Age of natural menopause onset in BRCA1/2 carriers – systematic review and meta-analysis

Łukasz Kępczyński1, Katarzyna Polatyńska2, Anna Nykel1, Jordan Sałamunia3, Tadeusz Kałużewski3, Andrzej Kużawczyk4, Agnieszka Gach1

1Department of Genetics, Polish Mother’s Memorial Hospital Research Institute, Lodz, Poland
2Department of Neurology, Polish Mother’s Memorial Hospital Research Institute, Lodz, Poland
3Laboratory of Medical Genetics of the “Genos” Partnership R&D Division, Lodz, Poland
4Institute IURISMED – Independent Medical Examiners, Kutno, Poland

Abstract

Introduction: Germinal pathogenic variants in BRCA1 and BRCA2 genes are associated with high risk of cancers, including breast, ovary, fallopian tubes and primary peritoneal. Non-oncological implications of germline pathogenic variants in BRCA1 and BRCA2 genes, complicating reproductive health are less described. The influence of BRCA1 and BRCA2 on age of natural menopause remains inconclusive and controversial.

Material and methods: PubMed database was searched for potentially relevant abstracts. Studies which were not case-control, cohort or cross-sectional studies were subsequently excluded. Reference lists from systematic reviews or meta-analyses, dealing with the topic of menopause and BRCA1 and BRCA2 germinal pathogenic variants, were also checked to identify eligible studies. We also included our original, unpublished data from families, affected by BRCA1 or BRCA2 pathogenic variant, consisted of at least two postmenopausal female siblings with differing variant status.

Results and conclusions: Initial database search retrieved 193 abstracts. We identified 4 eligible studies for meta-analysis. Two studies not reporting dispersion measures and not reporting age of natural menopause in control group were left in summary for illustrational purposes, yet were excluded from meta-analysis. 4 studies and our original, unpublished data, combining data from 1535 germinal BRCA1 and BRCA2 pathogenic variant carriers and 3191 control individuals, did not support the hypothesis of association between germinal pathogenic variants of “breast cancer genes” and premature menopause.

Key words: BRCA1, BRCA2, menopause.

Introduction

„Breast cancer genes” BRCA1 and BRCA2 are by far the most widely studied human genes, and consequences of germline pathogenic variants of both genes for cancer risk are very well described [1]. Non-oncological implications of germline BRCA1 and BRCA2 genes, complicating reproductive health, including early natural menopause, reduced ovarian reserve and unresolved association between BRCA1 and BRCA2 pathogenic variants, premature ovarian failure and CGG repeat number in FMR1 gene, are far less described [2-6].

Woman’s reproductive lifespan is limited by the age of menarche and age of natural menopause (ANM). Timing of both events are determined by genetic and environmental factors, with relatively high heritability for ANM, estimated on around 50% [7]. At least intragenic 3 loci (SYCP2L, UIMC1, and MCM8) and a least 1 intergenic locus (13q34) are associated with ANM across different ethnic populations [8], and can be treated as quantitative trait loci (QTL) for ANM. Loci for premature menopause were also identified, with most widely studied association between premature ovarian failure (POF) and number of CGG repeats in FMR1 gene [9].

The influence of germinal BRCA1 and BRCA2 on AMN remains inconclusive and controversial. Hence, we conducted a comprehensive systematic review and meta-analysis of BRCA1 and BRCA2 pathogenic variants on ANM.

Material and methods

PubMed database was searched for abstracts by two reviewers (ŁK and KP) using the keywords: (“BRCA1” OR “BRCA2” OR “hereditary breast can-
We identified 193 citations; both reviewers independently reviewed potentially relevant studies subsequently excluding studies which were not case-control, cohort or cross-sectional studies. Additionally, reference lists from systematic reviews or meta-analyses, dealing with the topic of menopause and BRCA1 and BRCA2 germline pathogenic variants, were also checked to identify eligible studies. Studies dealing only with risk-reducing salpingo-oophorectomy (RRSO) and influence of ANM on breast and/or ovarian cancer risk were excluded. Two studies (Table 1) not reporting dispersion measures and not reporting ANM in control group were left in tabular summary, yet were excluded from meta-analysis. Discrepancies in retrieved list were resolved by consensus. We also included our original, unpublished data from families, affected by BRCA1 or BRCA2 pathogenic variants, consisted of at least two postmenopausal female siblings with differing variant status (Table 2). None of our patients undergone RRSO prior to natural menopause. As most of the data reported median and range for ANM, we estimated mean and standard deviation using Hozo et al. approach [10]. Meta-analysis was done using random effects model on standardized mean differences. Statistical analysis was conducted using R (version 3.6.1. The R Foundation for Statistical Computing).

| Study                        | BRCA1/2 positive | BRCA1 positive | BRCA2 positive | Controls          | Geographical region |
|-----------------------------|------------------|----------------|----------------|-------------------|---------------------|
| Rzepka-Górńska et al., 2006 | Median = 45.5 [45] (Range: 39-52) | Median = 45.5 [45] (Range: 39-52) | NA1 | Median = 48.2 [90] (Range: 43-53) | Poland |
| Lin et al., 20122           | Median = 49 [166] (Range: 26-55) | Median = 48 [94] (Range: 26-55) | Median = 49 [72] (Range: 28-53) | Median = 53 [639] (Range: 18-53) | United States (California) |
| Collins et al., 20133       | NA               | Median = 51 [445] | Median = 51 [374] | Median = 52 [559] | Australia and New Zealand |
| Finch et al., 2013          | Mean = 50.3 [207] (Range: 38-53) | Mean = 49.9 [109] (Range: 39-65) | Mean = 50.8 [95] (Range: 38-59) | Mean = 49.0 [242] (Range: 30-63) | Canada and United States |
| Tea et al., 2013            | NA               | Mean = 40.7 [50] | Mean = 46.8 [49] | NA                | Austria |
| van Tilborg et al., 2016    | Median = 53 [1208] (Range: 28-59) | NA | NA | Median = 53 [2211] (Range: 35-62) | The Netherlands |
| Kępczyński et al., 2020 (this study) | Mean = 48.4 [7] (Range: 43-52) | Mean = 48.4 [7] (Range: 43-52) | NA1 | Mean = 46.2 [9] (Range: 41-52) | Poland |

1All cases were attributed to BRCA1 mutations, 2range derived from Figures 3 and 4, 3no dispersion measure nor range was given — excluded from analysis, 4controls for BRCA2 positive group, cancers for BRCA2 positive group, 5mean calculated as mean of menarche in whole group + mean reproductive lifespan, no actual data nor dispersion measure was given — excluded from analysis, 6only one family with BRCA2 mutation

| Family | BRCA1/BRCA2 pathogenic variant | Cancer status of affected sister | Age of natural menopause |
|--------|--------------------------------|--------------------------------|--------------------------|
| I      | BRCA1: c.5266dupC              | pre BRC                        | 43                       | 50                       |
| II     | BRCA1: c.5266dupC              | post BRC                       | 44                       | 46                       |
|        |                                 |                                |                          |                          |
| III    | BRCA1: c.5266dupC              | pre BRC                        | 50                       | 41                       |
| IV     | BRCA1: c.1687C>T               | pre BRC                        | 48                       | 44                       |
|        |                                 | unaffected                     | 52                       |                          |
| V      | BRCA1: c.1811T>G               | pre BRC                        | 52                       | 45                       |
|        |                                 |                                |                          |                          |
| VI     | BRCA2: c.6982G>T               | pre BRC                        | 50                       | 48                       |

BRCA1 variants nomenclature based on NM_007294.4 transcript sequence, BRCA2 variants based on NM_000059.3 transcript sequence, pre BRC — pre-menopausal breast cancer, post BRC — postmenopausal breast cancer
Results and discussion

Our database search retrieved 193 articles by initial strategy, and 6 studies, combining data from 2121 germlinal BRCA1 and BRCA2 pathogenic variant carriers and 3741 control subjects [11-16]. Four of the studies used Kaplan-Meier approach to assess the differences between carriers and non-carriers [12, 13, 16], two studies were excluded from meta-analysis, as they reported no dispersion measures (and we were unable unambiguously derive those data from Figures) [13] or did not report data from control group [15]. We also included original data from 7 pathogenic variant carriers and 9 non-carrier siblings, summarized in Table 2. Studies included in presented meta-analysis combined data from 1535 germlinal BRCA1 and BRCA2 pathogenic variant carriers and 3191 control individuals. Results of preformed meta-analysis are presented in Figure 1. Results only from group affected with BRCA1 pathogenic variant was similar to group combining carriers of either pathogenic variants (data not shown). Shortage of data from carriers of germlinal BRCA2 pathogenic variants did not enabled draw significant conclusions.

Three studies reported association BRCA1 and BRCA2 with premature menopause [11, 12, 14], two studies reported no evidence of that association [13, 16]. Meta-analysis results does not support the hypothesis of association between germlinal pathogenic variants of “breast cancer genes” and premature menopause. Nevertheless, data from all included studies are prone to selection biases as cessation of observation due to RRSO or cancer-related and treatment-related menopause. Only carefully designed prospective study may resolve the true association between BRCA1 and BRCA2 and early menopause.

Disclosure

The authors report no conflict of interest.

References

1. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA 2017; 317: 2402-2416.
2. de la Noval BD. Potential implications on female fertility and reproductive lifespan in BRCA germline mutation women. Arch Gynecol Obstet 2016; 294: 1099-1103.
3. Oktay K, Kim JY, Barad D, Babayev SN. Association of BRCA1 mutations with occult primary ovarian insufficiency: a possible explanation for the link between infertility and breast/ovarian cancer risks. J Clin Oncol 2010; 28: 240-244.
4. Cordeiro Mitchell CN, McGuinness B, Fene E, et al. Navigating the body of literature assessing BRCA1/2 mutations and markers of ovarian function: a systematic review and meta-analysis. J Assist Reprod Genet 2020; 37: 1037-1055.
5. Weghofer A, Tea MK, Barad DH, et al. BRCA1/2 mutations appear embryolethal unless rescued by low (CGG n<26) FMR1 sub-genotypes: explanation for the „BRCA paradox”? Plos One 2012; 7: e44753.
6. Laitman Y, Ries-Levavi L, Berkensdadt M, et al. FMR1 CGG allele length in Israeli BRCA1/BRCA2 mutation carriers and the general population display distinct distribution patterns. Genet Res (Camb) 2014; 96: e11.
7. Murabito JM, Yang Q, Fox C, et al. Heritability of age at natural menopause in the Framingham Heart Study. J Clin Endocrinol Metab 2005; 90: 3427-30.
8. Carty CL, Spencer KJ, Setiawan VW, et al. Replication of genetic loci for ages at menarche and menopause in the multi-ethnic Population Architecture using Genomics and Epidemiology (PAGE) study. Hum Reprod 2013; 28: 1695-706.
9. Nato V, Harrity C, Walsh D, Marmo K. The impact of FMR1 gene mutations on human reproduction and development: a systematic review. J Assist Reprod Genet 2016; 33: 1135-1147.
10. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5: 13.
11. Rzepka-Górska I, Tarnowski B, Chudecka-Claz A, et al. Premature menopause in patients with BRCA1 gene mutation. Menopause 2006; 100: 59-63.
12. Lin WT, Beattie M, Chen LM, et al. Comparison of age at natural menopause in BRCA1/2 mutation carriers with a non-clinic-based sample of women in northern California. Cancer 2011; 119: 1652-1659.
13. Collins IM, Milne RJ, McLachlan SA, et al. Do BRCA1 and BRCA2 mutation carriers have earlier natural menopause than their noncarrier relatives? Results from the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer. J Clin Oncol 2013; 31: 3920-3925.
14. Finch AI, Valentini A, Greenblatt E, et al. Frequency of premature menopause in women who carry a BRCA1 or BRCA2 mutation. Fertil Steril 2013; 99: 1724-1728.
15. Tea MK, Weghofer A, Wagner K, Singer CF. Association of BRCA1/2 mutations with FMR1 genotypes: effects on menarcheal and menopausal age. Maturitas 2013; 75: 148-151.
16. van Tilborg TC, Broekmans FJ, Piipe A, et al. Do BRCA1/2 mutation carriers have an earlier onset of natural menopause? Menopause 2016; 23: 903-910.