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Whether is the Logic of Russian Roulette Appropriate for Assessing Individual Cancer Risks of Breast Cancer Mutation Carriers among their Clusters?

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Abstract

Breast and ovarian cancers can result from an inherited mutation that runs in the family. An unsolved question is the individual risk for a mutation carrier within her family cluster at some point in time. This question is here interpreted using logic of the Russian roulette in which the revolver is spun only once. If the mean cancer risk for a certain mutation with SEM can be calculated for all clusters in the population, then the arithmetic mean cluster risk ±1.96*SEM can give the confidence interval to predict the probable number of cancers to happen in a similar cluster. This would allow us to estimate risks of carriers younger than 70 and help in making tough diagnostic and preventive decisions.

Keywords: BRCA1; BRCA2; Russian roulette; Cancer risk; Breast cancer; Ovarian cancer.

Introduction

Any healthy woman with a detected mutation related to the Breast Cancer (BC) or the Ovarian Cancer (OC) occurrence (i.e., mutations of BRCA1 and BRCA2 genes), has an age dependent increase in the risk for getting these cancer types. Risks differ between mutation types and among affected populations. Often it is expressed as a range of percentages of getting cancer, until a certain age [1]. Some mutations of these gens may seem not to be linked to increased cancer risks, so these mutations are possibly clinically unimportant.

It is assumed that among women with harmful BRCA1 mutations, some 50% to 65% of them will develop BC and 35% to 46% will develop OC, till the age of 70. For harmful BRCA2 mutations, the rate for BC is 40% to 57% and for OC 13% to 23%, both risks estimated till the age of 70 [1].

For verification of these mutations in oncological patients and their close relatives, genetic diagnostic is necessary. At least in the SE Europe, a very limited willingness to accept the proposed DNA testing is often encountered. This is particularly often, if the lady patient has no daughters and shows no interest in DNA testing, mainly due to the involved test price. A separate issue is iheir attitude towards possible procedures for confirmed mutation carriers that include preventive removal of breasts or ovaries. Most of the mutation carriers consider wide risk ranges not high enough to make prophylactic surgical procedure worthwhile.

The question of individual risks within a small family cluster of mutation carriers

Few years ago, the first author of this manuscript was asked by a medical student about the cancer risk for her aunt with a Breast Cancer (BC) linked mutation. The lady in question was told by a physician that near 70% of female mutation carriers will get BC before reaching seventy. The student has raised a more specific question:

What is the BC risk for my 45-year-old aunt, one of the six female BC-related mutation carriers in her family? Two ladies already got BC before seventy, while the two oldest ladies remained BC-free after 70.

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The first author recollects his answer: Although among these six ladies, four BC cases might be expected before the age of 70, the total number can also be three or five, and it will remain unknown until all of the involved ladies turn 70. It can be guessed, based on two BC-free ladies older than 70, that the remaining two younger ladies might have an increased BC risk, possibly larger than the supposed 70%.

The Russian roulette logic

Recently, we have stumbled on the statistics of the Russian roulette [2], and it reminded us of this question. In most of descriptions, this game of lethal challenge is done by using a six-shot revolver, with one bullet and five blanks or five empty chambers.

Often, the revolver is re-spun after each trigger pull, thus the probability of losing decreases with the later trigger pull. In a six-shot revolver, for any pull, the probability of firing is 1/6 or 16.7%. An alternative variant is to spin the revolver only once at the start of the game, with no further randomization. Then, probabilities of firing the single bullet are different for each of the six players are: 16.7%, 20%, 25%, 33.3%, 50% and even 100% for the 6th trigger pull. The progression of risks for later trigger pulls in the latter variant clearly possibly resemble the question described in the introductory section. Of course, if all bullets are already spent by previous players, later risks are reduced to zero, since no live bullets remain in the revolver.

In here proposed model, all mutation carriers are considered analogous to the chambers of a hypothetical revolver used in a Russian roulette session. Those who already got the cancer are analogous to live cartridges that have already been shut at the time of evacuation. Those cancer-free carriers who are older than 70 can be considered the blanks.

The remaining chambers can be either loaded or empty. If there are no more bullets in the remaining chambers, their risk drops to 0%. If all remaining chambers are loaded, their risk reaches 100%.

The vital information is how many bullets can be expected in the beginning of the cluster formation. Chances are expected to be equal among the remaining revolver chambers.

Comparison between the Russian roulette and the individual cancer chances in a family cluster

It seems as an attractive approach to apply the Russian roulette logic to the introductory question. Our current guess is that the described family situation (shown as the cluster A in the Table) seems similar to a session of the Russian roulette (the last column in Table 1).

The imagined revolver in Table 1, contains an unknown number of bullets (women with a BC related mutations that will surely develop BC before 70). The table proposes variants within the range between only two and four BC cases per setting.

At the time of cluster evaluation, the trigger has already been pulled four times with two blanks (healthy sisters older than 70) and two bullets fired (two BC cases younger than 70). This means that the chances of getting BC for the remaining cancer-free ladies younger than 70 can be 0%, 50% or 100% in their remaining years till 70.

The first assumption with two bullets is because of two BC cases before the age of 70 and two BC-free ladies older than 70. If the two remaining ladies stay cancer free, there were only two bullets initially. If both of them get BC before 70, the cluster contained four bullets. These three settings obviously have different chances to happen, due to the expected overall BC rate in large carrier groups of 70%.

In short, the author's guess several years ago has probably been wrong. The aunt's individual risk remains elusive, although probably altered from the overall BC risk of 70%, due to the small cluster size. Nevertheless, we can expect that the actual number of BC occurrences in a family cluster of mutation carriers alters chances of getting cancer for a particular lady before reaching 70.

Future perspective

In Table 1, two family clusters A and B, consisting of BC-related mutation female carriers are shown. Chance of getting BC for the youngest lady (A6 and B5) is estimated by analogy to a Russian roulette with six chambers in the Cluster A (analogous to the family described in the introductory section) and with five chambers in Cluster B.

In the cluster A, the number of bullets can range from two to four bullets (surrogates for BC cases). Similarly, the cluster B can take three or four bullets. Each setting has a different probability of occurrence, imposed by the overall BC probability of around 70%.

Some measure of confidence seems needed for interpretation. This means that risks within a small cluster are related to the general risk of a certain mutation. It is not identical. It can be lower or higher for a certain lady than the general risk, depending on the already existing BC cases among the mutation carriers.

More accurate population specific risk rates for common BRCA mutations are needed to allow individual cancer risk determination in a family cluster of mutation carriers. Then individual risks for still healthy carriers might be estimated relative to the reported cancer risks for that mutation in that population, possibly easing some tough decisions.

If this reasoning is acceptable, we believe that this issue is relevant to the clinical practice of genetic counseling. Developing a statistical model for calculating individual BC risks for a particular type of mutation within the population might be helpful.

If a certain mutation increases the risk of BC before reaching 70 years of age, this can be detected in a large cohort of mutation carriers. The mean cluster risk value can be calculated if the cohort data are divided in individual family clusters. This means that we can define the mean cluster risk rate ± SEM for a certain mutation in a certain population.

As shown in Table 2, the arithmetic mean ±1.96*SEM can give the confidence interval of the cluster risk, therefore the number of expected BC cases can be calculated as linked integer values. Often, several integer values for the total number of BC cases are expected (two settings shown in Table 3). Integer values within the confidence interval are more probable than the outlier values

At any point in time, individual BC cancer risks might be estimated by counting diagnosed BC cases (bullets), BC free carriers more than 70 years old (blanks) and carriers less than 70 that are yet under the BC risk. If a statistically significant risk can be estimated, this would help in making decisions regarding preventive interventions and scheduling of future examinations.

Table 1: Illustration of the Russian roulette logic in a family cluster of carriers of a BC related mutation. The evaluation moment is reached when the youngest carrier is near 70 years old. If older carriers have developed BC in previous years, the roulette logic suggests that the chances can be increased or decreased in comparison to the expected cluster risk. If there are enough BC cases already, the last carrier is less expected to develop BC.

A family cluster A of six ladies with a BC-related mutation							Approximated individual BC risk for the last unsolved patient A6 in comparison to the cluster risk	The Russian roulette logic
Codes of mutation carriers	A1	A2	A3	A4	A5	A6		
Age at the start	>70	>70	63	61	54	47		
The evaluations point in time: After 16 years of following up								
Age	>70	>70	79	77	70	63		
Setting 1: Expected two BC cases found within the cluster (2/6 cluster probability)							2 bullets, 4 blanks	
Breast cancer	NO	NO	YES	YES	NO	NO	reduced	Used 2 bullets, 3 blanks. no bullets expected
Setting 2: Expected three BC cases within the cluster (3/6 cluster probability)							3 bullets 3 blanks	
BC	NO	NO	YES	YES	YES	NO	reduced	used 3 bullets and 2 blanks, 1 blank expected
Setting 3: Four Breast cancer cases within the cluster (4/6 cluster probability)							4 bullets, 2 blanks	

Table 2: The hypothetical cluster of 6 mutation carriers with the mean risk of BC before the age of 70 of 0.70 (70%), with the SEM of 0.006. These data are used to calculate the 95% confidence interval of the cancer risk within the cluster and express it as a probable integer number of BC cases until all carriers are older than 70. The expectation of only three BC cases is outside of the 95% confidence interval, while the setting of 4 BC cases is within the interval and thus more probable. Data are used to analyze the hypothetical cluster C. The second setting is within the 95% confidence interval, thus much more probable than the first setting.

The mean cancer risk for cluster members with a BC related mutation, til the carriers reach the target age (the mean risk and the SEM)			The 95% confidence interval for the mutation carriers for that population	The expected decimal numbers of BC cases within a cluster of six carriers (6*cancer risk)		The expected integer numbers of BC cases
The arithmetic mean±SEM			**0.70±0.06**	Mean: 4.2 cancer cases		Expected total of 4 BC cases. (within the 95% confidence interval) 5 BC cases is slightly above the upper interval limit.
The arithmetic mean-1.96*SEM			0.58	**The low interval limit: 3.48 cancer cases**		
The arithmetic mean+1.96*SEM			0.82	**The upper interval limit: 4.92 cancer cases**		
Hypothetical family cluster C of six ladies with a BC-related mutation						Approximated individual BC risk for the last unsolved patient C6 in comparison to the cluster risk
Codes of mutation carriers	C1	C2	C3	C4	C5	C6
Age at the start	>70	58	63	61	54	47
The evaluation point in time: After 16 years of following up						
Age	>70	>70	79	77	70	63
Setting 1: Expected three BC cases within the cluster (3/6 cluster probability); outside the 95% confidence interval limit o 3.92						3 bullets 3 blanks expected
BC	NO	NO	YES	YES	YES	NO		a low risk, p<<0.025
Setting 2: Expected four BC cases within the cluster (4/6 cluster probability); within the 95% confidence interval						**4 bullets, 2 blanks expected**
BC	**NO**	**NO**	**YES**	**YES**	**YES**	**YES**		**a very high risk, p>0.95**
Setting 3: Expected five BC cases within the cluster (5/6 cluster probability); outside the 95% confidence interval limit of 4,92						**5 bullets and 1 blank expected**
BC	**NO**	**YES**	**YES**	**YES**	**YES**	**NO**		**low risk for the C6 carrier, p near 0.025**

Declarations

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