













Article

Endometriosis in Carriers of a Pathogenic Variant in *BRCA1* or *BRCA2*: A Descriptive Analysis of a Large Multicenteral *BRCA* Carrier Cohort

Aghaghia Mokhber ^{1,2,*} , Brynne Stewart ³ , Kathryn L. Terry ⁴, Jacek Gronwald ⁵ , Cezary Cybulski ⁵ , Raymond H. Kim ⁶ , Beth Y. Karlan ⁷ , Louise Bordeleau ⁸, Teresa Ramón y Cajal ⁹ , Tuya Pal ¹⁰ , Andrea Eisen ¹¹ , Fergus J. Couch ¹², Dana Zakalik ¹³, Nadine Tung ¹⁴, Robert Fruscio ^{15,16} , William D. Foulkes ¹⁷, Amber M. Aeilts ¹⁸, Ping Sun ¹, Jan Lubiński ⁵ , Steven Narod ^{1,19}  and Joanne Kotsopoulos ^{1,19,*}

¹ Women's College Research Institute, Women's College Hospital, Toronto, ON M5S 1B2, Canada

² Queen's School of Medicine, Queen's University, Kingston, ON K7L 3N6, Canada

³ Temerty Faculty of Medicine, University of Toronto, Toronto, ON M5S 1A1, Canada

⁴ Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA 02115, USA

⁵ Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University, 70-204 Szczecin, Poland; jan.lubinski@pum.edu.pl (J.L.)

⁶ Princess Margaret Cancer Centre, University Health Network, Toronto, ON M5G 2C4, Canada

⁷ Department of Obstetrics and Gynecology, David Geffen School of Medicine, University of California, Los Angeles, CA 90095, USA

⁸ Department of Oncology, Juravinski Cancer Centre, McMaster University, Hamilton, ON L8S 4L8, Canada

⁹ Department of Medical Oncology, Hospital de la Santa Creu i Sant Pau, 08025 Barcelona, Spain

¹⁰ Vanderbilt-Ingram Cancer Center, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN 37232, USA

¹¹ Department of Medical Oncology, Sunnybrook Odette Cancer Center, University of Toronto, Toronto, ON M5S 1A1, Canada

¹² Division of Experimental Pathology and Laboratory Medicine, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN 55901, USA

¹³ Cancer Genetics Program, Beaumont Hospital, Royal Oak, MI 48073, USA

¹⁴ Beth Israel Deaconess Medical Center, Boston, MA 02215, USA

¹⁵ Department of Medicine and Surgery, University of Milan-Bicocca, 20126 Milan, Italy

¹⁶ UO Gynecology, Fondazione IRCCS San Gerardo dei Tintori, 20900 Monza, Italy

¹⁷ McGill Program in Cancer Genetics, Department of Oncology, McGill University, Montreal, QC H3A 0G4, Canada

¹⁸ Division of Human Genetics, Comprehensive Cancer Center, The Ohio State University Medical Center, Columbus, OH 43202, USA

¹⁹ Dalla Lana School of Public Health, University of Toronto, Toronto, ON M5S 1A1, Canada

* Correspondence: aghia.mokhber@queensu.ca (A.M.); joanne.kotsopoulos@wchospital.ca (J.K.); Tel.: +1-(416)-351-3800 (J.K.)



Received: 20 October 2025

Revised: 22 November 2025

Accepted: 29 November 2025

Published: 1 December 2025

Citation: Mokhber, A.; Stewart, B.; Terry, K.L.; Gronwald, J.; Cybulski, C.; Kim, R.H.; Karlan, B.Y.; Bordeleau, L.; Ramón y Cajal, T.; Pal, T.; et al.

Endometriosis in Carriers of a Pathogenic Variant in *BRCA1* or *BRCA2*: A Descriptive Analysis of a Large Multicenteral *BRCA* Carrier Cohort. *Curr. Oncol.* **2025**, *32*, 675. <https://doi.org/10.3390/currenol32120675>

Copyright: © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Simple Summary

Endometriosis is a common condition that affects women during their reproductive years and is linked to chronic pain and fertility challenges. Some studies suggest that endometriosis may also increase the risk of ovarian cancer. Women who carry *BRCA* gene mutations already face a higher risk of ovarian cancer, but it is unclear whether they are also more likely to have endometriosis. In this large study of nearly 17,000 women with *BRCA* mutations, endometriosis was found to be much less common than in the general population, and it did not appear to increase ovarian cancer risk. These findings suggest that the connection between endometriosis and ovarian cancer may differ for women with *BRCA* mutations. Understanding these differences could help guide future research and inform personalized cancer prevention and reproductive health strategies for women at genetic risk.

Abstract

Background: Endometriosis affects an estimated 10% of reproductive-aged women and is associated with increased ovarian cancer risk. While *BRCA1/2* mutations are established risk factors for ovarian cancer, their association with endometriosis remains unclear. This study aimed to characterize the prevalence and clinical features of endometriosis within a large cohort of *BRCA* mutation carriers. **Methods:** A descriptive analysis was conducted using data from a multi-center longitudinal cohort of women with pathogenic *BRCA* variants. Reproductive history and related factors were collected through self-reported questionnaires and compared. **Results:** Among 16,950 *BRCA* carriers, the prevalence of endometriosis was 2.4%. Compared to *BRCA* carriers without endometriosis, those with endometriosis were more likely to carry a *BRCA2* mutation, have post-secondary education, and experience earlier menarche. *BRCA* carriers with endometriosis had a lower ovarian cancer prevalence than those without (10% vs. 15%, $p < 0.001$). **Conclusions:** This is the first study of this scale to report the prevalence of endometriosis among *BRCA* mutation carriers, which was lower than previously reported in the general population. The association between endometriosis and ovarian cancer does not appear to be generalizable to this population. Further prospective studies are warranted to clarify this association among *BRCA* mutation carriers.

Keywords: *BRCA* mutations; endometriosis; ovarian cancer; prevalence; reproductive epidemiology

1. Introduction

Endometriosis is a chronic gynecological disorder characterized by the presence of endometrial-like tissue outside the uterus, affecting approximately 10% of reproductive-aged women globally [1,2]. This multifactorial condition is associated with significant morbidity, notably chronic pelvic pain, dysmenorrhea, dyspareunia, infertility, and depression [1–7]. The pathophysiology of endometriosis is complex with potential contributions from retrograde menstruation, immune dysregulation, hormonal imbalances, and genetic predisposition [8–11]. Endometriosis is estrogen-dependent, with estrogen driving lesion growth and progesterone resistance limiting its suppression [10,11]. This condition has been associated with increased risk of ovarian cancer, particularly the clear cell and endometrioid subtypes [12,13], with some recent evidence also suggesting a modest link with high-grade serous subtypes [14].

Although twin studies have suggested a heritable component to endometriosis, no high-penetrance susceptibility genes have been identified [15,16]. Findings from genome-wide association studies suggest a role of genetic variation in *WNT4*, *FN1*, and *GREB1* genes, all of which are implicated in estrogen signaling and inflammation [1,17]. *BRCA1* and *BRCA2* are tumor suppressor genes that play a critical role in maintaining genomic stability, among other critical functions. Pathogenic (or likely pathogenic) *BRCA* variants confer the highest known lifetime risks of developing ovarian and/or fallopian tube cancer [18].

Given the association between endometriosis and ovarian cancer, it is important to understand how endometriosis presents in women at high genetic risk of ovarian cancer, including *BRCA* carriers. While *BRCA* mutations are well-established in hereditary cancer syndromes, their relationship to benign gynecologic conditions such as endometriosis is not evaluated. Moreover, other burdens of endometriosis, including chronic pain, infertility, and mental health impacts, remain underexplored in this high-risk population. This study aims to evaluate the prevalence and clinical characteristics of endometriosis in a

large multicenter cohort of *BRCA* carriers and to provide real-world insights into how endometriosis manifests in this high-risk population.

2. Methods

2.1. Study Population

Participants were identified from a longitudinal study of women aged 18 to 70 with a confirmed pathogenic or likely pathogenic variant in the *BRCA1* or *BRCA2* gene (carriers hereafter) and has been previously described in detail [19]. Briefly, eligible participants had undergone genetic testing based on a personal or family history of breast and/or ovarian cancer. While various methods were used to detect mutations, all identified variants were confirmed through direct DNA sequencing. Informed written consent was obtained from all participants. The study was conducted in accordance with the ethical standards of the relevant institutional or national research committees and with the 1964 Declaration of Helsinki and its later amendments. Ethical approval was obtained from the Institutional Review Boards of all participating centers.

2.2. Data Collection

Participants complete a research questionnaire at the time enrollment (between 1995 and 2024), which was administered either in person during a clinic visit or remotely via telephone or mail. The questionnaire gathered self-reported data on established and potential risk factors for breast and ovarian cancer, including personal and family cancer history, medical and reproductive history, medication use, and select lifestyle factors. Menopausal status was also assessed, with questions addressing natural, surgical, medication-induced, or other causes of menopause. Follow-up questionnaires were distributed every two years to collect updated information on exposures, new cancer diagnoses, treatments received, and vital status. These follow-ups were conducted by mail or telephone by a research assistant.

Self-reported diagnoses of primary invasive ovarian or fallopian tube cancer, collectively referred to as ovarian cancer, were collected. The questionnaires asked specifically about a personal diagnosis of endometriosis (yes/no), including details on the date of diagnosis and treatments received. We also included cases of endometriosis identified incidentally during surgery. Date of diagnosis was based on the participant's report where available.

2.3. Eligible Participants

All *BRCA1* and *BRCA2* mutation carriers who completed at least one follow-up questionnaire were eligible for inclusion. Participants were excluded if they reported a history of any malignancy other than breast or ovarian cancer ($n = 2301$). To limit misclassification, women who had undergone bilateral salpingo-oophorectomy (BSO) or hysterectomy prior to an endometriosis diagnosis were also excluded ($n = 20$). For analyses involving ovarian cancer, self-reported ovarian cancer diagnoses were included only if they occurred after the reported endometriosis diagnosis and in women without a history of prophylactic BSO. Women with missing data on endometriosis status or date of diagnosis were excluded from all analyses ($n = 263$). After applying these criteria, 16,950 women remained eligible: 402 with self-reported endometriosis and 16,547 without.

2.4. Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics, comparing *BRCA* carriers with and without endometriosis. Continuous variables were presented as means and corresponding minimum and maximum values (min–max) and compared using Student's *t*-test, while categorical variables were presented as counts and percentages and

compared using the χ^2 test. All statistical analyses were conducted using SAS On Demand for Academics (Cary, NC, USA), and statistical significance was set at $p \leq 0.05$.

3. Results

Among the 16,950 *BRCA* carriers included in the study, 403 (2.4%) had a self-reported diagnosis of endometriosis (Table 1). The mean age at diagnosis of endometriosis was 35.2 years (min–max: 13–72). The mean follow-up time for the cohort was 5.5 years (min–max: 2–26), with a longer average follow-up among women with endometriosis (8.1 years; min–max: 2–24) compared with those without endometriosis (5.5 years; min–max: 2–26). A greater proportion of participants with endometriosis had post-secondary education compared with those without endometriosis (75% vs. 67%). Women with endometriosis reported an earlier age at menarche (mean: 12.7 vs. 13.0 years) and were more likely to be postmenopausal at the time of data collection (85% vs. 72%). Among postmenopausal women, those with endometriosis experienced menopause at a younger age (41.5 vs. 44.3 years), with surgical menopause being more common (69% vs. 55%). Parity also differed significantly, with a higher proportion of women with endometriosis never having given birth (29% vs. 20%). Women with endometriosis were more likely to have a history of oral contraceptive (75% vs. 64%) and HRT use (31% vs. 20%). Rates of hysterectomy and BSO were also higher in women with endometriosis (53% vs. 32% and 68% vs. 45%, respectively).

Table 1. Descriptive characteristics of *BRCA* mutation carriers overall and by endometriosis diagnosis.

Characteristic	Total (n = 16,950)	No Endometriosis (n = 16,547)	Endometriosis ^a (n = 403)	<i>p</i> ^b
Year of birth, mean (min–max)	1961 (1903–2004)	1961 (1903–2004)	1962 (1921–1994)	0.40
Age at diagnosis, mean (min–max)	35.2 (13–72)	N/A	35.2 (13–72)	N/A
Follow-up time in years, mean (min–max)	5.5 (2–26)	5.5 (2–26)	8.1 (2–24)	<0.01
Country of residence, n (%)				
USA	5278 (31)	5147 (31)	131 (33)	<0.01
Canada	3743 (22)	3609 (22)	134 (33)	
Poland	5065 (30)	4944 (30)	121 (30)	
Other	2847 (17)	2830 (17)	17 (4)	
Education level, n (%)				
Primary	2548 (33)	2481 (33)	67 (25)	<0.01
Post-secondary	5238 (67)	5033 (67)	205 (75)	
Body Mass Index (BMI) at 18, mean (min–max)	20.9 (10–59)	20.9 (10–59)	20.7 (13–37)	0.32
Age at menarche, mean (min–max)	13.0 (8–30)	13.0 (8–30)	12.7 (9–17)	<0.01
Menopause status, n (%)				
Premenopuase	4651 (28)	4592 (28)	59 (15)	<0.01
Postmenopause	12,255 (72)	11,912 (72)	343 (85)	
Menopause age, mean (min–max)	44.17 (12–73)	44.3 (12–73)	41.5 (23–58)	<0.01
Menopause cause, n (%)				
Natural	2906 (27)	2860 (24)	46 (13)	<0.01
Surgical	6796 (64)	6558 (55)	238 (69)	

Table 1. Cont.

Characteristic	Total (n = 16,950)	No Endometriosis (n = 16,547)	Endometriosis ^a (n = 403)	p ^b
Medical Parity, n (%)	975 (9)	944 (8)	31 (9)	
Never	3433 (20)	3318 (20)	115 (29)	<0.01
Ever	13,517 (80)	13,229 (80)	288 (71)	
Oral contraceptive, n (%)				
Never	6096 (36)	5995 (36)	101 (25)	<0.01
Ever	10,854 (64)	10,552 (64)	302 (75)	
Postmenopausal HRT ^c , n (%)				
Never	9722 (79)	9487 (80)	235 (69)	<0.01
Ever	2533 (21)	2425 (20)	108 (31)	
Tubal ligation ^d , n (%)				
Never	12,984 (88)	12,637 (88)	347 (87)	0.85
Ever	1822 (12)	1772 (12)	50 (13)	
Hysterectomy, n (%)				
Never	11,477 (68)	11,288 (68)	189 (47)	<0.01
Ever	5473 (32)	5259 (32)	214 (53)	
BSO, n (%)				
Never	7794 (46)	7579 (46)	115 (28)	<0.01
Ever	9201 (54)	8906 (53)	295 (72)	

^a Women with BSO, hysterectomy and/or ovarian cancer diagnosis before endometriosis diagnosis were excluded.
^b The distributions of continuous and categorical variables were compared using the student's *t*-test and χ^2 test, respectively. ^c HRT use reflects ever use of hormone replacement therapy after surgical or natural menopause.
^d Differences between the total cohort size and the sums within individual variables are due to missing responses for specific questionnaire items. N/A= not applicable.

Participants with endometriosis were more likely to carry a *BRCA2* mutation compared with those without endometriosis (34% vs. 28%, *p* = 0.012) (Table 2). The prevalence of ovarian cancer was lower in women with endometriosis (10% vs. 15%, *p* < 0.01).

Table 2. Distribution of *BRCA* mutation type and ovarian cancer among carriers with and without endometriosis.

Characteristic	Total (n = 16,950)	No Endometriosis (n = 16,547)	Endometriosis ^a (n = 403)	p ^b
Mutation type, n (%)				0.012
Total	16,950			
<i>BRCA1</i>	12,169 (72)	11,902 (72)	267 (66)	
<i>BRCA2</i>	4781 (28)	4645 (28)	136 (34)	
Ovarian cancer ^c , n (%)				<0.0001
Total	7794			
Never	6662 (85)	6559 (85)	103 (90)	
Ever	1132 (15)	1120 (15)	12 (10)	

^a Women with BSO, hysterectomy and/or ovarian cancer diagnosis before endometriosis diagnosis were excluded.
^b The distributions of variables were compared using the χ^2 test. ^c Ovarian cancer reported only in patients with no history of prophylactic BSO.

4. Discussion

In this report of endometriosis in a large cohort of *BRCA* carriers, we observed a lower prevalence of endometriosis (2.4%) compared to that estimated from women in the general population (~10%) [1,2]. In addition, the prevalence of ovarian cancer was significantly lower in *BRCA* carriers with endometriosis compared to those without (10% vs. 15%). Although limited by small number of endometriosis cases and self-reported diagnosis, these findings suggest that *BRCA* carriers with endometriosis are not at an increased risk of ovarian cancer.

Despite the large number of *BRCA* carriers in our study, a very small proportion ever reported a history of endometriosis. Table 3 summarizes the small but growing body of literature that has investigated the prevalence of endometriosis among *BRCA* mutation carriers, with sample sizes ranging from 37 to 4926 participants [20–26]. Reported prevalence among *BRCA* carriers ranged from 1.6% to 34.2%, with some studies focusing solely on *BRCA* mutation carriers and others comparing carriers to non-carriers or women with other genetic mutations. Among studies that only analyzed *BRCA* mutation carriers, endometriosis prevalence was generally low, with rates under 5% in all cohorts [24,26]. While one study reported higher rates of endometriosis in *BRCA* carriers than in mutation-negative women [22], others found lower rates among carriers relative to non-carriers [20,23]. Among the case-only studies, which focused on cancer patients, prevalence rates were closer to the documented prevalence of endometriosis in the general population [1]. Rates ranged from approximately 8% to 10% across studies, with no significant differences between *BRCA* carriers and non-carriers [21,25,26]. Lower prevalence of endometriosis in this population may be explained by the high rates of prophylactic surgeries (BSO, Hysterectomy) among *BRCA* carriers [27–30], which remove the primary sites of endometriotic lesions and reduce the likelihood of a formal endometriosis diagnosis. Another potential factor is diagnostic bias due to cancer-focused medical surveillance [27], where clinical attention in *BRCA* carriers is directed toward malignancy risk rather than benign gynecologic conditions. As a result, endometriosis may be underdiagnosed or underreported in this population.

Table 3. Summary of studies investigating the prevalence of endometriosis among *BRCA* mutation carriers.

Study	Country	Population	Study Design	Results
Stratton et al., 1999 [20]	UK	37 women (<i>BRCA</i> : n = 11; Non-carriers: n = 26)	Cohort	Endometriosis prevalence was 9.1% (1/11) among <i>BRCA</i> mutation carriers and 15.3% (4/26) among non-carriers.
Casey et al., 2013 [21]	USA	174 women with invasive gynecological cancers (<i>BRCA</i> : n = 95; <i>MMR</i> : n = 79)	Case-only	Endometriosis prevalence was 9.1% (1/11) among <i>BRCA</i> mutation carriers and 8.9% (7/79) among women with <i>MMR</i> gene mutations. Of the endometriosis cases identified, 81.8% (9/11) were associated with endometrioid carcinomas.

Table 3. Cont.

Study	Country	Population	Study Design	Results
Seidman and Krishnan, 2016 [22]	USA	403 women (BRCA: n = 38; High-risk without mutation: n = 79; low-risk without mutation: n = 286)	Cohort	Endometriosis prevalence was 34.2% (13/38) among BRCA mutation carriers, 30.4% (24/79) in high-risk individuals without a mutation, and 18% (51/286) in non-high-risk individuals. The overall prevalence of endometriosis was 22% (88/403).
Thompson et al., 2018 [23]	IRL	130 women (BRCA: n = 46, Non-Carriers: n = 19, Untested: n = 65)	Cohort	Endometriosis prevalence was 2.2% (1/46) among BRCA mutation carriers and 7.1% (6/84) in non-carriers or untested individuals.
Grandi et al., 2020 [24]	ITA	116 women with BRCA mutations (Previous RRSO: n = 25; Actual RRSO: n = 29; No RRSO: n = 62)	Cohort	The overall prevalence of endometriosis was 4.3% (5/116).
Gersekowski et al., 2024 [25]	AUS	4926 women with ovarian cancer (BRCA: n = 637; Non-carriers n = 4289) * Data on endometriosis was missing for 1648 women	Pooled Case-only	Endometriosis prevalence was 8.6% (41/476) among BRCA mutation carriers and 10.2% (285/2802) among non-carriers The overall prevalence of endometriosis was 9.9% (326/3278) The positive association between endometriosis and ovarian cancer risk was weaker for BRCA carriers compared to non-carriers (IRR = 0.75, 95% CI: 0.54–1.01)
Loizzi et al., 2024 [26]	ITA	184 women with BRCA mutations (Personal history of cancer: n = 14)	Cohort	Endometriosis was reported in 1.6% (3/184) of patients, all of whom had no personal or family history of cancer.

* NS = Not statistically significant, numerical data not reported; N/A = Not available; RRSO = risk-reducing salpingo-oophorectomy; OR = Odds ratio; IRR = interaction risk ratio; CI = confidence interval.

Despite this lower prevalence, several well-established risk factors for endometriosis, including earlier menarche [31–33], lower early adulthood body mass [34,35], and nulliparity [33,36], were observed in our BRCA carrier cohort. These findings suggest that BRCA mutation status does not necessarily alter traditional risk profiles for endometriosis, reinforcing that hormonal and metabolic influences continue to play a role in disease development even within this high-risk genetic population. A particularly notable finding of our study was the lower prevalence of ovarian cancer among BRCA carriers with endometriosis compared to those without (10% vs. 15%, $p \leq 0.001$), a contrast to the general population, where endometriosis is associated with an increased risk of ovarian cancer [12–14]. Our findings are aligned with previous reports on the association between endometriosis and ovarian cancer risk among BRCA mutation carriers. Although limited by sample size, Gersekowski et al. reported a weaker association between endometriosis and ovarian can-

cer in *BRCA* mutation carriers compared to non-carriers (IRR = 0.75, 95% CI: 0.54–1.01) [25]. Similarly, none of the endometriosis patients with a *BRCA* mutation were found to have cancer in a study conducted by Loizzi et al. [26], while 81.8% of cancers associated with endometriosis in another study were associated with endometrioid carcinoma over other gynecological malignancies [21]. These findings may reflect differences in tumor histology [12,14,37]. Endometriosis has been most strongly linked to clear cell ovarian cancer [12], with emerging evidence suggesting a modest association with high-grade serous carcinomas (HGSC) [14]. In contrast, *BRCA*-driven ovarian cancers are predominantly HGSC [37]. Since endometriosis is not strongly linked to HGSC development, its impact on cancer risk may be less pronounced in *BRCA* carriers. It is also possible that, in *BRCA*-associated ovarian cancer, endometriosis may represent an incidental rather than causative finding, consistent with emerging histologic distinctions between endometriosis-correlated and endometriosis-incidental ovarian cancer [38]. Additionally, the low prevalence of ovarian cancer among *BRCA* carriers with endometriosis could be influenced by early risk-reducing surgeries [27–30], including bilateral oophorectomy which would dramatically reduce ovarian cancer risk. Socioeconomic and healthcare access factors may have also influenced the findings. Women with endometriosis in our *BRCA* cohort were more likely to have post-secondary education, a factor associated with improved access to specialist care and greater engagement in preventive health services [39–41]. This may have contributed to earlier diagnosis, timely surgical management, and lower observed rates of ovarian cancer in this group.

This descriptive analysis offers a real-world perspective on the relationship between germline *BRCA* mutations and endometriosis, leveraging a large, multicenter, longitudinal cohort. In contrast to previous studies, which were limited by small sample sizes, single-center recruitment, and short follow-up durations, the scale and design of this dataset allowed for a more robust evaluation of endometriosis prevalence and associated risk factors in *BRCA* carriers. Our study included both *BRCA1* and *BRCA2* mutation carriers, allowing for mutation-specific comparisons that remain underexplored in the existing literature. To our knowledge, this is the first study to systematically characterize reproductive, hormonal, and surgical factors associated with endometriosis within a large cohort of *BRCA* mutation carriers, enhancing the generalizability and clinical relevance of our finding.

This study had several limitations, notably that self-reported diagnoses may have led to underreporting or misclassification of endometriosis. Women with undiagnosed or asymptomatic disease may have been included in the comparison group, potentially underestimating differences in ovarian cancer prevalence. Although we did not report on the specific histology of the ovarian cancers, it has been well documented that *BRCA* mutations are associated with the development of serous and endometrioid subtypes [37]. In addition, ethnicity information was not available for this cohort, which is important to acknowledge as endometriosis prevalence varies by race and ethnicity [40]. Given the relatively small number of endometriosis cases and ovarian cancer events, the study was not powered to perform multivariable or time-to-event analyses. A descriptive approach was therefore adopted to characterize patterns and generate hypotheses. Future studies with larger samples, clinically confirmed diagnoses, and tumor histology data are needed to better understand the relationship between endometriosis and cancer risk in *BRCA* mutation carriers.

Overall, our findings suggest that *BRCA* mutations are likely not strongly associated with endometriosis and that endometriosis is unlikely to be a significant risk factor for *BRCA*-ovarian cancer. While traditional risk factors for endometriosis were still present, the influence of early surgical interventions and surveillance practices may help explain these patterns. To our knowledge, this is the first study to describe endometriosis preva-

lence and associated risk factors within a large cohort of *BRCA* mutation carriers. Future studies should prioritize prospective research to clarify these interactions and their clinical implications, particularly how endometriosis may affect ovarian cancer surveillance and reproductive health in women with a *BRCA* mutation.

Author Contributions: Conceptualization, A.M. and J.K.; Data curation, B.S., J.G., C.C., R.H.K., B.Y.K., L.B., T.R.y.C., T.P., A.E., F.J.C., D.Z., N.T., R.F., W.D.F., P.S. and J.L.; Investigation, A.M., B.S.; Methodology, A.M., K.L.T. and J.K.; Resources, J.G., C.C., R.H.K., B.Y.K., L.B., T.R.y.C., T.P., A.E., F.J.C., D.Z., N.T., R.F., W.D.F., A.M.A., P.S. and J.L.; Supervision, S.N. and J.K.; Writing—original draft, A.M. and J.K.; Writing—review and editing, A.M., K.L.T., B.Y.K., S.N. and J.K. All authors have read and agreed to the published version of the manuscript.

Funding: J.K. holds a Tier II Canada Research Chair (950231438), and Steven A. Narod holds a Tier I Canada Research Chair (453704). Funding for this research was provided by the Champions of Genetics Grant from the Canadian Gene Cure Foundation, in collaboration with the CIHR Institute of Genetics and the Canadian Cancer Society Research Institute (703058), and by the Peter Gilgan Centre for Women’s Cancers at Women’s College Hospital in partnership with the Canadian Cancer Society. The funding organizations were not involved in the study design, data collection and analysis, publication decisions, or manuscript preparation.

Institutional Review Board Statement: The study was approved by the institutional ethics review boards of Women’s College Hospital (Protocol Number (REB #): 2007-0036-B; Date of Approval: 29 February 2024) and all study subjects provided written informed consent. The study was performed in accordance with the Declaration of Helsinki.

Informed Consent Statement: Informed consent was obtained from all participants involved in the study.

Data Availability Statement: The data presented in this study are available on reasonable request from the corresponding author. The data are not publicly available due to institutional privacy policies.

Acknowledgments: We sincerely thank all the women who participated in this study, as their contributions were essential to our research. We also acknowledge the study staff, students, and volunteers for their assistance with data collection and data entry. We extend our gratitude to Shana Kim, for her valuable input and support throughout this project. We would like to thank the Hereditary Breast Cancer Clinical Study Group. (Other members of the Hereditary Breast Cancer Clinical Study Group: Kevin Sweet, Christine Elser, Seema Panchal, Georgia Wiesner, Susan Armel, Linda Steele, Howard Saal, Kim Serfas, Carey A. Cullinane, Robert E. Reilly, Daniel Rayson, Leanne Mercer, Jeffrey Dungan, Stephanie Cohen, Susan Neuhausen, Sophie Sun, Leigha Senter, Joanne L. Blum, Klaudia Stempa, Tracy Graham, Marta Seca, Martina Delle Marchette, Serena Negri, Adriana I. Apostol, Pal Moller, Intan Schrader, Christian F. Singer, Kelly Metcalfe, Olufunmilayo Olo-pade, Cristina Dell’Oro, Alessandra Inzoli, Rosa Alfonso, Consol Lopez and Francesco Cusco).

Conflicts of Interest: The authors declare no conflicts of interest relevant to this manuscript.

References

1. Horne, A.W.; Missmer, S.A. Pathophysiology, diagnosis, and management of endometriosis. *BMJ* **2022**, *379*, e070750. [[CrossRef](#)]
2. Shafrir, A.L.; Farland, L.V.; Shah, D.K.; Harris, H.R.; Kvaskoff, M.; Zondervan, K.; Missmer, S.A. Risk for and consequences of endometriosis: A critical epidemiologic review. *Best Pract. Res. Clin. Obstet. Gynaecol.* **2018**, *51*, 1–15. [[CrossRef](#)]
3. Prescott, J.; Farland, L.V.; Tobias, D.K.; Gaskins, A.J.; Spiegelman, D.; Chavarro, J.E.; Rich-Edwards, J.W.; Barbieri, R.L.; Missmer, S.A. A prospective cohort study of endometriosis and subsequent risk of infertility. *Hum. Reprod.* **2016**, *31*, 1475–1482. [[CrossRef](#)] [[PubMed](#)]
4. Gallagher, J.S.; DiVasta, A.D.; Vitonis, A.F.; Sarda, V.; Laufer, M.R.; Missmer, S.A. The Impact of Endometriosis on Quality of Life in Adolescents. *J. Adolesc. Health* **2018**, *63*, 766–772. [[CrossRef](#)] [[PubMed](#)]

5. Nnoaham, K.E.; Hummelshoj, L.; Webster, P.; d'Hooghe, T.; de Cicco Nardone, F.; de Cicco Nardone, C.; Jenkinson, C.; Kennedy, S.H.; Zondervan, K.T.; World Endometriosis Research Foundation Global Study of Women's Health Consortium. Impact of endometriosis on quality of life and work productivity: A multicenter study across ten countries. *Fertil. Steril.* **2011**, *96*, 366–373.e8. [[CrossRef](#)] [[PubMed](#)]
6. Rush, G.; Misajon, R.; Hunter, J.A.; Gardner, J.; O'Brien, K.S. The relationship between endometriosis-related pelvic pain and symptom frequency, and subjective wellbeing. *Health Qual. Life Outcomes* **2019**, *17*, 123. [[CrossRef](#)]
7. As-Sanie, S.; Mackenzie, S.C.; Morrison, L.; Schrepf, A.; Zondervan, K.T.; Horne, A.W.; Missmer, S.A. Endometriosis: A Review. *JAMA* **2025**, *334*, 64–78. [[CrossRef](#)]
8. Rahmioglu, N.; Mortlock, S.; Ghiasi, M.; Møller, P.L.; Stefansdottir, L.; Galarneau, G.; Turman, C.; Danning, R.; Law, M.H.; Sapkota, Y.; et al. The genetic basis of endometriosis and comorbidity with other pain and inflammatory conditions. *Nat. Genet.* **2023**, *55*, 423–436. [[CrossRef](#)]
9. Symons, L.K.; Miller, J.E.; Kay, V.R.; Marks, R.M.; Liblik, K.; Koti, M.; Tayade, C. The Immunopathophysiology of Endometriosis. *Trends Mol. Med.* **2018**, *24*, 748–762. [[CrossRef](#)]
10. Chantalat, E.; Valera, M.-C.; Vaysse, C.; Noirrit, E.; Rusidze, M.; Weyl, A.; Vergriete, K.; Buscail, E.; Lluel, P.; Fontaine, C.; et al. Estrogen Receptors and Endometriosis. *Int. J. Mol. Sci.* **2020**, *21*, 2815. [[CrossRef](#)]
11. McKinnon, B.; Mueller, M.; Montgomery, G. Progesterone Resistance in Endometriosis: An Acquired Property? *Trends Endocrinol. Metab.* **2018**, *29*, 535–548. [[CrossRef](#)] [[PubMed](#)]
12. Kvaskoff, M.; Mahamat-Saleh, Y.; Farland, L.V.; Shigesu, N.; Terry, K.L.; Harris, H.R.; Roman, H.; Becker, C.M.; As-Sanie, S.; Zondervan, K.T.; et al. Endometriosis and cancer: A systematic review and meta-analysis. *Hum. Reprod. Update* **2021**, *27*, 393–420. [[CrossRef](#)]
13. Pearce, C.L.; Templeman, C.; Rossing, M.A.; Lee, A.; Near, A.M.; Webb, P.M.; Nagle, C.M.; Doherty, J.A.; Cushing-Haugen, K.L.; Wicklund, K.G.; et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: A pooled analysis of case-control studies. *Lancet Oncol.* **2012**, *13*, 385–394. [[CrossRef](#)] [[PubMed](#)]
14. Harris, H.R.; Peres, L.C.; Johnson, C.E.; Guertin, K.A.; Beeghly, A.; Bandera, E.V.; Bethea, T.N.; Joslin, C.E.; Wu, A.H.; Moorman, P.G.; et al. Racial Differences in the Association of Endometriosis and Uterine Leiomyomas With the Risk of Ovarian Cancer. *Obstet. Gynecol.* **2023**, *141*, 1124–1138. [[CrossRef](#)] [[PubMed](#)]
15. Saha, R.; Pettersson, H.J.; Svedberg, P.; Olovsson, M.; Bergqvist, A.; Marions, L.; Tornvall, P.; Kuja-Halkola, R. Heritability of endometriosis. *Fertil. Steril.* **2015**, *104*, 947–952. [[CrossRef](#)]
16. Treloar, S.A.; O'Connor, D.T.; O'Connor, V.M.; Martin, N.G. Genetic influences on endometriosis in an Australian twin sample. *Fertil. Steril.* **1999**, *71*, 701–710. [[CrossRef](#)]
17. Sapkota, Y.; Steinthorsdottir, V.; Morris, A.P.; Fassbender, A.; Rahmioglu, N.; De Vivo, I.; Buring, J.E.; Zhang, F.; Edwards, T.L.; Jones, S.; et al. Meta-analysis identifies five novel loci associated with endometriosis highlighting key genes involved in hormone metabolism. *Nat. Commun.* **2017**, *8*, 15539. [[CrossRef](#)]
18. Kuchenbaecker, K.B.; Hopper, J.L.; Barnes, D.R.; Phillips, K.A.; Mooij, T.M.; Roos-Blom, M.J.; Jervis, S.; van Leeuwen, F.E.; Milne, R.L.; Andrieu, N.; et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA* **2017**, *317*, 2402–2416. [[CrossRef](#)]
19. McLaughlin, J.R.; Risch, H.A.; Lubinski, J.; Møller, P.; Ghadirian, P.; Lynch, H.; Karlan, B.; Fishman, D.; Rosen, B.; Neuhausen, S.L.; et al. Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: A case-control study. *Lancet Oncol.* **2007**, *8*, 26–34. [[CrossRef](#)]
20. Stratton, J.F.; Buckley, C.H.; Lowe, D.; Ponder, B.A.J. Comparison of Prophylactic Oophorectomy Specimens From Carriers and Noncarriers of a BRCA1 or BRCA2 Gene Mutation. *J. Natl. Cancer Inst.* **1999**, *91*, 626–628. [[CrossRef](#)]
21. Casey, M.J.; Bewtra, C.; Lynch, H.T.; Snyder, C.; Stacy, M.; Watson, P. Phenotypic heterogeneity of hereditary gynecologic cancers: A report from the Creighton hereditary cancer registry. *Fam. Cancer* **2013**, *12*, 719–740. [[CrossRef](#)]
22. Seidman, J.D.; Krishnan, J. Non-Neoplastic Conditions of the Ovaries in Grossly Normal Adnexa: A Clinicopathologic Study of 403 Completely Embedded Cases. *Int. J. Gynecol. Pathol.* **2016**, *35*, 544–548. [[CrossRef](#)]
23. Thompson, C.; McCormick, C.; Kamran, W.; O'Riain, C.; Norris, L.; Gallagher, D.; Gleeson, N. Risk reduction surgery (RRS) for tubo-ovarian cancer in an Irish gynaecological practice: An analysis of indications and outcomes. *Ir. J. Med. Sci.* **2018**, *187*, 789–794. [[CrossRef](#)]
24. Grandi, G.; Del Savio, M.C.; Sammarini, M.; Cortesi, L.; Toss, A.; Piombino, C.; Facchinetti, F. The reduction of CA 125 serum levels in BRCA 1/2 mutation carriers after risk-reducing salpingo-oophorectomy is only partially associated with surgery: A prospective cohort, other biomarker controlled, study. *Eur. J. Cancer Prev.* **2020**, *29*, 350–356. [[CrossRef](#)]
25. Gersekowski, K.; Na, R.; Alsop, K.; Delahunty, R.; Goode, E.L.; Cunningham, J.M.; Winham, S.J.; Pharoah, P.D.P.; Song, H.; Webb, P.M.; et al. Risk Factors for Ovarian Cancer by BRCA Status: A Collaborative Case-Only Analysis. *Cancer Epidemiol. Biomark. Prev.* **2024**, *33*, 586–592. [[CrossRef](#)] [[PubMed](#)]

26. Loizzi, V.; Mongelli, M.; Arezzo, F.; Romagno, I.; Cazzato, G.; Popescu, O.; Legge, F.; Trerotoli, P.; Silvestris, E.; Kardhashi, A.; et al. BRCA Mutation Patients: Are There Other Predisposing Factors for Ovarian Cancer Occurrence? A Multicenter Retrospective Study. *Gynecol. Obstet. Investig.* **2024**, *89*, 87–94. [[CrossRef](#)] [[PubMed](#)]
27. Metcalfe, K.; Eisen, A.; Senter, L.; Armel, S.; Bordeleau, L.; Meschino, W.S.; Pal, T.; Lynch, H.T.; Tung, N.M.; Kwong, A.; et al. International trends in the uptake of cancer risk reduction strategies in women with a BRCA1 or BRCA2 mutation. *Br. J. Cancer* **2019**, *121*, 15–21. [[CrossRef](#)]
28. Finch, A.; Beiner, M.; Lubinski, J.; Lynch, H.T.; Moller, P.; Rosen, B.; Murphy, J.; Ghadirian, P.; Friedman, E.; Foulkes, W.D.; et al. Salpingo-oophorectomy and the Risk of Ovarian, Fallopian Tube, and Peritoneal Cancers in Women With a BRCA1 or BRCA2 Mutation. *JAMA* **2006**, *296*, 185–192. [[CrossRef](#)]
29. Rebbeck, T.R.; Lynch, H.T.; Neuhausen, S.L.; Narod, S.A.; Van't Veer, L.; Garber, J.E.; Evans, G.; Isaacs, C.; Daly, M.B.; Matloff, E.; et al. Prophylactic Oophorectomy in Carriers of BRCA1 or BRCA2 Mutations. *N. Engl. J. Med.* **2002**, *346*, 1616–1622. [[CrossRef](#)]
30. Marchetti, C.; De Felice, F.; Palaia, I.; Perniola, G.; Musella, A.; Musio, D.; Muzii, L.; Tombolini, V.; Benedetti Panici, P. Risk-reducing salpingo-oophorectomy: A meta-analysis on impact on ovarian cancer risk and all cause mortality in BRCA 1 and BRCA 2 mutation carriers. *BMC Women's Health* **2014**, *14*, 1–6. [[CrossRef](#)]
31. Matalliotakis, I.M.; Cakmak, H.; Fragouli, Y.G.; Goumenou, A.G.; Mahutte, N.G.; Arici, A. Epidemiological characteristics in women with and without endometriosis in the Yale series. *Arch. Gynecol. Obstet.* **2008**, *277*, 389–393. [[CrossRef](#)] [[PubMed](#)]
32. Nnoaham, K.E.; Webster, P.; Kumbang, J.; Kennedy, S.H.; Zondervan, K.T. Is early age at menarche a risk factor for endometriosis? A systematic review and meta-analysis of case-control studies. *Fertil. Steril.* **2012**, *98*, 702–712.e6. [[CrossRef](#)] [[PubMed](#)]
33. Missmer, S.A.; Hankinson, S.E.; Spiegelman, D.; Barbieri, R.L.; Malspeis, S.; Willett, W.C.; Hunter, D.J. Reproductive History and Endometriosis Among Premenopausal Women. *Obstet. Gynecol.* **2004**, *104 Pt 1*, 965. [[CrossRef](#)] [[PubMed](#)]
34. Farland, L.V.; Missmer, S.A.; Bijon, A.; Gusto, G.; Gelot, A.; Clavel-Chapelon, F.; Mesrine, S.; Boutron-Ruault, M.C. Associations among body size across the life course, adult height and endometriosis. *Hum. Reprod.* **2017**, *32*, 1732–1742. [[CrossRef](#)]
35. Vitonis, A.F.; Baer, H.J.; Hankinson, S.E.; Laufer, M.R.; Missmer, S.A. A prospective study of body size during childhood and early adulthood and the incidence of endometriosis. *Hum. Reprod.* **2010**, *25*, 1325–1334. [[CrossRef](#)]
36. Peterson, C.M.; Johnstone, E.B.; Hammoud, A.O.; Stanford, J.B.; Varner, M.W.; Kennedy, A.; Dodge, J.E.; Hribar McCormick, D.; Missmer, S.A. Risk factors associated with endometriosis: Importance of study population for characterizing disease in the ENDO Study. *Am. J. Obstet. Gynecol.* **2013**, *208*, 451.e1–451.e11. [[CrossRef](#)]
37. Mavaddat, N.; Barrowdale, D.; Andrulis, I.L.; Domchek, S.M.; Eccles, D.; Nevanlinna, H.; Ramus, S.J.; Spurdle, A.B.; Robson, M.; Sherman, M.E.; et al. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: Results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). *Cancer Epidemiol. Biomark. Prev.* **2012**, *21*, 134–147. [[CrossRef](#)]
38. Mezzapesa, F.; Dondi, G.; Coada, C.A.; De Leo, A.; De Terlizzi, F.; Strigari, L.; Di Costanzo, S.; Ravegnini, G.; Santoro, M.; de Biase, D.; et al. Two possible entities of endometriosis-associated ovarian cancer: Correlated or incidental? *Int. J. Gynecol. Cancer* **2025**, *35*, 101634. [[CrossRef](#)]
39. Velarde, M.C.; Bucu, M.E.M.; Habana, M.A.E. Endometriosis as a highly relevant yet neglected gynecologic condition in Asian women. *Endocr. Connect.* **2023**, *12*, e230169. [[CrossRef](#)]
40. Bougie, O.; Yap, M.I.; Sikora, L.; Flaxman, T.; Singh, S. Influence of race/ethnicity on prevalence and presentation of endometriosis: A systematic review and meta-analysis. *BJOG Int. J. Obstet. Gynaecol.* **2019**, *126*, 1104–1115. [[CrossRef](#)]
41. Boychuk, A.V.; Miklashevskaya, O.A.; Khlibovskaya, O.I.; Yakymchuk, Y.B.; Nikitina, I.M.; Herevych, N.V. Comorbid pathology of the mammary glands and endometriosis: Risk factors and prognosis. *Wiad. Lek.* **2024**, *77*, 247–253. [[CrossRef](#)]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.