Breast Cancer Screening, Outside the Population-Screening Program, of Women from Breast Cancer Families without Proven BRCA1/BRCA2 Mutations: a Simulation Study

Catharina E. Jacobi,1 Nico J.D. Nagelkerke,2,3 J. (Hans) C. van Houwelingen,2 and Geertruida H. de Bock1,4

Departments of 1Medical Decision Making and 2Medical Statistics, Leiden University Medical Center, Leiden, the Netherlands; 3Department of Community Medicine, United Arab Emirates University, Al Ain, United Arab Emirates; and 4Department of Epidemiology and Biostatistics, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

Abstract

Purpose: We assessed the cost-effectiveness of mammography screening for women under the age of 50, from breast cancer families without proven BRCA1/BRCA2 mutations, because current criteria for screening healthy women from breast cancer families are not evidence-based.

Methods: We did simulation studies with mathematical models on the cost-effectiveness of mammography screening under the age of 50 with breast cancer family histories. Breast cancer screening was simulated with varying screening intervals (6, 12, 18, and 24 months) and screening cohorts (starting at ages 30, 35, 40, and 45, and continuing to age 50). Incremental costs of screening were compared with those of women ages 50 to 52 years, the youngest age group currently routinely screened in the nationwide screening program of the Netherlands, to determine cost-effectiveness. Sensitivity analyses were done to explore the effects of model assumptions. The cost-effectiveness of breast cancer screening for women over the age of 50 was not debated.

Results: The most effective screening interval was found to be 12 months, which, however, seems only to be cost-effective in a small group of women under the age of 50 with at least two affected relatives, including at least one affected in the first degree diagnosed under the age of 50. Significantly, early breast cancer screening never seemed to be cost-effective in women with only one affected first-degree or second-degree relative.

Conclusion: Annual breast cancer screening with mammography for women under the age of 50 seems to be cost-effective in women with strong family histories of breast cancer, even when no BRCA1/BRCA2 mutation was found in affected family members. (Cancer Epidemiol Biomarkers Prev 2006;15(3):429–36)

Introduction

Breast cancer is a common disease and is one of the leading causes of death in women. The lifetime risk of breast cancer is 10% to 11% in the Netherlands (1), and 13% to 14% in the U.S. (2). Most breast cancers are diagnosed at age 50 years or older, but about one-quarter of cases are diagnosed earlier (1).

The risk of breast cancer is increased by factors such as young age at menarche, older menopausal age, and null parity. Genetic predisposition, however, was found to be one of the most important risk factors (3-6). In ~20% of the individuals with breast cancer, a familial aggregation of breast cancer was found (7, 8), and in 5% to 10% of these cancers, this aggregation is explained by BRCA1/BRCA2 mutations (9). The lifetime risk of breast cancer in women who carry a BRCA1/BRCA2 mutation may be as high as 80% (e.g., refs. 6, 10-12).

In a growing number of countries, nationwide breast cancer screening programs are available for the general population for women of 50 years and older (13). Screening for breast cancer in all women under this age is considered cost-ineffective in most countries, primarily due to a lower incidence and lower sensitivity of mammography (13). Breast screening under the age of 50 in women from families with identified BRCA1/BRCA2 mutations on the other hand, is highly recommended and well accepted (e.g., refs. 14, 15), although not evidence-based. However, if no information is available on the presence of BRCA1/BRCA2 mutations in the family, women with relatives with breast cancer are also at increased risk of developing breast cancer (16). Consequently, breast cancer screening might also be advisable and cost-effective for such women under the age of 50.

We assessed the cost-effectiveness of mammography screening for women under the age of 50, from breast cancer families without proven BRCA1/BRCA2 mutations, using the incremental costs compared with costs and gains of the screening of all women ages 50 to 52 years in the Dutch nationwide breast cancer screening program. For this purpose, we assumed that this program, i.e., biannual screening of all women ages 50 to 75 years, is cost-effective.

Materials and Methods

Selection of the Study Population. A population of 1 million women ages 30 to 50 years was simulated using the Dutch demographic age structure (17). We simulated first- and second-degree relatives for these women using a lifetime approach, as described previously (18). In short, family structure was based on Dutch family structures and sizes over several generations (17). Using the Jonker genetic model I, breast cancer predispositions were assigned to families (19), so that the simulated breast cancer incidence reflected the observed incidence in the general population (1, 18). This approach enabled the linkage of incidence and familial clustering of breast cancer in the general population (18).
All simulated women with at least one first- or second-degree relative with breast cancer were used in this study. As we aimed to formulate screening recommendations for women from breast cancer families without proven BRCA1/BRCA2 mutations, we excluded all women with family histories associated with BRCA1/BRCA2 mutations, i.e., with bilateral breast cancer, ovarian cancer, and/or male breast cancer. We estimated the women’s lifetime risk of breast cancer, conditional on the absence of BRCA1/BRCA2 mutations (i.e., conditional lifetime risk; Appendix 1), using the Jonker model I (19). This approach, however, does not guarantee the exclusion of all BRCA1/BRCA2 carriers, or carriers of mutations of other cancer susceptibility genes, such as CHEK2-100delC (20) or ATM (21). In the Jonker model, all non-BRCA1/BRCA2 mutations and other familial risk factors have been grouped together into a single hypothetical susceptibility gene. The women were classified according to family history groups based on the number of affected relatives and the ages at diagnosis of these relatives. The estimated lifetime risks according to the Jonker model and according to the Claus model (3) are highly comparable, with a Spearman’s correlation coefficient of 0.87.

Mammography Screening Under the Age of 50. A simulation model for mammography screening was developed using all information currently available in the medical literature on sensitivity and specificity of mammography, tumor growth rates, cancer induction risk due to mammography radiation, and prognosis and survival after breast cancer diagnosis. An extensive description of all variables of the screening model can be found in Appendix 1. A summary can be found below. For mammography screening under the age of 50, we considered four cohorts with 5-year starting ages (30-50, 35-50, 40-50, and 45-50 years of age) and four screening intervals (6, 12, 18, and 24 months).

Values
- The sensitivity of mammography under the age of 50 was 64% (range, 22-82%) and 85% (range, 56-94%) over the age of 50 (22-24). The specificity of mammography was 0.967 to 0.996 under the age of 50 and 0.970 to 0.997 over the age of 50 (22, 25, 26).
- The median tumor volume doubling time (i.e., tumor growth) was 80 days under the age of 50 (95% confidence limits, 44-147) and 157 days over the age of 50 (95% confidence limits, 121-204; ref. 27).
- A two-view mammogram, i.e., two photos per breast, uses 4 mGy average radiation dose. The breast cancer induction risk due to mammography radiation was 0.0000165 under the age of 50, and 0.0000114 over the age of 50 (28).
- For calculation purposes, we divided patients with breast cancer into patients who would recover (cure) and those who would not recover from the disease (no cure). For no cure, the average remaining life expectancy was 5.1 years (29-31), and for the cured category: 0.52 – detection age) x 0.966, according to the remaining life expectancy for women ages 30 to 50 years (17).
- The survival rate of patients with breast cancer is higher among women with breast cancer diagnosed at older ages compared with diagnosis at younger ages (32). For women ages 30 to 50 years, the relative risk of dying from breast cancer is linearly, negatively, associated with age (17). We calculated a linear fit between ages and the relative risk of dying from breast cancer for women under the age of 50 compared with women over 50: (50 – detection age) x 0.0314 + 0.8835. For older women, no adaptation in survival rates was made.

Assumptions
- Screening causes a shift to finding tumors at earlier stages, leading to a 50% better survival rate among women with screen-detected breast cancer compared with women with clinically detected tumors (29). The proportion of women cured whose breast cancer was detected through screening was therefore higher than the proportion of women cured whose breast cancer was clinically detected.
- Women with a familial predisposition for breast cancer are at higher risk of radiation-induced cancer than women without such a predisposition (Appendix 1). This assumption has only been used in a sensitivity analysis.
- Hereditary and familial tumors have an underlying mechanism that causes unfavorable prognosis. We based this on the finding that tumors in BRCA1/BRCA2 carriers are, on average, larger-sized and of worse grade at diagnosis than tumors in individuals without BRCA1/BRCA2 mutations (Appendix 1). We included a worse prognosis up to 25% due to larger-sized and higher-graded tumors, based on the extent of the family history.
- The screening model showed the number of tumors found and missed, and the relative gain in life years, per 1,000 women screened.

Cost-Effectiveness of Screening Under the Age of 50
Quality adjusted life years. To adjust the relative gain in life-years for quality of life (QoL), we combined the changes in life expectancy with the expected changes in morbidity, according to de Koning et al. (33). We used a 10% reduction in QoL for women who would be cured from breast cancer, and a 50% QoL reduction for those not cured (Appendix 1). We assumed no effect of the screening process on QoL, if no cancers were detected (34).

Costs. Costs were based on current costs in the Netherlands (35), including the costs of a mammogram, the interpretation of the mammogram, and a related visit to the general practitioner. For additional tests, we included costs of biopsies. Costs were used independently of age.

Cost-effectiveness. We defined screening under the age of 50 as cost-effective if the costs of screening per life-year gained, per 1,000 screened women from a certain family history group, were equal or less than the screening costs per life-year gained among women from the general population ages 50 to 52 years. We determined cost-effectiveness of screening per 5-year age groups, i.e., 30 to 35, 35 to 40, 40 to 45, and 45 to 50 years of age. Costs in this study were incremental costs, and thus, relative costs compared with the older comparison group. These outcomes are, therefore, also applicable to other countries even if costs of screening would be different in those countries.

Sensitivity Analyses. To test the effect of assumptions in the simulation model, three independent sensitivity analyses were done. In each of these analyses, one assumption was tested, whereas the other values were similar to the main analysis.

Analysis 1. In this analysis, we omitted the correction factor regarding unfavorable prognosis due to larger-sized and worse-graded familial cancers, based on the fact that the medical literature showed no differences in survival after adjustment for prognostic variables such as histologic grade (Appendix 1).

Analysis 2. In this analysis, we omitted the two correction factors regarding unfavorable prognosis, i.e., the one due to larger-sized/worse-graded familial cancers and the one on young age at diagnosis.

Analysis 3. In this analysis, we tested the effect of increased sensitivity to radiation-induced breast cancer among women with a familial predisposition to cancer, based on the
assumption that women with BRCA1/BRCA2 mutations are at higher risk of radiation-induced breast cancer than women without such mutations (Appendix 1): an assumption that has been confirmed by several in vitro studies (36-38). Therefore, in this analysis, we assigned the excess tumor-induction risk to women depending on the extent of the familial aggregation of breast cancer instead of assigning this excess risk equally to all women in the population.

Results

Study Population. For this study, 216,320 simulated women with a family history of breast cancer were available. These women were stratified into family history groups based on the number of affected relatives and the ages at diagnosis of these relatives, and conditional lifetime risk of breast cancer per group were estimated (Table 1). This table shows that, for instance, a woman with two first-degree relatives with breast cancer of whom one was affected under the age of 50, and with one second-degree relative with breast cancer affected after the age of 50, has a lifetime risk of breast cancer of 27%.

Table 2. Tumors found per screening episode per 1,000 women screened over the complete period

<table>
<thead>
<tr>
<th>Second-degree relatives</th>
<th>Age(s) at diagnosis</th>
<th>First-degree relatives with breast cancer</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥50</td>
</tr>
<tr>
<td>0</td>
<td>not assessed</td>
<td>0.74</td>
</tr>
<tr>
<td>1</td>
<td>≥50</td>
<td>0.66</td>
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<tr>
<td></td>
<td>&lt;50</td>
<td>0.82</td>
</tr>
<tr>
<td>2+</td>
<td>≥50</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>&lt;50</td>
<td>0.84</td>
</tr>
<tr>
<td>1+ &lt; 50</td>
<td>0.87</td>
<td>0.74</td>
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<td></td>
<td>1.05</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>1.27</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>1.46</td>
<td>0.83</td>
</tr>
</tbody>
</table>

NOTE: Each 4 rows represent tumors found with 12-month screening intervals from 30 to 50, 35 to 50, 40 to 50, and 45 to 50 years, respectively.

*No individuals from the simulated population were classified into these cells.
Table 3. Screening recommendations based on sensitivity analyses

<table>
<thead>
<tr>
<th>Second-degree relatives</th>
<th>Age(s) at diagnosis</th>
<th>First-degree relatives with breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>≥50</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Sensitivity analysis 1 (a)</td>
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<td>50</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>≥50</td>
</tr>
<tr>
<td></td>
<td>2+</td>
<td>≥50</td>
</tr>
<tr>
<td>Sensitivity analysis 2 (b)</td>
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<td>50</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>≥50</td>
</tr>
<tr>
<td></td>
<td>2+</td>
<td>≥50</td>
</tr>
<tr>
<td>Sensitivity analysis 3 (c)</td>
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<td>50</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>≥50</td>
</tr>
<tr>
<td></td>
<td>2+</td>
<td>≥50</td>
</tr>
</tbody>
</table>

NOTE: (a) Main analysis without correction for worse prognosis due to size and grade. (b) Main analysis without correction for worse prognosis due to size, grade, and young age. (c) Main analysis with increased radiation sensitivity among women with a familial predisposition. Start of mammography screening at ages 30, 35, 40, 45 (12-month intervals), and 50 (24-month interval), respectively.

*Groups were empty; recommendations are based on surrounding cells.

high according to the European Guidelines of Mammography Screening (39). If screenings were done at 6-month intervals, more tumors would be identified by screening (i.e., >90%), at the expense of twice the dose of ionizing radiation per woman per year. Screening intervals of 18 and 24 months would result in a lower dose of ionizing radiation per woman per year, with substantially reduced numbers of screen-detected tumors (<50%), leading to an unacceptable number of interval cancers (39). Thus, we focused on the 12-month interval as the optimal screening interval for women under the age of 50.

Cost-Effectiveness of Screening Under the Age of 50. Table 1 presents the additional outcomes of the main screening analysis: mammography screening of women under the age of 50 from breast cancer families without proven BRCA1/BRCA2 mutations is cost-effective in women with at least two relatives with breast cancer, including a first-degree relative diagnosed before the age of 50. Hence, the woman with two first-degree relatives with breast cancer of whom one was affected under the age of 50, and with one second-degree relative with breast cancer affected over the age of 50, should receive annual mammography from age 45 onwards. Annual screening with mammography was found to be cost-effective in women with a lifetime risk of breast cancer of 27% and higher from age 45, for women with a lifetime risk of 32% and higher from age 40, for women with a lifetime risk of 38% and higher from age 35, and for women with a lifetime risk of 47% and higher from age 30. In this main analysis, a Quality Adjusted Life Years (QALY) correction was included. The outcomes would, however, be similar if the QALY correction had been excluded, as correcting for QALYs had no effect on the recommendations.

Sensitivity Analyses

Analysis 1. Assuming that familial breast cancers did not have a worse prognosis than sporadic tumors. The survival of women with breast cancer increases when the adjustment for unfavorable prognosis is omitted. Breast cancer screening would more often be in favor of screening women under the age of 50, at lower risk of breast cancer than is the case in our main analysis, i.e., by at least 24% (sensitivity analysis 1, Table 3).

Analysis 2. Assuming that young age and/or familial breast cancers did not have a worse prognosis than sporadic tumors. The survival of women with breast cancer increases when both these adjustments for unfavorable prognosis are omitted. Breast cancer screening would more often be in favor of screening women under 50, at lower risk of breast cancer than is the case in our main analysis, i.e., by at least 24% (sensitivity analysis 2, Table 3).

Analysis 3. Radiation-induced tumor risk assigned to women with a familial or hereditary predisposition to cancer. This analysis shows that more gain in life-years is needed to compensate for the years lost due to induced tumors among women with a familial predisposition. In this analysis, breast cancer screening is less often in favor of screening women under the age of 50. Women should have a stronger breast cancer family history than is the case in our main analysis (Table 1), i.e., women with lifetime risks of 32% and higher ought to be screened from age 45, and from age 40 with lifetime risks of at least 47% (sensitivity analysis 3, Table 3).

Discussion

We explored the cost-effectiveness of breast cancer screening in women under the age of 50, with a family history of breast cancer, using a simulation analysis applying the Jonker model (19). On the basis of these simulations, recommendations for early breast cancer screening have been suggested (Table 1). These recommendations are based on simulation models that include current insights of screening practice, genetic etiology of breast cancer, and the consensus that comprehensive biannual breast cancer screening with mammography from the age of 50 is cost-effective. As early breast cancer screening...
(i.e., <50 years old) is generally accepted in women from families with BRCA1/BRCA2 mutations, we focused on women from breast cancer families without proven BRCA1/BRCA2 mutations. Our results show that women with at least two relatives with breast cancer, including at least one affected first-degree relative diagnosed before the age of 50, might be eligible for screening before age 50.

Breast cancer risk assessment with the Jonker model (19) showed that many women with relatives with breast cancer have a higher risk of breast cancer than the 10% to 14% average population lifetime risk in Western countries (1, 2). The Jonker model has been fit on the population incidence of breast cancer, and it shows, in accordance with empirical evidence (9, 40), that mutations on the BRCA1/BRCA2 locus account for a small proportion of breast cancer in the population.

In a previous study, we estimated that ~35% of women ages 30 to 50 years in the general population have at least one first-degree or one second-degree relative with breast cancer (18), which is in line with other studies (16). According to current Dutch guidelines of early screening, about one-third of these women should receive early breast cancer screening starting at age 35 (41). According to our analysis, only a very small part of this group of women from non–BRCA1/BRCA2 breast cancer families would be eligible for early breast cancer screening. Our screening recommendations are more stringent than current screening guidelines (40-42). Although these current guidelines recommend annual mammography and breast examination from age 35 for both women with only one affected first-degree relative diagnosed under the age of 50 and for women with only second-degree relatives affected (i.e., ≥2) diagnosed under the age of 50 (41), these women are not eligible for early breast cancer screening according to our screening model. The breast cancer risk of these women, which is based on their family history, is too low to justify early breast cancer screening, given the assumptions in the model. These family histories, however, are very common in the general population. Although we used a simulated population based on the Dutch population, we believe that our results would not be much different if we would base the outcomes on populations of other Western countries.

We found that breast cancer screening under the age of 50 should not be done with screening intervals of 18 or 24 months, as the incidence of interval tumors would be too high. Corresponding to the tumor growth rates found by Peer et al. (27), other authors have also suggested that breast cancer screening under the age of 50, should be offered at least at 12-month intervals (5, 43, 44). We concur with this recommendation. Moreover, we showed that screening at 6-month intervals results in even higher tumor detection rates compared with screening at 12-month intervals, but also results in a higher risk of radiation-induced breast cancer (data not presented). The gain in tumor detection at 6-month screening intervals is, however, not that much higher than screening at 12-month intervals and does not justify the shorter interval and higher health care costs. Screening at 12-month intervals results in acceptable tumor detection rates with half the costs and half the dose of radiation. This latter point is particularly important, as we are dealing with young women. Young individuals are found to be more sensitive to radiation than older women (28, 45). Moreover, in vitro studies have shown that the cells of BRCA1/BRCA2 mutation carriers are more sensitive to radiation, independent of age. We focused on young women without proven BRCA1/BRCA2 mutations, but with a familial and probably genetic susceptibility to cancer. It seems, therefore, reasonable and prudent to assume that these women are also more sensitive to radiation-induced cancer. Screening with ionizing radiation should include as low a dose as possible, and with cancer detection as high as possible. Therefore, mammography at 12-month intervals should be preferred over 6-month intervals. Moreover, if it seems that women with a familial predisposition to cancer indeed have increased sensitivity to radiation-induced breast cancer, the recommendations according to sensitivity analysis 3 would apply.

Some limitations of this study should be mentioned. As the presented study is a simulation study, we included values and estimates that are presented in the medical literature. We discuss screening of women at increased risk of breast cancer. Some of the values and estimates may be correct for women from the general population, but may be different in such a specific group of women. We are unable to determine whether mammography (e.g., sensitivity and specificity of mammography) is different in our target group compared with women with non–BRCA1/BRCA2 breast cancer families. However, we believe that our results would not be much different if we would base the outcomes on unequivocal empirical data (32). Part of this difference may be due to differences in large numbers of clinically detected tumors in younger women compared with screen-detected tumors in older women. In sensitivity analysis 2, we omitted both the worse prognosis for young age at diagnosis and the worse prognosis due to larger-sized and worse-graded tumors, whereas sensitivity analysis 1 deals only with the latter. Sensitivity analysis 2 shows that, although the outcomes of screening are more favorable compared with sensitivity analysis 1 (data not shown), the screening recommendations only differ on one point. Women with one first-degree relative affected under the age of 50 combined with at least two affected second-degree relatives, of whom at least one was diagnosed under the age of 50, should be screened from the age of 30 instead of starting screening at age 35. We also included age-dependent sensitivity and specificity in our model. The values differed between the young age group (<50 years) and the older age group (≥50 years). Previous research has found these differences (e.g., refs. 24, 27), which were explained by differences in menopausal state and breast density between younger and older women (e.g., refs. 48, 49).

We feel, therefore, that it was justified to use the age of 50 as a sort of switch point between these values. However, in the model, this switch point is more gradual than might be expected as we used a wide range of these values, i.e., a sensitivity of mammography under the age of 50 varying from 22% to 82% and over age 50 from 56% to 94% and a specificity of mammography under the age of 50 varying from 0.967 to 0.996, and over age 50 from 0.970 to 0.997.

Screening with mammography was the focus of our analysis. Currently, magnetic resonance imaging has gained much attention as an alternative screening device, particularly in women with BRCA1/BRCA2 mutations. A large advantage of magnetic resonance imaging is the absence of any potential tumor induction due to ionizing radiation. If future research would show that women from non–BRCA1/BRCA2 breast cancer families have the same increased sensitivity for radiation-induced cancer as women from BRCA1/BRCA2 breast cancer families, it might be possible to recommend...
magnetic resonance imaging screening in all young women with a family history to prevent breast cancer induction due to mammographic radiation.

In the last decade, referrals to genetic departments have increased rapidly in all developed countries (50) and many BRCA1/BRCA2 DNA tests have been done. In the coming years, health care providers will more often be confronted with women with family histories that will involve BRCA1/BRCA2 test results. One should remember, however, that the absence of BRCA1/BRCA2 mutations in affected relatives does not rule out a genetic breast cancer predisposition in that family. It would seem key that women from families with a high prevalence of breast cancer, but without identified BRCA1/BRCA2 mutations, receive proper risk estimations and are followed-up carefully at specialized centers.

Studies on screening women of 50 years and older have shown a mortality reduction in their target age groups (e.g., refs. 51-53), but a mortality reduction in young women due to screening has not been observed in a clinical setting. Direct empirical evidence is lacking. It would seem essential to determine empirically whether screening under the age of 50 leads to a true mortality reduction and a gain in life expectancy. Furthermore, current screening recommendations, even for women with detected BRCA1/BRCA2 mutations, are not evidence-based (5). Our study shows that breast cancer screening in women apparently at high-risk is not necessarily cost-effective. It seems prudent that screening practices outside population screening programs should be evaluated within trial settings. Thus, healthy women with a high lifetime risk of breast cancer should be included in a prospective study to identify women who will really benefit from screening. Until new evidence is available, we conclude that annual breast cancer screening with mammography is cost-effective in women under the age of 50, from non—BRCA1/BRCA2 families, with at least two breast cancer cases, including at least one affected first-degree relative who was diagnosed before the age of 50.

Appendix

A.1 Estimation of Lifetime Risk and Conditional Lifetime Risk According to the Jonker Model

The estimation of a woman’s lifetime risk of breast cancer according to the Jonker model I is based on estimating the probabilities of carrying mutations on each of three genes: BRCA1, BRCA2, and BRCAu, given a woman’s family history of breast and ovarian cancer in first- and second-degree relatives. Table 1 presents the penetrance functions of the lifetime risk up to age 80 for the three genes and that of sporadic breast cancer are as follows. BRCA1, 0.96 × n (age, 53.0, 16.5); BRCA2, 1.00 × n (age, 58.3, 13.8); BRCAu, 0.48 × n (age, 56.3, 17.2); and non-carriers (sporadic), 0.08 × n (age, 66.3, 14.9), where n (x, y, z) denotes the normal cumulative distribution with x as age, y as the mean, and z as the SD (19). For example, based on her family history, the probability of carrying a mutation on BRCA1, BRCA2, and BRCAu for a particular woman is estimated as: 0.007930, 0.005141, and 0.467050, respectively. Using the abovementioned functions, her lifetime risk is estimated at 0.2515, i.e., [0.007930 × 0.96 × n (80, 53.0, 16.5)] + [0.005141 × 1.00 × n (80, 58.3, 13.8)] + [0.467050 × 0.48 × n (80, 56.3, 17.2)] + 0.08 × n (80, 66.3, 14.9). If we estimate this woman’s lifetime risk, conditional on the absence of BRCA1/BRCA2 mutations, it would be estimated at 0.2427, i.e., [0.467050 / 0.467050 + 0.519897] × 0.48 × n (80, 56.3, 17.2) + [0.519897 / 0.467050 + 0.519897] × 0.08 × n (80, 66.3, 14.9).

In this case, the estimated lifetime risk and conditional lifetime risk hardly differ, as the woman’s family history does not include specific characteristics associated with BRCA1 or BRCA2 mutations, such as the presence of bilateral breast cancer, ovarian cancer, and/or male breast cancer.

A.2 Literature Searches Regarding Input Values for the Model of Cost-Effectiveness of Screening

Sensitivity and specificity. We did a systematic search in MEDLINE with the following strategy: [breast cancer (ti) AND (age-specific OR age specific) AND (sensitivity OR specificity) AND screening (tw) AND (mammography OR mammographic) AND Human (MeSH)], up to December 2003, which yielded 18 articles. Of these, three articles could be used on the sensitivity (22-24) and two on the specificity (22, 25) of mammography, which could also be partly adapted from the National Evaluation Team Breast Cancer Screening of the Netherlands (26). The sensitivity of mammography was lower in women under the age of 50 (i.e., 64%, varying from 22% to 82%) than in women ages 50 to 69 years (i.e., 85%, varying from 56% to 94%). The specificity of mammography screening under the age of 50 was found to be 0.967 to 0.996 and over age 50 it was 0.970 to 0.997.

Tumor growth. We did a systematic search in MEDLINE with the following strategy [growth rate AND (age-specific OR age-dependent) AND breast cancer]. Ten articles were identified, of which one provided detailed information on tumor growth rates (27): the median volume doubling time of the primary breast cancers diagnosed in women ages 50 to 70 years was 157 days (95% confidence limits, 121-204 days). This was significantly longer than in women younger than 50 years of age at diagnosis (80 days; 95% confidence limits, 44-147 days).

Radiation. In the model, we used a two-view mammogram with a 2 mGy average dose per mammogram, leading to 4 mGy radiation per two-view mammogram (i.e., two mammograms of the same breast). We assumed that the breast cancer induction risk was equal to the average population risk with an age dependency: 0.0000165 in women under the age of 50 and 0.0000114 in those over 50 (28). A MEDLINE search was done to find information on the risk of tumor induction due to radiation in women at increased risk of breast cancer. We used the following strategy: ["Breast Neoplasms" (MAJR) AND (BRCA OR hereditary OR familial)] AND [radiation AND breast cancer]. Ten articles were identified, of which one provided detailed information on tumor growth (80 days; 95% confidence limits, 44-147 days). We did a systematic search in MEDLINE with the following strategy: [breast cancer (ti) AND (age-specific OR age-dependent)] AND [radiation AND breast cancer] AND (mammography or mammographic). The search was limited to articles in English between 1993 and 2003, and relating to humans of the female gender. It revealed five articles (28, 54-57). These studies showed that women who are susceptible to breast cancer due to a genetic mutation are at higher risk of radiation-induced breast cancer than women who do not carry such a mutation.

Prognosis and survival. Screen-detected breast cancers were found to have a 50% better survival rate than clinically detected cancers (29). Furthermore, we divided patients into those who would recover (cure) and those who would not recover from the disease (no cure). For no cure, we calculated an average remaining life expectancy of 5.1 years (29-31), and for the cured category, we assumed a remaining life expectancy of: (80.52 – detection age) × 0.966, which closely matches the remaining life expectancy for women ages 30 to 50 years (17). There is empirical evidence that, in general, the survival of patients with breast cancer is higher at older detection ages (32). As for women ages 30 to 50 years, the relationships between relative risk of dying from breast cancer and age seem to be linear (17), we calculated a linear fit between ages and cure rates for women under the age of 50. This yielded a relative risk of (50 – detection age) × 0.0314 + 0.8835. For older women, no adjustment in survival rates was made. In the literature, we searched for differences in prognostic factors and survival between individuals with and without a genetic susceptibility to breast cancer.

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6 Teeuwisse W, Geleijns J. Average glandular dose (AGD) per mammogram in 11 Dutch hospitals. Department of Radiology Leiden University Medical Center, the Netherlands; personal communication, September 1, 2003.

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We searched MEDLINE with: “Breast Neoplasms” (MAJR) AND BRCA* combined with the specific filter of prognostic studies, and systematic reviews, and limited it to articles in English with an abstract published from 1995 to 2001. This yielded five reviews (58-62). None of the reviews included pooled analyses of study outcomes, and thus, the included original articles were retrieved and examined. In addition, a second search was done to identify similar original articles that were published after the conduction of the reviews. The MEDLINE search was similar, but without the filter for systematic reviews and only for articles published in 2000 and 2001. All articles had to meet the following criteria: (a) provide information on tumor size, lymph node involvement, or histologic grade of breast cancers; and (b) point estimates and measures of variability or frequencies are presented for at least one of the relevant variables; or (a) provide information on breast cancer-specific or overall survival; and (b) hazard ratios or survival percentages are presented. The reviews provided 20 articles (63-82) and the second search provided five articles, of which only one was not yet identified through the reviews (83).

These articles showed no clear difference in lymph node involvement between genetically susceptible individuals and individuals without this susceptibility, but they showed that tumors in genetically susceptible individuals tend on average to be larger and clearly more often of worse grade at diagnosis than tumors in individuals without this proven genetic susceptibility. Therefore, we assumed that hereditary or familial tumors have an underlying mechanism that causes unfavorable prognosis, and we included a correction factor for unfavorable prognosis in the screening model (i.e., up to 25% worse prognosis based on the extent of the family history). Furthermore, after correction for prognostic factors, both breast cancer–specific and overall survival was, according to these studies, on average, similar in both groups.

QALYs. To adjust the gain in life years for QoL, we combined the changes in life expectancy with the expected changes in morbidity as described by de Koning et al. (33). We assumed that the QoL among women who would be cured from breast cancer would be reduced by 10% due to sequelae of the initial treatment, concerns about recurrent cancer, etc., thus, a QALY value of 0.90 was attained, where 1.00 refers to the woman’s health before screening. For those who would not be cured, we assumed a linear decline in QoL from 1 to 0, i.e., each residual life-year has, on average, a QALY of 0.50. These utilities were based on a large governmental study as published by Stouthard et al. (84). We assumed no effect of the screening process on QoL, if no cancers were detected, as was found by Rijnsburger et al. (34).

A.3 Program for Screening Simulation

Simulation was carried out using a specially written program. With this program, first, 100,000 women of each family history group were each randomly assigned to one of the four genetic groups (BRCA1, BRCA2, BRCAu, noncarrier) according to the probability of belonging to each of these groups, conditional on their family history of breast cancer. Second, for each woman, it was randomly decided whether she would develop breast cancer or not, depending on the penetrance function in the specific genetic group. If a woman would develop breast cancer, an age of onset was randomly generated with normal distribution. Third, for each of the breast tumors, the age at which the tumor would be clinically detected was calculated, taking the age of onset into account. The preclinical phase (i.e., the time between onset and clinical detection) depended on the tumor volume doubling times, as described earlier, which had a log-normal distribution. Fourth, for each of the screening episodes, we simulated whether a tumor would be detected depending on the sensitivity of mammography screening in the specific age group. For a tumor to be detected, the screening episode had to take place between tumor onset age and the clinical detection age. The number of tumors found and missed, the age at detection, and the relative size of each detected tumor was registered within each family history group. Output from the simulation program was further analyzed to calculate the relative gain in life-years by history group, and to compare costs per life-years gained to the marginal costs per life-years gained due to screening in women ages 50 to 52 from the general population.

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Breast Cancer Screening, Outside the Population-Screening Program, of Women from Breast Cancer Families without Proven BRCA1/BRCA2 Mutations: a Simulation Study

Catharina E. Jacobi, Nico J.D. Nagelkerke, J. (Hans) C. van Houwelingen, et al.


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