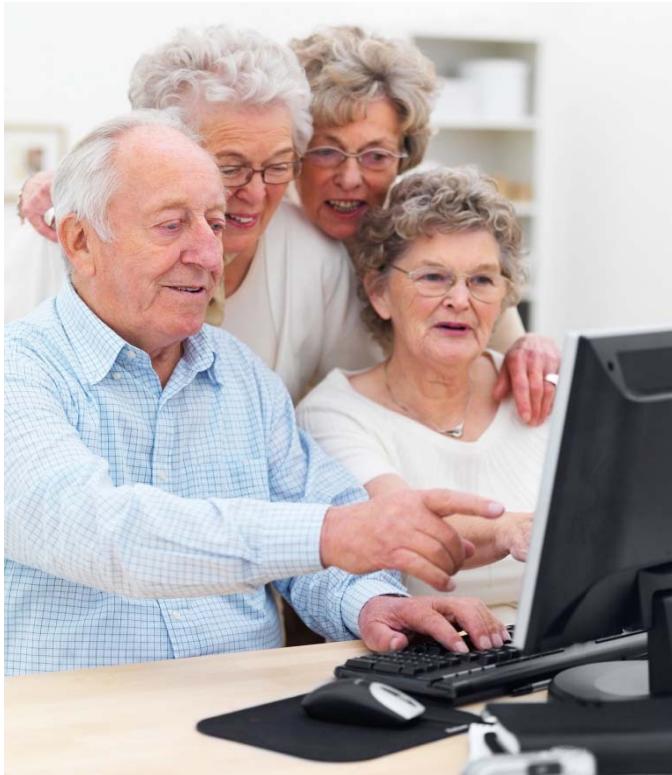


OPSPORING VAN BORSTKANKER TUSSEN 70 EN 74 JAAR





Het Federaal Kenniscentrum voor de Gezondheidszorg

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OPSPORING VAN BORSTKANKER TUSSEN 70 EN 74 JAAR

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Layout:	Ine Verhulst

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Publicatiedatum:	26 april 2012
Domein:	Good Clinical Practice (GCP)
MeSH:	Breast Neoplasms ; Mammography ; Mass Screening
NLM classificatie:	WP 870 - Breast - Neoplasms
Taal:	Nederlands, Engels



Formaat:	Adobe® PDF™ (A4)
Wettelijk depot:	D/2012/10.273/18
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Hoe refereren naar dit document?	Mambourg F, Robays J, Gerkens S. Opsporing van borstkanker tussen 70 en 74 jaar. Good Clinical Practice (GCP). Brussel: Federaal Kenniscentrum voor de Gezondheidszorg (KCE). 2012. KCE Report 176A. D/2012/10.273/18.
	Dit document is beschikbaar op de website van het Federaal Kenniscentrum voor de Gezondheidszorg.



■ VOORWOORD

Keuzes maken in de zorg – het lijkt snel op discriminatie, zeker wanneer de keuze gebeurt op basis van leeftijd. Hoe kan men bijvoorbeeld verantwoorden om aan een oudere patiënt de terugbetaling voor een dure hartingreep te ontzeggen, louter omdat van een leeftijds criterium, ook al is hij of zij voor het overige nog in goede algemene toestand? Dergelijke denkpistes roepen steeds een verhitte maatschappelijke discussie op, gevoed vanuit soms diametraal tegenover elkaar staande waardensystemen.

Met deze studie over het al dan niet aanbieden van een georganiseerde borstkancerscreening aan vrouwen tussen de 70 en 74 jaar begeven we ons dus andermaal op glad ijs. Maar ook om andere redenen moeten we hier extra waakzaam zijn. Zoals bij elke georganiseerde opsparing richt men zich tot mensen die a priori geen gezondheidsklachten hebben en dus ook niet noodzakelijk om dit onderzoek gevraagd hebben. Het adagium *primum non nocere* is hier dus des te belangrijker.

Ook op het vlak van het te gebruiken argumentarium staan we voor een bijzondere uitdaging. De clinicus is immers doorgaans veel vertrouwder met de logica van de diagnosestelling bij een persoon met klachten dan met deze van screening. In het eerste geval is het risico op vals positieve resultaten niet alleen kleiner, maar het wordt duidelijk ook als minder belangrijk gezien dan het risico op een vals negatief resultaat, namelijk het missen van een diagnose. Dit verklaart mede waarom de nadelen van screening systematisch worden onderschat. Bovendien laat het onderwerp de publieke opinie zeker niet onberoerd, er wordt druk rond gelobbyd en het ligt (dus) ook politiek gevoelig.

Ook al mobiliseert men alle op dit moment voorhanden zijnde wetenschappelijke bevindingen om een advies te funderen, toch kan men niet hopen dat hiermee de controverse zal ophouden. Alleen durven we hopen dat we met dit rapport beantwoorden aan wat men in een dergelijk debat van een wetenschappelijk adviesorgaan mag verwachten.

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■ KORTE SAMENVATTING

INLEIDING

Dit werk maakt deel uit van een groter project met als doel het updaten van het rapport: "Borstkancerscreening", gepubliceerd in 2005 (KCE-rapport nr. 11). Het gaat hier meer bepaald om de uitbreiding van de georganiseerde screening naar vrouwen van 70 tot 74 jaar die voor de rest geen enkel symptoom vertonen dat op borstkanker zou kunnen wijzen, noch enige specifieke risicofactor hebben.

Borstkancerscreening is een complex proces dat zowel voordelen als nadelen inhoudt. De voornaamste voordelen van borstkancerscreening zijn een daling van de mortaliteit en de morbiditeit door borstkanker. Een daling van de morbiditeit houdt ofwel in dat een minder zware behandeling kan worden gegeven, ofwel dat er minder recidieven optreden of de ziekte minder vaak het gemetastaseerde stadium bereikt.

De voornaamste nadelen van de screening hebben te maken met de levenskwaliteit. Een vals-positief resultaat, een ontijdige diagnose (overdiagnose) gevolgd door een behandeling en het vervroegen van de diagnose kunnen de levenskwaliteit inderdaad negatief beïnvloeden.

Vals-positieve resultaten doen gezonde vrouwen terechtkomen in een circuit van angstwekkende, en soms zelfs invasieve (biopsies) diagnostische onderzoeken.

Overdiagnose kan worden gedefinieerd als de opsporing van kankergevallen die zonder screening nooit klinisch zouden zijn opgemerkt, en de frequentie neemt toe naarmate de levensverwachting in de gescreende populatie lager wordt. Overbehandeling is een gevolg van overdiagnose. Omdat het op dit moment onmogelijk is te voorspellen hoe een kanker verder zal evolueren, wordt het overgrote deel van de gediagnosticeerde kancers behandeld.

Door screening komen kancers twee tot drie jaar eerder aan het licht dan door klinische diagnose. Hierdoor wordt de vrouw dus reeds vroeger in haar leven geconfronteerd met het feit dat zij aan kanker lijdt en met de invasieve behandelingen ertegen.



ONDERZOEKSVRAGEN

Dit rapport onderzoekt volgende vraag: moet men de georganiseerde borstkancerscreening uitbreiden tot de groep vrouwen van 70 tot 74 jaar?

Als het antwoord op deze vraag negatief is, stelt zich nog een bijkomende vraag: welk antwoord moet men geven aan een vrouw uit die leeftijdscategorie die om een screening vraagt?

METHODOLOGIE

Het onderzoek van de klinische voordelen van screening is gebaseerd op een literatuuroverzicht uitgevoerd in OVID Medline, EMBASE, CDSR en DARE. In dit overzicht werden artikels opgenomen die in het Engels, Duits, Nederlands en Frans werden gepubliceerd vanaf januari 2004 tot april 2011.

De evaluatie van de risico's/baten-verhouding van deze screening is gebaseerd op een overzicht van modelleringsonderzoeken uit Medline, Embase, NHS EED en Econlit. In dit overzicht werden artikels opgenomen die werden gepubliceerd in het Engels, Duits, Nederlands en Frans vanaf januari 2000 tot september 2011.

Om de risico's/baten-verhouding in de Belgische context te kwantificeren, werd een specifiek model uitgewerkt. Voor het opbouwen van dit model werd in Medline, Embase, HTA EED en Psycinfo (1950-10/2011) gezocht naar onderzoeken rond de levenskwaliteit tijdens en na screening en behandeling van borstkanker. Het model maakt maximaal gebruik van de beschikbare Belgische gegevens.

Tenslotte werden op basis van het verkregen bewijsmateriaal een aantal praktijkaanbevelingen uitgewerkt en aan externe experten voorgelegd. Er werd geen enkel belangенconflict gemeld.

RESULTATEN VAN HET LITERATUUR-ONDERZOEK

Mortaliteit

De beschikbare gerandomiseerde en gecontroleerde studies brachten volgende feiten aan het licht:

- Screening gaat gepaard met een daling van de mortaliteit van 23% op een follow-up-periode van 13 jaar bij vrouwen boven de 50 jaar die om de twee jaar een screening ondergingen.
- De daling van de sterfte komt tussen de 4 en 7 jaar na de screening tot uiting. Deze gegevens zijn te bekijken in het perspectief van de gemiddelde levensverwachting in deze leeftijdscategorie, nl. 16 jaar op 70 jaar en 13 jaar op 74 jaar (Belgische gegevens voor 2009).

Bij de interpretatie van deze buitenlandse studies moet men er wel rekening mee houden dat in de leeftijdsgroep van 70 tot 74 jaar het aantal vrouwen dat aan de studies deelneemt niet erg hoog is; het effect op de mortaliteit kon voor hen niet statistisch worden aangetoond.

Morbiditeit

Naast het aantal gewonnen levensjaren is het voornaamste voordeel dat men van screening verwacht de mogelijkheid om minder agressieve behandelingen te kunnen instellen, aangezien screening tot doel heeft om tumoren aan het licht te brengen wanneer ze nog kleiner zijn. De Belgische gegevens waarover wij momenteel beschikken laten ons niet toe om deze bewering te valideren. De meest recente gegevens (KCE-rapport 150) maken gewag van 58% borstsparende chirurgie versus 38% totale mastectomieën in de minder gevorderde stadia (Stadia I en II). Bijna 90% van de vrouwen die een borstsparende ingreep ondergingen, kregen ook radiotherapie, 38% van hen kregen neo-adjuvante chemotherapie en 41% een hormonale behandeling.

Anderzijds gaven de gerandomiseerde gecontroleerde onderzoeken geen uitsluitsel over het percentage recidieven, noch over de evolutie naar metastatische stadia van de ziekte. Op deze basis kan de hypothese van een daling van de morbiditeit noch worden ontkracht, noch bevestigd.



Daarentegen werd het verlies van levenskwaliteit bij een gemitastaseerde kanker wel in het model opgenomen (zie hieronder).

MODELLERING

De voornaamste modellingsonderzoeken werden uitgevoerd in het CISNET-project (Cancer Intervention and Surveillance Modeling Network). Het doel van deze modellen was het evalueren van het relatieve aandeel van screening door mammografie resp. van adjuvante behandeling in de daling van de mortaliteit door borstkanker vastgesteld in de Verenigde Staten van 1974 tot 2000. Ze maakten gebruik van gegevens afkomstig van het Breast Cancer Screening Consortium.

De resultaten van deze modellen wijzen op een winst gaande van 9 tot 22 levensjaren per 1000 gescreende vrouwen. In het wetenschappelijk rapport worden ook andere modellen beschreven die geen gebruik maken van de CISNET-methodologie.

Deze modellen zijn niet zonder meer aanpasbaar aan de Belgische situatie aangezien het invoegen van Belgische gegevens onmogelijk is. Daarom werd een nieuw, specifiek model ontwikkeld.

EEN COHORTMODEL VOOR BELGIE

Methodologie

Het model dat voor dit rapport werd ontworpen, is een cohortmodel dat evolueert via jaarcycli. In dit model worden twee theoretische cohorten van vrouwen ouder dan 70 jaar met elkaar vergeleken. Eén cohort krijgt geen uitnodiging voor een screening (huidige situatie), in de andere cohort worden vrouwen verder uitgenodigd om deel te nemen aan screening. Voor het deelnemingspercentage en de verdeling van de door screening opgespoorde kancers versus de intervalkancers worden dezelfde cijfers als in de leeftijdsgroep van 50-69 jaar genomen.

De bedoeling van screening is tumoren in een vroeg stadium (I en II) aan het licht te brengen teneinde een evolutie te voorkomen naar stadium IV (metastatisch stadium) dat ongeneeslijk is. Deze 'stage shift' houdt in dat bij de opgespoorde kancers het aantal vroege stadia (I, II) toeneemt terwijl tegelijkertijd het aantal gevorderde stadia (II en IV) verminderd.

Verder hebben we de hypothese vooropgesteld dat overleving en levenskwaliteit afhangen van de leeftijd van de patiënt en van het tumorstadium. Deze hypothese houdt geen rekening met het feit dat de prognose van de door screening opgespoorde kancers beter is dan die van klinisch opgespoorde kancers (intervalkancers en kancers die optreden bij vrouwen die niet aan screening deelnemen).

Parameters

Dit model maakt maximaal gebruik van Belgische gegevens, nl. de gemiddelde levensverwachting van de vrouwen volgens hun leeftijd (2009), de gegevens van het kankerregister (voor de Vlaamse Gemeenschap), de gegevens afkomstig van het huidige screeningsprogramma (50-69 jaar), de tijd nodig voor het ontkrachten van een vals-positief resultaat (IMA/AIM) en de gegevens over overleving na vijf jaar in functie van het stadium (kankerregister). De gegevens van de Vlaamse Gemeenschap werden gebruikt omdat ze vollediger zijn en omdat opportunistische screening na 70 jaar er minder vaak gebeurt dan in de rest van het land. Hoeveel vroeger de diagnose wordt gesteld en het percentage overdiagnose werden bepaald op basis van de literatuuranalyse.

Meting van de levenskwaliteit

De gegevens over de levenskwaliteit tijdens screening en behandeling zijn afkomstig uit de literatuur. Voor het beschrijven van de gezondheidstoestand werd het EQ-5D (European Quality of Life-5 Dimensions) instrument gebruikt; deze beschrijvingen werden gevaloriseerd door de algemene engelse bevolking ("UK tariffs"). We konden niet over gegevens beschikken met betrekking tot de Belgische bevolking.

De veranderingen in levenskwaliteit van vrouwen ouder dan 70 jaar die in de modellen werden gebruikt, zijn de volgende:

- Het verlies aan levenskwaliteit na een vals-positief screeningsresultaat wordt geraamd op 16%, gedurende 45 dagen.

- Voor de kankerpatiënten en tijdens het eerste jaar volgend op de diagnose (ongeacht het type behandeling) wordt het verlies aan levenskwaliteit geraamd op 16% voor de stadia I,II,III en op 18% voor de stadia IV. Tijdens de volgende jaren wordt het verlies aan levenskwaliteit geraamd op 6% voor de stadia I,II,III. Dit verlies blijft stationair (18%) voor de stadia IV.

Omdat aan deze benadering verschillende beperkingen verbonden zijn, moeten deze cijfers met de nodige omzichtigheid worden geïnterpreteerd.

Resultaten

Het basisscenario toont dat screening tussen 70 en 74 jaar 1,3 overlijden zou kunnen voorkomen per 1000 deelnemende vrouwen, hetgeen een daling van de sterfte met 21% vertegenwoordigt. Het globaal aantal gewonnen levensjaren wordt geraamd op 13,1 en de winst aan QALY's op 3,9.

Omdat er veel onzekerheid is met betrekking tot deze ramingen (voor details, zie de bespreking in het wetenschappelijk rapport), werd een sensitiviteitsanalyse op het model uitgevoerd. Deze analyse omvat een pessimistisch scenario en een optimistisch scenario.

Het pessimistisch scenario gaat uit van een hypothese met 20% overdiagnose en 10% vals-positieven, waardoor een verlies van levenskwaliteit optreedt van 0,19 dat gedurende 54 dagen aanhoudt (de tijd nodig om de resultaten te ontkrachten). Voor de gescreende groep werd de verdeling van de opgespoorde kancers per stadia gebruikt die momenteel wordt vastgesteld in het kader van de georganiseerde screening (50-69 jaar) in Vlaanderen. Dit pessimistisch scenario raamt een winst van 8,7 levensjaren, maar **een verlies** van 3,1 QALY's per 1000 vrouwen die aan de screening deelnamen. Dit betekent dat in bepaalde omstandigheden - en we blijven hierbij zeker realistisch - de screening kan leiden tot een daling van de levenskwaliteit.

Het optimistisch scenario gaat uit van een hypothese met 3% overdiagnose en 2% vals-positieven, waardoor een verlies van levenskwaliteit optreedt van 0,13 gedurende 36 dagen. Dit scenario past op de gescreende groep de verdeling per stadia toe die momenteel wordt vastgesteld in het kader van de in Nederland georganiseerde screening (70-74 jaar). Dit optimistisch scenario raamt een winst van 17,0 levensjaren en **een winst** van 16,3 QALY's per 1000 vrouwen die aan de screening deelnamen. Dit betekent dat het nodig is om gedurende vijf jaar 67 vrouwen voor een screening uit te nodigen om één QALY te winnen.

CONCLUSIE

Het doel van het organiseren van screenings is het verbeteren van het welzijn van de bevolking door voortijdige overlijdens te voorkomen. Uiteraard zou het uitbreiden van de screening naar de leeftijd van 74 jaar het mogelijk maken om voor een bepaald aantal vrouwen enkele levensjaren te winnen. De invloed van georganiseerde screening op de levenskwaliteit is echter veel onzekerder (erg laag niveau van bewijskracht, want gebaseerd op een model). Volgens bepaalde realistische hypothesen zou deze interventie zelfs een verlies van levenskwaliteit kunnen veroorzaken. In deze omstandigheden zou de balans tussen de voor- en nadelen van screening globaal eerder kunnen doorslaan naar de kant van een verlies van welzijn van de bevolking.

Er wordt dus niet aanbevolen om de georganiseerde borstkancerscreening uit te breiden tot de groep vrouwen van 70 tot 74 jaar.



■ AANBEVELINGEN^a

- Het systematisch uitnodigen van vrouwen tussen 70 en 74 jaar om deel te nemen aan georganiseerde borstkancerscreening wordt niet aanbevolen.
- Als een vrouw boven de 70 jaar vraagt om een mammografie in het kader van een screening zal de arts erover waken dat de vrouw goed op de hoogte wordt gebracht van de voordelen en mogelijke nadelen die deze screening met zich mee kan brengen.
- Elke screeningsmammografie moet beantwoorden aan de Europese vereisten op het vlak van kwaliteit, met name: de controle en kwaliteit van de installaties, de dubbele lezing, de registratie en de optimalisering van het *recall*-percentage. Daarom zal de arts de vrouw die om een screening vraagt, doorverwijzen naar een structuur die aan deze kwaliteitsvereisten beantwoordt.
- Om het risico op een verlies aan levenskwaliteit te wijten aan vals positieve resultaten te minimaliseren is het belangrijk dat de propotie vrouwen die teruggeroepen wordt voor verder onderzoek zo laag mogelijk is en onder de Europese vereisten blijft (<5%).

^a

Het KCE blijft als enige verantwoordelijk voor de aanbevelingen die aan de overheid worden geformuleerd.



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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
CPG	Clinical Practice Guideline
CCRT	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
DCIS	Ductal Carcinoma in situ
DET	Data Extraction Table
BCSC	Breast Cancer Surveillance Consortium (USA)
AHRQ	Agency for Health Care Research and Quality
BCR	Belgian Cancer Registry
DNETB	Dutch National Evaluation Team for Breast cancer screening
CISNET	Cancer Intervention and Surveillance Modelling Network
IMA/AIM	Intermutualistic Agency
INAMI/RIZIV	National Institute for Health and Disability Insurance
ICER	Incremental cost-effectiveness ratio
KCE	Belgian Healthcare Knowledge Centre
MST	Mean Sojourn Time
M-A	Meta-analysis
NIS	National Institute for Statistics
NBSS	Canadian National Breast Cancer Screening Study
NBCSP	Norwegian Breast Cancer Screening Programmes
NHS	National Health Service (UK)
NHS EED	NHS Economic Evaluation Database
NCI	National Cancer Institute (USA)
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomized Controlled Trial
RR	Relative Risk



SEER	Surveillance, Epidemiology and End Results (USA)
SR	Systematic Review
ST	Sojourn Time
TTO	Time-trade-off
UK	United Kingdom
USA	Unites States of America
USPSTF	US Preventive Services Task Force



■ SYNTHESE

1. CONTEXT

Het KCE publiceerde al drie rapporten over borskankerscreening. Het basisrapport, gepubliceerd in 2005 (KCE-rapport nr. 11) betrof borstkankerscreening in het algemeen, in de bevolking zonder risicofactoren. Borstkankerscreening bij vrouwen in de leeftijdsklasse van 40-49 jaar was het onderwerp van een gedeeltelijke bijwerking gepubliceerd in 2010. In dit rapport (KCE-rapport nr. 129) beval het KCE geen systematische screening aan bij vrouwen jonger dan 50 jaar. Het derde rapport (KCE-rapport nr. 172), gepubliceerd in 2012, stelde het probleem van de opsporing van vrouwen die een verhoogd risico op borstkanker hebben. In dit rapport wordt onderzocht of men de georganiseerde borstkankerscreening moet uitbreiden naar vrouwen van 70 tot 74 jaar.

Deze vraag wordt vaak gesteld aan politici omwille van de stijging van de levensverwachting van de vrouwelijke bevolking. Hoewel de meeste groepen die actief zijn bij screening deze uitbreiding vragen, zijn de openbare instanties hierover minder unaniem. Slechts vier lidstaten van de Europese Unie richten zich op de leeftijdsgroep van 70-74 jaar (Frankrijk, Nederland, Spanje en Zweden)¹. De andere landen benadrukken dat het noodzakelijk is om de vrouwen te informeren en de beslissing samen met hen te nemen.

2. ONDERZOEKSVRAGEN

Moet de georganiseerde borstkankerscreening worden uitgebreid tot de leeftijd van 74 jaar? Als het antwoord op deze vraag negatief is, wat moet men dan zeggen tegen een persoon die om deze screening vraagt?

De eerste vraag heeft meer specifiek betrekking op de openbare instanties en de tweede op de zorgverleners.



3. BESCHRIJVING VAN DE PROBLEMATIEK

3.1. Intuïtieve benadering

Op intuïtief vlak heeft borstkancerscreening zeker zin. De media zijn meestal erg enthousiast over screening. Deze houding werd aangetoond door Schwartz begin 21^{ste} eeuw². Een enquête uitgevoerd in de Verenigde Staten toonde aan dat 87% van de volwassenen van oordeel was dat screening een goed idee is. Drie vierde van de ondervraagde personen verklaarde dat het opsporen van kanker in een vroeg stadium in de meeste gevallen levens redt. Het enthousiasme van de respondenten was zo groot dat voor de meesten van hen screening geen te nemen beslissen was, maar een morele verplichting³.

Deze algemene houding die we als volgt kunnen samenvatten "vroegtijdige opsporing van kancers kan levens redden", kan onrealistische verwachtingen wekken bij vrouwen. Silverman realiseerde telefonische interviews om te evalueren hoe vrouwen borstkanker en het voordeel van screening via mammografie zien. De meeste respondenten beschouwden borstkanker als een uniform progressieve ziekte en geloofden dat alle kancers beginnen met een geneesbare en stille vorm⁴. Samengevat, deze vrouwen waren van oordeel dat indien borstkanker niet wordt opgespoord door een mammografie en vroegtijdig behandeld, de kanker groeit, zich vermeerderd en doodt. Omwille van deze opvattingen, gaan vrouwen ervan uit dat gevorderde kancers (en zonder enige twijfel de meeste dodelijke kancers) samenhangen met het falen van vroegtijdige opsporing.

Schwartz beklemtoonde dat 94% van de vrouwen niet weten dat screening kancers kan opsporen die zich nooit zullen ontwikkelen. Bovendien is 92% van de respondenten ervan overtuigd dat mammografie ongevaarlijk is voor een persoon die geen borstkanker heeft⁵.

Het medisch korps zelf begrijpt de screening niet altijd op een adequate manier. Daardoor blijven talrijke clinici zich concentreren op het percentage gediagnosticeerde kancers (tussentijds doel), terwijl het uiteindelijke doel van de opsporing het verlagen van de mortaliteit is. Anderzijds lijken clinici gevoeliger voor het risico van het miskennen van

een kanker (vals-negatief) dan voor de risico's die samenhangen met vals-positieve resultaten.

3.2. Epidemiologische benadering

Borstkanker is de meest voorkomende kanker bij de vrouw. In België werden 10.849 gevallen van borstkanker gediagnosticeerd in 2008. Meer dan drie vierde van de borstkancers wordt gediagnosticeerd na de leeftijd van 50 jaar. Het gemiddelde ogenblik van de diagnose is 62 jaar. De incidentie van borstkanker is **370,7/100.000** in de groep vrouwen van 70 tot 75 jaar⁶.

Nochtans verschilt het relatieve aandeel van mortaliteit veroorzaakt door borstkanker in het totale percentage mortaliteit in functie van de leeftijd. In 1999 was borstkanker verantwoordelijk voor 18% van de overlijdens bij vrouwen van 50 tot 54 jaar, 13% in de groep van 60 tot 64 jaar en 6% in de groep van 70 tot 74 jaar (KCE-rapport nr.11). In 2006 bedroeg dit percentage 14% voor vrouwen van 50 tot 54 jaar, 12% voor de groep van 60 tot 64 jaar, 7% voor de groep van 70 tot 74 jaar en 5% voor de groep van 75 tot 79 jaar⁶.

Essentiële kenmerken van screening:

1. Screening is bedoeld voor personen in goede gezondheid **In tegenstelling tot een patiënt die zijn arts raadpleegt omwille van een klacht of een symptoom, wordt ervan uitgegaan dat een persoon die deelneemt aan een screening niet lijdt aan de ziekte die wordt opgespoord.**
2. Screening heeft als doel om op korte termijn de afwezigheid van de ziekte te bevestigen.
3. Screening heeft als uiteindelijk doel de mortaliteit/morbiditeit die samenhangt met de ziekte te verminderen.
4. Het principe "primum non nocere" (in ieder geval geen kwaad doen) is vooral van toepassing op screening.

Wij wensen eraan te herinneren dat op duizend gescreende vrouwen tussen 70 en 74 jaar, meer dan 990 geen borstkanker hebben.



3.2.1. Doel op korte termijn

Screening heeft als doel om de afwezigheid van de ziekte te bevestigen. De persoon die aan screening deelneemt, geniet van "het vermoeden van onschuld" wat betreft borstkanker. Daarentegen wordt de patiënt die zijn arts raadpleegt omdat hij een klacht heeft of omdat hij iets ongewoon heeft opgemerkt, "verdacht" van ziekte. Het doel van de arts en de middelen die hiertoe worden gebruikt, staan in deze twee situaties diametraal tegenover elkaar. In het geval van het scherpstellen van een diagnose heeft de arts de plicht om alle middelen in te zetten om een etiologie te vinden voor de klacht of het symptoom. In het geval van screening daarentegen, heeft de arts de plicht om alleen de onontbeerlijke onderzoeken uit te voeren. De bedoeling hiervan is om de risico's en ongemakken van screening voor de vrouwen die geen borstkanker hebben zo gering mogelijk te houden.

Omdat de opleiding van artsen voornamelijk gebeurt in hospitalen bij zieken gaat deze verandering van gezichtspunt volledig in tegen de intuïtie van een clinicus.

3.2.2. Uiteindelijk doel

Diagnosticeren van kanker in een vroeg stadium vooraleer de ziekte zich kan ontwikkelen en uitzaaien (metastasen) is het basisprincipe van borstkancerscreening. Daarom verwacht men dat screening de mortaliteit die specifiek gekoppeld is aan de ziekte zal verminderen, en bijgevolg ook de totale mortaliteit. Het feit dat de gebruikte technologie toelaat om weinig gevorderde, en dus mogelijk nog geneesbare laesies te diagnosticeren, vormt een tussenstap in dit proces. Het betreft hier dus een noodzakelijke voorwaarde die echter onvoldoende is⁷.

Men kan ook de hypothese vooropstellen dat screening de morbiditeit die gepaard gaat met de ziekte vermindert, doordat het mogelijk wordt om minder invasieve behandelingen te gebruiken (gedeeltelijke mastectomie in plaats van totale mastectomie) en doordat men een deel van de progressie naar metastatische fasen kan voorkomen.

3.2.3. Vals-positieven en overtollige diagnoses

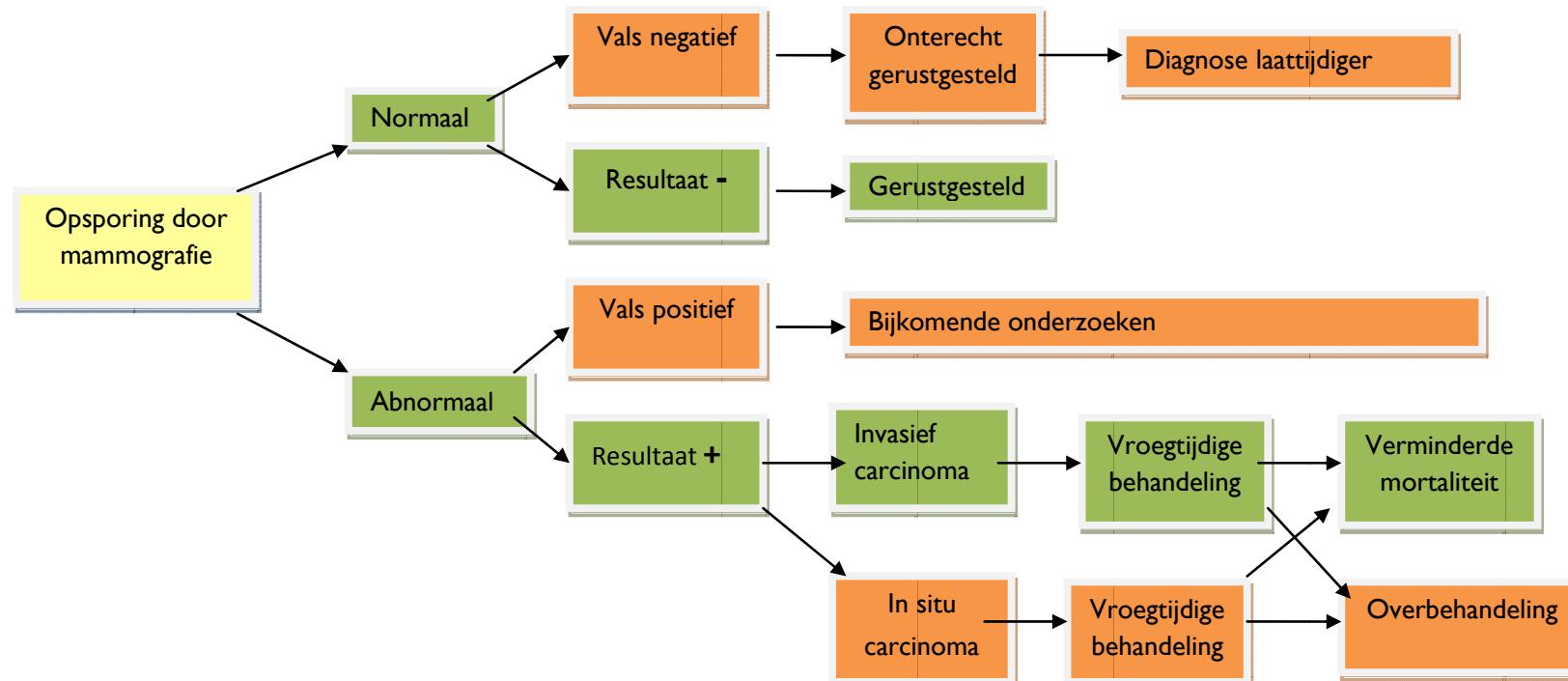
Vooraleer een georganiseerde screening in te voeren, is het nodig er zeker van te zijn dat de verhouding voordelen/nadelen van screening overhelt naar de kant van de voordelen. Om dit te doen moet de grootte van de daling van de mortaliteit het verlies aan levenskwaliteit compenseren veroorzaakt door ongemakken en risico's van de screening.

De zogenaamd "vals-positieve" resultaten (vermoeden van kankerlaesies zonder de aanwezigheid van kanker) zijn de ongewenste negatieve gevolgen van borstkancerscreening die het vaakst voorkomen. Deze vals-positieve resultaten zorgen voor heel veel angst en het uitvoeren van bijkomende onderzoeken.

Meer nog dan de vals-positieve resultaten is vooral het risico van overtollige diagnose het grootste risico van screening bij vrouwen van 70 tot 74 jaar. Overtollige diagnose kan worden gedefinieerd als het diagnosticeren van kanker waarvan de evolutie zodanig is dat ze zich nooit klinisch zou manifesteren wanneer er geen screening zou hebben plaatsgevonden⁸. Dit risico is des te groter naarmate de kanker slechts traag evolueert en de levensverwachting van de persoon laag is. Vooral dit risico is weinig bekend bij de bevolking. Zeer weinig vrouwen weten inderdaad dat sommige kankers zo langzaam evolueren dat, zelfs al worden ze niet behandeld, ze geen invloed zouden hebben op de gezondheid⁹.

Dit rapport heeft tot doel om de voor- en nadelen te bepalen (zie Fig. 1) van deze screening om ze in perspectief te kunnen plaatsen en ervoor te zorgen dat de voordelen grotendeels opwegen tegen het risico van verlies van levenskwaliteit.

Figuur 1 - mogelijke voor- en de nadelen van screening.





4. METHODOLOGIE

We hebben elementen voor een antwoord op voorgenomen vragen gezocht in de klinische literatuur, in modelleringsstudies en in nationale en internationale gegevens. Dit opzoekingswerk werd uitgevoerd volgens de bij het KCE geldende procedures. Ze worden gedetailleerd beschreven in hoofdstuk 2 van het wetenschappelijk rapport.

4.1. Raming van de voordelen van screening

4.1.1. Daling van de mortaliteit

De meest bewijskrachtige gegevens met betrekking tot borstkankerscreening komen uit acht gerandomiseerde gecontroleerde studies. Op basis van deze studies kunnen twee belangrijke vaststellingen worden gedaan:

1. Screening zorgt voor een daling van de mortaliteit met 23% over een opvolgingsperiode van 13 jaar voor vrouwen ouder dan 50 jaar die elke twee jaar een screening ondergingen.
2. Deze daling van de mortaliteit komt 4 tot 7 jaar na de screening tot uiting. Dit moet in perspectief geplaatst worden ten opzichte van de levensverwachting van de doelpopulatie. De gemiddelde levensverwachting in deze leeftijdscategorie is 16 jaar op 70 jaar en 13 jaar op 74 jaar (Belgische gegevens voor 2009).

De bewijskrachtige gegevens van deze gerandomiseerde gecontroleerde studies kunnen geen antwoord geven op onze basisvraag. Slechts één enkele gerandomiseerde studie, de Zweedse "Two County"-studie, bevatte ook vrouwen in de leeftijdscategorie van 70 tot 74 jaar en het aantal zeventigjarigen dat aan deze studie deelnam was te laag (10.000 voor de twee groepen) om een statistisch significant effect op de mortaliteit te kunnen aantonen. Bovendien werd deze studie gehinderd door methodologische bias.

4.1.2. Verbetering van de levenskwaliteit van patiënten

Hoewel screening als doel heeft kleine tumoren aan te tonen, is een van de verwachte voordelen dat het zal toelaten om minder agressieve behandelingen te gebruiken. Nog de gegevens afkomstig uit gerandomiseerde gecontroleerde studies, noch feitelijke gegevens verzameld in België laten toe om deze verwachtingen te bevestigen.

Gerandomiseerde gecontroleerde onderzoeken hebben nog het percentage recidieven, noch de evolutie naar metastatische stadia van de ziekte gekwantificeerd. Op deze basis kan de hypothese van een daling van de morbiditeit dus noch worden ontkracht, noch bevestigd. Daarentegen werd een verlies van levenskwaliteit door metastasen wel in het hieronder beschreven model opgenomen.

De Belgische gegevens waarover wij momenteel beschikken laten ons niet toe om deze bewering te valideren. De meest recente gegevens (KCE-rapport 150) maken gewag van 58% conservatieve chirurgie versus 38% totale mastectomieën in de minder gevorderde stadia (Stadia I en II). Bijna 90% van de vrouwen die een conservatieve chirurgische ingreep ondergingen, kregen ook een behandeling met radiotherapie, 38% van hen kregen een neo-adjuvante behandeling met chemotherapie en 41% een hormonale behandeling.



4.2. Raming van de nadelen van screening

4.2.1. Vermindering van de levenskwaliteit van patiënten

Screening veroorzaakt een vermindering van de levenskwaliteit van een deel van de gescreende personen. Dit kan worden verklaard door een reeks factoren:

1. De vals-positieve resultaten van screening worden door de patiënten ervaren als terecht-positieve resultaten gezien zolang de bijkomende onderzoeken ze niet hebben kunnen ontkrachten. Ze veroorzaken ongerustheid met betrekking tot borstkanker en de invasieve procedures zoals puncties.
2. De overtollige diagnoses en behandelingen die erop volgen (overdiagnose en overbehandeling (voor meer details zie het wetenschappelijk rapport), leiden tot ernstige ongerustheid en zware behandelingen waaronder borstamputaties die geen invloed hebben op de overleving van de persoon.
3. Een voortijdige diagnose kan leiden tot het verlies van meerdere levensjaren in goede gezondheid. Screening heeft als doel om kanker vroeger op te sporen dan met een klinische diagnose. De patiënt wordt hierdoor vroeger in haar leven ziek van kanker. Wanneer deze patiënt overlijdt aan een oorzaak die niets te maken heeft met haar kanker, dus voordat die kanker de kans kreeg te evolueren, zou ze enkele jaren te vroeg "aan kanker geleden hebben" terwijl deze voortijdige diagnose en behandeling geenszins een invloed had op haar levensverwachting¹⁰.

4.3. Benadering door modellisering

Met voornoemde literatuuronderzoeken konden we de verhouding tussen voor- en nadelen niet afwegen en daarom hebben we hiervoor een specifiek model uitgewerkt. Voor het uitwerken van dit model was het nodig studies te zoeken met betrekking tot de levenskwaliteit van vrouwen tijdens de screening en de levenskwaliteit van patiënten tijdens hun ziekte.

4.3.1. Meting van de levenskwaliteit

Er zijn verschillende instrumenten beschikbaar voor het meten van de levenskwaliteit. Bepaalde instrumenten zijn specifiek aangepast aan de ziekte zoals bijvoorbeeld de vragenlijst met betrekking tot de levenskwaliteit van patiënten die aan borstkanker lijden van de European Organization for Research and Treatment of Cancer (EORTC). Deze hulpmiddelen evalueren het beeld dat de patiënt heeft van haar lichaam, haar psychologisch functioneren, de angst voor hervallen... Het is echter niet mogelijk om met deze multidimensionale gezondheidsgegevens rekening te houden in een model. Ze moeten worden omgezet in een globale index voor levenskwaliteit, nl. de Quality-Adjusted Life-Year (QALY). De QALY's zijn het aantal levensjaren met een goede levenskwaliteit.

De farmaco-economische aanbevelingen van het KCE gaan ervan uit dat de vragenlijst EQ-5D een van de beste hulpmiddelen is die beschikbaar is voor het evalueren van de QALY's. Met dit hulpmiddel wordt de levenskwaliteit gekoppeld aan de gezondheidstoestand rekening houdend met vijf elementen: mobiliteit, autonomie van de persoon, dagelijkse activiteiten, pijn/hinder, angst/depressie. Voor elk van deze elementen zijn meerdere antwoorden mogelijk. Die verwijzen naar de ernst van het probleem (geen probleem, enkele problemen, matige problemen, ernstige problemen). Deze vragenlijst wordt voorgelegd aan de betrokken populatie, dus voor screening aan een populatie van vrouwen die niet aan borstkanker lijden, en voor de ziekte zelf aan een populatie patiënten met borstkanker. Via het literatuuroverzicht konden drie studies worden opgespoord die aan onze inclusiecriteria voldeden. Op basis van deze studies worden de variaties in levenskwaliteit bij zeventigjarigen als volgt geraamd:

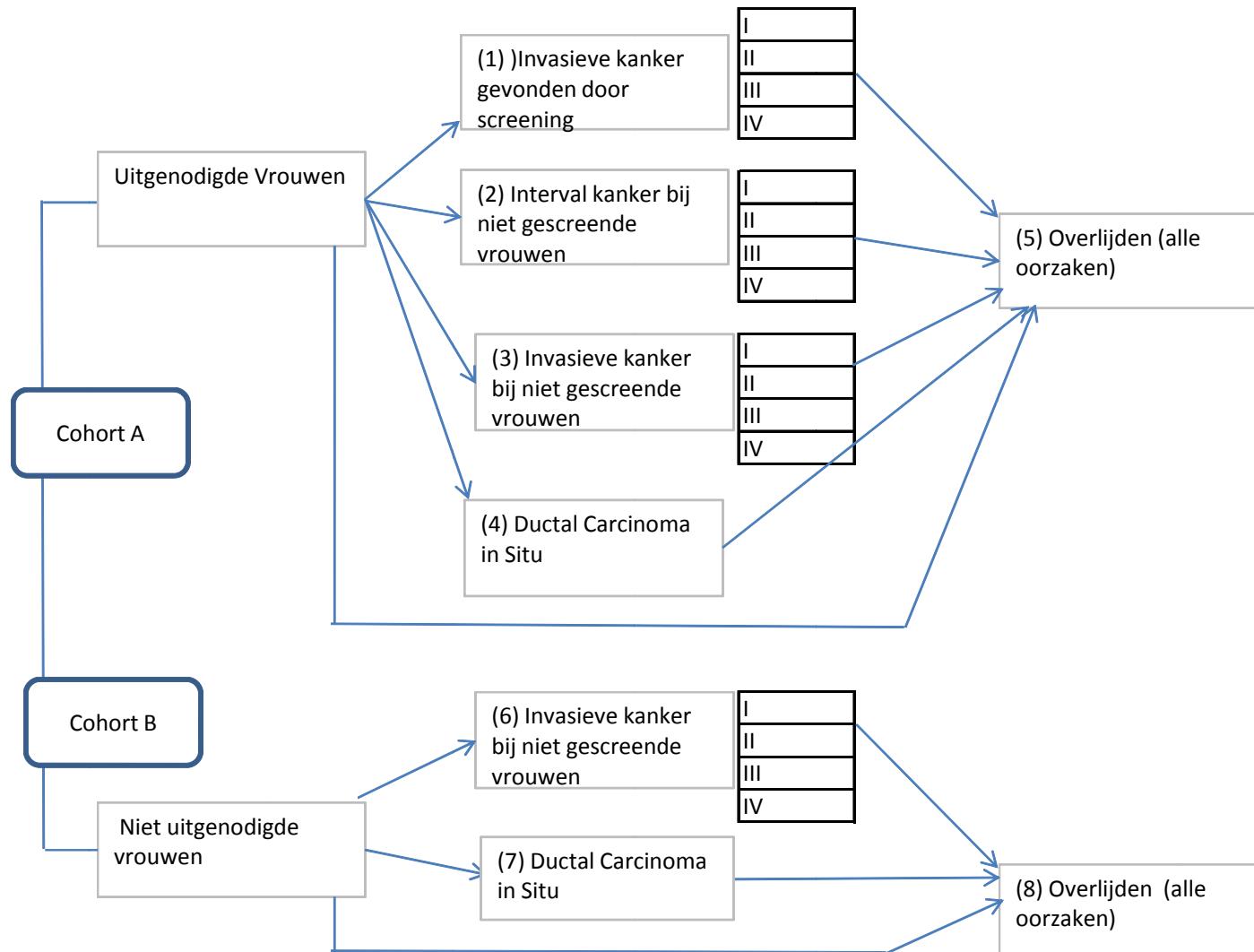


1. Het verlies aan levenskwaliteit voortvloeiend uit een vals-positief screeningresultaat wordt geraamd op 16% tijdens de periode die nodig is om dit vals-positieve resultaat te ontkrachten. In België duurt die periode gemiddeld 45 dagen (min. 36, max. 54 dagen) volgens de gegevens van het Intermutualistisch Agenschap (IMA).
2. Voor de kankerpatiënten, en tijdens het eerste jaar volgend op de diagnose (bij om het even welke behandeling), wordt het verlies aan levenskwaliteit geraamd op 16% voor de stadia I,II,III en op 18% voor de stadium IV. Tijdens de volgende jaren wordt het verlies aan levenskwaliteit geraamd op 6% voor de stadia I,II,III. Dit verlies blijft stationair (18%) voor de stadium IV.

Omdat aan deze benadering verschillende beperkingen verbonden zijn, moeten deze cijfers met de nodige omzichtigheid worden geïnterpreteerd. Het betreft hier resultaten uit Angelsaksische landen. De gebruikte vragenlijst, nl. EQS-5D, meet de algemene gezondheidsdimensies en niet de dimensies die specifiek zijn voor borstkanker. De maatregelen met betrekking tot de patiënten houden slechts in geringe mate rekening met de impact op korte termijn van de diagnose en de chirurgie. Deze vragenlijst werd gebruikt tijdens ambulante consultaties en de resultaten ervan weerspiegelen dus niet de levenskwaliteit van ernstig zieke patiënten die zich niet meer kunnen verplaatsen. Het bijzondere karakter van de gebruikte studie zou de geringe wijziging in levenskwaliteit kunnen verklaren die werd vastgesteld tussen patiënten met borstkanker en de algemene populatie of tussen patiënten met metastasen en zij die geen metastasen ontwikkelden.

4.3.2. Beschrijving van het product

Het model bevat twee theoretische cohorten. Deze twee cohorten zijn samengesteld uit 100.000 vrouwen waarvan de evolutie wordt gevolgd tot aan hun overlijden. Hieronder vindt u het schema dat deze evolutie weergeeft.



Cohort A illustreert de hypothese van een uitbreiding van de georganiseerde screening tot 74 jaar. Het cohort is samengesteld uit vrouwen die uitgenodigd werden om deel te nemen aan screening. Sommigen van hen namen deel (uitgenodigd/deelnemer) en anderen niet (uitgenodigd/niet-deelnemer). De kankers die zich voordeden in het cohort werden geïnventariseerd. Het betreft hier kankers die werden gediagnosticeerd tijdens de screening (1), of kankers die werden gediagnosticeerd in het interval tussen twee screenings (2), of kankers die gediagnosticeerd werden in de groep van de uitgenodigden/niet-deelnemers (3). De ductale carcinomen *in situ* tenslotte kunnen voorkomen in de groep uitgenodigden/deelnemers net zoals bij de groep van de uitgenodigden/niet-deelnemers (4). De overgrote meerderheid van de vrouwen die dit cohort uitmaakten overleden aan een andere aandoening dan borstkanker (5).

Cohort B (controle-cohort) komt overeen met de huidige situatie. De leden van dit cohort werden niet uitgenodigd voor de screening. Sommige vrouwen werden getroffen door een invasieve kanker (6), andere door een ductaal carcinoom *in situ* (7). De overgrote meerderheid van de vrouwen die dit cohort uitmaakten overleden aan een andere aandoening dan borstkanker (8).

Borstkanker evolueert in vier stadia (I, II, III, IV). Stadium I is het minst gevorderde stadium. Overleving is per definitie minder goed en de behandeling is des te zwaarder en meer invasief wanneer de kanker zich in een meer gevorderd stadium bevindt op het moment van de diagnose.

4.3.3. Basishypothesen

De basishypothese is de volgende: bij de kankers die worden opgespoord door screening, is het percentage weinig gevorderde kankers (stadia I en II) groter dan bij kanker die klinisch gediagnosticeerd wordt. Alle voordelen van screening komen voort uit de verschillen tussen de verdeling van de stadia (stage-shift) volgend op de screening.

De andere weerhouden hypothese is dat de overleving en de levenskwaliteit van de vrouwen uitsluitend afhankelijk is van het stadium van de tumor en de leeftijd van de vrouw op het ogenblik van de diagnose, of dit nu al dan niet volgt op een screening.

De cohorten werden jaar na jaar opgevolgd in functie van de overgangsparameters zoals het aantal vrouwen dat elk jaar getroffen wordt (incidentie) en het overlevingspercentage in functie van het kankerstadium.

4.3.4. Gegevensinvoer voor het model

Om deze oefening te kunnen doen, hebben we zo goed mogelijk de Belgische gegevens in ons model ingevoerd. Deze parameters worden gedetailleerd beschreven in hoofdstuk 3.3 van het rapport.

De levensverwachting van de onderzochte populatie is afkomstig van de overlevingstabellen van de vrouwelijke populatie van dezelfde leeftijdsgroep. De incidentie van kanker in functie van de leeftijd en de stadia van de ziekte is afkomstig van het Belgisch Kankerregister (Vlaamse Gemeenschap). De gegevens met betrekking tot de screening zijn afkomstig uit de huidige programma's (vrouwen van 50-69 jaar in Wallonië, Brussel en de Vlaamse Gemeenschap).

Voor elk compartiment van het model werd de levenskwaliteit gemeten. Het model bevat een basisscenario (base case) dat overeenstemt met de meest aannemelijke situatie.

"In wezen zijn alle modellen vals, maar sommige zijn nuttig"^a

4.3.5. Sensitiviteitsanalyse

In ons model zijn we uitgegaan van een zeker aantal simplificerende hypothesen omwille van de gegevens waarover we beschikken, en de noodzaak om te vermijden een te complex model te gebruiken. Deze keuze veroorzaakt onzekerheid die verband houdt met de structuur van het model, met de goede keuze van de parameters en met de bron van de informatie. Om aan deze verschillende soorten onzekerheden het hoofd te kunnen bieden, hebben we een diepgaande sensitiviteitsanalyse uitgevoerd waarbij we gebruik maakten van verschillende scenario's. Deze verschillende scenario's worden gedetailleerd beschreven in tabel 3.2 van het wetenschappelijk rapport.

^a citaat toegeschreven aan de statisticus George Box.



5. RESULTATEN

Het basisscenario toont dat uitbreiding van de screening tot 74 jaar 1,3 overlijdens zou kunnen voorkomen per 1000 deelnemende vrouwen, hetgeen een daling van de sterfte met 21% vertegenwoordigt. Het aantal gewonnen levensjaren wordt geraamd op 13,1 en de winst in QALY op 3,9.

Deze sensitiviteitsanalyse omvat een pessimistisch scenario en een optimistisch scenario.

Het pessimistisch scenario gaat uit van een hypothese met een overtollige diagnose van 20%, een percentage vals-positieven van 10% waardoor een verlies van levenskwaliteit wordt veroorzaakt van 0,19 dat gedurende 54 dagen aanhoudt (de tijd nodig om de resultaten te ontkrachten). Op de gescreende groep werd de verdeling van de opgespoorde kankers per stadia die momenteel wordt vastgesteld in het kader van de in Vlaanderen georganiseerde screening (50-69 jaar), toegepast. Dit pessimistisch scenario raamt een winst van 8,7 levensjaren, maar een **verlies van 3,1 QALY** per 1000 vrouwen die aan de screening deelnamen. Dit betekent dat in bepaalde omstandigheden - en we blijven hierbij zeker realistisch - de screening kan leiden tot een daling van de levenskwaliteit.

Het optimistisch scenario gaat uit van een hypothese met een overtollige diagnose van 3%, een percentage vals-positieven van 2% waardoor een verlies van levenskwaliteit wordt veroorzaakt van 0,13 dat gedurende 36 dagen aanhoudt. Dit scenario past op de gescreende groep de verdeling per stadia toe die momenteel wordt vastgesteld in het kader van de in Nederland georganiseerde screening (70-74 jaar). Dit optimistisch scenario raamt een winst van 17,0 levensjaren en een winst van 16,2 QALY per 1000 vrouwen die aan de screening deelnamen. Dit betekent dat het nodig is om gedurende vijf jaar 62 vrouwen voor een screening uit te nodigen om een QALY te winnen.

6. BESPREKING

De resultaten van het hierboven beschreven model wijzen erop dat, wat de basissituatie betreft, de winst in levensjaren 13 jaar bedraagt per 1000 gescreende vrouwen. Dit resultaat blijft betrouwbaar doorheen gans de sensitiviteitsanalyse. De QALY daarentegen variëren aanzienlijk in functie van de gekozen hypothesen, gaande van een relatief geringe winst tot, volgens sommige geloofwaardige hypothesen, een verlies aan levenskwaliteit.

6.1. Levensjaren toevoegen?

De verhoging van de levensverwachting van de vrouw is één van de argumenten die worden gebruikt om borstkancerscreening uit te breiden tot vrouwen die ouder zijn dan 69 jaar. Dit argument gaat uit van de veronderstelling dat de populatie van de zeventigjarigen dezelfde kenmerken heeft als de populatie van de zestigjarigen. Dit is helemaal niet het geval voor het aantal vrouwen dat overlijdt en hun doodsoorzaak.

Het aantal overlijdens vastgesteld in de leeftijdsgroep van 70-79 jaar is tweeënhalve keer zo hoog als die in de leeftijdsgroep van 60-69 jaar. De Belgische populatie verliest 4% van haar effectieve leden tussen 50 à 59 jaar, 8% tussen 60 à 69 jaar en 20% tussen 70 à 79 jaar (Belgian life table 2009).

De oorzaken van het overlijden verschillen eveneens. In België wijzigt het percentage overlijdens door borstkanker van 13% tussen 60 en 64 jaar naar 6% van alle overlijdens tussen 70 en 75 jaar. Op die leeftijd zijn de mortaliteit door kanker, en de cardiovasculaire mortaliteit praktisch gelijk en elk verantwoordelijk voor meer dan een derde van alle overlijdens. In het overlijdenspercentage daalt het aandeel van borstkanker dus met de leeftijd (KCE-rapport nr. 11).

6.2. Toevoegen van levenskwaliteit aan levensjaren?

6.2.1. Minder agressieve behandelingen?

Naast de winst in levensjaren is het voornaamste voordeel dat wordt verwacht van screening de mogelijkheid om minder agressieve behandelingen toe te passen. Echter, noch de gegevens afkomstig van gerandomiseerde gecontroleerde studies, noch de feitelijke gegevens die werden verzameld in België, konden deze verwachting bevestigen.

6.2.2. Vals-positieven

In ons model vertegenwoordigden de "vals-positieve" diagnoses een belangrijke bron van verlies aan levenskwaliteit. Een hoog percentage vals-positieve resultaten (dat tot 10% kan bedragen) gecombineerd met een relatief lange wachtpériode (gemiddeld 45 dagen) voor bijkomende onderzoeken kan leiden tot een totaal negatief screeningresultaat in termen van QALY. Als men erin slaagt om dit percentage binnen de Europese normen te houden (3,5%) zoals dit het geval is in één regio van het land (in Vlaanderen), is de winst aan QALY 3 op 1 000 vrouwen.

6.2.3. Overtollige diagnoses en behandelingen

Het risico van overtollige diagnoses is het grootste risico van screening voor zeventigjarigen. Wanneer we een percentage over-diagnose van 3% toepassen, kan men zich eraan verwachten dat in elk cohort van 100.000 vrouwen, 108 bijkomende vrouwen een diagnose van kanker zullen krijgen en waarschijnlijk een behandeling zullen ondergaan. Als we een percentage over-diagnose van 10% toepassen, stijgt dit aantal tot 367.

Anderzijds worden alle vrouwen bij wie de diagnose van kanker wordt gesteld door middel van screening, twee tot drie jaar eerder ziek dan in het geval van een klinische diagnose. Dit heeft een negatieve invloed op de kwaliteit van de levensjaren die zij nog hebben.

7. CONCLUSIES

7.1. Moet men de screening uitbreiden tot de leeftijd van 74 jaar?

De conclusie van deze studie is dat het antwoord op deze vraag neen is. Deze uitspraak is enerzijds gebaseerd op de resultaten van het model en anderzijds op de specifieke context van deze vraag. De resultaten van het model tonen een winst van 13 levensjaren aan per 1000 gescreeneerde vrouwen. Sommige hypothese, die helemaal niet onrealistisch zijn, wijzen er echter op dat het netto-resultaat van een uitbreiding van de screening een algemeen verlies in levenskwaliteit kan veroorzaken. Deze resultaten zijn dus als zodanig niet doorslaggevend in de bijzondere context van een georganiseerde screening. Georganiseerde screening richt zich per definitie op een individu die geen enkele klacht, noch vraag heeft. Deze specificiteit houdt in dat men des te meer waakzaamheid moet in acht nemen op het vlak van ethische principes¹¹. Drie ethische basisprincipes zijn met name op screening van toepassing: het principe van weldoen of geen schade toebrengen, het principe van rechtvaardigheid of van billijkheid en het principe van respect voor autonomie¹².

Het principe van weldoen of geen schade toebrengen wordt als volgt gedefinieerd: "Ten eerste geen kwaad doen, in ieder geval geen kwaad doen (primum non nocere). Dit moet gepaard gaan met een plicht tot weldoen die samengaat met een houding van welwillendheid"¹². Het principe van rechtvaardigheid of billijkheid is: "deze bezorgdheid die de collectieve dimensie van gezondheidsproblemen laat tussenbeide komen met van een voorkeur voor de meest zwakken, de meest achtergestelden"¹².

Het doel van het organiseren van screening is het verbeteren van het welzijn van de bevolking door voortijdige overlijdens te voorkomen. De resultaten die via het model werden verkregen lieten echter niet toe om uit te sluiten dat in sommige gevallen screening de levenskwaliteit van de onderzochte leeftijdsgroep negatief zou kunnen beïnvloeden. In deze omstandigheden zou dit kunnen leiden tot een schending van het basisprincipe: "primum non nocere" (in ieder geval geen kwaad doen).



Anderzijds is screening duidelijk minder doeltreffend voor vrouwen met een lagere levensverwachting. Dit verschil in doeltreffendheid bestaat zeker ook bij de andere leeftijdsgroepen, maar minder uitgesproken. Het respecteren van het principe van rechtvaardigheid of billijkheid blijkt dus een bijkomende reden te zijn om negatief te antwoorden op de gestelde vraag.

7.2. Wat moet men zeggen tegen een persoon die om screening vraagt?

De context van deze vraag onderscheidt zich van vorige vraag op twee punten: het individu zelf is hier vragende partij en het probleem moet op individueel vlak worden geëvalueerd. Het principe van het respecteren van de autonomie is zeer goed van toepassing in deze situatie. Dit principe wordt als volgt gedefinieerd: "het respecteren van de persoon is het basisprincipe, het respecteren van de autonomie van de persoon vloeit hieruit voort; het gaat om het erkennen van het vermogen van de individuele persoon om keuzes te maken voor zichzelf (zelfbeschikking en vrije keuze) en om zijn handelwijze te beheersen (zelfbestuur)¹²". Opdat de persoon een vrije keuze zou kunnen maken, is het belangrijk dat hij duidelijk en correct geïnformeerd wordt over de voor- en nadelen van screening in zijn persoonlijke situatie. Het recht op informatie (artikel 7) en het recht op geïnformeerde toestemming zijn beschreven in de Belgische wet betreffende de rechten van de patiënt. De geïnformeerde toestemming van de patiënt kan slechts worden verkregen na lezing van een informatieblad. Het gaat om een proces waarbij idealiter ook een uitwisseling van ideeën met de zorgverlener moet plaatsvinden

Tevens is het nuttig dat de arts voor zijn patiënt die om screening vraagt een strategie uitwerkt die de nadelen tot een minimum beperkt¹³. Zo kan een houding in drie stappen worden aanbevolen:

- Specifieke informatie voor de leeftijdsgroep
- Het nemen van een beslissing in functie van de persoonlijke beoordeling van de patiënt¹⁴.
- Oriëntatie van de persoon die screening wenst, naar een screening waarvan de modaliteiten de nadelen tot een minimum beperken.

De criteria die werden gedefinieerd in het kader van het Europese programma voorzien met name het toezicht op de technische kwaliteit van de gebruikte apparatuur, een dubbele lezing van de mammografieën en een optimalisatie van het trefpercentage¹. Aangezien in België de erkende mammografische afdelingen moeten beantwoorden aan welbepaalde criteria in het kader van het Europese programma, is het logisch om vrouwen die uitdrukkelijk om screening vragen naar deze structuren te oriënteren.

7.3. Kernboodschappen

Het doel van het organiseren van screening is het verbeteren van het welzijn van de bevolking door voortijdige overlijdens te voorkomen. Uiteraard zou het uitbreiden van de screening naar de leeftijd van 74 jaar het mogelijk maken om enkele levensjaren te winnen. Echter, de invloed van deze maatregel op de levenskwaliteit is duidelijk meer onzeker. Volgens billijke hypothesen zou deze interventie zelfs een verlies van levenskwaliteit kunnen veroorzaken. In deze omstandigheden zou de balans tussen de voor- en nadelen van screening eerder kunnen doorslaan naar de kant van een algemeen verlies van welzijn van de bevolking.

8. REFERENTIES

1. Perry N, Broeders M, de Wolf C, Tornberg S, Holland R, von Karsa L. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. Ann Oncol. 2008;19(4):614-22.
2. Schwartz LM, Woloshin S. News media coverage of screening mammography for women in their 40s and tamoxifen for primary prevention of breast cancer. JAMA. 2002;287(23):3136-42.
3. Schwartz LM, Woloshin S, Fowler FJ, Jr., Welch HG. Enthusiasm for cancer screening in the United States. JAMA. 2004;291(1):71-8.
4. Silverman E, Woloshin S, Schwartz LM, Byram SJ, Welch HG, Fischhoff B. Women's views on breast cancer risk and screening mammography: a qualitative interview study. Med Decis Making. 2001;21(3):231-40.
5. Schwartz LM, Woloshin S, Sox HC, Fischhoff B, Welch HG. US women's attitudes to false positive mammography results and detection of ductal carcinoma in situ: cross sectional survey. BMJ. 2000;320(7250):1635-40.
6. Belgian Cancer Registry, editor. Cancer incidence in Belgium, 2004-2005. Brussels; 2008.
7. Paulus D, Mambourg F, Bonneux L. [Breast cancer screening]. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2005 02/05/2005. KCE Reports 11 Available from:
http://kce.fgov.be/index_en.aspx?SGREF=5221&CREF=9348
8. Mandelblatt JS, Cronin KA, Bailey S, Berry DA, de Koning HJ, Draisma G, et al. Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms.[Erratum appears in Ann Intern Med. 2010 Jan 19;152(2):136]. Ann Intern Med. 2009;151(10):738-47.
9. Woloshin S, Schwartz LM, Byram SJ, Sox HC, Fischhoff B, Welch HG. Women's understanding of the mammography screening debate. Arch Intern Med. 2000;160(10):1434-40.
10. Mandelblatt JS, Silliman R. Hanging in the balance: making decisions about the benefits and harms of breast cancer screening among the oldest old without a safety net of scientific evidence. J Clin Oncol. 2009;27(4):487-90.
11. Doumont D, Verstraeten K. Enjeux éthiques du dépistage organisé. Santé en Communauté Française. 2012(7):3-7.
12. Gallois. Dépister les cancers, mais à quelle condition In: UNAFORMEC, editor. Médecine. Paris; 2005. p. 72-7.
13. USPSTF. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement Annals of Internal Medicine 2011(151):716-26.
14. Woloshin S, Schwartz LM. The benefits and harms of mammography screening: understanding the trade-offs. JAMA. 2010;303(2):164-5.



■ SCIENTIFIC REPORT

1. INTRODUCTION

1.1. Context of this report

This report is a partial update of the clinical practice guideline (CPG) on breast cancer screening published in 2005¹. Therefore, the KCE experts made a list of clinical questions related to breast cancer screening. Representatives of stakeholders' organizations were then invited to review the choice and the wording of the questions, to highlight the main problems related to each question and to score the relevance of clinical questions (see KCE report 172)². Selected questions were then divided over three KCE reports. A first KCE report published in 2010 is focused on breast cancer screening with mammography for women in the age group of 40-49 years (KCE report 129)³. The second is focused on identification of women at risk for breast cancer and technical methods for breast cancer screening (KCE report 172)².

1.2. Scope of this report

This report focuses on the extension of organized breast cancer screening with mammography to older women. Eligible population is defined as women between 70-74 years of age with average risk of breast cancer.

1.3. Breast cancer screening in Belgium

The Belgian federal and regional governments signed a protocol agreement in 2001 for an organized screening programme for women aged 50-69 years, to be organized by the regional governments with appropriate financial resources supplied by the federal government. Since 2001, Flanders, the Walloon region and the Brussels capital region have each introduced an organized screening programme within their specific context of already existing practices. Indeed, opportunistic screening remains quite frequent in the Walloon and Brussels region among women in the age-group 50-69, but also among younger (40-49 years of age) or older women (>70 years). In Flanders, screening mammographies are dominant in the age-group 50-69. In the age-group 70-79 overall coverage drops, mainly because organized screening stops at age 69. The coverage by means of diagnostic mammography decreases also with 3%, indicating that substitution of screening mammography by opportunistic screening at



the age of 70 is not frequent in Flanders. At this age, total coverage (including both diagnostic or follow up mammographies and opportunistic screening) remains at 18% in Flanders, 33% in Brussels and 30% in the Walloon region (KCE report 172)².

1.4. Clinical questions

This specific report addresses the following questions:

1. What are clinical benefits of an extension of breast cancer organized screening in women between 70 and 74 years?
 - 1.1. What is the effect of an extension (70-74 years) of breast cancer organized screening on the breast cancer related mortality?
 - 1.2. How long is the delay between the screening and the associated breast cancer related mortality reduction?
 - 1.3. What is the effect of an extension (70-74 years) of breast cancer organized screening on the overall mortality?
 - 1.4. What is the effect of an extension (70-74 years) of breast cancer organized screening on morbidity?
2. What are the specific harms of an extension of breast cancer organized screening in women between 70 and 74 years? Harms in terms of false positive or false negative results?
 - 2.2. Harms in terms of additional diagnostic tests?
 - 2.3. Harms in terms of over-diagnosis?
 - 2.4. Harms in terms of overtreatment?
3. What attitude should be recommended for women in case of self referral?

1.5. Scientific approach

For each clinical question, a systematic search of the literature was performed and discussed with the support of external experts chosen for their scientific competency in several fields: gynaecology, radiology, epidemiology, or health economics. For question 3, we searched for models. To quantify what the implications of our findings are on the Belgian situation we applied data from the Intermutualistic Agency (IMA/AIM), cancer registry and data from the literature on the Belgian life tables and constructed a simple time dependent Markov chain with annual cycles.

The methodology used and the results are described in each chapter.



2. LITERATURE REVIEWS

2.1. Review of clinical studies

2.1.1. Methodology

2.1.1.1. Sources

A broad search of the electronic databases OVID Medline, EMBASE, CDSR and DARE was conducted in April 2011. Search was conducted first for systematic reviews (SR) and meta-analysis (M-A).

2.1.1.2. Search terms

For searching on Medline database, the following MeSH terms were used in combination with usual language: Breast neoplasms (MESH) and mass screening (or early detection) (MESH) and mammography (MESH). For EMBASE, the following Emmtree terms were used: 'cancer screening', 'breast cancer' and 'mammography'. These MESH and Emmtree terms were combined with a standard search strategy to identify systematic reviews (SR) or meta-analysis (M-A).

2.1.1.3. In- and exclusion criteria

Databases were searched for SR and M-A in English, French, Dutch or German. This report is a update of previous KCE report¹ (search made in 2004), thus we used a date restriction (2004-2011) and a language restriction (English, Dutch, French and German). Inclusion criteria used for selection based on title, abstract or full text were: population (women without breast cancer and without particular breast cancer risk), intervention (mammography), outcome (mortality, morbidity, additional diagnosis tests, over diagnosis and over treatment), design (SR or meta-analysis or RCT), key question (screening), age of population (>70 and <75 years), and original publication. Relevant publications were selected independently by 2 reviewers (FM, JR).

2.1.1.4. Additional evidence

We identified two SR^{4, 5} as the more extensive source for the research question 2. Therefore the evidence-identified through those SR-was updated by searching Medline and the Cochrane Database of Systematic Reviews from the search date of the two SR's on (search date Nov-Dec 2008). Additional hand searching of reference lists was also undertaken to ensure that no potentially relevant studies were missed. We also scanned reference lists of SR and of our previous report on breast cancer screening³.

The identified studies were selected based on title and abstract. For all eligible studies, the full-text was retrieved. In case no full-text was available, the study was not taken into account.

The description and results of the literature searches and flow of studies search are in Appendix 1.1.

2.1.1.5. Quality appraisal

The methodological quality of systematic reviews and associated risk of bias were rated using the checklists of the Dutch Cochrane Centre (www.cochrane.nl). The assessment of the risk of bias in the included SR was conducted by a team of two reviewers (FM, JR).

The methodological quality of selected additional evidence was also rated using the adequate checklists of the Dutch Cochrane Centre (www.cochrane.nl).

The results of the quality appraisal are in Appendix 1.5.

2.1.1.6. Identified systematic reviews

In the systematic search for literature reviews, 53 citations on the topic were identified in database searches. The majority of citations were excluded on the basis of title and abstract; 10 citations were retrieved in full and reviewed in more detail. On the basis of the full text, 5 reviews were included⁴⁻⁸.

The reviews written by Götzsche and Nelson^{4, 5} are mainly focused on mortality as outcome, those from Biesheuvel and Jorgensen^{6, 7} on over-diagnosis and the review of Virnig⁸ on ductal carcinoma in situ (DCIS).

As a first step, a quality appraisal of all the reviews was carried out to determine their suitability for inclusion. Götsche and Nelson SR^{4, 5} were judged to be of high quality with a low risk of bias. Nelson review⁵ was an update of one other review performed by Humphrey for the U.S. Preventive Task Force⁹. Humphrey review was also judged to be of high quality and used here as complementary information source.

The review written by Biesheuvel⁶ was judged to be of good quality (quality appraisal of selected trials not sufficiently described) and those written by Jorgensen⁷ was judged to be of high quality. The review written by Virnig was also judged to be of high quality.

2.1.1.7. Identified RCT

The evidence was updated using the key words reported in Nelson SR⁵ by searching Medline and the Cochrane Database of Systematic Reviews from the search date of this SR on (search date Nov 2008). The literature search for relevant RCTs carried out in Medline, EMBASE and CCRT (in April 2011) identified 432 citations. The majority of citations were excluded on the basis of title and abstract; the other papers (n=8) were retrieved in full and reviewed in more detail. On the basis of the full text, all eight studies were excluded because of the study design (not an RCT) shows the flow of randomized controlled trials from selection to in-or exclusion.

By hand searching of reference lists of Götsche and Nelson^{4, 5}, the Swedish RCT's were identified. Among those, the Two County trials is the only RCT that includes women aged 70-74 years at the time of randomization. Quality appraisal of this RCT was carried out to determine their suitability for inclusion. The Two County trials was judged to be of fair quality by Nelson and of low quality by Götsche and included for further analysis¹⁰.

2.1.1.8. Identified additional evidence

For diagnostic errors and over-diagnosis, this update was carried out in July 2011 identifying 10 citations. The majority of citations were excluded on the basis of title and abstract; 2 papers on diagnostic errors were retrieved in full and reviewed in more detail. On the basis of the full text, those two studies were excluded. Most papers are discussions and comments on the two main SR^{4, 5}.

For DCIS, this update was carried out in July 2011 identifying 7 citations. All citations were excluded on the basis of title and abstract.

For overtreatment, this update was carried out in July 2011 identifying 19 citations on Medline and 7 citations on the Cochrane Library. The majority of citations were excluded on the basis of title and abstract; 2 papers on overtreatment were retrieved in full and reviewed in more detail. On the basis of the full text, we retrieved again the SR written by Götsche⁴ and selected one publication presenting data issued from the UK Breast Screening Programme¹¹. The description and results of those updates are in Appendix 1.4.

2.1.1.9. Ongoing clinical trials

In addition to the database searches, the ClinicalTrials.gov website was searched for clinical trials. The search terms 'breast neoplasm' as well as 'screening' and 'mammography' were used to search for studies. The majority of search results (n=135) were ongoing trials. Two potentially relevant trials (NCT00963911, NCT00247442) were identified but were considered as out of scope after receiving more information on the full protocol.

2.1.1.10. Data extraction

Data from systematic reviews and from trials were extracted into a data extraction table (DET) summarizing key design features and results. All data extraction table are in Appendix 1.6.

2.1.2. Description of screening benefit

2.1.2.1. Sources

In the years 1960-1980, USA, Sweden, Canada and United Kingdom conducted randomized controlled trials of mammography screening. In US, the HIP trial (N = 60 995) started in 1963. In Sweden, the Malmö trial (phase I and II, N = 60 076) started in 1976 and 1978, the Two county Trial (Kopparberg and Östergötland, N= 133 065) in 1977-78, the Stockholm trial (N= 60 117) in 1980 and finally the Göteborg trial (N= 51 611) in 1981. In Canada, the National Breast Screening Trials (NBSS-1 and 2, N = 89 835) were initiated in 1980. In United Kingdom, the Edinburgh, trial started in 1979 in 1980 (N=44 268) and the UK Age Trial in 1991 (trial limited to



women aged 40-49 years)¹². Numerous publications and some SR summarizing theirs results are now available.

This part is based on the SR (2002) commissioned to assist the US Preventive Services Task Force (USPTSF) and its update of 2009^{5,9} and on the Cochrane SR⁴. We analysed more in detail one RCT named the Swedish Two-County trial (Östergötland) which was included by both SR^{10,13,14}.

Both reviews included the same trials in their meta-analysis: the HIP trial, Malmö I and II, the Two county trial, the NBSS trials (1 and 2), the Stockholm trial, the Göteborg trial and the UK Age Trial. The Edinburgh study was rated as poor quality by both authors and excluded therefore^{4,9}.

Nelson updated the meta-analysis from Humphrey⁹ to include new findings about younger women (40-49 years of age). Therefore, we refer to the Humphrey publication for mortality analysis performed on women aged from 50 to 74 years. Götzsche⁴ performed first a meta-analysis among women 39 to 74 years of age. Then he did a separate analysis for women younger than 50 years and for women older than 50 years.

Two-County trial

We analysed the Swedish Two-County trial in order to find more information on our specific population (70-74 years). The Swedish Two-County trial is the largest of the first eight randomized trials. We used therefore three publications that describe this study. We used the first publication of the initiator¹⁰, the publication of Nyström¹³ who was selected by Nelson and the last publication of Tabar published in July 2011¹⁴. The Two-County trial was commissioned by the Swedish National Board of Health and Welfare and included women in two Swedish counties: Kopparberg and Östergötland. In 1977-78, 134 867 women aged 40 to 74 years were cluster-randomized by geographic area. They were also stratified by socioeconomic status, urban or rural residency, and size of cluster. Finally, 78 085 women were invited to the screening. Among those, they were 10 568 women aged 70-74 years in the screening group and 7 462 in the control group. At this age, women were invited to two screening rounds with a screening interval of 33 months. The trial was closed in 1984 after approximately 7 years of screening¹⁰.

In 2002, Nyström performed one review of the Swedish RCT's including the Malmö, Östergötland, Stockholm, Göteborg trials. Results of the Kopparberg trial were not available at this time. This publication assessed the age-dependency of the effect of screening. The author calculated mortality relative risks for consecutive 5-years age group based on results from the Östergötland trial. The median follow-up time was 17.9 years. Unfortunately, without the Kopparberg part of the Swedish trial, the number of women 70 to 74 years of aged enrolled was low (approximately 5000 in each group)¹³.

Finally, we found one publication summarizing long term data (29 years) on mammographic screening effect on mortality¹⁴.

Trials quality and bias

All studies included by Humphrey in 2002 and later by Nelson were rated as fair^{5,9}. Götzsche assessed the randomization quality. This author divided his results on results based on adequately randomized control trial and results based on suboptimally randomized control trial⁴.

Nevertheless, the third meta-analyses were judged of high quality with a low risk of bias (see Appendix 1.5.1).

Some publications based on The Swedish Two-County reported varying numbers of women enrolled. To explain this variation, Nyström replied that some studies analysed results by year-of-birth while some others used exact age at randomization¹³. Nevertheless, Götzsche assessed this trial as suboptimally randomized and likely to be biased. He argued that for Östergötland, a public notary allocated the clusters by tossing a coin while witnesses were present. Breast cancer mortality in the control group was almost twice as high in Kopparberg compared to Östergötland (0.0021 versus 0.0012, p = 0.02). The autopsy rate was 36% for all the Two-County trial and cause-of-death assessments were not blinded⁴. According to that the validity of local end point committee data was criticized, a third committee (named consensus committee) reviewed the records containing a doubtful cause of death¹⁴.

2.1.2.2. Breast cancer related mortality reduction

For women aged 39 to 74 years and at approximately 13 years of follow-up, the Humphrey meta-analysis (M-A)⁹ and the Cochrane review⁴ showed a significant reduction in breast cancer mortality of 16% (Relative Risk (RR) 0.84, 95% confidence interval (CI) 0.77 to 0.91) and 19% (Relative Risk (RR) 0.81, 95% (CI) (0.74, 0.87) respectively.

For women aged 39 to 74 years, the Review of Swedish randomized control trial showed a significant reduction in breast cancer mortality at 15.8 years (median follow up) of 21% (Relative Risk (RR) 0.79, 95% (CI) 0.70 to 0.89). This study showed that the effect of breast cancer screening in terms of breast cancer mortality reduction varies according to age range¹³.

For women aged at least 50 y at randomization, three trials with adequate randomization did not show a significant reduction in breast cancer mortality at 13 years (Relative Risk (RR) 0.94, 95% (CI) 0.77 to 1.15). Four trials with suboptimal randomization showed a significant reduction in breast cancer mortality (RR of 0.77 (95% CI 0.67 to 0.83)). The RR for all seven trials combined was 0.77 (95% CI 0.69 to 0.86)⁴.

The review of Swedish randomized control trial, applying a more conservative determination of cause of death for women aged at least 70 y at randomization, did not show a significant reduction in breast cancer mortality at 17.4 years ((RR) 1.12, 95% (CI) 0.73 to 1.72)). Unfortunately, this age group was relatively small (approximately 5000 women in each group) and this study is underpowered¹³. Consequently, we must conclude together with Nelson that data are insufficient for this age group⁵.

2.1.2.3. Delay between screening and specific mortality reduction

Tabar published in July 2011 the last follow-up result (29-year) of the Swedish Two-County Trial¹⁴. This publication modulated breast cancer mortality reduction in function of length of follow up. In this report both data issued from local end point committees and consensus-based data were presented. The validity of local end point committee data was criticized, we present here consensus data. For women aged 39 to 74 years, this publication showed specific mortality reductions of 20% ((RR) 0.80, 95% (CI) 0.62 to 1.05), 27% ((RR) 0.73, 95% (CI) 0.59 to 0.92), and 27% at respectively 10, 15 and 20 to 29 years of follow up. In the same time,

deaths from breast cancer prevented in the study group increased along length of follow-up. They were respectively 50, 99, 114, 122 and 126 deaths prevented at 10, 15, 20, 25 and 29 years of follow-up for all women included in this study. Author emphasized that breast cancer screening prevents deaths more in the medium to long term than in the immediate future. So most of the breast cancer deaths would have occurred (in the absence of screening) more than 10 years after randomization.

Authors did not calculate mortality relative risks for each age group separately. Results presented are based on 133 065 women aged 40-74 (77 080 in the screening group and 55 985 in the control group), while they were 10 568 women aged 70-74 years in the screening group and 7 462 in the control group. In Kopparberg, cancers diagnosed after the two screening rounds in women aged 70-74 years and breast cancer deaths from these cases were still included in the results¹⁴.

As cited on previous point, the group of women aged 70-74 years included in the Swedish Two-County Trial was relatively small (approximately 5000 women in each group) and this study is underpowered¹³.

2.1.2.4. All-cause mortality

The Cochrane SR has reported data on all-cause mortality. For women aged at least 50 y at randomization, two trials with adequate randomization (n=73654) did not show a significant reduction in all-cause mortality at 13 years (Relative Risk (RR) 1.00, 95% (CI) 0.95 to 1.04). The two trials with suboptimal randomization (n=98261) also did not show a significant reduction in all-cause breast cancer mortality (RR of 0.99 (95% CI 0.97 to 1.02))⁴.

Unfortunately studies did not have statistical power to detect an all-cause mortality reduction. According to that disease specific mortality is a small fraction of all-cause mortality in cancer screening trials, detect a mortality reduction would require inclusion of millions of subject.

2.1.2.5. Morbidity reduction

We found no data related to the cancer related morbidity in our selected sources. In other words, we do not accept or reject the hypothesis that screening reduces the morbidity of the breast cancer disease.



2.1.3. Description of screening harms

2.1.3.1. Sources

This part is based on the 5 SR selected in our main search⁴⁻⁸. As explained in part 2.3.5, we updated those in July 2011 starting from the last literature search date. See more details in appendix 1.4.

2.1.3.2. Study description

SR written by Götsche and Nelson are described in point 3.1.1. The reviews written by Biesheuvel and Jorgensen^{6, 7} were focused on over-diagnosis and subsequently on overtreatment. Each author used very different methods to address this issue. Biesheuvel analysed reports issued from the first RCTs while Jorgensen analysed data issued from publicly organized screening programmes. The review written by Virnig was focused on ductal carcinoma in situ (DCIS)⁸.

2.1.3.3. Performance of mammography

The sensitivity of first mammography for women aged 70-74 years was 81% in the Two County trial. This includes over-diagnosis and may be difficult to interpret. This data cannot be applied to individual patients because they are not adjusted for patient factors (use of hormone replacement therapy, mammographic breast density), technical factors (quality of mammography, number of mammographic views) or provider factors (the experience of radiologists and their propensity to label the results of an examination abnormal)⁹. Provider factors may explain that sensibility may vary between countries⁴. In the Two County trial, the specificity of a single mammographic examination was 95.6% for women aged 40-74 years. This indicates that 4% of women who did not have cancer underwent further diagnostic evaluation. The positive predictive value of one-time mammography was 12% for abnormal results requiring further evaluation and from 50% to 75% for abnormal results requiring biopsy. Positive predictive value increases with age and ranged from 18% to 20% among women 70 years of age or older⁹.

Nelson reported data from the Breast Cancer Surveillance Consortium (USA) BCSC for regularly screened women that are based on results from a single screening round. False-positive mammography results are less common among women aged 70-79 years (68.8 per 1000 women per

screening round). Conversely, false-negative mammography results are a little more common among women aged 70 to 79 years (1.5 per 1000 women per screening round)⁵.

2.1.3.4. Additional diagnostic tests

Rates of additional imaging are relatively low among women aged 70 to 79 years (64.03 per 1000 women per screening round). Biopsy rates are higher among women aged 70 to 79 years (12.2 per 1000 women per screening round) than among younger women. As expected, the number of screen detected cancer is highest in this age group. Results indicate 6.5 screen-detected invasive cancer and 1.4 screen-detected DCIS per 1000 women per screening round. The BCSC results indicate that for every case of invasive breast cancer detected by mammography screening in women aged 70 to 79 years, 154 women have additional mammography, 10 have other imaging test, and 2 have biopsies⁵.

2.1.3.5. Over-diagnosis

Over-diagnosis of breast cancer at screening may be defined as the detection with screening of cancer that would not have presented clinically during the woman's lifetime (and therefore would not be diagnosed in the absence of screening)⁶.

Nelson reported rates of over-diagnosis varying from less than 1% to 30% with most from 1% to 10%. She explained variations by inclusion or exclusion of DCIS cases, by whether cases are incident or prevalent, and by age. She concluded that the studies are too heterogeneous to combine statistically⁵.

Götsche reported that the level of over-diagnosis was about 30% in the RCT's that did not introduce early screening in the control group, and somewhat larger in the sub optimally randomized trials before screening of the control group. He found also a 40% to 60% increase in incidence of breast cancer in observational studies performed in Australia, Europe and USA after beginning of the screening⁴.

Biesheuvel analysed publications issued from the first RCTs (New York/HIP, Malm II, Two County, Canada a and b, Stockholm, Göteborg, Edinburgh) and from four population-based programme (Sweden, Norway, Netherlands and Italy). He selected papers that attempted to estimate over-detection of invasive breast cancer by mammography screening.

Note that he did not include DCIS. He excluded potentially biased publications. Bias were described as: different breast cancer risk in screened and unscreened population, low participation in screening group and high participation in non-screening group, offering screening to the control group before or during follow up, inappropriate adjustment for lead time. After exclusion, he selected 22 estimates of over-detection from several (some overlapping) sources. Publications were categorized as being based on cumulative-incidence or incidence-rate methods (definitions of terms are in appendix 1.4.3). Excluding biased studies as described before, he selected the least biased over-detection estimates. Excluding DCIS cases, over-detection ranged from 7% to 21% for women aged 60–69 years⁶.

Jorgensen analysed data issued from publicly organized screening programmes. He selected papers that published trends in incidence of breast cancer before and after the introduction of mammography screening. Note that when data were present, DCIS were included. If not, he estimated that they would contribute to 10% of the diagnoses in a screened population. After exclusion of the implementation phase of the screening, he compared data covering at least seven years before screening with data covering at least seven years after screening in screened and non screened age groups. The most common age-range for mammography screening programmes was 50–69 years. No data specific for women aged 70 to 79 years are available. The increase in incidence of breast cancer was closely related to the introduction of screening. Surprisingly, little of this increase was compensated for by a drop in incidence of breast cancer in women older than 70 years. Jorgensen calculated that over-diagnosis for invasive cancer was 35%. The rate of over-diagnosis including DCIS cases was 52% in this meta-analysis (95% CI 46% to 58%)⁷.

Discrepancies between results reported by Biesheuvel or by Jorgensen have led to a lot of controversial discussions.

The approach Biesheuvel et al. to adjusting for lead time was contested by Zahl, Jorgensen and Götzsche (2008), who stated that their estimations were substantially downwardly biased, due to over-adjustment, use of a hypothetical increase in incidence based on theoretical models and use of

long term follow up data that are considerably diluted. They also considered estimation unhelpfully wide.

Jorgensen & Götzsche used linear regression to compare observed incidence with a in an (hypothetical) population that did not undergo screening. They assume a linear increase extrapolated from prescreening trends, following the same pattern as the linear trend observed in women too young to be screened. It is difficult to judge if this assumption holds or not, the graphs the authors present show non-linear increases in incidences before screening was introduced in the UK and Norway for whom no explanation was given.

2.1.3.6. DCIS

Historically, DCIS was rare and diagnosed by surgical removal of a suspicious breast mass. Since the wide use of mammography, a increasing numbers of patients were diagnosed with DCIS. The prognosis of the disease is excellent. Maass reported data issued from the SEER database (Surveillance, Epidemiology and End Results database of the United States National Cancer Institute). Those data showed a 10-year survival rate of 96.6% for cases between 1978 and 1983, when no screening was performed. The rate was 98.1% between 1984 and 1989, when screening was performed^{3, 15}.

Recent changes in DCIS incidence in USA were emphasized by Virnig. This author performed a SR on incidence, treatment and outcomes of DCIS in name of Agency for Healthcare Research and Quality (AHRQ). She included 63 publications addressing incidence for analysis. She compared data obtained before the screening (1973–1975) with current century data collected in US where screening is common. DCIS incidence rose there from 1.87 per 100 000 in 1973–1975 to 32.5 per 100 000 in 2004. Incidence increased most in women older than 50 years. Increased use of mammography may explain some but not all of this increased incidence⁸.

2.1.3.7. Overtreatment

Götsche reported that the number of mastectomies and lumpectomies was significantly larger in the screened groups. Three trials with adequate randomization showed a significant increase in mastectomies and lumpectomies (Relative Risk (RR) 1.31, 95% (CI) 1.22 to 1.42). Two trials with suboptimal randomization showed the same increase in interventions (RR of 1.42 (95% CI 1.26 to 1.61)). The RR for all five trials combined was 1.35 (95% CI 1.26 to 1.44)⁴.

Based on recent data from the UK Breast Screening Programme, Dixon emphasized the increasing numbers of patients with DCIS. In 1998/99 there were approximately 1500 cases, but in 2007/08 there were close to 3500 cases. Although, most DCIS cases may be treated by breast-conserving surgery, the percentage of patients being treated with this method has remained constant at 30% during this period. Because of the increasing incidence of DCIS treatments, the absolute numbers of women having mastectomies has increased from just under 500 in 1998/99 to over 900 in 2007/08¹¹.

2.1.4. Screening conditions

The sojourn time (ST) is the average duration of the preclinical screen-detectable phase. Estimation of sojourn time can be performed by from simple mathematical estimates or using microsimulation techniques (mainly Markov Models)¹². Sojourn time provides an absolute upper limit to the lead time obtainable. If the sojourn time is long, the maximum attainable lead time is corresponding long¹⁶. A longer sojourn time results in higher number of additional breast cancer detected, more life-years gained and higher number of years with cancer due to lead-time¹⁷.

2.1.4.1. Literature search

In a first stage, studies assessing sojourn time were searched. Ovid Medline was consulted from 1948 to October Week 1 2011. The main search terms (MESH) were: Breast Neoplasms/ Mass Screening/ or Mammography/. Sojourn time was included in free text. The search was limited to papers written in English, Dutch, French, or German. Reference lists of the selected studies were checked for additional relevant citations. See more details in appendix 1.4.4.

Selection criteria

All retrieved references were assessed against pre-defined inclusion criteria (in terms of population, intervention, outcomes, and design-Table 1) in a two-step procedure: initial assessment of the title, abstract and keywords; followed by full-text assessment of the selected references. Estimation of sojourn time not based on data were excluded. After excluding of 3 duplicates, 40 unique citations were identified from the databases. Of this total of 40 references, 23 did not meet the inclusion criteria based on title and abstract evaluation. Among the 17 citations retained for full-text assessment, 6 did not fulfill the population criteria¹⁸⁻²³ and 1 did not fulfill the outcome criteria²⁴. Finally, 10 studies were retained^{16, 17, 25-32}.

Our search was based on ST duration estimations as search. We found several publications where ST estimations were issued from others studies cited as references by the author. For example, Zappa in 2003³² referred to data published by Tabar in 1995²⁹. Duffy in 2005²⁶ referred also to those data²⁹. Therefore, we used original publications. If one author published two or more articles based on the same data, we choose the most accurate for our study^{30, 31}. Finally, 7 publications are summarized in data extraction table (see appendix 1.6.7).

2.1.4.2. Results

Sojourn times calculated on RCT's data

We found 4 studies based on the results of the Two- County Trial. The Two- County Trial is described in chapter 2 (point 2.2.1.1.)^{10, 13}. First estimates of sojourn time published by Tabar and Duffy were based on approximately the same data. Both authors used the same Markov chain model, but results were not the same. Shen underlined that the difference in estimates published by the two authors^{25, 29} may be caused by different statistical methods or by discrepancy in the data. Shen applied his recently developed statistical methods based on the maximum likelihood estimates to data from the Two County Trial. Authors estimated the sensitivities of early detection modalities as 0.92 (SD, 0.09) and the mean ST as 4.4 years (SD, 0.76)²⁷.



Sojourn times calculated on screening programmes data

Spratt estimated the duration of breast cancer before detection by dividing prevalence rates at first screening round by incidence rates in the following years. Therefore, he used data from 10 000 women aged 35 to 70y at start included in the Breast Cancer Detection and Demonstration Project (Louisville). For women aged 70-74, he estimated that sojourn time ranged between 2.5 y to 3.8 y²⁸.

Fracheboud compared the results of the Dutch breast cancer screening programme for women aged 70-75 with the hypothesis developed by Boer in 1995. Boer had described optimistic and pessimistic assumptions for use in his MISCAN model. Optimistic assumption assumed no further increase in preclinical duration of breast cancer after 65years of age although pessimistic assumption assumed a further increase in preclinical duration with age³³. Based on 187 207 screening examinations (women aged 70-74 years), Fracheboud found that detection rates in both initial and subsequent screens increased steadily with age and got close to assumption which assume a continuously increasing sojourn time beyond the age of 69. This increasing sojourn time of breast tumours lead to a strong increase in detection of cancers, but also to more life- years in lead time¹⁷.

Weedon constructed one inventive solution for screening programme who do not have full registration of interval cancers or where opportunistic screening is common. Although Norwegian registration is of very high quality, incidence data from the first screening round, interval between screening examination or registration of interval cancer may be insufficient. Therefore, he replaced data lacking by data issued from questionnaire send to 336 533 women in the Norwegian Breast Cancer Screening Programme (NBCSP). This new approach gave estimation of MST to 6.9 years for women aged 60-69 years, although STS was estimated to 60%³⁰.

2.1.4.3. Discussion

Most estimates of sojourn time have been based on Models (mainly Markov chain models). Such models assume a chronological stepwise growth of cancer. Unfortunately, it remains unknown whether cancer really develop according to a chronological sequence. Estimations of sojourn time must consequently be interpreted with caution.

2.1.5. Key data

Data issued from literature search are summarized in table 2.1.

Table 2.1: Data issued from clinical literature review

Question 1: Should breast cancer organized screening extended in women between 70 and 74 years?

Population	Women between 70-74 years of age without breast cancer and without particular risk of breast cancer.
Intervention	Organized screening with mammography
Comparison	No organized screening
Outcomes:	
Mortality (specific)	For women >50 y at randomization, the specific mortality reduction after a follow-up of 13 years is 23% (RR: 0.77, (CI) 0.69 to 0.86). In the Two County trial, specific mortality reduction reach at significant reduction of 27% (RR: 0.73, (CI) 0.59 to 0.92) at 15 years of follow up and increases afterwards.
Mortality (all cause)	Studies did not have statistical power to detect an all-cause mortality reduction.
FP	68.8 per 1000 women aged 70 to 79 years per screening round (BCSC-USA)
FN	1.5 per 1000 women aged 70 to 79 years per screening round (BCSC-USA)
Additional imaging	64.03 per 1000 women aged 70 to 79 years per screening round (BCSC-USA)
Biopsy	12.2 per 1000 women aged 70 to 79 years per screening round (BCSC-USA)



DCIS	1.4 screen-detected DCIS per 1000 women aged 70 to 79 years per screening round (BCSC-USA)
Over-diagnosis	Over-detection (excluding DCIS cases), ranged from (7% to 21%) to 35% (no data specific for women aged 70 to 79 years are available).
Over-treatment	The number of mastectomies and lumpectomies was significantly larger in the screened groups (RR:1.35 (95% CI 1.26 to 1.44)).

2.1.6. Conclusion

At this age group, performance of mammography is high and rates of additional imaging are relatively low. Breast cancer screening achieves a specific mortality reduction of 23% to 27% according to authors. This mortality reduction did not appear in the first years after screening. The specific mortality reduction is not statistically significant before 10 years after screening ((RR) 0.80, (CI) 0.62 to 1.05). Breast cancer mortality reduction must be put in perspective with life-expectancy for this age-group in our country.

On the other hand, aspects related to quality of life raises questions pertinent to discussion of the benefit and harms of breast cancer screening in this age-group. First, over-diagnosis being an inevitable consequence of cancer screening, the risk of overtreatment persists. Secondly, the lead time bias although difficult to estimate, may be crucial for older women. Screening diagnosed breast cancer and consecutive treatment may mean the end of "the life in good health condition" some years earlier than clinical diagnosed breast cancer³⁴.

2.2. Review of modeling studies

2.2.1. Literature search strategy

In a first stage, randomized clinical trials analysing the impact of screening on morbidity and mortality were searched (see above). Then, because the effectiveness of screening require a lot of information from a wide range of sources to correctly inform decision makers, modeling studies were searched³⁵.

Medline, Embase, NHS EED and Econlit databases were consulted from January 2000 up to September 2011 (see appendix 2.1). The search was limited to papers written in English, Dutch, French, Spanish, or German. Reference lists of the selected studies were checked for additional relevant citations.

The keywords used and the results are detailed in appendix 2.1. The main search terms (MESH) were:

- Breast Neoplasms; and
- Mass Screening or Early Detection of Cancer ; and
- Mammography; and

2.2.2. Selection criteria

All retrieved references were assessed against pre-defined selection criteria (in terms of population, intervention, outcomes, and design - Table 2.2.) in a two-step procedure: initial assessment of the title, abstract and keywords; followed by full-text assessment of the selected references. It should be noted that studies assessing screening techniques (such as digital mammography) were excluded because such topic was investigated in KCE report 172².

**Table 2.2: Selection criteria**

	Inclusion criteria	Exclusion criteria
Population	caucasian women without breast cancer and without particular risk	Other (e.g. woman at risk, Asian women, etc.)
Intervention	Screening mammography	Other, including mammography techniques (e.g. digital mammography)
Outcomes	Morbidity and Mortality (e.g. LYG and QALYs)	Other outcomes (e.g. over diagnosis)
Design	Modeling studies	Other designs

LYG: life-year gained; QALY: Quality-adjusted life-year gained

2.2.3. Quantity of research available

After excluding 195 duplicates, 1058 unique citations were identified from the databases. Hand searching did not allow us to identify additional citations. Of this total of 1058 references, 1016 did not meet the inclusion criteria based on title and abstract evaluation. Among the 42 citations retained for full-text assessment, 2 did not fulfill the population criteria and 15 did not fulfill the design criteria. Finally, 25 modeling publications were retained, concerning 6 models developed by modeling groups involved in CISNET, 2 applications of these models on different context and 7 models developed by other groups or authors, as some models have several publications^{17, 36-59}. The flow chart of this selection is presented in the appendix 2.2.

Table 2.3: Modeling studies excluded after full-text assessment

Exclusion criteria	Studies
Population	Messsecar 2000; Wen 2005 ^{60, 61} .
Intervention	
Outcome	
Design	Advisory Committee on Breast Cancer 2006; Anonymous 2000; Barratt 2002a; Barratt 2002b; Bonneux 2009; Caplan 2001; Carney 2007; De Koning 2000; Feuer 2004; Grivegnee 2001; Habbema 2006; Mandelblatt 2003; Prevost 2000; Rautenstrauch 2000, Xu 2000 ⁶²⁻⁷⁶ .

2.2.4. Selected studies

2.2.4.1. The CISNET Project

The Cancer Intervention and Surveillance Modeling Network (CISNET) (<http://cisnet.cancer.gov>) is a consortium of National Cancer Institute (NCI)-sponsored investigators whose focus is modeling the impact of cancer control interventions on population trends in incidence and mortality for breast cancer. These models are also used to project future trends and to help determine optimal cancer control strategies⁴⁰. Seven groups developed their own breast cancer models spanning a wide range of modeling philosophies: The University of Texas M. D. Anderson Cancer Center model³⁷, University of Wisconsin model, Georgetown⁴⁷, Erasmus (MISCAN) model⁵⁷, Dana-Farber model⁴⁴ University of Rochester model⁴³ and Stanford model⁵¹.

The seven models were first used to assess the relative and absolute contributions of screening mammography and adjuvant treatment to the reduction in breast-cancer mortality in the United States from 1975 to 2000⁷⁷. Mandelblatt et al⁴⁸ used 6 of those CISNET models to provide estimates of potential benefits and harms of mammography screening under different screening schedules. One of the 7 models, the University of



Texas M. D. Anderson Cancer Center model³⁷ was not used as it was purely descriptive.

The models were developed by different groups but not independently, they were compared, discussed and adapted during the development process, they also used a common set of variables and inputs, based on US datasets BCSC (Breast Cancer Surveillance Consortium), SEER 9 (Surveillance, epidemiology and end results), Connecticut Tumor registry and the Berkeley mortality Database.

A detailed discussion of each of this models can be found in the publications and on the CISNET website, we will not discuss each model in detail, but summarize the pooled comparison of Mandelblatt et al.⁴⁸ and discuss the main limitations and implications for our research question. The models estimated a large number of scenarios, but we will only present the results of the part relevant to our research question, the comparison of a screening policy screening age 50-69 to a screening policy screening age 50-74.

Feuer et al.⁴⁰ identifies two dimensions to characterize the types of surveillance models used here. The first dimension incorporates micro simulation models at one end of the spectrum, where individuals are run through the model one at a time, where at each transition a random number is generated and individual life histories are generated, to mechanistic or analytic models, where a set of analytically derived equations describe the relationships between key health states and/or tumor growth and metastasis. The University of Texas M. D. Anderson Cancer Center, University of Wisconsin, Georgetown, and Erasmus models could be characterized as micro simulation models; the Dana-Farber model could be characterized as analytic; and the remaining two models (University of Rochester and Stanford) could be described as having some aspects of each. The second dimension of model characterization runs from biologic, where the model goes beyond observable quantities to model the underlying disease onset, growth, and progression of disease, to epidemiologic, where only a portion of the disease process is modeled (usually the observable portion).

The models start with estimates of breast cancer incidence and mortality trends without screening and treatment and then look at the effect of screening use and improvements in survival associated with treatment.

Breast cancer is assumed to have a preclinical, screening-detectable period (sojourn time) and a clinical detection point. On the basis of mammography sensitivity (or thresholds of detection), screening identifies disease in the preclinical screening-detection period and results in the identification of earlier-stage or smaller tumors than might be identified by clinical detection, resulting in reduction in breast cancer mortality. Age, estrogen receptor status, and tumor size— or stage—specific treatment have independent effects on mortality. Women can die of breast cancer or of other causes. As mentioned before, the 6 models use a common set of age-specific variables for breast cancer incidence, mammography test characteristics, treatment algorithms and effects, and non-breast cancer competing causes of death. On the other hand, unobserved variables such as preclinical detectable times (sojourn time), lead time, dwell time within stages of disease, were in these models estimated intermediate outputs that followed from the model structure and assumptions concerning tumor growth.

The stage distributions in unscreened versus screened women in these models were also intermediate outcomes, this in contrast to some other models that use this observable variable as input. As end output from the model reductions in mortality, life years gained were calculated, no QALYs were used. The harmful effects false positive mammograms, unnecessary biopsies and over diagnosis followed from the model, also here no direct observed input was used, no attempt was made to quantify those harms in terms of QALYs. Morbidity associated with surgery for screening-detected disease or decrements in quality of life associated with false-positive results living with earlier knowledge of a cancer diagnosis or over diagnosis was not considered, which makes the models less useful for our purposes.

Table 2.4 gives the results of the different models in terms of mortality reduction and years of life gained for the different models. Gains are fairly limited and there is some variability between models, with number years gained per 1000 women screened ranging from 9 to 17 and number of deaths averted ranging from 4 to 6.

This class of models relies heavily on unobservable variables, and as most models are individual bases they are not always very transparent. Independent validation was made difficult because results from trials and

the main US breast cancer registries were used to parameterize or calibrate the model. Model outputs are similar to the results from RCT's and some observational studies, but this does not say much about the validity of the model as data from those studies were partly used to calibrate the model.

Table 2.4: results of the different models in terms of mortality reduction and years of life gained per 1000 women screened for the different models

Model	D	E	G	M	S	W
Mortality (specific) reduction over the whole period in %						
Screening in agegroup 50-69	16	23	17	16	15	23
Screening in agegroup 50-74	22	27	21	21	20	28
Incremental mortality reduction screening in agegroup 50-74 compared to screening in agegroup 50-69	6	4	4	5	5	5
Years of life Gained per 1000 women screened						
Screening in agegroup 50-69	88	107	111	82	99	84
Screening in agegroup 50-74	106	116	128	96	121	95
Incremental years of life gained screening in agegroup 50-74 compared to screening in agegroup 50-69	18	9	17	14	22	11
Incremental days of life gained per women screened						
Screening in agegroup 50-74 compared to screening in agegroup 50-69 women screened	6,6	3,3	6,2	5,1	8,0	4,0

Model group abbreviations: D _ Dana-Farber Cancer Institute; E _ Erasmus Medical Center; G _ Georgetown University; M _ M.D. Anderson Cancer Center; S _ Stanford University; W _ University of Wisconsin/Harvard

Stout et al 2006⁵⁶ used the Wisconsin model to do a cost effectiveness analysis, including the use of QALYs, but comparisons of the age groups 50-74 with age groups 50 - 69 were not made.

Rue et al.⁵⁵ adapted de Dana-Farber Cancer Institute model of Lee and Zeelen⁴⁴ to data in Catalonia. Because there was insufficient information on Catalan survival they combined the survival data from the SEER in the US with Catalan data in a previous publication of Vilaprinyo, 2009⁵⁸. Obtained results were very similar to the ones Lee & Zeelen originally found, a mortality reduction of 21% and 131 life years gained per 1000

women screened for a biannual screening in the age group 50-74, with an incremental benefit for biannual screening 50- 74 of 1.7% in terms of mortality and 2 life years gained per 1000 women screened. As authors had no choice than to use US data for most key variables one can question in what degree this can really be called an adaptation to the Catalan context. Carles et al, 2011³⁸ finally used the results of Rue et al and Vilaprinyo et al⁵⁸ to do a cost effectiveness analysis, including QALYs. They found 3990 life years gained for a cohort of 100 000 women for a biannual screening in the age group 50-74, with an incremental benefit for biannual screening 50- 74 of 299 life years gained per 100 000 women. They found 3891 QALYs gained per 100 000 women screened with a biannual screening in the age group 50-74, with an incremental benefit for biannual screening 50- 74 of 277 life years gained per 100 000 women compared to a schedule 50-69. They did not report the QALYs gained with extending the screening to 50-74 from 50 -69, as it was dominated by screening from 45- 69, but reported that 186 QALYs per 100 000 were gained by extending the screening to 45-74 from 45 -69. Interestingly, they did not incorporate the results of Vilaprinyo et al, 2009⁵⁸ into their calculations, but used US survival data. They did not take into account over diagnosis.

2.2.4.2. Models not related or not using CISNET methodology

Carter et al, 2005^{39, 78} developed a micro simulation model based on tumor growth using mainly SEER data. The model lacks credibility though mainly because of unrealistic assumptions concerning stage specific survival, as they assume a fixed survival of 2 years for stage 4 and complete cure for stages 1, 2 and 3. This leads to considerably higher years of life gained for screening than other models but is in absolute contradiction to what we know about stage specific survival.

Rojnik et al, 2008 produced a time dependent Markov model with 4 stages, DCIS, local, regional and distant. Overall model structure was described but details on how the model was parameterized are lacking so we cannot judge how this was done or if assumptions were reasonable. They only report ICERs so we have no information on assumed gains in Life Years Gained and QALYs.



Neeser et al developed a simple Markov model comparing organized screening with a coverage of 70% with opportunistic screening with a coverage of 20%. They assumed that the organized screening reduces breast cancer mortality with 15% based on the IARC handbook, but it is unclear how they come to this figure as IARC postulates a reduction ranging from 5 to 20%. They calculated the years of life gained for a 10 years screening beginning at 70 (they evaluated other schedules not relevant for our research question as well. They found that organized screening would save 41 lives per 100 000 and add 0.008 life years (2.9 days) per women screened for 10 years. The model is somewhat overly simplistic by not taking into account lead time but applying assumed reductions immediately. No QALYs were used and effects on morbidity was not taken into account.

Rauner et al, 2010 developed an ant colonization optimization model but only evaluated the effect of screening amongst women 50-70 and their rather experimental model is not useful for our purposes. It is also unclear how they actually modeled stage specific survival.

Mahnken et al, 2008⁴⁶ developed a method to adjust for lead time bias, length bias and over-detection and applied this to SEER data, but provided only adjusted Hazard ratio's.

Rijnsburger et al, 2004⁵³ used the MISCAN micro-simulation model developed by the Rotterdam⁵⁷ (see above) to replicate the data of the Canadian CNBSS-2 trial on breast cancer screening among women aged 50–59, so their findings are not really useful for our purposes.

Barratt et al 2005³⁶ constructed a Markov model for two hypothetical cohorts, with one cohort women undergoing biennial screening and the other not, assuming 100% participation. Within this model, they evaluated the outcomes of women over 70 years old undergoing 10 years of biennial screening. They assume a 37% mortality reduction, adjusting the 25% reduction from non compliance, and assume that benefit accrues linearly to maximal level over first five years after starting screening and that benefit declines linearly to nothing over five years after stopping screening. For women who continue screening for 10 years after the age of 70s, two fewer women per thousand die from breast cancer than in women who stop screening (six v eight deaths from breast cancer). The number of diagnoses of breast cancer in screened women is about 41 and

the number in unscreened women about 26. assuming a risk reduction of 50% brings the number of deaths in the screened group down 6.2 to 5.1. This simple model has the advantage of transparency, but does not take into account the effects of lead time and stage-shifts on morbidity.

2.2.5. Conclusion

Models described are give useful insights and elements but it is difficult to adapt them to the Belgian situation as we do not have the necessary data to parameterize them. The CISNET models give a modest gain in year of life between 9 an 22 years per 1000 women screened.

2.3. Review of quality of life studies

Because breast cancer screening programs are expected to have an impact on the quality of life (QoL) of the patients, models with a one-dimensional health-outcome measure in terms of survival are not enough informative. It is important to take into account all the multidimensional health outcomes in the assessment of breast cancer screening programs. To value these multidimensional outcomes into a single measure, quality-adjusted life-year (QALY) must be used. QALYs permit to adjust the expected length of life by the health-related quality of life. These adjustments are made using utilities derived from individuals' preference for different health states.

Determination of utility values, needed for the calculation of QALYs, requires two steps:

1. The health state description. According to the pharmaco-economic guidelines of the Belgian Health Care Knowledge Centre (KCE), health states should be described on a standardized descriptive system. Ideally, the description should be done by Belgian patients using a generic descriptive system, such as the EQ-5D. If health states descriptions from Belgian patients are not available, descriptions from similar patients in other countries may be used⁷⁹.

2. The valuation of these health states. According to the pharmacoeconomic guidelines of the KCE, health state values should be valued on a 0 (=value for death) to 1 (=value for perfect health) scale by a representative sample of the general public. Ideally, they should be valued by the Belgian population but if no original Belgian data are collected, valuations from other countries can be used and discussed⁷⁹.

In this section, the availability and the quality of published utility values describing the burden of disease due to breast cancer (screening and treatment) is assessed.

2.3.1. Methods

2.3.1.1. Literature search strategy

Electronic databases were consulted for original publications on utility estimates for different health states associated with breast cancer screening and treatment. Systematic searches were carried out up to the end of October 2011 in the following databases: Medline (via OVID), Embase (via Embase.com), HTA and EED (via CRD NHS) and Psycinfo (via OVID).

Searches using various qualifiers for “quality of life” were used as Subject heading or text word. See appendix 3.1 for an overview of the search strategies and terms used.

2.3.1.2. Selection criteria

Identified references were assessed against pre-defined selection criteria (in terms of population, intervention, outcome and design –Table 2.5) in a two-step procedure: initial assessment of the title, abstract and keywords; followed by full-text assessment of the selected references. When no abstract was available and the citation was unclear or ambiguous, the citation was assessed based on keywords and full-text. Reference lists of the selected studies were scrutinized for additional relevant citations.

Table 2.5: Article selection criteria

	Inclusion criteria	Exclusion criteria
Population	Screened or treated patients for breast cancer, with a Caucasian origin and without high risk factors	Other diseases, non Caucasian, high risk women
Intervention	Any intervention relevant to the Belgian settings	Interventions not used in Belgium
Outcome	Unique QoL weights allowing to derive QALYs (=utilities)	Multi-dimension HRQoL scores, DALYs, HYEs, ...
Design	Direct (TTO, PTO, SG) or indirect (EQ-5D, SF-6D, HUI, QWB) valuation methods in primary studies	Letters, secondary studies, CUA with QALYs derived from the literature, ... Direct valuations using VAS (not recommended in the KCE pharmaco-economic guidelines) ⁷⁹ .

QoL: Quality of Life. QALY: Quality adjusted life year. HRQoL: Health-Related Quality of Life. DALY: Disability-Adjusted Life-Years. HYE: healthy-years-equivalent; TTO: Time-Trade-Off. PTO: Person Trade-Off. SG: Standard-Gamble. HUI: Health Utility Index. QWB: Quality of Well Being scale. CUA: cost-utility analysis. VAS: visual analogue scale



2.3.1.3. Selection process

The flowchart of the selection process is presented in appendix 3.2. The searches on the databases returned 524 citations. After exclusion of 172 duplicates, 352 unique citations were left (see also appendix 3.2). Hand searching allowed us to identify 3 additional citations. Two-hundred and ninety (290) references were discarded based on title and abstract, leaving 65 references for full-text evaluation. Another 49 references were excluded at this stage, mostly because of the unmet design and population criteria. Overall, we selected 16 primary studies (see appendix 3.2).

2.3.2. Results

A summary of the selected studies can be found in appendix 3.3. It should be noted that this summary only report methods used to derive utility values and their results. If other parameters were measured, they were not reported in the summary.

The selection of utilities was done according to the following stages:

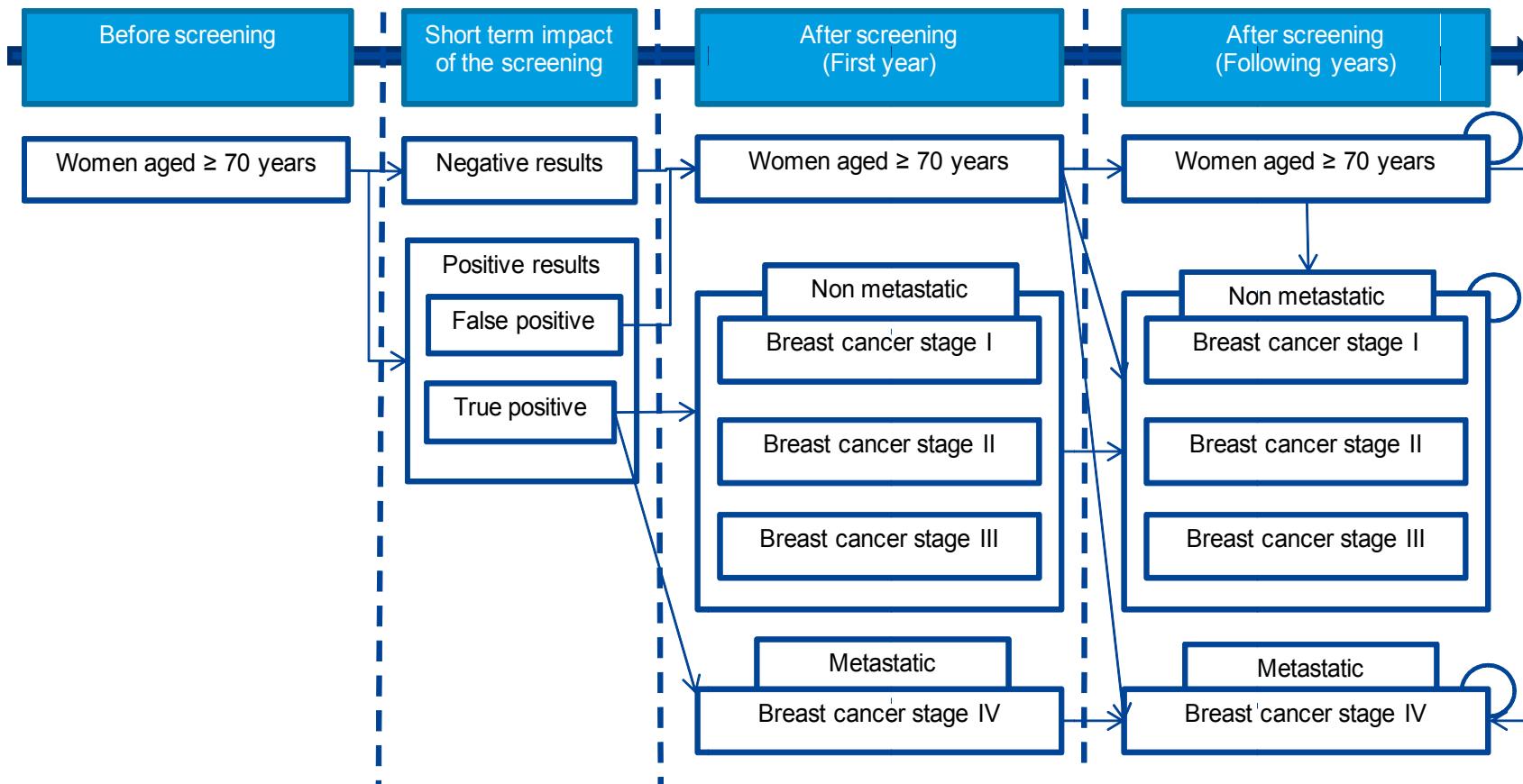
- Determination of health states for which utilities were needed
- Selection of utilities
 - Selection of a basecase study
 - Selection of other studies
- Pooling of selected utilities and calculation of percentage changes

2.3.2.1. Determination of health states

Health states for which utility values are needed are listed in Figure 2.1.

It should be noted that this figure is a schematic representation of the reflection process but not the model itself (described in section 3.2).

Figure 2.1: Health states for which utilities are needed (reflection process)



2.3.2.2. Selection of utilities

To select utility values, we first tried to find Belgian data as recommended by the pharmaco-economic guidelines of the KCE⁷⁹. However, no Belgian data could be found.

Then, we tried to find the most complete study which best fit with our model. The aim was to avoid as much as possible the use of multiple instruments and multiple populations to derive them. Indeed, according to the pharmaco-economic guidelines of the KCE, it is strongly recommended to use the same descriptive instrument and the same set of values for quality of life weights coming from different studies⁷⁹.

However, no study assessing all of the health states described in section 2.3.2.1 with the same design was found. We therefore tried to find the study with the greatest number of health states corresponding to our model and to use it at the starting point of the selection process.

Selection of the base case study

We found only one study having assessed utility values for both non-metastatic and metastatic patients, i.e. the study of Lidgren et al⁸⁰. We had the chance that this study also used the better available instrument according to the pharmaco-economic guidelines of the KCE, i.e. the EQ-5D⁷⁹. This study was therefore the starting point of our selection process.

Utility values in the study of Lidgren et al.⁸⁰ were derived from two methods, i.e. a direct valuation method (i.e. the time-trade-off (TTO) technique) by Swedish patients and an indirect valuation method using a generic instrument (i.e. the EQ-5D instrument). Because pharmaco-economic guidelines of the KCE recommend the use of the EQ-5D, only these valuations were retained (i.e. utility values from EQ-5D and not from TTO). In this study, health states were described by Swedish patients and valued using UK tariffs (because no tariffs from the Swedish population are available). Health states descriptions can be found in Table 2.6. Utility values for non-metastatic patients in the first year (i.e. the year of the treatment) and the following years as well as utility values for metastatic patients are described in Table 2.8.

This study had the following limitations:

- Utility values were measured during out-patient visits at a breast cancer outpatient clinic (Karolinska University hospital), implying the following limitations:

Utility values for non-metastatic patients did not fully take into account the short term impact of surgery. However, on an annual basis, this short term impact was expected to cover a limited length of time and was therefore not included in the model.

Utility values for metastatic patients did not represent patients in palliative care. It was therefore assumed that these utility values only reflected the quality of life of metastatic patients during the first year of diagnosis.

The short term impact of diagnosis is also not fully taken into account (not measured at the moment of the diagnosis), even if authors of this study reported that this impact was expected to be included in the valuation (measured the year of diagnosis).

- Non-metastatic patients were divided in only two groups, i.e. the first year of diagnosis and the following years. It was therefore assumed that after the year of treatment, utility values remained constant. This assumption is supported by an US study where no significant difference in utility values (from EQ-5D using US tariffs) was found at year 5, 10 and 15⁸¹. This US study is described in the appendix 3.3.
- It should also be noted that utility estimates for non-metastatic patients (primary breast cancer in the first year of diagnosis) and metastatic patients were similar (0.696 and 0.685 respectively). This inconsistency may be due to the following reasons:

Metastatic patients only include patients going in out-patient consultations (best cases).

Generic instruments such as the EQ-5D are less sensitive to capture relevant changes in health in a specific disease than disease-specific instruments. However, disease-specific instruments can only be used if validated mapping functions to derive utilities from these instruments are available, which was not the case⁷⁹.

Table 2.6: Health states descriptions for the study of Lidgren et al.

Primary breast cancer (year 0-1)	Patients who had primary diagnosis breast of cancer within 1 year or less prior to answering the questionnaire, no recurrence and no metastatic disease
Recurrence (year 0-1)	Patients who had at least one recurrence (loco-regional and/or contra-lateral) within 1 year or less prior to answering the questionnaire, and no metastatic disease.
Primary cancer and recurrence following years	Patients who had been diagnosed with a primary breast cancer or their last recurrence more than 1 year prior to answering the questionnaire, and no metastatic disease.
Metastatic patients	Patients who had metastatic disease

Selection of other studies

For other health states, we tried to find studies having used similar instruments for the same population. The study of Lidgren et al.⁸⁰ allowed us to identify a study assessing utility values for the general Swedish population stratified by age and gender using the same instrument (EQ-5D with UK tariffs), i.e. the study of Burström et al.⁸² These utility values were therefore used for women aged 70 and over (see Table 2.8).

For the short term impact of positive results after screening, one study using the EQ-5D instrument was identified (Gerard et al.)⁸³. This study assessed utility values for false positive, true positive, false negative and true negative. Health states were described by the UK population (and not the Swedish population) but UK tariffs were used to valuate these health states (as in the other selected studies). A description of the “false positive” state is given in Table 2.7.

As showed in this table, the description include the following stage: being invited for screening, having a breast screen, waiting for results, being recalled for further examinations, having further examinations and obtention of a diagnosis, i.e. no evidence of breast cancer. For the assessment, only three of the five EQ-5D dimensions were used, i.e. usual activity; pain/discomfort; and anxiety/distress and it was assumed that the remaining two dimensions (i.e. mobility and ability of self-care) were unaffected. The quality of life effects associated with true negatives and false positives lasted 12 months while true positive and false negative were measured for the remaining life expectancy. These values can therefore not be used to measure the short term impact of screening. We decided to make the following assumptions:

- True negative patients have utility values equal to the general population.
- The short term impact of positive results at screening is measured by the percentage change between true negative and false positive.
- This impact is present until the diagnosis, i.e. on average 45 days after screening according to IMA data. After, either valuations of Burström et al.⁸² (general population for false positive) or valuations of Lidgren et al.⁸⁰ (non metastatic or metastatic disease year 1 for true positive) were used.

Utility values for false positive and true negative can be found in Table 2.8. It should be noted that the study of Domeyer et al.⁸⁴ described in appendix 3.3 assessed the short term impact of biopsy. However, to avoid model complexity and because the biopsy is included in the description of a “false positive” in the study of Gerard et al.⁸³, we decided to not take the study of Domeyer et al.⁸⁴ into account.

Concerning the evolution of utility values for patients with metastatic breast cancer in the long term, no study was found.

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**Table 2.7: Description of a “false positive” state (Gerard et al)⁸³**

Routine breast screen	<ul style="list-style-type: none">• She is invited by letter for routine breast screening.• The appointment is about 2 weeks from receiving the invitation.• The visit at the breast screening centre takes about half an hour, which may include waiting time.• A female radiographer asks about any symptoms or history of breast disease and explains what will happen.• To take the X-ray she is asked to undress to the waist. Each breast is placed in turn between two special X-ray plates and compressed to get the best possible picture.
Further tests	<ul style="list-style-type: none">• She is asked by letter to go to the breast screening centre the following week.• Other tests are needed because the breast X-ray result is not clear.• This visit may take up to half a day.• The breast X-ray is repeated.• The doctor examines her breasts.• The doctor may carry out an ultrasound examination.• Fluid from the affected area is taken for laboratory analysis using a fine needle to do this her breast may again be compressed between the X-ray plates.
The results of the tests are ready within the week	<ul style="list-style-type: none">• The tests show no evidence of breast cancer.
Quality of life effects of routine breast screening (short term)	The QoL of some women is affected by the experience of routine breast screening and breast cancer diagnosis. The effects may continue for some time.
Receiving the invitation	<ul style="list-style-type: none">• Most women are pleased to receive the invitation.• Some women are made nervous, anxious or depressed, and are worried about having breast cancer.
Waiting for the day of the appointment	<ul style="list-style-type: none">• Most women carry on with their usual activities and interests.• Some women are anxious and depressed, unable to concentrate, sleep badly and are moody and irritable. They are unable to carry on with their usual activities and interests.• Personal and sexual relationships may be affected.

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|---------------------------------------|--|
| At the breast screening clinic | <ul style="list-style-type: none"> • Most women are nervous, but are not anxious or depressed. • Most women are not embarrassed by the screening procedure. • Most women are not unduly worried about breast cancer developing. • Most women find the breast X-ray is uncomfortable and slightly painful, but this is short lived. • Some women find the breast X-ray very uncomfortable and painful. |
| Waiting for the results | <ul style="list-style-type: none"> • Most women carry on with their usual activities and interests. • Some women are anxious and depressed, un-able to concentrate, sleep badly and are moody and irritable. They are unable to carry on with their usual activities and interests. • Personal and sexual relationships of some women may be affected. <p>If recalled for further tests:</p> <ul style="list-style-type: none"> • Most women are very anxious at being recalled for further tests. • One of the tests, where the doctor removes fluid from the affected area, is painful. |
| Clear results after the test | <ul style="list-style-type: none"> • Most women are reassured by the clear results. • Some women remain anxious for up to a year before they are back to their usual self. |
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Table 2.8: Description of the selected utilities

Author (year)	Instrument	Population for health state description	Population for valuation	Health state	Mean value
Lidgren et al. (2007) ⁸⁰	EQ-5D	Sweden patients (Mean age: see health states)	UK tariffs (general population)	Primary breast cancer (Year 0-1); Mean age: 56	0.696
			UK tariffs (general population)	Breast cancer (following years); Mean age: 58	0.779
			UK tariffs (general population)	Metastatic patients; Mean age 56	0.685
Burström et al. (2001) ⁸²	EQ-5D	Sweden patients (Mean age: see health states)	UK tariffs (general population)	Women aged 50-59	0.833
				Women aged 70-79	0.792
				Women aged 80-88	0.740
Gerard et al. (1999) ⁸³	EQ-5D	Women from UK aged 40-64 years (eligible for screening)	UK tariffs (general population)	True negative	0.940



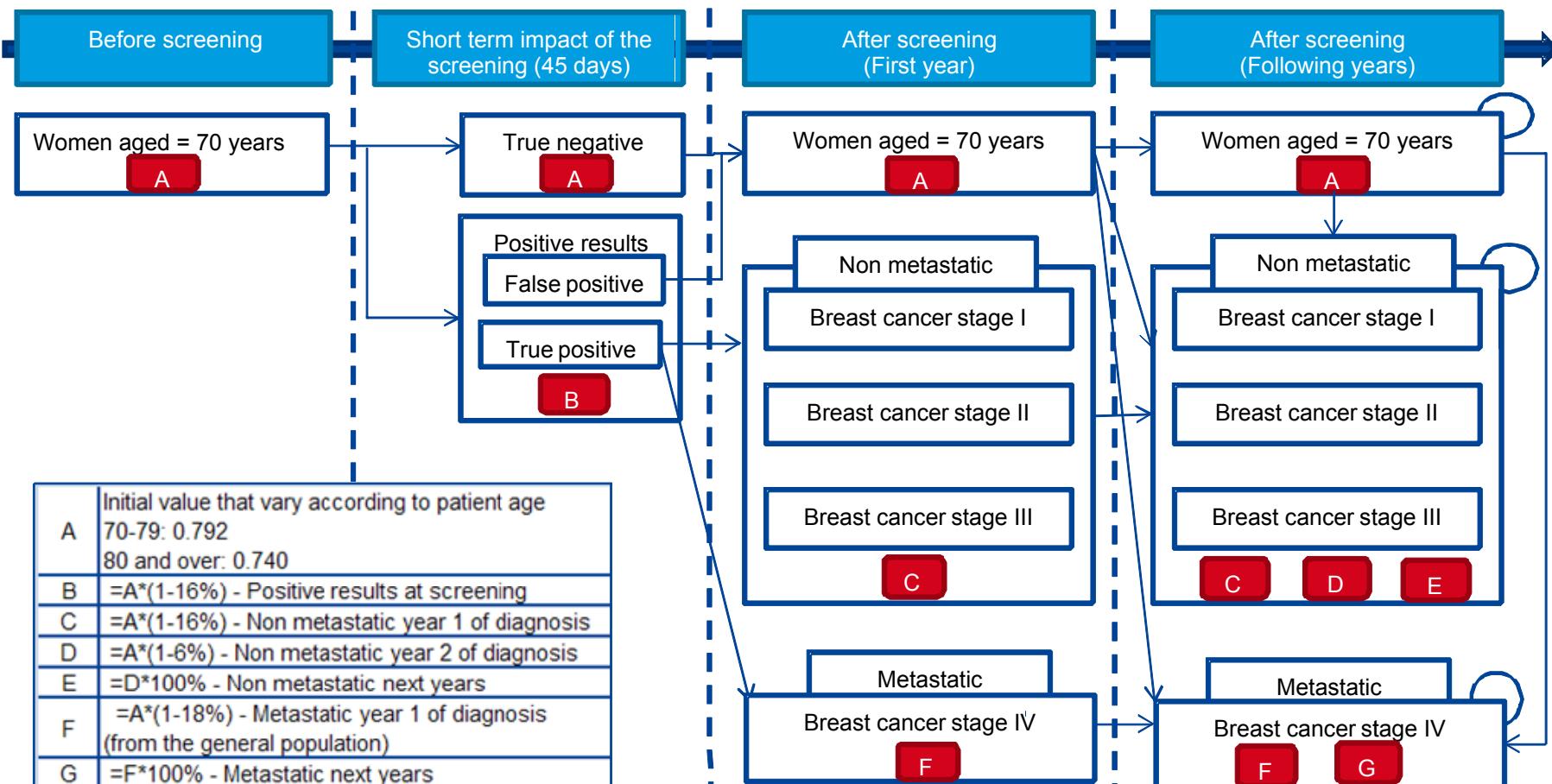
2.3.2.3. Pooling of selected studies and calculation of percentage changes

A summary of selected utilities and of calculation of percentage changes can be found in Figure 2.2. The utility values of the study of Burström et al.⁸² were chosen as the initial values of the model (first state of the model (A)). These values varied according to women age. Then, the percentage change relative to these values was applied. It was assumed that these percentage changes did not vary according to the women age (no data).

The next stage concerns the short term impact of the screening. It was assumed that utility values for true negative women were equal to utility values in the general population (A). Then, the percentage decrease in utilities between true negative women and false positive women was calculated, i.e. -16% (B). Initial values were thus maintained for true negative women and decreased by 16% for women with a positive result after screening (false or true positive). As mentioned in the section 0, these utilities will be maintained for 45 days.

For the first year of screening, women without breast cancer had utility values equal to the general population (A). For true positive, utility values of the study of Lidgren et al. were used.⁸⁰ To make the link between the study of Lidgren et al.⁸⁰ and the study of Burström et al.⁸², percentage changes between values for the same population were used, i.e. Swedish women aged 50-59 (and UK tariffs). Utility values were therefore reduced by 16% ((0.696-0.833)/0.833) for non metastatic patients (C) and by 18% ((0.685-0.833)/0.833) for metastatic patients (E).

For the next years, people from the general population who developed non-metastatic or metastatic breast cancer had utility values reduced by 16% (C) and 18% (E) respectively (as calculated above). Non-metastatic patients who stayed in this stage had their utility decreased by 6% compared to the general population ((0.779-0.833)/0.833) and maintained the years after (D). Metastatic patients maintained their utility until death (G).

Figure 2.2: Percentage change in utilities



2.3.3. Discussion

To include the quality of life impact of screening in the analysis, utility values for each health state of the model had to be identified. The aim of this chapter was therefore to select these values. The method was based on the KCE pharmaco-economic guidelines⁷⁹. We tried to avoid the use of multiple instruments and multiple valuations and focused on utility values derived from the EQ-5D instrument.

- The analysis had the following limitations:
- No Belgian data were available and a transferability analysis was not possible (no access to primary data). Even if we expected that using UK tariffs instead of Belgian valuations would not greatly influence results, Belgian data would be interesting for future models.
- The short term impact of surgery and of diagnosis was not taken into account because no valid data were available.
- Even if the EQ-5D is one of the best available instrument to assess these utilities (according to the KCE pharmaco-economic guidelines), this instrument is less sensitive than disease specific instruments. Consequently, it can be expected that the impact of some conditions such as a mastectomy (partial or total) would have been more important if a disease specific instrument instead of a generic instrument had been used. This lack of sensitivity could explain the low percentage change between patients with breast cancer and women in the general population or between metastatic and non metastatic patients. The assessment of the quality of life from disease specific instruments was nevertheless not investigated in this chapter because these instruments do not permit to derive QALYs.
- Finally, the review of the literature showed an important variability between reported utility estimates for breast cancer health states (see appendix 3.3), revealing a high level of uncertainty around these parameters. Because of this uncertainty, a sensitivity analysis on these parameters should be done in the chapter on model results.

3. DECISION ANALYSIS

To quantify what the implications of our findings are on the Belgian situation we constructed a decision analysis model using two different approaches. For the first simple approach, we applied data from IMA, cancer registry and data from the literature on the Belgian life tables (see below). For the second, we constructed a simple time dependent cohort with annual cycles.

We consider performing one Belgian decision analysis a better approach than trying to adapt the models discussed in chapter 2 to the Belgian situation. Indeed, Belgian data needed to parameterize these models are not available and we would merely reproduce the already published findings of these models, as we would be obliged to use the same (mainly US) data.

We look at the effect of introducing mammography screening in addition to the currently existing situation with the opportunistic screening going on at the current level. This has the advantage that we can use Belgian data as baseline without having to modify them, as this can only be done making use of an additional number of non verifiable assumptions. We describe here:

- Available data used in this decision analysis;
- Additional literature review focused on quality of life related to the screening and to the breast cancer as such;
- The model used for this decision analysis.



3.1. Data sources

Belgian life table (2009)

Overall survival was taken from the Belgian life table of 2009 from be.STAT (<http://statbel.fgov.be>)

Belgian Cancer Registry (BCR)

The Belgian Cancer Registry Foundation is a public institution which collects data concerning new cancer cases in Belgium and makes up statistics from these data (<http://www.kankerregister.org/>).

Belgian organized screening

As recommended by European Commission, Belgium started a national organized screening programme. The target age groups as defined by the program are women aged 50 to 69 years. Belgian breast cancer screening programs are organized by: Brumammo (Bruxelles, <http://www.brumammo.be/>), Centre Communautaire de Référence pour le dépistage des cancers (CCRef: <http://www.ccref.org/>) (Communauté Française) and BorstKankerOpsporing (BKO) (Vlaamse Gemeenschap: <http://www.zorg-en-gezondheid.be/>).

Intermutualistic Agency (IMA)

The Intermutualistic Agency (IMA) centralises data coming from all Belgian sickness funds. IMA compiled and published several reports on the national screening program containing data on the target age groups as defined by the program (50-69 years). IMA complemented this with information on persons outside the target age-group, with a particular focus on the tests used, delays between screening tests and possible confirmation and treatments following testing (<http://www.nic-ima.be/>).

Dutch National Evaluation Team for Breast cancer screening (DNETB)⁸⁵

The Dutch National Evaluation Team for Breast cancer screening published a report with their findings covering the period 1990-2007 containing information on age specific stage distributions in the screened population.

SEER database

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute works to provide information on cancer statistics in an effort to reduce the burden of cancer among the U.S. Population (<http://seer.cancer.gov/>). SEER collects data on cancer cases from various locations and sources throughout the United States. Data collection began in 1973. As they used an outdated distribution we could not incorporate these in the model.

3.2. Model description

In a first simple approach we applied the 22% reduction in breast cancer mortality caused by screening coming from RCT and its range, resulting from the results of the meta-analysis of Götzsche et al, 2008⁴ on the Belgian life table. We assume here that the reduction in women aged 70-74 is similar to the reduction in other age groups. We also assume, following Barratt et al 2005³⁶ that benefit accrues linearly to a maximal level over first five years after starting screening and that benefit declines linearly to nothing over five years after stopping screening. Life years saved can then be derived from the life table. However, effects of harms and effects on quality of life resulting from earlier diagnosis, over-diagnosis and stage-shift is more difficult to assess in this approach. Therefore this approach was only used for cross validation by comparing it with a more complex approach that makes use of the stage-shift caused by screening.

The second approach makes use of the Belgian Cancer Registry (BCR) data on incidence of invasive cancer and DCIS for the construction of a time dependent state transition cohort model with annual cycles.

The model compares 2 cohorts:

- A cohort of women starting at age 70 where screening is extended to the population in the age group 70-74, where a part of the women participates in the screening and where a part of the cancers is found by screening, depending on participation rate and sensitivity of the screening. There is a mix of screen detected and not screen detected cases (interval cancers and cancers amongst unscreened women). The screen detected cancers will have a different stage distribution than the cancers not detected by screening.



- A cohort of women starting at age 70 where the screening is not extended beyond the age of 69 years. For this cohort all women have the stage distribution of the non screened.

All women are followed to death. The cumulative number of life years, the number of QALYs and deaths to breast cancer of the two cohorts are compared. Overall mortality is not compared as in the end everybody dies.

We assume that:

- Survival and quality of life of the women depends only on the stage of the tumor at the moment the tumor is detected and the age of the women, and not on the presence or absence of screening;
- All benefit of the screening results from the stage-shift, the differences in stage-distribution caused by the screening.

Harm caused by false positives at the moment of the screening is accounted for separately, by assuming 3 screening rounds with a 2 years interval in the participation women and applying recall rates at the proportion women that are alive and without breast cancer at the moment the screening round actually takes place.

Figure 3.1 shows the different compartments in the two cohorts and the transitions between them.

In the unscreened cohort, transitions between compartments from year to year are determined by:

- Incidence of breast cancer;
- Stage distribution of unscreened cancers;
- Stage specific survival; and
- Age specific overall mortality due to other causes.

On top of that, for the cohort where screening takes place, transition is also determined by some aspects of the screening:

- Lead time as part of the cancers will be found earlier;
- The proportion of cancers found by screening and proportion not found by screening and their respective stage distributions.

As survival and quality of life depends on both age and time since diagnosis in the model, a separate compartment is made for each age of diagnosis and stage, and stage specific survival is than applied. As screening is applied during 5 years and there is an assumed lead time of 2 years (or 3 in sensitivity analysis) the number of compartments remained manageable.

Transitions between stages are not included as stages are assessed at the moment the diagnosis is made followed by treatment. Even if the cancer evolves after treatment it does not necessarily go through the 4 stages anymore.

Figure 3.1: Comparison of the two cohorts with and without a screening program

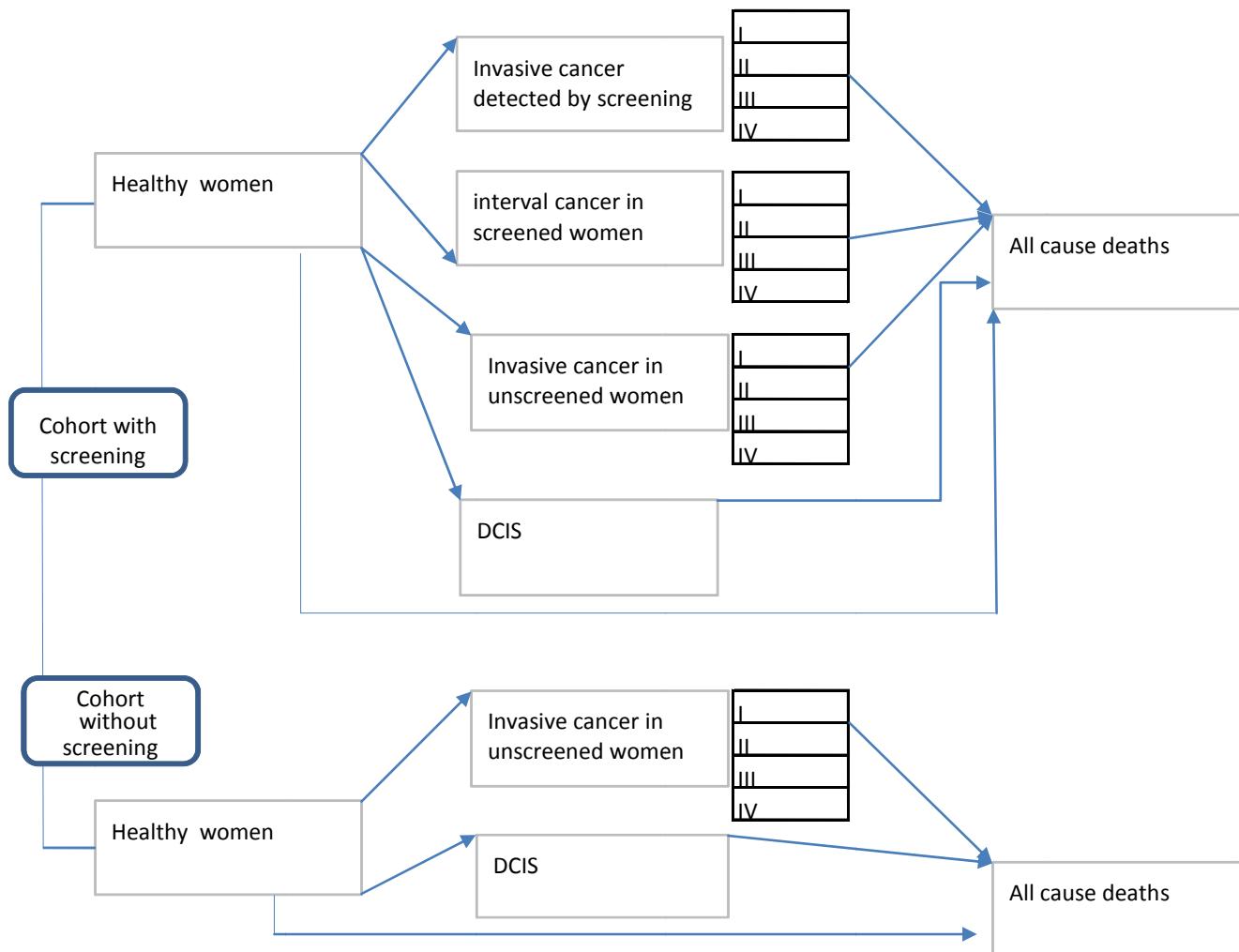
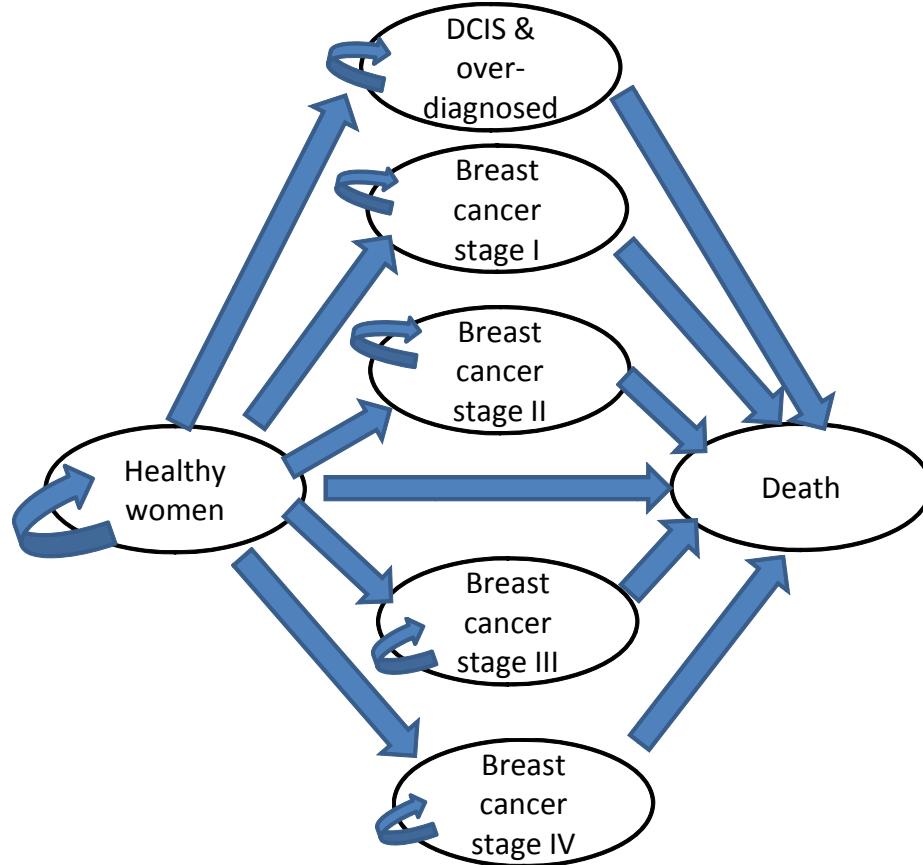


Figure 3.2: Compartments in the two cohorts and the transitions between them





3.3. Description of the parameters

3.3.1. Age specific overall survival

Overall survival was taken from the Belgian life table of 2009 from be.STAT (<http://statbel.fgov.be>) after adjusting for breast cancer specific mortality based on data from the Belgian Cancer register.

3.3.2. Breast cancer incidence

For the baseline without screening the BCR data on incidence of DCIS and the 4 stages for invasive for the age group 70-74 of the period 2004-2008 were used. There is some opportunistic screening in that age group. From the IMA data we infer that in Flanders the coverage with at least one mammography in the past 2 years is 18% (for details see the KCE report 172 on breast cancer screening in risk groups)². Given that we can assume that an important part of this is also for diagnostic and follows up purposes, so we choose to use data issued from Flanders because they are less contaminated by opportunistic screening.

For the situation where screening takes place, incidence in the 70-74 group will increase with a number of cancers coming from two sources:

- **Lead time**, cancers that would have appeared later but are found now because of lead time. This will lead to a compensatory decrease in number of cases in the following years. The moment and degree of this shift depends on the assumed lead time (see point 3.2.2). We used 2 years lead time in the baseline and 3 years in the sensitivity analysis.
- **Over diagnosis invasive cancer**, we modeled the over diagnosis based on the findings in the literature as described in the literature review above under 2.1.3.5. We assume a range of 2 to 30% for over diagnosis excluding DCIS.
- **Over diagnosis DCIS**, we model the over diagnosis of DCIS in a different way: we use the observation that in Flanders the incidence DCIS per 100 000 is twice in the group 60-69 where screening takes place compared to the age-groups 70-74 and 75-79 where only a limited amount of opportunistic screening takes place. This is in contrast with the Brussels capital region and Walloon region where the drop in DCIS is much less pronounced. So we take as an estimation of

over diagnosis the difference in DCIS incidence in Flanders between the age-groups 60-69 and 70-74, augmented by 1.5 to adjust for the fact that screening coverage is only 60% as a proxy for overdiagnosed DCIS. This brings us to an over diagnosis of DCIS of 40 per 100 000 women per year.

3.3.3. Participation rate

We used a 70% participation (plausible range 60% to 80%) as baseline.

3.3.4. Proportion of screen detected breast cancers

The data of the Belgian screening program show that in the age group 50-69, 49% of the cases are found by screening, and the rest is either interval cancer or not participating in the screening. Among the screened women, 75% of the found cancers are screen-detected and 25% is interval cancer. We used a proportion of cancers found among the women participating in screening of 70% (plausible range 60% to 80%).

3.3.5. Recall rate

We assume a recall rate of 3.5% based on the data from the Flemish screening program concerning follow up rounds (as the screening would be an extension of the screening among women aged 50-69. For the sensitivity analysis we used 2% in an optimistic scenario and 5 and 10% in the more pessimistic scenario (10% recall rates are observed for the moment in certain regions).

As a baseline we assume a delay of 45 days, based on IMA data, with a plausible range for the sensitivity analysis of 36 and 45 days (subtracting and adding 20%).

The short term impact of positive results at screening were measured by the percentage change in utility values between true negative and false positive results.

3.3.6. Stage distribution and stage shift

We take estimations of the stage distribution for breast cancer amongst screened and unscreened from the BCR data on the Flanders and data provided by the Flemish screening program.

For the stage distribution in the unscreened women, we can consider the stage distribution amongst women in the group 70-74 in Flanders for the years 2004 - 2008 a good estimation. The stage shift will be slightly underestimated as there is some opportunistic screening in that group going on, see above.

For stage distribution in the screened population, the base case estimation is based on the data from the Dutch National Evaluation Team for Breast cancer screening report of 2009 (DNETB)⁸⁵ who provide data specifically for the age group 70-74 from 1998-2007. Although using 2 stage distributions from different sources is a suboptimal way of modeling a stage shift we think this approximates best the Belgian situation, as we do not have date on screen detected cancer in this age group. We assume stage distribution of cases among the non screened and interval cancer to be the same, based on the data from the Flemish screening program.

The Flemish screening program provided data on the stages among screen detected cancers, interval cancers and cancers amongst non participants, collected amongst women who gave their consent in the period 2001-2006. Stage distribution of interval cancers and cancer among non participants is very similar.

Table 3.1: Stage distribution among screen detected breast cancers, interval cancers and cancers among non participants, age 50-69, Flemish screening program 2001-2006.

Screen detected cancers			Interval cancers		Cancers amongst non participants	
Stage	n	%	n	%	n	%
I	2586	62.5%	624	41.5%	1454	41.8%
II	1306	31.6%	656	43.6%	1460	42.0%
III	232	5.6%	200	13.3%	493	14.2%
IV	15	0.4%	24	1.6%	71	2.0%
TOTAL	4139	100%	1504	100%	3478	100%

This baseline stage shift we call Scenario 1:

Stage distribution of cancers not found by screening

BCR data (Flemish population, 70-74y, 2004-2008)

Stage	%
I	31.6%
II	42.3%
III	16.6%
IV	9.5%



Stage distribution of cancers found by screening
Data of the DNETB screening report 2009

Stage	%
I	80%
II	18.7%
III	0.8%
IV	0.5%

Important remark: It is important to note that this shift concerns **only screen detected cancers** and that in the cohort with screening interval cancers and nonparticipants keep the stage distribution of cancer not found by screening. In most cases this is around 50% but depends on the other parameter values of the screening and varies in time.

For the sensitivity analysis we use 2 supplementary scenario's:

As the stage distribution from the Dutch National Evaluation Team for Breast cancer screening report of 2009 may be more favorable than what can be achieved in the Belgian context, we used as an alternative scenario the stage-distribution for screen detected patients of the age group 50-69 from the Flemish cancer screening program.

This we call Scenario 2:

Stage distribution of cancers not found by screening

BCR data (Flemish population,70-74 years, 2004-2008)

Stage	%
I	31.6%
II	42.3%
III	16.6%
IV	9.5%



Stage distribution of cancers found by screening (Flemish screening programme (50-69 years))

Stage	%
I	62.5%
II	31.6%
III	5.6%
IV	0.4%

In a third scenario we use a slightly different modeling approach.

Instead of using stage distributions amongst screened and unscreened women, we assume that introducing screening in the group 69-74 will shift the stage distribution amongst **all breast cancer** cases in the population to the stage distribution of the women 60-69 in the same period, using data for Flanders from the Belgian breast cancer registry.

This we call scenario 3

Stage distribution of cancers not found by screening

BCR data (Flemish population,70-74 years, 2004-2008)

Stage	%
I	31.6%
II	42.3%
III	16.6%
IV	9.5%



Stage distribution amongst all breast cancers if screening levels are similar to levels among 60-69 in Flanders

Stage	%
I	45.7%
II	35.9%
III	12.5%
IV	5.9%

3.3.7. Stage specific relative survival

Stage specific survival was taken from Belgian stage specific annual survival data (taken from KCE report 150A)⁸⁶. We only have data up to 5 years. We used data from the Dutch cancer register taken from the website (<http://www.cijfersoverkanker.nl>) to supplement until 7 years (see appendix 4.1). We assumed that survival conditional on stage is similar in screened and unscreened breast cancer patients. As a sensitivity analysis we used also:

- Entirely the Dutch survival data for women above 70 years per stagegroup. The relative survival curve shows a lower relative survival for women above 70 compared with the overall survival. This may reflect the fact that older women support the invasive treatments less well but it is also possible that there is undertreatment of the elderly. Moreover, the data include patients that were treated more than 20 years ago, this may also explain the lower relative survival.
- British survival data coming from breast cancer research UK (<http://info.cancerresearchuk.org/>) They provide 10 years survival data but survival is considerably lower than the Dutch or Belgian data. One of the problems with 10 year survival data is the fact that it reflects survival of persons treated at least 11 years ago, given the fast evolution in breast cancer treatment this is a long time.



- Belgian survival data supplemented by French 10 year survival data coming from⁸⁷. The problem of the evolution in breast cancer treatment apply here as for the British data.

We did not use US SEER data as they use an outdated staging method, so that survival curves per stage are not comparable to the other sources and difficult to incorporate in the model.

The survival curves can be found in the annex.

3.3.8. QALY

Number of life years was calculated for each stage and a stage and this was adjusted for the quality of life (QALYs), based on a literature search (see point 2.3).

We made some assumptions:

- Utility values at start of the model (before screening) were stratified by age but percentage changes relative to these values were assumed to not vary according to the age of the women (we did not have data on this). For the sensitivity analysis, we apply a 20% reduction or increase.
- Patients with negative results had utility values equal to the general population.
- In the assessment of utility values for true negative and false positive results, mobility and ability of self-care were assumed to be unaffected by screening.

- In the study of Lidgren et al.⁸⁰, non-metastatic patients were divided in only two groups, i.e. the first year of diagnosis and the following years. Therefore patients in stage I, II, III (grouped as non metastatic patients) were assumed to have the same utility. This assumption is supported by the fact that for years 2001-2006, the treatment was the same for patients in stage I, II, III according to the KCE report on quality indicators in breast cancer⁸⁶. Note that more recent data may change this picture because many cancer found by screening are now treated by conservative surgery. Nevertheless, data to prove this assumption are not available and we found no study comparing the impact of partial versus total mastectomy on quality of life corresponding to our inclusion criteria.

- Utility values for non-metastatic patients (after the year of surgery) and metastatic patients were assumed to remain constant across years. For non-metastatic patients, this assumption is supported by an US study showing no significant differences at year 5, 10, and 15⁸¹. Nevertheless, as a sensitivity analysis we apply a 20% decrement in QALYs for taking into account a variation of utility values across years.
- At baseline, we did not discount QALYs. For the sensitivity analysis, discount rates of 1.5%, 3% and 5% were applied.

Parameters used in the model are shown in table 3.2.

**Table 3.2: Parameters used in the model**

Parameters	No screening	Base case	Sensitivity analysis
3.3.1 Age specific overall survival	Belgian life-table	Belgian life-table	Belgian life-table
3.3.2 Breast cancer incidence	BCR data (Flanders population, 2004-2008)	BCR data (Flemish population, 2004-2008) increased by lead time. over-diagnosis invasive cancer of DCIS	BCR data (Flemish population, 2004-2008) increased by lead time. over-diagnosis invasive cancer of DCIS
Lead time	2 years	3 years	
Over-diagnosis invasive cancer	10.0%	range from 3 to 30%	
Over-diagnosis DCIS	40/100 000 women per year	40/100 000 women per year	
3.3.3 Participation rate	70.0%	range from 60% to 80%	
3.3.4 Proportion of screened detected cancers	70.0%	range from 60% to 80%	
3.3.5 Recall rate	3.5% (Flemish screening program)	range from 2% to 10%	
Duration of period after positive result	45 days	range from 36 to 54 days	
QALYs lost in this period	16.0%	estimated between 13% to 19%	
		Scenario 2	Scenario 3
3.3.6 Stage distribution	BCR data (Flemish population, 70-74years, 2004-2008)	Data of the DNETB screening report 2009	Stage distribution of Flemish screening programme (50-69)
Stage I	31.6%	80.0%	62.5%
Stage II	42.3%	18.7%	31.6%
			45.7%
			35.9%

Stage III	16.6%	0.8%	5.6%	12.5%
Stage IV	9.5%	0.5%	0.4%	5.9%

3.3.7	Stage specific relative survival	Belgian stage specific annual survival data supplemented until 7 years by Dutch data	Belgian stage specific annual survival data supplemented until 7 years by Dutch data	Dutch survival or British survival or Belgian/French survival
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3.3.8 QALY

Stage II III IV	-constant	- constant	-20.0%
Stage III IV	-constant	-constant	-20.0%
Stage IV	-constant	-constant	-20.0%
Age related QALY	-constant	-constant	range from + 20% to -20%
Discounted QALY			discounting rate + 1.5%. 3% and 5%



3.4. Results

In the baseline scenario the model predicts that there would be 1307 years of life saved per 100 000 (13.1 per 1000) women invited for screening and 395 per 100 000 (3.9 per 1000) QALYs. The model also predicts that 128 deaths would be averted per 100 000 women screened (1.3 per 1000), being a reduction of 21% (number needed to be offered screening: 782).

Because of the considerable uncertainty surrounding the parameters and model structure we did an extensive sensitivity analysis. Most uncertainty is not due to random error but due to issues relating to the right choice of source of information on the parameter. We did not do a probabilistic sensitivity analysis, as it was not possible to choose appropriate probability-distributions in a meaningful way.

Table 3.4 shows the results of the sensitivity analysis, the plausible ranges used for this analysis was discussed in 3.3, description of the parameters and justification of chosen values.

The number of years of life gained remains fairly constant under different assumptions. The number of QALY gained or lost varies much more under different assumptions. This is partly due to the fact the a lot of the uncertain or variable parameters have an impact on the quality of life gained rather than on mortality, such as high recall rates, over diagnosis, apart from the values accorded to the QALYs.

Assumed degree of over-diagnosis has a strong impact on QALYs gained and under the higher assumed values of 20% or 30% even imply that QALY would be lost instead of gained. Years of life gained increases slightly, this due to the fact that an over diagnosed case cannot become a new case in the model, one could argue that this is somewhat of an artifact but the effect is very small.

Recall rates of 10% also can shift the balance towards a loss of QALYs. Ten per cent recall rates are actually found in some parts of Belgium.

Assumptions on the choice of the appropriate survival curve have both an impact on years of life gained and QALYs gained. The Dutch and the British survival data increase the number of life years gained but lead to a loss of QALYs in certain scenarios. Belgian survival data supplemented by French 10 year survival is somewhere in between.

Increasing the assumed lead time to 3 years has an impact on both years of life gained and QALYs.

The model's estimation of the number of QALYs gained or lost depends on the valuation of these QALYs. Diminishing the age related QALYs, this is the decrease in quality of life due to old age, decreases the number of QALYs gained, as could be expected.

The estimations coming from the Lidgren's paper are fairly uniform and do not vary much in function of the different stages. We introduced a larger decrement in quality of life due to increasing stage at diagnosis, with 3 scenarios: (i) decreasing stage II III and IV with 20%, (ii) decreasing stage III and IV with 20% or (iii) decreasing stage IV with 20%. This has the effect of increasing the number of QALYs gained, because there are also gains in QALYs due to the stage shift alone outside the effect on mortality, as persons in stage I have in this scenario a better assumed quality of life, in contrast to the Lidgren data.

As could be expected, introducing discount rates decreases the number of QALYs gained.

As a worst case scenario, we set the estimation of over diagnosis at 20%, recall rate at 10%, loss of QALYs per recall at 0.19 during a period of 54 days and using the stage distribution coming from the Flemish screening program (scenario 2). This gives a gain of 872 Years of Life but a loss of 307 QALYs per 100 000.

As a best case scenario, we set the estimation of over-diagnosis at 3%, recall rate at 2%, loss of QALYs per recall at 0.13 during a period of 36 days and using the stage distribution coming from the Dutch screening program (scenario 1). This gives a gain of 1704 Years of Life and a gain of 1626 QALYs per 100 000.

Applying the 22% reduction in mortality from the meta-analysis from Götsche et al. to the Belgian life table, as described above, gives a very similar result, 139 cancers deaths due to breast cancer avoided and 1145 years of life saved.



Table 3.3 Modeling results: baseline, worst and best case scenario.

Scenario	Assumptions	Years of life	Quality adjusted years of life
		Per 100 000 women	Per 100 000 women
Baseline	Over diagnosis: 10% recall rate at 3.5% loss of QALYs per recall 0.16 during a period of 45 days stage distribution coming Dutch screening program (scenario 1)	1307 gained	395 gained
Worst case	Over diagnosis: 20% recall rate at 10% loss of QALYs per recall 0.19 during a period of 54 days stage distribution coming Flemish screening program (scenario 2)	872 gained	307 lost
Best case	Over diagnosis: 3% recall rate at 2% loss of QALYs per recall 0.13 during a period of 36 days stage distribution coming Dutch screening program (scenario 1)	1704 gained	1626 gained

**Table 3.4 Modeling results: sensitivity analysis.**

	Stageshift scenario 1		Stageshift scenario 2		Stageshift scenario 3	
	Years of life	QALYs	Years of life	QALYs	Years of life	QALYs
Baseline	1307	395	1014	186	1246	420
Assumed overdiagnosis						
0.03	1304	526	1011	317	1245	551
0.05	1305	489	1012	280	1245	514
0.1	1307	395	1014	186	1246	420
0.2	1310	208	1018	0	1249	232
0.3	1314	22	1022	-187	1251	45
Recall rate						
0.02	1307	442	1014	234	1246	459
0.035	1307	395	1014	186	1246	420
0.05	1307	348	1014	139	1246	380
0.1	1307	190	1014	-19	1246	249
Period between false positive and confirmation test: duration						
36 days	1307	417	1014	208	1246	438
45 days	1307	395	1014	186	1246	420
54 days	1307	373	1014	164	1246	401
Period between false positive and confirmation test:% QALYs lost						
QALYs loss period 13%	1307	416	1014	207	1246	449
QALYs loss period 16%	1307	395	1014	186	1246	434
QALYs loss per period 19%	1307	374	1014	166	1246	420
Participation rate						
0.6	1120	281	869	102	na	na

0.7	1307	395	1014	186	na	na
0.8	1493	509	1159	270	na	na
Effectiveness screening amongst participants						
0.6	1120	281	869	102	na	na
0.7	1307	395	1014	186	na	na
0.8	1493	509	1159	270	na	na
Survival curve by stage from other sources						
Dutch survival	1607	710	1181	310	1481	505
Britisch survival	1714	399	1148	-3	1585	374
Belgian survival supplemented by French data	1460	473	1045	96	1365	477
Assumed lead time 3 years	1098	118	875	77	1169	187
All QALYs minus 20%	1307	-948	1014	-1089	1246	-787
All QALYs plus 20%	1307	1587	1014	1310	1246	1534
Stage II III IV -20	1307	903	1014	465	1246	na
Stage III IV -20	1307	648	1014	370	1246	na
Stage IV -20	1307	450	1014	241	1246	na
Discounted QALYs						
Discount rate 1.5% for QALYs	1307	297	1014	121	1246	274
Discount rate 3% for QALYs	1307	215	1014	67	1246	193
Discount rate 5% for QALYs	1307	138	1014	15	1246	114

3.5. Discussion

Under baseline assumptions, screening in the age group 70-74 has a limited impact on breast cancer deaths avoided and number of years of life saved, amounting to 1.4 death avoided per 1000 women offered screening in that period and 13 years of life saved per 1000 women, amounting to 4.7 days of life gained per women offered screening.

This results fall within the range that the modelers of the CISNET project found as reported by Mandelblatt et al in 2009⁴⁸, where years of life gained ranged from 9 to 22 per thousand women screened. This, despite the fact that completely different data and model structures were used.

Years of life gained remained fairly constant in the sensitivity analysis. We choose a worst and best case scenario, with years of life gained ranging from 872 to 1704. It corresponds also with the simplified estimation based on the meta-analysis of Götsche et al.⁴ and the Belgian life tables, despite that this estimation comes from a completely different source of data and estimation method. This indicates that the estimations of the years of life gained are fairly robust and consistent with other studies.

The gain in quality adjusted life years (QALYs) is considerably less, with only 3.9 QALYs per 1000 women (1.4 quality adjusted day of life per women) offered screening and uncertainty is larger. One can present these data in another way by stating that 250 women need to be offered screening for 5 years to gain one year of life. The sensitivity analysis shows that under certain assumptions introducing breast cancer screening in this age group would actually generate a loss of QALYs. The most important of these is an assumed recall rate of 10%, as is the case in certain parts of Belgium, so these high recall rates should certainly first be addressed before proceeding.

The worst case scenario would imply a loss of 3 QALYs per 1000 women screened, we made sure that the assumptions of this worst case scenario are still reasonable assumptions and not unduly extreme. A number of elements were not considered in the worst case scenario because the effect is sometimes mixed. Bringing down the baseline estimation for the quality of life per age-group increases or decreases the final number of QALYs gained depending on the chosen values of the other parameters. This is due to the fact that introducing screening induces losses due to false positives and over diagnosis but gains due to the stage shift.

Under the best case scenario one would gain 16 QALYs per 1000 women screened.

The higher variability seen in the estimation of the QALYs compared to years of life lost has a number of reasons. There is considerable uncertainty around key parameters that determine a loss of QALYs, in particular concerning over-diagnosis. Variability due to recall rates on the other hand rather reflects real underlying differences in practice between countries and in Belgium between regions. There is also considerable uncertainty around the valuation of the quality of life, and this is not only uncertainty concerning the quality of life surrounding different breast cancer states but also age specific quality of life in Belgium. If in the future cost-effectiveness analyses are considered, this problem should be addressed if we want to have meaningful results. Quality of life attributed to stage IV has only a limited impact on overall numbers of QALYs gained or lost as survival in this stage is short and proportion of stage IV patients is low.

Carles et al. 2011³⁸, in an adaptation of the CISNET model of Lee & Zeelen, found an incremental benefit for biannual screening 50-74 of 2.78 life years gained per 1000 women compared to a schedule 50-69. They did not report the QALYs gained with extending the screening to 50-74 from 50-69, as it was dominated by screening from 45- 69, but reported that 1.86 QALYs per 1 000 were gained by extending the screening to 45-74 from 45-69. Interestingly, they did not incorporate the results of Vilaprinyo et al. 2011⁵⁸ into their calculations, but used US survival data.

The model takes into account over-diagnosis and lead time bias. However, it does not take into account length bias, the fact that screen-detected cancers would have a slower clinical course and have a better survival because screening tends to pick-up slow growing tumors some of which are not life threatening. Follow up studies of screen detected cancers and non screen detected cancer in the literature show that survival of screen detected cases is better than cases among non participants, independent of stage, and that survival of interval cases is somewhat in between⁸⁸⁻⁹¹. This indicates that there may indeed be a length time bias, through selection of less aggressive cancers by screening. However, the fact that interval cancers have a better survival than cancer among women not attending screening indicates that other factors also play a role, such as



selection bias (such as the social class or other health related factors amongst women non attending screening) and residual confounding after adjustment for stage. However length time has no direct impact on efficacy and on effectiveness, as detection of slow growing tumors does not necessarily negatively correlate with the ability to detect potentially life-threatening cancers at an earlier stage. Length time has indeed a negative impact on efficiency, as detection of indolent tumors means more harm and greater cost for no benefit to women.

We unfortunately did not have data on stage specific survival for tumors in unscreened women, tumors found by screening and interval cancers. Moreover, there is in general considerable uncertainty around the survival curves that will apply in the future, as treatment evolves and actual data on survival may be outdated.

Another major source of uncertainty is the right choice of stage distributions of the diagnosed cancers and stage-shift. The Flemish data on stage distribution show that the stage distributions of the interval cancers and the cancer amongst the people who do not participate in the screening are very similar.

We choose a modeling approach that is essentially based on the stage shift and its consequences, in contrast to most CISNET models that are essentially tumor growth models. This has the advantage that it allowed us to stay closer to the data and make less use of unobserved variables, incorporating parameters based on Belgian data, but has the disadvantage that the model is less flexible and has more simplifications. We model an overall effect of screening on the proportion of cancers that are screen detected based on Belgian data in the group 50-69. This implies that we can only evaluate the effect of the screening schedules actually in place in Belgium, we cannot vary the screening interval. We do not have the data however needed to parameterize the CISNET models and would be forced to use the same parameters that are already used in the published models, we would just merely replicate them.

In conclusion, there is considerable structural uncertainty around the right choice of the parameters, so a lot of caution is needed when interpreting the results. This uncertainty is reflected in the wide range of estimated Years of Life gained and QALYs gained in the end result. Nevertheless, there is evidence that continuing screening until the age of 74 years has

modest effect on the number of Life Years Saved but there is considerable uncertainty on the effect on quality adjusted life years, and the data show that under reasonable assumptions the intervention may even lead to a loss of quality adjusted life years. It is important to bring the recall rates to acceptable level before extending screening.



4. ANSWER TO CLINICAL QUESTIONS

What are clinical benefits and specific harms of an extension of breast cancer organized screening in women between 70 and 74 years?

4.1. Breast cancer related mortality

What is the effect of an extension (70-74 years) of breast cancer organized screening on the breast cancer related mortality? The continued screening for breast cancer between the ages of 70 and 74 makes it possible to obtain an extra 13 years of life for 1,000 women screened. The model also predicts that 128 deaths would be averted per 100 000 women screened (1.3 per 1000), being a reduction of 21%.

4.2. Delay between the screening and the mortality reduction

How long is the delay between the screening and the associated breast cancer related mortality reduction? The mortality reduction appears between 4 and 7 years after screening

4.3. Overall mortality

What is the effect of an extension (70-74 years) of breast cancer organized screening on the overall mortality? The effect of an extension (70-74 years) of breast cancer organized screening on the overall mortality is unclear. Studies did not have statistical power to detect an all-cause mortality reduction.

4.4. Morbidity

What is the effect of an extension (70-74 years) of breast cancer organized screening on morbidity? We found no data related to the cancer morbidity in randomized control trials. In other words, on this basis we do not accept or reject the hypothesis that screening reduces the morbidity of the breast cancer disease. Aim of screening is to detect minor tumors. Consequently, morbidity may be diminish by less aggressive treatment. The Belgian data currently at our disposal do not enable us to ratify this assertion. Actually, the most recent data (KCE report 150)⁸⁶ show 58% of the interventions are conservative surgery versus 38% of total mastectomies in the least advanced stages (C Stage I and II). Nearly 90% of patients undergoing

conservative surgery also receive radiotherapy treatment, 38% are given a treatment of neo-adjuvant chemotherapy, and 41% receive hormone treatment.

4.5. False positive or false negative results

What are the specific harms in terms of false positive or false negative results? The Belgian data currently at our disposal show a recall rate of 3,5% in Flanders and of 10% in Walloon and Brussels region per screening round. At this age group, performance of mammography is high and rates of false negative results are relatively low. For USA, rate of false negative results are 1.5 per 1000 women aged 70 to 79 years per screening round (BCSC-USA).

4.6. Additional diagnostic tests

What are the specific harms in terms of additional diagnostic tests? Twenty to forty additional punctures or biopsies may be expected per 1000 women offered screening (three rounds).

4.7. Over-diagnosis and over-treatment

What are the specific harms in terms of over-diagnosis and over-treatment? Based on selected studies, over-detection (excluding DCIS cases), ranged from (7% to 21%) to 35% (no data specific for women aged 70 to 79 years are available). Götzsche reported that the number of mastectomies and lumpectomies was significantly larger in the screened groups (no data specific for women aged 70 to 79 years are available). Three trials with adequate randomization showed a significant increase in mastectomies and lumpectomies (Relative Risk (RR) 1.31, 95% (CI) 1.22 to 1.42). Two trials with suboptimal randomization showed the same increase in interventions (RR of 1.42 (95% CI 1.26 to 1.61)). The RR for all five trials combined was 1.35 (95% CI 1.26 to 1.44).



4.8. What attitude should be recommended for women in case of self referral?

It is advisable that when a patient asks her doctor for a screening, the doctor should develop a strategy minimizing the drawbacks of screening⁹². In this way, an attitude structured around three phases can be recommended:

- Information specific to the age bracket⁹³
- Decision making according to the patient personal assessment⁹⁴
- Steering of the person who so wishes towards a screening involving methods that minimize the drawbacks.

The criteria defined in the framework of the European Programme notably make provision for the monitoring of the technical quality of the equipment used, the double reading of the mammographies, and an optimization of the recall rate⁹⁵. In Belgium, the approved mammography units meet the criteria laid down in the context of the European Programme, and it is therefore logical to steer those women who explicitly request a screening towards these structures.

5. REFERENCES

1. Paulus D, Mambourg F, Bonneux L. [Breast cancer screening]. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2005 02/05/2005. KCE reports 11 Available from: http://kce.fgov.be/index_en.aspx?SGREF=5221&CREF=9348
2. Verleye L, Desomer A, Gailly J, Robays j. [Identifying women at risk for breast cancer/technical methods for breast cancer screening]. Good clinical Practice (GCP). Bruxelles: Centre fédéral d'expertise des soins de santé (KCE); 2012. KCE Reports 172 Available from: <http://www.kce.fgov.be/publication/report/identifying-women-at-risk-for-breast-cancertechnical-methods-for-breast-cancer-sc>
3. Mambourg F, Robays j, Camberlin C, Vlayen J, Gailly J. [Breast cancer screening with mammography for women in the agegroup of 40-49 years]. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2010 07/07/2010. KCE reports 129 Available from: http://kce.fgov.be/index_en.aspx?SGREF=14851&CREF=16581
4. Gotzsche PC, Nielsen M. Screening for breast cancer with mammography. Cochrane Database of Systematic Reviews. 2011(1).
5. Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;151(10):727-37, W237-42.
6. Biesheuvel C, Barratt A, Howard K, Houssami N, Irwig L. Effects of study methods and biases on estimates of invasive breast cancer overdiagnosis with mammography screening: a systematic review. Lancet Oncol. 2007;8(12):1129-38.
7. Jorgensen KJ, Götzsche PC. Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends. Bmj. 2009;339.
8. Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. J Natl Cancer Inst. 2010;102(3):170-8.
9. Humphrey LL, Helfand M, Chan BK, Woolf SH. Breast cancer screening: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2002;137(5 Part 1):347-60.
10. Tabar L, Fagerberg CJ, Gad A, Baldetorp L, Holmberg LH, Grontoft O, et al. Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. Lancet. 1985;1(8433):829-32.
11. Dixon JM. Breast screening has increased the number of mastectomies. Breast Cancer Res. 2009;11 Suppl 3:S19.
12. Smith RA, Duffy SW, Gabe R, Tabar L, Yen AM, Chen TH. The randomized trials of breast cancer screening: what have we learned? Radiol Clin North Am. 2004;42(5):793-806, v.
13. Nystrom L, Andersson I, Bjurstam N, Frisell J, Nordenskjold B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. Lancet. 2002;359(9310):909-19.
14. Tabar L, Vitak B, Chen TH, Yen AM, Cohen A, Tot T, et al. Swedish Two-County Trial: Impact of Mammographic Screening on Breast Cancer Mortality during 3 Decades. Radiology. 2011.
15. Maass N, Alkasi O, Bauer M, Jonat W, Souchon R, Meinhold-Heerlein I. Actual management of ductal carcinoma in situ of the breast. Arch Gynecol Obstet. 2009;280(5):699-705.
16. Duffy SW, Chen HH, Tabar L, Day NE. Estimation of mean sojourn time in breast cancer screening using a Markov chain model of both entry to and exit from the preclinical detectable phase. Stat Med. 1995;14(14):1531-43.
17. Fracheboud J, Groenewoud JH, Boer R, Draisma G, de Brujin AE, Verbeek AL, et al. Seventy-five years is an appropriate upper age limit for population-based mammography screening. Int J Cancer. 2006;118(8):2020-5.

18. Fett MJ. Computer modelling of the Swedish two county trial of mammographic screening and trade offs between participation and screening interval. *Journal of Medical Screening*. 2001;8(1):39-45.
19. Shen Y, Zelen M. Robust modeling in screening studies: estimation of sensitivity and preclinical sojourn time distribution. *Biostatistics*. 2005;6(4):604-14.
20. Wu JC, Hakama M, Anttila A, Yen AM, Malila N, Sarkeala T, et al. Estimation of natural history parameters of breast cancer based on non-randomized organized screening data: subsidiary analysis of effects of inter-screening interval, sensitivity, and attendance rate on reduction of advanced cancer. *Breast Cancer Research & Treatment*. 2010;122(2):553-66.
21. Olsen AH, Agbaje OF, Myles JP, Lynge E, Duffy SW. Overdiagnosis, sojourn time, and sensitivity in the Copenhagen mammography screening program. *Breast Journal*. 2006;12(4):338-42.
22. Frisell J, Eklund G, Hellstrom L, Somell A. Analysis of interval breast carcinomas in a randomized screening trial in Stockholm. *Breast Cancer Research & Treatment*. 1987;9(3):219-25.
23. Paci E, Duffy SW. Modelling the analysis of breast cancer screening programmes: sensitivity, lead time and predictive value in the Florence District Programme (1975-1986). *International Journal of Epidemiology*. 1991;20(4):852-8.
24. Boer R, de Koning HJ, van der Maas PJ. A longer breast carcinoma screening interval for women age older than 65 years? *Cancer*. 1999;86(8):1506-10.
25. Duffy SW, Day NE, Tabar L, Chen HH, Smith TC. Markov models of breast tumor progression: some age-specific results. *Journal of the National Cancer Institute. Monographs*. 1997;22:93-7.
26. Duffy SW, Gabe R. What should the detection rates of cancers be in breast screening programmes? *British Journal of Cancer*. 2005;92(3):597-600.
27. Shen Y, Zelen M. Screening sensitivity and sojourn time from breast cancer early detection clinical trials: mammograms and physical examinations. *Journal of Clinical Oncology*. 2001;19(15):3490-9.
28. Spratt JS, Greenberg RA, Heuser LS. Geometry, growth rates, and duration of cancer and carcinoma in situ of the breast before detection by screening. *Cancer Research*. 1986;46(2):970-4.
29. Tabar L, Fagerberg G, Chen HH, Duffy SW, Smart CR, Gad A, et al. Efficacy of breast cancer screening by age. New results from the Swedish Two-County Trial. *Cancer*. 1995;75(10):2507-17.
30. Weedon-Fekjaer H, Lindqvist BH, Vatten LJ, Aalen OO, Tretli S. Estimating mean sojourn time and screening sensitivity using questionnaire data on time since previous screening. *Journal of Medical Screening*. 2008;15(2):83-90.
31. Weedon-Fekjaer H, Vatten LJ, Aalen OO, Lindqvist B, Tretli S. Estimating mean sojourn time and screening test sensitivity in breast cancer mammography screening: new results. *Journal of Medical Screening*. 2005;12(4):172-8.
32. Zappa M, Visioli CB, Ciatto S. Mammography screening in elderly women: efficacy and cost-effectiveness. Review 16 refs. *Critical Reviews in Oncology Hematology*. 2003;46(3):235-9.
33. Boer R, de Koning HJ, van Oortmarsen GJ, van der Maas PJ. In search of the best upper age limit for breast cancer screening. *Eur J Cancer*. 1995;31A(12):2040-3.
34. Mandelblatt JS, Silliman R. Hanging in the balance: making decisions about the benefits and harms of breast cancer screening among the oldest old without a safety net of scientific evidence. *J Clin Oncol*. 2009;27(4):487-90.
35. Karon J, Goyder E, Tappenden P, McPhie S, Towers I, Brazier J, et al. A review and critique of modelling in prioritising and designing screening programmes. *Health Technol Assess*. 2007;11(52):iii-iv, ix-xi, 1-145.
36. Barratt A, Howard K, Irwig L, Salkeld G, Houssami N. Model of outcomes of screening mammography: information to support informed choices. *BMJ*. 2005;330(7497):936.
37. Berry DA, Inoue L, Shen Y, Venier J, Cohen D, Bondy M, et al. Modeling the impact of treatment and screening on U.S. breast

- cancer mortality: a Bayesian approach. *J Natl Cancer Inst Monogr.* 2006;Monographs.(36):30-6.
38. Carles M, Vilaprinyo E, Cots F, Gregori A, Pla R, Roman R, et al. Cost-effectiveness of early detection of breast cancer in Catalonia (Spain). *BMC Cancer.* 2011;11.
39. Carter KJ, Castro F, Kessler E, Erickson BA. Simulation of begin and end ages for mammography screening. *J Healthc Qual.* 2005;27(1):40-7.
40. Feuer EJ. Modeling the impact of adjuvant therapy and screening mammography on U.S. breast cancer mortality between 1975 and 2000: introduction to the problem. *J Natl Cancer Inst Monogr.* 2006;Monographs.(36):2-6.
41. Fryback DG, Stout NK, Rosenberg MA, Trentham-Dietz A, Kuruchittham V, Remington PL. The Wisconsin Breast Cancer Epidemiology Simulation Model. *J Natl Cancer Inst Monogr.* 2006;Monographs.(36):37-47.
42. Gyrd-Hansen D. Cost-benefit analysis of mammography screening in Denmark based on discrete ranking data. *Int J Technol Assess Health Care.* 2000;16(3):811-21.
43. Hanin LG, Miller A, Zorin AV, Yakovlev AY. The University of Rochester model of breast cancer detection and survival. *J Natl Cancer Inst Monogr.* 2006;Monographs.(36):66-78.
44. Lee S, Zelen M. A stochastic model for predicting the mortality of breast cancer. *J Natl Cancer Inst Monogr.* 2006;Monographs.(36):79-86.
45. Lee SJ, Zelen M. Modelling the early detection of breast cancer. *Ann Oncol.* 2003;14(8):1199-202.
46. Mahnken JD, Chan W, Freeman DH, Jr., Freeman JL. Reducing the effects of lead-time bias, length bias and over-detection in evaluating screening mammography: a censored bivariate data approach. *Stat Methods Med Res.* 2008;17(6):643-63.
47. Mandelblatt J, Schechter CB, Lawrence W, Yi B, Cullen J. The SPECTRUM population model of the impact of screening and treatment on U.S. breast cancer trends from 1975 to 2000: principles and practice of the model methods. *J Natl Cancer Inst Monogr.* 2006;Monographs.(36):47-55.
48. Mandelblatt JS, Cronin KA, Bailey S, Berry DA, de Koning HJ, Draisma G, et al. Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms.[Erratum appears in Ann Intern Med. 2010 Jan 19;152(2):136]. *Ann Intern Med.* 2009;151(10):738-47.
49. Mandelblatt JS, Schechter CB, Yabroff KR, Lawrence W, Dignam J, Extermann M, et al. Toward optimal screening strategies for older women: Costs, benefits, and harms of breast cancer screening by age, biology, and health status. *J. Gen. Intern. Med.* 2005;20(6):487-96.
50. Neeser K, Szucs T, Bulliard JL, Bachmann G, Schramm W. Cost-effectiveness analysis of a quality-controlled mammography screening program from the Swiss statutory health-care perspective: quantitative assessment of the most influential factors (Structured abstract). *2007;10(1):42-53.*
51. Plevritis SK, Sigal BM, Salzman P, Rosenberg J, Glynn P. A stochastic simulation model of U.S. breast cancer mortality trends from 1975 to 2000. *J Natl Cancer Inst Monogr.* 2006;Monographs.(36):86-95.
52. Rauner MS, Gutjahr WJ, Heidenberger K, Wagner J, Pasia J. Dynamic Policy Modeling for Chronic Diseases: Metaheuristic-Based Identification of Pareto-Optimal Screening Strategies. *Operations Research.* 2010;58(5):1269-86.
53. Rijnsburger AJ, van Oortmarsen GJ, Boer R, Draisma G, To T, Miller AB, et al. Mammography benefit in the Canadian National Breast Screening Study-2: a model evaluation. *Int J Cancer.* 2004;110(5):756-62.
54. Rojnik K, Naversnik K, Mateovic-Rojnik T, Primiczakelj M. Probabilistic cost-effectiveness modeling of different breast cancer screening policies in Slovenia. *Value Health.* 2008;11(2):139-48.
55. Rue M, Vilaprinyo E, Lee S, Martinez-Alonso M, Carles MD, Marcos-Gragera R, et al. Effectiveness of early detection on breast

- cancer mortality reduction in Catalonia (Spain). *BMC Cancer.* 2009;9(326).
56. Stout NK, Rosenberg MA, Trentham-Dietz A, Smith MA, Robinson SM, Fryback DG. Retrospective cost-effectiveness analysis of screening mammography. *J Natl Cancer Inst.* 2006;98(11):774-82.
57. Tan SY, van Oortmarsen GJ, de Koning HJ, Boer R, Habbema JD. The MISCAN-Fadia continuous tumor growth model for breast cancer. *J Natl Cancer Inst Monogr.* 2006;Monographs.(36):56-65.
58. Vilaprinyo E, Rue M, Marcos-Gragera R, Martinez-Alonso M. Estimation of age- and stage-specific Catalan breast cancer survival functions using US and Catalan survival data. *BMC Cancer.* 2009;9(98).
59. Wang H, Karesen R, Hervik A, Thoresen SA. Mammography screening in Norway: Results from the first screening round in four counties and cost-effectiveness of a modeled nationwide screening. *Cancer Causes Control.* 2001;12(1):39-45.
60. Messelcar DC. Mammography screening for older women with and without cognitive impairment. *J Gerontol Nurs.* 2000;26(4):14-24; quiz 52-3.
61. Wen YP, Sheu ML. A cost-benefit analysis of preventive care: The case of breast cancer screening. *Taiwan J. Public Health.* 2005;24(6):519-28.
62. Advisory Committee on Breast Cancer S. Screening for breast cancer in England: past and future. *J Med Screen.* 2006;13(2):59-61.
63. Anonymous. Landelijk bevolkingsonderzoek naar borstkanker volledig ingevoerd; resultaten van de implementatiefase 1990-1997. Landelijk Evaluatie Team voor bevolkingsonderzoek naar Borstkanker. *Ned Tijdschr Geneeskd.* 2000;144(23):1124-9.
64. Barratt A, Irwig L, Glasziou P, Salkeld G, Houssami N, Kerlikowske K, et al. Relative benefit of mammography reduces with age. *Evid.-Based Healthc.* 2002;6(4):156-7.
65. Barratt AL, Les Irwig M, Glasziou PP, Salkeld GP, Houssami N. Benefits, harms and costs of screening mammography in women 70 years and over: a systematic review. *Med J Aust.* 2002;176(6):266-71.
66. Bonneux L. De voor- en nadelen van borstkancerscreening: tijd voor evidence-based informatie. *Nederlands Tijdschrift voor Geneeskunde.* 2009;153.
67. Caplan LS. To screen or not to screen: the issue of breast cancer screening in older women. *Public Health Rev.* 2001;29(2-4):231-40.
68. Carney PA, Abraham LA, Miglioretti DL, Yabroff KR, Sickles EA, Buist DSM, et al. Factors associated with imaging and procedural events used to detect breast cancer after screening mammography. *Am. J. Roentgenol.* 2007;188(2):385-92.
69. De Koning HJ. Breast cancer screening: cost-effective in practice? *Eur J Radiol.* 2000;33(1):32-7.
70. Feuer EJ, Etzioni R, Cronin KA, Mariotto A. The use of modeling to understand the impact of screening on U.S. mortality: examples from mammography and PSA testing. *Stat Methods Med Res.* 2004;13(6):421-42.
71. Grivegnee AR, Autier P. Approche économique du dépistage du cancer du sein en Belgique. *Rev Med Brux.* 2001;22(4):A277-81.
72. Habbema JD, Tan SY, Cronin KA. Impact of mammography on U.S. breast cancer mortality, 1975-2000: are intermediate outcome measures informative? *J Natl Cancer Inst Monogr.* 2006;Monographs.(36):105-11.
73. Mandelblatt J, Saha S, Teutsch S, Hoerger T, Siu AL, Atkins D, et al. The cost-effectiveness of screening mammography beyond age 65 years: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2003;139(10):835-42.
74. Prevost TC, Abrams KR, Jones DR. Hierarchical models in generalized synthesis of evidence: an example based on studies of breast cancer screening. *Stat Med.* 2000;19(24):3359-76.
75. Rautenstrauch J. Is mammography screening only a pointless waste of money? *MMW-Fortschr. Med.* 2000;142(12):4-10.

76. Xu W, Vnenchak P, Smucny J. Screening mammography in women aged 70 to 79 years. *J*. 2000;49(3):266-7.
77. Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005;353(17):1784-92.
78. Carter KJ, Castro F, Kessler E, Erickson B. A computer model for the study of breast cancer. *Comput Biol Med*. 2003;33(4):345-60.
79. Cleemput I, Van Wilder P, Vrijens F, Huybrechts M, Ramaekers D. Recommandations pour les évaluations pharmacoéconomiques en Belgique. Health technology Assessment (HTA). Bruxelles: Centre fédéral d'expertise des soins de santé (KCE); 2008. KCE Reports 78B (D/2008/10.273/24)
80. Lidgren M, Wilking N, Jonsson B, Rehnberg C. Health related quality of life in different states of breast cancer. *Qual Life Res*. 2007;16(6):1073-81.
81. Freedman GM, Li T, Anderson PR, Nicolaou N, Konski A. Health states of women after conservative surgery and radiation for breast cancer. *Breast Cancer Res Treat*. 2010;121(2):519-26.
82. Burstrom K, Johannesson M, Diderichsen F. Health-related quality of life by disease and socio-economic group in the general population in Sweden. *Health Policy*. 2001;55(1):51-69.
83. Gerard K, Johnston K, Brown J. The role of a pre-scored multi-attribute health classification measure in validating condition-specific health state descriptions. *Health Econ*. 1999;8(8):685-99.
84. Domeyer PJ, Sergentanis TN, Zagouri F, Zografos GC. Health-related quality of life in vacuum-assisted breast biopsy: short-term effects, long-term effects and predictors. *Health & Quality of Life Outcomes*. 2010;8(11):2010.
85. Borstkanker LETvbn. Landelijke evaluatie van bevolkingsonderzoek naar borstkanker in Nederland 1990-2007. 2010.
86. Stordeur S, Vrijens F, Beirens K, Vlaijen J, Devriese S, Van Eycken E. Quality indicators in oncology: breast cancer. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2010. KCE reports 150C (D/2010/10.273/101) Available from: http://kce.fgov.be/index_en.aspx?SGREF=5211&CREF=18847
87. INC. Survie attendue des patients atteints de cancers en France : état des lieux. 2010.
88. Mook S, Van 't Veer LJ, Rutgers EJ, Ravdin PM, van de Velde AO, van Leeuwen FE, et al. Independent prognostic value of screen detection in invasive breast cancer. *J Natl Cancer Inst*. 2011;103(7):585-97.
89. Cortesi L, Chiuri VE, Ruscelli S, Bellelli V, Negri R, Rashid I, et al. Prognosis of screen-detected breast cancers: results of a population based study. *BMC Cancer*. 2006;6:17.
90. Joensuu H, Lehtimaki T, Holli K, Elomaa L, Turpeenniemi-Hujanen T, Kataja V, et al. Risk for distant recurrence of breast cancer detected by mammography screening or other methods. *Jama*. 2004;292(9):1064-73.
91. Olsson A, Borgquist S, Butt S, Zackrisson S, Landberg G, Manjer J. Tumour-related factors and prognosis in breast cancer detected by screening. *Br J Surg*. 2012;99(1):78-87.
92. Physicians AAoF. Summary of Recommendations for Clinical Preventive Services. In: AAFP Policy Action AAFP; 2010.
93. Woloshin S, Schwartz LM. The benefits and harms of mammography screening: understanding the trade-offs. *JAMA*. 2010;303(2):164-5.
94. Jorgensen KJ, Gotzsche PC. Content of invitations for publicly funded screening mammography. *BMJ*. 2006;332(7540):538-41.
95. Perry N, Broeders M, de Wolf C, Tornberg S, Holland R, von Karsa L. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. *Ann Oncol*. 2008;19(4):614-22.

- cancer mortality reduction in Catalonia (Spain). *BMC Cancer.* 2009;9(326).
56. Stout NK, Rosenberg MA, Trentham-Dietz A, Smith MA, Robinson SM, Fryback DG. Retrospective cost-effectiveness analysis of screening mammography. *J Natl Cancer Inst.* 2006;98(11):774-82.
57. Tan SY, van Oortmarsen GJ, de Koning HJ, Boer R, Habbema JD. The MISCAN-Fadia continuous tumor growth model for breast cancer. *J Natl Cancer Inst Monogr.* 2006;Monographs.(36):56-65.
58. Vilaprinyo E, Rue M, Marcos-Gragera R, Martinez-Alonso M. Estimation of age- and stage-specific Catalan breast cancer survival functions using US and Catalan survival data. *BMC Cancer.* 2009;9(98).
59. Wang H, Karesen R, Hervik A, Thoresen SA. Mammography screening in Norway: Results from the first screening round in four counties and cost-effectiveness of a modeled nationwide screening. *Cancer Causes Control.* 2001;12(1):39-45.
60. Messelcar DC. Mammography screening for older women with and without cognitive impairment. *J Gerontol Nurs.* 2000;26(4):14-24; quiz 52-3.
61. Wen YP, Sheu ML. A cost-benefit analysis of preventive care: The case of breast cancer screening. *Taiwan J. Public Health.* 2005;24(6):519-28.
62. Advisory Committee on Breast Cancer S. Screening for breast cancer in England: past and future. *J Med Screen.* 2006;13(2):59-61.
63. Anonymous. Landelijk bevolkingsonderzoek naar borstkanker volledig ingevoerd; resultaten van de implementatiefase 1990-1997. Landelijk Evaluatie Team voor bevolkingsonderzoek naar Borstkanker. *Ned Tijdschr Geneeskd.* 2000;144(23):1124-9.
64. Barratt A, Irwig L, Glasziou P, Salkeld G, Houssami N, Kerlikowske K, et al. Relative benefit of mammography reduces with age. *Evid.-Based Healthc.* 2002;6(4):156-7.
65. Barratt AL, Les Irwig M, Glasziou PP, Salkeld GP, Houssami N. Benefits, harms and costs of screening mammography in women 70 years and over: a systematic review. *Med J Aust.* 2002;176(6):266-71.
66. Bonneux L. De voor- en nadelen van borstkancerscreening: tijd voor evidence-based informatie. *Nederlands Tijdschrift voor Geneeskunde.* 2009;153.
67. Caplan LS. To screen or not to screen: the issue of breast cancer screening in older women. *Public Health Rev.* 2001;29(2-4):231-40.
68. Carney PA, Abraham LA, Miglioretti DL, Yabroff KR, Sickles EA, Buist DSM, et al. Factors associated with imaging and procedural events used to detect breast cancer after screening mammography. *Am. J. Roentgenol.* 2007;188(2):385-92.
69. De Koning HJ. Breast cancer screening: cost-effective in practice? *Eur J Radiol.* 2000;33(1):32-7.
70. Feuer EJ, Etzioni R, Cronin KA, Mariotto A. The use of modeling to understand the impact of screening on U.S. mortality: examples from mammography and PSA testing. *Stat Methods Med Res.* 2004;13(6):421-42.
71. Grivegnee AR, Autier P. Approche économique du dépistage du cancer du sein en Belgique. *Rev Med Brux.* 2001;22(4):A277-81.
72. Habbema JD, Tan SY, Cronin KA. Impact of mammography on U.S. breast cancer mortality, 1975-2000: are intermediate outcome measures informative? *J Natl Cancer Inst Monogr.* 2006;Monographs.(36):105-11.
73. Mandelblatt J, Saha S, Teutsch S, Hoerger T, Siu AL, Atkins D, et al. The cost-effectiveness of screening mammography beyond age 65 years: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2003;139(10):835-42.
74. Prevost TC, Abrams KR, Jones DR. Hierarchical models in generalized synthesis of evidence: an example based on studies of breast cancer screening. *Stat Med.* 2000;19(24):3359-76.
75. Rautenstrauch J. Is mammography screening only a pointless waste of money? *MMW-Fortschr. Med.* 2000;142(12):4-10.

76. Xu W, Vnenchak P, Smucny J. Screening mammography in women aged 70 to 79 years. *J*. 2000;49(3):266-7.
77. Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005;353(17):1784-92.
78. Carter KJ, Castro F, Kessler E, Erickson B. A computer model for the study of breast cancer. *Comput Biol Med*. 2003;33(4):345-60.
79. Cleemput I, Van Wilder P, Vrijens F, Huybrechts M, Ramaekers D. Recommandations pour les évaluations pharmacoéconomiques en Belgique. Health technology Assessment (HTA). Bruxelles: Centre fédéral d'expertise des soins de santé (KCE); 2008. KCE Reports 78B (D/2008/10.273/24)
80. Lidgren M, Wilking N, Jonsson B, Rehnberg C. Health related quality of life in different states of breast cancer. *Qual Life Res*. 2007;16(6):1073-81.
81. Freedman GM, Li T, Anderson PR, Nicolaou N, Konski A. Health states of women after conservative surgery and radiation for breast cancer. *Breast Cancer Res Treat*. 2010;121(2):519-26.
82. Burstrom K, Johannesson M, Diderichsen F. Health-related quality of life by disease and socio-economic group in the general population in Sweden. *Health Policy*. 2001;55(1):51-69.
83. Gerard K, Johnston K, Brown J. The role of a pre-scored multi-attribute health classification measure in validating condition-specific health state descriptions. *Health Econ*. 1999;8(8):685-99.
84. Domeyer PJ, Sergentanis TN, Zagouri F, Zografos GC. Health-related quality of life in vacuum-assisted breast biopsy: short-term effects, long-term effects and predictors. *Health & Quality of Life Outcomes*. 2010;8(11):2010.
85. Borstkanker LETvbn. Landelijke evaluatie van bevolkingsonderzoek naar borstkanker in Nederland 1990-2007. 2010.
86. Stordeur S, Vrijens F, Beirens K, Vlaijen J, Devriese S, Van Eycken E. Quality indicators in oncology: breast cancer. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2010. KCE reports 150C (D/2010/10.273/101) Available from: http://kce.fgov.be/index_en.aspx?SGREF=5211&CREF=18847
87. INC. Survie attendue des patients atteints de cancers en France : état des lieux. 2010.
88. Mook S, Van 't Veer LJ, Rutgers EJ, Ravdin PM, van de Velde AO, van Leeuwen FE, et al. Independent prognostic value of screen detection in invasive breast cancer. *J Natl Cancer Inst*. 2011;103(7):585-97.
89. Cortesi L, Chiuri VE, Ruscelli S, Bellelli V, Negri R, Rashid I, et al. Prognosis of screen-detected breast cancers: results of a population based study. *BMC Cancer*. 2006;6:17.
90. Joensuu H, Lehtimaki T, Holli K, Elomaa L, Turpeenniemi-Hujanen T, Kataja V, et al. Risk for distant recurrence of breast cancer detected by mammography screening or other methods. *Jama*. 2004;292(9):1064-73.
91. Olsson A, Borgquist S, Butt S, Zackrisson S, Landberg G, Manjer J. Tumour-related factors and prognosis in breast cancer detected by screening. *Br J Surg*. 2012;99(1):78-87.
92. Physicians AAoF. Summary of Recommendations for Clinical Preventive Services. In: AAFP Policy Action AAFP; 2010.
93. Woloshin S, Schwartz LM. The benefits and harms of mammography screening: understanding the trade-offs. *JAMA*. 2010;303(2):164-5.
94. Jorgensen KJ, Gotzsche PC. Content of invitations for publicly funded screening mammography. *BMJ*. 2006;332(7540):538-41.
95. Perry N, Broeders M, de Wolf C, Tornberg S, Holland R, von Karsa L. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. *Ann Oncol*. 2008;19(4):614-22.

