Stralingsrisico van mammascreening

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Nascholings- en Studiemiddag
Stralingsbeschermingseenheid
RuG en UMCG

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US Mortality, 2000

Rank	Cause of Death	No. of deaths	% of all deaths
1.	Heart Diseases	710,760	29.6
2.	Cancer	553,091	23.0
3.	Cerebrovascular diseases	167,661	7.0
4.	Chronic lower respiratory diseases	122,009	5.1
5.	Accidents (Unintentional injuries)	97,900	4.1
6.	Diabetes mellitus	69,301	2.9
7.	Influenza and Pneumonia	65,313	2.7
8.	Alzheimer's disease	49,558	2.1
9.	Nephritis	37,251	1.5
10.	Septicemia	31,224	1.3

US Mortality Public Use Data Tape 2000, National Center for Health Statistics, Centers for Disease Control and Prevention, 2002.

2003 Estimated US Cancer Deaths*

Men 285,900	
Lung & bronchus	31%
Prostate	10%
Colon & rectum	10%
Pancreas	5%
Non-Hodgkin lymphoma	4%
Leukemia	4%
Esophagus	4%
Liver/intrahepatic bile duct	3%
Urinary bladder	3%
Kidney	3%
All other sites	22%

Women 270,600	
25%	Lung & bronchus
15%	Breast
11%	Colon & rectum
6%	Pancreas
5%	Ovary
4%	Non-Hodgkin lymphoma
4%	Leukemia
3%	Uterine corpus
2%	Brain/ONS
2%	Multiple myeloma
23%	All other sites

ONS=Other nervous system.
***Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.**
Source: American Cancer Society, 2003.

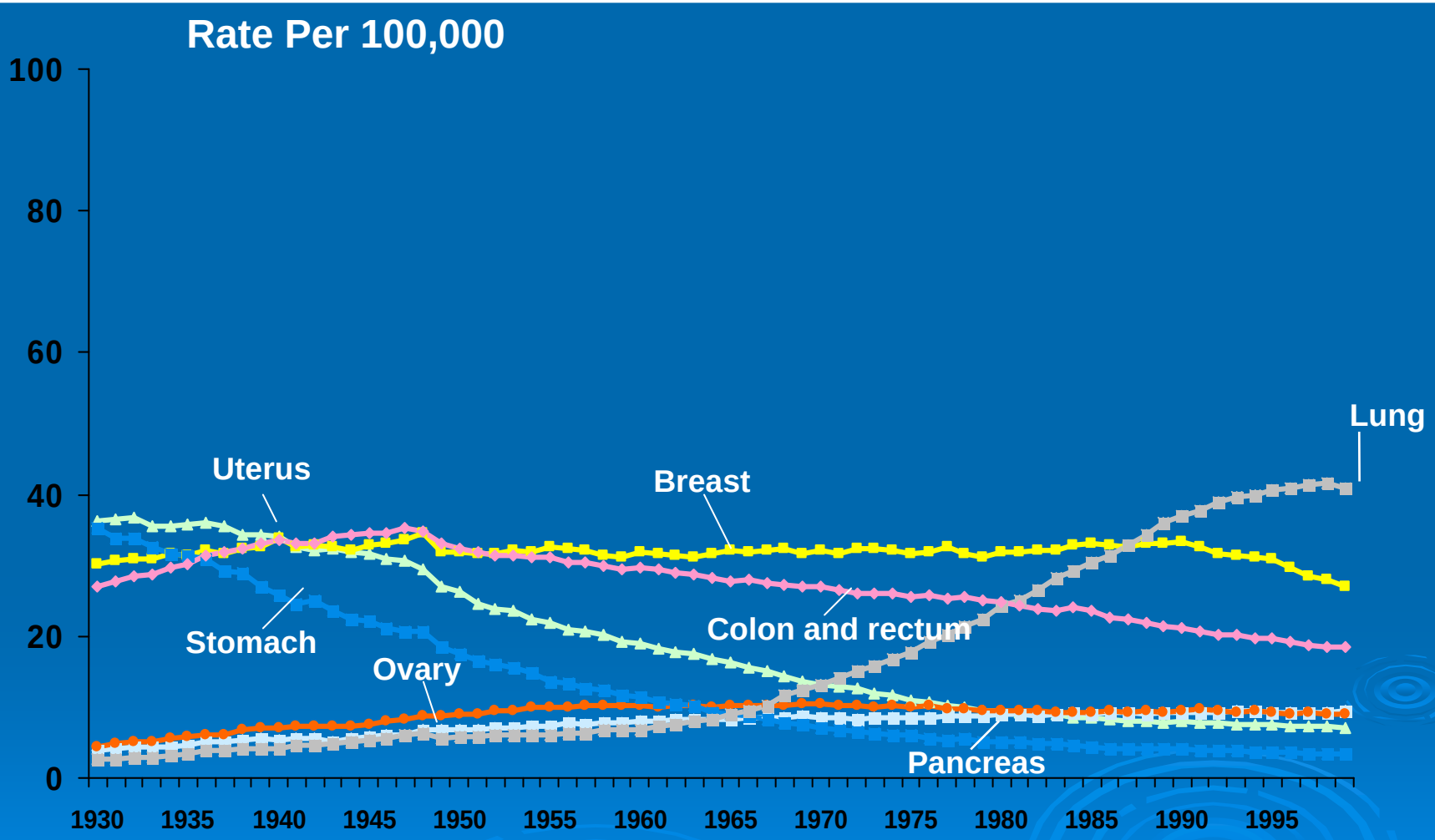
2003 Estimated US Cancer Cases*

Men 675,300	
Prostate	33%
Lung & bronchus	14%
Colon & rectum	11%
Urinary bladder	6%
Melanoma of skin	4%
Non-Hodgkin lymphoma	4%
Kidney	3%
Oral Cavity	3%
Leukemia	3%
Pancreas	2%
All Other Sites	17%

Women 658,800	
32%	Breast
12%	Lung & bronchus
11%	Colon & rectum
6%	Uterine corpus
4%	Ovary
4%	Non-Hodgkin lymphoma
3%	Melanoma of skin
3%	Thyroid
2%	Pancreas
2%	Urinary bladder
20%	All Other Sites

***Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.**
Source: American Cancer Society, 2003.

Cancer Death Rates*, for Women, US, 1930-1999



*Age-adjusted to the 2000 US standard population.

Source: US Mortality Public Use Data Tapes 1960-1999, US Mortality Volumes 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2002.

	Disease		
Exposure	Yes	No	Total
Yes	a	b	a+b
No	c	d	c+d
Total	a+c	b+d	N

Frequentie van ziekte onder blootgestelden: $R_e = a / (a + b)$

Frequentie van ziekte onder niet-blootgestelden: $R_0 = c / (c + d)$

RR relatief risico

$$RR = \frac{\text{mate van effect bij blootgestelde personen}}{\text{mate van effect bij niet blootgestelde personen}}$$

ERR excess relative risk

ERR = RR – 1

EAR excess attributive risico

– maat voor aantal effecten, toe te schrijven aan blootstelling

EAR = ERR x baseline

- R_0 = frequentie zonder blootstelling
- R_e = frequentie met blootstelling (exposure)
- $R_e - R_0$ = verschil in frequentie

Excess Absolute Risico EAR = $R_e - R_0$

Relatieve risico RR = R_e / R

Excess relatieve risico = bijdrage aan RR door blootstelling

$$ERR = RR - 1 = (R_e / R_0) - 1 = (R_e - R_0) / R_0$$

$$ERR = EAR / R_0 \qquad EAR = ERR \times R_0$$

National Academies Division on Earth and Life Studies – USA

Radiation Effects Research Foundation (RERF) – JPN / USA
www.rerf.or.jp

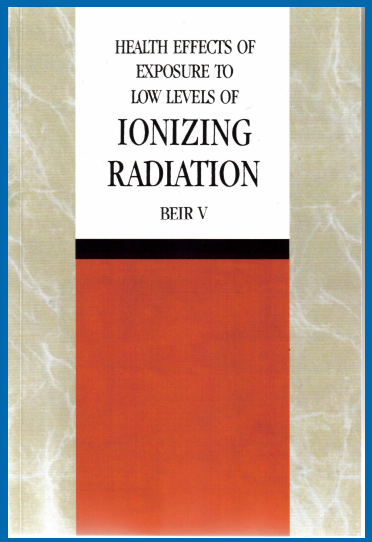
Board on Radiation Effects Research (BRER)
www7.nationalacademies.org/brer/index.html

RERF laboratory – Hiroshima, Japan

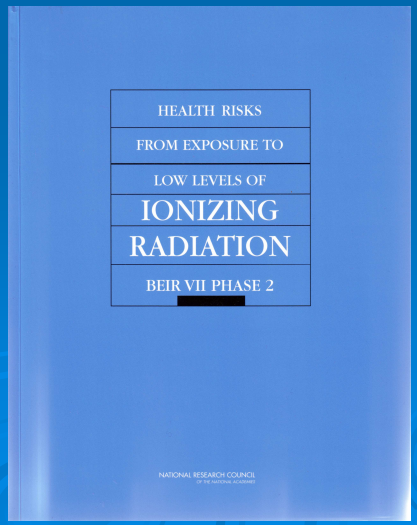
- **RERF - LLS Life Span Study overlevenden Hiroshima & Nagasaki**
  - **T65D Tentative 1965 Dose**
  - **DS86 Dosimetry System 1986**
  - **DS02 Dosimetry review 2002**
- **medische toepassingen**
  - **x - ray therapie**
  - **radium - injectie**
- **beroepsmatige blootstelling**
  - **radium painters, uranium mijnwerkers**
  - **radiologen en röntgentechnici**
- **nucleaire ongevallen**
  - **Marshall Islands - fall out**
  - **Tjernobyl**

Epidemiologische data

- **DS86**
  - **Dosimetry System 1986**
  - **BEIR V (1990)**



- **DS02**
  - **Dosimetry System 2002**
  - **BEIR VII (2006)**



Epidemiologische data

TABLE 6-1 Number of Subjects, Solid Cancer Deaths, and Noncancer Disease Deaths by Radiation Dose

	DS86 Weighted Colon Dose (Sv)[a]							
	Total	0 (<0.005)	0.005–0.1	0.1–0.2	0.2–0.5	0.5–1.0	1.0–2.0	2.0
Number of subjects	86,572	37,458	31,650	5,732	6,332	3,299	1,613	488
Solid cancer deaths (1950–1997)	9,335	3,833	3,277	668	763	438	274	82
Noncancer disease deaths (1950–1997)	31,881	13,832	11,633	2163	2,423	1,161	506	163

[a]These categories are defined using the estimated dose to the colon, obtained as the sum of the γ-ray dose to the colon plus 10 times the neutron dose to the colon.

SOURCE: Based on data from Preston and others (2003).

Risico op kanker: $\lambda(c,s,a,b)\left[1+ERR(s,e,a,t,d)\right]$

Met:

λ	achtergrond bij geen dosis en is afhankelijk van
c	stad
s	geslacht
a	huidige leeftijd
b	geboortejaar

En:

e	leeftijd ten tijde van de blootstelling
t	tijd sinds blootstelling (t = a-e)

Dosis respons

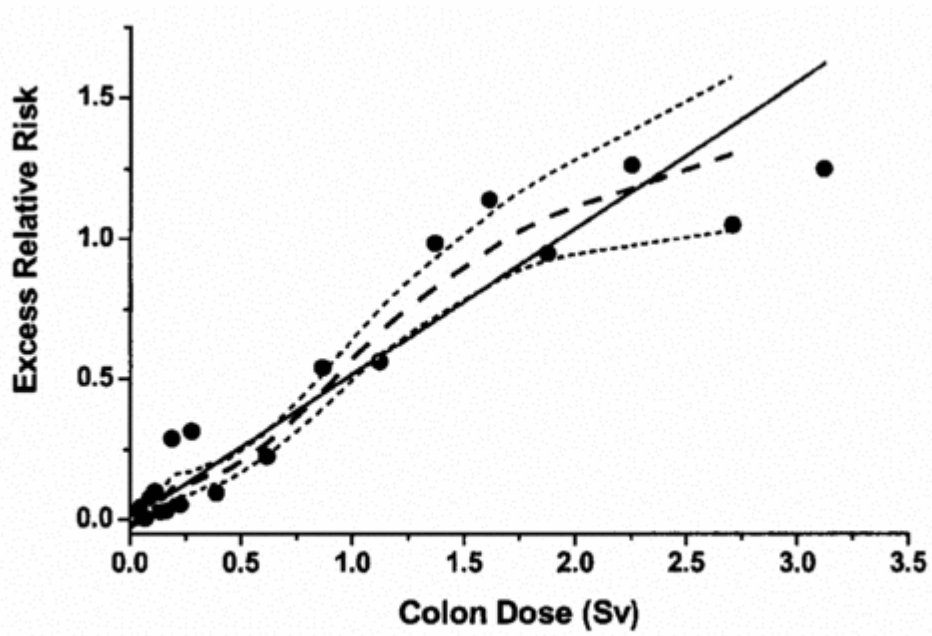


FIGURE 6-1 Solid cancer mortality dose-response function averaged over sex for attained age 70 after exposure at age 30. The solid straight line is the linear slope estimate, the points are dose-category-specific ERR estimates, the dashed curve is a smoothed estimate derived from the points. Dotted curves indicate upper and lower one-standard-error bounds on the smoothed estimate. SOURCE: Reproduced with permission from Preston and others (2003).

Conclusie BEIR VII:

"… the risk would continue in a linear fashion at lower doses without a threshold and that the smallest dose has the potential to cause a small risk To humans. This assumption is termed the linear no-threshold model".

Dosis respons

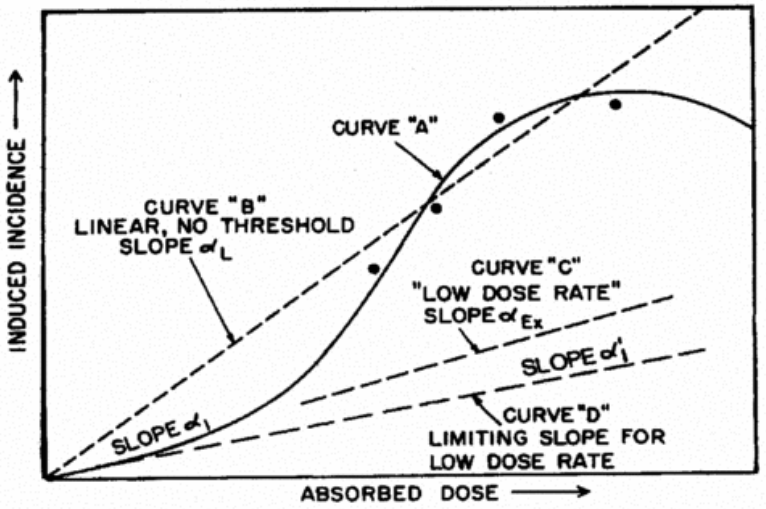


FIGURE 2-1 Schematic curves of incidence versus absorbed dose. The curved solid line for high absorbed doses and high dose rates (curve A) is the "true" curve. The linear, no-threshold dashed line (curve B) was fitted to the four indicated "experimental" points and the origin. Slope α_1 indicates the essentially linear portion of curve A at low doses. The dashed curve C, marked "low dose rate," slope α_{Ex}, represents experimental high-dose data obtained at low dose rates. SOURCE: Reproduced with permission of the National Council on Radiation Protection and Measurements, NCRP Report No. 64 (NCRP 1980).

Low dose response: $E = \alpha D + \beta D^2$

For extrapolating data from acute high-dose-rate experiments to results expected for low doses and low-dose-rate experiments, the dose and dose-rate effectiveness factor DDREF is given by:

$DDREF = \alpha_L / \alpha_1$

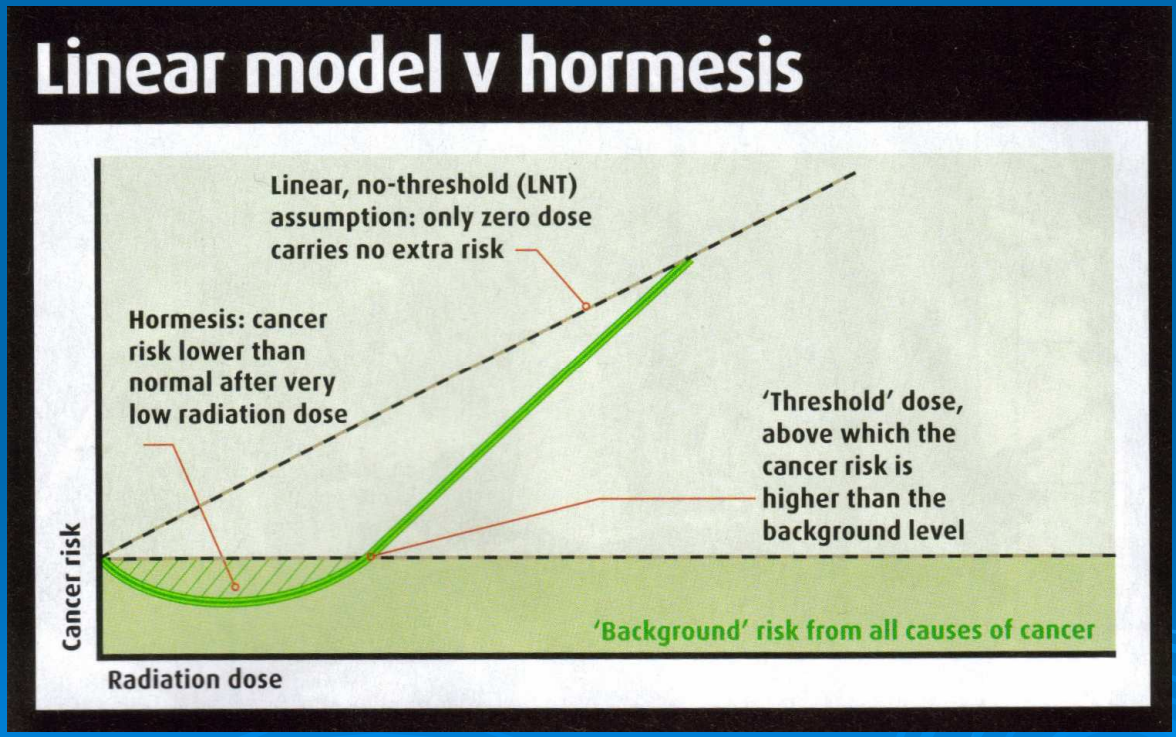
Dosis respons

DDREF geeft een reductie factor voor kansschattingen bij lage dosis en laag dosistempo op basis van kansschattingen bij hoge dosis en hoog dosistempo

1977 UNSCEAR	2,5
1980 BEIR III	2.25
1986 UNSCEAR	< 5
1988 UNSCEAR	2 - 10
1990 BEIR V	2 of meer
1991 ICRP 60	2
2006 BEIR VII	2
2006 ICRP 99	2

Hormesis?

Hormesis (Grieks: 'prikkeling') is het biologische effect dat een stof die in hoge dosis schadelijk is, bij lage dosis positieve effecten kan hebben.



BBC Focus, October 2007

Hormesis?

A vaccine for radiation

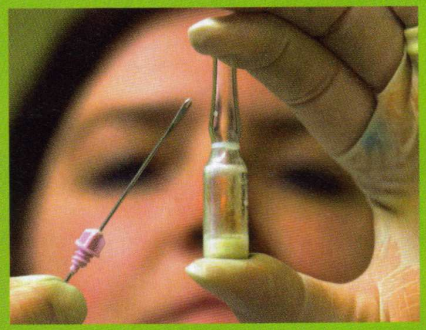
Inoculation is established medicine, but could it really apply to radiation?

For all the controversy about hormesis, the idea that living organisms actually benefit from brief exposure to toxins is widely accepted. Chinese doctors in the 10th Century knew they could protect patients by inoculating them with tiny doses of smallpox. Small doses of the deadly poisonous metal arsenic are also known to boost red blood cell production and stimulate the metabolism.

Hormesis is also attracting the interest of researchers investigating the causes of ageing. Exposure to low levels of X-rays and chemical toxins have been shown to increase the longevity of fruit flies, mice and guinea pigs. Research by biologist Joan Smith-Sonneborn of the University of Wyoming, Laramie, suggests that exposure to such 'stressors' could increase the typical human lifespan to around 90.

There are currently no detailed ideas on the mechanisms that may lead to radiation hormesis – just statistical evidence.

Actually proving the benefits exist is fraught with difficulty, however. For example, a study of British radiologists routinely exposed to low levels of X-rays suggested that they were less likely to die from cancer than other doctors. On the face of it, this suggested they were benefiting from radiation hormesis. However, later analysis revealed the radiologists also tended to smoke less, making them less susceptible to lung cancer – which accounted for most of the cancer deaths. For other cancers, their mortality rate was actually higher – exactly as expected if exposure to any level of X-rays is bad.



The benefits of inoculation are known – could low radiation doses have a similar effect?

Hormesis?

BEIR VII: "The possibility that low doses of radiation may have beneficial effects (a phenomenon often referred to as "hormesis") has been the subject of considerable debate. Evidence for hormetic effects was reviewed, with emphasis on material published since the 1990 BEIR V study on the health effects of exposure to low levels of ionizing radiation. Although examples of apparent stimulatory or protective effects can be found in cellular and animal biology, the preponderance of available experimental information does not support the contention that low levels of ionizing radiation have a beneficial effect. The mechanism of any such possible effect remains obscure. At this time, the assumption that any stimulatory hormetic effects from low doses of ionizing radiation will have a significant health benefit to humans that exceeds potential detrimental effects from radiation exposure at the same dose is unwarranted."

Vergelijkbare statements zijn gedaan door:
United States National Research Council
National Council on Radiation Protection and Measurements
United Nations Scientific Committee on the Effects of Atomic Radiation

Atomic bomb survivor studies

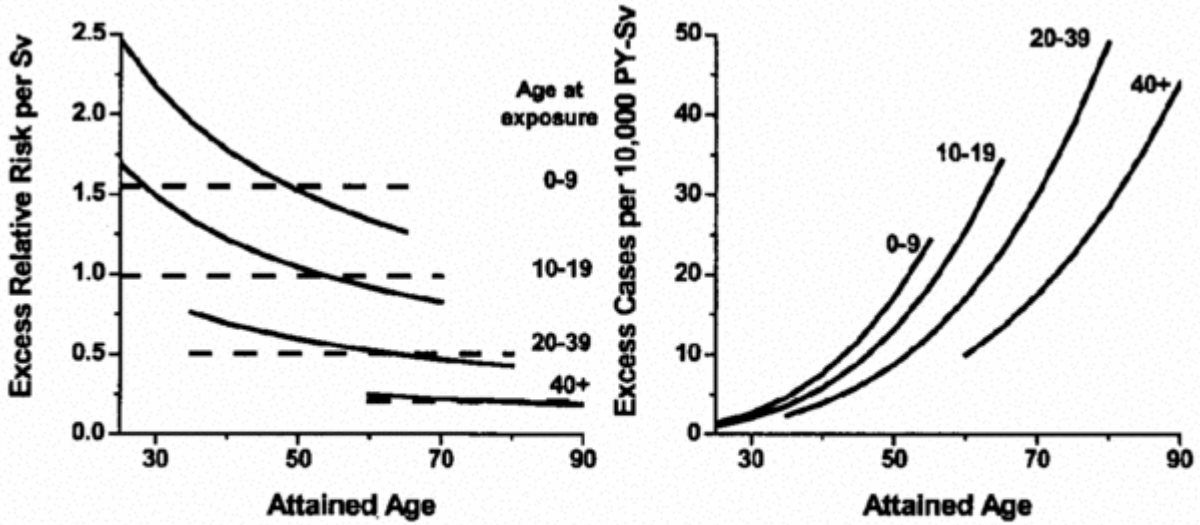


FIGURE 6-2 Primary descriptions of the excess risk of solid cancer mortality. Left panel: fitted sex-averaged ERR estimates using both attained-age-declining (solid black line) and attained-age-constant (dashed lines) forms, for age-at-exposure groups 0–9, 10–19, 20–39, and 40+. ERR estimates for women are about 25% greater, and ERR estimates for men 25% lower, than the values shown. Right panel: fitted EAR estimates for the same dose groups. There is no evidence of significant sex differences in the fitted EAR. SOURCE: Reproduced with permission from Preston and others (2003).

Atomic bomb survivor studies

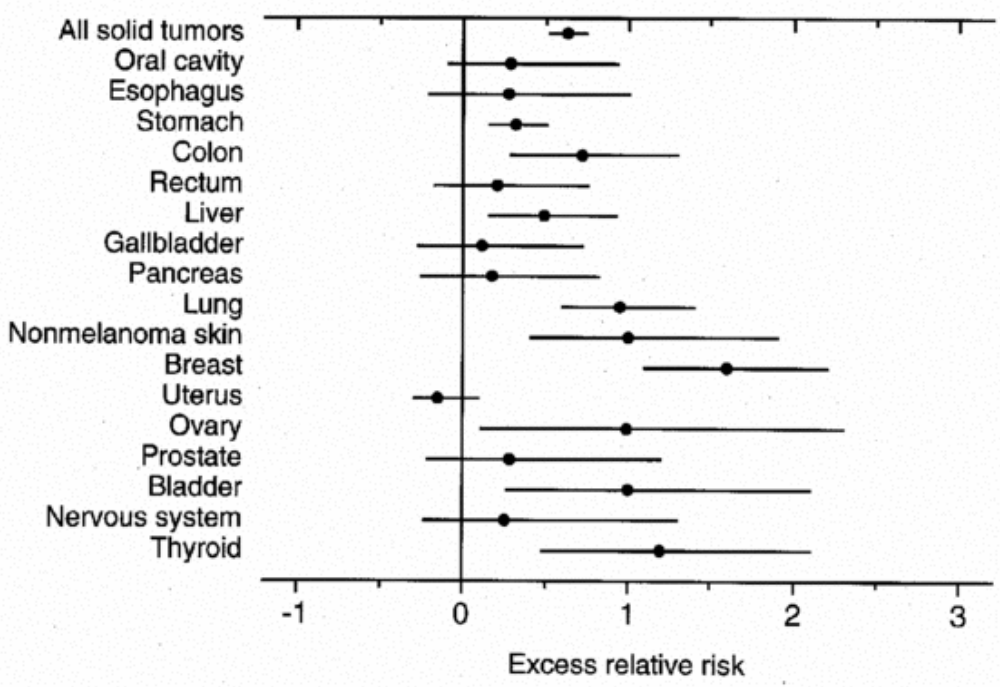


FIGURE 6-4 Excess relative risk at 1.0 Sv (RBE 10) for solid cancer incidence and 95% confidence interval, 1958–1987. SOURCE: Reproduced with permission from Thompson and others (1994).

Atomic bomb survivor studies

TABLE 12-4 Baseline Lifetime Risk Estimates of Cancer Incidence and Mortality

	Incidence		Mortality	
Cancer site	Males	Females	Males	Females
Solid cancer[a]	45,500	36,900	22,100 (11)	17,500 (11)
Stomach	1,300	720	670 (11)	430 (12)
Colon	4,200	4,200	2,200 (11)	2,100 (11)
Liver	640	280	490 (13)	260 (12)
Lung	7,700	5,400	7,700 (12)	4,600 (14)
Breast	—	12,000	—	3,000 (15)
Prostate	15,900	—	3,500 (8)	—
Uterus	—	3,000	—	750 (15)
Ovary	—	1,500	—	980 (14)
Bladder	3,400	1,100	770 (9)	330 (10)
Other solid cancer	12,500	8,800	6,800 (13)	5,100 (13)
Thyroid	230	550	40 (12)	60 (12)
Leukemia	830	590	710 (12)	530 (13)

NOTE: Number of estimated cancer cases or deaths in population of 100,000 (No. of years of life lost per death).

[a]Solid cancer incidence estimates exclude thyroid and nonmelanoma skin cancers.

TABLE 12-5A Lifetime Attributable Risk of Solid Cancer Incidence

	Males			Females		
Cancer Site	LAR Based on Relative Risk Transport[a]	LAR Based on Absolute Risk Transport[b]	Combined and Adjusted by DDREF[c] (Subjective 95% CI[d])	LAR Based on Relative Risk Transport[a]	LAR Based on Absolute Risk Transport[b]	Combined and Adjusted by DDREF[c] (Subjective 95% CI[d])
Incidence						
Stomach	25	280	34 (3, 350)	32	330	43 (5, 390)
Colon	260	180	160 (66, 360)	160	110	96 (34, 270)
Liver	23	150	27 (4, 180)	9	85	12 (1, 130)
Lung	250	190	140 (50, 380)	740	370	300 (120, 780)
Breast				510 Not used	460	310 (160, 610)
Prostate	190	6	44 (<0, 1860)			
Uterus				19	81	20 (<0, 131)
Ovary				66	47	40 (9, 170)
Bladder	160	120	98 (29, 330)	160	100	94 (30, 290)
Other	470	350	290 (120, 680)	490	320	290 (120, 680)
Thyroid	32	No model	21 (5, 80)	160	No model	130 (35, 410)
Sum of site-specific estimates	1400	1310[e]	800	2310[f]	2060[e]	1310
All solid cancer model[g]	1550	1250	970 (490, 1920)	2230	1880	1410 (740, 2690)

NOTE: Number of cases per 100,000 persons of mixed ages exposed to 0.1 Gy.

[a]Linear estimate based on ERR models shown in Table 12-2 with no DDREF adjustment.

[b]Linear estimate based on EAR models shown in Table 12-2 with no DDREF adjustment.

[c]Estimates obtained as a weighted average (on a logarithmic scale) of estimates based on relative and absolute risk transport. For sites other than lung, breast, and thyroid, relative risk transport was given a weight of 0.7 and absolute risk transport was given a weight of 0.3. These weights were reversed for lung cancer. Models for breast and thyroid cancer were based on data that included Caucasian subjects. The resulting estimates were reduced by a DDREF of 1.5.

[d]Including uncertainty from sampling variability, transport, and DDREF. Sampling uncertainty in the parameters that quantify the modifying effects of age at exposure and attained age is not included except for the all solid cancer model.

[e]Includes thyroid cancer estimate based on ERR model.

[f]Includes breast cancer estimate based on EAR model.

[g]Estimates based on model developed by analyzing LSS incidence data on all solid cancers excluding thyroid cancer and nonmelanoma skin cancer as a single category. See Table 12-1.

Gelijkmatige totale lichaamsblootstelling met 100 mSv effective dose
incidentie van kanker / morbiditeit

		Solide tumoren		Leukemie	
		mannen	Vrouwen	mannen	vrouwen
	Aantal nieuwe gevallen van kanker zonder blootstelling per 100.000	45.500	37.000	830	590
R0	Risico op kanker zonder blootstelling	455/1000	370/1000	8/1000	6/1000
	Extra aantal bij blootstelling 100 mSv	800	1300	100	70
	95% betrouwbaarheidsinterval	400-1600	700-2500	30-300	20-250
EAR	Toegevoegd absoluut risico bij blootstelling aan 100 mSv	8/1000	13/1000	1/1000	0,7/1000
ERR	Toegevoegd relatief risico bij blootstelling aan 100 mSv	2%	3,5%	12%	
	95% betrouwbaarheidsinterval	1-4%	2-7%	4-40%	
DD	Verdubbelingsdosis – Doubling Dose mSv	5.000	3.000	850	
	95% betrouwbaarheidsinterval	2.000-11.000		250-2.500	

Gelijkmatige totale lichaamsblootstelling met 100 mSv effective dose
kankersterfte / mortaliteit

		Solide tumoren		Leukemie	
		mannen	Vrouwen	mannen	vrouwen
	Aantal nieuwe gevallen van kanker zonder blootstelling per 100.000	22.100	17.500	710	530
R0	Risico op kanker zonder blootstelling	221/1000	175/1000	7/1000	5/1000
	Extra aantal bij blootstelling 100 mSv	410	610	70	50
	95% betrouwbaarheidsinterval	200-830	300-1200	20-220	10-190
EAR	Toegevoegd absoluut risico bij blootstelling aan 100 mSv	4/1000	6/1000	0,7/1000	0,5/1000
ERR	Toegevoegd relatief risico bij blootstelling aan 100 mSv	2%	3,5%	10%	
	95% betrouwbaarheidsinterval	1-4%	2-7%	3-35%	
DD	Verdubbelingsdosis – Doubling Dose mSv	5.000	3.000	1.000	
	95% betrouwbaarheidsinterval	2.000-11.000		300-3.000	

Atomic bomb survivor studies

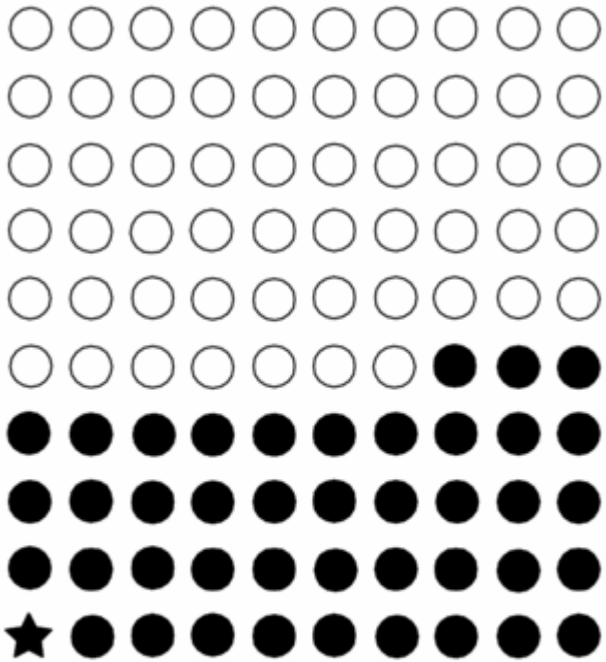


FIGURE PS-4 In a lifetime, approximately 42 (solid circles) of 100 people will be diagnosed with cancer (calculated from Table 12-4 of this report). Calculations in this report suggest that approximately one cancer (star) per 100 people could result from a single exposure to 0.1 Sv of low-LET radiation above background.

Borstkanker

RADIATION RESEARCH **158**, 220–235 (2002)
0033-7587/02 $5.00

Radiation Effects on Breast Cancer Risk: A Pooled Analysis of Eight Cohorts

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Preston, D. L., Mattsson, A., Holmberg, E., Shore, R., Hildreth, N. G. and Boice, J. D., Jr. Radiation Effects on Breast Cancer Risk: A Pooled Analysis of Eight Cohorts. ***Radiat. Res.*** **158, 220–235 (2002).**

protracted exposures. There is also a suggestion that women with some benign breast conditions may be at elevated risk of radiation-associated breast cancer.

Borstkanker

Population Size, Breast Cancer Cases, Woman-Years, and Radiation Dose by Cohort

Cohort	Abbreviation	Country	Women[a]	Exposed breasts[b]	Cases[a]	Woman-years[a]	Mean dose (Gy)[c] (range)	Type of exposure
Life span study	(LSS)	Japan	47,726	38,010	707	1,182,306	0.3 (0.02–5)	Atomic bomb radiation; γ rays with a small neutron component; single high-dose-rate exposure
Massachusetts original	(TBO)	US	1494	1608	103	44,616	1.0 (0.02–6)	Repeated chest fluoroscopies (X rays); many low-dose fractions at high dose rates
Massachusetts extension	(TBX)	US	3068	2576	108	45,410	0.7 (0.02–5)	Repeated chest fluoroscopies (X rays); many low-dose fractions at high dose rates
New York mastitis	(APM)	US	1811	767	114	35,585	3.8 (0.6–14)	175–250 kVp therapeutic X rays; small number of high-dose-rate fractions
Rochester thymus	(THY)	US	3312	2008	34	59,222	0.7 (0.02–7.5)	80–250 kVp therapeutic X rays; small number of high-dose-rate fractions
Benign breast disease	(BBD)	Sweden	3034	1778	210	63,417	5.8 (0.02–50)	170–175 kVp therapeutic X rays; small number of high-dose-rate fractions
Gothenburg hemangioma	(HMG)	Sweden	7469	11,115	71	169,635	0.17 (0.02–22)	External γ radiation from ^{226}Ra applicators; mainly protracted low-dose-rate exposures
Stockholm hemangioma	(HMS)	Sweden	9613	12,059	155	246,242	0.52 (0.02–35)	External γ radiation from ^{226}Ra applicators; mainly protracted low-dose-rate exposures
Total			77,527	69,921	1502	1,846,433		

[a] Total for exposed and unexposed women in the cohort.
[b] Total number of breasts exposed to at least 0.02 Gy.
[c] Values are for breasts that received a total dose in the range 0.02 to 10 Gy.

Borstkanker

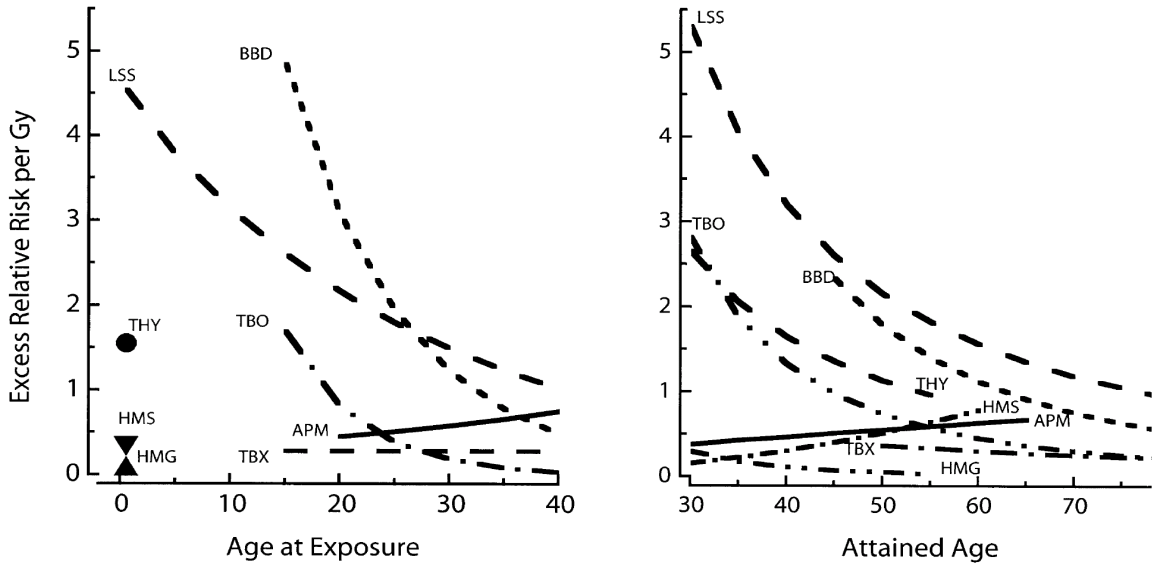


FIG. 3. Cohort-specific ERR models. The left panel presents the ERR estimates for the age-at-exposure models described in Table 7. These models assume a constant ERR (given age at exposure) for any attained age. Risks for the THY, HMG and HMS cohorts are shown as points since all of the exposures occurred in infancy. The right panel presents ERR estimates for the attained-age models. These fitted risks do not depend on age at exposure.

$$ERR(e) = \beta d \exp[\theta(e-25)]$$

$$ERR(a) = \beta d \left(\frac{a}{50}\right)^{\gamma}$$

Borstkanker

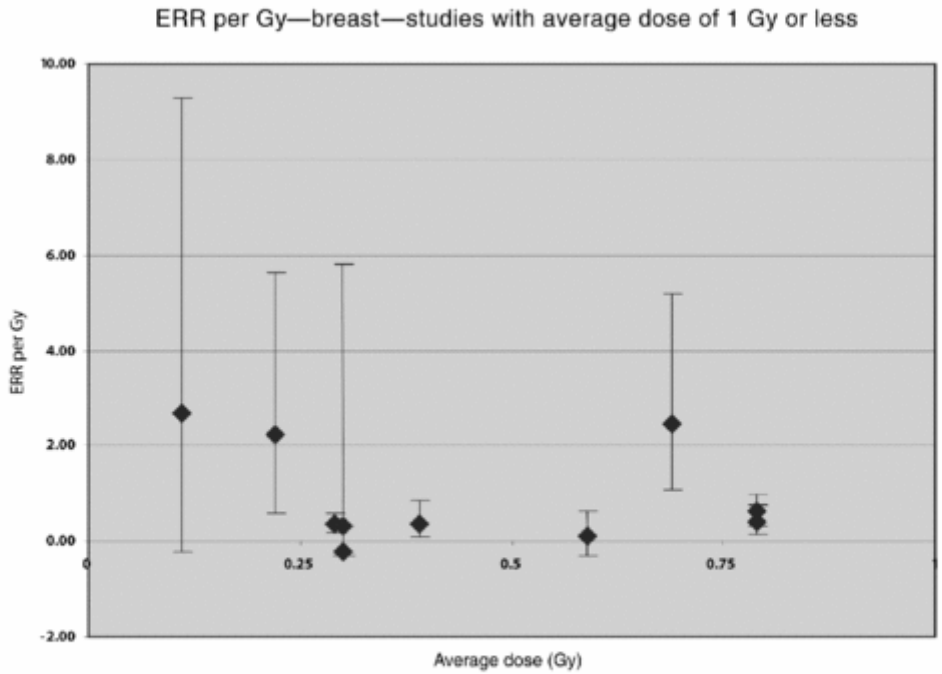


FIGURE 7-2 Distributions of study-specific estimates of ERR and EAR for breast cancer according to level of average dose to the breast.

Borstkanker

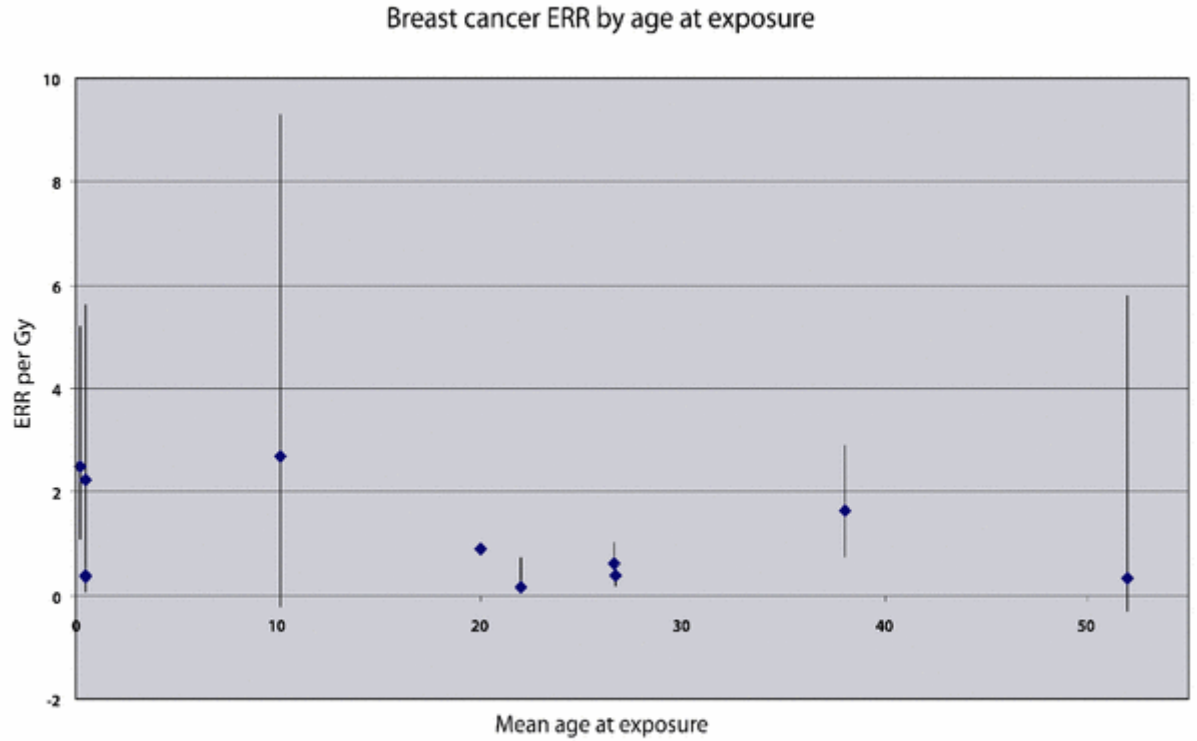


FIGURE 7-3 Distribution of study-specific estimates of ERR/Gy for breast cancer according to average age at exposure.

BEIR VII: $ERR/Sv = \beta(a/60)^{-2}$

β = 0.51 (0.28,0.83)

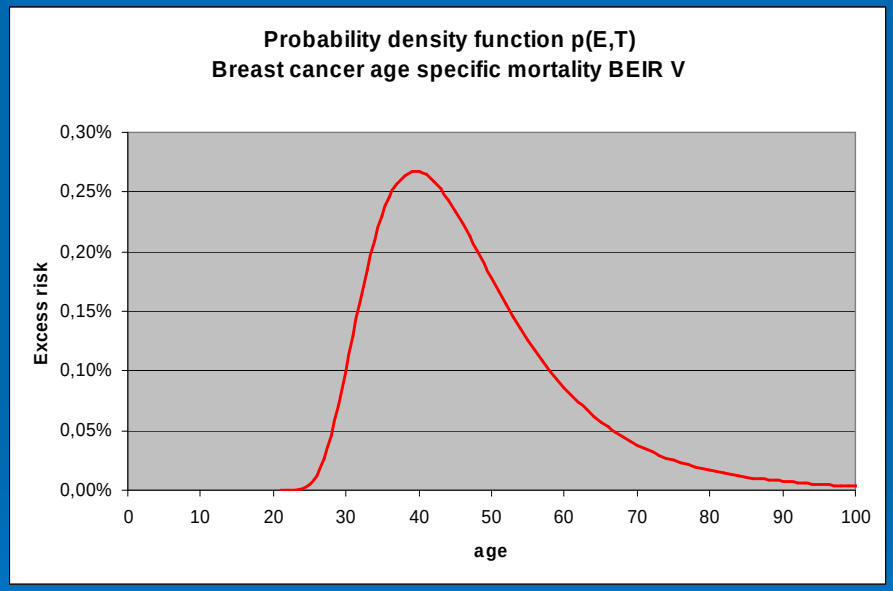
BEIR V:

$$ERR/Sv = \alpha_1 \cdot \begin{cases} e^{\beta_1+\beta_2\ln(t/20)+\beta_3\ln^2(t/20)} & e \le 15 \\ e^{\beta_2\ln(t/20)+\beta_3\ln^2(t/20)+\beta_4(e-15)} & e > 15 \end{cases}$$

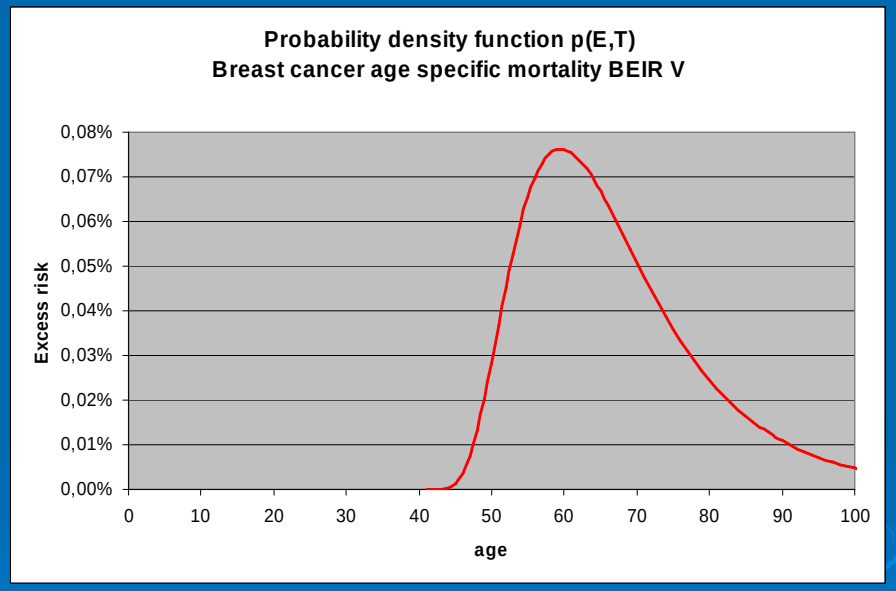
α1	1,220	0,610
β1	1,385	0,554
β2	-0,104	0,804
β3	-2,212	1,376
β4	-0,0628	0,0321

Borstkanker

d = 3 mSv

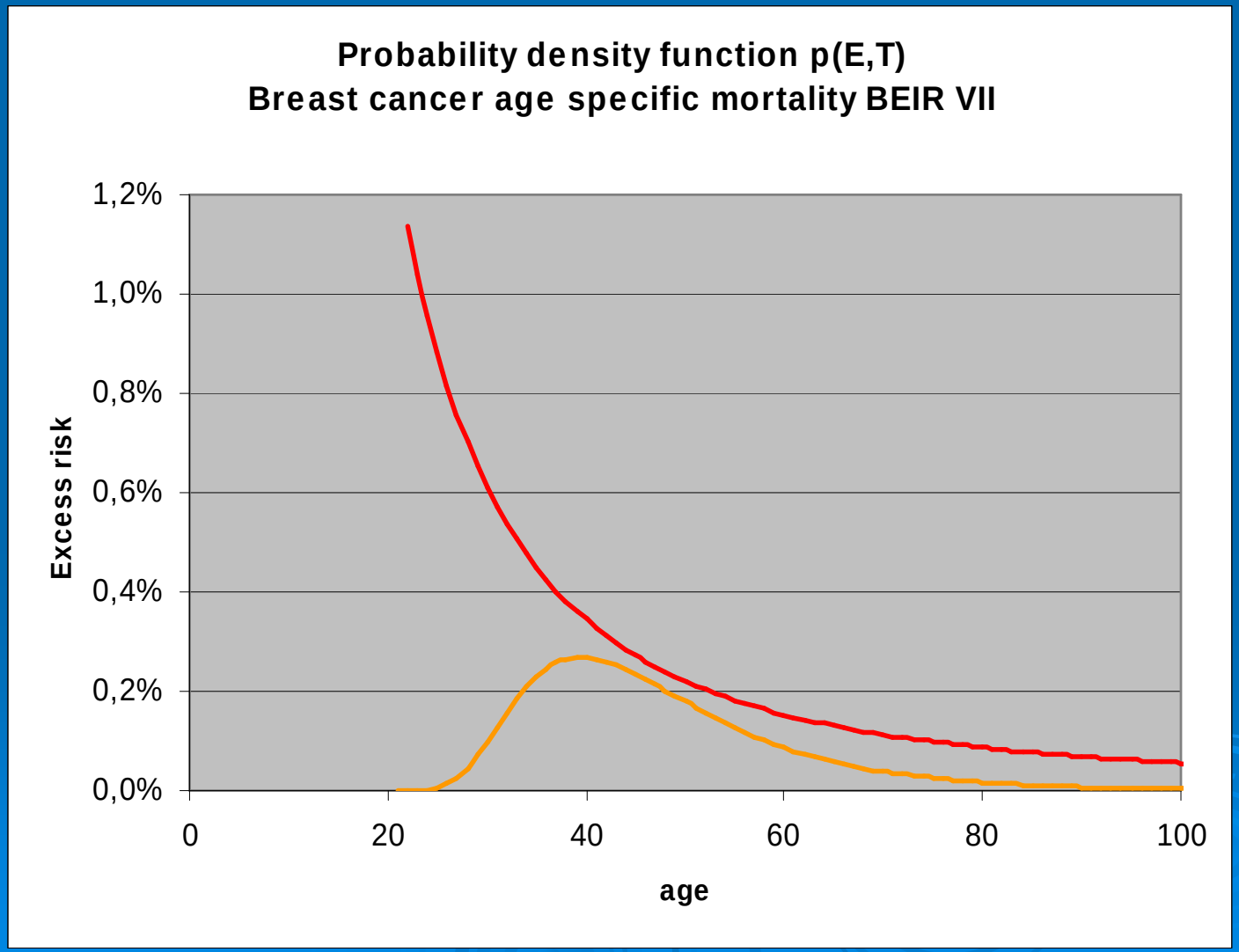


a = 20



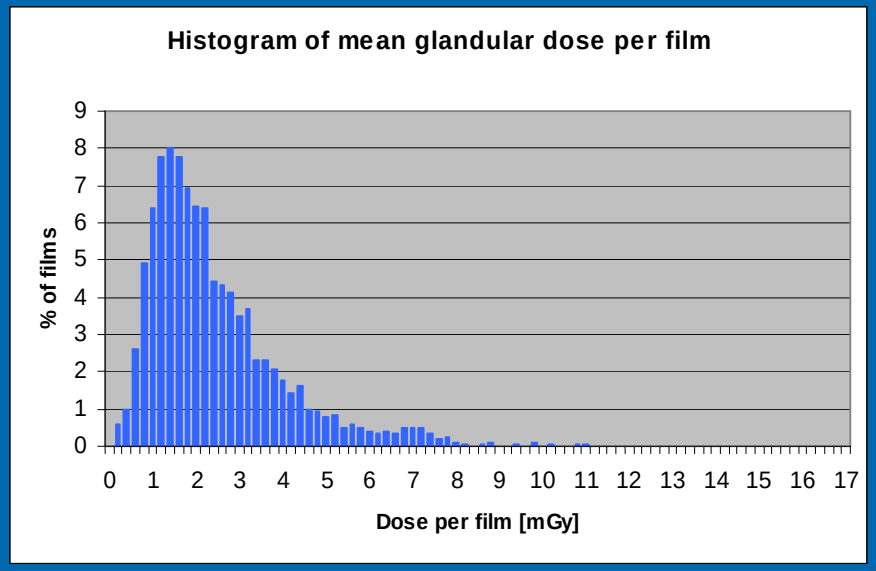
a = 40

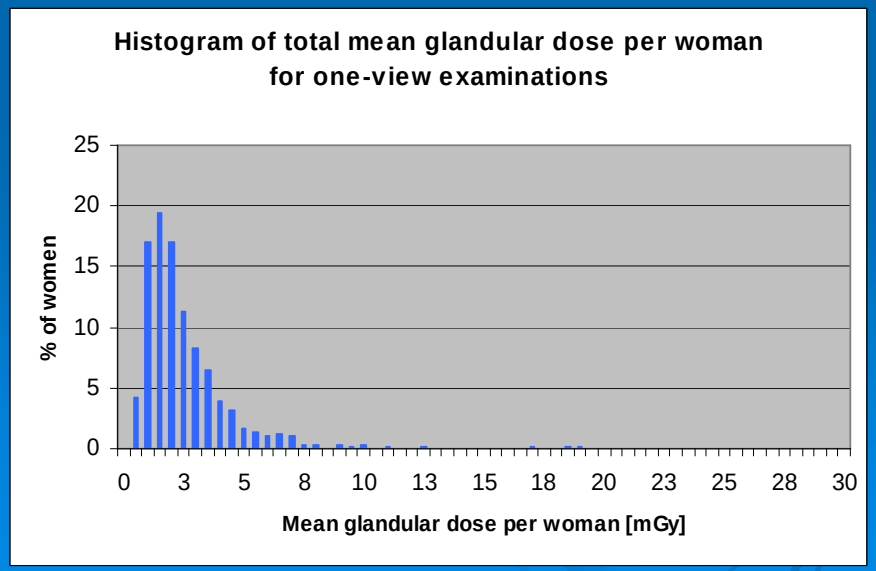
Borstkanker



d = 3 mSv
a = 20

Borstkanker





Examination type	MGD [mGy]
One-view	2,59±0,10
Two-view	4,70±0,52

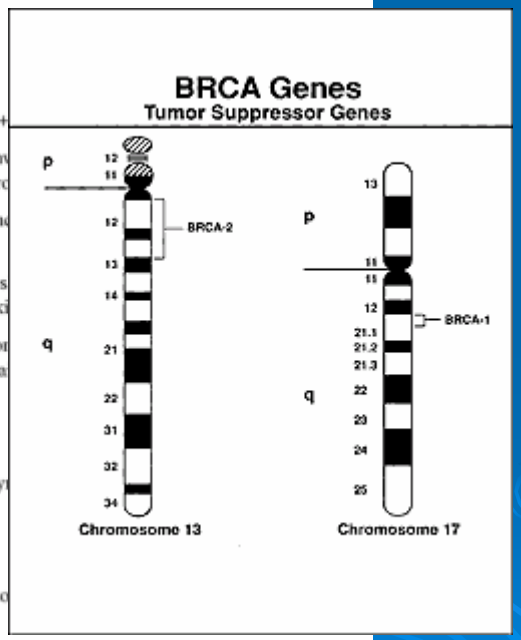
Young KC. Radiation doses in the UK trial of breast screening in women aged 40-48 years. The British Journal of Radiology 2002; 75:362-370.

- Beschikbaar:
  - Dosis respons curve voor tumor inductie
  - Gemiddelde dosis bij mammografie onderzoek
- Probleemstelling:
- Vrouwen met een verhoogd genetisch risico op borstkanker op jonge leeftijd
  - Screening?
  - Welke modaliteiten?
    - Mammografie
    - MRI
  - Vanaf welke leeftijd?
  - Tot welke leeftijd?
  - Welk interval?
- Aanpak: modelvorming
  - Validatie
  - Analyse

Model BRCA mammascreening

TABLE 3-4 Examples of Autosomal Dominant Disorders of Tumor Suppressor Genes, Proto-oncogenes, and DNA Damage Response or Repair Genes

Disorder	Genes or Locus	Defect Proposed	Cancer	Approximate Prevalence (per live births)
Tumor-Suppressor Disorders				
Familial adenomatous polyposis	*APC*	Transcriptional regulation	Colorectal cancer (multiple polyps)	
Von Hippel-Lindau disease	*VHL*	Transcriptional regulation	Renal cancer	
Denys Drash syndrome	*WT1*	Transcriptional regulation	Nephroblastoma (+	
Neurofibromatosis type 1 Neurofibromatosis type 2	*NF-1* *NF-2*	GTPase regulation Cytoskeletal linkage	Neurofibroma Schv Meningioma Neurc	
Nevoid basal cell carcinoma syndrome	*PTC*	Cellular signaling	Basal cell skin can Medulloblastoma	
Tuberous sclerosis	*TSC1* *TSC2*	Cellular signaling Cellular signaling	Benign lesions of s tissue, heart, and ki	
Retinoblastoma	*RB1*	Transcriptional regulation	Retinal tumors, bon tissue sarcoma, bra and melanoma	
Proto-oncogene Disorders				
Multiple endocrine neoplasia (2A and 2B) and familial medullary thyroid cancer	*RET*	Cellular signaling	Thyroid or parathyr neoplasms	
DNA Damage Response or Repair Disorders				
Hereditary nonpolyposis colon cancer	*MLH1*, *MSH2*, *PMS1*, *PMS2*	DNA mismatch repair, apoptosis	Colon cancer, endo cancer	
Li-Fraumeni syndrome	*TP53* (others?)	DNA damage recognition	Various	1 in 50,000
Heritable breast or ovarian cancer	*BRCA-1* *BRCA-2*	Transcriptional regulation, DNA repair	Breast or ovarian cancer Breast cancer (also male)	1 in 1000

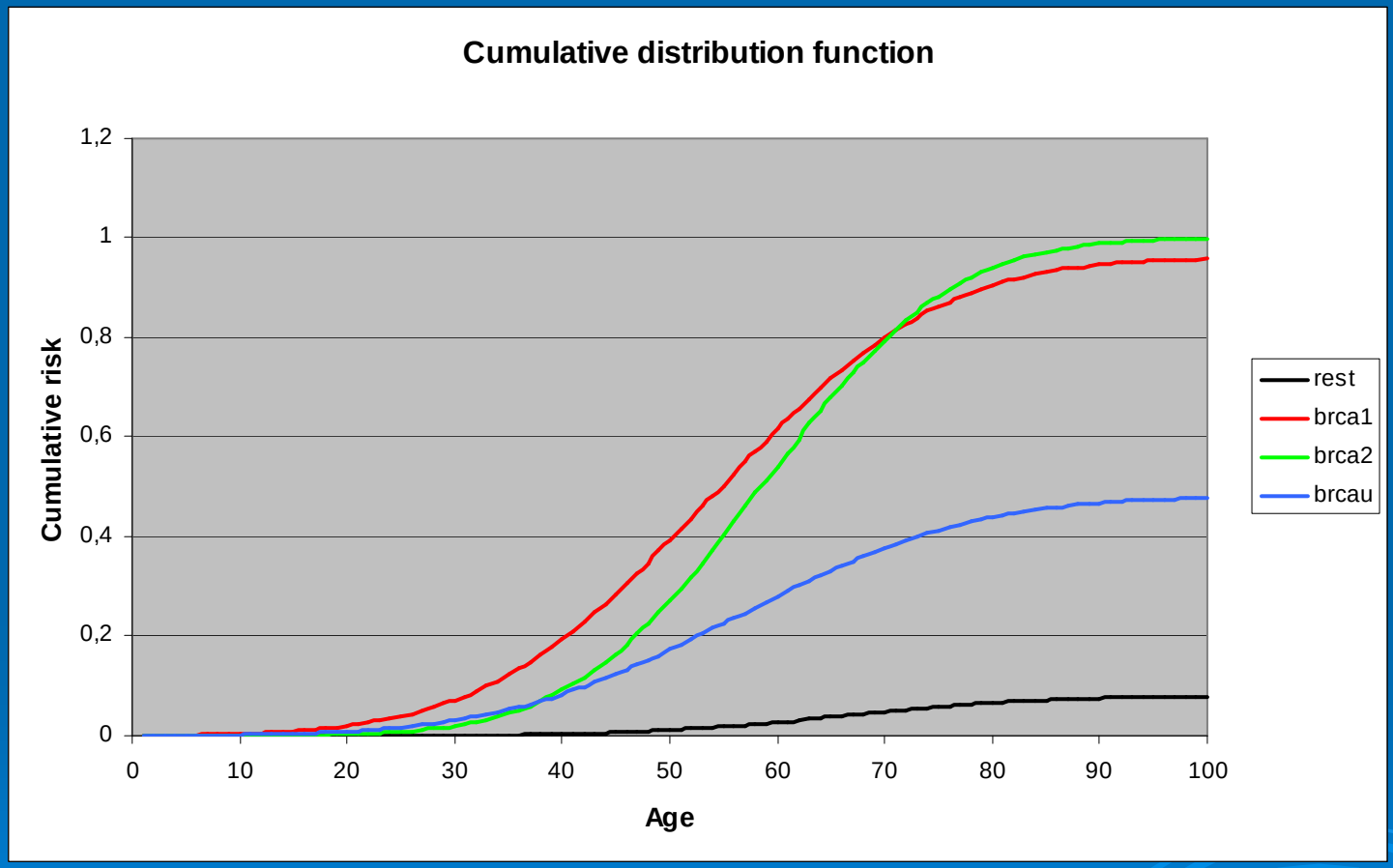


The probability density function $p(a_{bc},g)$ of breast cancer at age (a_{bc}) and genetic predisposition (g) (where g is equal to $brca_1$, $brca_2$, $brac_u$ or the population) is modeled by a normal distribution given by

$$p(a_{bc},g)=\frac{f_g}{\sigma_g\sqrt{2\pi}}e^{-\frac{1}{2}\left(\frac{a_{bc}-\mu_g}{\sigma_g}\right)^2}$$

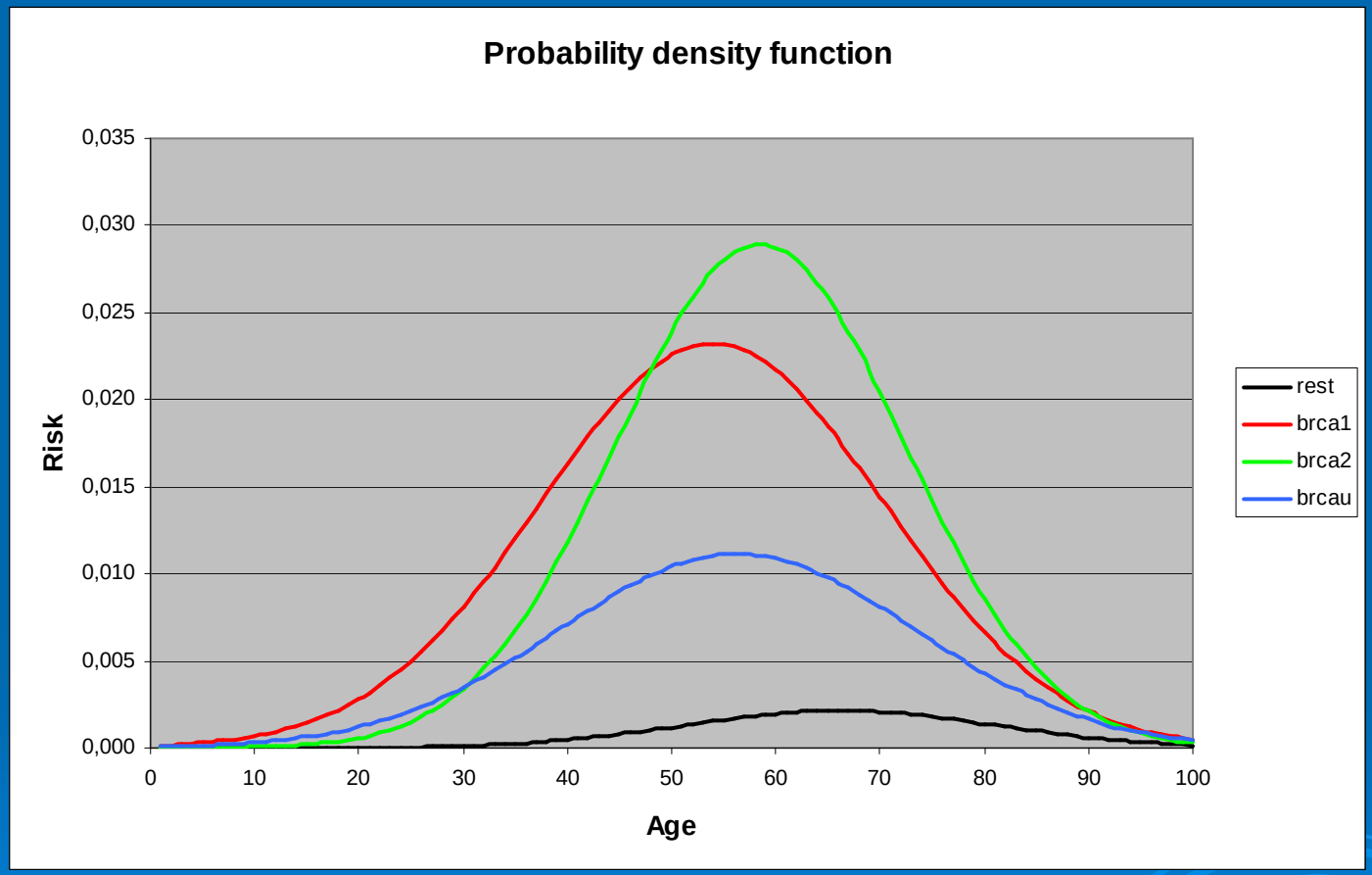
Where the mean breast cancer age is given by μ_g, the standard deviation is given by σ_g and the integral is given by f_g.

Model BRCA mammascreening



Jonker MA, Jacobi CE, Hoogendoorn WE, Nagelkerke NJ, de Bock GH, van Houwelingen JC.
Modeling familial clustered breast cancer using published data.
Cancer Epidemiol Biomarkers Prev. 2003 Dec;12(12):1479-85.

Model BRCA mammascreening



Jonker MA, Jacobi CE, Hoogendoorn WE, Nagelkerke NJ, de Bock GH, van Houwelingen JC.
Modeling familial clustered breast cancer using published data.
Cancer Epidemiol Biomarkers Prev. 2003 Dec;12(12):1479-85.

Model BRCA mammascreening

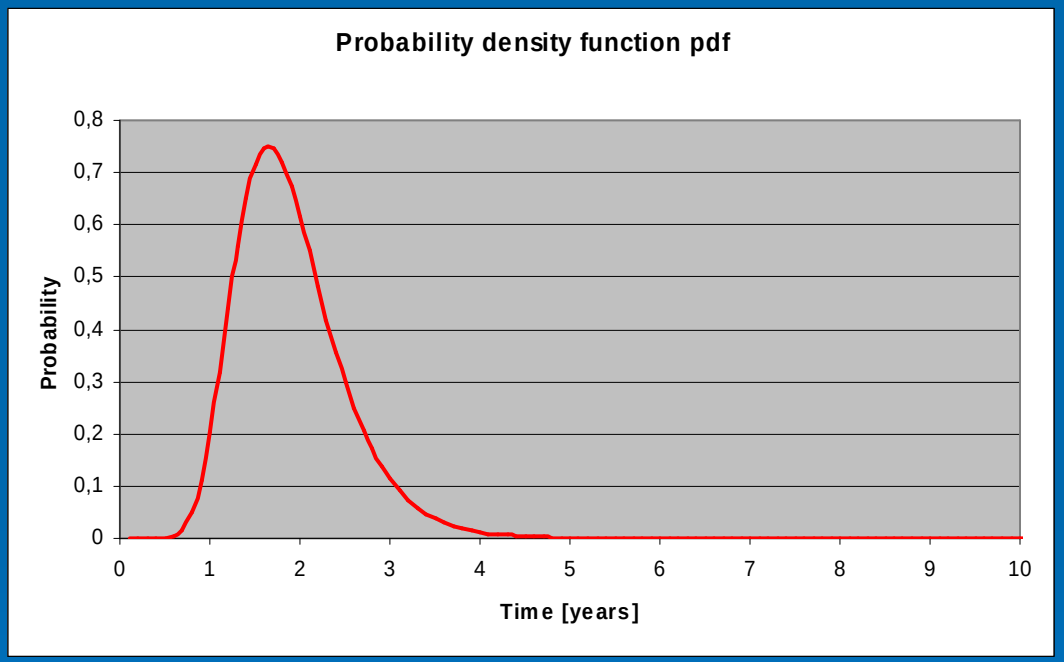
	Population	Brca1	Brca2	Brcau
F	0.08	0.60	0.52	0.49
M	66.30	45.00	52.00	56.30
S	14.90	5.00	11.50	17.20

A preclinical age is calculated using a log-normal distribution.
The probability distribution of this function is given by a normally distributed logarithm of the preclinical breast cancer period x_{pc}:

$$p(x_{pc}) = \frac{1}{x_{pc}\sigma_{pc}\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{\ln x_{pc} - \mu_{pc}}{\sigma_{pc}}\right)^2}$$

Where μ_{pc} and σ_{pc} are the mean and standard deviation of the logarithm of the preclinical breast cancer period x_{pc}.

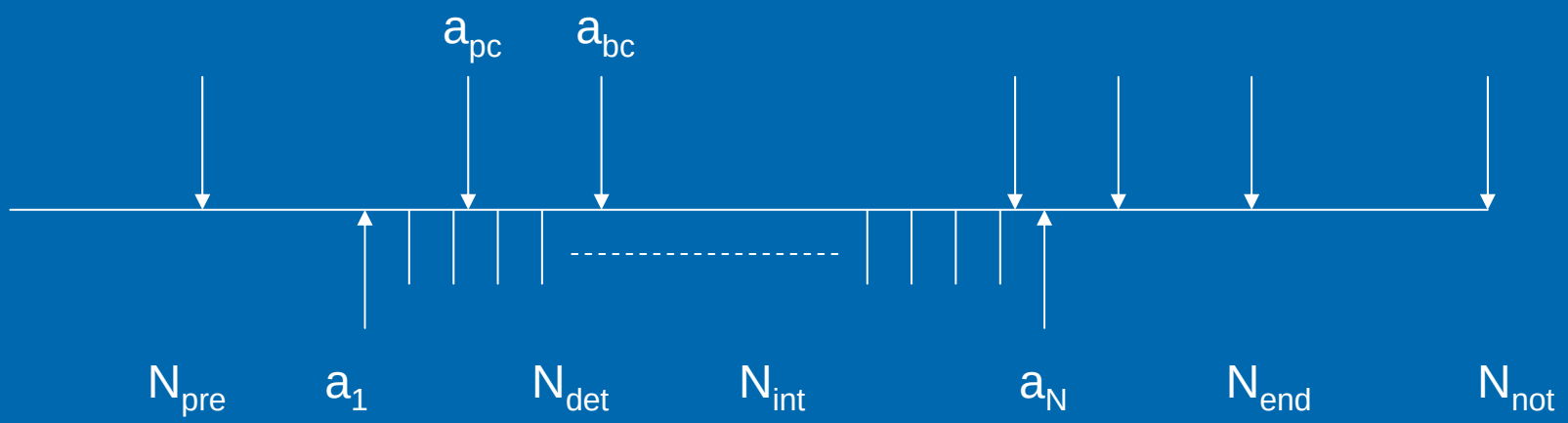
Model BRCA mammascreening



m = 1.9
sd = 0.6

Peer PG, Verbeek AL, Straatman H, Hendriks JH, Holland R.
Age-specific sensitivities of mammographic screening for breast cancer.
Breast Cancer Res Treat. 1996;38(2):153-60.

Model BRCA mammascreening



a1..aN	screening leeftijden
apc	preklinische borstkanker leeftijd
abc	klinische borstkanker leeftijd
Npre	aantal tumor voor start screening
Ndet	aantal door screening gedetecteerde tumoren
Nint	aantal in screening gemiste tumoren (interval tumoren)
Nend	aantal tumoren na einde screening
Nnot	aantal vrouwen zonder borstkanker

Incidentele kans op tumorinductie tgv dosis d op leeftijd ai:

$$CumERR(d,a_i) = \prod_{j=1}^{i}\left(1+ERR(a_j)\cdot d\right)-1$$

Totale indicentele kans op tumor tgv genetische aanleg g en tumorinductie op leeftijd ai met dosis d:

$$TotERR(d,a_i,g) = p(a_i,g)\left(1+CumERR(d,a_i)\right)$$

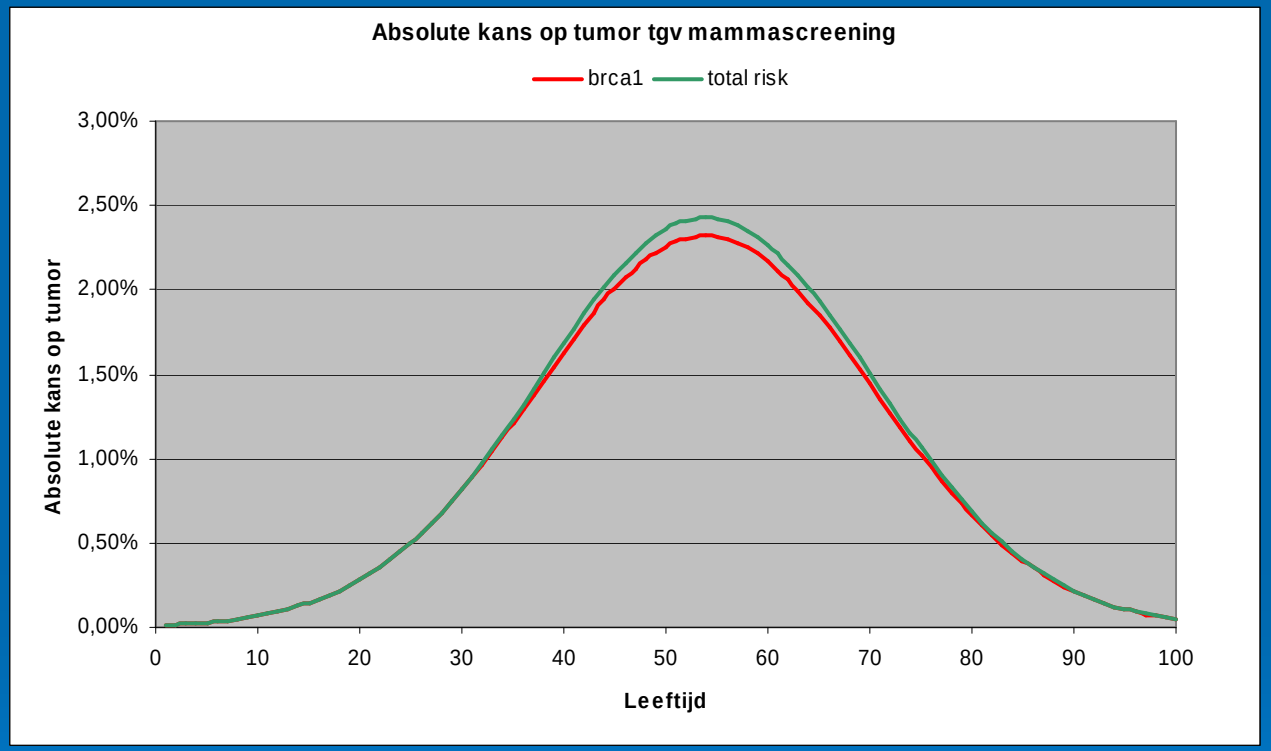
Totale cumulatieve kans op tumor tgv genetische aanleg g en tumorinductie op leeftijd a met dosis d:

$$p(d,a,g) = \int_{a'=0}^{a} TotERR(d,a',g)da'$$

Kansberekening mbv Monte Carlo. Los op tumorleeftijd a_{bc} met R = [0,1]

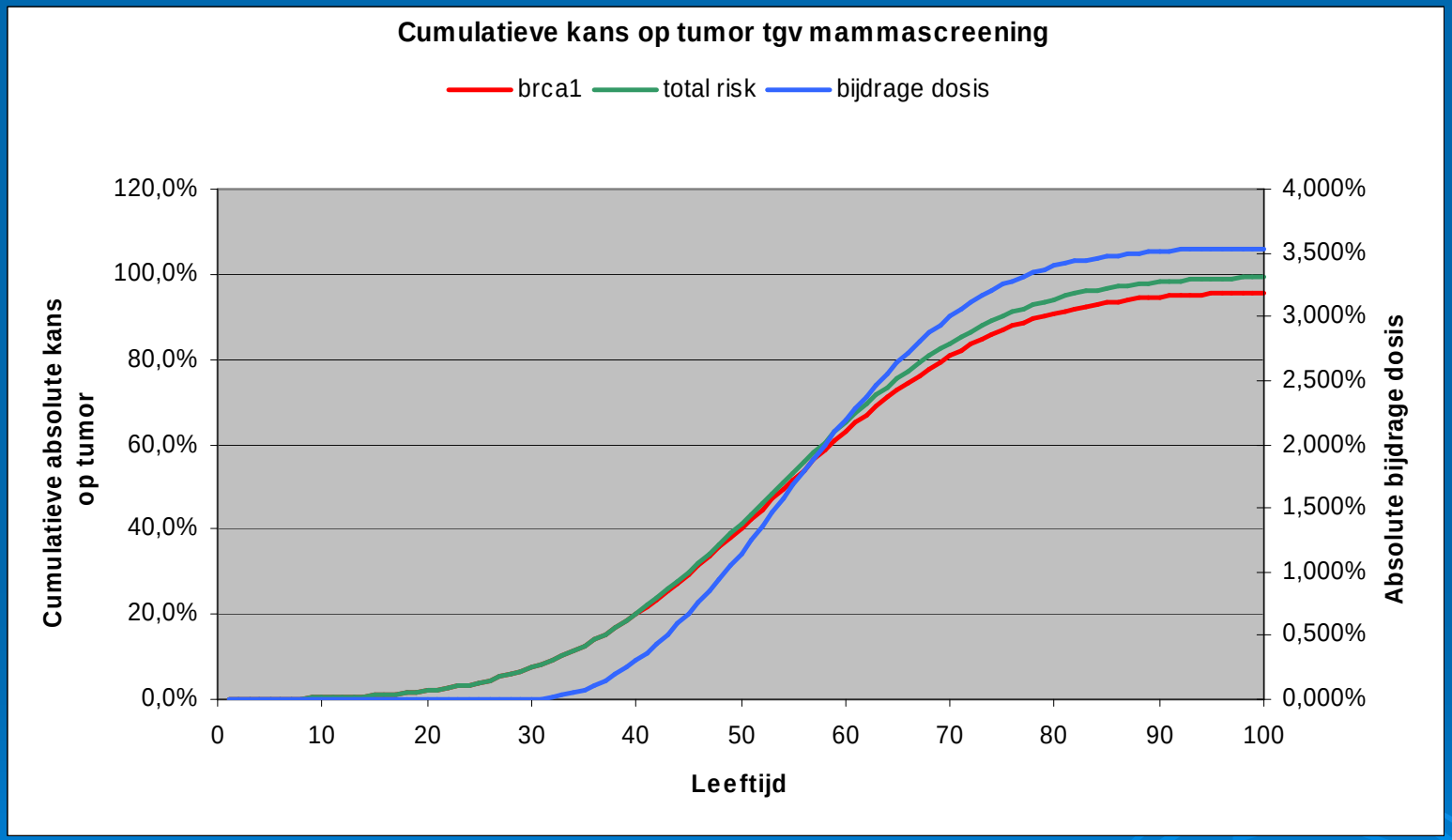
$$R = p(d,a_{bc},g)$$

Model BRCA mammascreening



Jaarlijkse screening 30 – 50 jaar
Dosis 3 mSv

Model BRCA mammascreening



Jaarlijkse screening 30 – 50 jaar
Dosis 3 mSv

Model BRCA mammascreening

VOLUME 23 · NUMBER 33 · NOVEMBER 20 2005

JOURNAL OF CLINICAL ONCOLOGY

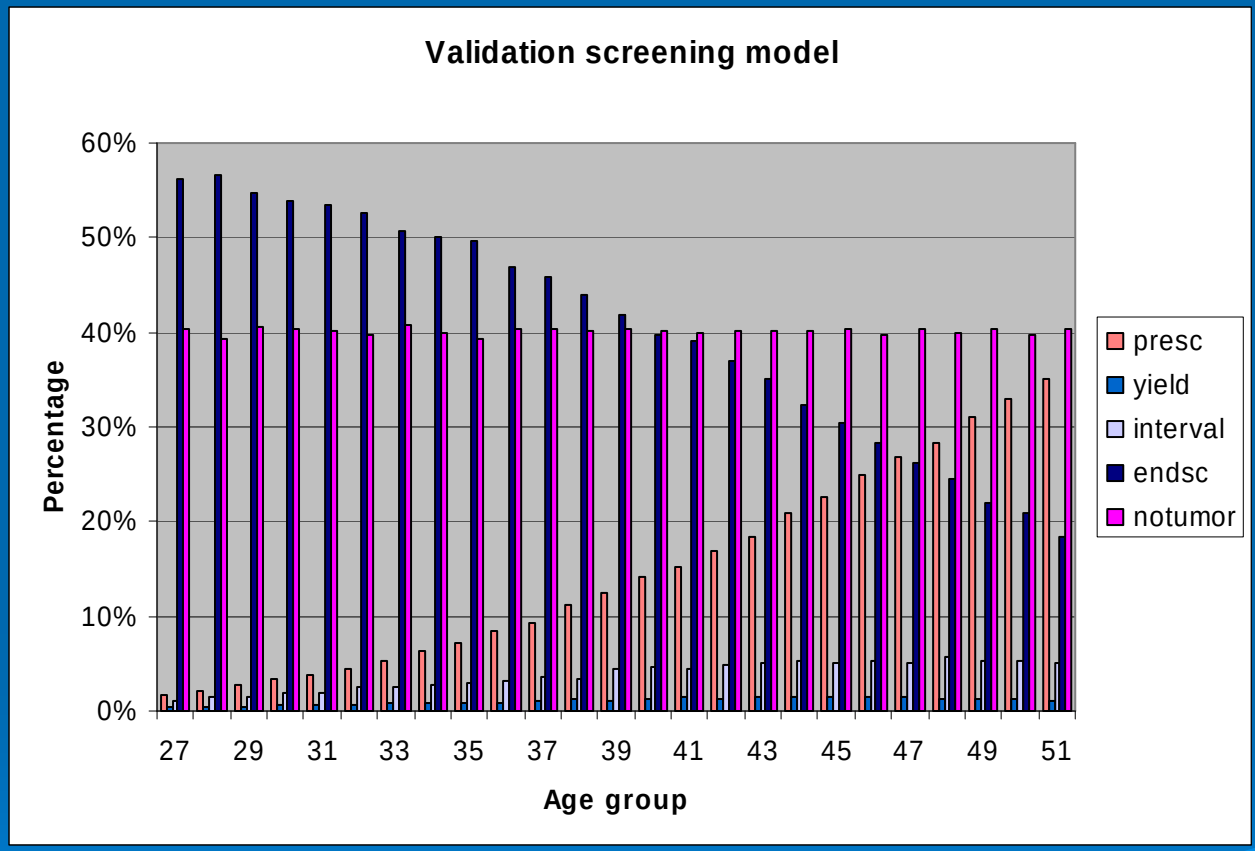
ORIGINAL REPORT

Mammography, Breast Ultrasound, and Magnetic Resonance Imaging for Surveillance of Women at High Familial Risk for Breast Cancer

Christiane K. Kuhl, Simone Schrading, Claudia C. Leutner, Nuschin Morakkabati-Spitz, Eva Wardelmann, Rolf Fimmers, Walther Kuhn, and Hans H. Schild

No of mutation carriers:	43
Mammography detected:	2
No of interval cancers:	6
Sensitivity:	25%
Age:	27-55
Screening:	4x1

Model BRCA mammascreening



Yield:	1,2	2 (95%CI:0-5)
Interval:	4,6	6 (95%CI:2-10)

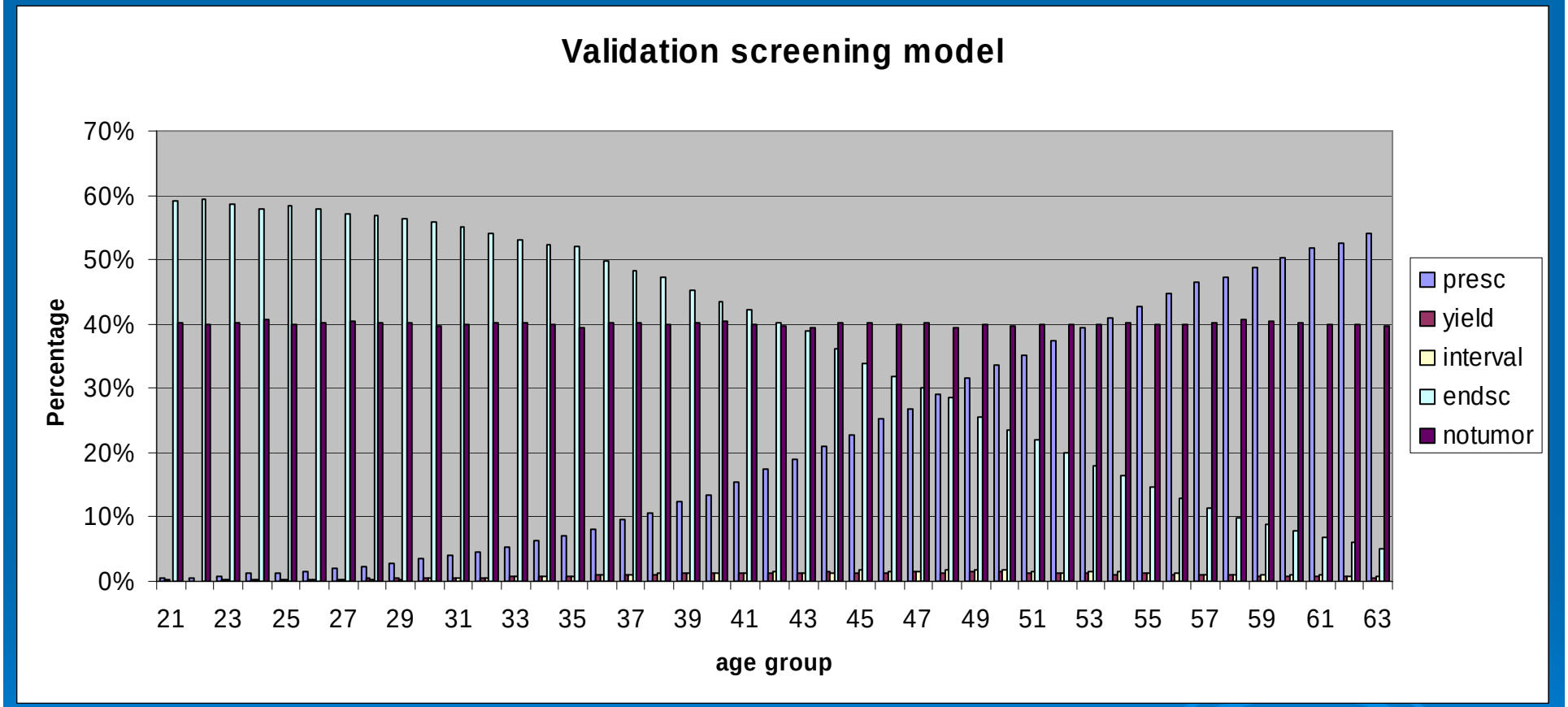
Effectiveness of Breast Cancer Surveillance in *BRCA1/2* Gene Mutation Carriers and Women With High Familial Risk

By C.T.M. Brekelmans, C. Seynaeve, C.C.M. Bartels, M.M.A. Tilanus-Linthorst, E.J. Meijers-Heijboer, C.M.G. Crepin, A.N. van Geel, M. Menke, L.C. Verhoog, A. van den Ouweland, I.M. Obdeijn, and J.G.M. Klijn
for the Rotterdam Committee for Medical and Genetic Counseling

Journal of Clinical Oncology, Vol 19, No 4 (February 15), 2001: pp 924-930

No of mutation carriers:	128
Mammography detected:	5
No of interval cancers:	4
Sensitivity:	56%
Age:	21-65
Screening:	2x1

Model BRCA mammascreening



Yield:	3,8	5 (1,9)	95% confidence intervals
Interval:	3,2	4 (0,8)	

- Model validatie aan epidemiologische data
  - Kuhl en Brekelmans
- Variatie van:
  - Dosis
  - Sensitiviteit
  - Start leeftijd
  - Eind leeftijd
  - Interval
  - Modaliteit
- Sensitiviteitsanalyse
- Uitkomstmaat?

Model BRCA mammascreening

Comparison of benefit / risk ratio

$$BRR(d) = 1 + \frac{\sum d_{ns} - \sum d_s}{\sum d_{sr}}$$

$$R(d) = 1 - \frac{\sum d_s}{\sum d_{ns}}$$

d_s no. breast cancer deaths in screened population

d_{ns} no. breast cancer deaths in non-screened population

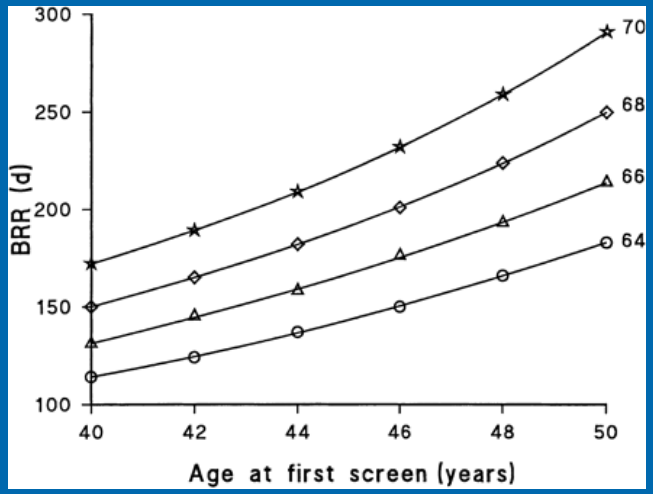
d_{sr} radiation induced breast cancer deaths

Screening age range, screening interval	BRR(d) [1]	BRR(d) [2]
50-69, 2 yr	242	206
40-69, 2 yr	97	111
40-69, 1 yr	73	72

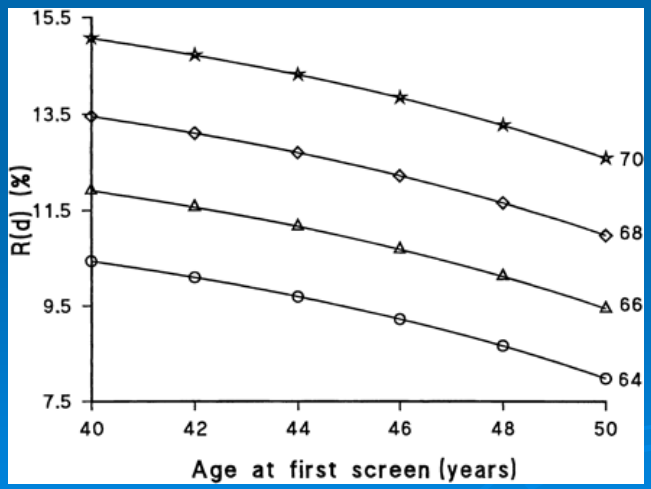
[1] Beemsterboer PMM, Warmerdam PG, Boer R, Koning HJ de. Radiation risk of mammography related to benefit in screening programmes: a favourable balance?. Journal of Medical Screening 1998; 5:81-87.

[2] Beckett JR, Kotre CJ, Michaelson JS. Analysis of benefit:risk ratio and mortality reduction for the UK Breast Screening Programme. The British Journal of Radiology 2003; 76:309-320.

Model BRCA mammascreening



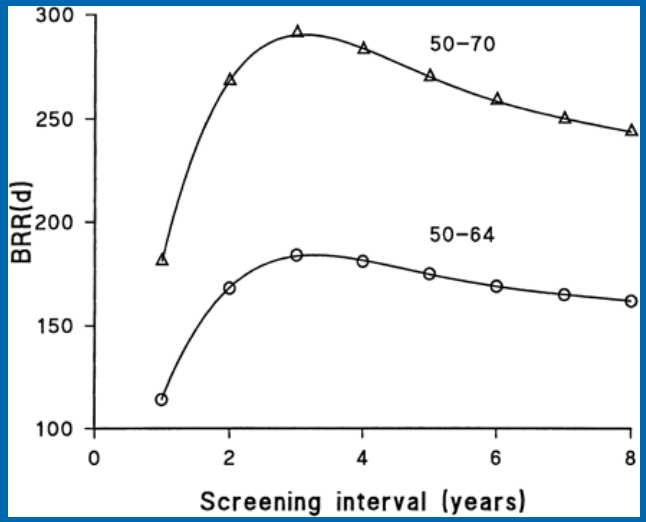
Benefit/risk ratio in terms of breast cancer mortality BRR(d) versus age at first screen with final screen at ages 64, 66, 68 and 70 years (3-year screen interval).



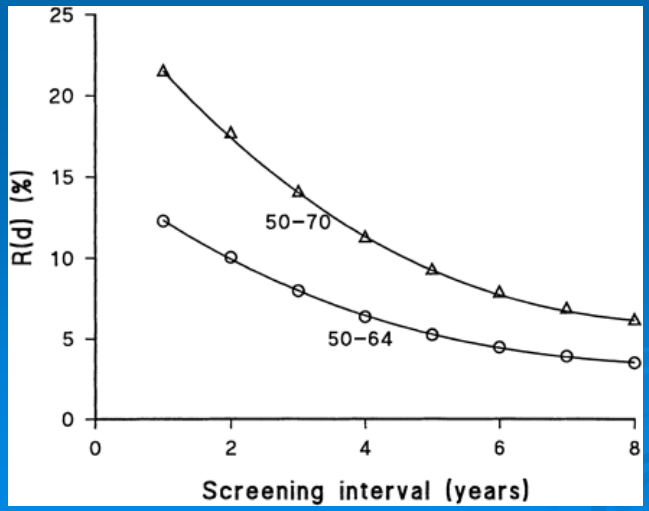
Reduction in breast cancer mortality R(d) versus age at first screen with final screen at ages 64, 66, 68 and 70 years (3-year screen interval).

Beckett JR, Kotre CJ, Michaelson JS. Analysis of benefit:risk ratio and mortality reduction for the UK Breast Screening Programme. The British Journal of Radiology 2003; 76:309-320.

Model BRCA mammascreening



Benefit/risk ratio in terms of breast cancer mortality BRR(d) versus interval between successive screen for age ranges 50-64 and 50-70.



Reduction in breast cancer mortality versus interval between successive screen for age ranges 50-64 and 50-70.

Conclusie

- Risico mammaonderzoek
  - Ongeveer 1% bij blootstelling op 20 jaar met 3 mSv
  - Neemt kwadratisch af met de leeftijd
- Risico borstkanker BRCA
  - 60-85% op 70 jarige leeftijd
- Jaarlijkse screening
  - Bijdrage 3.5% bij screening 30-50 jaar
- Model reproduceert epidemiologische data
- Ontwikkeling:
  - Benefit / risk ratio
  - Reduction of breast cancer mortality
  - Beantwoording screeningsvragen
  - Sensitiviteitsanalyse

Fernando Ureña Rib, Duo Turbantes

European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis
European Communities, 2006