PROCEEDINGS OF THE ROYAL SOCIETY B

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Proc. R. Soc. B (2012) **279**, 2926–2929
doi:10.1098/rspb.2012.0542
Published online 9 May 2012

Commentary

BRCA1/2 mutations, fertility and the grandmother effect

Various mutations in the 'breast cancer genes' *BRCA1* and *BRCA2* increase the lifetime risks of developing breast and ovarian cancers to high levels [1,2]. Because these cancers mostly develop after the cessation of reproduction—that is, after menopause—the responsible alleles may be selectively neutral, being neither selected for or against. However, there is some risk of developing these cancers before menopause, and the moderate negative selection that this generates, together with the recurrence of the alleles due to mutation, has been used to explain the frequency of *BRCA1* mutations of 1 in 3000 women in the USA [3]. However, a recent study showing that *BRCA1/2* mutations increase female fertility (number of children born) by nearly 50 per cent [4] demands a reanalysis of the selection operating on these alleles.

Smith *et al.* [4] used as their main source of data the Utah Population Database, which identifies putative obligate carriers of *BRCA1/2* mutations based on direct testing of descendants. They show that carriers born before 1930, who would not have used modern contraceptives in their mid-thirties, and who lived until age 45 (thereby completing their reproductive period), had nearly two more children than age-matched controls. After statistically controlling for birth year, age at first birth, age at marriage, the number of offspring that died as children and religious affiliation, carriers had an average of 1.91 more children than controls. For women born during 1930–1974, carriers had 0.61 more children than controls, the smaller (but still statistically significant) difference being presumably due to modern methods of birth control. The increased fertility of carriers was due to shorter birth intervals and a longer reproductive tenure.

These findings are extremely interesting for two reasons. First, *BRCA1* and *BRCA2* are among very few genes for which naturally occurring mutations cause a clear increase in reproduction early in life at a cost of increased mortality late in life, and the best example of these in humans [5]. The trade-off is predicted by one of the two main evolutionary theories of ageing. Both theories follow from the fact that the cumulative probability of death necessarily increases with age even in the absence of senescence (that is, with a constant rate of mortality) [6]. This makes selection weaker at later ages because individuals have a lower probability of being alive at those ages. Consequently, deleterious mutations whose effects are expressed only at later ages will accumulate, resulting in senescence, a scenario known as the mutation accumulation theory [6]. Following the same logic, the antagonistic pleiotropy theory of senescence states that any allele that increases early fertility (or survival) even at the expense of later survival will be favoured by selection [7]. Therefore, the surprising trade-off between early fertility and late survival reported for *BRCA1/2* mutations is strong confirmation of the antagonistic pleiotropy theory.

The second reason these findings are interesting is that the differences in fertility are substantial and imply strong selection for *BRCA1/2* mutations. For women born before 1930, a member of the control group gave birth to 4.19 children and a carrier gave birth to 6.22 children, on average. This represents a 48 per cent increase in fertility. All else (other components of fitness) being equal, such strong selection would quickly drive *BRCA1/2* mutations to fixation. Assuming a human mutation rate of 1.1×10^{-8} per nucleotide per generation [8] and assuming conservatively of the order of 1500 disease-causing mutations for both genes [2], the disease mutation rate for *BRCA1/2* is roughly $U = 1.65 \times 10^{-5}$ per generation. Then, even assuming a small effective population size for humans of $N_e = 2.3 \times 10^4$ [8], the stochastic theory of population genetics [9] tells us that a new mutation with a selection coefficient of $s = 0.48$ will spread to fixation with a probability of $\phi = 0.38$ and that it would take on average $1/(2N_eU\phi) = 3.5$ generations (approx. 105 years) for a new *BRCA1/2* mutation to reach a frequency of 100 per cent. Therefore, these mutations would have become extremely common over human history.

However, not all else is equal, and to estimate the strength of selection on these mutations other components of fitness have to be considered. To estimate the mean number of children that survived to adulthood we must subtract the number of children that died and factor in adult mortality, which are given by Smith *et al.* [4]. Twelve per cent of carriers and five per cent of controls were excluded from the study because they did not reach age 45. The difference in these percentages presumably reflects the difference in risk of developing associated cancers. Conservatively assuming that these women left no surviving offspring lets us calculate the average number of offspring reaching adulthood. After these adjustments, carriers had 5.13 surviving children, and controls 3.65 surviving children (table 1), reducing the increase in fitness due to *BRCA1/2* mutations to 41 per cent. This still represents extremely strong selection, and raises the question: why are these mutations not extremely common?

One answer may be the grandmother effect. This is the argument that the substantial post-menopausal survival of human females, in contrast to those of other primates, is selected because post-menopausal women may increase the number of their grandchildren by supporting their daughters and provisioning their grandchildren [10]. Therefore, the increased fertility of carriers may be

Received 9 March 2012
Accepted 18 April 2012

Table 1. Fitnesses of carriers and controls.

number of children	carrier	control
born	6.22	4.19
died	0.39	0.35
surviving	5.83	3.84
adjusted for adult mortality	5.13	3.65
relative fitness	1.41	1.00

countered by their higher post-menopausal mortality, which reduces the number of their grandchildren. Another possibility is the mother effect: the effect post-menopausal mothers have on the survival of their youngest children [7]. However, a recent comprehensive analysis of the mother effect shows it to be minor and confined to pre-weaning age children, and therefore to be insufficient to explain menopause [11]. Indeed, in the Smith *et al.* study, the mean age at last birth was in the mid-thirties for the pre-1930 cohort, and in the early thirties for the 1930–1974 cohort, meaning the youngest child would be age 10 or more on average when its mother reached menopause [4]. In contrast, grandmothers may increase the fertility of all their offspring. A study of the life histories of Finnish and Canadian women living in farming communities in the eighteenth and nineteenth centuries shows that for every year of survival beyond age 50 a woman produced an extra 0.2 grandchildren by reducing her daughters' birth intervals and increasing the survival of her grandchildren [12].

In the Smith *et al.* study [4], fertilities and childhood survival would have been affected by any grandmother effect present. However, this effect appears to have been small, judging from survival rates of children born to women in the pre-1930 cohort, which are marginally higher for carriers (94%), who had a lower probability of having a living grandmother, than controls (92%). And the children of women born in 1930–1974 had even higher survival rates: 99 per cent for carriers and 98 per cent for controls. This suggests that grandmothers may have little impact on the survival of their grandchildren in modern industrial societies. In contrast, children of Finnish women in eighteenth and nineteenth century farming communities had survival rates of only around 57 per cent [12]. So one possibility is that *BRCA1*/2 mutations are rare because the grandmother effect was stronger in the more distant past.

Because Smith *et al.* give the average birth and death years for the women in their study, it is possible to estimate what the impact of the pre-modern Finnish and Canadian grandmother effect would have been on the number of surviving children produced by carriers and controls born before 1930. Carriers survived past age 50 by 17.72 years and controls by 25.12 years. The impact of the grandmother effect on fitness is the number of a woman's extra grandchildren distributed among her children, whose number is also affected by the grandmother effect (owing to her own mother). And, because these mutations affect female fertility, it is the number of granddaughters that is relevant. If the number of daughters a woman (the daughter) produces is the sum of the number she produces on her own (without help from her mother), W_D, and the additional daughters produced with help from her mother, W_M, then the number of granddaughters she produces is $W_G = (W_D + W_M)^2$ (since her daughters will each produce the same number of daughters). The number of extra granddaughters produced due to the grandmother effect is $\Delta W_G = (W_D + W_M)^2 - W_D^2$. Therefore the number of extra daughters produced by a woman due to help from her mother is $W_M = \Delta W_G/(2W_D + W_M)$, which is estimated by iteration. For the pre-modern Finnish and Canadian grandmother effect of 0.2 extra grandchildren per year of survival after age 50, and assuming a 50 per cent sex ratio, carriers would produce an extra 0.32 daughters, giving them a total of 2.89 daughters, and controls would produce an extra 0.59 daughters, for a total of 2.42 daughters (table 2). Therefore, with this grandmother effect, carriers still have 20 per cent higher fitness than controls.

However, the grandmother effect may have been even stronger in the even more distant past. In hunter–gatherer societies, childhood survival rates may be even lower than in pre-modern agricultural societies, and there are greater opportunities for grandmothers to affect the production and survival of grandchildren because 'gathered' foods are typically difficult to acquire and process [10]. Therefore, grandmother effects ranging from 0.2 to 0.5 extra grandchildren per year of survival after age 50 were explored to determine if a plausible effect could explain the low frequency of *BRCA1*/2 mutations. But even with an effect of 0.5, carriers still have 7 per cent higher fitness than controls (table 2).

Therefore, it appears that the grandmother effect on its own is insufficient to explain the low frequencies of *BRCA1*/2 mutations. An additional factor may be that in hunter–gatherer societies women's fertilities are severely limited due to a short reproductive tenure and long inter-birth intervals, which would reduce the fertility differences between carriers and non-carriers. A typical hunter–gatherer woman reproduces for 15 years and has birth intervals of up to 4 years, meaning she may produce on average as few as 3.75 children over her lifetime [13,14]. If without the grandmother effect the maximum number of surviving children a woman may produce is 4, then a carrier would produce 2 daughters without help and 2.40 daughters with a grandmother effect of 0.2. A non-carrier would still produce 1.82 daughters on her own, but 2.42 with help. This results in 0.6 per cent *lower* fitness for carriers compared with controls. With this net disadvantage for carriers, the expected frequency of *BRCA1*/2 mutations at equilibrium between mutation and selection is approximately $U/s = 1.65 \times 10^{-5}/0.006 = 0.275\%$, which is similar to the geometric mean of recent estimates for modern populations: 0.227 per cent (0.051% [15] and 1.01% [16]). This idea could be tested by measuring the fertilities and survival rates of carriers and non-carriers and grandmother effects in modern hunter–gatherer societies.

Another factor possibly affecting selection on *BRCA1*/2 mutations is that the penetrance (disease risk) of mutations appears to have increased in recent decades [17,18], possibly due to changes in reproductive patterns [19,20]. If penetrance was much lower in our distant past, then selection against *BRCA1*/2 mutations through the grandmother effect would have been weaker because differences in post-menopausal survival between carriers

Table 2. Grandmother effect.

	carrier			control			
grandmother effect[a]	ΔW_G^b	W_M^c	W^d	ΔW_G^b	W_M^c	W^d	s^e
0	0	0	2.57	0	0	1.82	0.41
0.2	1.77	0.32	2.89	2.51	0.59	2.42	0.20
0.3	2.66	0.47	3.04	3.77	0.84	2.66	0.14
0.4	3.54	0.62	3.18	5.02	1.07	2.89	0.10
0.5	4.43	0.75	3.32	6.28	1.28	3.10	0.07

[a]Number of extra grandchildren per year after age 50.
[b]Total number of extra granddaughters due to grandmother effect.
[c]Number of extra daughters due to help from mother.
[d]Total number of daughters.
[e]Selection coefficient: proportion of fitness increase for carriers relative to controls.

and non-carriers would have been smaller. However, if the fertility effects of the mutations are correlated with their penetrance, then fertility differences between carriers and non-carriers would also have been diminished, reducing selection for *BRCA1*/2 mutations. Therefore, to predict frequencies of *BRCA1*/2 mutations in current populations accurately we would need historical values for the strength of the grandmother effect and for fertility and survival differences between carriers and non-carriers. Alternatively, we may assume similar levels of fertility and survival among natural fertility populations. Then, if the historical roles of grandmothers in supporting daughters and provisioning grandchildren vary among societies, or among populations with different demographics, we could test the prediction that *BRCA1*/2 mutation frequency is negatively correlated with the grandmother effect (after controlling for population founder effects on mutation frequencies [2]).

The substantial increase in fertility due to *BRCA1*/2 mutations would, on its own, predict these mutations to be extremely common in modern populations. The fact that they are not requires explanation. Here, it is proposed that the grandmother effect combined with limited female fertilities in hunter–gatherer societies resulted in weak net selection *against* *BRCA1*/2 mutations. This hypothesis may be tested by measuring fertility and survival rate of carriers and non-carriers, and grandmother effects, in modern hunter–gatherer populations.

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