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Clinical Heterogeneity of Hereditary Breast Cancer and its Impact on Screening Protocols: The Dutch Experience on 24 Families under Surveillance

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We investigated 24 families who satisfied a set of criteria for hereditary breast cancer. Five families had only breast cancer, four a combination of breast and ovarian cancer and the remaining 15 had also a variety of other cancers. The families include 86 patients, 78 of which had a malignant tumour and the rest had a benign lesion in the breast. The median age at diagnosis of the breast cancer was 47 years. Three of the 24 families were of a late onset variant. 58 of the 86 patients were symptomatic while 18 were identified during presymptomatic screening because of a positive family history. In 10 cases the reason for referral was not known. 56 of the symptomatic patients had a malignant breast lesion, 52% of which were with lymph node metastasis whereas 12 of the screening group had breast cancer with 2 patients showing lymph node involvement ($P = 0.06$). 22 of the symptomatic patients and none of the screening patients died of breast cancer after a median observation period of 6 and 7 years, respectively ($P < 0.05$).
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INTRODUCTION

OF ALL the breast cancer cases, 5% are due to hereditary causes [1, 2]. Hereditary breast cancer (HBC) is characterised by an early age of onset and a high incidence of bilateral tumours [3, 4]. Based on the association of breast cancer with other cancers HBC can operationally be subclassified into various categories. For example, the combination of breast cancer with sarcoma, brain tumour, lung cancer, adrenocortical carcinoma and leukaemia is designated as the Li–Fraumeni syndrome [5]. Another association of breast cancer is with ovarian cancer [6]. Surveillance in HBC may lead to the early detection of tumours and thus might improve the prognosis. An understanding of HBC heterogeneity with respect to its association with various other cancers and the variation in the age of onset is of paramount importance in developing appropriate management and surveillance protocols. Therefore, we set up a collaborative study in 24 suitable families to analyse the association of HBC with other cancers, to assess the age of onset of breast cancer and to evaluate

Table 1. Patients with breast lesions in the present study

Number of patients with breast lesions	86
Benign/premalignant lesions	8
Malignant lesions	78
Reasons for investigation	
Presentation of symptoms	58
Positive family history	18
Unknown	10

retrospectively, the results of screening the high risk family members.

PATIENTS AND METHODS

In 1985, the Dutch Foundation for the Detection of Hereditary Tumours (Stichting Opsporing Erfelijke Tumoren) set up a registry for families with hereditary cancer to promote and coordinate periodic screening in these families [7]. Since 1987, HBC families have been registered. The families were referred to the centre from all parts of The Netherlands, because they were suspected of having a predisposition for an inherited form of breast cancer. The family pedigrees were traced as far backward and laterally as possible. The collected data from medical records include information on the type of the cancer, the site of cancer, the age at diagnosis, the treatment given, the age at death and the histological findings. Written permissions for the release of primary medical as well as pathology documents facilitated us to secure such information for review. The screening protocol generally recommended in The Netherlands is self-examination once a month and mammography at 1- or 2-year intervals from the age of about 35 years [8]. The operational criteria for HBC families are that there are at least three relatives with breast cancer only or at least two relatives with breast cancer and one with ovarian cancer in one or two generations; at least one of them is a first-degree relative of the other two; or, in the case of paternal transmission, there are at least two affected first-degree and one affected second-degree relatives in two successive generations. The results are analysed with the standard procedures.

RESULTS

24 families met the criteria for selection. Five of these 24 families were classified as site-specific breast cancer (families with only breast cancer), and four as breast/ovarian cancer families. In 15 families there were, in addition to the 3 breast cancer cases, individuals with one or more other (non-ovarian) cancers. In one of the breast/ovarian cancer families there was a case of osteosarcoma.

The 24 families consisted of 86 patients who underwent surgery because of a breast lesion. A total of 78 patients (77 females and 1 male) were found to have breast cancer and 8 patients had benign or premalignant lesions (Table 1). The median age at diagnosis of breast cancer was 47 years (range 32–87). The distribution of the ages at diagnosis for all patients is shown in Fig. 1. In three families there were only postmenopausal cases. One of these "late onset families" had only breast cancer, the others had also one or more (non-ovarian) cancers outside the breast. The cumulative incidence of bilateral breast cancer was 10% after 7 years of follow-up.

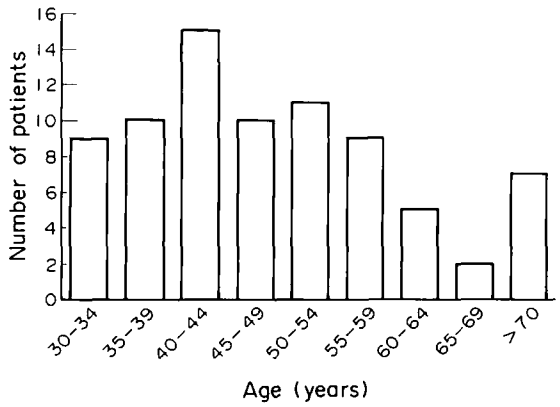

Fig. 1. Distribution of the ages at first diagnosis of breast cancer in the present series.

Of the 86 surgically treated patients, 58 (group A) were referred because of symptoms and 18 (group B) had been screened because of a positive family history. For 10 of the patients the reason for referral was not known (Table 1). 2 patients in the symptomatic group were found to have benign pathology, including 1 patient with cysts and 1 with a fibroadenoma, and 6 of the screening group had a benign or premalignant lesion, i.e. 2 patients with lobular dysplasia, 1 with cysts, 1 with a fibroadenoma, 1 with mild epithelial proliferation and 1 with ductal carcinoma *in situ*. 56 patients in group A and 12 patients in group B had breast cancer. Table 2 compares the occurrences of lymph node metastases and lethality in the symptomatic group with the screening group of the breast cancer patients. In the comparison only the first breast cancers or simultaneously diagnosed bilateral cancers were included. The screening group

Table 2. Data on pathology, the occurrence of lymph node metastasis and lethality in the symptomatic (A) and screening (B) groups of patients

	Group A	Group B
Number	58	18
Age		
Median	43	43
Range	21–87	23–60
Benign or premalignant lesions	2	6
Breast cancer	56	12
Median follow-up (years)	6	7
Lymph node metastasis	52%*	17%*
Lethality	22†	0†
Age at death		
Median	46	
Range	35–88	—

*χ^2 test, $P = 0.06$. †χ^2 test, $P < 0.05$.

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included 1 case from the late onset families. This patient was found to have a benign lesion.

Information on the presence of lymph node metastasis was available for 50 of the 56 group A patients and all the cases of group B. Lymph node metastasis was found in 26 of the 50 group A patients (52%) and in 2 of the 12 group B patients (17%) ($P = 0.06$). After a median observation time of 6 and 7 years, respectively, 22 of the symptomatic but none of the screening patients had died from breast cancer ($P < 0.05$).

DISCUSSION

Mortality from breast cancer has not changed during the last 30 years. Because the prognosis depends on tumour size at presentation, an accurate and early diagnosis is essential for the improvement of the quality of life and the reduction of mortality. Segregation analysis of population-based series of families indicated that an autosomal dominant gene with high penetrance could fully explain clustering of breast cancer in 4% of the families [2]. Identification of these high-risk families offers the possibility of early detection and radical cure. Screening of the relatives of these families may lead to early diagnosis and curative treatment.

Several reports indicate that hereditary breast cancer families are heterogeneous with respect to the age of onset of breast cancer and to integral association with cancer sites outside the breast. An awareness of the occurrence of such heterogeneity is important, because it can serve as the basis for choosing an appropriate screening protocol. Therefore, in the early onset families of which there are 21 in the present series, we recommend that screening should begin at the age of 25 or at least 5 years earlier than the youngest age of onset observed in the family. Thus, in families with a well-documented late age of onset of breast cancer (three of the 24 families), surveillance may be delayed until 5 years prior to the earliest age of diagnosis in the family history. The screening program generally recommended in the literature includes self-breast examination at regular intervals and semi-annual palpation by a clinician and mammography at 1- or 2-year intervals [9].

Five of our families showed a combination of breast and ovarian cancer. In such families the females should also be screened for ovarian cancers. Our screening program for these tumours includes yearly pelvic examinations by a gynaecologist, ultrasound, and estimation of CA125. The value of this screening program has not yet been established.

There is good evidence that screening for breast cancer reduces mortality in women older than 50 years [10], however, only a few data concerning the benefit of screening of breast cancer-prone families are available [11]. Moreover, previous reports have suggested that the benefits of mammography in women under age 50 are questionable [12–15]. The dense glandular tissue, usually associated with young women, obscures possible signs of malignancy. In the present study, we evaluated retrospectively the effect of screening of high-risk families by comparing symptomatic patients and patients found by screening with respect to the occurrence of lymph node metastases and lethality. The results suggest that screening of these families led to the reduction of lethality. However, because our methodology is subject to lead-time bias, length bias, and possibly to selection bias, a long-term prospective study is needed to establish the benefit of screening in these young women of high-risk families. The cumulative risk for the development of cancer in the contralateral breast in the present series was 10% after 7 years of follow-up. This is in agreement with the results reported by Harris [4], which showed a cumulative incidence of bilateral cancer of 10% after 7 years and 37% after 20 years. Although interstudy comparisons may be influenced by differences in methodology, these family rates are higher than published figures available from follow-up studies of unselected breast cancer patients, which showed a cumulative incidence of bilateral cancer of 7–10% after 10 years and 13–15% after 20 years of follow-up [16, 17]. On the basis of these findings we recommend semi-annual physical examination and annual mammography of the contralateral breast. A prophylactic mastectomy of the contralateral breast is an option to be considered in patients (where there is reasonable probability of long-term control of the primary cancer) who have a breast that is difficult to evaluate clinically and subsequent biopsies have revealed ductal carcinoma *in situ*, lobular carcinoma *in situ*, or atypical ductal hyperplasia, or in patients developing severe anxiety due to their increased risk of breast cancer.

Recent studies published by the group of Mary-Claire King have provided evidence pointing to the localisation of a putative breast cancer gene on chromosome 17q in families with early onset of breast cancer (mean age of onset of cancers younger than 46 years) [18]. Furthermore, the same gene on chromosome 17q has been suggested to be involved as well in families with breast and ovarian cancers [19]. These findings may have important implications for a subset of the HBC families, because once they have been extended and confirmed in individual families, screening can be focused on high-risk individuals and the family members at low risk can be less rigorously followed until the gene concerned is isolated and appropriate methodology for the detection of a specific mutation becomes available.

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The Management of Radiation-associated Oesophageal Carcinoma: a Report of 16 Cases

B.G. Taal, B.M.P. Aleman, J.V. Lebesque and R. Steinmetz

16 patients, presenting with squamous cell carcinoma in previously irradiated sections of the oesophagus, are described. Oesophagectomy could be performed in 2 patients, resulting in long-term disease-free survival (38 and 60 months after diagnosis). 14 patients were treated with palliative radiotherapy (external beam or intraluminal), oesophageal stenting, bougienage or chemotherapy. Although most patients previously received curative dosages of mediastinal irradiation, additional full courses of high-dose radiotherapy could be given on five occasions; no major complications were encountered and adequate palliation for up to 10 months was achieved. Similar results were observed after oesophageal stenting and/or bougienage. Relief of dysphagia following intraluminal radiotherapy or chemotherapy was only minimal (2 months or less). Median survival in the palliative treatment group was 6.5 months (range 2–27 months), which is in keeping with results observed in non-radiation-associated oesophageal carcinoma. We concluded that, in selected cases, both surgery and radiotherapy offer good prospects for patients with radiation-associated oesophageal cancer.
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INTRODUCTION

RADIATION-ASSOCIATED oesophageal carcinoma is defined as malignancy developing in a previously irradiated section of the oesophagus. Additional, but non-essential features are a long latent interval and evidence of radiation injury in surrounding tissue [1, 2]. This condition is rare. Since 1959, only 37 patients have been described in the literature [1–20] (Table 1).

In the present study, 16 additional cases from The Netherlands Cancer Institute are discussed, the largest series from a single hospital published thus far.

Apart from describing the clinical picture of radiation-associated oesophageal carcinoma, we summarise our experience in treating this condition. This appears to be of particular interest, as earlier publications contain very little information on this subject whereas even less is known about the prognosis of this type of malignancy.

PATIENTS AND METHODS

Scanning of tumour registry data and endoscopy reports revealed 16 patients, treated for radiation-associated oesophageal carcinoma in The Netherlands Cancer Institute between 1977 and 1991. We conducted a retrospective study which involved a review of their medical records, radiotherapy data and diagnostic X-rays.

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RESULTS

Of the 16 patients studied, 7 (44%) were men and 9 (56%) were women. The median age on diagnosis was 56 years (range: 32–83 years). Oesophageal carcinoma was demonstrated 2–63 years (median: 8.5 years) after therapeutic irradiation for malignancy (13 cases) or benign disorders (3 cases) (Table 2).

Most patients presented with a 1–6 month history of progressive dysphagia, occasionally accompanied by weight loss or fatigue.

Chronic intermittent dysphagia of 1–3 years duration was mentioned in 5 cases (numbers 2, 5, 6, 7, 9, Table 2); only one of them was examined endoscopically on an earlier occasion; at that time, biopsies were positive for chronic inflammation (case 9, Table 2). 1 patient did not suffer from dysphagia (case 2, Table 2); instead, she indicated intermittent retrosternal pain which had been present ever since irradiation of the internal mammary chain for inner quadrant breast carcinoma 2 years earlier. Endoscopy, performed after sudden deterioration of her complaints, quite surprisingly revealed squamous cell carcinoma of the oesophagus.

Endoscopic biopsies in the other 15 cases were also compatible with squamous cell carcinoma most of which occurred in the proximal third of the oesophagus (12/16 = 75%); tumour length, known in 14 patients, was assessed endoscopically in 12