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

3

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5

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23

24 **Abstract**

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

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

31  
32 The women of the nation-wide Swedish Family-Cancer Database were classified according to  
33 clinical criteria based on family history suggesting high risk for hereditary breast ovarian  
34 cancer syndrome. The relative risks of breast cancer were calculated as hazard ratio using Cox  
35 regression. Cumulative risks of breast cancer were estimated with a stratified Cox model  
36 based on Tsiatis' method.

37  
38 The hazard ratios of breast cancer for the considered criteria ranged from 1.50 to 5.99. The  
39 cumulative risks ranged from 1-10% by age 50. The age to reach the same cumulative risk as  
40 women lacking a family history at age 50 years ranged between 32.0-40.8 years.

41  
42 Relative and cumulative risks of women at high risk of breast cancer associated with different  
43 clinical criteria were diverse, which may be helpful to consider when current clinical criteria  
44 are revised. According to the present results, current recommendations of starting clinical  
45 interventions 10 years earlier in high risk women, based on expert opinions, appear justified at  
46 least for the largest high risk groups.

47 **Introduction**

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

68

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

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

75

## 76 **Materials & Methods**

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

88

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

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

107

## 108 **Results**

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

113

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

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

126

127 Hazard ratios were also calculated for women younger than 50 years and older women. The  
128 numbers of women affected by breast cancer before age 50 years were higher than for women  
129 who were diagnosed later. Expectedly, the hazard ratios were also higher for the young  
130 diagnostic group for any of the criteria; the highest hazard ratio of 8.98 was noted for criterion  
131 5.

132

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

143

144 The age to reach the same cumulative risk of breast cancer as women lacking a family history  
145 at the age 50 years (1.6%) and age 40 years (0.33%) is shown in Table 3. The difference 'Age  
146 difference' to reach the risk of 1.6% due to the family history was highest for women with ' $\geq$   
147 2 FDRs or SDRs with bc or oc and 1 FDR or SDR with oc', criterion 5, 18.0 years) and  
148 lowest for women with '1 FDR or SDR affected by bc  $\leq$  40 years', criterion 1, 9.2 years). The  
149 age difference to reach the risk of 0.33% was between 7.2 years ('1 FDR or SDR affected by

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

154

155 The considered criteria were overlapping. Table 4 shows the numbers of women that fulfilled  
156 two criteria. For example, 13 of 14 women with ' $\geq$  2 FDRs or SDRs with bc or oc and 1 FDR  
157 or SDR with oc' (criterion 5) also fulfilled the criterion '1 FDR or SDR with bc diagnosed  $\leq$   
158 50 y or bilateral and 1 FDR or SDR with oc' (criterion 4).

159

## 160 **Discussion**

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

172

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



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

196

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

202 probably due to a lack of power to prove the association for this criterion, the number of  
203 women fulfilling this criterion being small. The largest groups, criteria 1 and 3, included early  
204 onset breast cancers with intermediary hazard ratios. The cumulative incidence of breast  
205 cancer by age 50 was 1.6% in women lacking a family history while that cumulative  
206 incidence was reached between 9 years (95% CI 8 y – 11 y, criterion 1) and 18 years (95%  
207 CI 8 y-20 y, criterion 5) earlier in women belonging to any of the high risk groups (except  
208 criterion 7). The diversity of the risks depending on the criterion is likely to be explained in  
209 part by different proportions of BRCA1/2 mutation carriers in women fulfilling the criteria  
210 [17]. Empirically, mutation detection rates are highest in the groups where we found the  
211 highest risks [17,18] and the characteristics of these groups would also yield increased  
212 predictions for mutation positivity using the BRCAPRO and BOADICEA programs [19-22].  
213 For women carrying mutations in BRCA1/2, the estimated cumulative risk of breast cancer by  
214 the age of 50 years range from 28-39% (BRCA1) and 16-23% (BRCA2), respectively; by age  
215 70, the corresponding risk estimates are between 46-65% and between 45-56% [23-26]. We  
216 have found cumulative breast cancer risks between 1-10% at the age of 50 and between 7-  
217 17% at age 70. These proportions show that the majority of breast cancers even in the high  
218 risk groups are not associated with mutations in BRCA1/2, in agreement with mutation testing  
219 results [17,18]. A major weakness of our study is that we lack data on the mutation status of  
220 the subjects and we thus lack the possibility of risk estimation for women belonging to the  
221 high risk groups but who test negative. The risk of women outside mutation positive families  
222 should, at a minimum, exceed the familial risks of women with one affected FDR diagnosed  
223 with breast cancer, not fulfilling the high risk criteria (i.e., hazard ratio 1.74) [2]. Mutation  
224 negative women with a known familial mutation should be considered as average risk. [27]  
225  
226 Considering that 5257 index women with one FDR diagnosed with breast cancer and not  
227 fulfilling the high risk criteria showed an excess risk of 0.74 (1.74-1.00), the number of cases

228 due to family history was about 2240 ( $5257 \times (0.74/1.74)$ ), which was much higher than the  
229 12 (ie, extra risk of  $4.99 \times 14/5.99$ , criterion 5) to 209 ( $1.63 \times 338/2.63$ , criterion 1) extra  
230 number of cases among the high risk index cases. As these women reached the cumulative  
231 risk of 1.6% 4.8 years before the women lacking a family history, any screening efforts for  
232 these women should be started at 45 years if the others are offered screening at 50 years.

233

234 It has been shown that women with an increased risk of breast cancer might benefit from an  
235 intensified surveillance and risk reducing interventions, which includes an earlier start of  
236 mammography screening, MRI screening, chemoprevention and risk reducing surgery  
237 [9,10,28,29]. The starting age of mammography screening for women at increased risk is not  
238 well established. The American Cancer Society recommends average-risk women to start with  
239 mammography screening at the age of 40 years [30]. Women at increased risk of breast  
240 cancer, which includes women with a relative affected by breast cancer before 50 years, with  
241 two or more relatives affected by breast or ovarian cancer, with male breast cancer and with a  
242 relative affected by two independent breast cancers, are recommended to start 10 years earlier  
243 than average risk women, or 5-10 years earlier than the youngest patient in the family [3]. The  
244 above recommendations are mainly based on expert opinion, with support from the  
245 assessment of breast cancer risk with statistical models or epidemiological studies [6,31-33].  
246 The National Center for Clinical Excellence in the UK recommends for at-risk women annual  
247 mammography screening beginning at the age of 40 years, which is 10 years earlier than the  
248 recommended starting age in the UK for the general population [7]. For the surveillance  
249 between 30 and 40 years by mammography screening for women with BRCA1/2 mutations or  
250 at equivalent high risk, individual strategies are suggested [7].

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

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

267

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

276

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

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

283

284

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289

290 **References**

- 291 1. Hemminki K, Sundquist J, Bermejo JL (2008) How common is familial cancer? *Ann*  
292 *Oncol* 19:163-167
- 293 2. Evans DG, Lalloo F (2002) Risk assessment and management of high risk familial  
294 breast cancer. *J Med Genet* 39:865-871
- 295 3. Smith RA, Saslow D, Sawyer KA, Burke W, Costanza ME, Evans WP, 3rd, Foster  
296 RS, Jr., Hendrick E, Eyre HJ, Sener S (2003) American Cancer Society guidelines for  
297 breast cancer screening: update 2003. *CA Cancer J Clin* 53:141-169
- 298 4. Hampel H, Sweet K, Westman JA, Offit K, Eng C (2004) Referral for cancer genetics  
299 consultation: a review and compilation of risk assessment criteria. *J Med Genet* 41:81-  
300 91
- 301 5. U.S. Preventive Services Task Force (2005) Genetic risk assessment and BRCA  
302 mutation testing for breast and ovarian cancer susceptibility: recommendation  
303 statement. *Ann Intern Med* 143:355-361
- 304 6. Claus EB, Risch N, Thompson WD (1994) Autosomal dominant inheritance of early-  
305 onset breast cancer. Implications for risk prediction. *Cancer* 73:643-651
- 306 7. McIntosh A, Shaw C, Evans G, Turnbull N, Bahar N, Barclay M, Easton DF, Emery J,  
307 Gray J, Halpin J, Hopwood P, McKay J, Sheppard C, Sibbering M, Watson W,  
308 Wailoo A, Hutchinson A (2004) Clinical Guidelines and Evidence Review for The  
309 Classification and Care of Women at Risk of Familial Breast Cancer. National  
310 Collaborating Centre for Primary Care/University of Sheffield, London
- 311 8. Fackenthal JD, Olopade OI (2007) Breast cancer risk associated with BRCA1 and  
312 BRCA2 in diverse populations. *Nat Rev Cancer* 7:937-948
- 313 9. Moller P, Reis MM, Evans G, Vasen H, Haites N, Anderson E, Steel CM, Apold J,  
314 Lalloo F, Maehle L, Preece P, Gregory H, Heimdal K (1999) Efficacy of early

- 315 diagnosis and treatment in women with a family history of breast cancer. European  
316 Familial Breast Cancer Collaborative Group. *Dis Markers* 15:179-186
- 317 10. Brekelmans CT, Seynaeve C, Bartels CC, Tilanus-Linthorst MM, Meijers-Heijboer  
318 EJ, Crepin CM, van Geel AA, Menke M, Verhoog LC, van den Ouweland A, Obdeijn  
319 IM, Klijn JG (2001) Effectiveness of breast cancer surveillance in BRCA1/2 gene  
320 mutation carriers and women with high familial risk. *J Clin Oncol* 19:924-930
- 321 11. Hemminki K, Li X, Pina K, Granstrom C, Vaittinen P (2001) The nation-wide  
322 Swedish family-cancer database--updated structure and familial rates. *Acta Oncol*  
323 40:772-777
- 324 12. Centre for Epidemiology (2007) Cancer incidence in Sweden 2005. The National  
325 Board of Health and Welfare, Stockholm
- 326 13. Hemminki K, Granström C, Sundquist J, Lorenzo Bermejo J (2006) The updated  
327 Swedish family-cancer database used to assess familial risks of prostate cancer during  
328 rapidly increasing incidence *Heredit Cancer in Clin Pract* 4:186-192
- 329 14. Tsiatis A (1981) A Large Sample Study of the Estimates for the Integrated Hazard  
330 Function in Cox's Regression Model for Survival Data. *Annals of Statistics* 9:93-108
- 331 15. Lai TL, Su Z (2006) Confidence intervals for survival quantiles in the Cox regression  
332 model. *Lifetime Data Anal* 12:407-419
- 333 16. Turnbull C, Rahman N (2008) Genetic predisposition to breast cancer: past, present,  
334 and future. *Annu Rev Genomics Hum Genet* 9:321-345
- 335 17. German Consortium for Hereditary Breast and Ovarian Cancer (2002) Comprehensive  
336 analysis of 989 patients with breast or ovarian cancer provides BRCA1 and BRCA2  
337 mutation profiles and frequencies for the German population. *Int J Cancer* 97:472-480
- 338 18. Frank TS, Deffenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, Gumper  
339 KL, Scholl T, Tavtigian SV, Pruss DR, Critchfield GC (2002) Clinical characteristics

- 340 of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000  
341 individuals. *J Clin Oncol* 20:1480-1490
- 342 19. Parmigiani G, Berry D, Aguilar O (1998) Determining carrier probabilities for breast  
343 cancer-susceptibility genes BRCA1 and BRCA2. *Am J Hum Genet* 62:145-158
- 344 20. Antoniou AC, Pharoah PD, McMullan G, Day NE, Stratton MR, Peto J, Ponder BJ,  
345 Easton DF (2002) A comprehensive model for familial breast cancer incorporating  
346 BRCA1, BRCA2 and other genes. *Br J Cancer* 86:76-83
- 347 21. Berry DA, Iversen ES, Jr., Gudbjartsson DF, Hiller EH, Garber JE, Peshkin BN,  
348 Lerman C, Watson P, Lynch HT, Hilsenbeck SG, Rubinstein WS, Hughes KS,  
349 Parmigiani G (2002) BRCAPRO validation, sensitivity of genetic testing of  
350 BRCA1/BRCA2, and prevalence of other breast cancer susceptibility genes. *J Clin*  
351 *Oncol* 20:2701-2712
- 352 22. Antoniou AC, Pharoah PP, Smith P, Easton DF (2004) The BOADICEA model of  
353 genetic susceptibility to breast and ovarian cancer. *Br J Cancer* 91:1580-1590
- 354 23. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N,  
355 Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang  
356 N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H,  
357 Thorlacius S, Eerola H, Nevanlinna H, Syrjakoski K, Kallioniemi OP, Thompson D,  
358 Evans C, Peto J, Lalloo F, Evans DG, Easton DF (2003) Average risks of breast and  
359 ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series  
360 unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet*  
361 72:1117-1130
- 362 24. Chen S, Iversen ES, Friebel T, Finkelstein D, Weber BL, Eisen A, Peterson LE,  
363 Schildkraut JM, Isaacs C, Peshkin BN, Corio C, Leondaridis L, Tomlinson G, Dutson  
364 D, Kerber R, Amos CI, Strong LC, Berry DA, Euhus DM, Parmigiani G (2006)



- 365 Characterization of BRCA1 and BRCA2 mutations in a large United States sample. J  
366 Clin Oncol 24:863-871
- 367 25. Chen S, Parmigiani G (2007) Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin  
368 Oncol 25:1329-1333
- 369 26. Anglian Breast Cancer Study Group (2000) Prevalence and penetrance of BRCA1 and  
370 BRCA2 mutations in a population-based series of breast cancer cases. Br J Cancer  
371 83:1301-1308
- 372 27. Berliner JL, Fay AM (2007) Risk assessment and genetic counseling for hereditary  
373 breast and ovarian cancer: recommendations of the National Society of Genetic  
374 Counselors. J Genet Couns 16:241-260
- 375 28. Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Robidoux A,  
376 Bevers TB, Kavanah MT, Atkins JN, Margolese RG, Runowicz CD, James JM, Ford  
377 LG, Wolmark N (2005) Tamoxifen for the prevention of breast cancer: current status  
378 of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer  
379 Inst 97:1652-1662
- 380 29. Eccles DM (2004) Hereditary cancer: guidelines in clinical practice. Breast and  
381 ovarian cancer genetics. Ann Oncol 15 Suppl 4:iv133-138
- 382 30. Smith RA, Cokkinides V, Eyre HJ (2007) Cancer screening in the United States, 2007:  
383 a review of current guidelines, practices, and prospects. CA Cancer J Clin 57:90-104
- 384 31. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, Mulvihill JJ (1989)  
385 Projecting individualized probabilities of developing breast cancer for white females  
386 who are being examined annually. J Natl Cancer Inst 81:1879-1886
- 387 32. Tyrer J, Duffy SW, Cuzick J (2004) A breast cancer prediction model incorporating  
388 familial and personal risk factors. Stat Med 23:1111-1130
- 389 33. Decarli A, Calza S, Masala G, Specchia C, Palli D, Gail MH (2006) Gail model for  
390 prediction of absolute risk of invasive breast cancer: independent evaluation in the

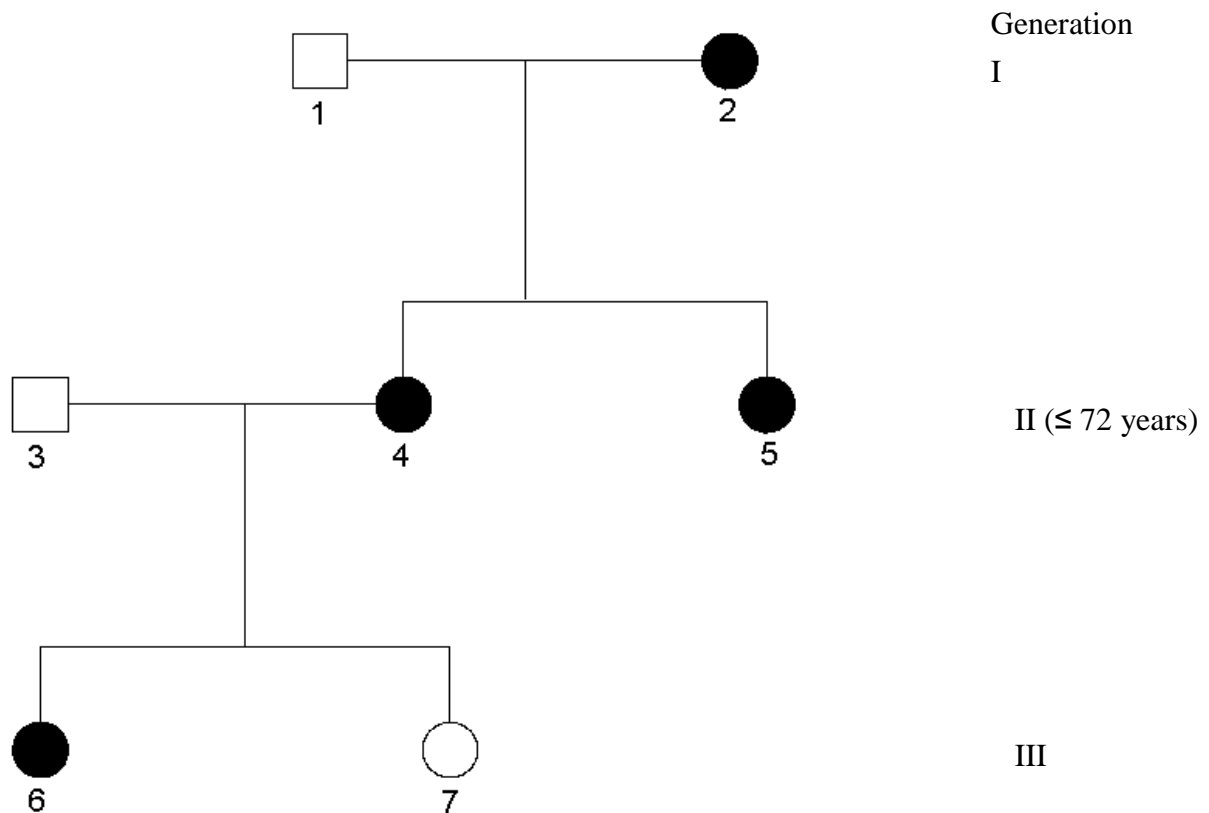
- 391 Florence-European Prospective Investigation Into Cancer and Nutrition cohort. *J Natl*  
392 *Cancer Inst* 98:1686-1693
- 393 34. Moss SM, Cuckle H, Evans A, Johns L, Waller M, Bobrow L (2006) Effect of  
394 mammographic screening from age 40 years on breast cancer mortality at 10 years'  
395 follow-up: a randomised controlled trial. *Lancet* 368:2053-2060
- 396 35. IARC (2002) Breast cancer screening. IARC Press, Lyon
- 397 36. Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, Morris E, Pisano E,  
398 Schnall M, Sener S, Smith RA, Warner E, Yaffe M, Andrews KS, Russell CA (2007)  
399 American Cancer Society guidelines for breast screening with MRI as an adjunct to  
400 mammography. *CA Cancer J Clin* 57:75-89
- 401 37. National Collaborating Centre for PrimaryCare (2006) The classification and care of  
402 women at risk of familial breast cancer in primary, secondary and tertiary care -  
403 Update. <http://www.nice.org.uk/nicemedia/pdf/CG41fullguidance.pdf>. Accessed 6  
404 May 2009
- 405 38. Cuzick J, Powles T, Veronesi U, Forbes J, Edwards R, Ashley S, Boyle P (2003)  
406 Overview of the main outcomes in breast-cancer prevention trials. *Lancet* 361:296-  
407 300
- 408 39. Gail MH, Costantino JP, Bryant J, Croyle R, Freedman L, Helzlsouer K, Vogel V  
409 (1999) Weighing the risks and benefits of tamoxifen treatment for preventing breast  
410 cancer. *J Natl Cancer Inst* 91:1829-1846

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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



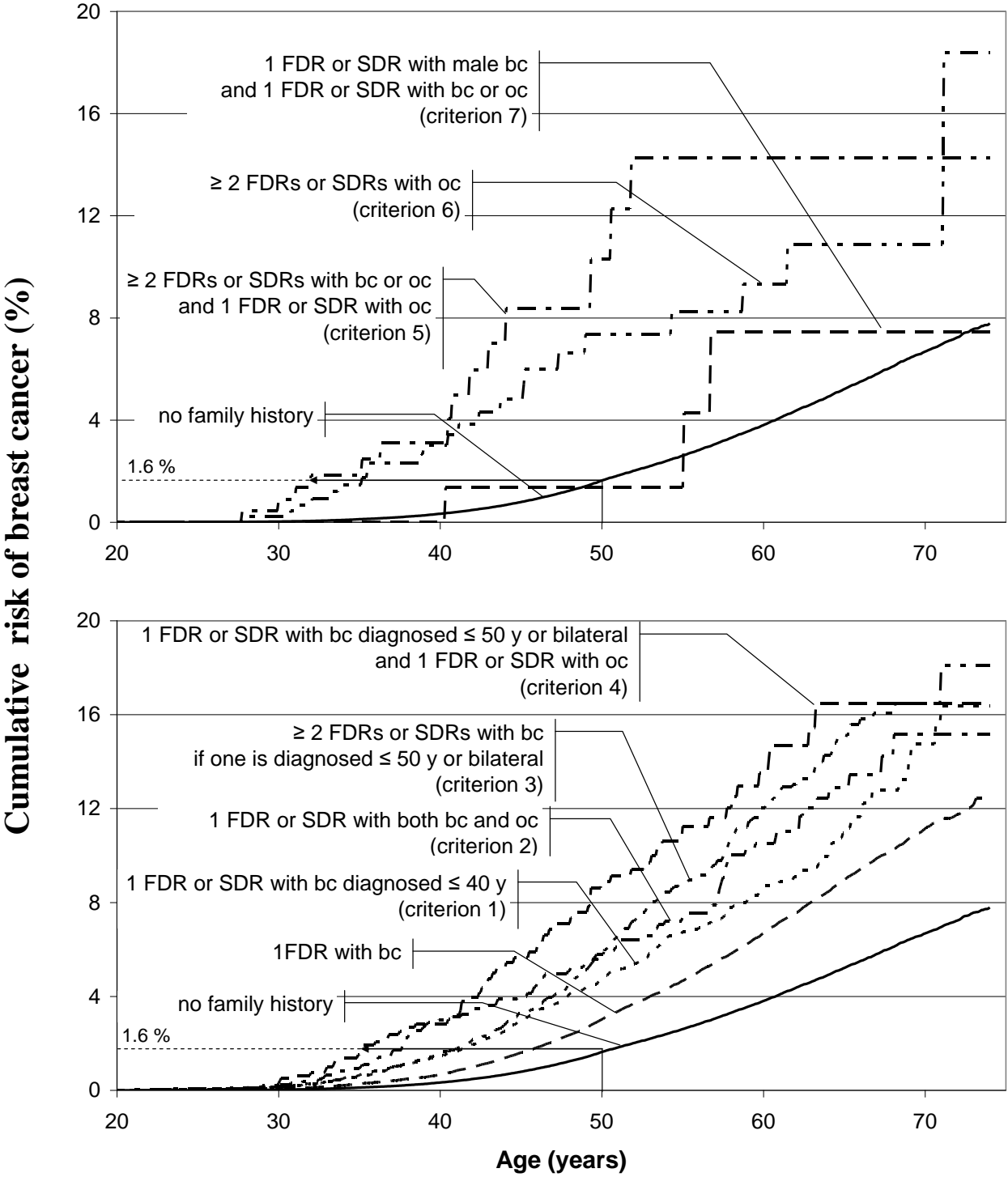
	Familial relationship	Example	Cancer site of relative	
			Breast	Ovary
First degree relatives	mother - daughter	2-4	3938	699
	sister - sister	4-5	2160	212
Second degree relatives	grandmother - granddaughter	2-6	399	80
	aunt - niece	5-6	211	44
	half-sister - half-sister	not shown	160	18

**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 <sup>a</sup> or SDR <sup>b</sup> with bc <sup>c</sup> 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 <sup>d</sup>	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	

<sup>a</sup> first degree relative (parent, sibling)<sup>b</sup> second degree relative (grandparent, aunt/uncle, half-sibling)<sup>c</sup> breast cancer<sup>d</sup> 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 <sup>a</sup> or SDR <sup>b</sup> with bc <sup>c</sup> diagnosed $\leq$ 40 y	4.7	4.1	5.4	14.7	12.0	17.5
2 1 FDR or SDR with both bc and oc <sup>d</sup>	5.8	4.2	7.4	15.2	11.3	19.0
3 $\geq$ 2 FDRs or SDRs with bc if one is diagnosed $\leq$ 50 y or bilateral	5.8	4.9	6.8	16.5	14.2	18.7
4 1 FDR or SDR with bc diagnosed $\leq$ 50 y or bilateral and 1 FDR or SDR with oc	8.9	6.4	11.4	16.5	12.0	20.9
5 $\geq$ 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 $\geq$ 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

<sup>a</sup> first degree relative (parent, sibling)<sup>b</sup> second degree relative (grandparent, aunt/uncle, half-sibling)<sup>c</sup> breast cancer<sup>d</sup> 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 <sup>e</sup>	Age <sup>f</sup>	50 years		Age difference	N <sup>e</sup>	40 years		Age difference	
			95% CI				95% CI			
1 1 FDR <sup>a</sup> or SDR <sup>b</sup> with bc <sup>c</sup> 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 <sup>d</sup>	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

<sup>a</sup> first degree relative (parent, sibling)

<sup>b</sup> second degree relative (grandparent, aunt/uncle, half-sibling)

<sup>c</sup> breast cancer

<sup>d</sup> ovarian cancer

<sup>e</sup> Number of cases until 'Age'

<sup>f</sup> Age to reach the same risk as women lacking a family history at age 50 years

<sup>g</sup> 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 <sup>a</sup> or SDR <sup>b</sup> with bc <sup>c</sup> diagnosed $\leq 40$ y	338						
2 1 FDR or SDR with both bc and oc <sup>d</sup>	14	88					
3 $\geq 2$ FDRs or SDRs with bc if one is diagnosed $\leq 50$ y or bilateral	71	11	289				
4 1 FDR or SDR with bc diagnosed $\leq 50$ y or bilateral and 1 FDR or SDR with oc	14	6	14	66			
5 $\geq 2$ FDRs or SDRs with bc or oc and 1 FDR or SDR with oc	5	2	11	13	14		
6 $\geq 2$ 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

<sup>a</sup> first degree relative (parent, sibling)

<sup>b</sup> second degree relative (grandparent, aunt/uncle, half-sibling)

<sup>c</sup> breast cancer

<sup>d</sup> ovarian cancer