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

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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 We also included our original, unpublished data from families, affected by *BRCA1* or *BRCA2* pathogenic variant, consisted of at least two postmenopausal female siblings with differing variant status.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were left in summary for illustrational purposes, yet were excluded from meta-analysis. 4 studies and our original, unpublished data, combining data from 1535 germinal *BRCA1* and *BRCA2* pathogenic variant carriers and 3191 control individuals, did not support the hypothesis of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-

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cer") AND ("menopause"). We identified 193 citation; both reviewers independently reviewed potentially relevant studies subsequently excluded 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* germinal pathogenic variants, were also checked to identify eligible studies. Studies dealing only with risk-reducing salpingo-oophrectomy (RRSO) and influence of ANM on breast and/or ovary 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).

Table 1. Studies included in systematic review and meta-analysis

Study	*BRCA1/2* positive	*BRCA1* positive	*BRCA2* positive	Controls	Geographical region
Rzepka-Górska *et al.*, 2006	Median = 45.5 [45] (Range: 39-52)	Median = 45.5 [45] (Range: 39-52)	NA[1]	Median = 48.2 [90] (Range: 43-53)	Poland
Lin *et al.*, 2012[2]	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.*, 2013[3]	NA	Median = 51.[445]	Median = 51 [374]	Median = 52 [559] Median = 51 [462]	Australia and New Zeland
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) Mean = 48.8 [126][4] (Range: 30-57) Mean = 49.2 [113][5] (Range: 36-62)	Canada and United States
Tea *et al.*, 2013[6]	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)	NA[7]	Mean = 46.2 [9] (Range: 41-52)	Poland

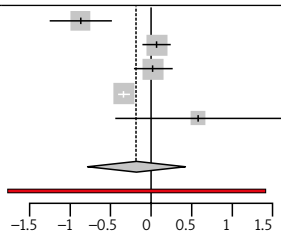
[1]All cases were attributed to *BRCA1* mutations, [2] range derived from Figures 3 and 4, [3] no dispersion measure nor range was given – excluded from analysis, [4] controls for *BRCA1* positive group, [5] controls for *BRCA2* positive group, [6] mean calculated as mean of menarche in whole group + mean reproductive lifespan, no actual data nor dispersion measure was given – excluded from analysis, [7] only one family with *BRCA2* mutation

Table 2. Characteristics of *BRCA1/2* positive probands and their BRCA1/2 negative siblings

Family	*BRCA1/BRCA2* pathogenic variant NM_007294.4	Cancer status of affected sister	Age of natural menopause	
			BRCA1/2(+) sister(s)	*BRCA1/2*(–) sister(s)
I	*BRCA1*: c.5266dupC	pre BRC	43	50
II	*BRCA1*: c.5266dupC	post BRC	44	46
				42
III	*BRCA1*: c.5266dupC	pre BRC	50	41
IV	*BRCA1*: c.1687C>T	pre BRC	48	44
		unaffected	52	
V	*BRCA1*: c.181T>G	pre BRC	52	45
				48
VI	*BRCA2*: c.6982G>T	pre BRC	50	48
				52

BRCA1 variants nomenclature based on NM_007294.4 transcript sequence, *BRCA2* variants based on NM_000059.3 transcript sequence, pre BRC – premenopausal breast cancer, post BRC – postmenopausal breast cancer

Study	*BRCA1/2* positive			Control			Standardized mean difference	SMD	95% CI	Weight
	Total	Mean	SD	Total	Mean	SD				
Rzepka-Gorska *et al.*, 2006 (Poland)	45	45.50	3.4359	90	48.10	2.6404		–0.88	[–1.26; –0.51]	20.3%
Lin *et al.*, 2013 (US, California)	166	44.67	7.7072	639	44.08	9.4755		0.06	[–0.11; 0.24]	23.1%
Finch *et al.*, 2013 (Canada and US)	109	47.85	4.0019	242	47.73	8.6443		0.02	[–0.21; 0.24]	22.5%
van Tilborg *et al.*, 2016 (The Netherlands)	1208	48.17	8.2120	2211	50.71	7.0917		–0.34	[–0.41; –0.27]	23.8%
Kepczynski *et al.*, 2020 (Poland)	7	48.43	3.6450	9	46.22	3.6324		0.57	[–0.44; 1.59]	10.3%
Random effects model	1535			3191				–0.18	[–0.78; 0.42]	100.0%
Prediction interval									[–1.77; 1.41]	
Heterogeneity: I^2 = 89%, τ^2 = 0.2025, p < 0.01										



Results and discussion

Our database search retrieved 193 articles by initial strategy, and 6 studies, combining data from 2121 germinal *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 germinal *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 germinal *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 germinal 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.

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