Health Technology Assessment prostate-specific-antigen (PSA) voor prostaatkankerscreening

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Voorwoord

Vorig jaar bracht het KCE haar rapport uit over borstkankerscreening dat pleitte voor kwaliteit en het correct informeren van vrouwen. Ditmaal gaat de aandacht naar mannen en prostaatkanker. Opnieuw blijkt het enorme belang van correcte informatieverstrekking aan de patiënt of in dit geval eerder de consument want het gaat bij screening over mannen zonder symptomen.

Prostaatkanker is een frequent voorkomende kanker bij mannen, die leidt tot heel wat morbiditeit en in sommige gevallen mortaliteit. Daartegenover staat dat op de leeftijd van 70 jaar bij de meerderheid van de mannen een 'slapende', niet-levensbedreigende prostaatkanker kan gevonden worden. De meesten zullen mét die kanker sterven en niet ervan. Die nuance is niet onbelangrijk.

Screening dient op de eerste plaats vanuit epidemiologisch populatiestandpunt bekeken. Screeningstesten vormen een tweesnijdend zwaard: ze kunnen een aantal personen helpen, maar vaak hebben ze slechts een beperkt of geen effect op de uiteindelijke mortaliteit en soms doen ze meer kwaad dan goed door te interveniëren bij mensen die dat nooit nodig zouden gehad hebben. In het geval van prostaatkanker zijn niet alleen de kenmerken van de test zelf belangrijk (vals positieven en vals negatieven), maar ook het evenwicht tussen enerzijds de mogelijk curatieve behandeling van een vroegtijdig opgespoorde, snel groeiende en gevaarlijke prostaatkanker en anderzijds de niet malse complicaties bij overbehandeling van de 'slapende' prostaatkankers waar niet ingrijpen beter zou zijn.

Niet iedereen zal de beschrijving van de wetenschappelijke stand van zaken over prostate-specific antigen (PSA) testing graag horen. Met dit HTA rapport hopen we echter een antidotum te bieden tegen de vaak simplistische slogans die de huidige promotie van screeningsonderzoeken in de media omringen, getuige de recente aandacht voor 'mannenklinieken' en de rondrijdende "prostamobielen". In welke mate de geprezen PSA-test voor de vroegtijdige opsporing van prostaatkanker een hulpmiddel kan zijn, kan u in dit rapport terugvinden.

Actuele beperkingen van een technologie mogen de aandacht voor prostaatkanker echter niet doen afnemen. De geneeskunde staat niet stil en in prostaatkankerbehandeling wordt er vooruitgang geboekt. De uitdaging voor de toekomst op het vlak van screening zal er in bestaan om de 'slapende' kankers, waarmee vele mannen zullen overlijden, te onderscheiden van de snel groeiende tumoren die in een vroegtijdig stadium mogelijk nog curatief kunnen behandeld worden.

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SAMENVATTING

INLEIDING

In het begin van de jaren negentig hebben verschillende studies aangetoond dat 'prostate specific antigen' (PSA) een onafhankelijke voorspeller is voor de aanwezigheid van prostaatkanker. Sindsdien werd deze test op grote schaal ingevoerd voor opsporing, diagnose en opvolging van prostaatkanker. Door het systematisch opsporen van prostaatkanker met de PSA test hoopt men om de mortaliteit en morbiditeit als gevolg van prostaatkanker te verminderen.

Volgens de Wereld Gezondheidsorganisatie (WGO) moet aan 3 criteria voldaan worden vooraleer een screeningsprogramma kan ingevoerd worden:

- het moet gaan om een belangrijk gezondheidsprobleem
- een test moet in staat zijn om de aandoening in een vroegtijdig stadium op te sporen
- een behandeling moet, indien toegepast in dit vroegtijdig stadium, een aangetoond positief effect hebben op mortaliteit en of morbiditeit.

Een man heeft een kans van 1 op 2 om ooit kanker te krijgen. Prostaatkanker is hiervan het meest frequent maar komt op het vlak van mortaliteit op de derde plaats. Deze paradox wordt veroorzaakt door het feit dat prostaatkanker vaak latent blijft, zoals blijkt uit het vinden van latent prostaatcarcinoom bij autopsie: in 32 % van de gevallen bij 50-plussers, 55 % bij 60-plussers, en 64 % na 70 jaar.

In België is de cumulatieve incidentie van prostaatkanker op de leeftijd van 75 jaar tussen 1990 en 1998 gestegen van 2 naar 6%. Een gelijkaardige stijging in incidentie werd gezien in alle landen waar de PSA test voor screening werd gebruikt.

Daarentegen blijft de cumulatieve oorzaak-specifieke mortaliteit constant : van 1,1% op 75 jaar naar 3,3% bij mannen ouder dan 75. Terwijl longkanker verantwoordelijk is voor 11% van de verloren levensjaren wegens kanker, is dit voor prostaatkanker 1%. Er zijn momenteel onvoldoende gegevens om de oorzaak-specifieke morbiditeit te schatten.

DOELSTELLINGEN

Deze studie evalueert de waarde van de PSA test voor prostaatkanker-screening bij gezonde aymptomatische mannen. Mannen die raciale of erfelijke risicofactoren hebben komen hier niet in aanmerking.

METHODOLOGIE

Dit rapport volgt een Health Technology Assessment (HTA) methodologie. Allereerst werd gezocht naar studies gepubliceerd door andere HTA agentschappen of wetenschappelijke instellingen. Deze werden vervolgens geselecteerd op basis van een kwaliteitsevaluatie. Vervolgens werd deze zoektocht aangevuld met primaire klinische studies gepubliceerd tot 15/01/2006. De economische, ethische en juridische aspecten zijn elk in een afzonderlijk literatuuroverzicht opgenomen.

Een multidisciplinaire groep experten heeft de tussentijdse versies van het rapport regelmatig ingezien en ze van waardevolle commentaar voorzien. Voor de ethische en juridische kwesties werden discussies gevoerd met deskundigen op juridisch resp. ethisch vlak.

Daarnaast werden Belgische gegevens verzameld om het gebruik van PSA testen en de daaruit volgende procedures gedurende de laatste tien jaar te beschrijven.

KLINISCHE DOELTREFFENDHEID

Prostaatkankerscreening verloopt in verschillende etappes. Bij een afwijkend resultaat van de PSA test worden patiënten eventueel verwezen voor verder onderzoek en wordt er een biopsie uitgevoerd indien er geen andere verklaring voor de PSA stijging gevonden werd. Indien deze biopsie positief is, wordt een behandeling voorgesteld. Het uiteindelijke doel van de screening is om oorzaak-specifieke mortaliteit en morbiditeit te doen dalen. De klinische doeltreffendheid zal dus afhangen van de diagnostische waarde van de PSA test en de biopsie, en van de doeltreffendheid van de daaropvolgende behandeling. Deze eventuele positieve effecten moeten afgewogen worden tegen de negatieve effecten van het hele proces.

PSA meting

Technische accuraatheid

Er is een aanzienlijke intra-individuele variatie tussen opeenvolgende PSA metingen. Daarenboven wordt het resultaat beïnvloed door urinaire infecties, ejaculatie en intense lichamelijke inspanning in de voorafgaande 48 uur, of een biopsie in de 6 voorafgaande maanden. Afhankelijk van de gebruikte methode in het laboratorium kan het resultaat variëren met 15-20%.

Diagnostische waarde

Onderzoek naar de diagnostische waarde van de PSA test wordt bemoeilijkt door het ontbreken van een betrouwbare referentietest. Het is op dit moment niet mogelijk om met biopsie de klinisch relevante kankers te identificeren. Daarnaast lijden veel studies aan verificatiebias, omdat enkel die mannen met een afwijkende PSA test werden geverifieerd met de referentietest, in dit geval biopsie. Een studie waarin alle mannen werden geverifieerd met biopsie vond een sensitiviteit van 20% en een specificiteit van boven de 90% bij een PSA waarde groter of gelijk aan 4,0 ng/ml.

De waarde van de PSA test kan correcter geschat worden als een klinisch gedetecteerde prostaatkanker als referentietest gebruikt wordt. Dergelijke onderzoeken vinden een sensitiviteit van ongeveer 50% en een specificiteit van meer dan 90% bij een PSA cut-off van 4,0 ng/ml.

Rectaal toucher

Rectaal toucher is op dit moment niet meer aanvaardbaar als enige screeningtest voor prostaatkanker, gezien zijn lage sensitiviteit (38%-79%). In de meeste trials wordt het rectaal toucher nog wel gebruikt als een aanvulling op de PSA test.

Biopsie

De prostaatbiopsie wordt gebruikt om maligniteit te bevestigen of uit te sluiten. De sensitiviteit is 60% en specificiteit 100% voor alle lesies inclusief latent kankers. Bij herhaalde biopsie wordt toch nog 10% tot 30% van de maligne lesies gemist. Een biopsie houdt risico's in zoals lokale complicaties en soms urosepsis.

De prognose van kanker is afhankelijk van het stadium van de kanker en de Gleason score. Van gelokaliseerde lesies (T1 tot T2b) met een Gleason score ≤ 7 en een PSA <15 ng/ml is het niet mogelijk te voorspellen welke uiteindelijk zullen evolueren naar een klinische kanker.

Behandeling

Naast watchful waiting, zijn mogelijke curatieve behandelingen voor prostaatkanker totale prostatectomie en radiotherapie. Gezien de trage evolutie van prostaatkanker, zijn deze mogelijks curatieve behandelingen een optie voor die patiënten met een levensverwachting van meer dan 10 jaar. Er wordt momenteel onderzocht of de behandeling van kleine lesies (≤ T1c) beter is dan 'watchful waiting'.

Positieve effecten

Er zijn vooralsnog onvoldoende gegevens om het effect op de oorzaak-specifieke mortaliteit door screening te schatten.

De meest betrouwbare schatting van het effect van PSA-screening komt van gerandomiseerde gecontroleerde studies. Hierdoor is het mogelijk om de voordelen af te wegen tegen de nadelen, wat absoluut noodzakelijk is gezien screening gericht is op gezonde mannen.

Momenteel lopen er twee grote gerandomiseerde gecontroleerde studies (PLCO, ERSPC) waarvan de resultaten ten vroegste in 2008 worden verwacht. Daarnaast zijn er tegenstrijdige observationele studies: in sommige werd een daling waargenomen van de mortaliteit in relatie met PSA-gebruik, terwijl in andere landen deze relatie niet werd teruggevonden. De kwaliteit van deze observationele studies varieert en voorzichtigheid is dan ook geboden bij het interpreteren van de resultaten.

Negatieve effecten

Het hele proces leidt tot een stijging van het aantal biopsies, met de bijbehorende ongerustheid en lichamelijk ongemak. Deze negatieve effecten zijn meestal beperkt. Belangrijker is het risico op toegenomen detectie van indolente tumorhaarden, ook wel overdiagnose[a] genoemd, dat wordt geschat op 18 tot 39%. Deze overdiagnose leidt tot ernstige negatieve effecten, gezien het van een gezonde persoon een zieke patiënt maakt, met de bijbehorende negatieve effecten van de behandeling. Het doet daarnaast de incidentie van prostaatkanker stijgen.

Radicale prostatectomie en radiotherapie kunnen levensreddend zijn, doch kunnen ook ernstige negatieve effecten voor de patiënt hebben op middellange en lange termijn. Schattingen voor het aantal negatieve effecten lopen uiteen naargelang de manier waarop negatieve effecten worden gedefinieerd en zijn afhankelijk van de ervaring van de chirurg. De voornaamste negatieve effecten van totale prostatectomie zijn erectiestoornissen bij driekwart van de patiënten en urine-incontinentie bij 10 tot 20% . Na radiotherapie hebben 30-35% van de patiënten maag/darmklachten het eerste jaar, het risico op impotentie op lange termijn ligt tussen de 45 en 63%.

KOSTENEFFECTIVITEIT

Zolang er geen overtuigend bewijs is voor de klinische doeltreffendheid van PSA-prostaatkankerscreening, zijn kosteneffectiviteitsanalyses louter speculatief.

ORGANISATORISCHE ASPECTEN

In 2003 werden er in België 1,1 miljoen tests aangevraagd, waarvan 80 % door een huisarts. De helft van de mannen tussen 65 en 74 jaar heeft minstens één test ondergaan, hetzelfde geldt voor de 75 plussers. Uit de nationale gegevens blijkt dat het aantal tests elk jaar met nagenoeg 10% toeneemt. Bovendien is er, ondanks het de facto bestaan van een onderste leeftijdsgrens voor terugbetaling, geen duidelijke bovenste leeftijdsgrens, wat zou kunnen verklaren dat meer dan de helft van de tachtigjarigen nog getest wordt. Ten slotte voeren

[a] Overdiagnose wordt gedefinieerd als de detectie van prostaatkanker door PSA testing dewelke zonder screening nooit aanleiding zou geven tot symptomen.

diverse (privé of openbare) organisaties en mannenklinieken preventie- of screeningsonderzoeken uit, inclusief dosering van PSA.

ETHISCHE EN JURIDISCHE ASPECTEN

Vanuit maatschappelijk oogpunt is het gebruik van PSA meting voor screening niet verantwoord aangezien de klinische doeltreffendheid van prostaatkanker screening niet bewezen is, en die middelen kunnen worden ingezet voor andere zorgen of procedures die hun efficiëntie wel bewezen hebben.

De Belgische wet over de rechten van de patiënt bepaalt dat de geïnformeerde toestemming van de patiënt noodzakelijk is alvorens een test uit te voeren. Als de patiënt zelf de test vraagt, wordt verwacht dat de arts volledige informatie geeft over de onzekerheden en de potentiële nadelen (bijvoorbeeld met een patiëntenbrochure), zodat de patiënt op grond van die informatie een bewuste keuze kan maken. Media of marketing campagnes die gezonde mannen aanzetten tot het vragen van een PSA test zijn een voorbeeld van aanbodsgeïnduceerde vraag.

CONCLUSIES

Teruggrijpend naar de criteria van de WGO voor screening, kunnen we besluiten dat prostaatkanker een belangrijk gezondheidsprobleem is van voornamelijk mannen ouder dan 75 jaar. PSA en het huidige testgebruik kunnen niet beschouwd worden als een valide screeningsstrategie. Het nut van een massascreening voor de vroegdetectie van prostaatkanker in asymptomatische mannen is onbekend en daarom ook niet te verantwoorden.

De huidige Belgische praktijk is gekenmerkt door een vaak routinematig gebruik van PSA in allerlei medische check-ups etc., niet steeds met voorafgaande informatieverstrekking aan de patiënt. Dit leidt tot een hoog aantal PSA-testen in het kader van opportunistische screening. Gezien de huidige stand van de wetenschap en de juridische en ethische aspecten is het aanvragen van een PSA test zonder informeren van de patiënt niet meer aanvaardbaar. Bij patiënten die een PSA test vragen, moet de arts de implicaties bespreken.

De conclusies van dit onderzoek dienen mogelijks aangepast na de publicatie van de lopende gerandomiseerde klinische studies.

BELEIDSAANBEVELINGEN

De PSA test in prostaatkankerscreening

Het gebruik van de PSA-test in een publiek georganiseerd screeningsprogramma, gericht op de mannelijke bevolking niet behorend tot een hoog-risico groep, kan niet aanbevolen worden zolang er geen evidence beschikbaar is over de doeltreffendheid ervan. Een publieke campagne die niet-geïnformeerde gezonde mannen mobiliseert voor een PSA-test is niet aan te raden.

Gezien de wetenschappelijke onzekerheden zou PSA-gebruik voor opportunistische screening - bij geïnformeerde mannen die een test vragen - moeten kaderen in een eenvormige aanbeveling met een duidelijk algoritme ontwikkeld door de wetenschappelijke verenigingen van urologen, huisartsen en de academische wereld. Dergelijk gevalideerd algoritme kan een kader bieden tot een meer restrictievere en oordeelkundige toepassing van PSA waarbij de frequentie van PSA-testen wordt gereduceerd tot éénmaal om de x-aantal jaar met start vanaf een bepaalde leeftijd. De terugbetalingscriteria van de PSA-test kunnen hierop aangepast worden. Deze leidraad zou alvast meer duidelijkheid scheppen en een gepast antwoord bieden op het huidige grote aantal PSA-testen. Dit impliceert ook dat in functie van het resultaat en de evolutie van de PSA-waarde frequenter kan gecontroleerd worden of integendeel minder frequent of gestopt vanaf een bepaalde leeftijd.

Het ontwikkelen van een informatiestrategie

Wereldwijd wordt aanbevolen om artsen te informeren over de onzekerheden die de PSA-test kenmerken en mannen en vrouwen te informeren over de implicaties van de test.

Hiervoor is samenwerking tussen verschillende organisaties betrokken in informatieverstrekking noodzakelijk zoals wetenschappelijke verenigingen, overheden en patiëntenverenigingen. Dit alles vergt een gecoördineerde en coherente informatie strategie, waarin beleidsmakers een belangrijke ondersteunende rol kunnen spelen. In het specifieke geval van prostaatkankerscreening zou de overheid initiatieven moeten nemen om de aanbods-geïnduceerde vraag voor de PSA test te verminderen door correcte informatieverstrekking aan de verschillende doelgroepen.

Nood aan gegevens en registratie

Een goede en actuele nationale registratie van de prostaatkankerincidentie, met gegevens over het anatomo-pathologisch onderzoek, de correcte staging, de initiële en latere behandelingen, en de oorzaak-specifieke morbiditeit en mortaliteit van de patiënt is essentieel voor kankerepidemiologie en voor kwaliteitszorg. Uit de literatuur blijkt daarenboven een grote variabiliteit in de kwaliteit van de verschillende heelkundige of bestralingsbehandelingen van prostaatkanker en in de indicatiestelling tot medicamenteuze en andere behandelingen. Deze punten dient gekaderd in de algemene problematiek van een performante Belgische kankerregistratie, niet alleen in het kader van een multidisciplinair consult, doch ook in de ambulante zorg.

Deze gegevens zouden uiteindelijk op nationaal niveau kunnen leiden tot een betere beoordeling en inschatting van de klinisch-economische doelmatigheid van PSA screening, niet enkel bij vroegtijdige behandeling van het lokaal beperkt prostaatcarcinoom, doch ook bij de mogelijke beïnvloeding van de incidentie van de meer uitgebreide en/of gemetastaseerde tumoren.

Samen met een meer performante Belgische kankerregistratie, is een nieuwe HTA analyse na de publicatie van de lopende gerandomiseerde klinische studies betreffende PSA screening wenselijk, waarbij opnieuw positieve en negatieve effecten van vroegtijdige opsporing en behandeling van prostaatkanker worden geëvalueerd.

1. INTRODUCTION

1.1. DESCRIPTION OF PROSTATE CANCER

Cancer is an illness characterized by uncontrolled proliferation of cells capable of penetrating other tissue either by direct invasion of adjoining tissue or after cell migration (metastasis).

Prostate cancer starts with progressive malignant transformation of glandular cells. Prostate cancer is considered "latent" as long as the cancer remains encapsulated. In post mortem examinations, the histological detection of latent prostate carcinoma increases with age: respectively 32% (> 50y), 55% (> 60y), and 64% (>70y)[1]. Latent prostate cancer does not produce symptoms: diagnosis is conducted either clinically (prostate nodule found with digital rectal examination), by imaging or biologically (increase in PSA levels). For latent prostate cancer with a Gleason score below 7 (see 3.4.2), it is currently not possible to predict which cancers will become invasive and potentially lethal, and which will remain latent. The presence of cancerous cells in the prostate does not imply a future malignant growth.

In contrast to latent cancer, an invasive cancer shows a malignant growth extending through the capsule, eventually reaching the lymph glands and resulting in bone metastasis. When symptoms like urinary obstruction and bone pain occur, the invasive cancer becomes incurable. Nevertheless, most urinary problems linked to the prostate are not caused by an invasive cancer but by benign hypertrophy of the prostate gland.

1.2. EPIDEMIOLOGY

1.2.1. Methodology

Age-standardized mortality and number of cases of prostate cancer per 100 000 men for the regions of the world were obtained from the GLOBOCAN database of the International Agency for Research on Cancer [2]. The world standard population was used for standardization. This source will be referred to in the text as GLOBOCAN.

Age-standardized mortality and number of cases of prostate cancer per 100 000 men for 15 European countries were obtained from the Comprehensive Cancer Monitoring Programme in Europe [3]. The European standard population was used for standardization. This source is referred to in the text as EUCCMP.

The number of prostate cancers in Belgium between 1990 and 1998 was obtained from the Nationaal Kankerregister (National registry of Cancer) [4]. This source is referred to in the text as NKR. Data was stratified by age group: 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, and over 85. Conversion to incidence per year per 100 000 men used population data for the relevant year and age groups, obtained from the ECODATA database of the Nationaal Instituut voor de Statistiek (National Institute for Statistics) [5].

Prostate cancer specific mortality in Belgium between 1990 and 1997 was obtained from The Centre for Operational Research in Public Health [6]. This source is referred to in the text as CORPH. Data was stratified by age group: 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, and over 85. Conversion to mortality per year per 100 000 men used the same procedure and source as conversion of incidence in Belgium.

The number of prostate cancers in the Flemish Region between 1995 and 1996 were obtained from NKR. The numbers from 1997 to 2000 were obtained from the Vlaamse Liga tegen Kanker (Flemish League against Cancer) [7]. This source is referred to in the text as VLK. Data was stratified by age group: 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, and over 85. Conversion to incidence per year per 100 000 men used the same procedure and source as conversion of incidence in Belgium, using population data of the Flemish Region.

Prostate cancer specific mortality in the Flemish Region between 1995 and 1997 was obtained from CORPH. Data from 1998 to 2000 were obtained from the Vlaamse Overheid, Administratie Gezondheidszorg (Flemish Government, Health Care Administration) [8]. This source is referred to in the text as VOAG. Data was stratified by age group: 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, and over 85. Conversion to incidence per year per 100 000 men used the same procedure and source as conversion of incidence in Belgium, using population data of the Flemish Region.

1.2.2. International incidence and mortality of prostate cancer

Incidence

Prostate cancer (latent or invasive) is the most common cancer, with a probability of being diagnosed of one in six [9].

The estimates for 2002 in the GLOBOCAN database of cancer incidence show the highest incidence of prostate cancer to occur in developed countries, while the lowest incidence is found in underdeveloped countries [2] (see figure 1). The standardized incidence per 100 000 men is 25.2 worldwide, 56.2 for the developed countries, and 9.4 for the underdeveloped countries. The highest standardized incidence per 100 000 men of 119.9 is found in North America, which is probably a consequence of intensive screening. Potosky[10] showed that incidence of prostate cancer in the United States increased with over 40% between 1986 and 1991, accompanied by an increase in the use of the PSA test and the transrectal echography for the same period.

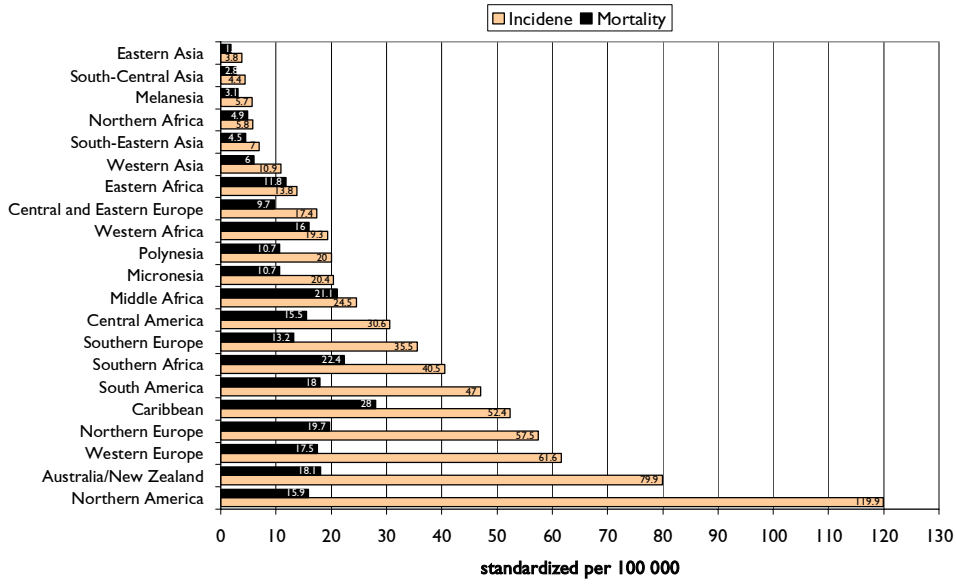


Figure 1. Standardized incidence and mortality per 100 000 of prostate cancer in the world in 2002 (source: GLOBOCAN)

Mortality

The difference in mortality of prostate cancer between the developed and underdeveloped countries is less pronounced than the difference in incidence (see figure 1). Standardized mortality of prostate cancer per 100 000 men is 8.2 worldwide, 13.5 for the developed countries and 5.2 for the underdeveloped countries. The highest levels of mortality of prostate cancer are found in the Caribbean (28), South Africa (22.4), and Central Africa (21.1). (source: GLOBOCAN)

Caution should be taken when interpreting these data, given the diversity in registration methods for cause of death and the non-comprehensiveness of the databases.

1.2.3. Belgium

Incidence of prostate cancer

Between 1990 and 1998, the cumulative incidence[b] of prostate cancer up to the age of 75 increased from 2% to 6% [11] The cancer register of the province of Limburg (LIKAR) reports for 2001 to 2003 age-standardized incidences of respectively 134, 113.2, and 145.2 per 100 000 men [12]. The results of a study in the province of Limburg showed that this increase in incidence can be explained in part by a variation in the use of the PSA test in different municipalities, although the relation between use of the PSA test and incidence was not statistically significant [13].

Prostate cancer and other causes of death

Cancer is the primary cause of natural death for men between 50 and 75 years of age. Together with cardiovascular disease, cancer causes three quarters of natural deaths up to the age of 70, and two thirds of natural deaths from 70 years of age onwards (see figure 2).

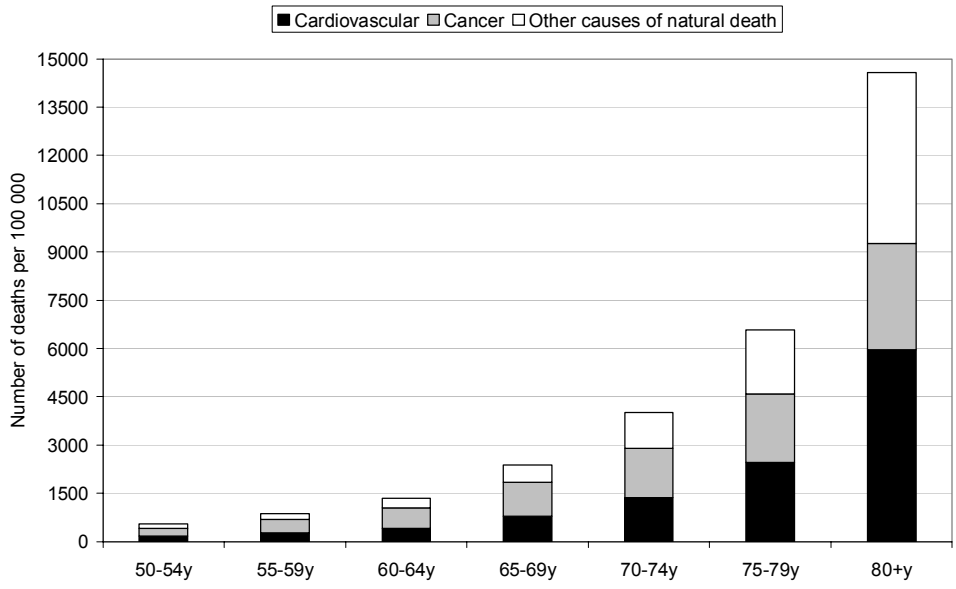


Figure 2. Number of deaths per 100 000 men in function of cause of death by category of age in 1997 (source CORPH)

Lung cancer is the most common cause of death by cancer between 50 and 80 years of age, (see figure 3). Up to 70 years of age, colon cancer is the second most common cancer, followed by prostate cancer. The importance of prostate cancer mortality relative to other cancers increases with age. From the age of 75 onwards, cardiovascular diseases become the primary cause of natural death for men.

[b] The cumulative incidence is the probability of occurrence by time t for a particular type of failure in the presence of other.

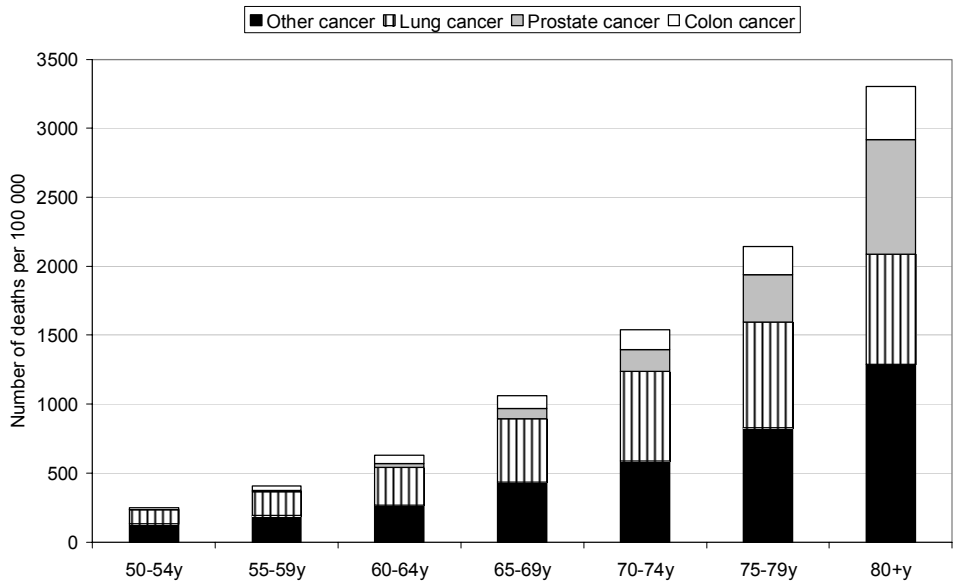


Figure 3. Number of deaths per 100 000 men in function of type of cancer by category of age in 1997 (source CORPH)

Years of life lost by cancer in Belgium

Prostate cancer, as "the male cancer", is often equated with breast cancer ("the female cancer"). However, the potential years of life lost (PYLL) [c] for prostate cancer are considerably lower than the PYLL for breast cancer (see table 1). In contrast to breast cancer in women, prostate cancer kills relatively few men before the age of 75.

Table 1. Potential years of life lost for four types of cancer in men and women (% from all deaths because cancers)(Source: National Registry of Cancer, 1997).

	PYLL men	PYLL women
Lung cancer	10.9%	4.4%
Colon cancer	2.4%	3.3%
Breast cancer		12.0%
Prostate cancer	1.1%	

Lung cancer is the fourth most common cause of PYLL, colon cancer is the tenth most common cause of PYLL, while prostate cancer does not figure in the top ten [14].

Evolution of mortality of prostate cancer

In Belgium, the cumulative mortality remained about 1.1% between 1990 and 1997 (see figure 4) (1.25% in the Netherlands) [11]. In other words, out of 100 Belgians who reached or should have reached the age of 75, 64 have a latent prostate carcinoma, two to six have been diagnosed with prostate cancer, and one has died of prostate cancer.

[c] The potential years of life lost (PYLL) are the number of years lost due to a specific cause given a particular age.

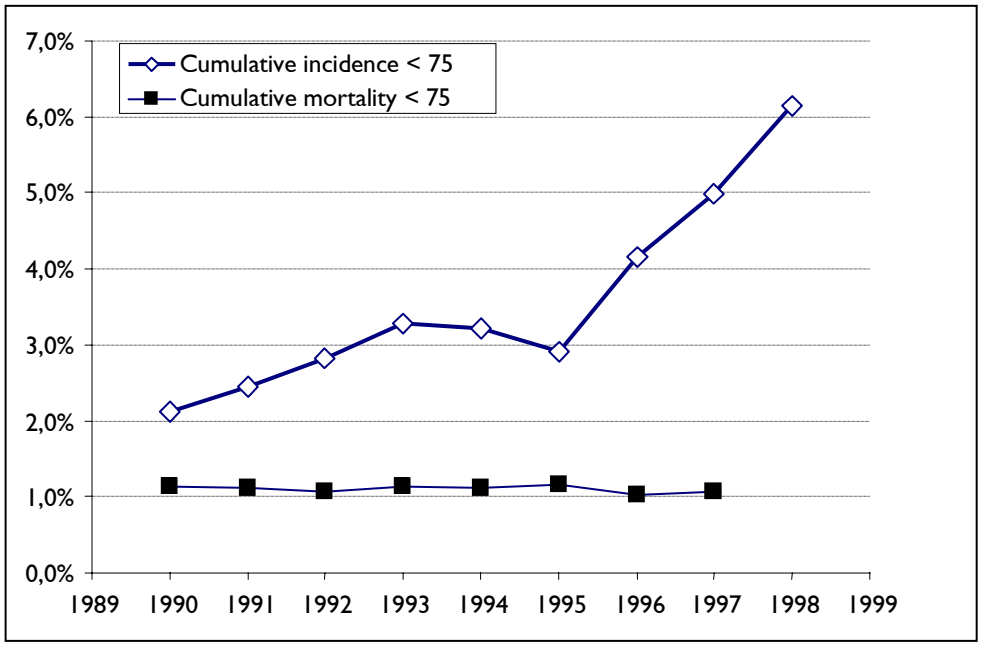


Figure 4. Probability of having prostate cancer of having died of prostate cancer before the age of 75 (source incidence: NKR; source mortality: CORPH).

1.2.4. Flemish Region

For the Flemish Region, more recent figures of incidence and mortality are available, confirming the general tendencies on the national level. Figure 5 shows a strong increase in standardized incidence of prostate cancer between 1995 and 2000, while the mortality remains stable in the same period. The somewhat lower mortality observed in the figure from 1998 onwards is due to the use of two different sources of mortality data. These sources each use a slightly different methodology in calculating the mortality.

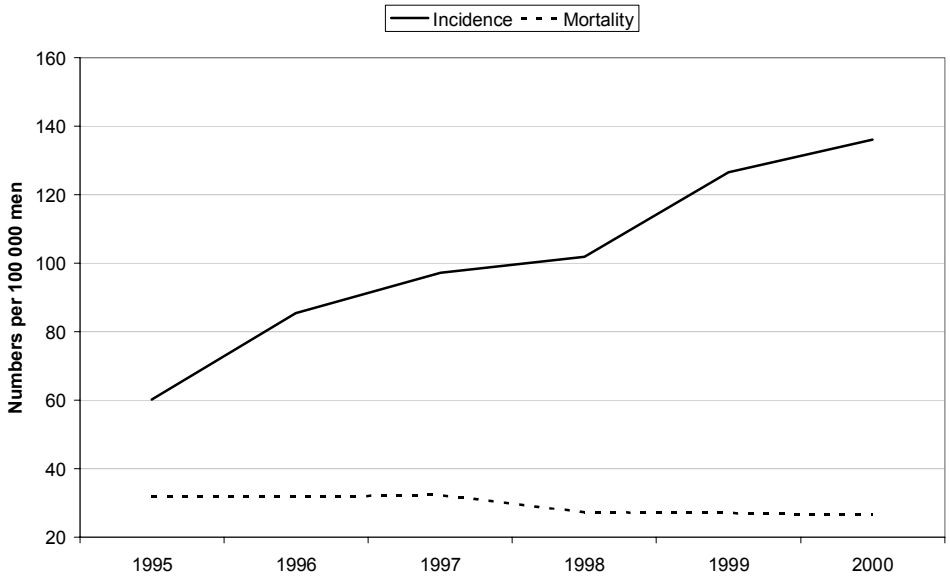


Figure 5. Incidence and mortality per year per 100 000 men of prostate cancer in the period 1995-2000 in the Flemish Region (source incidence NKR & VLK; source mortality: CORPH & VOAG).

Stratification to eight five-year categories of age shows a peak in incidence for the age categories 65-69 and 70-74 (see figure 6). The increase of incidence of prostate cancer is noticeable in almost all categories of age.

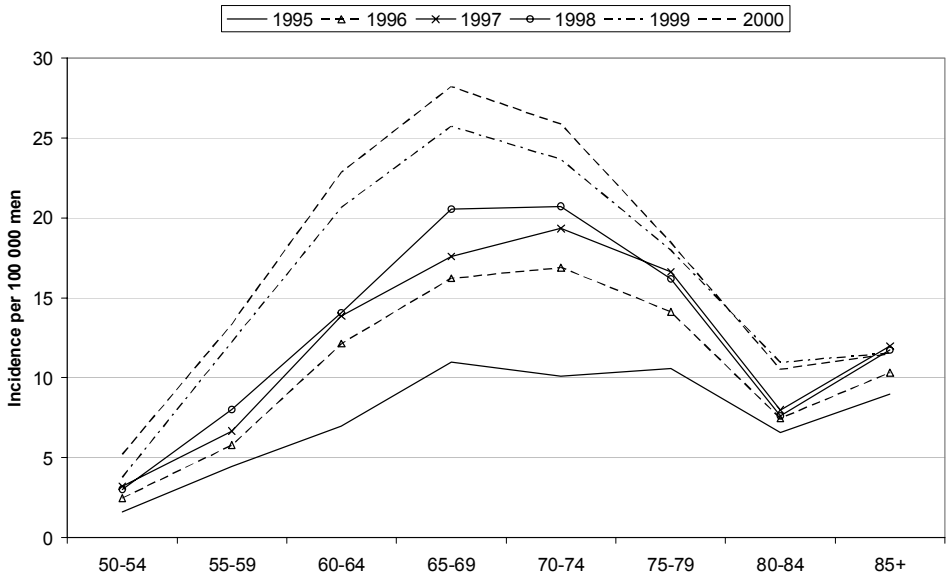


Figure 6. Age-specific incidence per year per 100 000 men of prostate cancer in function of category of age in the period 1995-2000 in the Flemish Region (source NKR & VLK).

Stratification of mortality to eight categories of age confirms the stability of mortality between 1995 and 2000 (see figure 7). The data suggest a slight decrease of mortality after the age of 70 since 1998. However, this could be due to the different source used for mortality figures from 1998 onwards.

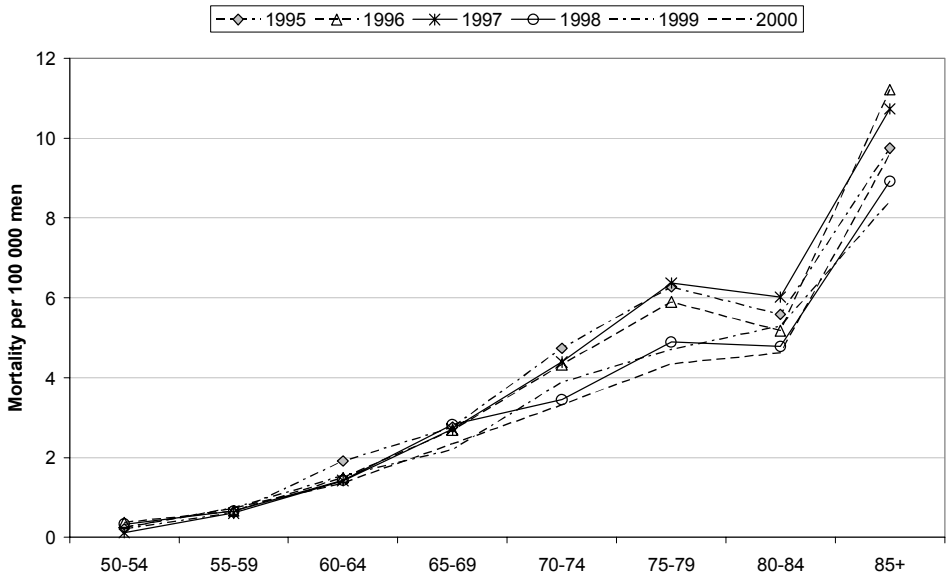


Figure 7. Age-specific mortality per year per 100 000 men of prostate cancer in function of category of age in the period 1995-2000 in the Flemish Region (source: CORPH & VOAG).

1.2.5. Discussion

Prostate cancer is something of a paradox. Although it is the most frequently diagnosed cancer in men, it is only the third most common cause of death by cancer in Belgium. Autopsy studies suggest the following explanation: irrespective of cause of death, half of the men aged 60 years have latent prostate cancer as shown by histological examination. This means, because of the slow progression of prostate cancer, more men die with than from prostate cancer. At present, it is not possible to reliably predict the outcome of latent prostate cancer with a Gleason score below seven. Of these, a small number are fatal, others become clinically relevant cancers, while most remain latent. If a man dies of prostate cancer, it occurs fairly late in life: mostly after the age of 75. This fact puts the relative importance of prostate cancer as a cause of death into perspective.

1.3. SCREENING OF PROSTATE CANCER

1.3.1. Context

In our culture, the statement "prevention is good for you" is assumed good practice in any case. Citizens are made aware of pre-symptomatic health problems, and urged to check for these. Men have become a particular target audience for cancer prevention in general and prostate cancer in particular. Especially for middle-aged men campaigns are being set up to pay considerable (preventive) attention on one's health status. Medical check-ups are being proposed as a good "preventive" strategy, often by direct stakeholders and the culture of medical "preventive" checkups is endorsed by some medical associations. For example, the American Medical Association suggests that people have medical check-ups every five years until age 40 and then every one to three years thereafter. As a rule of thumb it is suggested: For individuals in their twenties — two exams during that time period; in their thirties — three exams; forties — four exams. An annual health exam is recommended for most patients after age 50. (http://www.oznet.ksu.edu/library/hlsaf2/mf2357.pdf; see also the chapter on Organisational Issues below).

Screening for prostate cancer has become a particular part of these check-ups: In the '90s hospitals campaigned for men to undergo PSA-testing.

Some striking examples of "awareness-building" of the public can easily be found on the internet:

- The Arkansas prostate screening programme "encourage(s) men to be tested early and regularly" by providing information on prostate cancer screening and treatments and sponsoring free prostate cancer screening throughout the state (http://www.arprostatecancer.org/free.htm). Other programmes offer free prostate cancer screening and organize "awareness" programmes (http://www.cancerwise.org/September_2000/display.cfm?id=93C711D3-DC50-484E-D5B6E1EF315498B&method=displayFull&color=red)
- Specific websites are offering PSA-test-kits, and are explicitly advising to do regular PSA-test (e.g. http://www.mirates.nl/read/prostaat_PSA_info). Other websites clearly offer PSA-testing as an element of a regular medical check-up (http://www.ehcoaching.nl/publish/persoonlijkecheckup.shtml).

Within the Belgian context, "medical check-ups" are frequently offered by employers as a service to their employees. These check-ups are organised by private organisations responsible for labour related preventive activities, and are thus not part of the "public health care system". They consist of a combination of clinical examination, and testing of urine and blood, among which the PSA-test is used. More recently, the Belgian media paid particular attention to the creation of male clinics ("mannenkliniek" in Hasselt and Ghent). Other preventive initiatives are taken such as the Prostamobil in the province of Liège. However, some clinicians and epidemiologists opposed to these initiatives.

Against this medicalisation and marketing background of prevention, the use of PSA-testing has become a relevant public health issue. It is of particular interest to address the question of effectiveness and cost--effectiveness of early detection of prostate cancer screening by PSA.

1.3.2. Principles

The World Health Organisation has formulated several criteria to evaluate the appropriateness of screening for disease [15].

The disease must be considered as an "important" health problem. The progression of the disease must be well known and it must be possible to detect the disease in a localised stage by means of a marker or a test. The test used in screening must be acceptable to the public, which should be informed in advance of any alternatives. The availability of a valid screening test is crucial to a screening program. The test has to be able to detect cancer at an earlier stage. In addition, in order to reliably exclude cancer in those patients testing negative, the test's sensitivity should be as high as possible, while maintaining an acceptable specificity to minimise further invasive procedures in those patients testing positive. Finally, the test should ignore clinically irrelevant lesions, thus minimizing the detection of lesions that would never cause harm to the patient in his lifetime if left untreated.

It is necessary to have an effective treatment of lesions detected early by the screening test. Also, there must be convincing evidence for the superiority of the early treatment compared to treatment at a later stage of the disease. The choice of which patients to treat and which treatments are appropriate should depend on evidence based guidelines. Health care providers must take care to optimise both treatment and treatment outcome.

Prior to setting up a screening program, convincing evidence must be available on a decrease of disease specific mortality related to screening. The entire screening protocol must be accepted both by health care professionals and the public, from a medical, social, and ethical point of view. The benefits for the patient must outweigh the physical and psychological side effects of the test, the subsequent examinations and treatment. The screening must be cost-effective. An evaluation program must be in place, and documents explaining the consequences of the test, subsequent examinations and treatment should be publicly available. Scientifically based responses to issues raised by the public and patient organisations must be prepared.

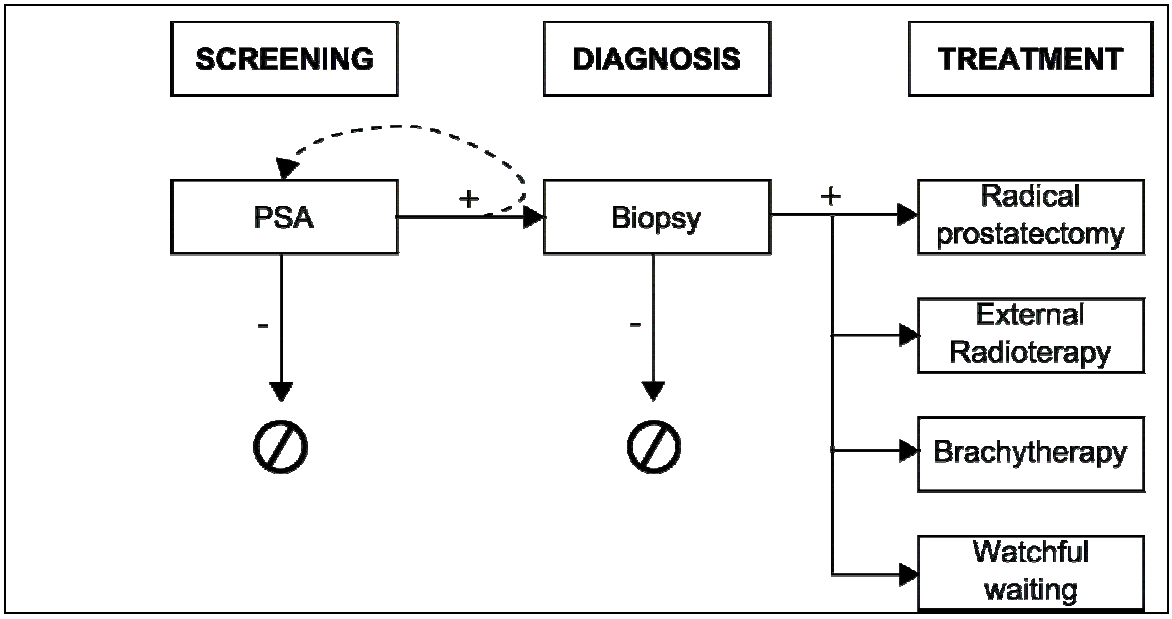
These aspects of screening are discussed in more detail in the next chapters.

1.3.3. Description of prostate cancer screening

In current practice, prostate cancer screening consists of two stages. First-line tests are used to screen the population, using the PSA level, digital rectal examination or both. Whenever one of these tests shows any abnormality, they are followed by a 'second line' test, being biopsy in most of the cases. Whenever a tumour is identified with biopsy, the patient is subsequently referred to treatment.

The principal objective of the present study is to evaluate the PSA test for screening purposes. It is not possible to evaluate the performance of the PSA test without considering the entire process of screening of prostate cancer and its consequences. Therefore, the third chapter describes in more detail the steps depicted in figure 8.

Figure 8. Prostate cancer screening process.



Key messages

- All regions using PSA tests for screening of prostate cancer have contributed to an important increase in incidence of prostate cancer.
- Between 1990 and 1998 the cumulative mortality of prostate cancer to the age of 75 has remained constant: approximately 1.1% (Belgium).
- According to autopsy studies, about half of the men aged 60 have localised prostate cancer irrespective of the cause of death.
- Prostate cancer causes about 1% of potential years of life lost, while lung cancer causes about 11% of potential years of life lost.

2. GENERAL METHODOLOGY

This research uses an HTA approach. The purpose is to support the process of decision making in health care at policy level by providing reliable information. HTA collects and analyses evidence in a systematic and reproducible way (and organizes it in an accessible and usable way for the decision makers). The principles of gathering, analyzing and using information are identical to the principles of Evidence Based Medicine (EBM) and Clinical Practice guidelines (GCP), but the purpose is different. EBM and GCP aim to support decision making at individual clinical or patient group level. In contrast, HTA aims to support decision making al policy level, leading to a different kind of recommendations and answers.

2.1. OBJECTIVES

In this report the clinical effectiveness, cost-effectiveness, organizational issues and ethical patient issues on the use of PSA-tests in prostate cancer screening are described. This question of decision-making will be addressed against the background of the appropriate use of collective means.

2.2. DEFINITION OF THE TARGET GROUP

This report applies to men of 50 years old or more, who are in good health and do not have any clinical sign that warrants an examination of the prostate: men with risk factors or men suffering from prostatic symptoms are not considered in this report.

Risk factors that increase the risk of prostate cancer are ethnicity (increased risk in African Americans) and family history [16, 17]. The relative risk of prostate cancer is increased 2-fold with one first-degree relative diagnosed at age 70 or under and rises to 4-fold with 2 relatives (if one of them is diagnosed under the age of 65)[16]. The risk with three or more relatives affected is increased 7–10 fold.

Key messages

- **This report applies to men of 50 years old or more, who are in good health.**
- **The clinical effectiveness, cost-effectiveness, organizational issues and ethical patient issues on the use of PSA-tests in prostate cancer screening are described.**

2.3. RESEARCH QUESTIONS

- What is the accuracy of the PSA test in prostate cancer screening?
- What is the accuracy of biopsy when indicated?
- What is the efficacy of PSA screening on patient related outcomes?
- What are the adverse effects of PSA screening?
- What is the cost-effectiveness of PSA screening?
- How is the PSA test currently used in Belgium?
- What ethical issues are involved in prostate cancer screening?

2.4. LITERATURE REVIEW

For questions 1 to 4, the literature has been reviewed by searching for reports first, published between 2000 and 2005 by other health Technology Assessment agencies or

scientific organisations. The reports thus identified were subsequently appraised for quality using validated checklists (checklists of INAHTA and AGREE). Of those reports, the reports by the U.S. Preventive Task Force[18], the Agence nationale d'évaluation en santé (France) [16] and the National Health Committee (New Zealand)[17] had the highest quality rates.

This search was subsequently updated by searching for original studies up until the 15th of January 2006. A more detailed description of the literature review and critical appraisal can be found in the appendix of this chapter.

All studies that were included were discussed repeatedly in a multidisciplinary group of experts (family physicians and urologists). The participation of an expert does not necessarily mean that he or she fully agrees with the entire content of the report

The literature on cost-effectiveness studies (research question 5) was searched in Medline and the CRD database (DARE, HTA, EED), by using the search terms ('screening' OR 'early') AND ('prostate cancer' OR PSA) AND ('cost' OR 'cost-effectiveness'). Studies were included if they were published from 1990 to 2005 and had an abstract in English, Dutch or French.

In order to answer the 6th research question on the current use of the PSA test in Belgium, primary data were collected. More details on the source and methodology are given in chapter 5.

Finally, the ethical issues were debated in a discussion group consisting of ethical and legal experts. The literature search was done in Medline, the Cochrane Library and the Campbell library with the search terms PSA AND (screening OR mass screening) AND (informed consent OR informed decision making OR shared decision making OR preventive screening ethical aspects OR ethics OR precaution principle OR precautionary principle); MESH : "Prostate-Specific Antigen" "Mass screening", informed consent, ethics.

Publication type	Source	Search terms
Guidelines	INAHTA, GIN, ICSI, NHG, ANAES, SSMG,	Prostate and PSA [free text]
Meta-analyses, RCTs, controlled studies	Medline (Ovid), Cochrane, CRD, ACP Journal Club, DARE, Embase,	« Prostatic neoplasm », «Prostate-Specific Antigen », « Mass screening » (MESH)
Ethics	Medline (Ovid), Cochrane, Campbell	Free text : PSA, screening, mass screening, informed consent, informed decision making, shared decision making, preventive screening ethical aspects , ethics. precaution principle, precautionary principle MESH : "Prostate-Specific Antigen" "Mass screening", informed consent, ethics.

3. CLINICAL EFFECTIVENESS

When assessing the value of a diagnostic test used in screening, several levels of efficacy should be addressed.

First of all, the technical accuracy of a test should be reviewed. This level deals with the technical performance of the test in terms of analytical sensitivity and specificity, inter- and intraobserver variation, limits of agreement etc.

The second level addresses the test's diagnostic accuracy: the test's ability to detect or exclude a target condition or disease in patients compared with a reference test. Test characteristics can be expressed as sensitivity, specificity, predictive values, likelihood ratios, ROC curves, area under the curve, odds ratio.

Finally, the effect of screening on patient outcome should be reviewed. Screening programs are set up in order to detect cancer at an earlier stage in which treatment is more likely to be beneficial. Therefore, the efficacy of a screening program can be assessed by examining its effect on mortality and morbidity, at the same time accounting for its adverse effects[19].

3.1. PROSTATE SPECIFIC ANTIGEN

Prostate specific antigen (PSA) is a glycoprotein with proteolytic activity. The antigen is produced by the epithelial cells of the prostate and prevents the coagulation of the ejaculate in order not to hamper spermatozoa motility.

A proportion of the PSA enters the blood where some will bind with a protein inhibitor. Total serum PSA is therefore made up of two fractions: free plus bound PSA. The PSA index is the ratio between the serum level of free PSA and the serum level of total PSA.

Although the rise of serum PSA may be due to other pathologies, the level of total serum PSA is mainly used in the screening for prostate cancer.

3.2. TECHNICAL ACCURACY OF THE PSA TEST

ANAES [16] produced a summary of the physiological or pathological circumstances that influence the level of PSA in blood:

There is an intra-individual physiological variation between PSA serum levels measured at various intervals. For patients with PSA levels between 4 and 10 ng/ml, the mean intra-individual coefficient is 23.5%. The PSA serum level may be increased in benign prostatic hypertrophy, acute prostatitis and prostate cancer. Physical exercise and ejaculation cause variations in the serum level of PSA.

Urinary endoscopy, biopsy of the prostate or surgical intervention on the prostate may cause a significant rise in serum PSA. In contrast, digital rectal examination does not cause a significant rise in PSA. The administration of 5-alpha-reductase inhibitors (finasteride and dutasteride used for the treatment of benign prostatic hypertrophy) causes a fall in the serum level of PSA of about 50%.

There are many testing kits on the market. Depending on the method, the results vary by 15 to 20%. The stability of PSA, especially in its free form, is affected by its proteolytic properties. It is therefore necessary to analyse the sample within maximum 18 hours of it being taken, or centrifuge and freeze it for later analysis. Therefore, together with physiological variations and measurement variations (5%), every test has to be evaluated critically.

Key message

The total serum PSA level is among others influenced by technical conditions and by benign prostate hypertrophy, urinary infection, ejaculation and physical exercise within 48 hours.

3.3. DIAGNOSTIC ACCURACY OF THE PSA TEST

The total serum PSA

Several studies have found the total serum PSA level to be an independent predictor of prostate cancer[20]. This does not necessarily mean that the PSA level can be transformed in a clinically meaningful test to diagnose or screen for prostate cancer. In order to correctly diagnose those patients with prostate cancer from a large, healthy population, a cut-off point needs to be defined below which prostate cancer is highly unlikely and above which the probability of prostate cancer is sufficiently high to justify further invasive testing.

But, research has yet to clarify which tumours should be targeted in screening to show a benefit on patient outcome. The natural history and progression of the disease are insufficiently understood to identify with certainty the clinically relevant tumours at a premature stage. This has important consequences for any diagnostic research on the PSA level. Ideally, a reference test identifies only those tumours that are clinically relevant, and the PSA is subsequently compared to this reference test. However, as further explained in the text, biopsy results are currently not able to differentiate clinically relevant tumours from clinically irrelevant ones. To avoid this problem, the PSA test is evaluated in its ability to predict the occurrence of a clinical prostate cancer, as a prognostic marker.

Most of the diagnostic accuracy studies on PSA level suffer from *verification bias*. Patients with an abnormal test result are verified with biopsy, patients with a normal test result are verified with clinical follow-up. This form of verification bias is called differential verification bias, and has an average effect of 1.69 (95% CI 1.03-2.78) on the odds ratio (Rutjes, PhD thesis 2005). However, in this specific situation, verification bias may be even more important, as tumours found by biopsy are markedly different from clinical tumours.

Studies using biopsy as a reference test

The evidence on the diagnostic accuracy of the total serum PSA has been summarized in several systematic reviews. The most recent was published in 2003[21]. However, this meta-analysis is of low quality in terms of search method, quality appraisal, and reporting. Only studies suffering from verification bias were included, and data were pooled despite the presence of marked clinical and statistical heterogeneity, for example studies with healthy volunteers were pooled with studies using referred patients. The results from this meta-analysis were therefore not included in this review.

Another recent literature search was performed by Harris et al. for their update of the evidence for the U.S. Preventive Services Task Force (search up until September 2002)[22]. The authors conclude that great uncertainty remains on the value of the PSA level on patient outcome, including age-adjusted PSA levels, f/t[d] PSA, and PSA velocity[e].

Two HTA reports summarized the available evidence[23, 16] of which that made by the ANAES is the most recent. Positive predictive value of the PSA level is estimated at around 30%, with biopsy results as the reference standard. Sensitivity and specificity measures are less trustworthy in this situtation due to verification bias.

One study has tried to overcome the problem of verification bias, by verifying all subjects, regardless of the PSA level[24]. Thompson et al. subjected all patients of the placebo-arm of

[d] f/t is the ratio of free to total PSA
[e] Velocity is defined as the rate of change in total PSA level per year

a trial on the efficacy of finasteride in preventing prostate cancer to biopsy. All patients had 3.0 ng/ml PSA at the beginning of the trial 7 years earlier. Measurement of PSA and DRE were performed annually. Patients with PSA 3.0 ng/ml or a suspicious DRE had prostate biopsy. At the end of the trial all participants not previously diagnosed with prostate cancer had an end-of-study biopsy. At a cut-off of 4.0 ng/ml, sensitivity was 20.5% and specificity 93.8%.

It becomes more and more clear that it is not possible to define a cut-off below which prostate cancer is highly unlikely, as is also illustrated in another study in which 478 (67%) of 760 detectable cancers were diagnosed irrespective of PSA in men screened with digital rectal examination, transrectal ultrasonography and PSA. 127 of 348 detectable prostate cancers (36.5%) were actually diagnosed in men with PSA 2 to 4 mg/ml. Approximately half of the tumours missed with PSA 0 to 4 ng/ml had aggressive characteristics[25].

Studies using clinical outcome as a reference test

As already discussed earlier, biopsy results are thought to overdiagnose prostate cancer as they fail to distinguish the clinically relevant cancers from the irrelevant ones. A few studies have assessed the value of PSA using clinically detected prostate cancer as a reference standard. In a nested case-control study based on the Physicians's Health Study[26], the value of the PSA test was related to the clinical occurrence of prostate cancer retrospectively. It is unclear how the cases of prostate cancer were diagnosed, as screening with digital rectal examination and presurgical PSA testing were included as well. This study found a sensitivity of 46% (95% CI 41-52) and specificity 91% (95% CI 89-93) after 10 years of follow-up for all prostate cancers at a cut-off of 4.0 ng/ml. Reconstructing the 2x2 table, it is possible to calculate the corresponding positive and negative predictive values, being 9.8% and 98.5% respectively, which is only just better than the pretest probability of 2.4%. The lower predictive value in this study as compared to those summarized by the HTA reports is due to the difference in disease definition: in this study, although not perfectly clear, only clinical cases of prostate cancer were included, whereas the other studies used biopsy results following screening as a reference standard.

A similar but smaller study found a sensitivity and specificity of a prostate-specific antigen level 4 ng/ml up to 3 years prior to the time of clinical diagnosis of both 75% and up to 6 years of 67% and 85%, respectively[27].

f/tPSA

It has been argued that the ratio of free to total PSA raises the test's specificity, leading to a lower proportion of men who need to undergo biopsy. Only recently, a meta-analysis was published that summarized the evidence up until December 2004[28]. Studies were included if they assessed the value of f/t PSA in patients with a total PSA level between 2-10 ng/ml and all patients were verified with biopsy. The authors conclude that in patients with total PSA 4-10 ng/ml, f/tPSA has a sensitivity of 95% and specificity of 18% at an estimated cut-off of 0.25. The complexed PSA (cPSA) is equivalent to the f/tPSA. In patients with 2-4 ng/ml total PSA level, specificity declines to 6% if sensitivity remains 95% at an estimated cut-off of 0.28.

PSA velocity

The mean PSA velocity is defined as the rate of change in total PSA level per year. Studies have found that velocity is higher in prostate cancer patients than in patients without prostate cancer[29]. However, although this difference has been found to be significant, it is not possible to define a clinically useful cut-off to predict biopsy outcomes, as was illustrated in recent studies[30, 31]. In addition, the available HTA reports and systematic review find the value of PSA velocity uncertain in terms of impact on clinical outcome[23, 22].

PSA screening intervals

The European Randomized Study of Screening for Prostate Cancer (ERSPC) is an ongoing trial on the efficacy of prostate cancer screening in Europe. Participants are screened at 4 year intervals. From the preliminary results of the study, it becomes apparent that the test characteristics of the total PSA level change after the first screening round. Larger

tumours are harvested and tumour volumes in the second round are subsequently smaller. In fact, tumour volume becomes a negative predictor of prostate cancer, indicating that elevated PSA levels are in large caused by benign prostatic hyperplasia instead of prostate cancer[32].

Key message

- **The diagnostic accuracy of the PSA level is different in studies using biopsy as a reference test than in studies using clinically detected prostate cancer**
- **When compared to biopsy, the sensitivity of total serum PSA is 20%, specificity is over 90%.**
- **When compared to clinically detected prostate cancer, specificity is similar, but sensitivity is around 50%.**
- **The incremental value of f/tPSA or PSA velocity is unclear.**

3.4. DIAGNOSTIC ACCURACY OF THE DIGITAL RECTAL EXAMINATION

Levels of sensitivity and specificity of digital rectal examination (DRE) are generally believed to be lower than those of PSA testing[23, 22]. DRE has now become unacceptable as a sole method of prostate cancer detection. But, most ongoing trials have included DRE as an adjunct to PSA testing.

The evidence on the value of digital rectal examination was summarized in a good-quality meta-analysis by Hoogendam et al[33]. The authors found that in a primary care screening situation, the DRE appears to be a test with a high specificity and negative predictive value, but a low sensitivity and positive predictive value. Sensitivity ranges between 38% and 79%. Neither a positive nor a negative test result is sufficient to enable conclusions without further confirmation. Some studies suggest that DRE is able to detect some tumours that are not detectable by PSA[34].

Key message

- **Neither a positive nor a negative DRE result is sufficient to enable conclusions on the presence of prostate cancer without further confirmation.**

3.5. BIOPSY

In case of an abnormal result on PSA level or DRE, needle biopsy is used to confirm the diagnosis of prostate cancer. The numbers of biopsies are rising due to the increasing numbers of men found to have raised PSA levels. In the ERSPC study [35], the decision to biopsy is based on an assay of total PSA only, if the result is above the cut-off value (4 ng/ml in general, 3 ng/ml in The Netherlands and in Spain). Elsewhere, authors recommend performing a biopsy on the basis of a number of factors such as PSA, age, rectal digital examination and total/free PSA [36 499]. Benign prostatic hypertrophy, which causes a rise in the PSA level, should also be taken into account. The combined use of PSA and DRE leads to the detection of one prostate cancer and 40 additional biopsies per one thousand men [37].).

The reported detection rate of prostate cancer, lesions suspicious for cancer, and prostatic intraepithelial neoplasia (PIN) in needle biopsies is highly variable. In part, technical factors, including the quality of the biopsies, the tissue processing, and histopathological reporting, may account for these differences[38].

Biopsy misses some cases of cancer; 10-30% of men who have negative biopsies have cancer on repeated biopsy series[39], with an overall sensitivity for sextant biopsies of 60%, and a specificity of 100%[40]. Using a strategy where the number of cores is dependent on age and prostate volume has equal cancer detection rates as the standard octant biopsy technique with systematic repeat biopsies in case of a negative result[41]. On the other hand, in a recent study on 12-core transperineal prostate biopsies in patients undergoing radical cystoprostatectomy for high-grade bladder cancer, 17.2% of patients had a positive biopsy and 54% had prostate cancer on definitive histology. Sensitivity of biopsy was 32.3% overall and 75% for clinically significant cancers. The PSA levels did not correlate with the presence of prostate cancer[42]. In a United Kingdom modeling study [17], it is necessary to perform 1,000 PSA tests and 136 biopsies in order to detect 33 cancerous lesions. Conversely, 23 lesions (15 false-negatives due to PSA and 8 false-negatives due to biopsy) will not be diagnosed. The detection rate of 33/1000 observed above is comparable to a mean rate of 34/1000 observed in the first round of the ERSPC study for The Netherlands [43]. Currently, we do not have such data for Belgium.

Obviously, this specificity of 100% relates to histologically proven tumours, which are not necessarily clinically relevant tumours. Several attempts have been made to improve the prognostic value of the biopsy results. If the PSA level is >15ng/ml or the Gleason score (see appendix to chapter 3) is 8 or the lesion is more thanT2b, prognosis is considered poor. Tumours in stage T1 with PSA <10ng/ml and a Gleason <7 have a good prognosis. Tumours in stage T2a, T2b and with PSA >10 and <15 and a Gleason score of 7 are considered as having an intermediate prognosis[44] .

In a certain number of cases, the diagnosis of latent histological lesions may lead to overtreatment (see 3.8.2). This phenomenon is illustrated by a study conducted from 1971 to 1984 in Connecticut [45] in which the patients received conservative treatment. Patients whose tumour had a Gleason score of 2 to 4 ran a 4 to 7% risk of dying from prostate cancer within 15 years. If the Gleason score was 6, the risk rose to 18-30%, and if the score was 8 to 10 the risk reached 60 to 80%.

Key message

Biopsy has a sensitivity of 60%.

Among localised lesions (T1 to T2b) with a Gleason score ≤ 7 and a PSA < 15ng/ml, it is not possible to predict which lesion will evolve to a clinically relevant cancer.

3.6. TREATMENT

The choice of treatment depends first and foremost on the patient's state of health. Considering the expected benefits and negative effects, a patient should have a life expectancy of more than 10 years; considering current median life expectancy, a limit at 70 years of age is suggested in order to benefit from curative treatment. For a lower life expectancy, watchful waiting as treatment seems preferable. (ANAES 2001).

For patients with a life expectancy of more than 10 years, the standard curative treatments of prostate cancer are radical prostatectomy and radiotherapy (external or internal). There is no definitive argument for the superiority of one treatment above another [46] Hormonal therapy is not mentioned in this context because it is not used as a sole curative treatment.

The optimum treatment for localized stages with an intermediate or good prognosis remains unknown. This would necessitate reliable long-term studies comparing the outcome of patients who have undergone curative treatment with that of patients monitored with active surveillance. The latter [47] consists of performing regular checks of PSA velocity (doubling time) and biopsies (evolution of the Gleason score); curative treatment is only proposed if an evolution is observed. This strategy differs from watchful waiting, which only proposes (palliative) hormonal treatment in the case of symptoms.

Some studies compared watchful waiting with agressive treatment in early stages of the disease. The Bill-Axelson study [48] concludes that radical prostatectomy reduces cause-specific mortality, all-cause mortality as well as the risk of metastases or local invasion after 10 years of follow-up. However, the study population comprised of 76% T2 patients (tumours with poor prognosis) and of only 12% T1c patients whose tumour had been detected by PSA testing. Therefore, it is not possible [47] to extrapolate the improvement in morbidity and mortality observed in the long term (10 years) in this study to the population screened with PSA. In addition, the improved survival, although statistically significant, is small in absolute numbers with overlapping confidence intervals and occurring in men under the age of 65 only.

Key messages

- **Curative treatments are reserved for patients whose life expectancy is greater than ten years (a limit of 70 years is suggested).**
- **The standard curative treatments for cancer are radical prostatectomy and radiotherapy.**
- **The optimum treatment of localised stages with a favourable or intermediate prognosis remains unknown.**

3.7. EFFECTIVENESS OF SCREENING

The positive effects expected from the use of PSA in screening are a reduction in disease-specific morbidity and mortality (total effectiveness), conditioned by the effectiveness of the test to detect potentially invasive cancers but also by the effectiveness of subsequent treatment.

3.7.1. Effectiveness of the total process

Evidence concerning the effectiveness of screening of prostate cancer (by PSA testing) in terms of reduction in mortality was first assessed by searching for randomised controlled trials. Other types of study were also considered.

Randomized controlled trials

Three randomized controlled trials were identified.

- Canada [49]: The Quebec prospective randomized control trial started in 1988, aims to evaluate the impact of prostate cancer screening on cancer-specific mortality. But, the participation was poor (23%); 46.486 men (aged 45-80 y.) were randomized between screening and no screening. This study suffers from several methodological problems, notably contamination of the control group by opportunistic screening and late inclusion without adjustment and analysis per protocol. [50]. If intention to treat analysis is performed, the probability of death from prostate cancer is 4.73/1,000 for the persons not invited to the screening versus 4.47/1,000 for the persons invited. At this moment, the difference is not statistically significant (lack of power).
- USA: the PLCO Cancer Study Trial, started in 1993, is a multicenter, randomized, two-arm trial designed to evaluate the effect of screening for prostate, lung, colorectal and ovarian cancer on disease specific mortality. The study combines the data from ten screening centres including more than 70,000 men (33,795 in the screened group and 33,805 in the control group). Interim findings are expected from 2005 on [51] and long-term results in 2015.
- Europe: the ERSPC (European Randomised Screening for Prostate Cancer) study was started in 7 European countries (Belgium Finland, Italy, Portugal, Spain, Sweden and The Netherlands). To date, 267,994 men have been included on a gradual basis. This trial should have sufficient power in 2008 to detect a 20% reduction in potential mortality related to the screening if contamination remains limited to 10% [52]. Numerous scientific articles citing preliminary data were already published.

The last two studies will be able to provide level 1 evidence on the effectiveness of PSA testing in reducing cause-specific mortality. Given the differences observed between the recruitment methods, the age of the participants and the PSA threshold value (cut-off), it is advisable to remain prudent when interpreting the results.

Cohort studies

The study conducted in Austria [53] started in 1993 compared the mortality in Tyrol (where the PSA test was offered at no charge) with that of the rest of Austria, which did not benefit from reimbursement. This study showed a decline in death rate from prostate cancer that was significantly greater in Tyrol than in the other parts of Austria ($p = 0.006$). This decline was concomitant with an increase in the number of cancers detected at an early stage. It is advisable to interpret these data with prudence as it is not a randomized study. The authors themselves conclude that the observed decline in mortality in the first years of the study is probably due to an improvement in treatment and that the contribution of screening can not be evaluated before several years.

Other cohort studies were performed by comparing regions where screening is frequent (heavy screening pressure) with regions where screening is less frequent. The Seattle study [54] cited in point 3.8.1 concluded that there seems to be no relationship between screening pressure, number of treatments and cause-specific mortality over a period of 11 years. In fact, the same reductions in mortality from prostate cancer were observed between 1987 and 1997. However, this study involved only men over 65 years and it is possible that screening has a greater impact in younger men.

Recently, Concato et al. performed a case-control study on cause-specific mortality of prostate cancer and screening. A benefit of screening was not found in the primary analysis assessing PSA screening and all-cause mortality (adjusted odds ratio, 1.08; 95% confidence interval, 0.71-1.64; $P = .72$), nor in a secondary analysis of PSA and/or DRE screening and cause-specific mortality (adjusted odds ratio, 1.13; 95% confidence interval, 0.63-2.06; $P = .68$) (Concato 2006). However, confidence intervals are wide, as a consequence of the rather small sample size.

Epidemiological data

The cause-specific mortality of prostate cancer has been falling in the United States since 1991. The study of the epidemiological data does not permit to attribute this reduction to screening, because the differences between treatments, risk factors and registration methods for cause of deaths can introduce bias into analysis of the data [22]. Likewise in Canada, the fall in the death rate of prostate cancer seems to have occurred too soon after the start of routine use of PSA to be one of the consequences of the screening [55]. In addition, a reduction in deaths is observed in countries where little PSA testing is performed [56]

Other types of studies

In terms of opportunistic screening, the only studies identified that might be indicative are studies based on registers. They examine the relationship between the frequency of screening and the mortality of prostate cancer; they do not allow to conclude that screening leads to a lower mortality of prostate cancer (evidence level 4) [16].

Key message

- **No evidence was found that screening decreases disease specific mortality.**
- **Two large RCTs studying the effect of PSA test screening of prostate cancer (PLCO and ERSPC) are currently conducted.**

3.8. NEGATIVE EFFECTS OF THE WHOLE PROCESS

3.8.1. Consequences of PSA testing and biopsy

PSA testing may be followed by a biopsy. Biopsy is a disagreeable experience for 70% of men [57]. It interferes little with everyday activities (less than ten percent of patients) and is responsible for infectious or local complications (1%). Minimal haematuria (15%) and haemospermia are common, but are not considered as complications [16]. The screening process is associated with an increase in anxiety but the number of men who are affected and the significance of this increase are not known [22].

The number of biopsies is greater in regions that practice screening. An American study [54] compared the outcome of two cohorts of patients in Seattle (region with screening) and in Connecticut (region without screening). The prostate specific antigen testing rate in Seattle was 5.39 (95% confidence interval 4.76 to 6.11) times that of Connecticut, and the prostate biopsy rate was 2.20 (1.81 to 2.68) times that of Connecticut during 1987-90.

3.8.2. Overdiagnosis and overtreatment

Overdiagnosis is defined as the detection of prostate cancer through PSA testing that otherwise would not have been diagnosed within the patient's lifetime. Overdiagnosis in screening effectively changes a healthy person into a diseased one; it causes overestimation of sensitivity, specificity and predictive values of tests and increases the incidence of disease[58].

Overdiagnosis is reflected in the rise in incidence of prostate cancer, and documented in several studies. For example, a 66% excess incidence rate was observed in the screened subjects over a 9-year period in Florence[59]. In another study by Etzioni et al., the authors used data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) population-based cancer registry to estimate the potential extent of overdiagnosis associated with PSA screening[60]. The authors found that among men aged 60–84 years, 18%–39% of Caucasian men and 20%–44% of African-American men may be overdiagnosed

with PSA screening. Draisma found overdiagnosis in 27-56%[61]. But, another study calculated overdiagnosis to be as high as 84%[62].

3.8.3. Complications of curative treatments

Treatment-related mortality is very low (0.1 to 0.2 for surgery, <1% for radiotherapy). Erectile dysfunction, urinary incontinence and bowel dysfunction are well-known and relatively common negative effects of surgery or radiotherapy. It is difficult to obtain an exact estimation of these effects, because they are surgeon-dependent and the definition of negative effects varies between the studies. For example, as far as sexual problems are concerned, some studies are interested in erectile dysfunction whereas others address the question of sexual relations (Harris 2003) (see annexe to chapter 4.). Furthermore, the patient's age and his previous sexual function should be taken into account. The duration of follow-up is also important: some problems (incontinence) can disappear after a few months, whereas others become stable after a number of years (impotence after radiotherapy). The following comparative tables come from a recent Belgian study [63] and present data from the most recent multicentre studies.

Table 2 : Erectile dysfunction after radical prostatectomy

Author	Definition	Follow-up	Quality of the study [f]	Risk
Hu 2004	Recovery of sexual function <75%	>1 year	7.5/10	80%
Potosky 2004	Erection not permitting penetration	>1 year	10/10	79.3%
Potosky 2000	Erection not permitting penetration	>1 year	10/10	79.6%
	Erection not permitting penetration (taking into account previous sexual function)	>1 year	10/10	76%

Table 3 : Erectile dysfunction after external radiotherapy

Author	Definition	Follow-up	Quality of the study	Risk
Hamilton 2001	Erection not permitting penetration	24 months	10/10	60.8%
	No erection	24 months	10/10	39.6%
Potosky 2000	Erection not permitting penetration	>1 year	10/10	61%
	Erection not permitting penetration (taking into account previous sexual function)	>1 year	10/10	45%
Potosky2004	Erection not permitting penetration	>1 year	10/10	63.5%

Table 4 : Bowel dysfunction after radical prostatectomy

Author	Definition	Follow-up	Quality of the study	Risk
Potosky 2000	Diarrhoea	>1 year	10/10	20.9%
	Cramps	>1 year	10/10	9.2%
Potosky	Diarrhoea	>1 year	10/10	23.9%

[f] Score from author : 1 point /item (see appendix to chapter 3)

2004	Cramps	>1 year	10/10	11.5%

Table 5 : Bowel dysfunction after external radiotherapy

Author	Definition	Follow-up	Quality of the study	Risk
Hamilton 2001	Cramps	24 months	10/10	14%
	False urge	24 months	10/10	34.4%
Potosky 2000	Diarrhoea	>1 year	10/10	37.2%
	Cramps	>1 year	10/10	13.6%
Potosky2004	Diarrhoea	>1 year	10/10	26.7
	Cramps	>1 year	10/10	9.4%
Talcott 2003	Diarrhoea (occasional)	< 1 year	7.5/10	43%
	Rectal blood loss	>1 year	10/10	25%
Little 2003	Weekly blood loss	36 months	10/10	8%

An original study carried out in Belgium by Van Poppel [64]reveals the variation caused by volume of surgery in the incidence of incontinence problems after radical prostatectomy (table 6).

Table 6 : Incidence of incontinence at 3 months after radical prostatectomy

Volume of surgery	Incontinence: none	Incontinence: drops	Incontinence: >1 pad
	[content text]	[contents figures centred]	
Low	7.6%	82.4%	10%
Medium	2.9%	76.0%	21.1%
High	2.0%	75.8%	22.2%

3.8.4. Repercussions on the quality of life

In the face of the wide variability of the data on negative effects, it is useful to consider their impact on the patients' quality of life. Litwin et al. [65] used generic questionnaires (type SF-36 Mental Health and Vitality) and concluded that in spite of negative effects, the quality of life in men treated for prostate cancer differed little at 5 years from that in age-matched controls. A recent thesis (Korfage) written in the margin of the Dutch arm of the ERSPC explains the discordance between the favourable results obtained by means of generic questionnaires (type SF-36 Mental Health and Vitality) and the unfavourable results from questionnaires focused on sexual, urinary and digestive problems. The author explains this difference by the inability of generic questionnaires to reveal specific problems and also by the fact that patients accept the negative effects of treatment as being the price to pay for staying alive. In this context, Madalinska [66] performed a prospective study using a specific questionnaire (Dutch version of the UCLA PCI). Patients who underwent radical prostatectomy complained of urinary incontinence (39-49%) and erectile dysfunction (80-91%). Patients undergoind radiotherapy were more affected by digestive type problems (30-35%). After radical prostatectomy, 64% of those fewer than 65 years said they were very dissatisfied with the change in their sexual life. Another study [67] evaluated the quality of life of patients who had undergone radical prostatectomy, external radiotherapy or brachytherapy compared with control groups of the same age.

The questionnaires evaluated specifically the consequences of treatments (urinary, bowel or sexual dysfunctions) and revealed significantly worse scores in the patients treated. There is no evidence to support the superiority of brachytherapy compared with external radiotherapy as far as quality of life is concerned [68]

Key messages

- **After radical prostatectomy, the risk of moderate to severe incontinence varies from 10 to 20% and the risk of impotence from 76 to 80% (recent multicentre studies).**
- **After radiotherapy, patients are affected initially by bowel dysfunctions (30-35%). The risk of impotence in the long term is between 45 and 63%.**
- **In the studies on quality of life, 64% of the patients under the age of 65 reported to be very dissatisfied with the change in their sexual life after being treated with radical prostatectomy.**

4. COST-EFFECTIVENESS

4.1. INTRODUCTION

Before starting an economic evaluation, we can question whether it is possible to provide carefully thought-out advice. Not only resources devoted to health care should be invested wisely but also resources devoted to performing economic evaluations. There is currently no sufficient evidence that patients will benefit from screening programs [69] and it is still not known whether introducing treatment in the early stage of prostate cancer improves survival[70]. Since the clinical benefit of a prostate screening program is questioned, the evidence for cost-effectiveness of such programs can only be weak or unreliable.

4.2. AVAILABLE ECONOMIC EVALUATIONS

Table 1 and 2 present costs for prostate screening, respectively with and without including costs of subsequent treatment. Simply calculating prostate cancer screening costs is insufficient to inform decision makers on whether or not this is acceptable from an economic point of view. Such decisions require cost-effectiveness analyses. No data concerning life years gained through screening for prostate cancer are available. Several authors ([71]; [72]; [69]) have therefore chosen to calculate intermediate cost-effectiveness ratios. The costs of cancer screening programs were expressed in terms of cost per cancer detected or cost per curable cancer detected.

Table 7: Cost of prostate cancer screening programs in which costs of subsequent treatment are included

	Cost/ participant	Cost/cancer detected	cost/early (small) cancer detected	Cost/cancer treated for cure
Abramson: USA (1992, US$)				
DRE[g] + TRUS[h]	$520	$16,300		
Holmberg: Sweden (1996, US $): 12 Year follow-up				
DRE + PSA (4 rounds)		$18,285		$49,075
incremental cost with screening compared with non-screening		$20,951	$22,144	$33,017
Sennfält : Sweden (1999, US $): 15 Year follow-up				
DRE + PSA (4 rounds)				
incremental cost with screening compared with non-screening			$22,144	$47,206

[g] DRE : digital rectal examination
[h] TRUS : trans rectal ultrasound

Table 8: Cost of prostate cancer screening, where costs included are those associated with screening and biopsy, but not subsequent cancer treatment

	Cost/ participant	Cost/cancer detected	cost/early (small) cancer detected	Cost/cancer treated for cure	Marginal cost/cancer treated for cure
Abramson: USA (1992,US$)					
DRE + TRUS	$231	$7240			
Chadwick: UK (1991+, £)					
PSA + TRUS if PSA > 4 ng/ml	£25	£1654			
Gustafsson: Sweden (1990, US $)					
St 1: DRE	$74*	$3100*	$12,420*	$4970*	$1100 (St 4→St 1)
St 2: TRUS	$98*	$2950*	$9750*	$4880*	$7450 (St 5→St 2)
St 3: DRE, TRUS, PSA + re-examination > 7 ng/ml	$161*	$4470*	$13,410*	$7000*	$22,400 (St 6→St 3)
St 4: PSA + DRE if PSA > 4 ng/ml	$71*	$3560*	$17,800*	$5930*	Baseline
St 5: PSA + TRUS if PSA > 4 ng/ml	$83*	$3180*	$13,770*	$4590*	$2700 (St 1→St 5)
St 6: DRE, PSA + TRUS if PSA > 4 ng/ml	$116*	$3630*	$12,900*	$5530*	$18,600 (St 2→St 6)
Holmberg: Sweden (1996, US$)					
DRE + PSA : 4 rounds	$36	$2466		$6603	
(+ fine-needle aspiration biopsy if suspicion of prostate cancer because of positive DRE and or PSA >4µg/l)	$147				
Benoit RM: (1992, US $)					
PSA (+DRE)					
Multicentre study : age-groups 50-59	$86	$2953			
Multicentre study : age-groups 60-69	$128	$2137			
Multicentre study : age-groups 50-69	$109	$2372			
single center study : age-groups 50-70	$55	$2205			
Kantrowitz: (1995+, US $)					
DRE+PSA + TRUS/biopsie if DRE/PSA abnormal		$6011			
Littrup PJ: (1997+, US $)		$2905			
DRE+PSA					
* Includes estimates of indirect costs					

The usefulness of these studies for decision makers is very limited. All studies do not answer the crucial question whether screening is cost-effective relative to other health care interventions. A full economic evaluation should compare the alternative courses, i.e. with or without prostate screening, in terms of both their costs and consequences. However, evidence from large randomized controlled trials is lacking. A possible solution to provide a full economic evaluation would be to link the intermediate outcomes with final outcomes such as life-years gained. However, doing so is not straightforward. When researchers want to undertake a cost-effectiveness analysis using effectiveness data relating to an intermediate endpoint, the economic analyst should make a case for this link.[73] An argument in favor of this approach would be that patients with clinically localized cancer of a lower grade are considered to be the best candidates for curative treatment. However, this link between the intermediate and final outcome has been questioned before. If data show that patients with prostate cancer in the screening group would live longer than those with prostate cancer in a control group, one would have to be careful in interpreting these results. Men in a screening program receive their diagnosis at an earlier stage than those in the control group. Those in the control group already lived a while with the disease before it was diagnosed. Consequently, the difference in life expectancy after diagnosis can probably be mainly explained by lead-time bias.[61] Without well funded arguments for linking the intermediate outcomes to final outcomes, the cost-effectiveness analysis of PSA screening are primarily based on assumptions and are highly speculative.

Furthermore, these studies should also take into account the potential harms of screening. A rate of over-detection has been calculated in the European Randomized Study of Screening for Prostate Cancer, which would be around 27-56%.[61] Another study even calculated this rate to be 84%.[62] These cases do not require treatment but, because they are detected, they may consequently receive unnecessary and potentially harmful treatment. A complete economic evaluation should also take into account the resulting costs and life-years lost.

Since no cost-effectiveness studies can prove value for money, i.e. the program's acceptability, there is no added value in calculating budget impact, i.e. the program's affordability. If one would do so for Belgium, the large scale of the program would very probably result in a high extra burden on budgets which cannot be justified by better health outcomes. The little evidence that has so far been collected in Sweden and the USA from uncontrolled studies suggests that a screening programme for prostate cancer would be prohibitively expensive.[23]

4.3. CONCLUSION

Decision makers could question whether it is worth to start up a prostate screening program to be able to detect cases of prostate cancer in an early stage of the disease and treat it appropriately. From an economic point of view, several factors are not in favor of such a screening program. First of all, and most importantly, no conclusive direct evidence has been provided yet to show that screening reduces morbidity or mortality while setting up a screening program would require the use of scarce health care resources. Secondly, due to over-detection, extra costs would be incurred and life years could even be lost. Combining these two arguments would even entail that such a program would do more harm than good.

Screening programs for the early detection of prostate cancer entail higher costs, and are also controversial because of uncertainty concerning the advantage of screening and the effectiveness of therapy. As mentioned before by Holmberg et al,[72] as long as knowledge is lacking about the long-term effects on quality of life and mortality, general screening can not be recommended, neither form a clinical point of view, nor from an economic point of view.

Key message

- No conclusive evidence has been provided yet to show that screening reduces morbidity or mortality
- As long as knowledge is lacking about the long-term effects on quality of life and mortality, general screening can not be recommended from an economic point of view.

5. ORGANISATIONAL ISSUES

The section on organisational issues deals with the international and national use of the PSA test for screening of prostate cancer. The use of the PSA test in screening purposes is described for a number of countries providing public documents on the use of the PSA test. A more detailed description of the use of the PSA test is presented for Belgium.

5.1. INTERNATIONAL

5.1.1. World Health Organisation (WHO)

The WHO discourages nation wide screening for prostate cancer unless results of the ongoing trials (see chapter on clinical effectiveness) would support mass screening [74]. The WHO also advises to control opportunistic screening to a certain extent by informing clinicians on the uncertainties of the tests and by informing the target population on the consequences of screening for prostate cancer.

5.1.2. Canada

Both governmental and non-governmental organisations discourage the routine use of the PSA test for the detection of prostate cancer (see Appendix to chapter 5). Some organisations advise against any use of the PSA test for screening purposes [75]. Others are more restrained in their advice and propose careful consideration by the patient of advantages and disadvantages in consultation with a clinician (e.g. [76]).

Currently, the PSA test is not reimbursed by the governmental health insurances in the provinces of Alberta [77] and Ontario [78]. Our search on Web for reimbursement regulations in the other provinces has not returned any publicly available documents. Reimbursement in the other provinces seems unlikely, considering the advice of the national Centre for Chronic Disease Prevention and Control against the use of the PSA test for screening,

We did not find nation wide data on the evolution of the use of the PSA test in Canada in the scientific literature. However, studies have been conducted on a regional level. For example, in Ontario, physicians were asked to complete a questionnaire on the use of the PSA test in screening for prostate cancer [79]. The results showed an increase in the use of the PSA test in 2002 compared to 1995.

5.1.3. New Zealand

Governmental and non-governmental organisations discourage the use of the PSA test in screening of prostate cancer. The PSA test is not reimbursed by governmental health insurance [80].

5.1.4. United States of America (USA)

The advices of different organisations in the USA differ widely (see Appendix to chapter 5) Organisations discourage the use of the PSA test in screening (e.g. [81]). Others postpone any recommendation anticipating the availability of further evidence. Yet other organisations encourage the use of the PSA test for screening purposes in men over 50[82].

Men over 50 entitled to Medicare or Veterans Affairs are reimbursed one PSA test yearly [83, 84].

Nation wide data on the use of the PSA test in screening of prostate cancer were not found in the scientific literature. However, studies relying on a more limited sample are available. For example, the results of one study using the New Jersey Veterans Affairs data showed a steady increase of the use of the PSA test between 1992 and 1998 [85]. The results of a larger study using a sample from Medicare showed a steady increase in use of the PSA test between 1998 and 1994

[60]. The results of another study in which 176 physicians completed a questionnaire, showed an increase of 8% between 1993 and 1998 [86].

5.1.5. United Kingdom (UK)

The National Health Service (NHS) discourages the use of the PSA test in prostate cancer screening. A PSA test should only be performed on asymptomatic men after careful consultation with a physician on the advantages and disadvantages of PSA testing (see Appendix to chapter 5).

5.1.6. France

ANAES discourages routine use of the PSA test for screening purposes [16]. Individual screening is considered appropriate in particular cases (e.g. familial history of prostate cancer). Nonetheless, ANAES advises the patient to consult a physician on the advantages and disadvantages of the PSA test prior to testing.

The PSA test is reimbursed by the governmental health insurance.

Nation wide data on the use of the PSA test are not available yet, but a recent study used data from the Région Centre [87]. The study considered the number of PSA tests prescribed in an ambulatory setting stratified by age and prescriber in 2000. In the four age categories between 65 years old and 84 years old, a PSA test was reimbursed for at least one out of four patients included in the study. Approximately 87% of those tests were prescribed by general practitioners. Other prescribers included urologists, cardiologists, and gastroenterologists.

5.1.7. Conclusions

Most countries discussed in this chapter are very cautious about the use of the PSA test in screening for prostate cancer. With the exception of some USA organisations, no organisation advises a general screening for prostate cancer in men over 50. Governmental health insurances do not reimburse the PSA test for screening, with the exception of the USA and France. Most countries anticipate further evidence in favour of or against screening of prostate cancer prior to revision of current recommendations. Few nation wide data on the use of PSA tests are available.

5.2. BELGIUM

5.2.1. Campaigns, directives and reimbursment

Currently, no federal or regional agency organizes screening campaigns for prostate cancer, with the exception of the province of Liège. In the province of Liège, screening for prostate cancer is done by means of a mobile lab visiting local communities on a regular base (“prostamobile”). In 2004 and 2005, a number of non-governmental organisations in cooperation with a pharmaceutical company organised an information campaign on prostate cancer.

Patient information and guidelines on screening for prostate cancer are available from scientific organisations of general practitioners. The ‘Société Scientifique de Médecine Générale’ (“scientific association of general practioners”) discourages the general use of the PSA test for screening purposes (SSMG [88]). The ‘Wetenschappelijke Vereniging van Vlaamse Huisartsen’ (“scientific association of flemish general practitioners”) proposes general practitioners to disseminate information on advantages and disadvantages of early detection of prostate cancer to men over 50 (WVVH [89]). A similar recommendation is made by the Stichting tegen Kanker (“foundation against cancer”) [90].

The PSA test (nomenclature 443016, 433020, 542010 en 542021) is reimbursed by the ‘Rijksinstituut voor ziekte-en invaliditeitsverzekering’ (RIZIV; “state institute for illness and disability insurance”) under certain conditions:

"Rule of diagnosis 5: the provisions 433016 - 433020 and 542010 – 542021 can be debited to the health insurance only for diagnostic purposes in men over 50, with a maximum of twice a year; or for therapeutic follow-up independent of the age of the patient "

["Diagnoseregel 5: De verstrekkingen 433016 - 433020 en 542010 - 542021 mogen slechts met een diagnostisch doel worden aangerekend aan de Z.I.V. bij mannen die tenminste 50 jaar oud zijn, met een maximum van 2 keer per jaar of voor de therapeutische follow-up ongeacht de leeftijd van de patiënt. "K.B. 9.12.1994" (in werking 1.3.1995) + "K.B. 29.11.1996" (in werking 1.4.1997) + "K.B. 16.7.2001" (in werking 1.12.2001)"]

Use of the PSA test in screening is not mentioned explicitly, nor is it prohibited in the rule of diagnosis.

5.2.2. Use of the PSA test, biopsy, and radical prostatectomy

PSA tests were first reimbursed in 1995 and their use has increased ever since (see figure 9). In 2004, three times the number of PSA tests was reimbursed by the health insurance in 1995, with an average annual increase of 17.7%.

A similar increase was found for radical prostatectomy. In 2004, twice the number of radical prostatectomies in 1995 was performed, with an average annual increase of 7.5%.

Likewise, the number of biopsies increased but to a lesser extent. In 2004, about one and a half times the number of biopsies in 1995 was carried out, with an average annual increase of 3%.

The number of visits to urologists increased with about 15% between 1995 and 2003, with an average annual increase of 2%.

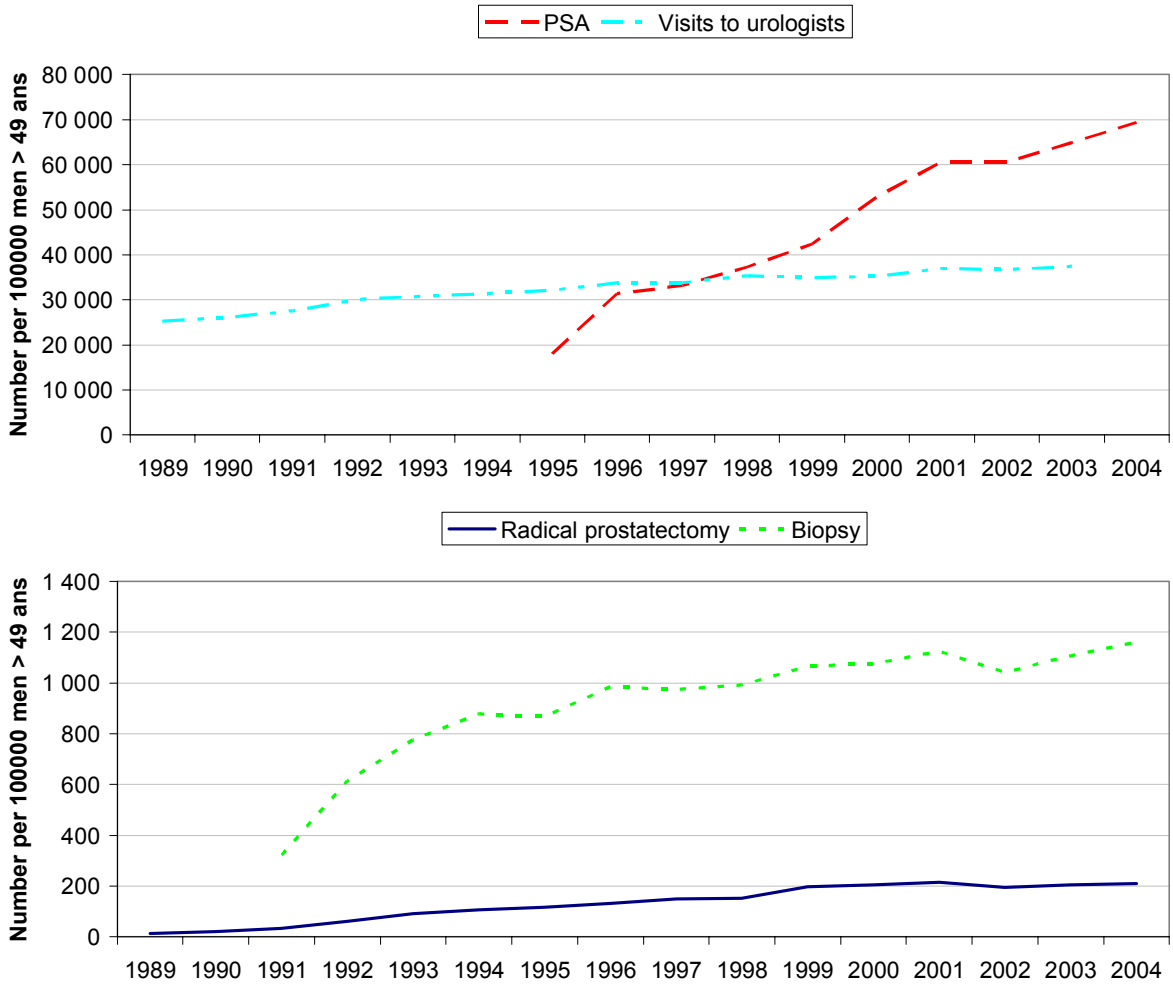


Figure 9 Number of PSA tests and visits to urologists (upper panel), and number of radical prostatectomies and biopsies (lower panel) per 100 000 men over 50 in Belgium between 1989 and 2004 (Source : INAMI, 2005).

As expected, total cost of reimbursement of the PSA test increased in accordance with the number of tests (see figure 10). The drop in cost in 2000 is due to adjustements to the amount reimbursed. Likewise, total cost of reimbursement of radical prostatectomy, biopsy, and visits to urologists increased with their numbers.

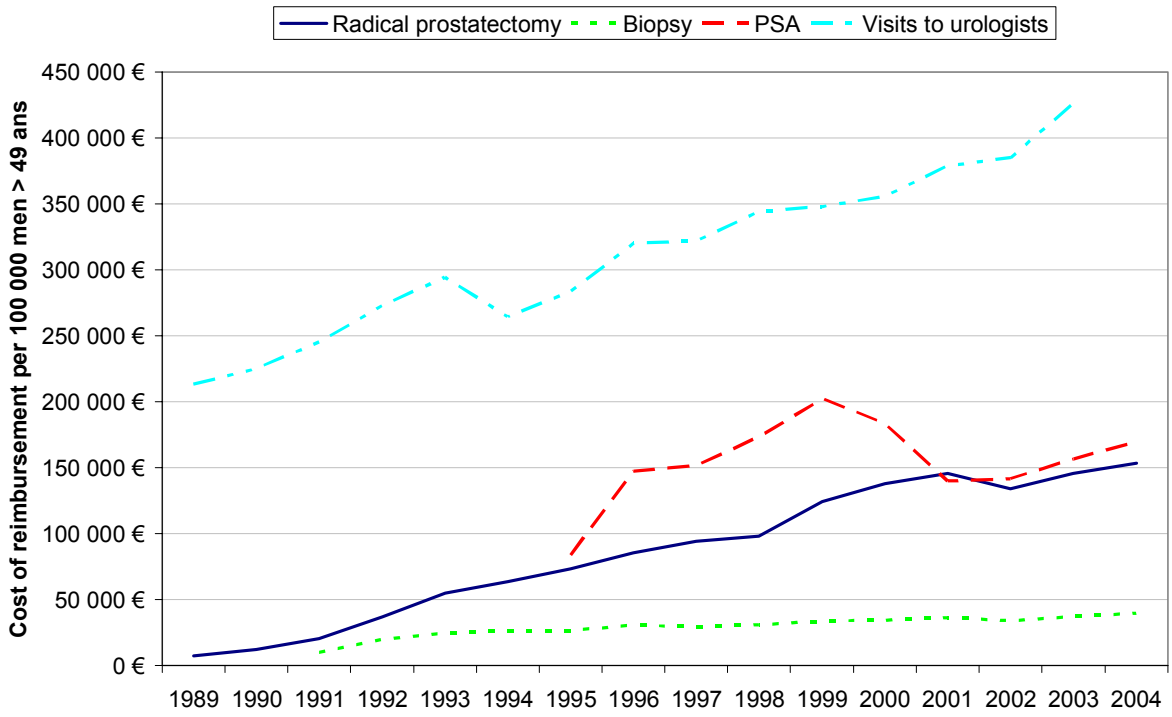


Figure 10 Cost of reimbursement of PSA test, radical prostatectomy, biopsy, and visits to urologists per 100 000 men over 50 in Belgium between 1989 and 2004 (Source: RIZIV, 2005).

5.2.3. The use of the PSA test and its relation to consumption of health care

To study the use of the PSA test in Belgium and its possible consequences in terms of diagnosis and treatment of prostate cancer, we analyzed consumption of health care data.

Method

The number of PSA tests and associated cost of reimbursement in 2003 (01-01-2003 to 28-02-2004) were retrieved from two health insurers: the 'Nationaal Verbond van Socialistische Mutualiteiten' ("national union of socialist health services") en de Landsbond der Christelijke Mutualiteiten ("national union of christian health services"). Data per five year of age interval were obtained for all affiliated men over 50. The nomenclature in use in Belgium did not allow distinguishing of PSA tests for screening, PSA tests for diagnosis, or PSA tests for treatment follow-up (see appendix to chapter 5). The proportion of each test in the total number of PSA tests was estimated using incidence and prevalence of prostate cancer in Belgium (see chapter 1). For the treatment follow-up estimate, we used an estimate of prevalence of 36 500 to 42 200 cases. For the diagnosis estimate, we used a recent incidence of prostate cancer in Belgium: approximately 5 000 new cases in 1998 [4]. Furthermore, we used following assumptions based on a panel discussion with several Belgian experts (see colofon): a) one PSA test is needed for the diagnosis of prostate cancer b) follow-up of treatment requires three test annually.

Number of biopsies and associated cost of reimbursement in 2003 (01-01-2003 to 31-12-2003) in men over 50 were retrieved from the same sources as cited above. Of all men in which a biopsy was performed, we retrieved number and associated cost of reimbursement up to six months after biopsy from 01-01-2003 to 30-06-2004 of four possible treatments: radical prostatectomy, external radiation therapy, brachytherapy, and hormonal therapy. No data were available on watchful waiting.

The data of both cooperating health insurers represent 71.6% of all health insurers' data in Belgium.

Eight 'Centra voor Radiotherapie' ("centres for radiation therapy") completed a questionnaire on the use of external radiation therapy and brachytherapy. They participated voluntarily and were

not a representative sample. We retrieved the number of patients treated for prostate cancer for each treatment in 2003.

Results

Over half of the men aged 65 years or older received at least one PSA test in 2003, even those over 75 (see figure 11).

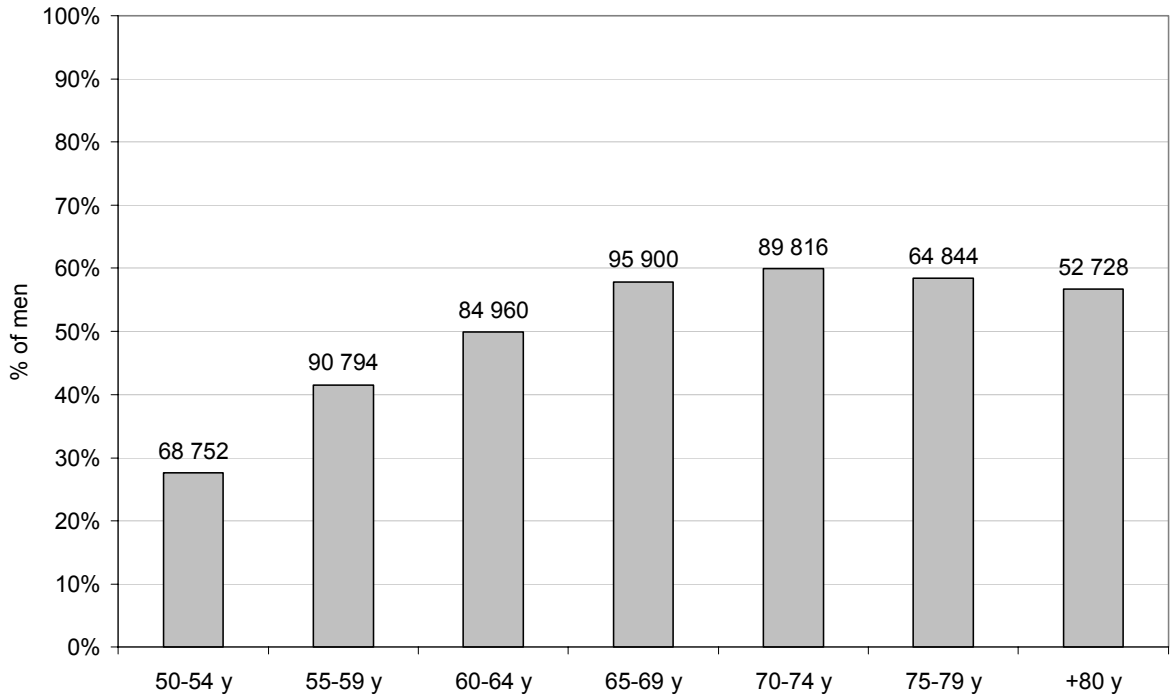


Figure 11 Percentage of men having at least one PSA test in 2003 in function of age (absolute numbers are indicated on top of the bars) (source: health insurers).

We estimated the number of PSA tests for screening, for diagnosis, and for treatment follow-up. In 2003, 1 072 499 PSA test were conducted (RIZIV). We estimated that approximately 5 000 (0.5%) PSA tests were performed for diagnosis of prostate cancer, and 109 500 (10%) to 126 600 (12%) for treatment follow-up in 2003. Subtracting these tests from the total number of tests in 2003 leaves 941 000 (87.5%) to 958 000 (89.5%) tests of which a large part were probably conducted for screening purposes.

Of the men obtaining a PSA test result, only a small percentage actually received a biopsy within six months of the test (see figure 12).

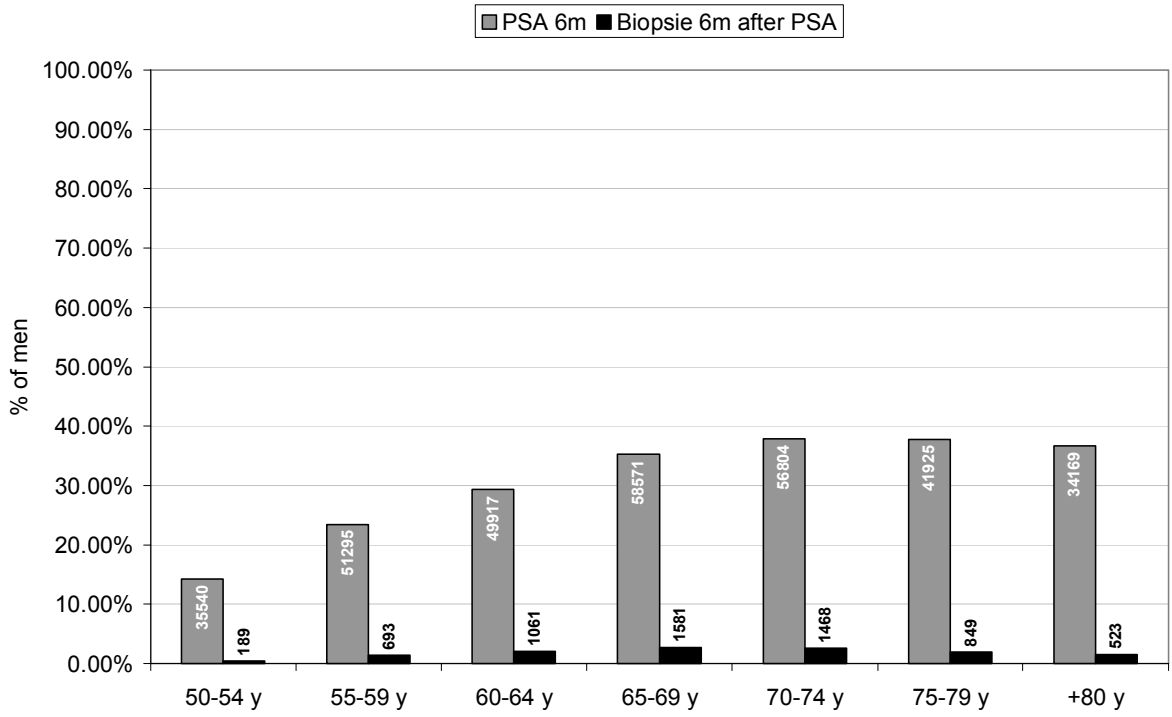


Figure 12 Percentage of men over 50 receiving a PSA test in the first half of 2003 (PSA 6m). Percentage of men receiving a biopsy within six months after a PSA test (Biopsy 6m after PSA). (absolute numbers are indicated at the top of the bars) (source: health insurers).

Men over 50 with at least one PSA test received on average 1.4 PSA tests (Q1=1, Q3=2) in 2003. Stratified by age, the average number of PSA tests per man increases by age: 1.2 tests between 50 and 54 years old (Q1=1, Q3=1) to 1.5 tests for men over 80 (Q1=1, Q3=2).

Eighty percent of PSA tests in 2003 were prescribed by general practitioners (see figure 13). The remaining tests were prescribed by urologists and internists among others.

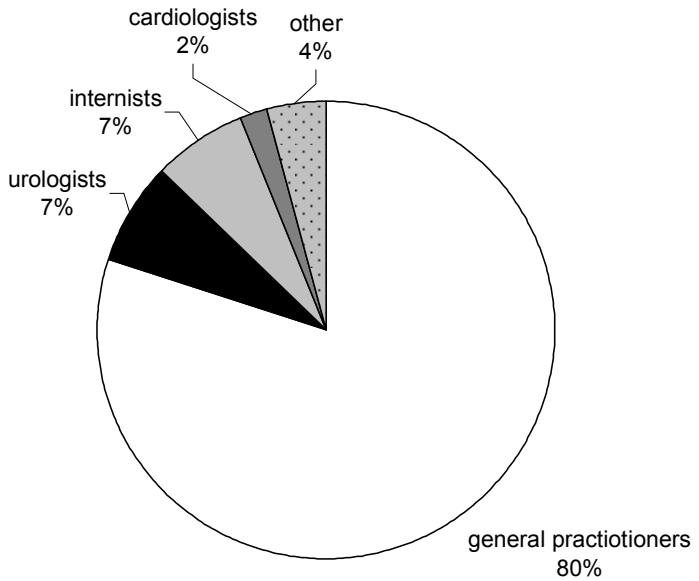


Figure 13 Percentage of PSA tests in function of prescriber in 2003 (source: health insurers).

In 2003, 25% to 30% of men between 50 and 75 years old were treated within six months after a biopsy. Within this group, radical prostatectomy was the preferred treatment (see figure 14). In contrast, men over 75 were mostly treated by non-surgical procedures.

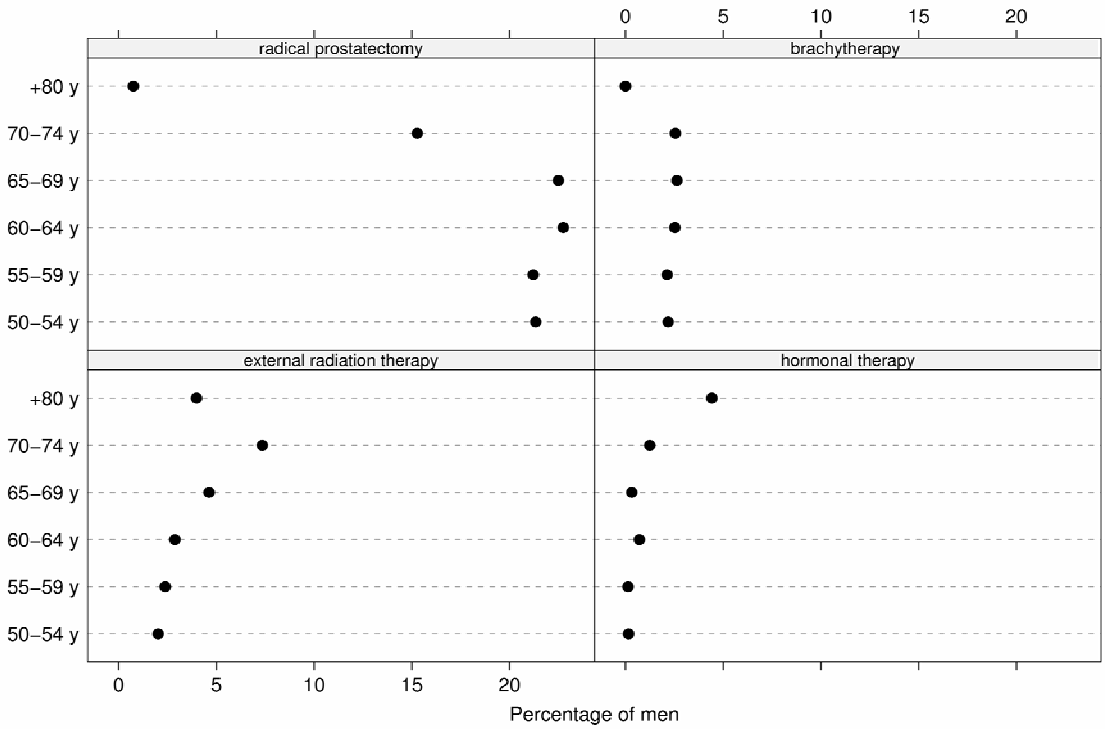


Figure 14 Percentage of men treated within six months after a biopsy in function of treatment type and age (absolute numbers are indicated on top of the bars) (source: health insurers).

The use of external radiation therapy or brachytherapy in treating prostate cancer varies widely from centre to centre, as illustrated by the data of eight 'Centra voor Radiotherapie' (see figure 15).

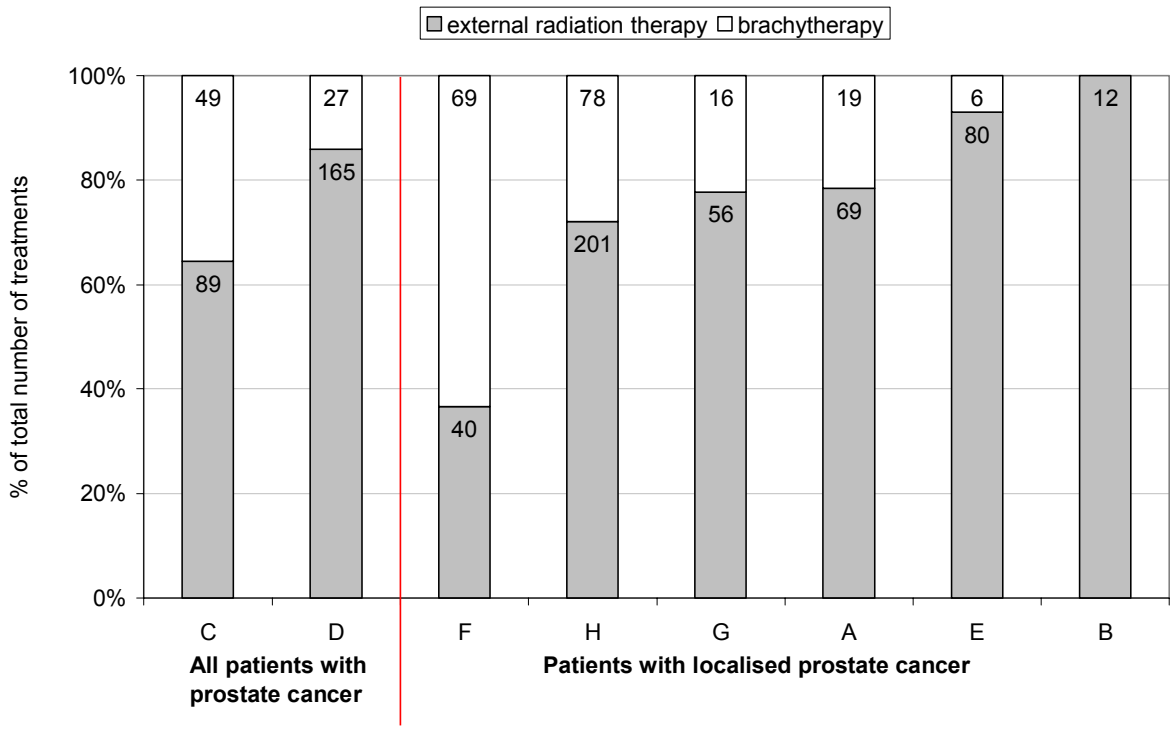


Figure 15 Percentage of total number of treatments for external radiation therapy and brachytherapy in eight 'Centra voor Radiotherapie' (absolute numbers are indicated on top of the bars). Centre able to distinguish patients with a localised prostate cancer from other prostate cancer patients, are presented separately (source: 'Centra voor Radiotherapie).

5.2.4. Discussion

The results showed an increase in the number of PSA tests, biopsies, and radical prostatectomies since 1995, albeit each with a different magnitude. While the number of PSA tests in 2004 is increased fourfold since 1995, the number of biopsies is increased one and a half times, and the number of radical prostatectomies has doubled. The number of visits to urologists also showed a more modest increase. The cost of reimbursement for PSA tests, biopsies, and radical prostatectomies corresponds to the increase in numbers.

The PSA test

The increase of the PSA test in screening for prostate cancer is found in other countries as well (see first section of this chapter: "International"). However, in contrast to the nation wide data used in the present study, most of these studies use relatively small samples from various databases or use questionnaire data obtained from physicians. Few of these studies provide an explanation for the increase of use of the PSA test in spite of the recommendations to the contrary of many evidence based guidelines. In a limited study (n=65), physicians from the USA and France were confronted with this apparent contradiction [91]. The participants responded that the recommendations of several guidelines are often contradictory themselves. Also, they even interpreted the guidelines as positive towards screening. Moreover, the fear to miss a prostate cancer prompted an increase in use of the PSA test in the participating physicians.

We asked a number of Belgian experts (among which urologists, general practitioners, and radiotherapists; see colophon) their opinion on the increase of the use of PSA tests. One hypothesis is the more frequent use of the PSA test in preventive check-ups in men over 50. In research, this hypothesis has been suggested as well. In Ottowa (Canada), the results of an enquiry among 285 general practitioners showed that more patients were screened with the PSA test during a routine medical examination in 2002 compared to 1995 [79].

Our results from the two health insurers showed that in 2003 about 47% of the men over 50 received at least one PSA test. This is a larger proportion of coverage than reported in a study of Lousbergh et al. [13]. They reported coverage of 23% (range 0% to 31%) of men between 1996 and 1998 in the province of Limburg.

One of the more striking results from the health insurers data showed that even at an advanced age (over 75), half of the men received at least one PSA test in 2003. Most guidelines set an upper age limit for prostate cancer screening, but this limit seems to be unfamiliar in the Belgian medical practice.

In the present study, the Belgian nomenclature does not differentiate between PSA tests used in screening and PSA tests used for diagnosis of symptomatic men or treatment follow-up of prostate cancer. However, we tried to estimate the proportion of PSA tests used in screening. Given some assumptions, we found that approximately 10% of the PSA tests in 2003 were used for either diagnosis or treatment follow-up. Because we have no data on hypertrophy of the prostate, we could not estimate the number of symptomatic men receiving a PSA test who were eventually diagnosed with hypertrophy. Hence, the percentage of PSA tests for diagnosis of symptomatic men is probably underestimated.

Biopsy

Proportionally, PSA tests induce few biopsies in Belgium. Possibly, only few of the conducted PSA tests have an abnormal result. Our data do not allow verification of this hypothesis because we do not have the clinical results of the PSA tests. However, let us assume that, like in France, approximately 10% of the PSA tests in men over 50 have a value larger than 4 ng/ml [16] (see [92] for a similar estimate). In the ERSPC study, each PSA test 4 ng/ml is followed by a biopsy. In Belgium, given our estimate for the number of PSA tests in screening, only one out of five PSA tests for screening purposes in 2003 is followed by a biopsy. Another explanation for the relatively low ratio of biopsies and PSA tests was provided by a number of Belgian experts (see colophon). Biopsies in Belgium are rarely conducted based on only one PSA test result, but usually require a combination of examinations (repeated PSA tests, DRE). The finding that in 2003, each tested man received on average 1.5 PSA tests, supports this hypothesis.

Treatment of prostate cancer

A quarter of all patients receiving a biopsy in 2003 were treated for prostate cancer within six months with either radical prostatectomy, or external radiation therapy, or brachytherapy, or hormonal therapy. Prostatectomy was used most frequently, except at an advanced age (over 75). Both external radiation therapy and brachytherapy are used to varying degrees, as shown by the results of our limited sample of 'Centra voor Radiotherapie'. A more thorough evaluation of the treatment for prostate cancer, however, is beyond the scope of this study.

Key messages

- **In Belgium, with the exception of a non-governmental information campaign and some local initiatives, no mass screening for prostate cancer exists. However, opportunistic screening is conducted on a large scale and is increasing.**
- **The number of the PSA tests has increased sharply since 1995. In 2004, more than a million PSA tests were reimbursed.**
- **In 2003, more than half of the men over 50 received at least one PSA test, even when older than 75.**
- **Eighty percent of the PSA tests in 2003 were prescribed by general practitioners. Only a limited number of these men received a biopsy and even less received treatment for prostate cancer.**

6. ETHICAL AND LEGAL CONSIDERATIONS IN PSA-SCREENING

Introduction

As has been argued in previous chapters, screening cannot be viewed in isolation from the overall management of the disease including diagnosis, treatment and possible rehabilitation issues. The issue and practice of screening for specific diseases raises several ethical considerations about the detection in presymptomatic stages *as well as* consecutive treatment.

The ethical approach is to a large degree inspired by what is generally defined as the "principles approach"[93]. Some basic moral principles (normative generalizations) are used to evaluate human actions: respect for autonomy, beneficence and nonmaleficence, and justice. This "instrumental" approach is often used in bioethical reasoning, although some criticisms are formulated.

In the particular case of PSA-screening the difference between the "public health issue" and "medical decision making" in clinical practice has to be considered carefully. Both issues require "ethical" reflection.

- medical decision making deals with the issue of doing a medical intervention (prevention, treatment, diagnosis, testing) on an individual, within a physician-patient relationship. The outcome of a reflection on an individual does not necessarily, from an ethical point of view, be congruent with a public health view.
- In a public health perspective, ethical guiding principles are used when deciding about an intervention on a (target) population, and an appropriate allocation of (public) resources.

This project is mainly focussing on the public health perspective, addressing the fairness and social justice of use of public resources. "Harm" could also be the diversion of public means from health care issues needing more priorities.

6.1. PRECAUTION, RISK AND HEALTH CARE

Although the principle of precaution is rather "new" for the public health domain, the issue is since long a leading principle to balance benefits and harms of any emerging technology in different societal domains. The precautionary principle is a guiding tool to assess whether an intervention or technology holds an acceptable level of risk and leads to an optimal use of public resources for the benefit of a population or a society. It provides some basic norms when taking decisions in situations of uncertainty [94].

The guiding principle is to prevent or refrain from contributing to irreversible harm to health and/or environment. Two dimensions of the precautionary principle should be put in balance: one must not only fear adverse effects that will follow from technological innovation but also the adverse effects that will follow from its absence. According to Kaiser the precautionary principle has the same status as other ethical principles as for example justice, equity, human dignity and solidarity. (quoted in [95]) The precautionary principle in health care practice implies the balancing the health care professionals' knowledge of the medical, social and psychological situation of the patient [95]. Based on these ethical principles screening recommendations are only justified if the benefits of the test (and the consecutive medical interventions) can reasonably be expected to outweigh the risks [96].

The principle of precaution fits easily in two important moral principles that are supposed to guide medical decision making (amongst others): "*primum non nocere*", or "above all do no harm" and the general acting principle of "*responsibility*".

- The first principle requires that any recommended procedure is reasonably expected to be good for the patient. This principle of nonmaleficence ("above all do not harm") has to be distinguished from the principle of beneficence, establishing the obligation to act for the benefit of others (promote good, prevent and remove harm). It is clear that these two principles are closely linked, be it that the principle of beneficence is often regarded as slightly less obligatory than the principle of not unnecessary harming

others [95] Beneficence requires taking action by helping, whereas nonmaleficence requires *intentionally refraining* from actions that cause harm. Obligations of nonmaleficence are not only obligations of not inflicting harms, but also include obligations of not imposing *risk* of harm. "*Due care is taking sufficient and appropriate care to avoid causing harm, as the circumstances demand of a reasonable and prudent person*" [93]

- The principle of responsibility is based on the idea that the more one encourages one (from an authority position) to engage in a given activity, the more responsible the person that encourages another person is for the outcome of that activity. Although we have moved away from paternalistic health care relationships, people and patients still assume that health care professionals would not recommend any procedure if they do not expect it to be good for the recipient.

Physicians have a professional obligation to do well to their patients and to weigh the benefits against possible harms and burdens. Prudence means that risk should be taken into account and should be minimized as much as possible *"One should take reasonable measures to prevent or mitigate threats that are plausible and serious"* [97]

Key messages

- **One of the basic principles of medical ethics is "*primum non nocere*".**
- **"Responsibility" is a fundamental ethical principle for people in an authority position, such as physicians. People assume that health care professionals would not recommend any procedure if they do not expect it to be good for the recipient.**

6.1.1. The precautionary principle and the PSA test

The precautionary principle urges to approach the debate on PSA testing mainly from the perspective of "reasonableness" of different options [97].

From a narrow medical-decision making point of view, a PSA test (identified as a single medical intervention, isolated from possible later interventions) can be reasonable as the intervention itself is relatively minor compared to the threat (taking a blood sample vs. the risk of not identifying cancer). It can be expected that on individual level, and regardless of the result of the screening, taking the test "in se" will be evaluated as positive by the patient. A negative result makes a patient grateful for reassurance and a positive result could make a patient grateful for early detection [98, 99], be it that it will also induce anxiety and emotional distress. The major problem however, rises when one is confronted with the results of the test. The available evidence clearly demonstrates that the test is unable to detect prostate cancer in a precise way. Moreover, an indication of cancerous cells has not been proven to save lives or improve quality of life. The consideration of harms and risks should not be limited to the test itself. It needs to take into account the potential benefits and harms of the medical activities following the results of the test. It is well documented that there are several potential risks relating to the *consequences* of having a PSA-test (possible harms of biopsy, side effects of treatments and psychological impact of the results of the test and of possible interventions).

When weighing the benefits and the risks in the consecutive stages of interventions, PSA screening does noet seem to offer benefits. Therefore PSA-screening should not be recommended, solely on the assumption that early detection is always in favour of the patient. The precautionary principle will automatically question the assumption that screening of asymptomatic men is better than waiting and detecting the disease in its symptomatic stage. This approach will avoid overdetection and overtreatment with all possible physical harm, psychological distress and public and individual costs involved (see appendix to chapter 6).

Key messages

- **The precautionary principle urges to approach the debate on PSA testing mainly from the perspective of "reasonableness" of different options**
- **The consideration of harms and risks should take into account the potential benefits and harms of the *whole trajectory* of medical interventions of the results of the PSA-test.**
- **Applying the precautionary principle urges not to recommend PSA-screening, solely on the assumption that early detection is always in favour of the patient.**

6.2. INFORMED DECISION MAKING

A particular ethical and legal issue to be discussed is informing and decision making (see appendix to chapter 6) about testing. In the particular situation where no definitive answers can be given to the effectiveness of prostate cancer screening, the issue of informed decision making is a difficult one. Although the majority of governmental and professional government organisations do not support routine population screening for asymptomatic men, most organisations do stress the importance of providing information to men and enabling them to discuss this information with the health professional. This recommendation is congruent with the general "cultural" attention paid to informing patients, based on guaranteeing the principle of autonomy. But, the controversy about the utility of opportunistic prostate cancer screening greatly affects the provision of information to men [100, 101].

6.2.1. Advantages and disadvantages of informed and shared decision making

A review group has focussed on making an inventory of potential advantages and disadvantages of informed and shared decision making.[102]

- Ethical considerations are one of the main drivers, and thus advantages, of informed decision making
- Increased patient involvement may lead to better decision-making, as the likelihood increases that decision reflects the patient's needs, preferences and values
- Increased patient participation might help to improve patient satisfaction and patient's adherence
- Although not al patients necessarily want to get involved in a decision making process, the vast majority wants more health information.
- Greater participation is useful for tailoring health care to the needs of the patients

However some problems have to be considered too,

- Communicating complex information to the public is difficult: information must be kept up to date, no excessive information can be offered, contradictory messages lead to problems, and unbiased information is necessary. The way information is presented influences the interpretation
- Admitting uncertainty is not comforting, neither for policymakers, clinicians or patients. Some individuals are unprepared to deal with uncertainty
- More involvement of patients in decision-making will take time, energy and resources that could be put in more effective and cost –effective interventions. Informed decisions making could also lead to an increase in demand of unproven, expensive or even harmful interventions.

- Shared decision-making is a very difficult process to conduct effectively, and requires very specific competences. Moreover finding a balance between patients' anxieties, wishes, needs and medical interventions is seldom easy.

Key message

- **Informing the patient and making health care choices is a far more complex issue than just offering technical information to the citizen or patient.**
- **Increased patient involvement may lead to better decision-making, as the likelihood increases that decisions reflect the patients needs, preferences and values**
- **Probabilistic thinking, including admitting uncertainty, is not comforting, neither for policymakers, clinicians or patients, and makes the process of informed decision difficult.**

6.3. CANCER "SCREENING" AND INFORMED DECISION MAKING

The English General Medical Council (http://www.gmc-uk.org/standards/CONSENT.htm) has identified ethical considerations about seeking patients' consent.

"You must ensure that anyone considering whether to consent to screening can make a properly informed decision. As far as possible, you should ensure that screening would not be contrary to the individual's interest. You must pay particular attention to ensuring that the information the person wants or ought to have is identified and provided. You should be careful to explain clearly:

- the purpose of the screening;
- the likelihood of positive/negative findings and possibility of false positive/negative results;
- the uncertainties and risks attached to the screening process;
- any significant medical, social or financial implications of screening for the particular condition or predisposition;
- Follow-up plans, including availability of counselling and support services."

But different research is demonstrating that these principles are not always applied, and that the way information is presented, even according to these principles, can have different "persuasive" effects [103, 100, 104]

Cognitive and emotional aspects do affect the decision making process [105, 106 107, 108] Cultural barriers and differences in literacy of patients also affect the shared decision making process.

A review of evidence on informed decision making interventions and decision aids, lead Rimer and colleagues [109]to identify seven lessons regarding informed decision making in cancer screening

- Informed decision making interventions increase short-term improvements in knowledge, beliefs, and accuracy of cancer risk perceptions.
- There is insufficient evidence to conclude whether informed decision making interventions result in decisions that are consistent with patients' preferences.
- The impact of informed decision making interventions on screening is modest. Informed decision making interventions generally have resulted in small decreases in prostate cancer testing and small increases in testing for breast and cervical cancers.
- Informed decision making interventions are needed, especially for those cancer screening tests for which the evidence is uncertain or is very sensitive to patients' preferences.

- In the short run, participation in informed decision making should be facilitated for those patients who want it. Greater numbers of individuals should be encouraged to participate more fully in their health care.
- Decision-making information can be provided to individuals outside clinical encounters. This not only may attenuate health disparities but may enhance the efficiency of patient-physician interactions.

6.3.1. Providing information on PSA-screening: a multifactorial issue

A specific literature review [101] focused on the main topics important for providing information to men about the PSA-test and its consequences. The review elucidated that providing people with information about a medical procedure is effective in several ways:

- it can improve knowledge,
- it helps to increase patient-participation in the decision-making process, and
- It allows patients to develop more realistic expectations about the benefits and harms of a procedure.

The literature review demonstrated for the specific topic of prostate cancer screening that information about PSA testing should be of the highest standards. However, many studies reviewed, did not incorporate clear outcome measures for evaluation of the informed decision making materials or the effectiveness of decision aids.

The review of psycho-social studies suggests that there is no dramatic increase in either distress or anxiety, but the instruments used in available studies evaluating the psychosocial impact may lack the sensitivity to detect changes in emotional state.

A particular challenging "communication" problem is to develop information about such complex issue, taking into account the different literacy levels and cultural backgrounds of the different patients. As it is known and proved in education and communication sciences, information always needs to be embedded in a particular support system that is helping the receiver of information to organise the information, and adapt the information to its particular background.

The potential role of decision aids

Especially in prostate cancer (screening) rather extensive research has been done on the use of decision aids for patients. Patient decision aids aim to facilitate informed, value based decisions about health [110]. Decision aids, such as folders (ANAES, NHS, WVVH,), videos, and other instruments seem to have an effect on screening behaviour, and appear to promote informed decision making [111, 112] However, decision aids are not always having the same effect: e. g. results of a research on internet information about screening suggest that online consumer health information does not adequately support decisions about screening [104] Greater use of written or electronic tools can help to clarify choices for patients, but decision aids cannot replace the human element in facilitating informed choice. The ideal solution would be to couple *information* with high-quality decision *counselling* to help patients understand the potential risks, benefits, and uncertainties of clinical options and to assist them in selecting the option that best accommodates their personal preferences. [113]

Emotions and characteristics of the patient

Informing men about PSA-testing is a difficult issue. [114] Taking a decision about testing is thus more than developing knowledge about the consequences of cancer screening. Despite increasing literature on the outcomes of counselling, it is still unclear how patients use the information within particular circumstances [115, 116].

Different elements seem influence the process of informed decision making [117] Thornton and Dixon Woods [118] have mentioned that risk-conscious patients demand a test, even when evidence is lacking and information about uncertainties is provided. Cognitive, socioeconomic, cultural and psychosocial differences affect the need for information, and the response to this information. Moreover, socio-demographic and disease specific factors affect the preference

about taking up an active role in decision making. Most patients are also unfamiliar with probabilistic thinking and the notion of risk and uncertainty. Seeking peace of mind is one of the main drivers for men to undergo screening [119] Informed decision making does not always reassure people [120] Underlying patient beliefs, as the result of personal stories from friends, family or media, can affect physician-patient communication about PSA-testing. Most men who underwent PSA-counseling cited underlying beliefs rather than the content of counselled information as the basis for their decision. Interestingly, the impact and endorsement of respected public figures (with prostate cancer) has for some men more impact than the information provided by the physician. Also the belief that "prevention is a vital goal" affected the choices of men[121].

Physician's perspectives

Research has demonstrated that the attitudes of physicians towards informed decision making on the one hand, and PSA-screening on the other, vary considerably. Specifically for PSA-testing informed decision making does not routinely occur [122, 123] also because of different beliefs and perspectives of the medical domains.

An American study analysing physicians' rating of the importance of key facts men ought to know about PSA, showed differences between urologists and non-urologists (family doctors and internists). Eight of the nine statements that urologists and non-urologists disagreed upon, concerned facts reflecting uncertainty: non-urologists were more likely to rate facts reflecting uncertainty as highly important for men to know. Non-urologists, female physicians and physicians under the age of 50 rated the fact "PSA screening is a controversial screening test" of significantly higher importance for men to know.[124]

In another study, four determinants have been identified to affect a physician's decision to order a cancer screening test in situations where recommendations are unclear or conflicting.[125]:

- The patients anxiety about having cancer;
- Patients' expectations to undergo screening
- The patients family history of cancer
- The quality of the patients-physicians relationship: in situations of a trust relationship between physician and patient, mutually agreeable and informed decisions can be reached

Moreover, physicians see the lack of time and problems of reimbursement as serious constraints to get involved in informed or shared decision making.[113] Providing support for informed choice is not straightforward because of challenges faced by clinicians, health systems, and consumers. Doctors are not particularly trained in discussing with patients about uncertainties and making choices. Some authors also suggest that physicians are not always capable of assessing the preferences of patients [126].

Key messages

- **Informed and shared decision making is far more complex than "just" providing information. Cognitive and emotional aspects affect the decision making process, as well as cultural barriers and differences in literacy.**
- **The attitudes of physicians towards informed decision making on the one hand, and PSA-screening on the other, vary considerably. Doctors are not particularly trained in discussing with patients about uncertainties and making choices**
- **Physicians consider the lack of time and problems of reimbursement as serious constraints to get involved in informed or shared decision making.**

6.4. INFORMING THE PATIENT IN THE BELGIAN PATIENTS RIGHTS ACT

6.4.1. Applicability of the Belgian Patients' rights act on PSA testing

The Belgian Patients rights[9] act states that a patient is the natural person[10] to whom health care is provided, regardless if this occurs at his own request. Health care is defined as services provided by a health care professional with a view of promoting, diagnosing, maintaining, curing or improving the health of the patient or supporting the patient during the process of dying. This definition implies that PSA testing and the possible following treatment are acts of health care and that asymptomatic men are regarded as patients when starting the process of PSA testing. Consequently the Patients' rights act is applicable.

6.4.2. Applicable regulations of the Patients' rights act

The right to be (not) informed

Article 7 of the Patients' rights act regulates the right to information about the health status (e.g. the diagnosis, the level of PSA). The right to know about the health status has to be distinguished from the right to informed consent. The right to information about the health status is not linked to a decision.

The patient has the right to be informed by the health care provider about all information concerning him/her that is required to understand his health status and the probable evolution. The information has to be communicated in a clear language. Information is given orally but the patient can request that the information will be confirmed in writing. Since some medical information can have major consequences on patients' life, it's likely that patients react so emotionally that they don't grasp all information. Written information gives patients the opportunity to clarify the situation. The law also states that the content of the information and the way of presentation has to be adapted to the individual patient.

In exceptional cases, not informing the patient is more beneficiary for the patient's health than informing the patient. In those cases the physician is not obliged to inform the patient (therapeutic exception) (e.g. if the physician foresees that the patient will get extremely depressed or expresses suicidal behaviour). It has to be stressed however that the application of this principle is very exceptional. The therapeutic exception can only be applied if the physician contacted a colleague about the problem; the physician has to add a written motivation to the medical file. Moreover, the therapeutic exception cannot be applied in case of decision related information (informed consent). Consequently a physician can not withhold information because he fears that the patient will not consent if all relevant information is given.

The right to information is considered as part of the free choice of the patient. As a consequence, everyone can refuse information, the so called right not to know (art. 7 § 3)[11]. The right not to know can be derived from the right to self – determination, the right to physical integrity, the right to confidentiality and autonomy: "Sometimes the most rational decision is to risk the consequences of not knowing. Sometimes, the taking of such risk is the most likely way to protect one's autonomy". Therefore, the law provides that the patient has to express his will not to be informed on his health status. The request of the patient will be registered or added to the patient's file. When the patient has expressed his wish not to be informed, no information shall be passed on except when not informing causes obviously serious disadvantage for the patient or for thirds (e.g. in casu of risk of contagion) on condition that the health care provider had consulted a colleague in advance and has heard – when that is the case – the designated person of confidence.

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[9] Wet betreffende de rechten van de patiënt van 22 augustus 2002, B.S. 26 september 2002 (naar achter bij andere referenties)

[10] which refers to a human and is the opposite of a legal/corporate person

[11] zie ook H. NYS, Het recht op niet – weten bij genetische diagnostiek, in J. DUTE, Omzien naar de toekomst. 35 preadviezen. Vereniging voor gezondheidsrecht, Bohn Stafleu van Loghum, Diegem, 2002, 263 - 277

Informed consent

The right to informed consent can be derived from the right to physical integrity and to self-determination. The right to receive information prior to consent is regulated in article 8 of the Patients' rights act and concerns every medical intervention. Information has to be provided in advance and timely.

According to the content a non exhaustive list is enumerated: The patient has to be informed about the nature, the purpose, the urgency, the frequency, the follow – up care of the intervention, the relevant contraindications, the risks and the side effects of the intervention, alternatives and the financial information.

The explanatory report[12] of the law states that consent has to be given explicitly, except when the physician, after having sufficiently informed the patient, can reasonably deduce from the behaviour of the patient that he/she consents. This exception particularly applies to minor interventions, e.g. the patient presents his arm to the physician in order to take a blood sample. In case of major interventions as screening however, one can state that explicit consent is required. Explicitly implies that consent can be given orally as well as written. The patient has the right to ask for a written form of his consent and that it will be added to the medical file. The physician too has the right to record the consent and to add it to the medical file, but only if the patient agrees. The patient also has the right not to consent or to withdraw the former given consent (art. 8 § 4).

Possibility of liability

Liability (see Appendix to chapter 6) implies the existence of three elements: fault, damage and a causal link between the fault and the damage. In that scope, several questions with regard to PSA testing can be raised.

First question: Can a physician possibly be held liable for not informing about the existence of the testing? In this situation one can imagine a claim of a patient that got prostate cancer and blames the physician for not having offered a PSA test. Responsibility will be very hypothetical because actually, there is no evidence that PSA testing decreases mortality caused by prostate cancer. Consequently the proof of the fault en the causal link between the fault and the damage will probably fail.

Second question: Can a physician possibly be held liable if he performs the test without the informed consent of the patient? A lack of informed consent is not in accordance with the Patients' rights act, but responsibility will only be established if the patient can prove that he had refused the test if he had known the risks and the negative consequences.

According to these questions, there is no Belgian (published) jurisprudence on the use of the PSA-test.

Key message

- **The right to information is legally considered as part of the free choice of the patient.**
- **Article 7 of the Patients' rights act regulates the right to information about the health status (e.g. the diagnosis, the level of PSA).**
- **The right to receive information prior to consent is regulated in article 8 of the Patients' rights act.**

[12] Memorie van toelichting, Parl. St, 2001 – 2002, 1642/001

7. DISCUSSION

The topics discussed in the previous chapters allow us to evaluate to what extent screening for prostate cancer with the PSA test corresponds to the Wilson criteria concerning the appropriateness of screening as presented in the introduction.

Prostate cancer is the third most common cause of death by cancer for men. Death occurs fairly late in life: mostly after the age of 75. This puts relative importance of prostate cancer as a cause of death into perspective the. The progression of the disease is not well known and is somewhat paradoxical. Half of the men aged 60 years have latent prostate cancer as shown by histological examination but more men die with than from prostate cancer. Because of the slow progression of prostate cancer, it is not possible to predict the outcome of latent prostate cancer.

The availability of a valid screening test is crucial to a screening program. The test's sensitivity should be as high as possible in order to exclude cancer with confidence in those patients testing negative, while maintaining an acceptable specificity to minimise further invasive procedures in those patients testing positive. Unfortunately, for a cut-off point of 4ng/ml, the diagnostic value of the total PSA level is insufficient for screening conditions, with sensitivity ranging from 20% in biopsy verified patients to 50% in patients eventually diagnosed with clinical prostate cancer. The test is not able to identify only those tumours that are clinically relevant and thus may not minimise overdiagnosis. There is insufficient evidence on other tests, such as the PSA velocity or free/total PSA.

Treatment alternatives are radical prostatectomy, radiotherapy or watchful waiting. The standard curative treatments of prostate cancer are radical prostatectomy and radiotherapy (external or internal). Diagnosis of histologically latent lesions might, in a number of cases, lead to overtreatment. The optimum treatment for localised stages with an intermediate or good prognosis (stade T1 to T2b, PSA<15 and Gleason ≤ 7) remains unknown. The treatment-induced harms for the patient vary greatly, but affect the quality of live to a great extent.

No convincing evidence was found that screening decreases disease-specific mortality. Two large RCTs studying the effect of prostate cancer screening using the PSA test (PLCO and ERSPC) are currently conducted.

Given the current lack of evidence, it is difficult to estimate the cost-effectiveness of prostate cancer screening with the PSA test.

A screening recommendation is only justified if the benefits of the test can "reasonably" be expected to outweigh the risks of the whole treatment trajectory. A judgement that a test is beneficial cannot, for instance, be based on an assumption and current high value of early detection. This assumption focuses primarily on the benefits for the sick, and is not paying enough attention to the potential harms for the healthy. Irrespective of the variability in reported overdiagnosis rates, even the seemingly modest rates reported by Etzioni et al. can be considerable from a patient's point of view. Assuming that PSA screening is effective, overdiagnosis might be acceptable (as it often is in other diseases) were it not for the fact that many of the 18%–44% (or more, considering data from the other aforementioned studies) of men diagnosed with prostate cancer by PSA testing would be subject to the substantial and sometimes uniquely enduring morbidities of treatment, even though they do not benefit from it.

If physicians are steering a patient towards a certain diagnosis and treatment path, they also become ethically implicated and responsible in outcome (both harms and benefits) of the treatment trajectory. From this responsibility, the least obligation of the physician is to inform the patient about benefits and potential harms and uncertainties of certain choices and decisions. Therefore, the important possibility of overdiagnosis should not be underestimated or overlooked [54]. If it can be proven that the patient was clearly and well informed, the patient becomes responsible for the decision, as he should be aware of his right to refuse the test and treatment.

Mass media or marketing campaigns urging asymptomatic men to ask for PSA-tests will lead to a further supplier-induced demand for the test. The PSA test is considered more and more a routine test and the number of PSA tests shows an average annual increase of about 18% since 1995 in Belgium. Our estimations show that currently over half of all men above 50 undergo a PSA test.

The uncertainties surrounding PSA test screening can explain the discrepancy between the strong increase in the use of the PSA test and the more moderate increase in the use of biopsy and prostate cancer treatment as found in the Belgian health insurance data.

8. RECOMMENDATIONS

8.1. ABOUT THE USE OF PSA IN PROSTATE CANCER SCREENING

Based on the current available evidence, it is not recommended to install or develop a programme on PSA mass screening. The risk of iatrogenic problems (overdiagnosis)[13], as a result of the medical interventions after the PSA-test, is substantial whereas the possible reduction in prostate cancer specific mortality and potential health gain is not proven.

Opportunistic screening ought to be limited to those individuals requesting to be tested after receiving sufficient information and time to give their informed consent. For these requests and awaiting future developments, it is useful that national experts in the field develop a decision algorithm developed by urologists and GPs, based on the most recent evidence. Such an algoritm should include:

- The selection of men at higher risk. Better screeningtests are urgently needed, as the total PSA, free/total PSA, PSA velocity nor digital rectal examination offer sufficient test characteristics.
- The frequency of tests. Opinions differ on the optimal screening interval: Roobol[127] recommends to test every 8 years in patients with a PSA 1.0 ng/ml, Paez[128] every 4 years and Gunnar[129] every 3 years.
- When to stop screening. All guidelines agree that screening is no longer useful in men with a life expectancy of less than 10 years, an upper age limit between 70 and 75 years has been proposed.

The introduction of an algoritm leading to a reduced frequency of current PSA-testing should be linked to a future evaluation of the epidemiology of prostate cancer in Belgium, e.g. via the National Cancer Registry.

In the specific case of prostate cancer screening, the supplier-induced demand for PSA-testing ought to be reduced. The current practice of medical check-ups, the routine use of PSA-tests for asymptomatic men and information campaigns urging asymptomatic men to demand or undergo prostate cancer screening should be scrutinized.

8.2. DEVELOPING AN INFORMATION STRATEGY

Policy makers should play an important role in the development of a coordinated and coherent information strategy. The target audiences should be the medical professionals (and specifically the general practitioners and urologists) as well as the "preventive services" and the general public. The authorities have the responsibility to avoid ambiguous messages from the media and preventive services to the public. Different health care actors, taking the responsibility to inform citizens, should pay more attention to the quality and validity of the information provided. To accomplish this, representatives of the Communities, the League against Cancer, the health insurers, and the scientific associations of general practitioners were asked to what extent they wished or could contribute in their field to the propagation of coherent message on prostate cancer screening with the PSA test.

The unclear and opposing guidelines and recommendations about PSA prostate cancer screening should be streamlined towards a uniform message. The content of the information provided should be of high quality and avoid confusion or even controversy. For this purpose, collaboration between authorities and professional organisations can be set up.

Individual medical professionals should get easy access to this information and should be better supported by (internet or ICT supported) decision aid tools leading to evidence based practice, by which it can be expected that the growing workload for general practitioners, resulting from informing the patient, can be reduced.

[13] Overdiagnosis is defined as the detection of prostate cancer through PSA testing that otherwise would not have been diagnosed within the patient's lifetime

8.3. THE RESPONSIBILITY OF THE MEDICAL PROFESSION

Physicians are ethically and legally bound to provide the necessary information about any diagnostic test they are performing on a patient. It is expected that in the case of prostate cancer screening, the physician is not persuading a patient to undergo a PSA-test or applying it as a routine test. From an ethical perspective it can be expected that the physician informs the patient (in due time) about uncertainties of the test and potential benefits and harms of the entire diagnostic and treatment path. Information should be provided in a clear, open and personally adapted way, in order to come to an informed choice.

Further research is definitely needed and will be necessary to guide future decisions on prostate cancer screening.

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10. APPENDIXES

APPENDIX TO CHAPTER 2

LITERATURE REVIEW

Recommandations

La revue de littérature a été limitée aux documents parus en Anglais en Français ou en Néerlandais, depuis le 01/01/2000 , vu qu'il s'agit d'une mise au point actuelle de la question. Les mots-clés : « prostate » and « PSA » (free text) ont été introduits sur les sites suivants : National Guidelines Clearinghouse (NGC), Guidelines International Network (GIN), Institute for Clinical Systems Improvement (ICSI) .). Cette recherche a été complétée par une recherche sur d'autres sites présentant des recommandations pour la pratique tels que celui de l'Association des médecins généralistes des Pays-Bas (NHG), de l'Agence Nationale d'Evaluation et d'Accreditation en Santé (ANAES , France) de la Société Scientifique de Médecine générale (SSMG, Belgique) et de la Wetenchappelijke Vereniging voor Vlaamse Huisartsen (WVVH, Belgique) et sur des sites référencés par l'ICES .

Les agences d'évaluation en santé ayant réalisé des travaux récents sont : Institute for Clinical Evaluative Sciences (ICES)[130], US Preventive Services Task Force[22] (USPSTF), le Singapore Ministry of Health, le National Health Committee (new Zealand 2004) et l'Agence Nationale d'Evaluation en Santé (ANAES) [16].

Les sociétés scientifiques ayant réalisé des travaux récents sont : Société Scientifique de Médecine Générale [88], le Canadian Task Force on the Periodic Health Examination[131], update, American Cancer Society[132] (ACS), Association française d'urologie [133], American Urology Association (AUA). Le guideline de l'Institute for Clinical System Improvement[134] (ICSI) adopte les conclusions de l'USPSTF[22].

Autres types d'études

A ICES review was published in 2002, reviewing all randomised clinical trials up till 2002. Hence, we limited our search to articles published between January 2002 and 30 April 2005. Articles written in English, Dutch, French or Spanish were considered for review.

Limits:

Years: January 2002 – April 2005

Search strategy:

Medline (Ovid) :

(*Prostatic Neoplasms/pc limit to (controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial), limit to "diagnosis (optimized)"), (Prostate-Specific Antigen/du)

CRD :

prostatic neoplasm (MESH) and screening (MESH)

CDSR, ACP Journal Club, DARE, and CCTR:

((prostat$ adj2 cancer).mp. and(prostat$ adj2 neoplasm?).mp. and screening.mp.

Embase:

(prostate specific antigen'/mj AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [embase]/lim)

La recherche a été achevée le 30/04/2005. La parution de nombreux articles d'actualité plus récents a nécessité la réalisation d'un update achevé le 15/01/2006.

Systematic reviews on the diagnostic accuracy of the PSA test were searched in Medline. The following search terms were used:

"Prostate-Specific Antigen"[MeSH] AND systematic[sb].

Articles were included if they evaluated the PSA test in an asymptomatic population for early detection.

Validation

La validation de la recherche de recommandations a été effectuée en comparaison avec les résultats de la revue de littérature effectuée par l'ANAES. La revue de l'ANAES comporte plus de références car elle n'a appliqué pas les mêmes limites, toutefois, il n'y avait pas de discordance quant aux guidelines. Le document de l'International Netwerk of Agencies for Health Technology Assesment (INAHTA)[135] qui est antérieur à 2000, mais est un document de synthèse a été intégré à ce travail à la suite de la lecture du rapport de l'ANAES. De même, la validation de la recherche des études en cours a été effectuée en comparaison avec les résultats de la revue de littérature effectuée par l'ANAES, mais les grands essais étant bien connus, cette validation n'a pas permis d'en trouver d'autres.

Critères de sélection

Les guidelines disponibles ont été analysés par les auteurs de ce document à l'aide de l'instrument AGREE[14]. Aucun des guidelines ne s'est intéressé à l'impact économique de l'application des recommandations. Seul le NHC[17] a mentionné s'être enquis des préférences des patients. Ce dernier item s'explique sans-doute par le fait que dans le cadre d'un dépistage, il s'agit de personnes et non de patients et qu'il est très difficile d'interroger la population sans une information neutre préalable. D'une manière générale, , les travaux des agences se caractérisent par une plus grande rigueur d'élaboration que ceux des sociétés scientifiques.

Parmi les recommandations des sociétés scientifiques, celle de la SSMG obtient les score le plus élevé, ce qui s'explique par le fait qu' il y à un lien explicite entre les recommandations et les données probantes sur lesquelles elles reposent et aussi par un pré-test auprès des futurs utilisateurs (médecins généralistes). Pour les agences, les rapports de l'US Preventive Task Force, de l'ANAES et du NHC présentent le score de qualité le plus élevé.

Les rapports des agences en Health Technology Assesment ont été évalués au moyen du checklist de l'INAHTA[15].et d'une lecture attentive. A l'issue de cette évaluation, les rapport de l'INAHTA et celui de l'ICES sont également recommandés. Les travaux mentionnés ci-dessus ont servi de base au présent rapport (voir les tableaux récapitulatifs).

Les articles ont été sélectionnés sur base des abstracts en fonction de leur pertinence par rapport au sujet. Les études qui avaient comme sujet principal le dosage des PSA dans le cadre du dépistage chez les patients sans risque particulier ont été retenues ainsi que celles qui abordaient les avantages et inconvénients du dépistage et de son rapport du coût- efficacité. Etant donné l'importance du consentement du patient, les articles trouvés dans la revue primitive ou référencés dans les recommandations ont également été étudiés. Les recommandations destinées au patient n'ont pas été étudiées.

[14] Grille d'Evaluation de la Qualité des Recommandations pour la Pratique Clinique (AGREE Collaboration -01/2002) : www.agree.org

[15] Grille pour l'élaboration et la lecture des rapports d'évaluation des technologies HTA INAHTA : http://www.inahta.org/Reports.asp?name=/Content11/Dokument/HTAChecklistFrench.pdf

Tableau 1 : cotations des guidelines selon AGREE

AGREE	Champ et objectif / 12	participation des groupes / 16	rigeur d'élaboration / 16	clarté et présentation / 16	applicabilité / 12	indépendance éditoriale: / 8	TOTAL	Remarques	Evaluation globale
Guidelines									
AUA 2000	8	10	12	11	5	8	54	pas de critères de sélection des articles pas de niveaux de preuve	Non recommandé (expert consensus)
SSMG 2000	8	12	16	15	5	6	62	mention des niveaux de preuves recommandation testée par les généralistes, utilisateurs	Recommandé malgré quelques lacunes dans la description de la méthodologie
ACS 2001	9	1	15	9	3	4	41	pas de niveaux de preuve constatent l'absence de RCT pas de praticien de terrain dans le groupe de développement (cancer society)	Non recommandé (expert consensus)
AFU	9	6	15	9	3	4	46	un seul niveau de	Non

AGREE	Champ et objectif / 12	participation des groupes / 16	rigeur d'élaboration / 16	clarté et présentation / 16	applicabilité / 12	indépendance éditoriale: / 8	TOTAL	Remarques	Evaluation globale
2002								preuve méthodologie non décrite pas de généralistes utilisateurs dans le groupe	recommandé (expert consensus)
Singapore 2000								Non étudié car le risque est plus faible dans la population asiatique que dans la population caucasienne.	
USPSTF 2003	11	8	27	13	8	5	72	Méthodologie très précise	Recommandé à cause de la rigueur méthodologique, mais réserves à cause de l'absence de conclusion : la responsablité est reporté sur le patient.
ANAES 2004	11	10	26	14	4	7	72	Méthodologie très précise	Fortement recommandé

AGREE	Champ et objectif / 12	participation des groupes / 16	rigeur d'élaboration / 16	clarté et présentation / 16	applicabilité / 12	indépendance éditoriale: / 8	TOTAL	Remarques	Evaluation globale
NHC 2004	11	13	27	13	8	6	78	Méthodologie très précise	Fortement recommandé

Ce tableau synthétique est conçu comme une aide pour mesurer comment un rapport d'évaluation des technologies de santé répond aux 17 questions de la grille. Il n'a pas pour objet de constituer un tableau d'évaluation de rapports ETS : ceux-ci pourront s'avérer tout à fait valides et utiles sans pour autant satisfaire à tous les critères qu'il contient.

Tableau 2 : Grille de lecture (INAHTA)

ELEMENT	INAHTA[135]	ICES[130]
Préliminaires		
1. Présence de coordonnées permettant d'obtenir des informations complémentaires ?	+	-
2. Identification des auteurs ?	+	-
3. Déclaration sur les conflits d'intérêts ?	-	-
4. Indication d'une validation externe du rapport ?	+	+
5. Bref résumé en langage non technique ?	-	-
Pourquoi ?		
6. Question posée et contexte de l'évaluation ?	+/-	+
7. Indication du champ de l'évaluation ?	+	+
8. Description de la technologie de santé évaluée ?	+	+
Comment ?		
9. Détails sur les sources d'informations ?	+	++
10. Informations sur le choix des éléments d'évaluation ?	-	++
11. Informations sur l'interprétation des données recueillies ?	NP	NP
Quoi ?		
12. Présentation des résultats de l'évaluation ?	+	+
13. Interprétation des résultats de l'évaluation ?	+	++
Implications		

14. Présentation des conclusions de l'évaluation ?	+	+
15. Enoncé des conséquences médico-légales ?	-	+
16. Enoncé clair des conclusions de l'évaluation ?	+	+
17. Suggestions d'actions complémentaires ?	+	-

+ = OUI, +/- = partiellement, - = non. NP = non pertinent (pas de données)

Tableau 3 : Appréciation globale

Organisme pays	Titre	Méthodologie	Commentaires	Appréciation globale
Singapour 2000[136]	Clinical Pratice Guidelines: Prostate Cancer	Non précisée	La population de base est différente : le risque est plus faible dans la population asiatique que dans la population caucasienne	Non étudié
US Preventive Services Task Force 2003[22]	Screening for Prostate Cancer: recommendation and rationale	Explicite Recherche systématisée de la littérature	**Méthodologie très précise**	**Recommandé à cause de la rigueur méthodologique, mais réserves à cause de l'absence de conclusion explicite:**
ANAES 2004 [16]	Indications du dosage sérique de l'Antigène Prostatique Spécifique	Explicite Recherche systématisée de la littérature	**Méthodologie très précise**	**Fortement recommandé**
NHC 2004[37]	Prostate cancer screening in New Zealand		**Méthodologie très précise**	**Fortement recommandé**
AUA 2000[137]	Prostate specific antigen Best Practice Policy	Consensus Panel Experts	**pas de critères de sélection des articles** **pas de niveaux de preuve**	**Non recommandé (expert consensus)**
SSMG 2000 [88]	Recommandations de bonne pratique : l'Antigène Prostatique Spécifique	Explicite Recherche systématisée de la littérature	**mention des niveaux de preuves** **recommandation testée par les généralistes, utilisateurs**	**Recommandé malgré quelques lacunes dans la description de la méthodologie**

Organisme pays	Titre	Méthodologie	Commentaires	Appréciation globale
American Cancer Society 2004[82]	Update of Early Detection Guidelines for Prostate […] Cancer	Explicite Recherche systématisée de la littérature	**pas de niveaux de preuve** **constatent l'absence de RCT** **pas de praticien de terrain dans le groupe de développement (cancer society)**	**Non recommandé (expert consensus)**
Association Française d'urologie 2002[133]	Recommandation 2002 du comité de Cancérologie : cancer de la prostate	Consensus Experts	**un seul niveau de preuve** **méthodologie non décrite** **pas de généralistes utilisateurs dans le groupe**	**Non recommandé (expert consensus)**

AGREE : Appraisal of Guidelines Research and Evaluation : www.cochrane.org

Organisme pays	Titre	Méthodologie	Commentaires	Appréciation globale
INAHTA [135]	Prostate cancer screening.	Explicite	les critères de choix des revues de base ne sont pas mentionnés.	**Recommandé malgré quelques lacunes dans la description de la méthodologie**
ICES [130]	Prostate-specific Antigen (PSA) Screening in asymptomatic Men	Explicite, très bonne méthodologie (littérature), conclusions très claires		**Fortement recommandé,**

INAHTA : grille pour l'élaboration et la lecture des rapports d'évaluation des technologies

Tableau 4 : Conclusions

Organisme et pays	Titre	Conclusions
US Preventive Services Task Force 2003	Screening for Prostate Cancer: recommendation and rationale	**Conclusion par défaut : en l'absence de données probantes suffisantes (« evidence is insufficient to recommend for or against » , recommandation de grade I) : la responsablité de la décision est reportée sur le patient.**
ANAES 2004	Indications du dosage sérique de l'Antigène Prostatique Spécifique	**Conclusion : le dépistage de masse n'est pas recommandé. Les résultats des études portant sur le dépistage systématique ne permettent pas de conclure sur l'efficacité du dépistage individuel.** **Si le patient a une demande individuelle, une information claire sur les avantages/inconvénients est nécessaire**
NHC 2004	Prostate cancer screening in New Zealend	**Ni le dépistage systématique, ni le dépistage opportuniste ne sont recommandés. Si le patient a une demande, il doit recevoir une information claire sur les avantages/inconvénients de celui-ci et du traitement.**
INAHTA 135	Prostate cancer screening.	**Le dépistage en routine n'est pas recommandé à cause du manque de preuve concernat les bénéfices et du risque considérable d'effets négatifs.**
ICES Canada 2002	Prostate-specific Antigen Screening in asymptomatic Men	**Le dosage du PSA n'est pas remboursé actuellement dans le cadre du dépistage. Pour l'avenir, les experts sont divisés : statu quo ou dosage si patient informé.**

APPENDIX TO CHAPTER 3

ANNEXE 1. CANCER DE LA PROSTATE. CLASSIFICATION TNM 1997

La classification TNM permet de décrire l'extension de la maladie. Elle est fondée sur l'évaluation de 3 critères :

- T définit l'extension de la tumeur primitive ;
- N définit l'absence, la présence ou l'extension des atteintes métastatiques des aires ganglionnaires régionales ;
- M définit l'absence ou la présence de métastases à distance.

TNM correspond à la classification clinique ; le classement utilisé pour les constatations histologiques est le même, mais est précédé de la lettre « p » : pT, pN, pM.
La classification TNM donne un groupement par stade qui tient compte du TNM et de la différenciation histopathologique, notée G.

T tumeur primitive

T1 Tumeur non palpable et non visible à l'imagerie
T1a ≤ 5 % des copeaux
T1b > 5 % des copeaux
T1c Découverte par biopsie (élévation du PSA)

T2 Tumeur limité à la prostate (apex et capsule compris)
T2a Atteinte d'un lobe (ancien T2a et b)
T2b Atteinte des deux lobes

T3 Extension au-delà de la capsule
T3a Extension extracapsulaire (ancien T3a et b)
T3b Extension aux vésicules séminales

T4 Extension aux organes adjacents (col vésical, sphincter, rectum, paroi pelvienne) ou tumeur fixée.

N ganglions régionaux

N0 Absence de métastase ganglionnaire
N1 Atteinte ganglionnaire régionale (ancien N1, 2, 3)

ANNEXE 2. SCORE DE GLEASON

Description de la classification de Gleason

La classification de Gleason (310) est fondée sur le degré de différenciation de la tumeur, coté du grade 1 à 5. Le score de Gleason, coté de 2 à 10, est la somme des deux grades le plus fréquemment représentés dans la tumeur analysée.

Grade	Glandes tumorales/épithélium	Aspects histologiques
1	Prolifération monotone de glandes simples, arrondies, étroitement regroupées.	Nodules arrondis aux bords bien dessinés
2	Glandes simples, arrondies, plus dispersées.	Masses vaguement arrondies, aux bords mal définis.
3A	Glandes simples, de taille moyenne, de forme, de taille et d'espacement irréguliers.	Masses irrégulières aux bords déchiquetés.
3B	Glandes simples, de très petite taille, de forme, de taille et d'espacement irréguliers	Masses irrégulières aux bords déchiquetés
3C	Massifs épithéliaux cribriformes ou papillaires, à bords réguliers.	Zones irrégulières constituées de cylindres et massifs arrondis
4A	Massifs épithéliaux de glande fusionnées	Massifs et cordons irréguliers de glandes fusionnées.
4B	Même aspect que 4A, avec présence de cellules claires	Massifs et cordons irréguliers. Aspects d'« hyper-néphrome ».
5A	Massifs arrondis, papillaires ou cribriformes avec nécrose centrale.	Cylindres et massifs arrondis disposés de façon variable, avec nécrose (« comédocarcinome »).
5B	Adénocarcinome anaplasique.	Massifs très irréguliers.

Side effects of treatments [63]

Kwaliteitscore : 1 punt per item : prospectieve manier voor het verzamelen van de gegevens, een patiëntenaantal van honderd of meer, een follow-up van twalf maand of langer, een eenduidige operationalisatie van het neveneffect in kwestie en het vermelden van de patïentenkenmerken , een onderscheid maken tussen een zenuwsparende en een niet-zenusparende ingreep, het aantal patiënten (n>100).

Kwaliteitsanalyse artikels over gastro-intestinale klachten na radicale prostatectomie

Referentie artikel	Type gastro-intestinale klacht	Prospectief/ retrospectief	Groot/klein aantal patiënten	Lange/korte follow-up	Goede/lakse definitie	Multicentrische studie	score	risico
[66] Potosky	Diarree	+1	+1	+1	+1	JA	10/10	20.9%
	Abdominale krampen	+1	+1	+1	+1	JA	10/10	9.2%
	Verhoogde stoelgangsdrang	+1	+1	+1	+1	JA	10/10	14.5%
[65] Potosky	Diarree	+1	+1	+1	+1	JA	10/10	23.9%
	Krampen	+1	+1	+1	+1	JA	10/10	11.5%
	Verhoogde stoelgangsdrang	+1	+1	+1	+1	JA	10/10	19.3%

Kwaliteitsanalyse artikels over gastro-intestinale klachten na externe radiotherapie

Referentie artikel	Type gastro-intestinale klacht	Prospectief/ retrospectief	Groot/klein Aantal patiënten	Lange/ korte follow-up	Goede/ lakse definitie	Multicentrische studie	score	risico
[66] Potosky	Diarree	+1	+1	+1	+1	JA	10/10	37.2%
	Abdominale krampen	+1	+1	+1	+1	JA	10/10	13.6%
	Verhoogde stoelgangsdrang	+1	+1	+1	+1	JA	10/10	35.7%
[64] Talcott	Diarree • Occasioneel • Verschillende keren/week	+1	+1	0	+1	JA	7.5/10	 43% 13%
	Rectaal bloedverlies	+1	+1	+1	+1	JA	10/10	25%
[71] Hamilton	Krampen (sommige dagen tot elke dag)	+1	+1	6 maand: 0 12 maand: +1 24 maand: +1	+1	JA	7.5/10 10/10 10/10	25.6% 13.6% 14%
	Verhoogde ontlastingsdrang	+1	+1	6 maand: 0 12 maand: +1 24 maand: +1	+1	JA	7.5/10 10/10 10/10	46.7% 36.4% 34.4%
[65] Potosky	Diarree	+1	+1	+1	+1	JA	10/10	26.7%
	krampen	+1	+1	+1	+1	JA	10/10	9.4%
	Verhoogde stoelgangsdrang	+1	+1	+1	+1	JA	10/10	28.5%
[68] Little	Wekelijks rectaal bloedverlies	+1	+1	24 maand: +1 36 maand: +1	+1 +1	JA JA	10/10 10/10	9% 8%

BIJLAGE 2: Tabellen overzichtsartikels: urinaire incontinentie

neveneffect	URINAIRE INCONTINENTIE								
referentie		**Aantal patiënten**	**Definitie incontinentie**	**Bepaling incontinentie na X maand**	**Chirurgie (RP)**	**Externe radiotherapie (EBRT)**	**Interne radiotherapie (BT)**	**Zorgvuldig opvolgen (WW)**	**opmerkingen**
[60] Kirschner-Hermanns R, Jakse G. Quality of life following radical prostatectomy. Crit Rev Oncol Hematol 2002;43:141-151.	Studie door Kirschner-Hermanns et al	137	Frequent urineverlies	Na 33.7 maand	8.2%				
	Studie door Kao et al	1013	Urineverlies van gelijk welke graad die het dragen van verbanden noodzakelijk maakt	?	65.5%				
[55] Grise P, Thurman S. Urinary incontinence following treatment of localized prostate cancer. Cancer Control 2001 Nov/Dec;8(6):532-9.	Studie door Catalona et al	1870	Het dragen van verbanden om urineverlies op te vangen	Na 48 maand	8%				
	Studie door Bates et al	87	Urineverlies van eender welke graad	Na 22 maand	69%				
	Studie door McCammon et al	203	Het dragen van verbanden om urineverlies op te vangen	Na 40 maand		8.7%			
			Urineverlies van eender welke graad	Na 40 maand		29%			
	Studie door Arterbery et al	51	?	Na 6 maand			3%		
	Studie door Benoit et al	2124	?	Na 24 -36 maand			6.6%		
	Deense studie	?	Urineverlies van eender welke graad	Na 40 maand				27%	

neveneffect	URINAIRE INCONTINENTIE								
referentie		**Aantal patiënten**	**Definitie incontinentie**	**Bepaling incontinentie na X maand**	**Chirurgie (RP)**	**Externe radiotherapie (EBRT)**	**Interne radiotherapie (BT)**	**Zorgvuldig opvolgen (WW)**	**opmerking**
[56] Bukkapatnam R, Pow-Sang JM. Radical prostatectomy in the management of clinically localized prostate cancer. Cancer Control 2001 Nov/Dec;8 (6):496-502.	Studie door Walsh et al	64	Het dragen van verbanden om urineverlies op te vangen	Na 12-18 maand	7%				
	Studie door Abbou et al	43	?	Na 1 maand	16%				
[57] Crook J, Lukka H, Klotz L, Bestic N, Johnston M, The Genitourinary Cancer Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative. Systematic overview of the evidence for brachytherapy in clinically localized prostate cancer. Can Med Assoc J 2001 Apr 3;164 (7):975-981.	Studie (review) door Crook et al	/	/	Na > 12 maand			5-6%		Indien na TURP: 13%
[58] Stone NN, Stock RG. Complications following permanent prostate brachytherapy. Eur Urol 2002;41:427-433.	Studie door Stone et al	301	?	?			0%		
	Studie door Nag et al	32	?	?			19%		
	Studie door Stone et al	43	?	?			TURP+BT: 0%		
	Studie door Talcott et al	13	?	?			TURP+BT: 85%		
	Studie door Terk et al	6	?	?			BT+TURP: 0%		
	Studie door Gelblum et al	28	?	?			BT+TURP: 17%		
[61] Henderson A, Laing RW, Langley SEM. Quality of life following treatment for early prostate cancer: does low dose rate (LDR) brachytherapy offer a better outcome? A review. Eur Urol 2004;45:134-141.	Studie door Henderson et al	/	/	Na 12 maand			1-2%		

BIJLAGE 3: Tabellen overzichtsartikels: erectiestoornissen

Neveneffect	**ERECTIESTOORNISSEN**											
Referentie		**Aantal patiënten**	**Definitie erectiestoornissen**	**Bepaling impotentie na X maand**	**Chirurgie (RP)**					**Externe radiotherapie (EBRT)**	**Interne radiotherapie (BT)**	**Zorgvuldig opvolgen (WW)**	**opmerkingen**
					RP	*NNS-RP*	*NS-RP*	*UNS-RP*	*BNS-RP*				
[59] Incrocci L, Slob AK, Levendag P. Sexual (dys)function after radiotherapy for prostate cancer: a review. Int J Radiat Oncol Biol Phys 2002;52 (3):681-693.	Studie door Lilleby et al	108	Het onvermogen om een erectie te bekomen en te behouden voldoende stevig voor betrekking	Na 12 maand	48%								
	Studie door Yarbo en Ferrans	68	Idem	Na 30 maand	98%								
	Studie door Lilleby et al	154	Idem	Na 12 maand						31%			
	Studie door Siegel et al	319	Idem	Na ? maand						85%			61% van de patiënten was potent voor EBRT
	Studie door Koutrouvelis	130	Idem	Na 6-24 maand							5%		
	Studie door Joly et al	71	Idem	?							89%		

Neveneffect	**ERECTIESTOORNISSEN**											
Referentie		**Aantal patiënten**	**Definitie erectiestoornissen**	**Bepaling impotentie na X maand**	**Chrirugie (RP)**					**Externe radiotherapie**	**Interne radiotherapie**	**Zorgvuldig opvolgen**	**Opmerkingen**
					RP	*NNS-RP*	*NS-RP*	*UNS-RP*	*BNS-RP*				
[56] Bukkapatnam R, Pow-Sang JM. Radical prostatectomy in the management of clinically localized prostate cancer. Cancer Control 2001 Nov/Dec;8 (6):496-502.	Studie door Walsh et al	64	Het onvermogen om zelfstandig betrekking te kunnen hebben, met of zonder het gebruik van sildenafil	Na 18 maand	14%								
	Studie door Stanford et al	3533	?	Na 18 maand	59.9%								
[63] Telöken C. Management of erectile dysfunction secondary to treatment for localized prostate cancer. Cancer Control 2001 Nov/Dec;8 (6):540-545.	Studie door Madalinska et al	278	het onvermogen om een erectie te bekomen en te behouden voldoende stevig voor betrekking	Na 12 maand						41-55%			
	Studie door Siegel et al	315	Idem	Na ? maand						85.4%			
	Studie door Matzkin et al	63	Idem	Na 15 maand							30%		
	Studie door Zelefsky et al	50	Idem	Na 60 maand							53%		
	Studie door Stanford et al	1291	Idem	Na 18 maand		65.5%		58.6%					
	Studie door Gralnek et al	163	Idem	Na 12 maand		83%							
	Studie door Walsh et al	62	Idem	Na 18 maand					14%				
	Studie door Formentie et al	94	Idem	Na 36 maand					60%				
	Studie door Catalona et al	798	Idem	Na 18 maand				53%					

neveneffect	ERECTIESTOORNISSEN												
referentie		**Aantal patiënten**	**Definitie erectiestoornissen**	**Bepaling impotentie na X maand**	**Chirurgie (RP)**					**Externe radiotherapie (EBRT)**	**Interne radiotherapie (BT)**	**Zorgvuldig opvolgen (WW)**	**opmerkingen**
					RP	*NNS-RP*	*NS-RP*	*UNS-RP*	*BNS-RP*				
[60] Kirschner-Hermanns R, Jakse G. Quality of life following radical prostatectomy. Crit Rev Oncol Hematol 2002;43:141-151.	Studie door Walsh et al	?	?	Na 12-18 maand			14%						
	Studie door Fossa et al	96	Het niet kunnen krijgen van een erectie die stevig genoeg is voor betrekking	Na ? maand	78%								18% van de patiënten was impotent voor de operatie
	Studie door Potosky et al	?	Het niet kunnen krijgen van een erecite stevig genoeg voor betrekking	Na ? maand						45%			Alle patiënten waren potent voor de behandeling
[61] Henderson A, Laing RW, Langley SEM. Quality of life following treatment for early prostate cancer: does low dose rate (LDR) brachytherapy offer a better outcome? A review. Eur Urol 2004;45:134-141.	Studie (review) door Henderson et al	/	/	Na 72 maand							39%		Alleen de mannen die voordien potent waren, werden in rekening gebracht
[62] Mirone V, Imbimbo C, Palmieri A, Longo N, Fusco F. Erectile dysfunction after surgical treatment. Int J Androl 2003;26:137-140.	Studie door Catalona et al	?	?	?	16%-82%			53%	32%	2-34%			
	Studie door Siegel et al	?	?	?	41%-85%								
[58] Stone NN, Stock RG. Complications following permanent prostate brachytherapy. Eur Urol 2002;41:427-433.	Studie door Wallner et al	92	?	Na 36 maand							14%		
	Studie door Kao et al	236	?	Na 72 maand							30%		Alle patiënten waren potent voor BT
		77	?	Na 72 maand							66%		Alle patiënten hadden reeds een verminderde erectiele functie voor BT
[57] Crook J, Lukka H, Klotz L, Bestic N, Johnston M, The Genitourinary Cancer Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative. Systematic overview of the evidence for brachytherapy in clinically localized prostate cancer. Can Med Assoc J 2001 Apr 3;164 (7):975-981.	Studie (review) door Crook et al	/	/	Na > 12 maand							4-14%		

BIJLAGE 4: Tabellen overzichtsartikels: gastro-intestinale klachten en urinaire retentie

Neveneffect	GASTRO-INTESTINALE KLACHTEN				
Referentie		**Aantal patiënten**	**Bepaling neveneffect na X maand**	**Definitie outcome**	**Radicale prostatectomie (RP)**
[60] Kirschner-Hermanns R, Jakse G. Quality of life following radical prostatectomy. Crit Rev Oncol Hematol 2002;43:141-151.	Studie door Helgason et al	314	Na ? maand	Fecale incontinentie: verlies van controle over de anale sfincter wat leidt tot ongewild verlies van feces of gas	4%
	Studie door Potosky et al	961	Na 24 maand	Verhoogde stoelgangsdrang	14.5%

neveneffect	URINAIRE RETENTIE			
referentie		**Aantal patiënten**	**Bepaling neveneffect na X maand**	**brachytherapie**
[61] Henderson A, Laing RW, Langley SEM. Quality of life following treatment for early prostate cancer: does low dose rate (LDR) brachytherapy offer a better outcome? A review. Eur Urol 2004;45:134-141.	Studie door Henderson et al	?	Na 2 weken	12%
[58] Stone NN, Stock RG. Complications following permanent prostate brachytherapy. Eur Urol 2002;41:427-433.	Studie door Terk et al	251	?	5%
	Studie door Vijverberg et al	46	?	22%

APPENDIX TO CHAPTER 4

In this appendix we provided summary sheets for those studies which also calculated costs per cancer treated for cure since this is a more interesting intermediate endpoint than just calculating cost per cancer detected.

1) Gustafsson O, Carlsson P, Norming U, Nyman CR, Svensson H. Cost-effectiveness analysis in early detection of prostate cancer: an evaluation of six screening strategies in a randomly selected population of 2,400 men. Prostate. 1995;26(6):299-309.

Author	Gustafsson O, Carlsson P, Norming U, Nyman CR, Svensson H
Country	Sweden
Design	A cost-effectiveness study was performed based on 6 screening strategies
Perspective	Not specified
Time window	1990
Interventions	Six strategies: 1) DRE (digital rectal examination) of all individuals 2) TRUS (transrectal ultrasonography) of all individuals 3) DRE of all individuals followed by TRUS on the subgroup with normal findings on DRE and finally re-examination of all individuals with a PSAs (prostate-specific antigen) >=7ng/ml 4) PSA of all individuals followed by DRE of the riskgroup with PSAs >=4ng/ml 5) PSA of all individuals followed by TRUS of the riskgroup with PSAs >=4ng/ml 6) DRE and PSA of all individuals followed by TRUS of the riskgroup with PSAs >=4ng/ml
Population	Men 55-70 years old Lower limit: because of the low detection rate of prostate cancer among younger persons in earlier studies Upper limit: because in Sweden, patients above this age have traditionally been considered not to benefit from radical prostatectomy
Assumptions	
Data source for costs	Cost calculations were based on the actual annual costs according to internal hospital accounts for 1990 (1$ = 5.90 SEK)
Cost items included	Total costs, i.e. direct plus indirect costs The total costs for each strategy have been subdivided into: 1) invitation costs 2) examination costs, i.e., costs associated with the examination only 3) costs for diagnostic procedures, consisting of costs for histopathological or cytological analysis and additional time spent due to biopsy and informing subjects of biopsy results 4) costs due to complications 5) indirect costs comprising participants' travel costs, costs due to their absence from work, or, for rehired participants, loss of leisure time
Data source for outcomes	The diagnostic results concerning the different methods have been reported earlier.[138]
Discounting	no

<table>
<tr><td>Costs</td><td>Total costs to examine 1000 individuals
intervention 1: 74,500$
intervention 2: 97,500$
intervention 3: 160,900$
intervention 4: 71,200$
intervention 5: 82,600$
intervention 6: 116,100$</td></tr>
<tr><td>Outcomes</td><td>1) number of cancers detected
2) number of small cancers diagnosed (T2A or less)
3) number of patients given treatment for cure</td></tr>
<tr><td>Cost-effectiveness</td><td>Decision tree
<table>
<tr><th></th><th>Cost / cancer detected</th><th>Cost / cancer T2A or less</th><th>Cost / cancer treated for cure</th><th>Marginal costs / cancer treated for cure</th></tr>
<tr><td>intervention 1</td><td>3,100$</td><td>12,420$</td><td>4,970$</td><td>1,100$</td></tr>
<tr><td>intervention 2</td><td>2,950$</td><td>9,750$</td><td>4,880$</td><td>7,450$</td></tr>
<tr><td>intervention 3</td><td>4,470$</td><td>13,410$</td><td>7,000$</td><td>22,400$</td></tr>
<tr><td>intervention 4</td><td>3,560$</td><td>17,800$</td><td>5,930$</td><td>baseline</td></tr>
<tr><td>intervention 5</td><td>3,180$</td><td>13,770$</td><td>4,590$</td><td>2,700$</td></tr>
<tr><td>intervention 6</td><td>3,630$</td><td>12,900$</td><td>5,530$</td><td>18,600$</td></tr>
</table></td></tr>
<tr><td>Sensitivity analysis</td><td>No</td></tr>
<tr><td>Conclusions</td><td>TRUS (transrectal ultrasound) of individuals with PSAs (prostate-specific antigen) >= 4ng/ml was the most cost-effective strategy and detected 80% of the cancers actually treated for cure. Screening with DRE (digital rectal examination) and PSA analysis followed by TRUS of individuals with PSAs >= 4ng/ml had a somewhat lower cost-effectiveness, but detected 90% of the cancers treated for cure.</td></tr>
</table>

2) Holmberg H, Carlsson P, Lofman O, Varenhorst E. Economic evaluation of screening for prostate cancer: a randomized population based programme during a 10-year period in Sweden. Health Policy. 1998;45(2):133-47.

Author	Holmberg H, Carlsson P, Lögman O, Varenhorst E
Country	Sweden
Design	The cost-effectiveness of the programme and the economic consequences of introducing a similar programme throughout the whole country have been calculated based on a limited trial
Perspective	Not specified
Time window	The study group was invited to participate in repeat screenings, at 3-year intervals, from 1987 to 1996. A total of four screening rounds were done.
Interventions	At the start of the study, DRE (digital rectal examination) was the only established screening method for early cancer detection. The PSA-test was not considered to be adequately evaluated and established as a diagnostic method for prostate cancer until the third screening in 1993, when it was included in the programme. During the whole study period, fine-needle aspiration biopsy was performed when there was a suspicion of prostate cancer because of positive DRE and or PSA > 4µg/l.
Population	A random selection of 1492 men (50-69 years) was invited to repeated screening in 1987. The remaining 7679 men constituted the control group.
Assumptions	
Data source for costs	Costs for different services are based on a medical record study.
Cost items included	Costs for particular measures in the screening, diagnosis and management of prostate cancer patients
Data source for outcomes	The Norrköping trial
Discounting	No
Costs	Costs related to measures in the screening programme (1996 prices) DRE 144 SEK (€ 16) PSA 131 SEK (€ 14) Fine-needle aspiration biopsy 1104 SEK (€ 119) Mean accumulated costs for management of prostatic cancer in different patient groups according to stage and primary treatment (1996 prices) Advanced cancer Expectant management 76,800 SEK (€ 8,291) Palliative treatment 217,300 SEK (€ 23,460) Localized cancer Expectant management 65,000 SEK (€ 7,018) Curative treatment 138,400 SEK (€ 14,942)

<table>
<tr><td>Outcomes</td><td>Number of detected cases of cancer distributed according to stages and primary therapy in the intervention and control group (cancer per 1000 men)

<table>
<tr><th></th><th>Intervention group</th><th>Control group</th><th>P-value</th></tr>
<tr><td>Stage</td><td></td><td></td><td></td></tr>
<tr><td>Advanced</td><td>10.7</td><td>8.9</td><td>0.35</td></tr>
<tr><td>Localized</td><td>23.5</td><td>10.2</td><td>0.013</td></tr>
<tr><td>Primary treatment</td><td></td><td></td><td></td></tr>
<tr><td>Curative</td><td>12.7</td><td>4.2</td><td>0.066</td></tr>
<tr><td>Palliative</td><td>9.4</td><td>8.5</td><td>0.161</td></tr>
<tr><td>Expectant management</td><td>11.4</td><td>6.4</td><td>0.051</td></tr>
</table>
The screening programme generates a larger number of cases of prostate cancer that are detected earlier than in the no-screening alternative. The probability that detected cases of cancer are localized and that therapy will be potentially curative is therefore larger in the screening alternative. Those cancers detected in the control group are more frequently advanced and lead less frequently to curative therapy.</td></tr>
<tr><td>Cost-effectiveness</td><td>Decision tree
Cost-effectiveness ratio: (direct costs)
Cost per detected cancer 18,600 SEK (€ 2,008)
Cost per curative treated patient 49,800 SEK (€ 5,376)

Cost-effectiveness ratio of the screening-programme when costs for treatment are included
Cost per detected cancer 137,900 SEK (€ 14,889)
Cost per potentially curative treatment 370,100 SEK (€ 39,960)

Incremental cost with screening compared to no-screening
Cost per detected cancer 158,000 SEK (€ 17,059)
Cost per detected localized cancer 167,000 SEK (€ 18,031)
Cost per potentially curative treatment 249,000 SEK (€ 26,884)</td></tr>
<tr><td>Sensitivity analysis</td><td>No</td></tr>
<tr><td>Conclusions</td><td>The results show that the total incremental heath care costs for prostate cancer will increase by 179 million SEK (= €19,326,899) per year with screening compared to no-screening. This was an evaluation of a general screening programme in Sweden for men aged 50-69 years. The number of men at risk in the first screening was 943000. The number of detected cases of localized cancer will increase by about 1000, which represents an additional cost of about 158000 SEK (= €17,060). In conclusion, general screening for prostate cancer can be performed with a reasonable cost per detected localized cancer.</td></tr>
</table>

3) Sennfalt K, Sandblom G, Carlsson P, Varenhorst E. Costs and effects of prostate cancer screening in Sweden--a 15-year follow-up of a randomized trial. Scandinavian Journal of Urology & Nephrology. 2004;38(4):291-8.

Author	Sennfält K, Sandblom G, Carlsson P, Varenhorst E
Country	Sweden
Design	See summary sheet: 'Holmberg H, Carlsson P, Lofman O, Varenhorst E. Economic evaluation of screening for prostate cancer: a randomized population based programme during a 10-year period in Sweden. Health Policy. 1998;45(2):133-47.'
Perspective	This study extends the follow-up until 2001.
Time window	
Interventions	
Population	
Assumptions	
Data source for costs	
Discounting	
Costs	Costs related to measures in the screening programme (1999 prices, i.e. 1996 prices adjusted upwards by 2% annually) Administration of the screening programme 40 SEK (€4) Loss of working and leisure time 155 SEK (€17) DRE 153 SEK (€17) PSA 139 SEK (€15) Fine-needle aspiration biopsy 1172 SEK (€126) Cost of thescreening programme in Norrköping. The average cost per man in the intervention group was 10,260 SEK (€1,107), compared to 6,620 SEK (€714) in the control group. Expected cost from time of diagnosis to death of four different management options Advanced cancer Expectant management 45,000 SEK (€4,853) Palliative treatment 198,400 SEK (€21,395) Localized cancer Expectant management 94,000 SEK (€10,137) Curative treatment 173,000 SEK (€18,656)

Outcomes	Number of detected localized and advanced prostate cancers and treatments with curative intents in the intervention and control groups (1987-2001)		
		Intervention group (n=1492)	Control group (n=7679)
	Advanced cancer	31	158
	Localized cancer	63	185
	Treatment with curative intent	23	40
Cost-effectiveness	Decision tree The incremental cost per extra detected localized cancer was calculated to be 168,000 SEK (€18,119). The incremental cost per extra treatment with curative intent was calculated to be 356,000 SEK (€38,395).		
Sensitivity analysis	No		
Conclusions	The incremental cost per extra detected localized cancer was 168,000 SEK (€18,119) and per potentially curable cancer 356,000 SEK (€38,395). Introducing this screening programme for prostate cancer in Sweden would incur 244 million SEK (€26,318,440) annually in additional costs for screening and treatment compared to a non-screening strategy. There is still no scientific evidence that patients will benefit from screening programmes. Prostate cancer screening would probably be perceived as cost-effective if potentially curable patients gained on average at least 1 year of survival.		

APPENDIX TO CHAPTER 5

INTERNATIONAL

Canada

Organisatie	Laatste herziening	Samenvatting van het advies / beleid
Canadian Cancer Society[76]	05 april 2005	Asymptomatische mannen boven de 50 moeten met hun arts overleggen over de voor- en nadelen van de PSA test voor screening van prostaatkanker. Asymptomatische mannen onder de 50 moeten dit overwegen indien zij behoren tot een hogere risicocategorie (familiale voorgeschiedenis of van Afrikaanse afkomst).
Canadian Task Force on Preventive Health Care[75]	01 augustus 2002	De laatste aanbeveling dateren van 1994. Een bijwerking van de aanbeveling is pas voorzien wanneer meer evidentie beschikbaar komt. 1994 aanbeveling: de PSA test is niet geschikt voor gebruik in periodieke medisch onderzoek voor mannen boven de 50.
Canadian Urological Association[139]	-	Op dit ogenblik geen aanbevelingen.
Centre for Chronic Disease Prevention and Control [140]	20 oktober 2003	Asymptomatische mannen boven de 50 moeten met hun arts overleggen over de voor- en nadelen van de PSA test voor screening van prostaatkanker. Asymptomatischa mannen onder de 50 moeten dit overwegen indien zij behoren tot een hogere risicocategorie (familiale voorgeschiedenis of van Afrikaanse afkomst).

Nieuw Zeeland

Organisatie	Laatste herziening	Samenvatting van het advies / beleid
New Zealand Guidelines Group [141]	september 2003	Screening van prostaatkanker bij asymptomatische mannen wordt ontraden.
Cancer Society of New Zealand [142]	november 1999	Voor huidige methoden voor screening van prostaatkanker in asymptomatische mannen is niet aangetoond dat de mortaliteit gereduceerd wordt. Het testen van asymptomatische mannen wordt ontraden.
Urological Society of Australasia [143]	juni 2003	Geen voorstander van de screening van asymptomatische mannen met de PSA test. Aanbeveling om de beschikbaarheid van de PSA test publiek te maken zodat deze een geïnformeerde beslissing kunnen nemen over het al dan niet laten afnemen van de PSA test.

Verenigde Staten van Amerika

Organisatie	Laatste herziening	Samenvatting van het advies / beleid
American College of Preventive Medicine [81]	2001	Ontraadt een algemene screening met de PSA test. Asymptomatische mannen boven de 50 moeten overleggen met hun arts over de voor- en nadelen, en de over de beperkte evidentie van de PSA test voor de screening van prostaatkanker.
American College of Physicians – Amercian society of internal medicine[144]	2002	Guideline (1997) is gedateerd (status is inactief): Ontraadt een algemene screening met de PSA test. Asymptomatische mannen boven de 50 moeten overleggen met hun arts over de voor- en nadelen, en de over de beperkte evidentie van de PSA test voor de screening van prostaatkanker. Een herziening van de evidentie in 2002 leidde niet tot een aanpassing van de voorgaande aanbelingen.
American Cancer Society [82]	6 januari 2004	Het niet aanbieden of het ontraden van de PSA test wordt als niet aangewezen beschouwd. De PSA test moet jaarlijks aangeboden worden aan alle mannen boven de 50 met een levensverwachting van minstens 10 jaar. Mannen met een hoger risico op prostaatkanker (van Afrikaans-Amerikaanse oorsprong of met prostaatkanker in eerstegraadsverwanten) moeten getest worden vanaf 45 jaar. Mannen met meerdere gevallen van prostaatkanker in eerstegraadsverwanten moeten getest worden vanaf 40 jaar. Bij deze mannen bepaalt het resultaat van de eerste test de noodzaak voor verder jaarlijkse testen tot hun 45ste jaar. Mannen moeten overleggen met hun arts over de voor- en nadelen, en de over de beperkte evidentie van de PSA test voor de screening van prostaatkanker.
American Academy of Family Physicians [145]	2005	Er is niet voldoende evidentie om een aanbeveling te doen voor of tegen screening voor prostaatkanker met de PSA test.
American Medical Association [139]	juni 2000	Grootschalige screening programma's zijn voorbarig. Asymptomatische mannen boven de 50 moeten overleggen met hun arts over de voor- en nadelen, en de over de beperkte evidentie van de PSA test voor de screening van prostaatkanker. Mannen met een hoger risico op prostaatkanker (van Afrikaans-Amerikaanse oorsprong of met prostaatkanker in eerstegraadsverwanten) moeten getest worden vanaf 40 jaar.
American Urological Association [146]	2000	Asymptomatische mannen boven de 50 moeten overleggen met hun arts over de voor- en nadelen, en de over de beperkte evidentie van de PSA test voor de screening van prostaatkanker. Alhoewel niet alle mannen boven de 50 beschouwd worden als geschikte kandidaten voor screening op prostaatkanker, moet vroegtijdige detectie aan hen aangeboden worden indien zij een levensverwachting van meer dan 10 jaar hebben.
National Cancer Institute [147]	20 mei 2005	Er is niet voldoende evidentie om een aanbeveling te doen voor of tegen screening voor prostaatkanker met de PSA test.
U.S. Preventive Services Task Force [18]	december 2002	Er is niet voldoende evidentie om een aanbeveling te doen voor of tegen screening voor prostaatkanker met de PSA test.
Department of Veterans Affairs [148]	13 juli 2005	Volgt de aanbevelingen van de American Cancer Society.

Verenigd Koninkrijk

Organisatie	Laatste herziening	Samenvatting van het advies / beleid
National Health Service – Cancer Screening Programs [149]	onbekend	De PSA test mag niet gebruikt worden voor grootschalige screening van prostaatkanker. Deze aanbeveling is gebaseerd op een HTA uit 1997 [23]. Omwille van het gebrek aan evidentie voor of tegen het nut van de PSA test in screening is een PSA Informed Choice Programme opgestart als reactie op de toegenomen vraag naar vroegtijdige detectie van prostaatkanker.
British Association of Urological Surgeons	-	Geen beschikbare aanbevelingen.

Belgium

Nomenclatuurcodes PSA, biopsie, totale radicale prostatectomie, brachytherapie en hormoontherapie

PSA

433016-433020	Tests ou dosages par produits marqués - 1/ Chimie 1/ Sang : Dosage de l'antigène prostatique spécifique (P S A) (Maximum 1) (Règle de cumul 316) (Règle diagnostique 5) Classe 15
542010-540021	1/Chimie 1/Sang : Dosage de l'antigène prostatique spécifique (P S A) par méthode non-isotopique (Maximum 1) (Règle de cumul 316) (Règle diagnostique 5) Classe 15

Biopsie de la prostate

355832-355843	Ponctions : Ponction biopsique de la prostate sous contrôle échographique.

Prostatectomies

261796-261800	Prostatectomie totale, y compris l'exérèse du bloc vésiculaire avec suture urétro-vésicale

Radiothérapie externe

444113/444124	Honoraires forfaitaires pour une série d'irradiations externes simples de 1 à 10 fractions chez un patient qui répond aux critères ou pathologie repris en catégorie 1
444135/444146	Honoraires forfaitaires pour une série d'irradiations externes simples de 11 à 35 fractions chez un patient qui répond aux critères ou pathologie repris en catégorie 2
444150/444161	Honoraires forfaitaires pour une série d'irradiations externes complexes chez un patient qui répond aux critères ou pathologie repris en catégorie 3
444172/444183	Honoraires forfaitaires pour une série d'irradiations externes complexes chez un patient qui répond aux critères ou pathologie repris en catégorie 4

Brachythérapie

260654/260665	Intervention chirurgicale pour application de matériel radio-actif dans la vessie ou la prostate
444253/444264	Traitement par curiethérapie : une ou plusieurs localisations dans un même volume cible avec une fraction ou avec curiethérapie fractionnée avec un inter valle d'au moins 5 jours : Honoraires forfaitaires pour curiethérapie

	exclusive chez un patient qui répond aux critères ou pathologie repris en catégorie 8
444290/444301	Traitement par curiethérapie : une ou plusieurs localisations dans un même volume cible avec une fraction ou avec curiethérapie fractionnée avec un intervalle d'au moins 5 jours : Honoraires forfaitaires pour curiethérapie combinée à une série d'irradiations externes chez un patient qui répond aux critères ou pathologie repris en catégorie 5

Hormonothérapie

Type	Nom ATC	Classification ATC
Oestrogènes	Oestrogènes	G03C
Anti-androgènes	Antiandrogens	GO3H
Analogue LHRH	Antigonadotropins and similar agents "Other sex hormones and moderators of the genital system"	G03XA

APPENDIX TO CHAPTER 6

PRECAUTION, RISK AND HEALTH CARE

Resnik [97] discusses three issues related to the principle of precaution when applied to medicine. Similar problems are discussed by Malm [96]

Lack of full scientific certainty

Due to a "lack of full scientific certainty" the crucial issue is to approach the idea of proof and evidence in a probabilistic way. To offer proof is to offer evidence that has some bearing on the degree of probability assigned to a statement or hypothesis. The degree of probability depends on the practical applications and implications of the statements we are attempting to prove. ·The more drastic the implications of the statement, the lesser the level of probability acquired is needed to consider action. But in order to avoid discussion about issues that are not probable or solely completely hypothetic, the threats have to be at least "plausible". A threat can be considered as *probable* when there are enough data to assign an objective probability to a statement describing the threat. A threat is *plausible* when there's no sufficient evidence for objective probability but there's some indication.

Reasonableness

Reasonableness involves the careful balancing of competing norms and goals in moral and political decision-making. Within that framework, measures taken in response to a threat should be proportional to the level of the threat. Proportionality means tailoring measures to the chosen level of protection which implies a careful balancing of harms and benefits. A reasonable measure is one that is proportional to degree of the threat, consistent with other decisions, carefully weighs benefits and harms, and takes a realistic attitude toward the threat and its prevention. Reasonableness implies the carefully weighing and balancing of possibilities based on underlying values. A lot depends on the choice of the values that will serve as a basis for the proper balance. A realistic attitude implies that the measures can reasonably limit the harm.

Seriousness

The seriousness of the threat is an important issue. Tubiana [150] argues in environmental issues that the assessment of the risks' seriousness should take into account the magnitude of the exposure, its' plausibility and the number of individuals at risk. Resnik follows a similar line and states that seriousness depends on the potential harm and on the reversibility. The bigger the potential harm the more serious the threat will be. A risk that is reversible (can be undone) can be less serious than an irreversible threat. However the principle of precaution does not need to be restricted to irreversible threat [151]. If reversing the damage could be more costly than preventing it, the principle of precaution can be applied.

INFORMED DECISION MAKING, INFORMED CHOICE AND SHARED DECISION MAKING

Traditionally information has been provided to patients in order to enable them to "understand" an intervention or a disease. However, currently it is more and more accepted that patients should be offered balanced and relevant information to allow them to take decisions or make choices. Contemporary culture is inducing a shift from an expert-oriented, paternalistic health care model, towards a model of active patient participation and informed choice. It is becoming an ethical principle, to respect the patients autonomy, avoiding paternalism and involving patients in health decision – making processes [152] [153]. Greater patient involvement in decision making is consistent with the changing ideas about quality of care.

Several factors have been mentioned in literature affecting this "role shift" in medical practice: the increased patient autonomy as an underlying principle in health practice, creating expectations and opportunities to take personal preferences in account; the broader access to information for citizens; the expanding clinical options opening a range of choices in stead of a single standard of care; the rising costs in health care bringing consumers to cost-considerations; the increase in chronic conditions stimulating patients for active engagement in health management; growing complexity of trade-offs (weighing benefits and harms) [113] controversies in medical and health care, growing role of consumer and advocacy organisations and developments in informatics [109].

Informed choice and informed decision making

"Informed choice" holds that a patient is getting enough information on an intervention or medical practice, and deals with this information on an individual, personal basis. The notion can hold the idea that the information is acquired in interaction with other professionals, but does not necessarily require this interaction.

Very related to the notion of informed choice is "informed decision making". Information has to be provided to patients, and information should be designed in such a way that it empowers patients, to enable them to make informed decisions.

Informed decision making has to be consonant with different prerequisites. It occurs when the individual [154]:

- understands the situation, condition or disease being addressed, and also comprehends what the clinical service involves, including the benefits, risks, limitations, alternatives and uncertainties;
- has considered his or her preferences, as appropriate
- believes she or he has participated in decision making at a level she or he desires;
- makes a decision consistent with these desires

A "truly" informed decision making process requires that patients understand the complexity of the different health care options, including a true understanding of the difficult to grasp risks and benefits of either decision [100]

Informed decision making need not *necessarily* to involve providers directly, but the "intuitive" use of this concept in literature generally holds an interaction with the health care provider

Shared decision making

Shared decision making, explicitly holds the notion (longer term) interaction between provider and patient through face-to face encounters, in the different steps a decision-making process requires [109, 113] Shared decision making is a widely promoted ethical approach in health care. However, in daily practice, the notion of shared decision making is far more contested than informed decision making, based on the argument that physicians lack the time to get involved in this often intensive process.

Whitney and colleagues [155, 156]have developed a typology of shared decision making considering the practical "constraints", and argue that shared decision making is only relevant in settings that really require difficult decisions. Briss [102]argues that shared decision making cannot bear the entire burden of informing the patient, and that population oriented interventions to promote informed decision making should also be explored.

THE PROCESS OF INFORMED DECISION MAKING

General factors

Based on a literature search Bekker and colleagues[157] identified factors pertaining to (a) the decision context (b) the decision maker and (c) other influences.

The decision context refers to

- *the type of health decision* (eg. Decisions about Smoking or drinking alcohol, adhering to medication, having a diagnostic test, leads to different decision-making processes,
- the seriousness of the outcome, (eg. Deciding to donate an organ, or decision to take a sleeping pill)
- *the familiarity with the decision* (eg. Decision about exercise, versus decision about a genetic test),
- *the level of certainty*, (e.g. effects of insulin uptake in diabetes versus a decision of prenatal screening for Down syndrome)
- *the health domain* (e.g. Making decisions in primary care, versus surgery or medicine)
- and *the "recipient"* (e.g. deciding for ones self or for one's child).

The characteristics of the decision makers have also to be taken into account. Individual differences (anxiety, state of illness, personality traits, cognitive competencies..) will affect the degree to which informed decisions are made. People do vary in their preferred degree of involvement in health decisions; some want all possible information, while others want to rely entirely on the advise of the health care provider.

The third group of "other" factors holds a broader spectrum: As individuals are often unable to deal systematically with large amounts of information, the employ heuristics to reduce the processing required, leading to decisions made from the "context" rather than the content of the information. It has been demonstrated that decisions can change, when the same factual information is presented slightly different. Contextual factors do have an important impact on the decision making process ((perceived) time pressure, extreme affect (angry, anxiety,..), the need to "justify" a decision. The use of decision aids (including presentation of information) does affect the decision taken.

The most important general message from this review is thus that "giving more information" in a decision making process is a very complex issue, and is not simply resolved by simple solutions such as "simply giving information". It is clear that information is a necessary condition, but not the only one that affects informed decision making.

INFORMING THE PATIENT IN THE BELGIAN PATIENTS RIGHTS ACT

Informed consent

Informed consent is linked to the explicit "authorization" of the patient.

Informed consent is generally seen as the legal process referring to a patient's *written* consent[P] to a surgical or medical procedure or other course of treatment, given after the physician has told the patient all of the potential benefits, risks, and alternatives involved.

[P] The Belgian Patients' Rights act however doesn't link informed consent to "written" consent crf. infra

The concept of informed consent is based on the principle that a physician has a duty to disclose to a patient, information that allows the patient to make a reasonable decision regarding his or her own treatment. Informed consent is also required for participation in clinical studies or medical experiments after a subject achieved an understanding of what is involved and especially of the risks.

Informed and shared decision making are often confused with informed consent, both on aspects of content as well as elements of process. Informed consent has a legal authority, shared decision making has a moral authority [156]. Shared and informed decision making may be far more flexible in the amount of participation that a patient may choose (ranging from delegating decision making to a provider or someone else, to making a decision about what to do before seeing the physician) and because informed or shared decision making is focusing a lot more on patient preferences [109].

Possibility of liability

Liability implies three elements: fault, damage and a causal link between the fault and the damage.

- Fault: One commits a fault if a regulation has been violated or if one violates the general standard of care.
  Since the Belgian Patients' Rights act states that informed consent is needed for any intervention of the health care professional, a PSA test or any other following treatment (biopsy, etc..) without obtaining the informed consent implies a violation of the law and thus a fault.
  The law on patients rights does not express who (the patient or the physician) has the burden of proof of the lack of information or consent to perform the test. Since the law provides that information or informed consent can be given orally it will be hard to prove that information was (not) given or that informed consent was (not) obtained. Jurisprudence however states that the burden of proof of the lack of informed consent or information on the health status relies on the patientq. It is the judge who has to consider if the physician has properly informed the patient.

- Damage: The damage that can result from performing a PSA test without obtaining the informed consent of the patient can include the fact that the patient has been deprived of his right not to know and that he is consequently obliged to take a decision concerning the result of the PSA test. Once they enter into PSA testing, patients might experience problems include the anxiety of waiting for the test results, the discomfort of a biopsy, and the potential need for treatment that will possibly lead to incontinence and impotence. In that way the decision to undergo PSA testing may have huge consequences.

- Causal Link: One has to prove a causal link between the fault and the damage. There 's a causal link if the facts indicate that the damage would not have occurred if the fault would not have been arisen. In the case of PSA testing the patient will have to prove that he had refused the test if he had known the risks and the negative consequences (if he had been informed correctly).

If these three aspects can be proven by the patient, the physician can be held liable. At the moment however there is no such (Belgian) jurisprudence.

Another question that can be raised is the possible liability in case a physician did not propose to undergo a test to the patient and prostate cancer occurs afterwards. As mentioned above the proof of liability requires the existence of the elements fault, damage and a causal link.

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q Cass. 16 december 2004, *R.W.* 2004 - 2005, afl. 39, 1553, noot H. NYS; *T. Gez.* 2004 – 2005, afl. 299, noot S. LIERMAN; Cass. 14 december 2001, *T. Gez.* 2001 – 2002, 239, noot J.T. FAGNART; *J.T.* 2002, 261, noot C. TROUET; Cass. 28 februari 2002, *T. Gez.* 2002 – 2003, 12,

- Fault? Did the physician act in conformity with the general standard of care if he lacks to propose a PSA test? The general standard of care can be defined as the level of carefulness that can be expected from a reasonably competent and reasonably acting physician of the same category and in the same circumstances. In principle, the judge, often assisted by some experts, will decide if the physician acted conform the standard of care. Their opinion is mostly based on the current medical literature or clinical practice guidelines. Since the results of the report in question show that systematically offering the test by means of prevention in a no risk population is not recommended, it can be assumed that there's no violation of the general standard of care if the physician didn't offer a PSA test.

- Damage? The damage consists in the fact that there is a "loss of chance[r]" of prostate cancer at an earlier stage in which treatment is more likely to be beneficial.

- Causal link? The omission of the PSA test has to be an element that necessarily caused the damage. This element too will be very hard to prove. Even if a PSA test was performed there is a considerable chance to false negatives. Consequently the PSA test doesn't guarantee the early detection of prostate cancer. Moreover a positive PSA test doesn't necessarily imply a more effective treatment of prostate cancer. Actually, there is no evidence that PSA testing decreases mortality caused by prostate cancer. Consequently, even if a fault would have been assumed to be proven, the proof of a causal link between the fault and the damage will probably fail.

Physician's liability for not offering a PSA test is thus very hypothetical. Moreover there's no such jurisprudence.

[r] for an profound consideration of the loss of chance theory in situations of uncertainty of evidence: S. LIERMAN, *Een juridische analyse van het gebruik van ioniserende straling in de klinische geneeskunde: een onderzoek naar de invloed van voorzorg en preventie op gezondheidsbescherming en aansprakelijkheid*, Antwerpen, Intersentia, 2004, p. 380 e.v.

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Wettelijk depot : D/2006/10.273/17

KCE reports

1. Effectiviteit en kosten-effectiviteit van behandelingen voor rookstop. D/2004/10.273/1.
2. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid (fase 1). D/2004/10.273/2.
3. Antibioticagebruik in ziekenhuizen bij acute pyelonefritis. D/2004/10.273/5.
4. Leukoreductie. Een mogelijke maatregel in het kader van een nationaal beleid voor bloedtransfusieveiligheid. D/2004/10.273/7.
5. Het preoperatief onderzoek. D/2004/10.273/9.
6. Validatie van het rapport van de Onderzoekscommissie over de onderfinanciering van de ziekenhuizen. D/2004/10.273/11.
7. Nationale richtlijn prenatale zorg. Een basis voor een klinisch pad voor de opvolging van zwangerschappen. D/2004/10.273/13.
8. Financieringssystemen van ziekenhuisgeneesmiddelen: een beschrijvende studie van een aantal Europese landen en Canada. D/2004/10.273/15.
9. Feedback: onderzoek naar de impact en barrières bij implementatie – Onderzoeksrapport: deel 1. D/2005/10.273/01.
10. De kost van tandprothesen. D/2005/10.273/03.
11. Borstkankerscreening. D/2005/10.273/05.
12. Studie naar een alternatieve financiering van bloed en labiele bloedderivaten in de ziekenhuizen. D/2005/10.273/07.
13. Endovasculaire behandeling van Carotisstenose. D/2005/10.273/09.
14. Variaties in de ziekenhuispraktijk bij acuut myocardinfarct in België. D/2005/10.273/11.
15. Evolutie van de uitgaven voor gezondheidszorg. D/2005/10.273/13.
16. Studie naar de mogelijke kosten van een eventuele wijziging van de rechtsregels inzake medische aansprakelijkheid. Fase II : ontwikkeling van een actuarieel model en eerste schattingen. D/2005/10.273/15.
17. Evaluatie van de referentiebedragen. D/2005/10.273/17.
18. Prospectief bepalen van de honoraria van ziekenhuisartsen op basis van klinische paden en guidelines: makkelijker gezegd dan gedaan.. D/2005/10.273/19.
19. Evaluatie van forfaitaire persoonlijk bijdrage op het gebruik van spoedgevallendienst. D/2005/10.273/21.
20. HTA Moleculaire Diagnostiek in België. D/2005/10.273/23, D/2005/10.273/25.
21. HTA Stomamateriaal in België. D/2005/10.273/27.
22. HTA Positronen Emissie Tomografie in België. D/2005/10.273/29.
23. HTA De electieve endovasculaire behandeling van het abdominale aorta aneurysma (AAA). D/2005/10.273/32.
24. Het gebruik van natriuretische peptides in de diagnostische aanpak van patiënten met vermoeden van hartfalen. D/2005/10.273/34.
25. Capsule endoscopie. D/2006/10.273/01.
26. Medico–legale aspecten van klinische praktijkrichtlijnen. D2006/10.273/05.
27. De kwaliteit en de organisatie van type 2 diabeteszorg. D2006/10.273/07.
28. Voorlopige richtlijnen voor farmaco-economisch onderzoek in België. D2006/10.273/10.
29. Nationale Richtlijnen College voor Oncologie: A. algemeen kader oncologisch kwaliteitshandboek B. wetenschappelijke basis voor klinische paden voor diagnose en behandeling colorectale kanker en testiskanker. D2006/10.273/12.
30. Inventaris van databanken gezondheidszorg. D2006/10.273/14.
31. Health Technology Assessment prostate-specific-antigen (PSA) voor prostaatkankerscreening. D2006/10.273/17.