BRIEF REPORT

Null effect of circulating sphingomyelins on risk for breast cancer: a Mendelian randomization report using Breast Cancer Association Consortium (BCAC) data. [version 1; peer review: awaiting peer review]

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Abstract

Background: Changes in cellular metabolism are a hallmark of cancer and are linked with sphingolipid synthesis. Due to immense interest in how sphingolipids influence chemoresistance, more is known about the impact of sphingolipids during cancer treatment and progression than about the potential role of sphingolipids in the induction of tumors in humans.

Methods: Because estrogen triggers sphingolipid signaling cascades, the causal role of circulating levels of sphingomyelin (a type of sphingolipid) on breast cancer was investigated with a well-powered Mendelian randomization design.

Results: The results reveal a null effect (OR = 0.94; 95% CI = 0.85, 1.05; \( P = 0.30 \)).

Conclusion: Despite the role sphingomyelins play during chemoresistance and cancer progression, circulating sphingomyelins do not appear to initiate or protect from breast cancer. This finding comprises the first causal report in humans that sphingomyelins on breast cancer initiation is null. Future investigations of risk in other cancer types are needed to further explore the potential role of sphingolipid biology in cancer etiology.

Keywords

Mendelian randomization, breast cancer, sphingomyelins, lipids, metabolism
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Author roles: Adams CD: Conceptualization, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The breast cancer genome-wide association analyses were supported by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research, the ‘Ministère de l’Économie, de la Science et de l’Innovation du Québec’ through Genome Québec and grant PSR-SIIRI-701, The National Institutes of Health (U19 CA148065, X01HG007492), Cancer Research UK (C1287/A10118, C1287/A16563, C1287/A10710) and The European Union (HEALTH-F2-2009-223175 and H2020 633784 and 634935). All studies and funders are listed in Michailidou et al (2017).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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How to cite this article: Adams CD. Null effect of circulating sphingomyelins on risk for breast cancer: a Mendelian randomization report using Breast Cancer Association Consortium (BCAC) data. [version 1; peer review: awaiting peer review] F1000Research 2019, 8:2119 (https://doi.org/10.12688/f1000research.21650.1)

First published: 18 Dec 2019, 8:2119 (https://doi.org/10.12688/f1000research.21650.1)
Introduction
Changes in cellular metabolism are a hallmark of cancer. Sphingolipids can control the rate of cell proliferation during malignant transformation and affect chemoresistance. Sphingomyelin is a type of sphingolipid, a class of lipids containing sphingoid bases (Figure 1). As a response to cellular stress, sphingolipids mediate apoptosis and autophagy, through the synthesis and/or accumulation of ceramide. Ceramide can be hydrolyzed from sphingomyelin. Due to immense interest in how sphingolipids influence chemoresistance, much is known about the impact of sphingolipids on cancer treatment and little is known about role sphingolipids in the induction of tumors in humans.

Estrogen triggers sphingolipid signaling cascades. Due to this, it was hypothesized that circulating sphingomyelins might be involved in acquisition of breast cancer. The causal impact of circulating levels of sphingomyelins on risk for breast cancer was appraised with Mendelian randomization (MR).

Methods
Conceptual framework
MR is an instrumental variables technique; i.e., genetic variants (typically single-nucleotide polymorphisms, SNPs) strongly associated with traits are used in statistical models instead of the traits themselves. This avoids most environmental sources of confounding and averts reverse causation, which preclude causal inference in observational studies. Two-sample MR is an adaptation of the procedure that uses summary statistics from two genome-wide association (GWA) studies.

MR assumptions
MR depends on the validity of three assumptions: (i) the SNPs acting as the instrumental variables must be strongly associated with the exposure; (ii) the instrumental variables must be independent of confounders of the exposure and the outcome; and (iii) the instrumental variables must be associated with the outcome only through the exposure.

Data sources
Step 1. Kettunen et al. (2016) performed a genome-wide association (GWA) study of 123 circulating metabolites—including sphingomyelins—in European participants (n=13,476 for sphingomyelins). From this, independent (those not in linkage disequilibrium; $R^2 < 0.01$) SNPs associated at genome-wide significance ($P < 5 \times 10^{-8}$) with a standard-deviation (SD) increase in circulating sphingomyelins were identified. The Kettunen GWA is available through MR-Base.

Discussion
This is the first causal report in humans that sphingomyelins on breast cancer initiation is null. The null effect might reflect the complex interplay of pro-apoptotic and pro-growth ceramides, perhaps with greater upregulation of the pro-apoptotic pathways, which may be different for different tissues. Future investigations of risk in other cancer types are needed to further explore the potential role of sphingolipid biology in cancer etiology.

One potential limitation of this analysis is that unwanted pleiotropy cannot be entirely ruled out in MR studies. However, the sensitivity estimators provide evidence against this. Given the many

Figure 1. Cartoon of a sphingomyelin. The bolder print indicates the lipidic sphingoid base that is carrying a saturated fatty acid amine bonded to an amino group at the C2 position. Attached to the polar head is a phosphocholine. The cartoon has been reproduced with permission from Holthuis et al. (2001).
ways in which a finding could be a false-positive, null findings from well-powered MR studies are, in some ways, more believable than reports of causal associations. A major strength of this two-sample MR analysis is that it capitalized on the power of very large GWA studies. If sphingomyelins were causal for breast cancer initiation, it is highly unlikely that the effect would go undetected with more than 100,000 cases and 100,000 controls in BCAC.

### Data availability

The sphingomyelin data are publicly available through the MR-Base repository (http://www.mrbase.org/) under a GNU General Public License v3.

The breast cancer outcome data are freely available on the BCAC website (http://bcac.ccge.medschl.cam.ac.uk/).

### Table 1. Causal estimates for the association of circulating sphingomyelin levels on risk breast cancer.

<table>
<thead>
<tr>
<th>Method</th>
<th>OR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P value</th>
<th>Q-statistic</th>
<th>Q-diff</th>
<th>Q P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVW</td>
<td>0.94</td>
<td>0.85</td>
<td>1.05</td>
<td>0.30</td>
<td>8</td>
<td>6</td>
<td>0.27</td>
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<tr>
<td>MR Egger*</td>
<td>0.88</td>
<td>0.68</td>
<td>1.13</td>
<td>0.36</td>
<td>7</td>
<td>5</td>
<td>0.22</td>
</tr>
<tr>
<td>Weighted median*</td>
<td>0.92</td>
<td>0.81</td>
<td>1.04</td>
<td>0.19</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Weighted mode*</td>
<td>0.91</td>
<td>0.78</td>
<td>1.06</td>
<td>0.26</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

IVW, inverse-weighted variance. *Denotes a sensitivity estimator.

### References

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