The assessment of genetic risk of breast cancer: a set of GP guidelines

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Background. Assessing a genetic risk for developing breast cancer is not an easy task for a GP. Current expert guidelines for referring and counselling women with a family history positive for breast cancer are complex and difficult to apply in general practice, and have only two strategies (to refer or not to refer for genetic counselling), giving no guidance for the GP on the management of women with a moderately increased risk of familial breast cancer.

Objectives. We aimed to develop a set of simple practical guidelines for use in primary care for assessing risk and advising women with a positive family history in general practice and aimed to explore its performance.

Methods. Based on a consensus meeting of the Leiden working party of hereditary tumours, the GPs of a university-related health care centre developed a set of GP guidelines to assess risk and advise women with a family history positive for breast cancer in general practice. The GP guidelines include four therapeutic strategies (reassuring, starting surveillance, starting surveillance and contacting a family cancer clinic, referring to a family cancer clinic). Its performance was tested in 67 patients whose pedigrees were available together with the risk assessment of a clinical geneticist using Claus’ tables as a gold standard. The gold standard was dichotomized regarding (i) referral to a family cancer clinic and (ii) surveillance. Two existing expert guidelines were similarly compared.

Results. Regarding referral to a family cancer clinic, the GP guidelines were very specific, whereas the expert guidelines were more sensitive. Regarding surveillance, the GP guidelines were very sensitive, whereas the expert guidelines were very specific. The total number of misclassified patients was lowest when using the GP guidelines, and higher when using the expert guidelines.

Conclusions. The GP guidelines provide a simplification of current guidelines. Before using them on a larger scale, more testing and refining are needed to increase their sensitivity regarding a referral to a family cancer clinic and their specificity regarding surveillance. They incorporate a role for the GP in the care for women with a family history positive for breast cancer with a moderately increased risk.

Keywords. Breast cancer, familial cancer, genetic counselling, genetic risk, GP guidelines.

Introduction

Breast cancer is a common disease among women. The lifetime risk of breast cancer is about 1 in 12 women in the UK, 1 in 10 in The Netherlands and 1 in 8 in the USA. The majority of the women are affected in the peri- or postmenopausal years: the population risk for women of developing breast cancer before the age of 30 years is about 1 in 4878, and for women of developing breast cancer between the ages of 50 and 60 years is about
1 in 78. Mutations in BRCA1 and BRCA2 genes give an inherited predisposition to breast and ovarian cancer. About 5% of the breast cancer cases are thought to be due to such mutations. The lifetime risk of cancer in mutation carriers is high, and women are generally affected at younger ages.

The recent detection of these cancer genes has led to much media attention. As a consequence, women with one or more relatives with breast cancer may visit their GP to seek advice on their own personal risk for breast cancer. Assessing a genetic risk for developing breast cancer is not an easy task in general practice. The best current risk assessments presently available may come from a clinical geneticist using Claus’ tables. However, in general practice, no such expertise is (readily) available.

To solve this problem, Claus’ tables have been translated and simplified into guidelines for referring and counselling women with a family history positive for breast cancer (further referred to as expert guidelines). Two sets of recently published guidelines, the Evans’ guidelines and the Dutch South West Cancer Centre (SWCC) guidelines are presented in Figures 1 and 2. Both sets of guidelines have limitations in their use in general practice. They are still complex and difficult to apply. They have only two strategies (to refer or not to refer for genetic counselling), and provide no guidance for the

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**FIGURE 1** Guidelines for consultation or referral to a family cancer clinic according to Evans et al.

**Reasons for referral**

- Mother or sister developed breast cancer before the age of 40.
- Mother or sister developed breast cancer before age of 50, and another close relative on same side of family developed cancer of breast, ovary, colon, or endometrium, or a sarcoma before the age of 65.
- Mother or sister developed breast cancer when aged 50–65, and one other closer relative on same side of family developed cancer of breast, ovary, colon, or endometrium, or sarcoma before the age of 50.
- Mother or sister developed double primary cancer (of the breast and any of ovary, colon or endometrium, or a sarcoma); at least one of the tumours occurred before the age of 50 and the breast cancer occurred before the age 65.
- Dominant history of breast cancer (four or more cases of breast or ovarian cancer, or both, or same side of family at any age).
- History of related malignancy in mother or father (cancer of colorectum, ovary or endometrium, or sarcoma before the age of 50) and at least one of the first-degree relatives developed breast cancer before the age of 50.
- Two or more cancers or related types (breast, ovary, endometrium or a sarcoma) in close relatives on father’s side, but not necessarily including fathers, with one cancer diagnosed before the age of 50.

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**FIGURE 2** Guidelines for consultation or referral to a family cancer clinic according to the Dutch South West Cancer Centre (Oosterwijk and Klijn)

**Reasons for referral**

- Three or more close relatives with breast and/or ovarian cancer at any age on the same side of the family.
- Two or more cancers of related types (breast, ovary, colorectum, prostate, endometrium, or sarcoma) in close relatives on the father’s side, but not necessarily including the father (one cancer diagnosed before the age of 50).
- Mother or sister developed double primary cancer: breast cancer before the age of 65 and ovary, colorectum, endometrium, or sarcoma (at least one tumour before the age of 50).
- Mother or sister with breast cancer before the age of 50 and another close relative on the same side with sarcoma or breast, ovary, colorectum, or endometrium cancer before the age of 65.
- Mother or sister with breast cancer before the age of 65 and another close relative on the same side with sarcoma or breast, ovary, colorectum, or endometrium cancer before the age of 50.
- Mother or sister with breast cancer before the age of 40.
- Chronic psychological distress by frequent occurrence of cancer in the family.
GP on the management of women with a moderately increased familial breast cancer risk.

In this paper we present a set of guidelines for counselling and referring women with a family history positive for breast cancer in primary care which is simple and practical and which defines four strategies (further referred to as GP guidelines). Its performance was tested in a set of patients where pedigree information was available, with the risk assessment of a clinical geneticist using Claus' tables taken as a gold standard. In the same patient set we evaluated the performance of the two previously mentioned sets of expert guidelines, and compared their performance with that of the GP guidelines.

### Method

**Development of a set of GP guidelines**

Based on a consensus meeting of the Leiden working party of hereditary tumours, the GPs of the university-linked primary health-care centre developed a set of consensus guidelines for advising women with a family history of breast cancer in general practice (see Figure 3). It is a simplification of current guidelines for referral of women with a family history of breast cancer, and the risk assessment of a clinical geneticist using Claus' tables. It includes the two important variables of closeness of relation (first and second degree), and age of onset of the breast cancer (aged under 50 years and aged 50 years and over). It divides relatives with breast cancer into four groups: first degree, age of onset under the age of 50 years; second degree, age of onset under the age of 50 years; first degree, age of onset at the age of 50 years and over; and second degree, age of onset at the age of 50 years and over. The guidelines lead to the following strategies: (i) reassure; (ii) start surveillance (monthly breast self-examination, palpation by a GP every 6 months and yearly mammography); (iii) start surveillance and contact (by telephone) a family cancer clinic for discussing the patient and (iv) refer to a family cancer clinic. An addition to the guidelines is to contact (by telephone) a family cancer clinic or consultant clinical geneticist to discuss every patient in the case of ovarian cancer in the family.

**Evaluation of the GP guidelines**

To evaluate the GP guidelines, we used a set of patients of whom information on pedigrees was collected in general practice. In our university-linked primary health care centre, female patients without breast cancer, between 15 and 50 years of age, who consulted their GP for advice between April 1994 and July 1995 about their risk of developing breast cancer because of a positive family history regarding breast cancer (n = 81) were asked to participate in a study. Sixty-seven of them complied, and for each case of breast cancer in the family, information.
was gathered by a researcher of the Department of General Practice on the following topics: age of onset, family relationship, bilaterality and breast cancer mortality. Additional information on other cancers, especially ovarian cancer, was also recorded. All data were based on family history only; no medical records were checked.

For each patient a family tree was drawn. These family trees were reviewed by a clinical geneticist who assessed each woman’s risk, on the basis of the tables by Claus, taking into account all available data. Based on these risk estimates, the clinical geneticist divided the family trees into three groups according to the relative breast cancer risk. The first group had a highly increased familial breast cancer risk \((RR \geq 3)\), the second a moderately increased familial breast cancer risk \((2 \leq RR < 3)\) and the third a mildly increased familial breast cancer risk \((RR < 2)\). A description of the relative risks for these patients was reported elsewhere in more detail: about a quarter of the sample group \((n=18)\) had a moderately increased familial breast cancer risk \((2 \leq RR < 3)\), and another quarter of the sample group \((n=17)\) had a highly increased familial breast cancer risk \((RR \geq 3)\).

The GP guidelines include therapeutic strategies instead of RRs, so these RRs were linked to therapeutic strategies, based on current practice in family cancer clinics. An \(RR \geq 3\) is often taken as a threshold for considering further genetic assessment, including DNA testing.

An \(2 \leq RR < 3\) is often taken as a threshold for surveillance. Surveillance may include: monthly breast self-examination, palpation by GP every 6 months and mammography once a year. An \(RR < 2\) is often used to imply that special interventions will not be cost-effective.

In the analysis, the risk assessment of a clinical geneticist using Claus’ tables was taken as a gold standard, including three categories: \(RR < 2\); \(2 \leq RR < 3\); \(RR \geq 3\).

The GP guidelines, the Evans’ guidelines (see Figure 1) and the SWCC guidelines (see Figure 2) were taken as tests. In the first step of the analysis, data were classified. In the second step of the analysis, the gold standard was dichotomized regarding (i) referral to a family cancer clinic \((RR \geq 3\) versus \(RR < 3\)), and (ii) surveillance \((RR \geq 2\) versus \(RR < 2\)). Sensitivity and specificity were calculated. In the third step, the total number of misclassified patients was calculated for the three guidelines.

Results

If the GP guidelines had been used, nine out of 67 (14%) patients would have been referred to a family cancer clinic, whereas in four (6%) patients, surveillance would have started, while they were discussed with a clinical geneticist from a family cancer clinic. This might have resulted in further referral. For 29 (43%) patients there was an indication to start surveillance according to the GP guidelines. If the Evans’ guidelines had been used, 25 patients (37%), and in the case of the SWCC guidelines 28 patients (42%), would have been referred to a family cancer clinic (see Table 1).

Referral to a family cancer clinic

See Table 2. Regarding referral to a family cancer clinic, the specificity of the GP guidelines was 100%, indicating that there were no false-positive referrals. The sensitivity was 76%, indicating that four patients were missed for a referral to a family cancer clinic. These four patients were high-risk women (two women with a mother or sister who developed double primary breast cancer before the

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<td>RR ≥ 3</td>
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<tr>
<td>Evans’ guidelines</td>
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<td>SWCC guidelines</td>
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a Three or more close relatives with breast and/or ovarian cancer at any age on the same side of the family (3).
b Mother or sister developed breast cancer between the age of 40 and 50 years, whereas there were fewer than five female relatives (first and second degree in the same side of the family) (7).
c Mother or sister developed double primary cancer before the age of 50 years (2). Three or more close relatives with breast cancer at any age on the same side of the family (2).
d Mother or sister developed breast cancer between the age of 40 and 50 years, whereas there were five or more female relatives (first and second degree in the same side of the family) (7).
age of 50 years, and two women with three or more close relatives with breast cancer at any age on the same side of the family). The specificity of the expert guidelines was 78%, indicating that there were false-positive referrals. These concerned 11 women with a moderately increased risk that would have been referred to a family cancer clinic. The sensitivity of the Evans’ guidelines was 82%, indicating that three high-risk patients were missed for a referral to a family cancer clinic. These three patients concerned three women with three or more close relatives with breast and/or ovarian cancer at any age on the same side of the family. The sensitivity of the SWCC guidelines was 100%, indicating that no one was missed for a referral to a family cancer clinic.

**Surveillance**

See Table 3. Regarding surveillance, the sensitivity of the GP guidelines was 100%, indicating that no patients were missed for surveillance. The specificity was 78%, indicating that there were false positives. Seven women with a mildly increased familial breast cancer risk got surveillance instead of reassurance. The specificity of the expert guidelines was 100% (both guidelines). The sensitivity of Evans’ guidelines was 71% and the sensitivity of the SWCC guidelines was 80%, indicating that there were false negatives. The seven patients with a moderately increased familial breast cancer risk that were missed for follow-up when using the Evans’ or SWCC guidelines were all women from small families with one mother or sister who developed breast cancer between the ages of 40 and 50 years.

The total number of misclassified patients was lowest when using the GP guidelines (11 patients). Use of Evans’ guidelines gave a misclassification of 21 patients in total, while the SWCC guidelines gave a misclassification of 18 patients in total.

**Discussion**

The increasing emergence of knowledge about a genetic predisposition to breast cancer in a minority of families raises practical problems for the GP. The GP is concerned not to miss early diagnosis in high-risk patients, but is equally concerned not to raise concerns in the majority of women for whom surveillance or genetic testing will bring no health gain. This study presents a set of simple practical guidelines for use in primary care for assessing risk in women with a positive family history in general practice and explores its performance in 67 patients, with the risk assessment of a clinical geneticist using Claus’ tables as a gold standard. Regarding referral to a family cancer clinic, the GP guidelines were very specific but less sensitive. The expert guidelines were more sensitive but less specific. Regarding surveillance, the GP guidelines were very sensitive but less specific. The expert guidelines were very specific but less sensitive. The total number of misclassified patients was lowest when using the GP guidelines.

By using the GP guidelines, four women with a highly increased familial breast cancer risk were not referred to a family cancer clinic. The addition of information regarding the risk of double primary breast cancers would have increased the sensitivity of the GP guideline regarding referral: in this case two women having a highly increased risk would have been recognized as such. Additionally, the addition of information regarding the risk of having three or more close relatives with breast cancer at any age on the same side of the family would have increased the sensitivity of the GP guidelines. When using the GP guidelines, surveillance was started in seven women with a mildly increased familial breast cancer risk while there was no indication. Adding the point that ‘a mother or sister with breast cancer between the age of

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<th>RR ≥ 3 versus RR &lt; 3</th>
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<th>Accuracy 53/67 = 0.79</th>
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<td>GP guidelines</td>
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<th>RR ≥ 2 versus RR &lt; 2</th>
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<th>Accuracy 57/67 = 0.78</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>25/35 = 0.71</td>
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<td>SWCC guidelines</td>
<td>Sensitivity 28/35 = 0.80</td>
<td>Specificity 32/32 = 1.00</td>
<td>Accuracy 60/67 = 0.90</td>
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<tr>
<td>GP guidelines</td>
<td>Sensitivity 35/35 = 1.00</td>
<td>Specificity 25/32 = 0.78</td>
<td>Accuracy 60/67 = 0.90</td>
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their own genetic predisposition. These GP guidelines, about the changes in quality of life due to knowledge of answer questions about the value of surveillance, about specificity of the GP guidelines regarding surveillance. 

Indication for surveillance would have increased the 40 and 50 years where the family is large’ is not an referral to a family cancer clinic have been proposed. In order to prevent women without an increased risk from being overmanaged, guidelines for referral to a family cancer clinic have been proposed. Current expert guidelines are complex and difficult to apply in general practice, and give no guidance for the GP on the management of women with a moderately increased familial breast cancer risk. These GP guidelines provide a simplification of current guidelines. They incorporate a role for the GP in the care for women with a family history positive for breast cancer in the moderately increased risk group. It was tested in a small sample of pedigrees, recruited in general practice. Before using it on a larger scale, more testing and perhaps refining is needed, in larger groups and in other patient groups. However, it demonstrates that the current criteria for referral to a family cancer clinic in the case of breast cancer in the family may be simplified adequately to make it suitable for use in general practice. Despite its current limitations, the GP guidelines facilitate the GP's interpretation of a positive family history without the need to refer all women with a relative with breast cancer to a family cancer clinic.

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References


