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Breast cancer risk in women that fulfill high risk criteria: at what age should surveillance start?

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Abstract

Family history is a strong predictor of hereditary breast cancer, particularly when it includes cases of early onset or bilateral breast cancers and multiple cases of breast or ovarian cancers.

This article provides relative risks and cumulative risks of breast cancer of women whose family history indicates high risk. Specifically, the aim was to determine how many years earlier the high risk women reach the cumulative risk of women without family history at the age at which screening in average risk women is initiated.

The women of the nation-wide Swedish Family-Cancer Database were classified according to clinical criteria based on family history suggesting high risk for hereditary breast ovarian cancer syndrome. The relative risks of breast cancer were calculated as hazard ratio using Cox regression. Cumulative risks of breast cancer were estimated with a stratified Cox model based on Tsiatis' method.

The hazard ratios of breast cancer for the considered criteria ranged from 1.50 to 5.99. The cumulative risks ranged from 1-10% by age 50. The age to reach the same cumulative risk as women lacking a family history at age 50 years ranged between 32.0-40.8 years.

Relative and cumulative risks of women at high risk of breast cancer associated with different clinical criteria were diverse, which may be helpful to consider when current clinical criteria are revised. According to the present results, current recommendations of starting clinical interventions 10 years earlier in high risk women, based on expert opinions, appear justified at least for the largest high risk groups.

Introduction

In the Swedish Family-Cancer Database, 14% of women with breast cancer have a mother or sister also diagnosed with this disease [1]. Family history is a strong predictor of hereditary breast cancer, particularly when it includes cases of early onset breast cancer, bilateral breast cancer and multiple cases of breast or ovarian cancers [2]. Therefore, clinical criteria based on family history have been developed to assess the risk of breast cancer as well as to assess risk of an autosomal dominant hereditary breast and ovarian cancer gene mutation [3-7]. Genetic testing for known cancer susceptibility genes, such as BRCA1 and BRCA2, is recommended for women at high risk of breast cancer according to such criteria [5]. For example, Hampel et al. reviewed professional society guidelines, which were based on the empirical likelihood that a family history was attributable to a mutation in BRCA1/2, and developed seven criteria to identify women at increased risk for a mutation in BRCA1/2 [4]. However, the proportion of breast cancer attributable to BRCA1/2 among women at high risk according to clinical criteria has ranged from 0.7-29% (BRCA1) and from 1.5-25% (BRCA2) for different populations [8]. Thus, women with a strong family history of breast or ovarian cancer are at high risk of breast cancer in spite of a negative genetic test for mutations in BRCA1/2 [2]. Women at high risk of breast cancer might benefit from increased surveillance and risk reducing interventions [9,10]. However, the recommendations for the starting age of screening in high risk women are mainly based on expert opinion [3]. Therefore, scientifically-based estimates of the risk associated with the criteria used to assess the risk of breast cancer are needed.

In the present population-based study covering the country of Sweden, the clinical criteria developed by Hampel et al. were used to classify the women in the nation-wide Swedish Family-Cancer Database. We estimated the relative risks and the cumulative incidences of breast cancer according to these criteria. The results show how many years earlier high risk

women reach a defined risk compared to women lacking a family history, thereby providing scientific basis for antedating screening recommendations for high risk women.

Materials & Methods

The Swedish Family-Cancer Database was created in the 1990s by linking information from the Multigeneration Register, national censuses, Swedish Cancer Registry and death notifications [11]. Data on family relationships were obtained from the Multigeneration Register, where children born in Sweden in 1932 and later are registered with their biological parents as families. The Swedish Cancer Registry is based on compulsory reports of diagnosed cases, with coverage of the cancer registration close to 100% [12]. The 2008 update of the Database includes more than 11.8 million individuals and their cancers from years 1958 to 2006 [13]. Women without identified parents were excluded from the study. The age structure of the Database (children born after 1932) implicates that the maximum age of diagnosis in the second generation is 74 years. The age of women in the first generation is not limited.

We have classified the women in the second and third generation of the Database according to seven criteria proposed by Hampel et al. which suggest a high risk of breast and ovarian cancer syndrome [4]. Women fulfilling several criteria were accounted for each criterion independently. The criteria are based on cancers in first and second degree relatives. We have defined parents and siblings as first degree relatives and grandparents, aunts, uncles and half-siblings as second degree relatives. If a criterion called for more than one affected relative, women were classified to fulfill the criterion only if the affected relatives were blood relatives of each other. The relative risks of breast cancer were estimated as a hazard ratio (HR) using Cox regression for any of the criteria (PROC PHREG; SAS Version 9.1; SAS Institute, Cary, NC). Individuals of the second and third generation entered the risk period at birth,

immigration, or first year of the study (1990). Censoring events were death, emigration, December 31, 2006, absence at census and diagnosis of malignancy at sites other than breast. Socioeconomic status, calendar period, age at first birth, number of children and region were taken into account as covariates. Cumulative risks of breast cancer according to family history were estimated using a stratified Cox model based on Tsiatis' method [14] (PROC PHREG; SAS Version 9.1; SAS Institute, Cary, NC). The strata were defined according to the criteria. For any of the criteria, we calculated the age at which the cumulative risk of women without a family history at the age of 50 years was reached [15].

Results

Figure 1 shows examples for the considered familial relationships and the numbers of women affected by breast cancer with a first degree relative (FDR) or second degree relative (SDR) affected by breast cancer or ovarian cancer. Among the affected pairs of individuals shown in Figure 1, mother-daughter pairs outnumbered sister pairs and FDRs outnumbered SDRs.

The hazard ratios of breast cancer in women at high risk of breast and ovarian cancer syndrome according to seven criteria from Hampel et al. are shown in Table 1. The numbers of women affected by breast cancer who fulfilled the criteria were variable. For example, 338 women with '1 FDR or SDR with bc diagnosed ≤ 40 ' (criterion 1) were affected while 3 women were affected with '1 FDR or SDR with male bc and 1 FDR or SDR with bc or oc' (criterion 7). The hazard ratios ranged from 1.50 ('1 FDR or SDR with male bc and 1 FDR or SDR relative with bc or oc', criterion 7) to 5.99 (' ≥ 2 FDRs or SDRs with bc or oc and 1 FDR or SDR with oc', criterion 5). For all but one criterion ('1 FDR or SDR with male bc and 1 FDR or SDR relative with bc or oc', criterion 7), the hazard ratios were higher than for women with one first degree relative affected by breast cancer (hazard ratio 1.74). However,

the number of affected women with a diseased first degree relative, 5257, was over 7 times higher than the number of women fulfilling criteria 1-7 (689 index cases).

Hazard ratios were also calculated for women younger than 50 years and older women. The numbers of women affected by breast cancer before age 50 years were higher than for women who were diagnosed later. Expectedly, the hazard ratios were also higher for the young diagnostic group for any of the criteria; the highest hazard ratio of 8.98 was noted for criterion 5.

Figure 2 represents the cumulative risk of breast cancer according to the criteria. The solid curves in the bottom show the cumulative risk of women without a family history; in these curves, the cumulative risk at age 50 years (1.6%) is marked. The cumulative incidence of breast cancer by age 50 years and 70 years is presented in Table 2. By age 50 years, the cumulative incidence ranged from 1.4% ('1 FDR or SDR with male bc and 1 FDR or SDR relative with bc or oc', criterion 7) to 10.3% (' ≥ 2 FDRs or SDRs with bc or oc and 1 FDR or SDR with oc', criterion 5); the percentages ranged from 7.5 to 16.5 by age 70 years. Notably, from age 50 to 70 years, the cumulative incidence in women lacking a family history increased from 1.6 to 6.7%, 4.2-fold or 5.1 percentage units. For many of the high risk women, the increases between ages 50 and 70 were relatively modest.

The age to reach the same cumulative risk of breast cancer as women lacking a family history at the age 50 years (1.6%) and age 40 years (0.33%) is shown in Table 3. The difference 'Age difference' to reach the risk of 1.6% due to the family history was highest for women with ' ≥ 2 FDRs or SDRs with bc or oc and 1 FDR or SDR with oc', criterion 5, 18.0 years) and lowest for women with '1 FDR or SDR affected by bc ≤ 40 years', criterion 1, 9.2 years). The age difference to reach the risk of 0.33% was between 7.2 years ('1 FDR or SDR affected by

bc \leq 40 years', criterion 1, ' \geq 2 FDRs or SDRs with bc if one is diagnosed \leq 50 y or bilateral', criterion 3) and 10.0 years ('1 FDR or SDR with bc diagnosed \leq 50 y or bilateral and 1 FDR or SDR with oc', criterion 4). However, for criterion 5 – 7, the number of cases was too small for the analysis of the age to reach the risk of 0.33%.

The considered criteria were overlapping. Table 4 shows the numbers of women that fulfilled two criteria. For example, 13 of 14 women with ' \geq 2 FDRs or SDRs with bc or oc and 1 FDR or SDR with oc' (criterion 5) also fulfilled the criterion '1 FDR or SDR with bc diagnosed \leq 50 y or bilateral and 1 FDR or SDR with oc' (criterion 4).

Discussion

The novel findings of the present study included a nation-wide definition of age-related relative and cumulative risks for women at high risk of breast cancer, which included 689 index cases. The largest high risk groups reached the cumulative risk of 1.6%, which was the cumulative risk of sporadic cases at the age of 50 years, some 10 years before the sporadic group. Another novel finding of also major practical importance was the description of familial breast cancers outside the high risk families. These included 5263 patients with a FDR with breast cancer and over 1400 patients with SDR with breast cancer or FDR with ovarian cancer. The number of potentially detectable cases in the latter groups far exceeded the cases in the high risk groups, as will be discussed below. Familial breast cancer cases, not belonging to the high risk groups, reached the cumulative risk of 1.6% about 5 years before sporadic cases.

The present study includes the whole Swedish population up to age 74 years and their parents, whose family relationships and cancer data originated from reliable and practically complete registered sources. Although the study included the whole Swedish population, the number of

women affected by breast cancer fulfilling any of the criteria was small. This was expected as the criteria aim at identifying women at risk of hereditary breast ovarian syndrome, which is rare [16]. Furthermore, the structure of the Database implies that the identification of grandparents, aunts and uncles was only possible for women whose parents were born in 1932 or later, i.e., three generations were to be identified where the youngest one aged ~ 50 years or less. The relatively small numbers of women diagnosed with breast cancer with a SDR affected is in part explained by the young age of the third generation. This might also be a reason for the relatively low proportion of breast cancers over 50 years in women fulfilling a criterion. Furthermore, women who fulfill the criteria are probably younger than the average women in the second generation, which might lead to an overestimation of the risks because familial cancer is associated with an earlier age of onset. As a further technical point, the present calculations were based on the register-based definition of the family history which did not consider the time of family member's diagnosis. In clinical counseling and screening situations, women enter the familial group only from the diagnosis date of the affected relative(s). We have carried out some analyses using the latter definition with practically unchanged results. However, a major problem with the latter definition is a reduction of case numbers because the familial group only includes cases after the relative's diagnosis. Identical results following both types of calculations for familial risk in groups with large enough case numbers reassure that the present results should be applicable to the clinical and screening situations.

The numbers of index cases and the risks that we found for the different high risk criteria were diverse, ranging from three cases and no increased risk in criterion 7 with male breast cancers to 14 cases and a hazard ratio of 5.99 in criterion 5 with multiple affected family members. Nevertheless, it is known that male breast cancer is a strong predictor of hereditary breast ovarian cancer syndrome. The finding that the risk was not increased in criterion 7 was

probably due to a lack of power to prove the association for this criterion, the number of women fulfilling this criterion being small. The largest groups, criteria 1 and 3, included early onset breast cancers with intermediary hazard ratios. The cumulative incidence of breast cancer by age 50 was 1.6% in women lacking a family history while that cumulative incidence was reached between 9 years (95% CI 8 y – 11 y, criterion 1) and 18 years (95% CI 8 y-20 y, criterion 5) earlier in women belonging to any of the high risk groups (except criterion 7). The diversity of the risks depending on the criterion is likely to be explained in part by different proportions of BRCA1/2 mutation carriers in women fulfilling the criteria [17]. Empirically, mutation detection rates are highest in the groups where we found the highest risks [17,18] and the characteristics of these groups would also yield increased predictions for mutation positivity using the BRCAPRO and BOADICEA programs [19-22]. For women carrying mutations in BRCA1/2, the estimated cumulative risk of breast cancer by the age of 50 years range from 28-39% (BRCA1) and 16-23% (BRCA2), respectively; by age 70, the corresponding risk estimates are between 46-65% and between 45-56% [23-26]. We have found cumulative breast cancer risks between 1-10% at the age of 50 and between 7-17% at age 70. These proportions show that the majority of breast cancers even in the high risk groups are not associated with mutations in BRCA1/2, in agreement with mutation testing results [17,18]. A major weakness of our study is that we lack data on the mutation status of the subjects and we thus lack the possibility of risk estimation for women belonging to the high risk groups but who test negative. The risk of women outside mutation positive families should, at a minimum, exceed the familial risks of women with one affected FDR diagnosed with breast cancer, not fulfilling the high risk criteria (i.e., hazard ratio 1.74) [2]. Mutation negative women with a known familial mutation should be considered as average risk. [27]

Considering that 5257 index women with one FDR diagnosed with breast cancer and not fulfilling the high risk criteria showed an excess risk of 0.74 (1.74-1.00), the number of cases

due to family history was about 2240 ($5257 \times (0.74/1.74)$), which was much higher than the 12 (ie, extra risk of $4.99 \times 14/5.99$, criterion 5) to 209 ($1.63 \times 338/2.63$, criterion 1) extra number of cases among the high risk index cases. As these women reached the cumulative risk of 1.6% 4.8 years before the women lacking a family history, any screening efforts for these women should be started at 45 years if the others are offered screening at 50 years.

It has been shown that women with an increased risk of breast cancer might benefit from an intensified surveillance and risk reducing interventions, which includes an earlier start of mammography screening, MRI screening, chemoprevention and risk reducing surgery [9,10,28,29]. The starting age of mammography screening for women at increased risk is not well established. The American Cancer Society recommends average-risk women to start with mammography screening at the age of 40 years [30]. Women at increased risk of breast cancer, which includes women with a relative affected by breast cancer before 50 years, with two or more relatives affected by breast or ovarian cancer, with male breast cancer and with a relative affected by two independent breast cancers, are recommended to start 10 years earlier than average risk women, or 5-10 years earlier than the youngest patient in the family [3]. The above recommendations are mainly based on expert opinion, with support from the assessment of breast cancer risk with statistical models or epidemiological studies [6,31-33]. The National Center for Clinical Excellence in the UK recommends for at-risk women annual mammography screening beginning at the age of 40 years, which is 10 years earlier than the recommended starting age in the UK for the general population [7]. For the surveillance between 30 and 40 years by mammography screening for women with BRCA1/2 mutations or at equivalent high risk, individual strategies are suggested [7].

There is good evidence that the efficacy of mammography screening in average risk women is lower in women aged 40-49 years than in those aged 50-69 years [34,35]. No evidence has been found for the efficacy of screening under the age 40 years. Furthermore, a poor

performance of mammography screening in BRCA1/2 carriers has been reported [35]. Nevertheless, women with increased risk might benefit of earlier mammography screening but a mortality reduction has not yet been shown [29]. Therefore, the American Cancer Society recommends MRI screening as an adjunct to mammography screening for women with an estimated 20-25% or greater lifetime risk of breast cancer [36]. Annual MRI screening between 30 and 40 years is recommended for women with an estimated breast cancer risk > 8% in this period by the National Center for Clinical Excellence [37]. Our risk estimates are well below these risks for any of the considered criteria. Thus, according to the above recommendations, our results indicate that MRI screening is not eligible solely on the basis of these clinical criteria. Our present data show the age differences for the cumulative risks for women at various risk levels estimated with a large population-based data set, and thus provide some justification for the timing of interventions. However, they cannot suggest the methods of intervention nor predict their success.

Another application of the present data may be in the adjuvant therapy of breast cancer. A combined analysis of 6 studies has shown a reduction of 38% of the breast cancer incidence by tamoxifen treatment [38]. Tamoxifen has, however, serious side-effects. Gail et al. have shown that the risk-benefit ratio is dependent on the age and the risk to develop breast cancer within the period of tamoxifen use [39]. They have demonstrated that tamoxifen is most beneficial for younger women with an increased risk of breast cancer. Thus, our risk estimations might support the decision for or against tamoxifen treatment as a risk reducing intervention.

In conclusion, the relative and cumulative risk of women at high risk of breast cancer associated with different clinical criteria is diverse. With the discussed limitations, the present data may help to evaluate and to improve current clinical criteria for the assessment of breast

cancer risk. They offer scientific bases for clinical counseling and screening activities targeted at high risk patients; these should commence some 10 years before sporadic patients. For familial patients outside the high risk groups the activities should commence 5 years earlier.

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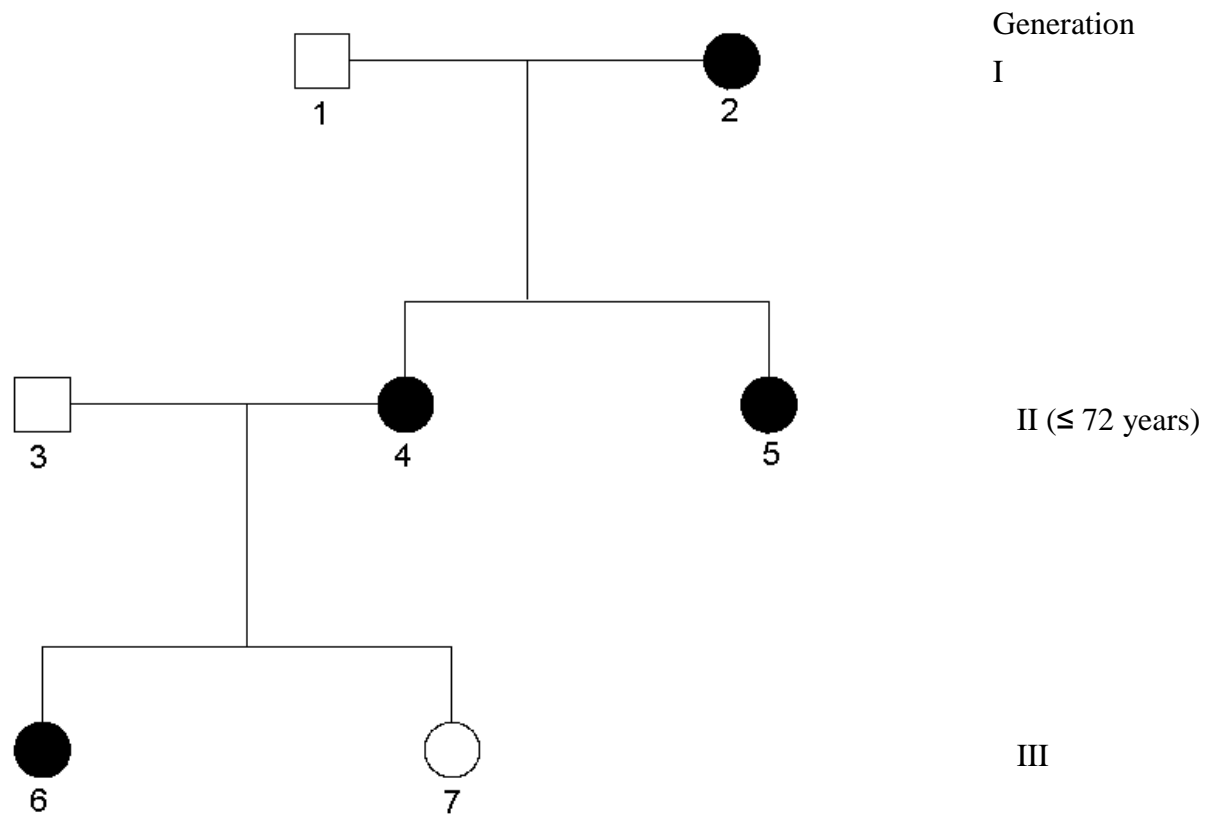
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Figure 1 Examples of the considered familial relationships and numbers of women affected by breast cancer with a first or second degree relative affected by breast or ovarian cancer.

Squares are men, circles are women; filled circles are affected women



			Cancer site of relative	
	Familial relationship	Example	Breast	Ovary
First degree relatives	mother - daughter	2-4	3938	699
	sister - sister	4-5	2160	212
Second degree relatives	grandmother - granddaughter	2-6	399	80
	aunt - niece	5-6	211	44
	half-sister - half-sister	not shown	160	18

Table 1 Hazard ratios of breast cancer for women that fulfilled high risk criteria for breast and ovarian cancer syndrome by age at diagnosis

Criterion	N	HR	Any age		P	N	< 50 years			P	No.	≥ 50 years			P
			95% CI				HR	95% CI	HR			95% CI			
1 1 FDR ^a or SDR ^b with bc ^c diagnosed ≤ 40 y	338	2.63	2.36	2.93	< 0.0001	229	3.24	2.84	3.69	< 0.0001	109	1.90	1.57	2.29	< 0.0001
2 1 FDR or SDR with both bc and oc ^d	88	2.92	2.37	3.60	< 0.0001	52	4.09	3.11	5.37	< 0.0001	36	2.07	1.49	2.87	< 0.0001
3 ≥ 2 FDRs or SDRs with bc if one is diagnosed ≤ 50 y or bilateral	289	3.27	2.91	3.67	< 0.0001	158	3.87	3.31	4.26	< 0.0001	131	2.74	2.31	3.26	< 0.0001
4 1 FDR or SDR with bc diagnosed ≤ 50 y or bilateral and 1 FDR or SDR with oc	66	4.25	3.34	5.41	< 0.0001	49	6.42	4.85	8.49	< 0.0001	17	2.16	1.34	3.47	0.002
5 ≥ 2 FDRs or SDRs with bc or oc and 1 FDR or SDR with oc	14	5.99	3.55	10.10	< 0.0001	12	8.98	5.10	15.81	< 0.0001	2	1.98	0.50	7.91	0.33
6 ≥ 2 FDRs or SDRs with oc	23	3.45	2.30	5.19	< 0.0001	19	5.92	3.78	9.27	< 0.0001	4	1.16	0.43	3.09	0.77
7 1 FDR or SDR with male bc and 1 FDR or SDR with bc or oc	3	1.50	0.49	4.65	0.48	1	1.00	0.14	7.11	0.99	2	2.06	0.53	8.04	0.30
1 bc in FDR, none of criteria 1-7	5257	1.74	1.69	1.79	< 0.0001	1906	1.84	1.76	1.94	< 0.0001	3351	1.68	1.62	1.74	< 0.0001
1 bc in SDR, none of criteria 1-7	612	1.46	1.34	1.58	< 0.0001	527	1.41	1.29	1.54	< 0.0001	85	1.73	1.39	2.13	< 0.0001
1 oc in FDR, none of criteria 1-7	817	1.36	1.27	1.45	< 0.0001	323	1.60	1.43	1.79	< 0.0001	494	1.23	1.13	1.35	< 0.0001
1 oc in SDR, none of criteria 1-7	101	1.19	0.97	1.44	0.09	93	1.21	0.98	1.48	0.07	8	0.98	0.49	1.95	0.94

^a first degree relative (parent, sibling)^b second degree relative (grandparent, aunt/uncle, half-sibling)^c breast cancer^d ovarian cancer

Figure 2 Cumulative risk of breast cancer for women that fulfilled high risk criteria for breast and ovarian cancer syndrome

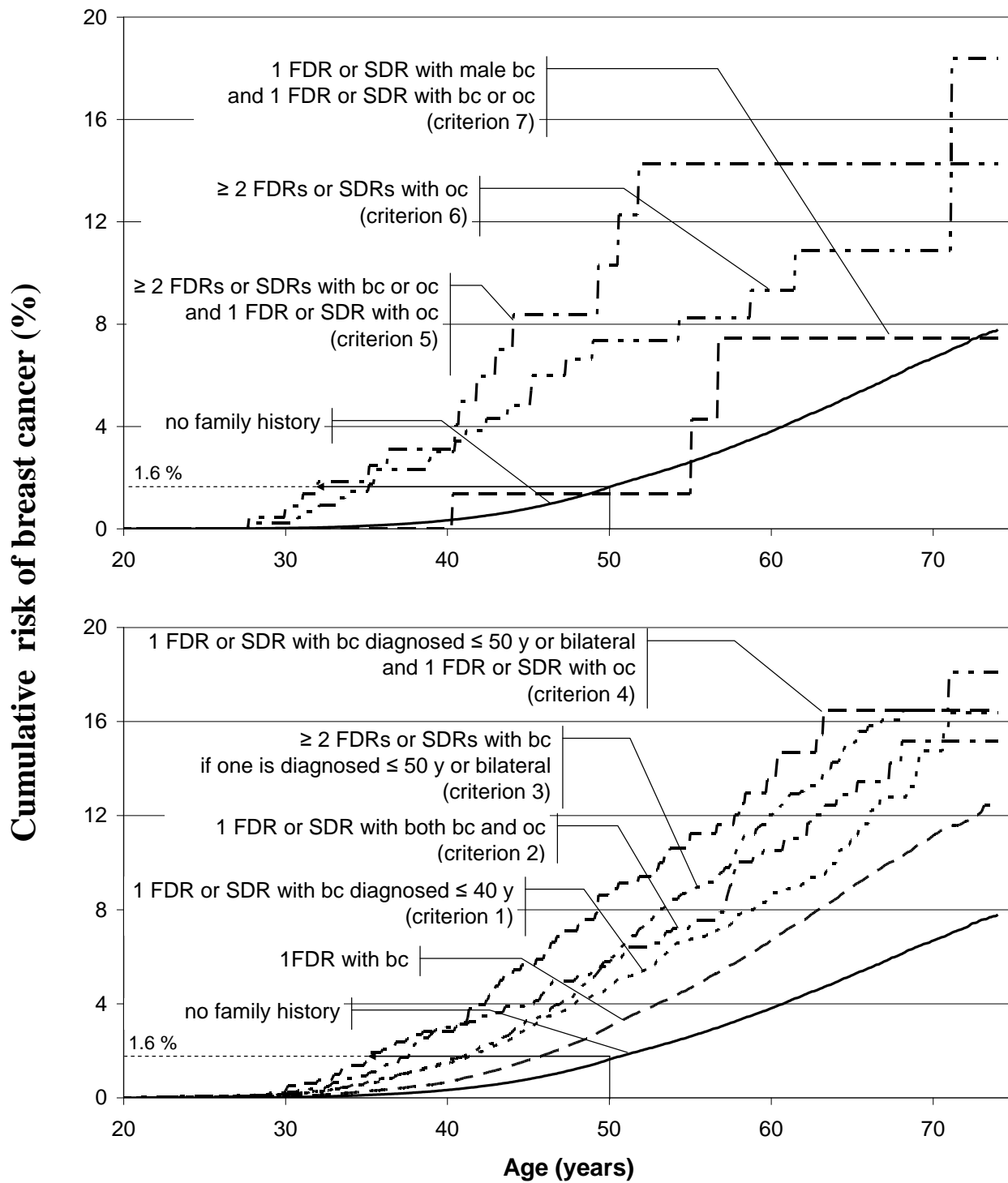


Table 2 Cumulative risk of breast cancer by age 50 and 70 years

Criterion	50 years			70 years		
	CR(%)	95% CI		CR (%)	95% CI	
1 1 FDR ^a or SDR ^b with bc ^c diagnosed ≤ 40 y	4.7	4.1	5.4	14.7	12.0	17.5
2 1 FDR or SDR with both bc and oc ^d	5.8	4.2	7.4	15.2	11.3	19.0
3 ≥ 2 FDRs or SDRs with bc if one is diagnosed ≤ 50 y or bilateral	5.8	4.9	6.8	16.5	14.2	18.7
4 1 FDR or SDR with bc diagnosed ≤ 50 y or bilateral and 1 FDR or SDR with oc	8.9	6.4	11.4	16.5	12.0	20.9
5 ≥ 2 FDRs or SDRs with bc or oc and 1 FDR or SDR with oc	10.3	4.0	16.5	14.3	6.2	22.3
6 ≥ 2 FDRs or SDRs with oc	7.4	3.9	10.8	10.9	5.7	16.1
7 1 FDR or SDR with male bc and 1 FDR or SDR with bc or oc	1.4	0.0	4.0	7.5	0.0	16.0
1 bc in FDR, none of criteria 1-7	3.0	2.9	3.2	11.1	10.7	11.6
1 bc in SDR, none of criteria 1-7	2.1	1.8	2.4	10.1	7.8	12.4
1 oc in FDR, none of criteria 1-7	2.7	2.4	3.0	8.8	8.0	9.5
1 oc in SDR, none of criteria 1-7	2.3	1.6	3.0	8.3	3.1	13.5
No family history	1.6	1.6	1.7	6.7	6.5	6.9

^a first degree relative (parent, sibling)^b second degree relative (grandparent, aunt/uncle, half-sibling)^c breast cancer^d ovarian cancer

Table 3 Age at which women that fulfilled high risk criteria for breast and ovarian cancer syndrome reach the cumulative risk of women lacking a family history at age 50 years and 40 years.

Criterion	N ^e	Age ^f	50 years			Age difference	N ^e	40 years			Age difference
			95% CI		Age ^g			95% CI			
1 1 FDR ^a or SDR ^b with bc ^c diagnosed \leq 40 y	110	40.8	39.4	42.3	9.2	27	32.8	31.4	33.8	7.3	
2 1 FDR or SDR with both bc and oc ^d	18	37.0	35.3	38.8	13.0	4	31.4	28.7	34.3	8.6	
3 \geq 2 FDRs or SDRs with bc if one is diagnosed \leq 50 y or bilateral	66	40.4	38.8	41.9	9.6	17	32.8	31.4	34.1	7.3	
4 1 FDR or SDR with bc diagnosed \leq 50 y or bilateral and 1 FDR or SDR with oc	14	35.1	33.4	38.4	14.9	4	30.0	29.0	32.9	10.0	
5 \geq 2 FDRs or SDRs with bc or oc and 1 FDR or SDR with oc	4	32.0	30.0	41.8	18.0						
6 \geq 2 FDRs or SDRs with oc	6	35.4	32.1	41.1	14.6						
7 1 FDR or SDR with male bc and 1 FDR or SDR with bc or oc											
1 bc in FDR, none of criteria 1-7	952	45.2	44.8	45.7	4.8	153	35.9	35.3	36.8	4.1	
1 bc in SDR, none of criteria 1-7	512	47.3	46.5	48.5	2.7	246	38.2	37.5	38.6	1.8	
1 oc in FDR, none of criteria 1-7	172	45.4	44.5	46.8	4.6	22	33.3	31.7	37.1	6.7	
1 oc in SDR, none of criteria 1-7	84	48.5	47.3	51.3	1.5	47	39.2	38.0	41.1	0.8	

^a first degree relative (parent, sibling)

^b second degree relative (grandparent, aunt/uncle, half-sibling)

^c breast cancer

^d ovarian cancer

^e Number of cases until 'Age'

^f Age to reach the same risk as women lacking a family history at age 50 years

^g Age to reach the same risk as women lacking a family history at age 40 years

Table 3 Number of women that fulfilled two criteria

Criterion	Women that fulfilled two criteria						
	1	2	3	4	5	6	7
1 1 FDR ^a or SDR ^b with bc ^c diagnosed ≤ 40 y	338						
2 1 FDR or SDR with both bc and oc ^d	14	88					
3 ≥ 2 FDRs or SDRs with bc if one is diagnosed ≤ 50 y or bilateral	71	11	289				
4 1 FDR or SDR with bc diagnosed ≤ 50 y or bilateral and 1 FDR or SDR with oc	14	6	14	66			
5 ≥ 2 FDRs or SDRs with bc or oc and 1 FDR or SDR with oc	5	2	11	13	14		
6 ≥ 2 FDRs or SDRs with oc	0	0	0	2	3	23	
7 1 FDR or SDR with male bc and 1 FDR or SDR with bc or oc	0	0	0	0	0	0	3

^a first degree relative (parent, sibling)^b second degree relative (grandparent, aunt/uncle, half-sibling)^c breast cancer^d ovarian cancer