$= 0,04250$

PSA : n_5

$= p\ [\alpha_0\ \alpha_3\ (1 - \alpha_4)] + (1 - p)(1 - \beta_0)(1 - \beta_3)\ \beta_4$
$= 0,03\ (0,428 \times 0,710 \times 0,034) + 0,97\ (0,244 \times 0,141 \times 0,267)$
$= 0,0092$

Biopsies: n_6

$= p\,[\alpha_0\,\alpha_3\,\alpha_4 + \alpha_0\,\alpha_3\,(1 - \beta_4)\,\beta_5]$
$+ (1 - p)\,[(1 - \beta_0)(1 - \beta_3)(1 - \beta_4) + (1 - \beta_0)(1 - \beta_3)\,\beta_4(1 - \beta_5)]$
$= 0{,}03\,(0{,}428 \times 0{,}710 \times 0{,}966 + 0{,}428 \times 0{,}710 \times 0{,}034 \times 0{,}676) +$
$0{,}97\,(0{,}244 \times 0{,}141 \times 0{,}732 + 0{,}244 \times 0{,}141 \times 0{,}267 \times 0{,}169)$
$= 0{,}3490$

Positive biopsies : n_7

$= p\,[\alpha_0\,\alpha_3\,\alpha 4 + \alpha_0\,\alpha_3\,(1 - \alpha_4)\,\beta_5]$
$= 0{,}03\,(0{,}428 \times 0{,}710 \times 0{,}966 + 0{,}428 \times 0{,}710 \times 0{,}034 \times 0{,}676)$
$= 0{,}0092$

The number of examinations applied to a population of 100.000 persons at risk amounts to :

Consultation with GP : $v_0 = 100\,000$
Consultation with specialist : $N_3 = 0{,}2495 \times 100\,000 = 24\,950$
US scans : $N_4 = 0{,}0424 \times 100\,000 = 4\,250$
PSA : $N_5 = 0{,}0092 \times 100\,000 = 920$
Biopsies : $N_6 = 0{,}0349 \times 100\,000 = 3\,490$

The cost of each item, from the National Health Insurance point of view, is calculated according to Relative scale value laid down by the Department of Public Heath.

Table 14 : Current cost data in France

Consultation with GP			85
Consultation with specialist			125
PSA	BM 70		123
US	K 30		360
Biopsy			
+ Tests	E C B U	B70	123
	hemostasis	B40	70
+ Antibio-prophylaxy			
	Noxorine 400 mg box of 10		68
	Peflacine 400 mg box of 2		139
	Bactrine box of 10		19
	Flagyl 500 mg box of 15		62
+ Surgery	K 30 + K 20/2		520
+ Histological examination	B 100		176
Total cost to the National Health insurance of biopsy between 957 FF and 1300 FF according to the type of antibiotic used			

Expenses for programme 1 amount to 16,560,825 FF per 100 000 screenees, when the G.P., S.P., US, PSA and biopsy costs are respectively estimated to be 85, 125, 360, 123 and 957 FF and when the prevalence is supposed to be 0.03 (Central assumption).

2. RESULTS

Table 15 : Volume of consumption

Pv = 0.03

Medical Acts	Programmes (1)	(2)	(3)	(4)	(5)	(6)
Consultation with GP	100,000	100,000	100,000	100,000	100,000	100,000
Consultation with specialist	24,952	24,952	24,952	57,937	68,194	57,937
US Scan	4,249	24,952	0	9,786	11,272	0
PSA 1st round	0	0	24,952	100,000	100,000	100,000
PSA 2nd round	922	0	0	2,142	2,528	0
Total no PSA	922	0	24,952	102,142	102,528	100,000
Biopsies	3,447	11,937	16,150	7,919	9,066	57,937
Tumours detected	902	1,037	1,264	1,995	2,046	2,841
False positives	2,545	10,900	14,886	5,924	7,020	55,096

Table 16 : Value of consumption

Pv = 0.03

Medical Acts	Programmes (1) (F)	(2) (F)	(3) (F)	(4) (F)	(5) (F)	(6) (F)
Consultation with GP	8,500,000	8,500,000	8,500,000	8,500,000	8,500,000	8,500,000
Consultation with specialist	3,119,000	3,119,000	3,119,000	7,242,125	8,524,250	7,242,125
US Scan	1,529,640	8,982,720	0	3,522,960	4,056,120	0
PSA	113,406	0	3,069,096	12,563,466	12,610,944	12,300,000
Biopsies	3,298,779	11,423,709	15,455,550	7,578,483	8,676,162	55,445,709
Total	16,560,825	32,025,429	30,143,646	39,407,034	42,367,476	83,487,834

Table 17 : Synthesis of results

	Total Cost Ct	Total no tumours Ca
Pr0 : nothing	0	0
Pr1 : DREx2->USE->PSA2	16,560,825	902
Pr2 : DREx2->USS	32,025,429	1,037
Pr3 : DREx2->PSA2->Biop	30,143,646	1,264
Pr4 : PSA1->DRE->USE->PSA2	39,407,034	1,995
Pr5 : PSA1->DREx2->USE->PSA2	42,367,476	2,046
Pr6 : PSA1->DRE->Biop	83,847,834	2,841

Note :

DREx2 = two DREs
US S = systematic US
PSA2 = PSA 2nd round
US E = elective US
PSA1 = PSA 1st round

The search for the best programme is divided into two stages. The first selects those programmes that are efficient according to the principle of dominance. The second determines the value judgment that must be made to select one efficient strategy over its alternatives. The search for an optimal allocation aims to achieve the maximum consistency possible and takes the place of empirical quest for efficiency. [2]The purpose of such procedure is to prevent more sickness for a given budget. This can be done by equalizing the marginal health return between preventative actions, no matter the illness being considered.

The axiom of dominance enables a number of possible choices to be ruled out. A situation dominates another when the cost per unit of effectiveness is less than or equal to that of the reference situation (average cost-effectiveness ratio). If the different programmes are classified according to this criterion, the programme Pr2 will never be used, since all the other programmes detected more cancers for a lower expenditure per unit (table 18a).

By extension, when several programmes are mutually exclusive, it is agreed that one option is dominated by another when the incremental cost of moving from one option to the next is less than the one before (incremental cost effectiveness ratio). The rule to apply is simple: a programme can be eliminated if, and only if, the incremental cost entailed in its replacement by another is lower th an the incremental cost per cancer detected which would have been associated with its implementation. On the basis of this criterion, programme Pr1 is dominated by programme Pr3. The same applies to Pr5 in relation to Pr6 (Table 18b).

Table 18a : Feasible programmes : average cost-effectiveness ratio

	Pr0	Pr1	Pr2	Pr3	Pr4	Pr5	Pr6
Ca	0	902	1,037	1,264	1,995	2,046	2,841
Ct (kf)	0	16,560	32,025	30,143	39,407	42,367	83,487
Ct/Ca (f)	0	18,360	30,883 (dominated)	23,848	19,753	20,707	29,387

(kf) : thousands of French Francs (f) : French Francs

Table 18b : Feasible programmes : marginal ccst-effectiveness ratio

		Pr1-Pr0	Pr3-Pr1	Pr4-Pr3	Pr5-Pr4	Pr6-Pr5
Δ Ca	0	902	362	731	51	795
Δ Ct (kf)	0	16,560	13,582	9,263	2,960	41,120
Δ Ct/Ca (f)	0	18,360	37,521 (dominated)	12,672	58,048 (dominated)	51,724

(kf) : thousands of French Francs (f) : French Francs

Table 19a : Efficient programmes : average cost-effectiveness ratio

	Pr0	Pr1	Pr4	Pr6
Ca	0	902	1,995	2,841
Ct (kf)	0	16,560	39,407	83,487
Ct/Ca (f)	0	18,360	19,753	29,387

(kf) : thousands of French Francs (f) : French Francs

Table 19b : Efficient programmes : marginal cost-effectiveness ratio

	Pr1-Pr0	Pr4-Pr1	Pr6-Pr4
Δ Ca	902	1,093	846
Δ Ct (kf)	16,560	22,846	44,080
Δ Ct/Ca (f)	18,360	20,902	52,104

(kf) : thousands of French Francs (f) : French Francs

Intuitive reasoning is as follows (supposing that returns are constant to scale) : if (Table 18b) the country believes that it is justified in spending an additional 13.5 million francs to detect 362 new cancers at a marginal cost of 37,521 F per cancer discovered, it will be willing, in the absence of any financial ccnstraint, tc adopt programme Pr4, for which an additional expense of 9,263.000 F has tc be paid for finding 731 new cancers at a lesser incremental ccst of 12,672 F. Programme Pr3 will therefore never be used, for it will always be possible to do better by using programme Pr4.

One may query the soundness of possibly replacing programme 1 by programme 4 on the effectiveness interval of 0-902 of detected cancers. This choice cannot be advocated, since the marginal cost per cancer discovered by programme 1 is less than that of programme 4 on this interval.

Efficient programmes are those for which health outcome cannot be improved without an increase in cost. The one that society will prefer remains to be defined. This supposes that society will adopt a criterion for assessment by deciding the maximum amount of money it is prepared to spend per additional cancer discovered. Choice in this field is mainly arbitrary, since the marginal cost of each new tumour detected ranges from 18,360 to 52, 104 :

$$\frac{\Delta Ct}{\Delta Ca} \begin{cases} 0 & Ca = & 0 \\ 18\,377 & Ca < & 904 \\ 20\,890 & 904 \leq & Ca < 1\,995 \\ 51\,799 & 1\,995 \leq & Ca < 2\,841 \end{cases}$$

Society has no means of choosing between the different options on the basis of truly scientific criteria. The choice is a political one. The same reasoning applies when the results are presented in terms of cost per life year saved, which varies between 102,230 FF for strategy 1 to 115,970 FF for strategy 4 and 288,110 FF for strategy 6. There is no theoretical justification for asserting that the efficient strategy with a higher cost per life year is least desirable. The crucial value jugdment is left to decision makers.

The ranking of the mutually exclusive programmes can also be described in terms of extra units of outcomes per extra franc spent. The procedure adopted is symetric to the one previously described. First, the best initial increment is selected, using the point with the maximum incremental cost effectiveness ratio. Second, the best programme from the list of the next possible increments is entered into the solution. The procedure is repeated until all programmes under consideration are exhausted. At each step, one cautiously checks that the additional outcome per extra franc is less that it was after choosing the previous best alternative. When the criterion is not satisfied, the programme previously entered into the solution is dominated and should be discarded. Finally, the incremental cost ratio of the selected option has to be recalculated with the dominated variant excluded.

The non dominated programmes are on the boundary of the set of the production possibilities. Interior points, which are obiously inefficient, are dominated by options on the "frontier" : a greater outcome can be obtained for the same cost or the same outcome can be produced for a lower cost. Resources are employed in a wasteful manner, and the corresponding options should be ruled out. Options on the boundary are cost effective in the sense that there are no other options that are both more effective and less expensive. Programmes Pr1, Pr4 and Pr6 are the only efficient ones.

However, because the willingness of the society to pay is unknown, it is not possible to identify a single strategy as being the most cost-effective.

3. SENSITIVITY ANAL YSIS

The central analysis was performed with the clinical prevalence equal to 3% and based upon clinical estimates of sensitivity and specificity. But it is known that incidental and latent prevalence might be much higher than the clinical one. Furthermore, it might be erroneous to extrapolate findings of the biopsied group of patients to the general population. We tried to check whether our results were robust by varying those parameters.

3.1 Variabilitv according to prevalence rate

The prevalence of adenocarcinoma varies widely according to age subgroups (50-59, 60-69 and over 70) and the criteria used to assess the pretest likelihood of prostatic cancer : clinical exam (Feldman 1986), randomized biopsy (Vallancien 1990) and autopsy study (Franks 1954). Alteration in prevalence has no effect on the relative ranking of the strategies when the end-point chosen is the number of cancers found. Strategies 1, 4, 6 are still the dominating strategies. However, the magnitude of the cost-effectiveness ratios decreases dramatically .The cost per cancer found is divided by 3 for the 50-59 year group when prevalence increases from 0.13% to 29%, by 4 for the 60-69 year old when prevalence varies from 0.9 to 30%, and by 16 for the over 70 year old when the prevalence range is between 3.6% and 40%.

Table 20 : Incremental cost Der cancer for different aae-Groups and Prevalence assumptions

Age	Strategy	Feldman	Vallancien	Franks
		0.13%	8.5%	29%
50-59 years	1	396,478	7,305	3,042
	4	458,201	8,127	3,287
	6	1,224,660	17,479	4,027
		0.90%	11%	30%
60-69 years	1	57,857	5,955	2,983
	4	66,403	6,609	3,145
	6	175,694	13,104	3,842
		3.6%	24%	40%
> 70 years	1	15,258	3,409	D
	4	17,104	3,707	D
	6	42,057	5,182	2,605

French Francs

* Se : sensitivity, Sp : specificity, B : biopsy

3.2. Correcting for work-up bias

Two decisions have to be taken for the fourfold tables to be filled in: was the result of the examination positive or negative and was disease present or not according to the reference diagnostic gold standard (biopsy) ? When these two aspects are not investigated independently, statistical bias is introduced into the analysis. This is mainly the case when the physician is reluctant to perform a reference examination, which may be expensive or hazardous, on all patients. For example, in the study conducted by Teillac in 1989, of 600 patients entered into the study, 11 had inassessable DRE. Of the remaining 589 patients, 33 had a positive DRE and 556 a negative DRE. Biopsy was requested for all positive DREs, but some patients refused and only 26 biopsies were carried out. For the 556 negative DREs, only 67 biopsies were performed following abnormally elevated PSA levels or positive US scans. The biopsy rate is therefore 78% for positive DREs versus 12% for negative DREs. The positive results are therefore over-represented in patients who had complementary examinations and *this* increases the sensitivity of DRE. On the other hand, negative DREs are under-represented which reduces the specificity of the test.

In the sub-population that had biopsies, classification of subjects as normal or not is unequivocal, since the corresponding procedure is considered as the criterion according to which cancer is or is not present. On the other hand, allocating people taken from the population in general to one or the other of these two groups is not possible, since the negative clinical examination has not been histologically confirmed. Clinical estimates of sensitivity and specificity are therefore highly distorted. Fortunately, it is possible to correct the bias. To extrapolate the results for the biopsied population to the population in general, it must be assumed that the disease is totally independent of the verification procedure selected (Begg and al. 1983, 1984, 1988). To eliminate the work-up bias, it is therefore accepted that biopsy is only requested when an anomaly is found on clinical examination, independently of any a priori idea as to whether cancer is present or not in the patients under consideration. In this case, the positivity of the sign alone determines the suspect population, whatever the true underlying pathological condition may be. Therefore :

$$P\,(V/R) = P\,(V/R, D\,)$$

where :

R = R +	disease found
R = R -	findings normal
V = V +	suspect case chosen for histological confirmation
V = V -	case not suspect, no biopsy
D = D +	patients with the disease
D = D -	normal subjects

The probability of having the disease when the sign is present is therefore the same whether there has been histological confirmation or not :

$$P\,(D+/R+, V+) = P(D+/R+)$$

When Bayes' theorem is applied to the results of the examination rather than to the presence or absence of the disease, it can be rewritten as follows :

$$P(R+/D+) = \frac{P(R+) \times P(D+/R+, V+)}{P(R+) \times P(D+/R+,V+) + P(R-) \times P(D+/R-, V+)}$$

The probability of a positive DRE among all patients with cancer P(R+/D+), i.e. the corrected sensitivity Se, is equal to the product of the frequency with which an anomaly is detected by DRE P(R+) in the population at large and the frequency of cancer in the sub-population of biopsied subjects who had a positive DRE P(D+/R+, V+). The result is divided by the probability for the whole of the subjects studied of having cancer, whether their DRE was normal or not. The probability of a negative DRE among normal subjects P(R-/D-) i.e. specificity Sp, is calculated in the same way.
The following Table illustrates these calculations using the figures taken from Teillac's study (1990) :

Table 21a : Verification Sample

V+	D+	D-	Tot
R+	8	18	26
R-	11	56	67
	19	74	93

Table 21b : Source Population

Pop	D+	D-	Tot
R+			33
R-			556
			589

P(R+) = 33/589 = 0,056
P(D+/R+V+) = 8/26 = 0,307
P(R-) = 556/589 = 0,944
P(D+/R-V+) = 11/67 = 0,164

$$Se = \frac{0,056 \times 0,307}{0,056 \times 0,307 \times 0,944 \times 0,164} = 0,099$$

$$P(R-/D-) = \frac{P(R-) \times P(D-/R-, V+)}{P(R-) \times P(D-/R-,V+) + P(R+) \times P(D-/R+,V+)}$$

P(R-) = 556/589 = 0,943
P(D-/R-V+) = 56/67 = 0,835
P(R+) = 33/589 = 0,056
P(D-/R+,V+) = 18/26 = 0,692

$$Sp = \frac{0,943 \times 0,835}{0,943 \times 0,835 + 0,056 \times 0,692} = 0,953$$

When the corrected values of the coefficients of sensitivity and a specificity are taken to calculate the positive likelihood ratio, the probability of detecting a tumour by DRE, when disease prevalence is about the same as for Connecticut, USA (0.38%, all ages taken together), is about 1%. This theoretical result seems to concord with the rates of detection (R of D) effectively found in most studies on the effectiveness of mass screening (Table 22).

Table 22 : Results of DRE Prostate Cancer Screenina Studies

	Follow up	Patients	Age	Nodules (DRE+)	Cancers	PPV %	R of D %
Screening exams							
Gibertsen 1971 (USA)	1948-1964 (5 years)	5,856	48-72	ND	75	ND	1.2
Faul 1982 (Germany)	1978 (1 year)	1,500,000	> 45	21,308	1,951	9.1	1.28
Thompson 1984 (USA)	1978-1983 (4 years)	2,005	40-92	65	19	29.2	0.85
Vicko 1985 (Finland)	1979-1984 (5 years)	771	54-76	27	9	39.3	1.16
Lee 1988 (USA)	1985-1987 (19 months)	784	60-86	29	10	34.0	1.20
Mueller 1988 (USA)	1979-1985 (6 years)	4,883	40-79	312	122	39.1	2.49
Imai 1988 (Japan)	1981-1985 (4 years)	5,770	> 50	202	54	26.7	0.93
Chodack 1989 (USA)	1981-1987 (6 years)	2,131	45-80	144	37	25.6	1.73
Perrin 1989 (France)	1988 (6 months)	863	50-60	19	3	15.7	0.34
Perrin 1989 (France)	01.87/04/89 (28 months)	530	$\bar{X} = 67$	59	6	10.1	1.6
Teillac 1990 (France)	ND	600	> 50	26	8	30.7	1.3
Hospital visits							
Devonec 1990 (France)	01.87/01/88 (12 months)	666	$\bar{X} = 67$	64	34	53.0	5.10
Perrin 1989 (France)	10.88/04.89 (6 months)	481	$\bar{X} = 67$	115	59	51.3	13.5
Vallancien 1990 (France)	ND	167	46-89	44	32	72.7	19.1

PPV : positive predictive value defined as the ratio of the number of true positive to the total number of postive tests.
R of D : rate of detection defined as the ratio of the number of cancers found to the total number of people screened.

Changing sensitivity and specificity (table 23) of the test alters substantial/y the strategy ranking (table 24) :

Table 23 : Assessing the sensitivity and specificity of tests subject to selection bias

	DRE	PSA	DRE+PSA
"naive" sensitivity corrected sensitivty	0.428 0.100	0.947 0.676	0.969 0.708
"naive" specificity corrected specificity	0.757 0.950	0.432 0.889	0.326 0.847

Table 24 : Incremental cost per cancer

Age	Strategy	Feldman	Vallancien	Franks
50-59 years		0.13%	8.5%	29%
	1	D	D	D
	4	D	D	D
	6	1,264,984	22,058	8,594
60-69 years		0.90%	11%	30%
	1	D	D	D
	4	D	D	D
	6	182,317	17,729	8,407
> 70 years		3.6%	24%	40%
	1	D	D	D
	4	D	D	D
	6	46,823	9,756	7,059

Strategy 6 is dominating all the other strategies, whatever the criteria chosen, i.e. number of cancers found or of life-years saved. The cost effectiveness ratios per life saved becomes acceptable: 243,500 FF for the 70 year-old versus 196,500 FF for the 60-69 age bracket and 122,600 FF for the 50-59 when the prevalence is respectively 24%, 11% and 8.5% (67). When the probability of prostatic cancer is so high, even invasive testing might be desirable. PSA + biopsy appears to be more efficient, because the greater cost is offset by the lower incidence of false positives. In the event that PSA + biopsy is used in asymptomatic patients, it is more cost-effective to perform biopsy in patients with positive PSA rather than proceeding directly to DRE or US. Strategy 6 is the dominating strategy.

CONCLUSION

The advantages and costs of a case finding program could have been compared with th ose that could be expected from a mass screening program. But this aspect has not been studied. We have limited our analysis to calculating the financial cost to society and to refer it back to the theoretical effectiveness of screening examinations in order to bring out the dominant programs. When key-parameters are not corrected for work-up bias, a range of strategies are efficient. When the bias is corrected, it appears that strategy 6 is the dominant one. In both cases, the implementation of the strategies depends of the collective marginal willingness to pay. No particular technique has been used to propose a choice, decisions taken in other are as could be used as guidelines : values observed a posteriori in other fields of prevention (marginal cost for colorectal cancer or carcinoma of the breast) can be applied a priori. But this would suppose that the previous decisions had been optimal. In reality, only the authorities can select one particular value in the screened case. The work of the assessor is to make explicit the scale of values on which their decisions are based and make it transparent. But as Marc Guillaume (1971) underlined twenty years ago "one cannot propose anything without transforming oneself into a political advisor".

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