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► **To cite this version:**

D Gareth Evans, Insiya Susnerwala, John Dawson, Emma Woodward, Eamonn R Maher, et al..
Risk of breast cancer in male BRCA2 carriers. *Journal of Medical Genetics*, 2010, 47 (10), pp.710.
10.1136/jmg.2009.075176 . hal-00557385

HAL Id: hal-00557385

<https://hal.science/hal-00557385>

Submitted on 19 Jan 2011

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Risk of breast cancer in male *BRCA2* carriers

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Word count 1126

Abstract

The risk of breast cancer for unaffected men who test positive for a *BRCA2* mutation is based on very few retrospective studies. We have used both retrospective and prospective analysis in 321 families with pathogenic *BRCA2* mutations. Three breast cancers occurred in male first degree relatives after family ascertainment in 4140 years of follow up suggesting a risk of breast cancer to 80 years of 8.9%. A second analysis excluding index cases identified 16 breast cancers in 905 first degree male relatives on which Kaplan Meier analysis was performed after assigning carrier status. This analysis confirmed that breast cancer risk in males was 7.1% (standard error 5.2-8.6%) by age 70 years and 8.4% (standard error 6.2-10.6%) by age 80 years.

The risk of breast cancer in male *BRCA2* carriers is still in question. Only three previous studies have assessed lifetime risk in males [1-3]. The second of these emphasised the need for further studies [2]. We have assessed the risk of breast cancer amongst males in families with proven *BRCA2* mutations from the adjoining health regions centralised around Manchester and Birmingham in Central North West England. Families were ascertained in the two genetic centres covering a population of around 10 million people. Testing generally starts with an affected family member in a family with more than one affected individual and was cascaded out from the index case as requested by the family. Uptake of testing in males was considerably lower than in females [3]. We have developed a dedicated database that enters all male first degree relatives (FDRs) of mutation carriers aged >20 years [4,5].

There were 321 families with proven pathogenic *BRCA2* mutations. In these families there were 20 male index cases of whom 15 had developed breast cancer (age range 29-79 years median 65.3) One had bilateral breast cancer. There were 905 male FDRs of proven *BRCA2* mutation carriers. 18/905 (2%) had developed breast cancer (age range 46.8-74 years median 61.7). Eight further male breast cancers occurred amongst second degree relatives including one with bilateral disease, two were confirmed as mutation positive. In 4140 years of follow up from date of family ascertainment in the genetics departments breast cancers had occurred in 3/667 male FDRs (0.72 per 1000). 238 male FDRs had died before the family ascertainment date. As all male FDRs >20 years were on the dataset this would mean that each male had a potential 60 years of risk. This would amount to a lifetime risk of 4.32%. However, only half of the FDRs would be mutation carriers as such the estimated risk in males would be 8.6%. Given the small number of male cancers in follow up we validated this risk by assessing male breast cancer amongst proven or assumed *BRCA2* mutation carriers excluding the index case. In this mostly retrospective analysis in addition to all males testing positive, FDR males were assigned mutation status on a 50% basis omitting every other male on the basis of

successive age at last follow up. FDR males with breast cancer were assumed to be mutation carriers as the relative risk of breast cancer in male *BRCA2* carriers is at least 100 fold [7] and male breast cancer phenocopies have not been described to our knowledge [6]. Male FDRs with pancreatic, and prostate cancer were assigned mutation status on a 4:1 basis omitting the fifth case in successive age order of cancer. Stomach cancers were assigned on a 2:1 basis. This decision was based on the described 2.5-5.9 fold relative risk in *BRCA2* carriers for pancreas (3.51-5.9) and prostate cancer (2.5-4.65) and 1.2-2.59 relative risk of stomach cancer [2,8]. After exclusion of the index case 122 males were identified as proven carriers from family testing six of these had breast cancer. Forty one male FDRs had tested negative in predictive testing. Ten male FDRs of unknown mutation status were assumed to be carriers as they had suffered from breast cancer. Of 29 prostate cancers of unknown mutation status in FDRs 24 were assigned mutation positive status as were 5/6 with pancreatic cancer and 10/14 stomach cancers. Of the remaining 683 male FDRs of unknown status 333 were assigned as positive (table 1). Thus 508 male *BRCA2* carriers or assumed carriers were identified. Cumulative risk of breast cancer was assessed by Kaplan Meier analysis (Figure 1). This showed a risk of 7.1% (standard error 5.2-8.6%) by age 70 years and 8.4% (standard error 6.2-10.6%) by age 80.

In the first report to assess male breast cancer risks two large *BRCA2*-linked families that contained four male breast carcinoma cases were evaluated [1]. The estimated cumulative risk for male breast carcinoma by age 70 years was 6.3%. In a separate study of 164 families with *BRCA2* mutations, the estimated cumulative risk of breast cancer for male *BRCA2* mutations carriers was 2.8% by 70 years of age and 6.9% by 80 years [2]. More recently, the estimated cumulative risk of breast carcinoma for male *BRCA2* mutation carriers was 6.8% (95% CI = 3.2-12%) by age 70 years and 8.3% to age 80 years [3]. The latter study was based on 23 families ascertained

through a male breast cancer. This study based risk estimates on the relative risks of male breast cancer in *BRCA2* versus population risks assuming certain *BRCA2* allele frequencies. A further study found that the relative risk of breast cancer for male *BRCA2* carriers was estimated to be 102 fold [6]. Our study is the first to have assessed male breast cancer risk prospectively from family ascertainment. Although the numbers are small and confidence intervals will clearly be wide the rates of breast cancer prospectively are in keeping with a lifetime risk to 80 years of close to 9%. To corroborate this we carried out an analysis of cumulative risk in male FDRs taking advantage of clinical testing but excluding the bias of the index case. There are flaws in such a study in that excluding the index case alone may not be sufficient, but a contrary argument would be that there would be a tendency to preferentially test a male breast cancer case first in families with multiple affected individuals. In any case the risks to 70 and 80 years are similar to those found in the most recent study using a different approach to analysis [3]. Ours is also now the largest study of *BRCA2* affected families. Based on the now four studies to assess male breast cancer risks using different study designs it would appear appropriate to quote lifetime risks (to age 70-80 years) of breast cancer to males in the Western world of between 6-9%. These risk are sufficient to increase awareness of breast cancer amongst males in *BRCA2* families and to stress the importance of early presentation with breast symptoms.

Acknowledgements: This work was supported by the Biomedical Research Centre at Central Manchester Foundation Trust and a grant from the Genesis Appeal.

Conflict of interest: None

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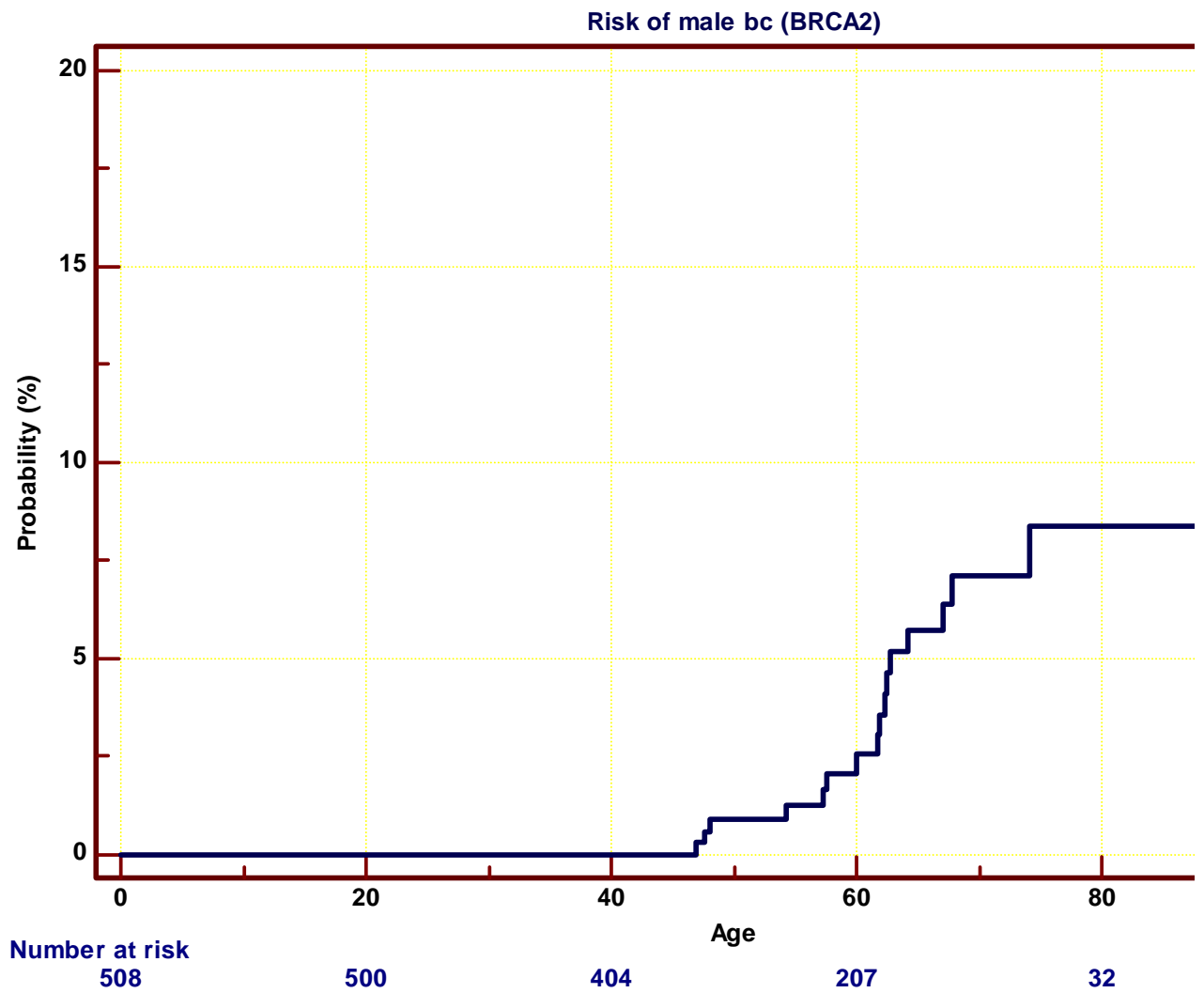
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Table 1: Assignment of male FDRs based on cancer diagnosis

Cancer	Number testing positive or (obligate carriers)	Number testing negative	Number at risk with unknown mutation status	Number assigned positive status	Total number in analysis
Breast cancer	6 (1)	0	10	10	16
Pancreatic cancer	4 (2)	0	6	5	9
Stomach cancer	5 (4)	0	14	10	15
Prostate cancer	17 (7)	0	29	24	41
melanoma	1	1	4	2	3
Lung cancer	0	0	22	11	11
Bladder cancer	3 (1)	1	3	2	5
Cholangiocarcinoma	1	0	2	2	3
Ampullary cancer	0	0	1	1	1
Other cancer	13 (11)	0	33	16	29
Unaffected	72 (19)	39	606	303	375
Total	122 (45)	41	752	386	508

Figure 1: Kaplan Meier cumulative onset of breast cancer in 508 male *BRCA2* carriers and presumed carriers.



Risk to age 70 years: 7.1% standard error 5.2-8.6%

Risk to age 80 years: 8.4% standard error 6.2-10.6%