Arch Gynecol Obstet (2016) 293:5–10
DOI 10.1007/s00404-015-3809-8

REVIEW

Association of endometriosis and breast cancer: mini review of the literature

Foteini Anifantaki[1] · Ioannis Boutas[1] · Theodoros Kalampokas[1] · Emmanouil Kalampokas[1] · Chrisostomos Sofoudis[1] · Nikolaos Salakos[1]

Received: 1 February 2015 / Accepted: 26 June 2015 / Published online: 3 July 2015

Abstract
Background Endometriosis is a common, estrogen-dependent, gynecological disease, which is defined as the presence of endometrial tissue outside the uterine cavity. Current data have associated endometriosis with specific malignancies, including ovarian and breast cancer.
Purpose The purpose of our study is to summarize and present published literature providing evidence regarding the possible relationship between endometriosis and breast cancer.
Methods Pubmed and Scopus databases were searched systematically for studies that sought to identify a potential association of endometriosis and breast cancer. 15 relevant articles were retrieved and included in the present review.
Results A small number of observational studies have shown a correlation of endometriosis and breast cancer. Other studies found that the risk of breast cancer increases with age. The scenario of an early interruption of the inflammatory process, derived from endometriosis, by oophorectomy and a possible consequent decrease in the risk of breast cancer has also been proposed. The hypothesis that both conditions could be related through common mutations on BRAC1 and BRAC2 genes has also been investigated.
Conclusion The available published evidence is inconclusive. Further studies are needed to evaluate the association of endometriosis and breast cancer and the possible pathogenetic pathways that relate the two disorders.

✉ Foteini Anifantaki
f.anifantaki@gmail.com

[1] Second Department of Obstetrics and Gynecology, University of Athens Aretaieion Hospital, Vas. Sofias Avenue 76, 11528 Athens, Greece

Keywords Endometriosis · Breast cancer · Breast neoplasm · Breast malignancies

Introduction

Endometriosis is a benign, estrogen-dependent gynecological disorder, which is frequently diagnosed in women with infertility. The estimated prevalence of endometriosis among women of reproductive age, ranges from 7 to 15 % and exceeds 50 % in women with infertility problems [1–3]. The disease is characterized by the implantation of hormonally sensitive endometrial tissue (endometrial glands and stroma) in locations outside the uterine cavity. The presence of ectopic endometrial tissue in distant locations such as lungs, pericardium and bladder has also been reported [2, 4, 5].

Several theories on etiology and origin of endometriosis have been proposed. The reflux of endometrial tissue via the fallopian tubes, during menstruation, and the consequent implantation of such tissue in distant places, is the prevailing theory [6]. Although endometriosis is a benign lesion, certain characteristics of it are also noted in malignancies. Specifically, similar to cancer, endometriosis presents with local and distant metastasis, attachment, damage of affected tissues and invasion [7].

Numerous studies have evaluated the risk of various cancers deriving from endometriosis [8]. Most of them have focused on the association of endometriosis and ovarian cancer and showed an increased risk for specific subtypes, including endometrioid and clear cell carcinoma [3, 9]. Recent genome and targeted sequencing studies have identified specific mutations on ARID1A, PIK3CA, PTEN and other genes that seem to associate endometriosis and ovarian cancer [10, 11]. Limited data have also

mentioned a potential correlation of endometriosis with other types of cancer, such as breast cancer (BC), non-Hodgkin lymphoma, melanoma, kidney cancer and endocrine cancers [3, 12, 13]. The existence of such relationship, as well as the possible background that relates such conditions has not been clarified yet.

BC is the most frequently diagnosed cancer among women. Family history and increasing exposure of breast tissue to estrogens are significant risk factors for BC [14]. It is generally accepted that both conditions are hormone-dependent conditions and also share some common risk factors and reproductive characteristics. However, whether endometriosis alters BC risk is unclear and the currently available data are inconsistent and not sufficient to support such association. The clarification of the existence of a possible pathophysiological relation between the two conditions needs further investigation as it would change the preventive and therapeutic approach of women with endometriosis.

The purpose of our study is to summarize and present published literature providing evidence regarding the possible relationship between endometriosis and BC, as well as the possible backgrounds that associate these conditions.

Methods

Literature search

PubMed and Scopus databases were searched systematically, until November 2014. The terms combined in both databases were "endometriosis", "breast cancer", "breast neoplasm" and "breast malignancies". Additional hand searches of reference lists and relevant articles were performed.

Study selection criteria

Studies were considered eligible if they provided data concerning the association of endometriosis and BC. Studies of any design that enrolled women of any age were included. Articles published in language other than English were excluded. Reviews, case reports and animal studies were also excluded from the present review.

Definitions and outcomes

The primary outcome of the present review was the existing evidence and possible pathways that associate endometriosis and breast carcinoma. Diagnosis of BC and endometriosis was defined according to criteria determined by investigators of each study.

Results

The electronic search generated 235 articles from PubMed and 240 articles from Scopus. After exclusion of articles that were not relevant to the focus of our study, a total of 15 articles were finally selected for the review. The selection process is depicted in Fig. 1. Table 1 summarizes the characteristics of the included studies.

Evidence from epidemiological studies on the association of endometriosis and breast cancer

In a population-based study, which evaluated the risk of cancer among women with endometriosis, an excess of BC was documented (standardized incidence ratio, SIR 1.3, 95 % confidence interval, CI 1.1–1.4) [9]. Furthermore, a second study showed a slightly increased risk of BC in women with a diagnosis of endometriosis (odds ratio, OR 1.10; 95 % CI 1.0–1.2) [15]. Contrary to the above data, Baron et al. observed a modest reduction in risk of BC in women with endometriosis (OR 0.8, 95 % CI 0.7–1.0) [16]. The latter was also supported by another study which showed that having a history of endometriosis

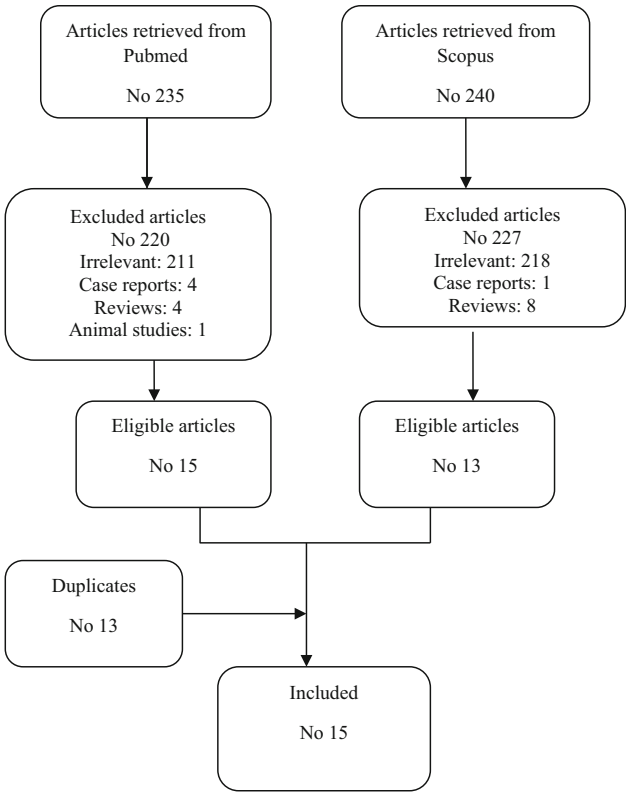

Fig. 1 Study selection process

Table 1 Characteristics of the included studies

References	Study design	No. of patients enrolled/study population	Scope of the study
Brinton et al. [9]	Cohort	20,686	Endometriosis and cancer risk
Schairer et al. [22]	Cohort	15,844	BC risk associated with gynecologic surgery
Weiss et al. [23]	Case–control	2173 cases/1990 controls	BC and medical conditions
Olson et al. [19]	Cohort	37,434	Association of endometriosis and BC, ovarian cancer, and NHL
Borgfeldt and Andolf [15]	Nested case–control	28,163 (to each case 3 controls were matched)	Endometriosis and risk of gynaecologic cancers
Melin et al. [12]	Cohort	64,492	Endometriosis and risk of ovarian cancer and other malignancies
Bertelsen et al. [20]	Nested case–control	114,327	Endometriosis and BC
Govindan et al. [25]	Case–control	337 cases/108 controls	Polymorphisms of progesterone receptor gene (PROGINS) in hormone responsive disorders
Matalliotakis et al. [26]	Case–control	352 cases/180 controls	Endometriosis and familial risk of BC
Gemmill et al. [18]	Cross-sectional	4331	Endometriosis and medical conditions
Nichols et al. [24]	Case–control	4935 cases/5111 controls	Bilateral oophorectomy due to nonmalignant indications and BC risk
Baron et al. [16]	Case–control	5659 cases/5928 controls	BC and metabolic disorders
Melin et al. [27]	Cohort	4278 (41,831 selected matched women)	Endometriosis as a prognostic factor for malignancies
Morales et al. [17]	Case–control	465 cases/661 controls	Risk factors for BC in Puerto Rican women
Aviel-Ronen et al. [21]	Mutation analysis	76 cases/50 controls	BRCA1/2 mutations in endometriosis

BC breast cancer, *NHL* non-Hodgkin lymphoma

decreased the risk of BC by 39 % ($p = 0.039$) [17]. Other two studies found that endometriosis was not associated with breast carcinoma (OR 0.54; 95 % CI 0.32–0.90, $p = 0.016$ and rate ratio, RR 1.0; 95 % CI 0.8–1.3, respectively) [18, 19].

Contribution of age on the risk of breast cancer among women with endometriosis

In two studies, the risk of BC in women with endometriosis seemed to increase with age. Specifically, in a study that evaluated the risk of endometriosis and other malignancies, women between the ages of 50 and 60 had an increased risk of BC (SIR 1.28, 95 % CI 1.13–1.45). In the same study, authors did not observe an elevation in the overall risk of BC [12]. In a second study, investigators observed that women in whom endometriosis was diagnosed earlier (approximately <40 years) had a reduced risk for BC comparing with women in whom diagnosis was done after the age of 40 and the risk of BC was higher. The same study showed that the crude overall RR for BC in women with endometriosis was 1.00 [20].

Mutations in BRAC1/2 genes

Regarding the mutations in common genes that possibly associate both conditions, one mutation analysis, in Ashkenazi Jewish women, did not find a statistically significant difference in the rate of mutations in BRAC1/2 genes in women with endometriotic cysts when compared with women with non-endometriotic cysts [study group vs control, 1/76 (1.3 %) vs 1/50(2 %), $p = 0.84$] [21].

Surgical intervention in endometriosis and risk of breast cancer

A case–cohort analysis has shown that women underwent hysterectomy without oophorectomy had a greater risk for BC when the indication was severe endometriosis [22]. In another case–control study, investigators did not find an overall association between BC and surgery for endometriosis. However, the risk was greater among premenopausal women (OR 1.68), especially among those with recent surgery (OR 2.38, 95 % CI 1.0–5.5) [23]. Furthermore, one study found a 58 % reduction in risk of BC in women with bilateral oophorectomy with hysterectomy, due to endometriosis. The latter probably could be

explained by the early interruption of an inflammatory process that may contribute to BC risk [24].

Other published data on the association of endometriosis and breast cancer

Another study, in an effort to identify a possible association between specific polymorphisms of progesterone receptor gene and disorders that are hormone responsive, found that such mechanism could be predisposing risk marker for breast cancer but not for endometriosis [25].

In a retrospective study, which evaluated the familial risk of BC in women with endometriosis, it was observed that 26.7 % of women with endometriosis and 5 % of women without endometriosis had a positive family history of BC ($p < 0001$) [26]. Finally, endometriosis as a prognostic factor for malignancies was studied by Melin and colleagues. Investigators showed that women with a diagnosis of endometriosis had a better prognosis for malignancies when compared with women without endometriosis and malignancies, including BC (HR 0.86, 95 % CI 0.75–0.97) [27].

Discussion

The potential carcinogenic pathways relating endometriosis and specific cancers have been extensively studied during last decade. The oxidative stress, the inflammatory process with cytokines and mediators derived from an environment of endometriosis, as well as the higher levels of estrogens observed in the disorder, have been proposed as possible mechanisms through which endometriosis contributes in the development of ovarian carcinogenesis [11].

Regarding the relevance between BC and endometriosis, the evidence from studies published so far is limited and their results are inconclusive. An increased risk was found in two studies, which were based on the hospital records of patients with endometriosis [9, 15]. Other studies failed to prove an overall increased risk of BC among women with the disease [16–19]. In two studies, authors observed that the risk of BC was depended on age, with an excess in older women [12, 20].

The hypothesis that both conditions probably share a common genetic pathway failed to be supported by a study, which examined mutations in BRAC1 and BRAC2 genes [21]. Other studies based on such hypothesis, showed a greater familial risk of BC in women with endometriosis [26]. Furthermore, a coexistence of congenital pyloric stenosis, endometriosis and BC was observed in two families from cancer clinics. Despite reported evidence, there are no specific data yet to prove that genetic factors may relate both conditions [14].

It has also been suggested that endometriosis promotes distant carcinogenesis through specific alterations in sex steroid hormones and inflammatory mediators. Higher secretion of cytokines and growth factors, abnormal B cell function and antibody production, as well as local elevation of estrogen levels, are some conditions observed in endometriosis and probably favor cancer progression [28–33]. The scenario of an early interruption of such inflammatory process by oophorectomy that may contribute to a limited risk of BC was also investigated in some studies, whose results were discrepant [22–24].

Additionally, the treatment of endometriosis could also be implicated in breast carcinogenesis. Specifically, before the introduction of GnRH agonists in the treatment of endometriosis, estrogens in combination with progestins were widely used. Studies have mentioned an increased risk of BC in those women who received the above combination as treatment [34]. Such agents may interact with members of the nuclear receptor superfamily and lead to deleterious impact on BC [35]. Limited studies have also examined the impact of drugs used by infertile women with endometriosis on breast tissue. However, such interaction could not be confirmed [36–38].

Polymorphisms of estrogen receptor and progesterone receptor genes have also been studied in hormone-related disorders, including BC and endometriosis [39–42]. The association of PROGINS (polymorphisms of the PR gene) with such disorders was studied by Govindan and colleagues. Authors mentioned that PROGINS can be regarded as risk marker of BC but not for endometriosis [25].

Data on the association of BC and endometriosis should be interpreted with caution due to certain limitations; the study design as well as the patients' history and characteristics differed among studies. Such heterogeneity does not permit us to conduct definitive conclusions regarding the association of such diseases. The association of both conditions is an area of great interest which needs further understanding. Further research is needed to evaluate the potential pathophysiological relation and determine the risk of breast carcinogenesis in women with endometriosis.

Conflict of interest We declare that we have no conflict of interest.

References

1. Panidis DK, Matalliotakis IM (1998) Subfertility associated with minimal to mild endometriosis. Main mechanisms. J Reprod Med 43:1034–1042
2. Ozkan S, Murk W, Arici A (2008) Endometriosis and infertility, epidemiology and evidence-based treatments. Ann N Y Acad Sci 1127:92–100

3. Somigliana E, Vigano P, Parazzini F, Stoppelli S, Giambattista E, Vercellini P (2006) Association between endometriosis and cancer: a comprehensive review and a critical analysis of clinical and epidemiological evidence. Gynecol Oncol 101:331–341
4. Genc M, Genc B, Karaarslan S, Solak A, Saracoglu M (2014) Endometriosis localized to urinary bladder wall mimicking urinary bladder carcinoma. Arch Ital Urol Androl 86:233–234
5. Ceccaroni M, Clarizia R, Placci A (2010) Pericardial, pleural, and diaphragmatic endometriosis. J Thorac Cardiovasc Surg 140:1189–1190
6. Zorbas KA, Economopoulos KP, Vlahos NF (2015) Continuous versus cyclic oral contraceptives for the treatment of endometriosis: a systematic review. Arch Gynecol Obstet 292(1):37–43
7. Garry R (2006) Diagnosis of endometriosis and pelvic pain. Fertil Steril 86:1307–1309
8. Kokcu A (2011) Relationship between endometriosis and cancer from current perspective. Arch Gynecol Obstet 284:1473–1479
9. Brinton LA, Gridley G, Persson I, Baron J, Bergqvist A (1997) Cancer risk after a hospital discharge diagnosis of endometriosis. Am J Obstet Gynecol 176:572–579
10. Wiegand KC, Shah SP, Al-Agha OM, Zhao Y, Tse K, Zeng T, Senz J, McConechy MK, Anglesio MS, Kalloger SE et al (2010) ARID1A mutations in endometriosis-associated ovarian carcinomas. N Engl J Med 363:1532–1543
11. Worley MJ, Welch WR, Berkowitz RS, Ng SW (2013) Endometriosis-associated ovarian cancer: a review of pathogenesis. Int J Mol Sci 14:5367–5379
12. Melin A, Sparen P, Persson I, Bergqvist A (2006) Endometriosis and the risk of cancer with special emphasis on ovarian cancer. Hum Reprod 21:1237–1242
13. Melin A, Sparen P, Bergqvist A (2007) The risk of cancer and the role of parity among women with endometriosis. Hum Reprod 22:3021–3026
14. Liede A, Pal T, Mitchell M, Narod SA (2000) Delineation of a new syndrome: clustering of pyloric stenosis, endometriosis, and breast cancer in two families. J Med Genet 37:794–796
15. Borgfeldt C, Andolf E (2004) Cancer risk after hospital discharge diagnosis of benign ovarian cysts and endometriosis. Acta Obstet Gynecol Scand 83:395–400
16. Baron JA, Weiderpass E, Newcomb PA, Stampfer M, Titus-Ernstoff L, Egan KM, Greenberg ER (2001) Metabolic disorders and breast cancer risk (United States). Cancer Causes Control 12:875–880
17. Morales L, Alvarez-Garriga C, Matta J, Ortiz C, Vergne Y, Vargas W, Acosta H, Ramirez J, Perez-Mayoral J, Bayona M (2013) Factors associated with breast cancer in Puerto Rican women. J Epidemiol Glob Health 3:205–215
18. Gemmill JA, Stratton P, Cleary SD, Ballweg ML, Sinaii N (2010) Cancers, infections, and endocrine diseases in women with endometriosis. Fertil Steril 94:1627–1631
19. Olson JE, Cerhan JR, Janney CA, Anderson KE, Vachon CM, Sellers TA (2002) Postmenopausal cancer risk after self-reported endometriosis diagnosis in the Iowa Women's Health Study. Cancer 94:1612–1618
20. Bertelsen L, Mellemkjaer L, Frederiksen K, Kjaer SK, Brinton LA, Sakoda LC, van Valkengoed I, Olsen JH (2007) Risk for breast cancer among women with endometriosis. Int J Cancer 120:1372–1375
21. Aviel-Ronen S, Soriano D, Shmuel E, Schonman R, Rosenblatt K, Zadok O, Vituri A, Seidman D, Barshack I, Cohen Y (2014) Surgically treated ovarian endometriosis association with BRCA1 and BRCA2 mutations. Pathol Res Pract 210:250–255
22. Schairer C, Persson I, Falkeborn M, Naessen T, Troisi R, Brinton LA (1997) Breast cancer risk associated with gynecologic surgery and indications for such surgery. Int J Cancer 70:150–154
23. Weiss HA, Brinton LA, Potischman NA, Brogan D, Coates RJ, Gammon MD, Malone KE, Schoenberg JB (1999) Breast cancer risk in young women and history of selected medical conditions. Int J Epidemiol 28:816–823
24. Nichols HB, Visvanathan K, Newcomb PA, Hampton JM, Egan KM, Titus-Ernstoff L, Trentham-Dietz A (2011) Bilateral oophorectomy in relation to risk of postmenopausal breast cancer: confounding by nonmalignant indications for surgery? Am J Epidemiol 173:1111–1120
25. Govindan S, Ahmad SN, Vedicherla B, Kodati V, Jahan P, Rao KP, Ahuja YR, Hasan Q (2007) Association of progesterone receptor gene polymorphism (PROGINS) with endometriosis, uterine fibroids and breast cancer. Cancer Biomark 3:73–78
26. Matalliotakis IM, Cakmak H, Mahutte N, Goumenou AG, Koumantakis G, Arici A (2008) The familial risk of breast cancer in women with endometriosis from Yale series. Surg Oncol 17:289–293
27. Melin A, Lundholm C, Malki N, Swahn ML, Sparen P, Bergqvist A (2011) Endometriosis as a prognostic factor for cancer survival. Int J Cancer 129:948–955
28. Ness RB, Modugno F (2006) Endometriosis as a model for inflammation-hormone interactions in ovarian and breast cancers. Eur J Cancer 42:691–703
29. Lebovic DI, Mueller MD, Taylor RN (2001) Immunobiology of endometriosis. Fertil Steril 75:1–10
30. Gazvani R, Templeton A (2002) New considerations for the pathogenesis of endometriosis. Int J Gynaecol Obstet 76:117–126
31. Reed MJ, Purohit A (1997) Breast cancer and the role of cytokines in regulating estrogen synthesis: an emerging hypothesis. Endocr Rev 18:701–715
32. Singer CF, Kronsteiner N, Hudelist G, Marton E, Walter I, Kubista M, Czerwenka K, Schreiber M, Seifert M, Kubista E (2003) Interleukin 1 system and sex steroid receptor expression in human breast cancer: interleukin 1alpha protein secretion is correlated with malignant phenotype. Clin Cancer Res 9:4877–4883
33. Zeitoun KM, Bulun SE (1999) Aromatase: a key molecule in the pathophysiology of endometriosis and a therapeutic target. Fertil Steril 72:961–969
34. Collins JA, Blake JM, Crosignani PG (2005) Breast cancer risk with postmenopausal hormonal treatment. Hum Reprod Update 11:545–560
35. Prentice RL, Chlebowski RT, Stefanick ML, Manson JE, Langer RD, Pettinger M, Hendrix SL, Hubbell FA, Kooperberg C, Kuller LH et al (2008) Conjugated equine estrogens and breast cancer risk in the Women's Health Initiative clinical trial and observational study. Am J Epidemiol 167:1407–1415
36. Ron E, Lunenfeld B, Menczer J, Blumstein T, Katz L, Oelsner G, Serr D (1987) Cancer incidence in a cohort of infertile women. Am J Epidemiol 125:780–790
37. Orgeas CC, Sanner K, Hall P, Conner P, Holte J, Nilsson SJ, Sundfeldt K, Persson I, Chia KS, Wedren S et al (2009) Breast cancer incidence after hormonal infertility treatment in Sweden: a cohort study. Am J Obstet Gynecol 200(72):e71–e77
38. Doyle P, Maconochie N, Beral V, Swerdlow AJ, Tan SL (2002) Cancer incidence following treatment for infertility at a clinic in the UK. Hum Reprod 17:2209–2213
39. Kitawaki J, Obayashi H, Ishihara H, Koshiba H, Kusuki I, Kado N, Tsukamoto K, Hasegawa G, Nakamura N, Honjo H (2001) Oestrogen receptor-alpha gene polymorphism is associated with endometriosis, adenomyosis and leiomyomata. Hum Reprod 16:51–55
40. Massart F, Becherini L, Marini F, Noci I, Piciocchi L, Del Monte F, Masi L, Falchetti A, Tanini A, Scarselli G, Brandi L (2003) Analysis of estrogen receptor (ERalpha and ERbeta) and

progesterone receptor (PR) polymorphisms in uterine leiomyomas. Med Sci Monit 9:BR25–BR30
41. Conneely OM, Mulac-Jericevic B, DeMayo F, Lydon JP, O'Malley BW (2002) Reproductive functions of progesterone receptors. Recent Prog Horm Res 57:339–355
42. Lattuada D, Somigliana E, Vigano P, Candiani M, Pardi G, Di Blasio AM (2004) Genetics of endometriosis: a role for the progesterone receptor gene polymorphism PROGINS? Clin Endocrinol (Oxf) 61:190–194