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Differences and similarities in breast cancer risk assessment models in clinical practice: which model to choose?

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Abstract To show differences and similarities between risk estimation models for breast cancer in healthy women from BRCA1/2-negative or untested families. After a systematic literature search seven models were selected: Gail-2, Claus Model, Claus Tables, BOADICEA, Jonker Model, Claus-Extended Formula, and Tyrer–Cuzick. Life-time risks (LTRs) for developing breast cancer were estimated for two healthy counsellees, aged 40, with a variety in family histories and personal risk factors. Comparisons were made with guideline thresholds for individual screening. Without a clinically significant family history LTRs varied from 6.7% (Gail-2 Model) to 12.8% (Tyrer–Cuzick Model). Adding more information on personal risk factors increased the LTRs and yearly mammography will be advised in most situations. Older models (i.e. Gail-2 and Claus) are likely to underestimate the LTR for developing breast cancer as their baseline risk for women is too low. When models include personal risk factors, surveillance thresholds have to be reformulated. For current clinical practice, the Tyrer–Cuzick Model and the BOADICEA Model seem good choices.

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Introduction

Breast cancer is the most common type of cancer in women in western countries, and is an important cause of death for women, especially in the age group 30–59 [1]. The most important risk factor for the development of breast cancer, besides advanced age, is a family history of breast cancer [2]. In the past decades, many empirical and statistical models have been developed to estimate the risk of developing breast cancer during life, the life-time risk (LTR). These models have been developed to guide clinicians to decide whether or not surveillance is indicated [3–5]. Most of these models focus on family history of breast cancer alone, but some use other risk factors additionally. Although generally applicable to all women, the models are mostly developed for healthy women who have relatives with breast cancer and who are BRCA1/2 negative or untested. For those healthy women who want more certainty about their breast cancer risk, the risk can only be estimated by examining their pedigree. As the diversity of models available is large, it is often difficult for clinicians to decide which model to use for an individual counsellee.

The aim of this study is to show and evaluate the differences and similarities between the different models in risk estimates for breast cancer in healthy women. To be able to provide a complete overview of risk assessment models, a systematic literature search was performed to find all available risk assessment models. Often used and recently developed models of which risk assessment software was available were selected and applied to cousellees with varying personal risk factors and different pedigrees

varying in affected relatives. The risk estimates of the models were compared with the thresholds for individual mammographic screening in guidelines.

The provided overview of observed strengths and weaknesses of the models in these different individual situations might help clinicians to make a founded choice of a risk assessment model for their clinical practice.

Methods

Literature search for risk assessment models

The medical literature was searched systematically to find a complete overview of existing breast cancer risk assessment models, in PubMed (1950–September 2006), EMBASE (1980–September 2006), and Web of Science (1945–September 2006). The combination of two concepts, i.e. familial breast cancer AND risk models, was extensively searched either by the use of subject headings or free text words (Appendix 1). The search revealed 522 unique articles.

Three independent reviewers made a first selection based on title and abstract, and a second selection based on complete article readings. Excluded were: models dealing with risk assessment using invasive or surveillance techniques; models intended for non-healthy individuals; models for psychological outcome; or models only focusing on carrier status of genetic mutations. We selected 29 articles to be of interest. After studying the references to check whether we may have missed relevant models, we included an additional ten articles, leading to a total of 39 selected articles [6–44]. Among the total of 39 articles, 18 were related to 12 different breast cancer risk assessment models or methods [6–23].

Risk assessment models and methods

From the identified models, we selected those models or methods that are still in use: Gail2-Model, Claus Model and Claus Tables [8–10, 15], and for which risk estimates could be obtained by software availability or because a formula or reading tables are included in the article: BOADICEA Model, Jonker Model, Tyrer–Cuzick Model, and Claus-Extended Formula [16–18, 21, 22] (Table 1). The models of Gail and Tyrer–Cuzick [8, 21] incorporate, next to family history and age, information on personal risk factors. The selected models vary upon the life-time age for which the risks are estimated. The Claus Model, Claus Tables, Claus-Extended Formula, Jonker Model, Tyrer–Cuzick Model, and BOADICEA Model use an end-age of 80 years, and the Gail-2 Model 90 years.

When using the available software, the Gail-2 and Tyrer–Cuzick Model provide remaining life-time risks (i.e. 40–80 or 90 years), whereas the other models provide full life-time risks (i.e. 0–80 years).

Counsellees and pedigrees

The counsellees are examples of women who might ask to be informed about their LTR for breast cancer and additional management strategies if needed. The first concerns Counsellee A, 40 years of age, of Caucasian origin, without a history of LCIS/DCIS. She reflects a counsellee of whom family cancer data were included, but no questions were asked about personal risk factors. The second concerns Counsellee B, with identical characteristics as Counsellee A, but additional information was asked for; she has had one biopsy, is 170 cm (5.6 ft) in height and 65 kg (143 lbs) in weight. Additionally she provided information on two other personal risk factors, i.e. age at first menstrual period and age at first born child. These two factors are varied to study the impact on risk estimates.

In addition, these two counsellee's have identical family history for breast and ovarian cancer, which we varied in six different pedigrees (Fig. 1). Each of these pedigrees consisted of a counsellee (Counsellee A *without* information on personal risk factors or Counsellee B *with* information on personal risk factors), with a brother and a sister aged 46 and 45, respectively. The mother died 60 years old and the father is alive and 74 years old. In case of a maternal or paternal aunt, this aunt died at age 55. In case of presented grandparents, whether they are from the maternal or paternal side, the grandmother died at age 55 and the grandfather at age 74.

Breast cancer risk estimation and analysis

We calculated the breast cancer risk for Counsellee A, using her age and family history, and for Counsellee B, including age, family history, medical history and personal risk factors. Risks for Counsellee B were only estimated using the Gail-2 and the Tyrer–Cuzick Model, as these are the only models including personal risk factors into the estimation. Her risks are identical with the risks of Counsellee A according to the other models. By calculating the risks for Counsellee A using the Gail-2 and the Tyrer–Cuzick Model, the personal risk factors included in these models were set to unknown or not available. By reading the Claus Tables, we included as many affected family members as possible. The Claus Tables seem to use strict combinations of affected family members, such as an affected mother and maternal aunt in Table 5. However, we used these tables more freely by reading them as affected first degree relatives combined with second-degree maternal or paternal relatives (Personal communication by

Table 1 Overview of the risk assessment models

Author	Input for development	Population for development	Analyses	Output	Software
Gail, 1989 [8]	Number of breast cancer in first degree relatives Risk factors %	Case–control data: 2,852 screened breast cancer cases and 3,146 controls, all white with complete data on risk factors	Logistic regression	Regression formula regarding the risk of breast cancer; start time age 35; end time age 90	BRISK tool www.cancer.gov/bcrisktool
Claus, 1991 [9]	Age and number of breast cancers in first degree relative (mother or sisters)	Case–control data: 4,730 breast cancers aged 20–54 and 4,688 matched controls	Segregation analysis and goodness of fit test	A function for the effect of age and genotype on the risk of breast cancer; end time age 80	Not applicable & Included in Cyrillic
Claus, 1994 [11]	Age and number of breast cancers in first degree relative (mother or sisters)	Case–control data: 4,730 breast cancers aged 20–54 and 4,688 matched controls	Segregation analysis and goodness of fit test	Tables with age-specific risks for the risk of breast cancer; end time age 80	Not applicable Reading tables are included in the paper
Antoniou, 2004 [18]	Age of breast or ovarian cancer and BRCA1 and 2 mutation prevalence and penetrance	1. 1,484 breast cancers diagnosed before age 50. 2. 156 families including at least two cases with breast cancer, at least one under the age of 50	Segregation analysis	Computer software for the risk of breast cancer; end time age 80	BOADICEA Available from author*, website recently available.
Jonker, 2003 [17]	Age of breast or ovarian cancer BRCA1 and 2 mutation prevalence and penetrance	1. National cancer incidence rates 2. Meta-analyzed risks related to family history of breast cancer 3. Published penetrances for BRCA1 and BRCA2	Model fitting	Computer software for the risk of breast cancer; end time age 80	Available from author
Van Asperen, 2004 [22]	Age of breast or ovarian cancer and BRCA1 and 2 mutation prevalence and penetrance	196 breast/ovarian cancer families	Linear regression analysis	Scorings formula; only lifetime risk; end time age 80	Not applicable; Formula is available from paper
Tyrer, 2004 [21]	Family history, BRCA1 and 2 mutation prevalence and penetrance, and environmental and personal risk factors $	1. National cancer incidence rates 2. Cohort of daughters of patients with breast cancer 3. Published risk figures	Model fitting	Computer software for the risk of breast cancer; end time age 80	IBIS version 6.0.0 Available from author; ibis@cancer.org.uk

% Risk factors included are: medical history of DCIS or LCIS; current age; age of first menstrual period; age of first live birth of a child; breast biopsy in history; ethnicity

* http://www.srl.cam.ac.uk/genepi/boadicea/boadicea_interface.html $ Risk factors included are: age of menarche; parity; age at first child; menopausal status; menopausal age; BMI; hyperplasia; LCIS; ovarian status; age at ovarian status; ashkenazi inheritance; HRT use; genetic test results

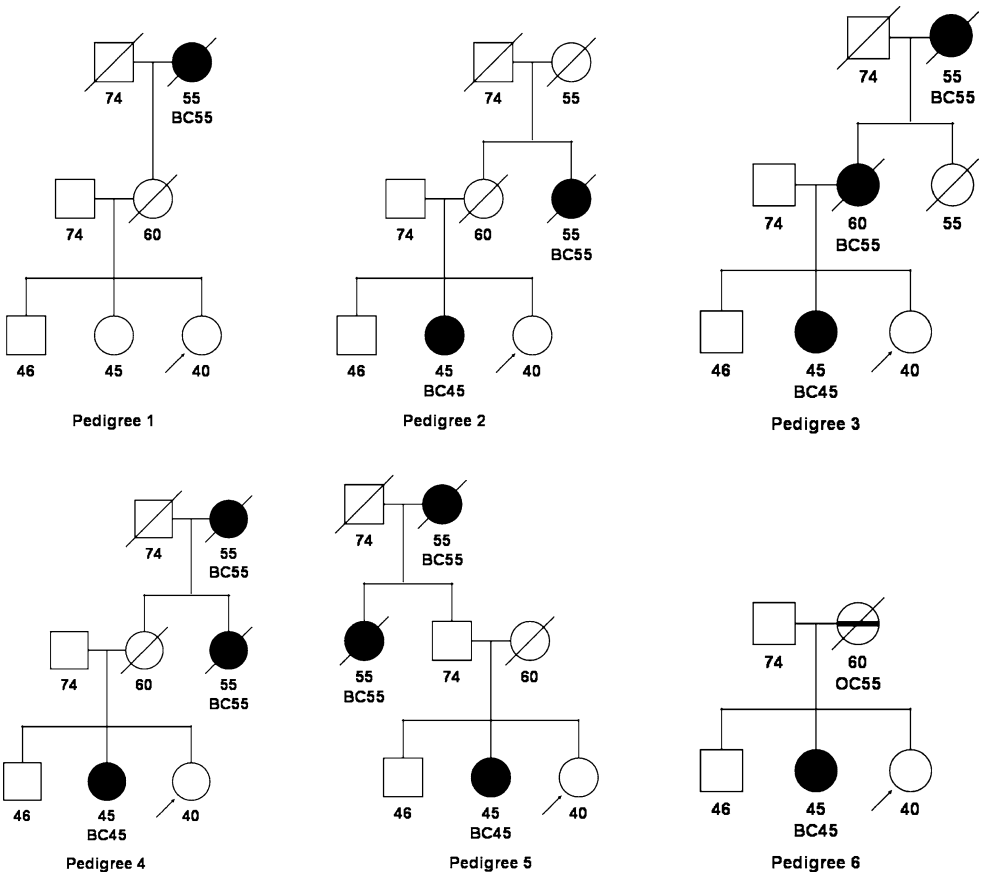

Fig. 1 Drawings of the six pedigrees, for which breast cancer risks were assessed. (a square represents male; a circle represents a female; a full black circle represents a female with breast cancer (BC), circles with a black horizontal line represent a female with ovarian cancer (OC); the number below the circles and square represent the current age or age at death of that person; if that person had breast or ovarian cancer, the age at diagnosis follows the type of cancer on the line below, e.g. BC45 means breast cancer at age 45)

e-mail with dr. Elizabeth Claus at date Sept. 24, 2005). So, for pedigree 1 we used Claus Table number 3, for pedigree 2 table number 5, for pedigree 3 table number 4 (with exclusion of the grandmother), for pedigree 4 table number 5 (with exclusion of the grandmother), for pedigree 5 table number 6 (with exclusion of the grandmother), and for pedigree 6 table number 2 (without a possibility of including the ovarian cancer of the mother).

The outcomes of the models were compared with the threshold in national guidelines for individual mammographic screening. In the UK, a LTR of 17% or higher is an indication for an increased LTR, i.e. 'moderate risk', whereas in the Netherlands this threshold is 20%. Both guidelines classify women with risks of 30 and over as the 'high risk' group (www.nice.org.uk/CG041; www.cbo.nl/product/richtlijnen/folder20021023121843/mammac_rl_2005.pdf/view). In this analysis, both guidelines were applied.

Recommended surveillance for those in the moderate risk group is a mammography annually aged 40–49 years. From age 50 years, population screening is offered. For those with a high risk, surveillance is usually offered at age 35 years (NL) or 40 years (UK) and continues up to 50 years (UK) or up to 60 years (NL), after which population screening is offered.

Results

Estimated LTRs developing breast cancer for Counsellee A

Counsellee A in pedigree 1 represents a woman without a significant family history for breast cancer. Her risk according to all models was below the threshold for moderate risk, i.e. 17%, with 6.7% (Gail-2 Model) as the lowest and 12.8% (Tyrer–Cuzick Model) as the highest estimate (Table 2). In pedigree 2 with an affected sister and maternal aunt the risk estimates were more divided with 16.4% as the lowest (Gail-2 Model) and 28.9% as the highest estimate (Claus Tables). A difference of 20% between the lowest and highest estimate was observed in pedigree 3 (breast cancer in three generations). The BOADICEA model estimated the lowest risk (22.6%) and the Claus Tables the highest risk (43.0%), all at least a moderate risk. In pedigree 4 with one-first- and two-second-degree affected relatives in the maternal family, the lowest risk estimate for Counsellee A was 16.4% (Gail-2 Model) and the highest was 33.2% (Claus Model). In pedigree 5, a similar situation but in the paternal family, the lowest risk estimate was 14.4% (Claus Tables) and the highest 39.4% (Claus Model). In pedigree 6 there was also an ovarian

Table 2 Risk assessment for Counsellee A, applying the seven models

pedigree		Gail-2 Model	Claus Model	Claus Tables	BOADICEA Model	Jonker Model	Claus Extended Formula	Tyrer-Cuzick Model
1	Mat-GM BC55	6.7%	8.4%	9.4%	10.4%	10.1%	11.8%	12.8%
2	Mat-aunt BC55 Sister BC45	16.4%	17.1%	28.9%	16.6%	19.4%	19.6%	20.4%
3	Mat-GM BC55 Mother BC55 Sister BC45	36.8%	43.0%	30.0%	22.6%	29.6%	27.0%	24.1%
4	Mat-GM BC55 Mat-aunt BC55 Sister BC45	16.4%	33.2%	28.9%	19.0%	24.9%	26.6%	22.2%
5	Pat-GM BC55 Mat-aunt BC55 Sister BC45	16.4%	39.4%	14.4%	20.2%	27.3%	20.8%	23.1%
6	Mother OC55 Sister BC45	16.4%	12.1%	13.2%	18.8%	25.2%	20.3%	19.8%

30% gray	Moderate risk
50% gray	High risk

cancer diagnosed, leading to a lowest risk estimate of 12.1% (Claus Model) and a highest of 25.2% (Jonker Model).

Estimated LTRs developing breast cancer for Counsellee B

Adding information on the age at first menstrual period and the age at first born child always resulted in an increase of the estimated LTR for developing breast cancer of Counsellee B, except when the counsellee had her first child at the age of 19 (Table 3). In this situation, the Tyrer–Cuzick model estimates her risk as lower than the risk for Counsellee A, for whom no information on the personal risk factors was available.

Without a significant family history of breast cancer, as in pedigree 1, the estimates of the Tyrer–Cuzick Model are always higher than those of the Gail2 Model, but these differences are clinically not significant. For Counsellee B in pedigree 3, with breast cancer in three generations, the estimates of the Gail-2 Model are for all, but one, variants of the personal risk factors higher, varying from 29.6% to 49.1%, than those of the Tyrer–Cuzick Model (20.2–33.7%). For Counsellee B in pedigrees 2, 4, 5 and 6, the estimates are rather comparable.

Related management strategies

Using the thresholds for individual mammographic screening of guidelines (≥17% LTR in UK and ≥20% LTR in the Netherlands), different decisions regarding the optimal management strategy were found when different models were used. Without a significant family history (pedigree 1), the models all agreed that there is no indication to offer her mammographic screening before the age of 50. All models agreed that Counsellee A in pedigree 3 had at least a moderate LTR for developing breast cancer (≥17%). The models differed in their advice for Counsellee A in pedigrees 2, 4, 5 and 6, where the newer models (BOADICEA, Jonker Model, Claus-Extended Formula and Tyrer–Cuzick Model) had a high level of agreement. For Counsellee A in pedigree 2, two models, i.e. Gail-2 Model and BOADICEA Model, advised not to start early screening according to the UK guideline, while three models, i.e. Claus Model, Jonker Model, and Claus-Extended Formula, reached an estimate between the UK and Dutch threshold of moderate risk. The newer models agreed that Counsellee A in pedigree 3, 4, 5 and 6 had a moderate risk, while the older models also reached risks below the moderate threshold.

Using the guidelines with risk thresholds based on family history alone, for Counsellee B, the management strategies are somewhat different. In pedigree 1, without a significant family history of breast cancer, the Gail-2 Model and the Tyrer–Cuzick Model reached a moderate risk when the menstrual period had started at the age 11 and when her first child was born at age 30 or when she had had no children at all. The two models also agreed for most situations that Counsellee B had an indication for yearly mammography in nearly all other pedigrees, irrespective of the age of the first menstrual period or the age at first born child.

Discussion

In this study we report on breast cancer LTR estimates using several risk assessment models for two healthy counsellees with different risk factors included in six different pedigrees. When we compared the risk estimates of the different models with the thresholds for individual mammographic screening (≥17% LTR in UK and ≥20% LTR in the Netherlands), different decisions regarding optimal management strategies were found.

Table 3 Risk assessment for Counsellee B, given six different pedigrees and two different risk factors, applying the Gail-2 Model and the Tyrer–Cuzick Model

Pedigree 1		Gail-2 Model	Tyrer Cuzick
Menstrual period:	Age at first birth		
No information	No information	6.7%	12.8%
11	19	9.8%	12.1%
15	19	8.2%	10.6%
11	25	14.7%	15.4%
15	25	12.4%	13.5%
11	30	17.9%	18.3%
15	30	15.1%	16.1%
11	No child	14.7%	18.4%
15	No child	12.4%	16.2%

Pedigree 2		Gail-2 Model	Tyrer Cuzick
Menstrual period:	Age at first birth		
No information	No information	16.4%	20.4%
11	19	23.4%	19.3%
15	19	19.9%	17.0%
11	25	24.5%	24.4%
15	25	20.9%	21.5%
11	30	25.1%	28.6%
15	30	21.4%	25.4%
11	No child	24.5%	23.2%
15	No child	20.9%	20.5%

Pedigree 3		Gail-2 Model	Tyrer Cuzick
Menstrual period:	Age at first birth		
No information	No information	36.8%	24.1%
11	19	49.1%	22.8%
15	19	43.1%	20.2%
11	25	39.0%	28.6%
15	25	33.7%	25.4%
11	30	34.4%	33.5%
15	30	29.6%	29.8%
11	No child	39.0%	33.7%
15	No child	33.7%	30.1%

Pedigree 4		Gail-2 Model	Tyrer Cuzick
Menstrual period:	Age at first birth		
No information	No information	16.4%	22.2%
11	19	23.4%	21.0%
15	19	19.9%	18.6%
11	25	24.5%	26.5%
15	25	20.9%	23.4%
11	30	25.1%	31.0%
15	30	21.4%	27.6%
11	No child	24.5%	31.3%
15	No child	20.9%	27.8%

Pedigree 5		Gail-2 Model	Tyrer Cuzick
Menstrual period:	Age at first birth		
No information	No information	16.4%	23.1%
11	19	23.4%	21.9%
15	19	19.9%	19.3%
11	25	24.5%	27.5%
15	25	20.9%	24.4%
11	30	25.1%	32.2%
15	30	21.4%	28.7%
11	No child	24.5%	32.5%
15	No child	20.9%	28.9%

Pedigree 6		Gail-2 Model	Tyrer Cuzick
Menstrual period:	Age at first birth		
No information	No information	16.4%	19.8%
11	19	23.4%	18.7%
15	19	19.9%	16.5%
11	25	24.5%	23.6%
15	25	20.9%	20.9%
11	30	25.1%	27.8%
15	30	21.4%	24.6%
11	No child	24.5%	28.0%
15	No child	20.9%	24.8%

	Moderate risk
	High risk

On the first row the risks for Counselee A, with unknown personal risk factors, is given as a reference

Counsellee A in pedigree 1 represents a woman without a clinically significant family history of breast cancer. Her risk varied from 6.7% to 12.8%. The older models and methods, providing 6.7% (Gail-2 Model), 8.4% (Claus Model) and 9.4% (Claus Tables), were developed in the eighties and nineties, when the incidence of breast cancer was significantly lower than now-a-days. The four newer models have baseline risks more likely representing the current incidence of breast cancer in the USA and Western-European countries [45], with baseline risks varying from 10.1% to 12.8% at age 40. It is important for breast cancer risk assessment models that their estimated risks for a population represent the current overall population incidence. As the breast cancer incidence has risen over the years, it is likely that the older models underestimate the overall breast cancer incidence.

Counsellee A in pedigree 6 represents a woman with a family history of breast and ovarian cancer. Only the four newer models have incorporated ovarian cancer. It is therefore according to the expectation that these models, i.e. BOADICEA Model, Jonker Model, Claus-Extended Formula and Tyrer–Cuzick Model, yield higher estimates for this situation compared to the models that ignore ovarian cancer in relatives, i.e. Gail-2 Model, Claus Model and Claus Tables.

We have shown that information on the age of the first menstrual period and the age at first born child increases the estimated LTRs for developing breast cancer, except for the situation in which the counsellee had her first child at the age of 19 (Tyrer–Cuzick Model estimate). It can be expected that adding more information on risk factors to the counsellee will further increase these risk estimates,

and yearly mammography will then be advised more often if models including this information are used. One has to remember, however, that in this current situation the risk estimate of the counsellee reached a level above the 17% through adding personal factors into the model, while the screening thresholds from current guidelines are based on family history risks only (www.nice.org.uk/CG041). Remarkable in this respect are the risk estimates outcomes in our study for a counsellee without a significant family history and a first menstrual period at the age of 11 and the age at her first born child of 30 or when she had had no children at all. The Gail-2 Model and the Tyrer–Cuzick Model agreed in these situations and gave a LTR between 17.9 and 18.4% for which a yearly mammography is offered in the UK based on the threshold for moderate risk.

Interesting to note is that in the example of pedigree 5, which includes a sister, a paternal aunt and the paternal grandmother with breast cancer, large differences in risk estimates between the Claus Tables, i.e. 14.4%, and the Claus Model, i.e. 39.4%, were found. Although the Claus Tables were developed as summary tables of the Claus Model, the Tables apparently do not represent the Claus Model estimates in a very precise manner. The Claus Model is able to include all three family members into the risk estimate. The Claus Tables can only include two family members of this three generation breast cancer family.

For women at increased risk to develop breast cancer, surveillance and preventive measures may be provided as an attempt to decrease mortality. In this study we have evaluated the results in breast cancer risk estimates of seven different models or methods. All models base their risk estimates on the family history for breast cancer. In four models, the presence of ovarian cancer could be used, and two of the seven models also incorporate personal risk factors. The only situations in which similar advice to start screening was reached were for Counsellee A in pedigree 1 regarding no-screening and in pedigree 3 (a sister with breast cancer at 45 and a maternal aunt with breast cancer at 55 years) for screening. In the latter situation, all models reached at least a moderate risk, but three models (Gail Model, Claus Model and Claus Tables) even reached a high risk estimate for this counsellee. For clinical counsellors, however, women at the lowest and highest ranges of risk are usually not the problem for decisions regarding surveillance. Pedigrees that reach breast cancer risks in the group extremes, such as between 29% and 31% or around 17% or 20%, are the ones that make decision making hard. The models that we have tested in this study do not provide consensus in these matters. Another problem that we have encountered was that some of the models actually provide remaining life-time risks, thus from age 40 up to age 80 or 90 instead of full life-time risks (e.g. Tyrer–Cuzick and Gail Model). In the final risk overviews that these models provide, they use the term life-time risk and not remaining life-time risk. One may be confused by this. A problem with the remaining life-time risk strategy is that current guidelines have been formulated upon full life-time risks. Although an estimate of remaining life-time risk is more accurate for the individual woman, it feels unjust to relate this risk to current guideline thresholds. In the overview here provided the full life-time risks and remaining life-time risks do not differ that much, as the breast cancer risk for any woman is relatively low up to age 40; varying from 0.4% to 4.1%, depending on the different models and the varying pedigrees presented here (data not shown).

For women with the other pedigrees (Counsellee A with pedigree 2, 4, 5 or 6), the use of risk assessment models seems useful, as the decision regarding screening or no-screening is not self-evident. In these cases, objective decision support would make it possible to standardize clinical behaviour. The varying outcomes of the different models for an identical pedigree present the current problem for clinical practice. Clinical counsellors often depend on their years of experience by judging a pedigree. This experience, however, cannot be transferred to young, inexperienced, health care professionals. Evidence-based clinical behaviour is therefore of utmost importance, because it is reproducible and not coloured by clinical experience. Although each of the existing models shows limitations, the documented use of such a model will make the risk estimation process more uniform and reproducible.

When a decision should be made for the use of risk assessment models in clinical practice, several factors play a role. First, a model should be easy to use. Although, the Claus Tables are easy to use in clinical practice, these tables ignore much information from the pedigree, e.g. presence of bilateral breast cancer and ovarian cancer, so these Tables should not be recommended for use. Also Amir et al. [33] concluded that the Claus Model, among others, significantly underestimate breast cancer risk. The Claus-Extended Formula was developed to overcome these problems.

A second point is that the model should be validated. In validating a risk assessment model, the most important characteristics of risk model performance are calibration, discrimination, and accuracy [46]. Validation studies regarding these models have shown that the Tyrer–Cuzick Model as well as the BOADICEA perform well [33, 47, 48], although improvements are always possible.

A third point concerns the question which factors should be included in the preferred model. As it is widely acknowledged that personal risk factors may play a role in a person's breast cancer risk, it may be recommendable to use a model that includes these personal risk factors into the risk assessment. Familial factors have been acknowledged to be one of the most important for breast cancer with relative risks up to 6–8, but personal risk

factors such as atypical hyperplasia have been shown to also increase breast cancer risk considerable with a relative risk of 3–4 [2]. In addition, it can be argued that information regarding genetic modifiers such as CHEK2-1100delC and a number of SNP's should be also included in an optimal model [49, 50]. On the other hand, thus far, the LTRs related to these genetic modifiers and the interaction between these and personal risk factors are unknown, as is the interaction between the different personal risk factors. It is unlikely that the personal risk factors each have an independent impact on breast cancer risk. This problem makes it hard to include these factors into a risk assessment model that contains more than one breast cancer risk factor. However, the Tyrer–Cuzick Model proves to be a good example of a multiple factor model, as the validation study by Amir et al. showed [33]. They concluded that the Tyrer–Cuzick Model is the most consistently accurate model for prediction of breast cancer, among the models they tested.

Finally, a model should be up-to-date. The incidence of breast cancer is increasing, for that the LTRs for developing breast cancer are increasing. The occurrence of risk factors is also increasing. There is a trend that more women will have their first born child after the age of 30 and the age of the first menstrual period is decreasing. For that reasons, a model should be fit on the target population. Another option is to start yearly mammography for women aged 40–50 [51, 52]; the question for which women screening for breast cancer is indicated outside the population screening for breast cancer will become obsolete.

One has to keep in mind that the management strategies proposed in current guidelines have been formulated based on cancer family history alone, and are not based on the combination of family history and *personal risk factors* of the counsellee.

Our results show that it is recommendable to use one of the newer models. Older models underestimate the baseline life-time risk for breast cancer. Using a model including personal risk factors will increase insight in the variation in risk estimates. Therefore we conclude that the Tyrer–Cuzick Model and the BOADICEA Model seem a good choice for current clinical practice.

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Appendix 1: Literature search

In all search engines, the two concepts "Familial breast cancer" and "Risk models" are represented by different variations or permutations of relevant terms.

PubMed (1950–2006)

In PubMed, words or phrases without field descriptions are mapped automatically to the appropriate field descriptions such as title, abstract, MeSH (Medical Subject Headings), MaJR (Major Medical Subject Headings). The concepts are combined, using the following search strategy:

("familial breast cancer risk" OR ("breast cancer families" AND risk) OR ("breast cancer family" AND risk) OR ("risk assessment" AND "familial breast cancer")) AND ((risk[ti] AND (model[ti] OR assessment[ti]) OR (("Models, Statistical"[Majr] OR "Models, Genetic"[Majr]) AND "Probability"[Mesh]))) OR ("Breast Neoplasms/genetics"[Majr] OR (breast cancer AND ("Mass Screening"[MeSH] OR "Genetic Services"[MeSH] OR familial OR family OR families OR gene OR genes OR "Genetic Predisposition to Disease"[MeSH]))) AND ((risk[ti] AND (model[ti] OR assessment[ti]) OR (("Models, Statistical"[Majr] OR "Models, Genetic"[Majr]) AND "Probability"[Mesh])))

EMBASE (1980–2006)

In EMBASE, subject headings and free text words are used in combination. Subject headings are marked with '/' at the end of the specific term and are "exploded", i.e. the narrower subject headings are also selected automatically. The following field descriptions were used for free text terms: mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; ti = title. The concepts are combined, using the following search strategy:

(familial breast cancer risk.mp OR (breast cancer families AND risk).mp OR (breast cancer family AND risk).mp OR (risk assessment AND familial breast cancer).mp) AND ((risk.ti AND (model.ti OR assessment.ti) OR ((exp mathematical model/) AND exp risk/))) OR ((exp *Breast Cancer/AND genetic$.mp) OR (exp Breast Cancer/AND (exp genetic service/OR exp cancer screening/OR familial.mp OR family.mp OR families.mp OR gene.mp OR genes.mp OR exp multifactorial inheritance/))) AND ((risk.ti AND (model.ti OR assessment.ti) OR ((exp mathematical model/) AND exp risk/)))

Web of Science (1945–2006)

In the Web of Science, free text words are used in combination. Words preceded by TI are searched in the field title. Words preceded by TS are searched in the fields abstract, keywords, or title. The concepts are combined, using the following search strategy:

(((TS="risk assessment" AND TS="familial breast cancer") OR TS="familial breast cancer risk" OR

(TS="breast cancer families" AND TS=risk) OR (TS="breast cancer family" AND TS=risk)) AND ((TI=risk AND (TI=model OR TI=assessment)) OR (TS=model* AND TS=risk*))) OR (((TI="Breast Cancer" OR TI="breast tumor*" OR TI="breast tumour*" OR TI="breast carcin*" OR TI="breast neoplas*") AND (TS="genetic screen*" OR TS="cancer screen*" OR TS=famil* OR TS=gene OR TS=genes OR TS=predispos* OR TS=susceptib*)) AND ((TI=risk* AND (TI=model* OR TI=assessment)) OR (TS=model* AND TI=risk*))) OR ((((TI="Breast Cancer" OR TI="breast tumor*" OR TI="breast tumour*" OR TI="breast carcin*" OR TI="breast neoplas*") AND TI=genetic*)) AND ((TI=risk* AND (TI=model* OR TI=assessment)) OR (TS=model* AND TI=risk*)))

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