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Early detection of breast and ovarian cancer in families with BRCA mutations

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Abstract

Women at risk of breast and ovarian cancer due to a genetic predisposition may opt for preventive surgery or surveillance. The aim of this study was to determine the effectiveness of surveillance in families with a BRCA mutation. Sixty-eight BRCA-families underwent surveillance using annual mammography, transvaginal ultrasound, and estimation of CA125. Two hundred and two women had at least one breast examination, and 138 at least one examination of the ovaries. After a mean follow-up of 33 months, breast cancer was detected in 21 women, four with lymph node metastases. After a mean follow-up of 37 months, six advanced ovarian cancers were detected. The percentage of metastatic breast cancers in the current study appeared to be acceptable. However, because these women have a high-risk of developing breast cancer, they still have a substantial risk of developing metastatic disease under surveillance. Surveillance for ovarian cancer was not effective.

Keywords: Breast cancer; Ovarian cancer; BRCA; Surveillance

1. Introduction

An increasing number of carriers of mutations in *BRCA1* and *BRCA2* are now being identified, thanks both to the awareness of hereditary breast cancer among the medical community and the general public, and also to the availability of improved techniques for mutation detection. Nowadays, a pathogenic mutation can be identified in approximately 25–30% of families suspected of hereditary breast/ovarian cancer. A recent meta-analysis showed that the cumulative lifetime risk in *BRCA1* carriers by age 70 was 65% (95% CL 44–78) for breast cancer, and 39% (18–54) for ovarian cancer [1]. The corresponding estimates for *BRCA2* were 45% (31–56) and 11% (2.4–19).

The surveillance programme generally recommended for the early detection of breast cancer consists of annual mammography, bi-annual clinical breast examination, and monthly self-palpation [2]. The protocol for surveillance of the ovaries comprises annual gynaecological examination, transvaginal ultrasound, and estimation of serum CA 125 [2].

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Various large studies on the effectiveness of surveillance by mammography in women with an increased risk of breast cancer have indicated that screening of these high-risk groups might lead to the detection of breast cancer at an early stage [3–6]. Unfortunately, however, there have been very few studies on the value of mammographic screening of mutation carriers. Brekelmans and colleagues [6] reported rather disappointing results of mammographic screening of 128 BRCA mutation carriers, identifying nine cancers, five of them with lymph node metastasis. Four of the nine tumours were so-called interval cancers detected between the screening examinations. Another study of 165 mutation carriers showed that mammographic screening led to the identification of 12 cancers, three of which were node-positive [7]. Six of the 12 cancers were interval cancers. A third recently published study reported the results of combined screening by mammography and magnetic resonance imaging (MRI) in women with a familial or genetic predisposition. The overall sensitivity of MRI (79%) was found to be significantly higher than the sensitivity of mammography (33%). However, for the detection of ductal carcinoma *in situ*, mammography had a higher sensitivity. Among a subgroup of 358 mutation carriers, 23 tumours (16 invasive tumours) were identified, four of which were node-positive. Four of the 23 cancers were detected between the screenings [8].

There have also been a number of studies on the surveillance of women who are at increased risk of ovarian cancer [7,9,10]. One recent British study in 1017 women from families with site-specific ovarian cancer, or from families with multiple-site cancer, showed that ultrasound screening led to the detection of six ovarian cancers (two borderline tumours, one stage I, one stage II and two stage III) [9]. A Norwegian study described the outcome of surveillance by ultrasound of 845 women from hereditary breast and/or ovarian cancer families: this detected four borderline tumours and 12 cancers, most of them at an advanced stage (one stage I, one stage II, 10 stage III) [10]. In contrast, a recent North American study showed that surveillance of 89 BRCA mutation carriers led to the detection of early stage ovarian cancers (two stage I, two stage IIc) [7].

The aim of the present prospective study was to evaluate the effectiveness of breast and ovarian screening in a large cohort of families with an identified mutation in the *BRCA1* or *BRCA2* genes.

2. Patients and methods

Patients were drawn from 68 families registered in the Hereditary Breast Cancer Registry, a national registry of families with hereditary breast cancer (HBC) established in 1987 at The Netherlands Foundation for the Detection of Hereditary Tumours.

The aims of the registry are: (1) to promote the identification of families with hereditary breast cancer (HBC) and hereditary breast and ovarian cancer (HBOC); (2) to encourage the participation of these families in surveillance programmes; (3) to guarantee long-term follow-up; (4) to assess the value of surveillance. Data collected for the registry comprise personal data, pedigree data, medical data including age at diagnosis, mode of diagnosis, treatment, pathology, and results of surveillance. The methods used by the registry have been reported previously in [11].

All families suspected of HBC or HBOC are referred to the registry by clinical genetic centres, oncologists or surgeons from all parts of The Netherlands. Pedigree analysis is then performed by social workers or clinical geneticists. Data collection includes results of screening, medical reports and pathology reports.

The surveillance programme for the early detection of breast cancer recommended in all subjects consists of annual mammography, bi-annual clinical breast examination, and monthly self-palpation starting from age 25 years. The programme for the early detection of ovarian cancer includes annual gynaecological examination, transvaginal ultrasound, and estimation of serum CA 125 starting from age 30 to 35 years. The examinations are performed at various centres in The Netherlands. To ensure continuity of follow-up at regular times, reminders are sent to the specialists to inform them they are due for screening. All screening results are collected at the registry.

3. Results

Since the establishment of the Hereditary Breast Cancer Registry, data have been collected on more than 250 families suspected of hereditary breast cancer, including 90 families with an identified mutation. The data collection in the first 68 families was complete; a *BRCA1* mutation was detected in 53 of these families, and a *BRCA2* mutation in 15 families.

3.1. Breast surveillance group

A group of 202 relatives underwent at least one surveillance examination of the breast. Thirty-one patients had one screening examination, 58 patients had two examinations, 31 patients three examinations, 34 four examinations and the remaining patients five or more screening examinations. A hundred and two relatives were carriers of a *BRCA1* mutation, and 26 of a *BRCA2* mutation; the remaining relatives were untested. The mean follow-up time was 33 months (0–222 months), as calculated from the date of the first screening until the detection of breast cancer, the date of prophylactic

bilateral mastectomy, or the date of last contact. The information on follow-up is shown in Table 1.

During the screening programme, a total of 21 breast cancers were detected. Out of the 21 screen-detected breast cancers, four were detected at first screening, 10 were detected at follow-up screening, and seven were identified between the screening examinations (interval cancers). The interval detection rate (defined as the number of tumours detected during the interval divided by the total number of cancers detected during the programme) was 33%. With one exception, all screen-detected cancers were visible on the mammogram; the exception was detected by MRI only. In one other patient in whom MRI was performed at the same time as the mammogram, the tumour was detected by both screening modalities. The clinical and pathological features of these cancers are shown in Table 2. Detailed information on the findings of screening are shown in Table 3.

Lymph node metastases were observed in four of the 20 cases with invasive tumours, in two of 14 screen-detected tumours, and in two of six interval cancers. In one of the 10 incident tumours and in one of the four prevalent tumours, the patient had lymph node metastasis. All patients with breast cancer detected during the surveillance programme are alive at the date of the present study after a mean follow-up of 87 months (range: 8–230 months).

A total of 24 benign tumours were detected in 21 patients. Pathology examination revealed cystic mastopathy in 10 tumours, fibro-adenomas in seven, and adenosis in two.

Table 1
Outcome of relatives in the breast surveillance group

Women with at least one breast surveillance examination	202
Secondary prophylactic mastectomy	31
Screen-detected breast cancer	21
Deceased	5
Lost to follow-up	8
Surveillance discontinued due to subject's old age	3
Under surveillance as of 1-1-2001	134

Table 2
Clinical and pathological features of the 21 screen-detected breast cancers

Breast cancers detected during the screening programme	21
Screen-detected	14
Incident/prevalent	10/4
Interval cancers	7
Pathology LCIS	1
Ductal carcinomas	18
Adenocarcinoma unspecified	2
Lymph node metastasis	4/20
Size $\leqslant$20 mm	80%

LCIS, lobular carcinoma *in situ*.

3.2. Symptomatic breast cancer

The 68 families included 96 relatives with clinically reported symptomatic breast cancer. All cancers were confirmed by medical or pathology reports. Eighty-six patients were found to have one or more family members with a *BRCA1* mutation; 10 more patients were found to have one or more family members with a *BRCA2* mutation. The mean age at diagnosis of breast cancer was 44.4 years (range: 22–69 years). Lymph node metastases were detected in 48% of the cases. The five-year survival rate was 74%.

3.3. Prophylactic mastectomy

A total of 77 relatives from the 68 families underwent prophylactic mastectomy. Thirty-six of them had previously had breast cancer, and underwent prophylactic contralateral mastectomy. Four other women had breast-conserving surgery for breast cancer followed by a bilateral mastectomy. The remaining patients were asymptomatic women in whom no evidence of breast cancer was detected before surgery. In four women, examination of the surgical specimen revealed a breast cancer. The mean age at bilateral mastectomy was 38.9 years (range: 24–56 years). The mean follow-up was 28 months (range: 2–94 months). None of the women who underwent prophylactic mastectomy developed breast cancer.

3.4. Ovarian surveillance group

A total of 138 relatives from the 68 families underwent at least one ultrasound screening examination of the ovaries. Forty-five women had one screening examination, 30 had two examinations, 30 had three examinations and 33 had four examinations or more. Seventy-seven harbored a *BRCA1* mutation, and 18 had a *BRCA2* mutation. The remaining women were untested relatives from families with a known mutation. The mean follow-up time was 37 months (1–90 months), as calculated from the date of the first screening until the detection of ovarian cancer, the date of prophylactic oophorectomy, or the date of last contact. Detailed information on the follow-up is shown in Table 4.

In six patients, surveillance led to the detection of ovarian cancer. Two out of the six screen-detected ovarian cancers were identified at first screening, three at follow-up screening and one between the screening examinations. The clinical and pathological features of these patients are summarised in Table 5. The mean age at diagnosis was 47 years (range: 38–70 years). Two of the patients died after the diagnosis (after 69 months and 162 months). A total of 30 benign lesions were detected by screening: 16 cysts, 6 uterine myomas,

Table 3
Detailed information on the 21 screen-detected breast cancers

Number	Age at diagnosis (years)	Incident, prevalent or interval tumour	Screening round	Time since previous exam (months)	Size (mm)	Lymph node metastasis
1	51	Prevalent	1st	n.a.[a]	5	No
2	58	Incident	6th	12	7	No
3	46	Interval	n.a.	unknown	15	Yes
4	61	Incident	2nd	12	6	No
5	69	Interval	n.a.	7	20	No
6	59	Incident	19th	12	35	Yes
7	40	Prevalent	1st	n.a.	?	No
8	36	Interval	n.a.	12	20	No
9	52	Incident	2nd	24	10	No
10	32	Prevalent	1st	n.a	30	Yes
11	42	Interval	n.a.	5	11	No
12	33	Interval	n.a.	2	8[b]	No
13	50	Prevalent	1st	n.a.	6	No
14	58	Incident	5th	24	15	No
15	55	Interval	n.a.	12	25	Yes
16	52	Interval	n.a.	3	5	No
17	43	Incident	2nd	12	22	No
18	72	Incident	6th	12	6	No
19	43	Incident	2nd	12	16	No
20	49	Incident	2nd	16	?	No
21	40	Incident	>5th	12	10	No

[a] n.a, not applicable.
[b] Lobular carcinoma *in situ*.

Table 4
Outcome of relatives of the ovarian surveillance group

Women with at least one screening examination of the ovaries	138
Secondary prophylactic oophorectomy	26
Screen-detected ovarian cancer	6
Deceased	2
Lost to follow-up	3
Surveillance discontinued due to young age of subjects	5
Under surveillance as of 1-1-2001	96

Table 5
Clinical and pathological features of the screen-detected ovarian cancers

Case	Age at diagnosis (years)	Mutation	CA125	Incident/prevalent/interval	Interval since last screening examination (months)	Pathology	FIGO stage
1	50	*BRCA1*	–	Incident (3rd screening)	9	Serous cystadenocarcinoma	III
2	70	*BRCA2*	56	Incident (5th screening)	12	Serous cystadenocarcinoma	III
3	46	*BRCA1*	69	Prevalent	–	Undifferentiated adenocarcinoma	III
4	38	*BRCA1*	1450	Interval	11	Mucinous cystadenocarcinoma	III
5	38	*BRCA1*	363	Prevalent	–	Endometroid adenocarcinoma	III
6	40	*BRCA1*	162	Incident (2nd screening)	6	Serous cystadenocarcinoma	IV

FIGO, International Federation of Gynecology and Obstetrics.

2 endometrial polyps, 1 endometriosis, 1 benign cervical lesion, and 1 benign unspecified.

3.5. Symptomatic ovarian cancer

The 68 families included 91 women with clinically reported symptomatic ovarian cancer. Seventy-eight were from *BRCA1* families and 12 from *BRCA2* families. There was one patient with an ovarian cancer who was found not to carry the mutation identified in her family. The mean age at diagnosis was 52 years (range: 33–76 years). Stage III or IV was observed in 70% (45/64) of the patients in whom the stage of the disease was known. The five-year survival rate was 35%.

3.6. Prophylactic oophorectomy

Ninety-seven patients underwent prophylactic bilateral oophorectomy. In 61 cases, the ovaries and fallopian tubes were removed. In 19 cases, only the ovaries were removed. In 17 cases, the exact surgical procedure had not been described in the records. Pathological examination of the surgical specimens revealed three cancers: two cancers of the fallopian tubes (stage I and II), and one ovarian cancer (stage IIc). After a mean follow-up time of 34 months (range: 0–283 months), none of the patients who underwent prophylactic surgery had developed ovarian cancer.

4. Discussion

The present study showed that surveillance by mammography of a large series of families with a BRCA mutation led to the detection of breast cancer at a relatively early stage. In contrast, surveillance of the ovaries led to the detection of ovarian cancers only at an advanced stage. After a mean follow-up time of 28 months, none of the patients who had a prophylactic bilateral mastectomy had developed breast cancer. Similarly, after a mean follow-up time of 34 months, no one who had prophylactic bilateral oophorectomy or salpingo-oophorectomy had developed peritoneal cancer.

Two options are available to carriers of a BRCA mutation with their high risk of breast cancer: prophylactic bilateral mastectomy, or intensive surveillance by mammography. Decision analysis comparing prophylactic mastectomy to intensive surveillance indicated that, depending on the age at which surgery took place, mastectomy would lead to a 4–5 year increase in life-expectancy [12]. Similarly, a large retrospective study showed that prophylactic mastectomy reduces breast cancer by more than 95% [13]. The only study performed in mutation carriers showed that none of 76 carriers developed breast cancer after a mean follow-up of three years after surgery [14].

Unfortunately, the literature contains very little data on the adverse effects of prophylactic mastectomy, although one preliminary study of the adverse effects of mastectomy followed by immediate breast reconstruction showed that the procedure led to substantial morbidity [15]. Almost half of the patients in question had sexual problems, and there were complications in 33%. Such morbidity suggests that intensive surveillance of the breasts by mammography might be a better option.

Perhaps the most important question in decision-making is whether mammographic surveillance of mutation carriers will prevent death. A few studies available in the literature on the value of mammographic surveillance of mutation carriers produced conflicting results. One study suggested that surveillance did not work at all, as lymph node metastases were observed in more than half of the patients [6]. Another study was more encouraging, suggesting that mammography led to detection of local metastatic disease in 25% of screen-detected cancers [7]. The present study provides even better results, with lymph node metastasis in only 20% of the cases. Monthly self-examination appeared to be an important part of the surveillance program: in our study, it led to the diagnosis of seven interval cancers. Another recent study showed that with combined use of MRI and mammography, the proportion of positive axillary nodes was 17% of the screen-detected cancers [8]. The large variation in results published in the literature is probably an effect of the low numbers of patients in the studies. Therefore, more studies are needed to establish the true value of mammographic and/or MRI screening in mutation carriers.

With regard to mutation carriers with a high-risk of ovarian cancers, there are two main options. The first is prophylactic bilateral salpingo-oophorectomy. Although this prevents ovarian cancer, a minimum long-term risk of 4% of peritoneal cancer remains after surgery. The second option is intensive surveillance, on which there is little agreement in the literature: although two studies suggested that surveillance by ultrasound led to the early detection of ovarian cancer, one large study showed that it led mainly to the detection of advanced cancers [7,9,10]. The present study showed that surveillance of the ovaries in mutation carriers was not effective, as all screen-detected tumours were advanced cancers.

So what are the implications of our findings for the management of mutation carriers? Although our results on mammographic screening seem encouraging, we should remember that because mutation carriers have a high lifetime risk of developing breast cancer (65–70%), they also have a high absolute risk of developing local metastatic disease under surveillance: this is at least 13% ($20\% \times 65\%$). In view of this substantial risk, we might conclude that long-term mammographic surveillance of mutation carriers is not sufficiently effective, and that, so far, only one method of preventing mortality due to breast cancer in mutation carriers has proved effective, i.e. prophylactic mastectomy. However, as a possible alternative for women who do not wish to undergo prophylactic mastectomy, it might be possible to reduce the risk of breast cancer by prophylactic oophorectomy and/or hormonal chemoprevention subsequently offering additional screening by MRI [16–20]. Because interval cancers appear to occur relatively frequently in the follow-up of BRCA-mutation carriers, even when patients are screened both by mammography and MRI, it might be appropriate to perform screening examinations every six months, alternating mammography and MRI [8].

In view of the disappointing results of ovarian cancer screening by transvaginal ultrasound, prophylactic

bilateral oophorectomy appears to be the management of first choice in *BRCA1* carriers who have had their children, perhaps at the age of 35–40 years. Because ovarian cancer rarely develops in *BRCA2* mutation carriers before the age of 50 years, the appropriate age for prophylactic salpingo-oophorectomy is approximately 50 years.

A recent study has suggested that the fallopian tubes are also at risk in BRCA mutation carriers [21]. This is confirmed by our findings that examination of the surgical specimens of prophylactic oophorectomy revealed two cancers in the fallopian tubes. Prophylactic oophorectomy should therefore include removal of the fallopian tubes.

If each mutation carrier is to make the most appropriate decision, she should be informed about all of the advantages and disadvantages of the options open to her. Such information is best provided by a multidisciplinary team consisting of at least a clinical geneticist, surgeon, gynaecologist, radiologist, oncologist and plastic surgeon. Choosing between options for preventing breast cancer often depends not only on a range of highly personal considerations, but also on a patient's psychosocial background. For this reason, counselling should be non-directive.

Conflict of interest statement

None declared.

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