LETTER TO JMG

Change in the penetrance of founder *BRCA1/2* mutations? A retrospective cohort study

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There has been much discussion regarding the penetrance of breast cancer in *BRCA1/2* mutation carriers (hereafter "carriers"). Both genetic and epigenetic factors could be influencing the reported penetrance estimates. We wanted to establish whether the penetrance of *BRCA1/2* mutations is changing over time. To limit the genetic variability, we studied a cohort of 292 Ashkenazi Jewish (AJ) women diagnosed with first primary invasive breast cancer between 1 January 1980 and 1 November 1995 at a single Montreal Hospital, without regard to family history. All women were diagnosed at less than 65 years of age. Pathology blocks were identified from all women and the three AJ founder mutations in *BRCA1/2* (185delAG, 5382insC (*BRCA1*) and 6174delT (*BRCA2*)) were identified in archival samples using PCR based techniques described previously.[1] We identified 41 (14%, 95% CI 10.2-18.6) *BRCA1/2* carriers (31 in *BRCA1* and 10 in *BRCA2*). The difference in mutation frequency between *BRCA1* and *BRCA2* carriers (10.6% *v* 3.4%) is statistically significant (Z=3.40, p=0.0007). Given that the population allele frequencies of AJ founder mutations in *BRCA1* and *BRCA2* are approximately equal (~1%), this would suggest that *BRCA1* has a higher penetrance than *BRCA2* by age 65. This observation supports previous data from Canada.[2] We then divided the data into quartiles by year of diagnosis and determined whether the proportion of mutation carriers was changing over time. The number of founder *BRCA1/2* mutations per quartile of year of diagnosis increased from eight (11.0%) to 15 (20.5%) over the 15 year period of the study, and the χ^2 p value for the trend in mean scores was 0.047 (table 1). This suggests that the penetrance of *BRCA1/2* mutations to the age of 65 years is increasing. This is important, as previous studies of penetrance have not taken into account the year of diagnosis of the mutation carriers.[3]

The median age at diagnosis for all subjects was 53.6 years. Interestingly, *BRCA2* carriers were diagnosed at a statistically significantly older median age than were *BRCA1* carriers (59.8 years *v* 47.5 years, p=0.02, Mann-Whitney test). To study further the change in penetrance over time, we studied the effect of year of diagnosis (YOD) on age at diagnosis. The median YOD for all subjects was 1988.5. The median age at diagnosis for *BRCA1* carriers diagnosed below the 50th centile was 50.7 years. For those diagnosed in the second half of the cohort study, the median age at diagnosis was 44.9 years (p=0.21). Although this difference does not reach statistical significance, in 251 non-carriers the equivalent ages were 54.5 and 53.3 years respectively, a much closer difference in age at diagnosis (p=0.98). For the 10 *BRCA2* carriers, this difference was almost 10 years (60.4 years *v* 50.6 years, dichotomised at the median YOD, p=0.38). To show the change in age at diagnosis over time, we plotted the YOD against the age of diagnosis in *BRCA1* carriers, in *BRCA2* carriers, and in non-carriers (fig 1). The slopes for *BRCA1* (point estimate of the slope –0.724, p=0.066) and *BRCA2* (slope –0.303, p=0.68) clearly deviate from the non-carrier slope (–0.024, p=0.85), suggesting an interaction between mutation status and YOD. However, perhaps because of the small numbers of mutation carriers, these slopes are not statistically different, and their confidence intervals overlap (fig 1). The age at diagnosis of breast cancer among the non-carriers is virtually constant over time, whereas the age at diagnosis is falling for women diagnosed more recently with *BRCA1* or *BRCA2* related breast cancer. Taken together, these findings suggest that the age dependent penetrance of *BRCA1/2* mutations could be increasing.

Table 1 *BRCA1/2* mutation frequencies by year of diagnosis

Quartile	Median age at diagnosis (y)	No mutation (%)	*BRCA1* (%)	*BRCA2* (%)
1980.1-1984.72	57.9	65 (89)	6 (8)	2 (3)
1984.72-1988.51	53.8	66 (90)	6 (8)	1 (1)
1988.51-1992.50	55.5	62 (85)	9 (12)	2 (3)
1992.50-1995.87	50.6	58 (79)	10 (14)	5 (7)
1980-1995	53.6	251 (86)	31 (11)	10 (3)

Overall χ^2=5.86, df=6, p=0.44.
χ^2 for trend in mean scores 3.50, df=1, p=0.047.
When *BRCA1/2* combined, χ^2 for linear trend 3.55, p=0.060.

Some previous pedigree based studies have found that the age of diagnosis of familial and/or hereditary breast cancer is falling. Genetic anticipation,[4] birth cohort effects,[5] or ascertainment bias[6] have all been suggested as possible underlying mechanisms. It is important to note that bias cannot be ruled out in any series of mutation carriers that were not ascertained at the time of diagnosis and without reference to family history.

Another possible reason why we might observe an increase in mutation frequency and a fall in age at diagnosis is that there were changes in referral patterns to the single hospital where all the subjects were diagnosed. For example, young women with a family history of breast cancer could have been preferentially referred in the latter years (1990-1995) of the study period to this hospital, whereas those without a family history or older women were referred to other hospitals. This would result in more *BRCA1/2* mutation carriers being diagnosed at the study hospital without any change in penetrance. This is possible, but we cannot confirm or refute this suggestion as our study is anonymised and we have no family history information. It does, however, seem a somewhat implausible scenario. Notably, in fig 1, there is virtually no change in the age at diagnosis of non-carriers, so whatever is causing the fall in the overall median age at diagnosis per quartile (table 1) can only be acting on the carrier subgroup.

Another possible explanation for our observation is that from the mid-1980s onwards, some young high risk women decided to undergo preventive oophorectomy, which may have

Abbreviations: AJ, Ashkenazi Jewish; YOD, year of diagnosis

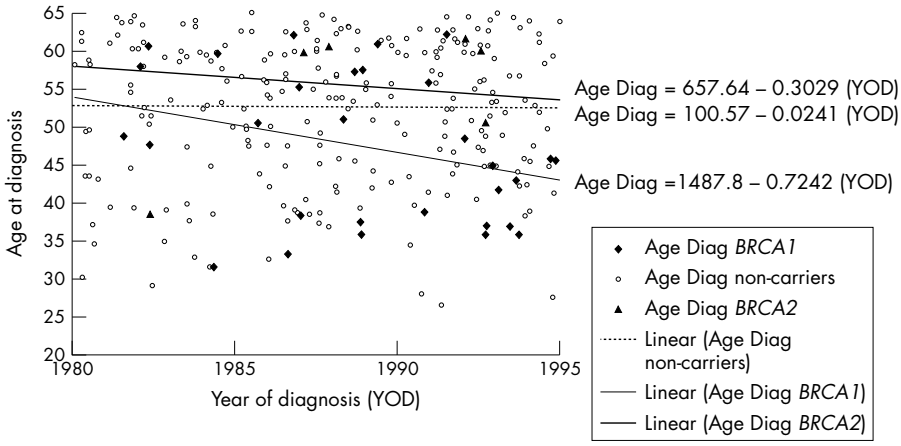

Figure 1 Age at diagnosis (Y axis) is plotted against year of diagnosis (X axis). All 292 subjects recruited into the study are included. The key for the figure is shown in the box inset into the figure. The characteristics of the slopes are as follows: *BRCA1*, slope –0.72 (95% CI –1.56-0.12), r^2=0.097, p=0.066; *BRCA2*, slope –0.30 (95% CI –1.98-1.37), r^2=0.021, p=0.69; non-carriers, slope –0.02 (95% CI –0.28-0.23), p=0.85.

delayed or prevented their breast cancer diagnosis.[7] This would result in a recent deficiency of late onset cases, and could resemble the pattern of an excess of early onset cases. This is a possible explanation for the decrease in the age of diagnosis of mutation carriers over time, but cannot explain the increase in the total number of mutation carriers in recent years.

In the general population, mammographic screening is likely to downstage those cancers identified. To consider this potential source of bias, we analysed the change over time in the size of the primary tumour and the probability of associated positive lymph nodes. Cancers in non-carriers diagnosed more recently were indeed smaller (median size 1.5 cm) when compared to those diagnosed earlier (1.8 cm, p=0.02, dichotomised at median YOD). In contrast, *BRCA1/2* related cancers were not different in size (median size of 2.0 cm for those diagnosed before and after the median YOD, p=0.73). We noticed that among non-carriers, the proportion of women with node positive breast cancers was decreasing with time, whereas this effect was not seen in *BRCA1/2* carriers. In a logistic regression model developed to predict nodal status over time, there was a noticeable interaction between mutation status and YOD. *BRCA1/2* carriers diagnosed recently were twice as likely (odds ratio 2.1) to be node positive than were those diagnosed earlier, whereas in non-carriers the effect was reversed: non-carriers diagnosed earlier were twice as likely (odds ratio 1.9) as were those diagnosed recently to be node positive (p=0.07). Neither of these results suggest that mammography has resulted in a downstaging of *BRCA1/2* related breast cancer. Mammography may also diagnose invasive breast cancer at younger ages than in non-screened subjects, and in recent years *BRCA1/2* carriers may have used screening mammography at younger ages than non-carriers because of a positive family history of breast cancer. However, in another analysis of the same dataset, we showed that mammography is particularly ineffective in detecting small tumours in young *BRCA1/2* mutation carriers,[8] which is just the group that might be expected to be artificially skewing our results. It therefore seems unlikely that either potential biases are present in our dataset.

The importance of our observation is that the potential benefit of preventive interventions is intimately related to the incidence rate of cancer in those at risk. If the age dependent penetrance is increasing, then this should be taken into account when counselling unaffected women. Moreover, as our study is genetically restricted, it is likely that the change in penetrance we observed is the result of epigenetic (that is, reversible) factors. If such factors could be identified, then it would seem possible that the effect could be diminished, or even reversed. Several unmeasured factors could be contributing separately to the increase in number of mutations and the decrease in age at diagnosis with time, but it is important to note that these factors appear to be acting on the carriers only. This could suggest that the carriers are responding differently to pre-existing environmental or hormonal exposures. Nevertheless, we recognise that proving a change in penetrance of a cancer related gene over time is challenging and, therefore, these data can be regarded only as suggestive early evidence for such an effect. Large population based prospective cohort studies will be required to confirm or refute our preliminary observations.

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ECHO

HLA-DR4 and risk of spondyloarthropathy

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French investigators have identified in 70 families a second allele predisposing to a group of inflammatory rhematic diseases—the spondyloarthropathies (SpA). MHC HLA-B27 is associated with all familial SpA—ankylosing spondylitis; reactive arthritis; a subspecies of psoriatic arthritis; arthritis with inflammatory bowel disease; and undifferentiated spondyloarthropathy—but now HLA-DR4 has also been shown to be significantly associated, independently of linkage disequilibrium with HLA-B27.

The investigators found that the gene frequencies of HLA-A, B, C in the HLA-B27 haplotypes in these families were similar to those in a random sample of the French population; the same was true for HLA-DR except for DR 13, which was overrepresented. Transmission disequilibrium tests for HLA-DR alleles performed on all haplotypes showed excess transmission of HLA-DR4 to family members affected with SpA (52 positive *v* 20 negative; 169 tested) and reduced transmission in unaffected siblings with HLA-B27 (10 positive *v* 18 negative; 71 tested). Repeating the test with HLA-B27 negative haplotypes showed excess transmission of HLA-DR4 to family members with SpA (20 positive *v* 6 negative; 156 tested) but the reverse for unaffected siblings with HLA-B27 (2 positive *v* 8 negative; 70 tested), confirming HLA-DR4 was not in linkage disequilibrium with HLA-B27.

The study population included 188 patients and first degree relatives from 70 families with at least two affected members and 198 HLA-B27 negative haplotypes randomly selected from the French population.

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