Archives of Gynecology and Obstetrics
https://doi.org/10.1007/s00404-018-4991-2

REVIEW

Malignant transformation of adenomyosis: literature review and meta-analysis

Hang Yuan[1] · **Shiqian Zhang**[1]

Received: 8 June 2017 / Accepted: 23 November 2018

Abstract

Purpose To review and analyze risk factors and the pathology of malignant transformation of adenomyosis.

Methods In this paper, the relevant research on current risks factors and the pathology of malignant transformation of adenomyosis was reviewed and analyzed by metaanalysis. All studies included were retrieved from the PUBMED.

Results Analysis of existing studies revealed that most malignant transformation of adenomyosis occurs in elderly or post-menopausal patients. Adenomyosis with uterine leiomyoma or benign endometrial hyperplasia and other benign diseases appears to be more prone to malignancy, but there is currently no strong evidence to confirm this finding.

Conclusions At present, the malignant transformation of adenomyosis is thought to be due to its endometrial epithelium transition to monolayer tumor cells before malignant transformation, which eventually develops to varying degrees of cancer. However, the specific molecular mechanism of adenomyosis is not yet clear. Because of its low incidence of malignant transformation, lack of large-sample, multi-center clinical trials, and large heterogeneity of the existing research, the evidence based on the high-risk factors of malignant transformation of adenomyosis is weak.

Keywords Adenomyosis · Malignant transformation · Meta-analysis

Introduction

Adenomyosis is a benign but refractory gynecological disease. It involves myometrial damage characterized by ectopic myometrium surrounding deep endometrial glands and the stroma accompanied by hyperplasia and hypertrophy of the adjacent myometrium. Most cases occur in women of childbearing age between 30 and 50 years. Common symptoms include menorrhagia, dysmenorrhea, pelvic pain, abnormal uterine bleeding and uterine enlargement-related symptoms [1–3]. Adenomyosis may exhibit malignant features in some respects such as angiogenesis and invasive behavior. Adenomyosis is common in endometrial adenocarcinoma hysterectomy specimens [4], and its malignant results are mostly endometrial adenocarcinoma [4]. In this paper, the relevant research on current risk factors and the pathology of malignant transformation of adenomyosis was reviewed and analyzed by meta-analysis.

✉ Shiqian Zhang
zhangshiqian370112@126.com

Hang Yuan
yuanhang940611@outlook.com

[1] Department of Gynecology, Qilu Hospital of Shandong University, Jinan, Shandong Province, China

Incidence of malignant transformation of adenomyosis and clinical manifestation

Approximately 1% of endometriosis cases are malignant; by contrast, the malignant transformation of adenomyosis is quite rare, and the malignant rate has not yet been reported. In 1897, Rolly first reported a case of malignant transformation of adenomyosis into endometrial adenocarcinoma. Only 50 cases of malignant transformation of adenomyosis into endometrial adenocarcinoma have been reported in the Chinese and English literature to date [5]. The vast majority occur in post-menopausal women, and the malignant transformation of pre-menopausal cases is rarer [6].

The malignant transformation of adenomyosis into endometrial adenocarcinoma lacks specific clinical manifestations. Its main symptoms include abnormal vaginal bleeding, menorrhea, anemia, and weight loss [1]. Compared with non-malignant changes, malignant transformation is difficult to distinguish owing to the lack of specific

Published online: 05 December 2018

clinical manifestations. Primary endometrial adenocarcinoma patients often present with hypertension, diabetes, and obesity, which are known as "triad syndrome". There has been no relevant study to show the relationship between malignant transformation of adenomyosis and endometrial adenocarcinoma "triad syndrome".

Pathological diagnostic criteria for the malignant transformation of adenomyosis

For endometrial adenocarcinoma from the malignant transformation of adenomyosis, the internationally accepted pathology diagnostic criteria are the Sampson Standard and the Scott Supplemental Standard [1, 7, 20, 21]. The Sampson Standard includes the following: (1) cancerous tissue and ectopic endometrial tissue coexist in the same lesion; (2) glandular cells and/or endometrial stromal cells exist to support the diagnosis of adenomyosis; (3) transformation evidence between benign and malignant gland structures is present; (4) other sources of tumor invasion or metastasis are excluded [1]. The Scott Supplemental Standard includes morphological evidence of ectopic endometrial metastases under the microscope, e.g., normal endometrial epithelium, borderline, and invasive carcinoma coexist [7] (Fig. 1).

Risk factors of the malignant transformation of adenomyosis

Based on the low malignancy rate of adenomyosis, there is a lack of large sample, multi-center RCT studies, and seven cohort studies have examined the leading factors of the malignant transformation of adenomyosis [4, 8–12, 22]. It has been suggested that adenomyosis can be malignant, transforming into endometrial adenocarcinoma, with the vast majority of cases occurring in post-menopausal women and rarely occurring in pre-menopausal women [6]. It has been suggested that adenomyosis associated with uterine leiomyoma and/or benign endometrial polyp appears to be more prone to malignancy [4, 8–12, 22]. A meta-analysis has been conducted for existing studies, and the main results are as follows (Figs. 2, 3, 4, 5). Malignant transformation of adenomyosis mostly occurs in elderly or post-menopausal patients and is rare in young or pre-menopausal patients (Fig. 2). Based on this finding, being elderly or post-menopausal may be included as high-risk factors for the malignant transformation of adenomyosis. As for endocrine therapy, based on existing studies, it may be correlated with malignant transformation of adenomyosis (Fig. 3). Adenomyosis with uterine leiomyoma and/or benign endometrial polyp appears to be more prone to malignancy, but there is insufficient evidence for it to be included as a major risk factor for the malignant transformation of adenomyosis (Figs. 4, 5).

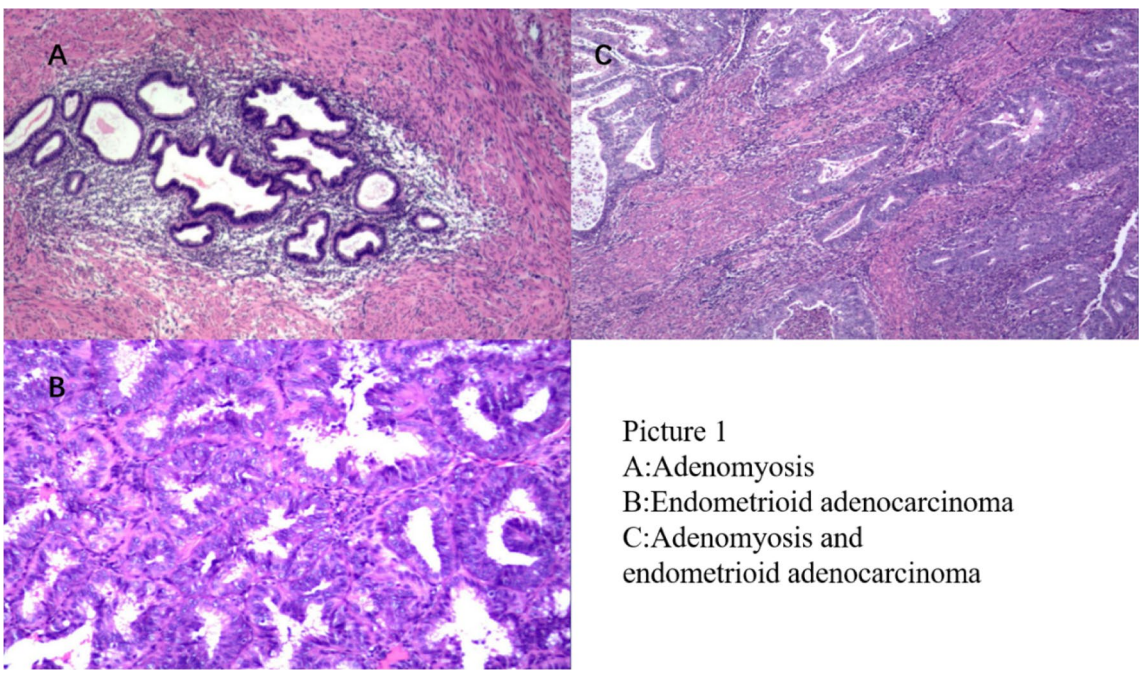

Fig. 1 Transformation of adenomyosis

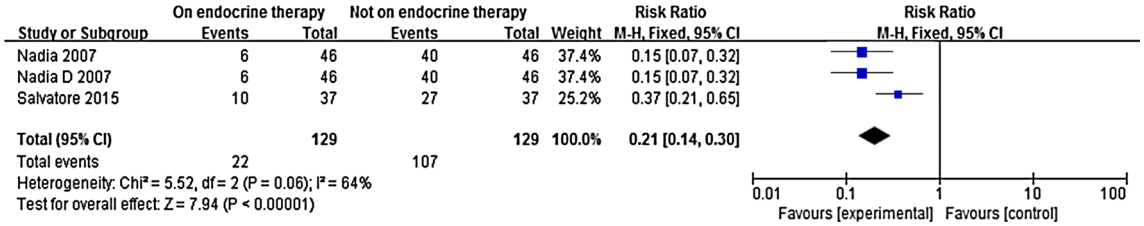

Fig. 2 Relationship between menopause and malignant transformation of adenomyosis

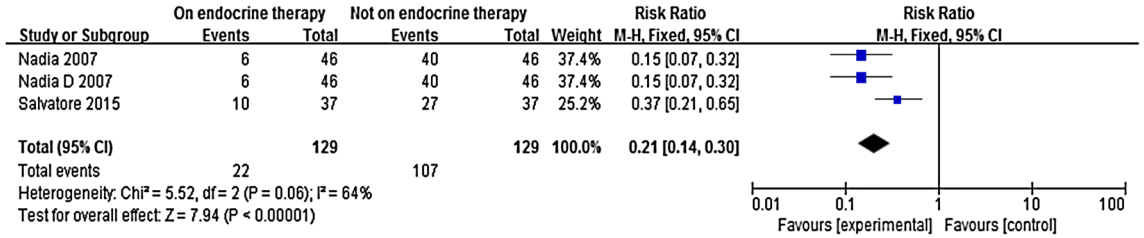

Fig. 3 Relationship between endocrine therapy and malignant transformation of adenomyosis

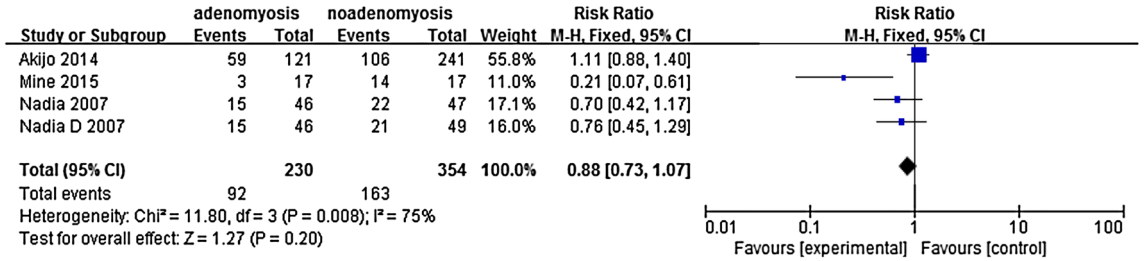

Fig. 4 Relationship between leiomyoma(s) and malignant transformation of adenomyosis

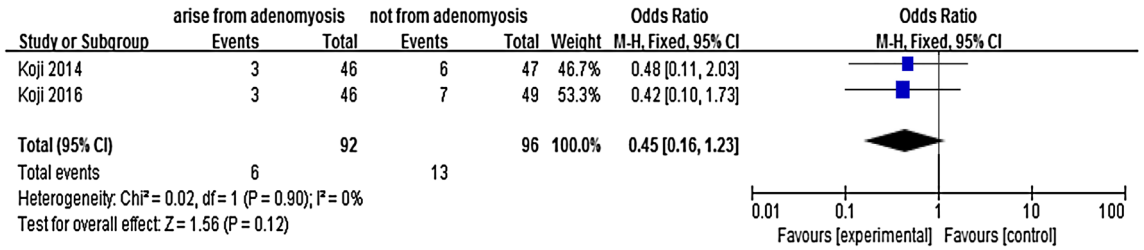

Fig. 5 Relationship between benign endometrial polyp and malignant transformation of adenomyosis

Pathological findings of malignant transformation of adenomyosis

Endometrioid adenocarcinoma is most common for the malignant transformation of adenomyosis into endometrial adenocarcinoma followed by serous carcinoma, clear cell carcinoma and poorly differentiated adenocarcinoma [13]. Serous endometrial intraepithelial carcinoma due to malignant transformation of adenomyosis (serous EIC) is rare [14, 15].

Three studies have investigated the relationship between lymphovascular invasion and malignant transformation of adenomyosis [4, 9, 16]. However, regardless of the cause of endometrial adenocarcinoma, its lymphovascular invasion had no significant differences (Fig. 6). Several studies

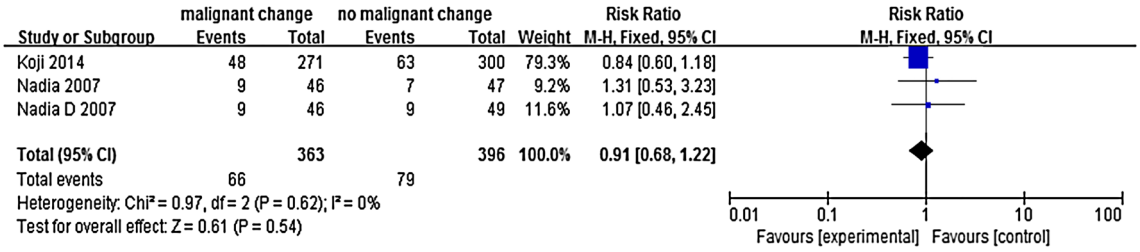

Fig. 6 Relationship between lymphovascular invasion and malignant transformation of adenomyosis

have investigated the FIGO staging and histological grade of endometrial adenocarcinoma due to malignant transformation of adenomyosis [8, 10, 11, 16]. Existing studies have shown that, regardless of the cause of endometrial adenocarcinoma, its FIGO staging was not significant (Fig. 7). However, for the histological grade, the endometrial adenocarcinoma caused by the malignant transformation of adenomyosis tends to be low (Fig. 8). Based on subgroup analysis, FIGO I staging was more common in endometrial adenocarcinoma due to non-malignant transformation of adenomyosis, while FIGO II staging was more common in endometrial adenocarcinoma caused by malignant transformation of adenomyosis (Fig. 7). As for histological grade, grade 3 was more common in malignant transformation of adenomyosis and grade 1 was more common in endometrial adenocarcinoma due to non-malignant transformation of adenomyosis (Fig. 8).

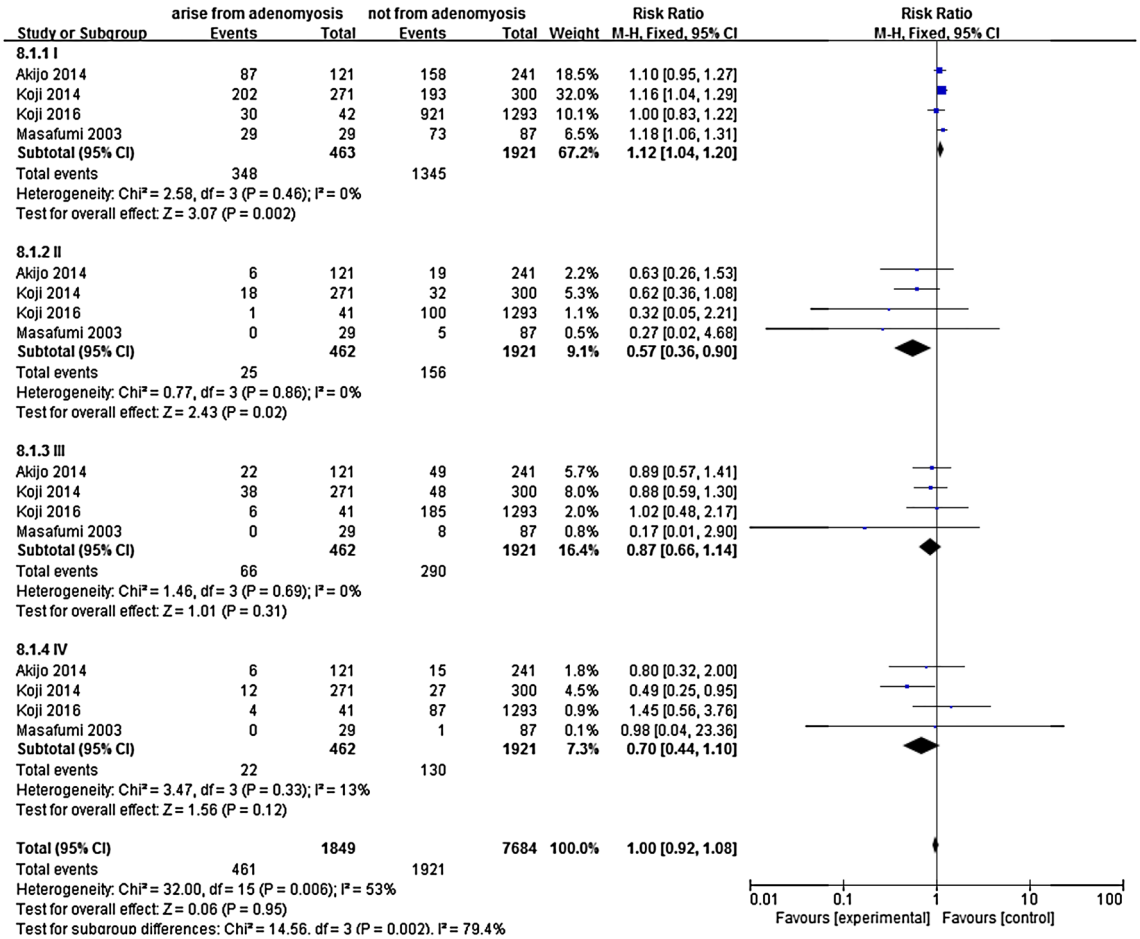

Fig. 7 FIGO staging of malignant transformation of adenomyosis

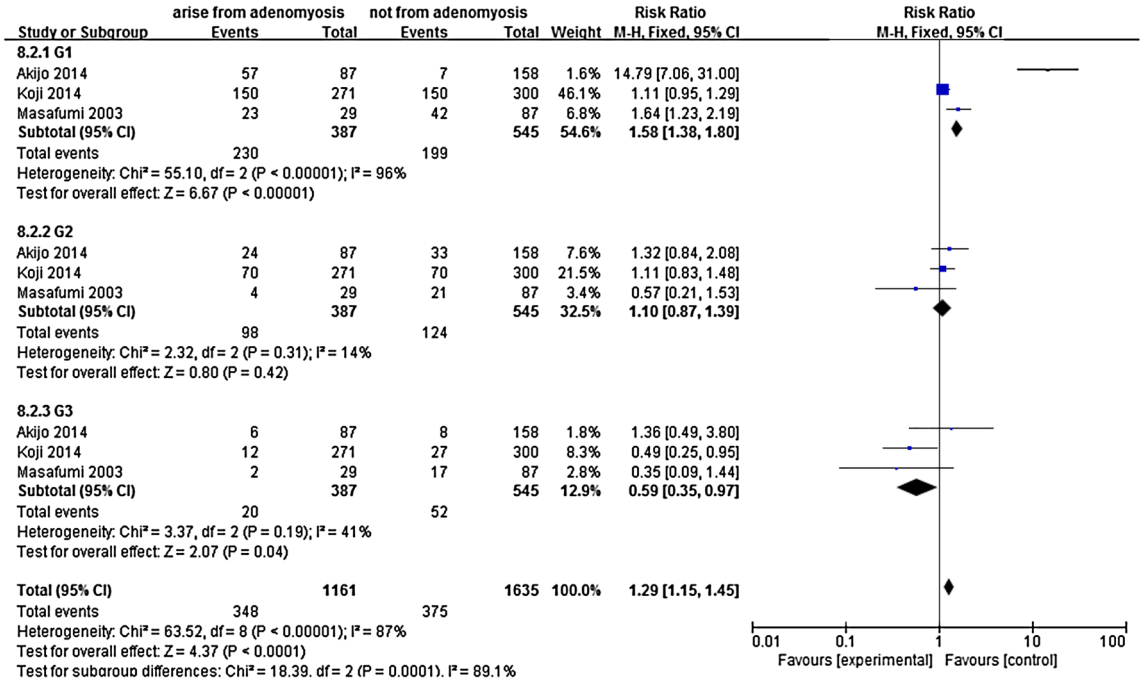

Fig. 8 Histological grade of malignant transformation of adenomyosis

Pathological mechanism of the malignant transformation of adenomyosis

Possible mechanism for the malignant transformation of adenomyosis

Adenomyosis shows malignant features in some areas such as rapid growth, angiogenesis and invasion. Malignant disease progress rarely occurs [1]. It is now believed that adenomyosis endometrial epithelium transitions to monolayer tumor cells before malignant transformation and eventually develops to varying degrees of cancer [1]. However, the specific molecules that cause myometrial cell transformation and its subsequent regulation are not yet clear. There is still a lack of strong confirmation in the pathology and rationality of the molecular mechanism.

Some data indicate that there are genetic alterations, mutation analysis, and inactivation of specific tumor suppressor genes in adenomyosis, which may be associated with its malignant transformation [17–19]. Goumenou et al. reported for the first time that there was a loss of heterozygosity (LOH) in adenomyosis, which may be involved in the initiation of adenomyosis and the early onset of the disorder [17]. DNA mismatch repair genes (hMSH2, hMLH1), p16Ink4 (CDKN2A, cyclin-dependent kinase inhibitor 2A) and the GALT (galactose-1-phosphate uridyltransferase) gene are associated with the occurrence and development of adenomyosis [17]. DNA mismatch repair genes (hMSH2, hMLH1) have been found at 2p22.3-pl6.1 and 3p24.2-p22. LOH on these sites may associate with cancer pre-disposition of adenomyosis [17]. Adenomyosis stroma Bcl-2 expression is maintained at a low level and may have a negative effect on ectopic endometrial growth and survival [18]. Jones et al. found that, compared with the eutopic endometrium, stromal bcl-2 expression in endometriotic foci was significantly increased, and did not vary with menstrual cycle [18]. In contrast, stromal bcl-2 expression in adenomyosis was at low levels and did not show significant cyclical variation [18]. Adenomyosis shows epigenetic variation related to the methylation of the progesterone receptor gene promoter region [19]. Progesterone receptor isoform B (PR-B) promoter is hypermethylated in adenomyosis, with concomitant reduced expression. In addition [19], the biological function of other genes in the occurrence and malignant transformation of adenomyosis remains to be determined. At present, the molecular continuity between benign and malignant lesions of adenomyosis requires strong evidence to confirm [1].

Relationship between adenomyosis and myometrial invasion

At present, five cohort studies have explored the relationship between adenomyosis and myometrial invasion in endometrial adenocarcinoma [4, 8, 9, 11, 16]. This review incorporates these five studies and provides a meta-analysis of their research data. Analysis of the available data suggests that adenomyosis may not contribute to the development

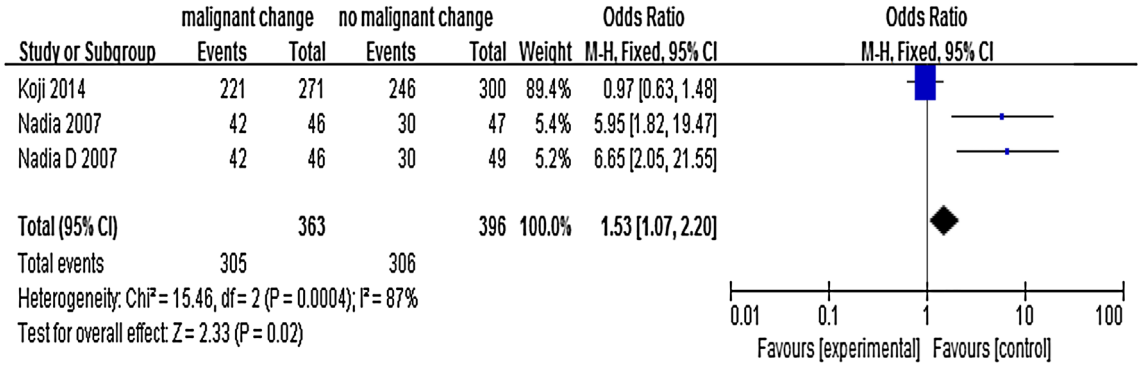

Fig. 9 Relationship between myometrial invasion and malignant transformation of adenomyosis

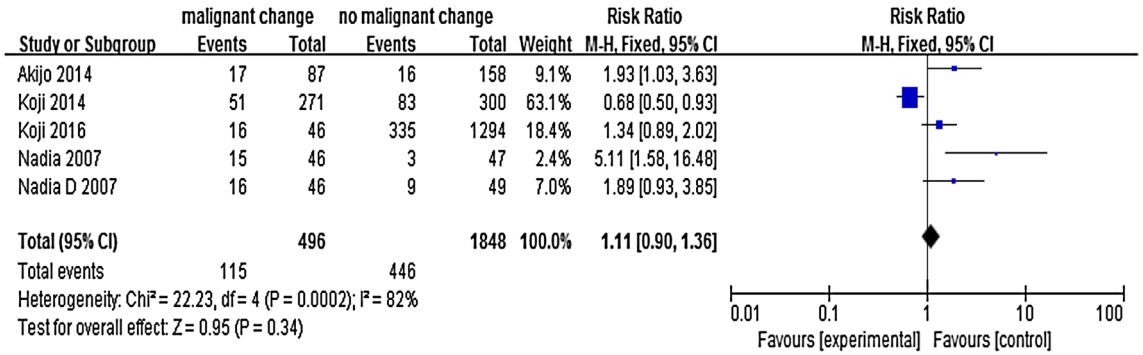

Fig. 10 Relationship between deep myometrial invasion and malignant transformation of adenomyosis

of myometrial invasion in endometrial adenocarcinoma (Fig. 9). However, there is still a lack of data from a large sample of multi-center randomized controlled clinical trials; thus, existing evidence is insufficient. In terms of the depth of myometrial invasion, the available data suggest that adenomyosis may not be associated with deep myometrial invasion (depth of invasion ≥ 1/2) (Fig. 10). Overall, the relationship between adenomyosis and endometrial myometrial invasion endometrial adenocarcinoma is not clear.

Conclusion

Adenomyosis is a benign but refractory gynecological disease. Adenomyosis shows malignant features in some areas such as rapid growth, angiogenesis and invasion. Adenomyosis may be associated with certain malignant tumors. At present, the malignant transformation of adenomyosis is thought to be due to its endometrial epithelium transition to monolayer tumor cells before malignant transformation, which eventually develops to varying degrees of cancer. However, the specific molecular mechanism of adenomyosis is not yet clear. Because of its low incidence of malignant transformation, lack of large- sample, multi-center clinical trials, and large heterogeneity of the existing research, the high-risk factors of malignant transformation of adenomyosis is still unclear. Analysis of existing studies revealed that most malignant transformation of adenomyosis occurs in elderly or post-menopausal patients. Adenomyosis with uterine leiomyoma or benign endometrial hyperplasia and other benign diseases appears to be more prone to malignancy, but there is currently no strong evidence to confirm this finding.

Author contributions HY Data Collection, Manuscript writing. SZ Data Collection, Manuscript writing

Compliance with ethical standards

Conflict of interest Hang Yuan declares that she has no conflict of interest. Shiqian Zhang declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Koike N, Tsunemi T, Uekuri C, Akasaka J, Ito F, Shigemitsu A, Kobayashi H (2013) Pathogenesis and malignant transformation of adenomyosis (review). Oncol Rep 29:861–867 **(Published online EpubMar (10.3892/or.2012.2184))**
2. Taran FA, Stewart EA, Brucker S (2013) Adenomyosis: epidemiology, risk factors, clinical phenotype and surgical and interventional alternatives to hysterectomy. Geburtshilfe und Frauenheilkunde 73:924–931 **(Published online EpubSep (10.1055/s-0033-1350840))**
3. Hong SC, Khoo CK (2016) An update on adenomyosis uteri. Gynecol Min Invas Ther 5:106–108. https://doi.org/10.1016/j.gmit.2015.08.003
4. Ismiil ND, Rasty G, Ghorab Z, Nofech-Mozes S, Bernardini M, Thomas G, Ackerman I, Covens A, Khalifa MA (2007) Adenomyosis is associated with myometrial invasion by FIGO 1 endometrial adenocarcinoma. Int J Gynecol Pathol 26:278–283. https://doi.org/10.1097/01.pgp.0000235064.93182.ec
5. Mori M, Furusawa A, Kino N, Uno M, Ozaki Y, Yasugi T (2015) Rare case of endometrioid adenocarcinoma arising from cystic adenomyosis. J Obstet Gynaecol Res 41:324–328 **(Published online EpubFeb 10.1111/jog.12513)**
6. Kazandi M, Zeybek B, Terek MC, Zekioglu O, Ozdemir N, Oztekin K (2010) Grade 2 endometrioid adenocarcinoma arising from adenomyosis of the uterus: report of a case. Eur J Gynaecol Oncol 31:719–721
7. Hsu MI, Chou SY, Lin SE, Liang SJ, Chiu HC, Hsu CS (2006) Very early stage adenocarcinoma arising from adenomyosis in the uterus. Taiwan J Obstet Gynecol 45:346–349 **(Published online EpubDec (10.1016/s1028-4559(09)60258-8))**
8. Matsuo K, Moeini A, Machida H, Scannell CA, Casabar JK, Kakuda M, Adachi S, Garcia-Sayre J, Ueda Y, Roman LD (2016) Tumor characteristics and survival outcome of endometrial cancer arising in adenomyosis: an exploratory analysis. Ann Surg Oncol 23:959–967 **(Published online EpubMar (10.1245/s10434-015-4952-y))**
9. Ismiil N, Rasty G, Ghorab Z, Nofech-Mozes S, Bernardini M, Ackerman I, Thomas G, Covens A, Khalifa MA (2007) Adenomyosis involved by endometrial adenocarcinoma is a significant risk factor for deep myometrial invasion. Annals of diagnostic pathology 11:252–257 **(Published online epubaug (10.1016/j.anndiagpath.2006.08.011))**
10. Koshiyama M, Okamoto T, Ueta M (2004) The relationship between endometrial carcinoma and coexistent adenomyosis uteri, endometriosis externa and myoma uteri. Cancer Detect Prev 28:94–98. https://doi.org/10.1016/j.cdp.2003.12.008
11. Taneichi A, Fujiwara H, Takahashi Y, Takei Y, Machida S, Saga Y, Takahashi S, Suzuki M (2014) Influences of uterine adenomyosis on muscle invasion and prognosis of endometrioid adenocarcinoma. Int J Gynecol Cancer 24:1429–1433 **(Published online EpubOct (10.1097/IGC.0000000000000243))**
12. Genc M, Genc B, Cengiz H (2015) Adenomyosis and accompanying gynecological pathologies. Arch Gynecol Obstet 291:877–881 **(Published online EpubApr (10.1007/s00404-014-3498-8))**
13. Baba A, Yamazoe S, Dogru M, Ogawa M, Takamatsu K, Miyauchi J (2016) Clear cell adenocarcinoma arising from adenomyotic cyst: A case report and literature review. The journal of obstetrics and gynaecology research 42:217–223 **(Published online EpubFeb (10.1111/jog.12866))**
14. Lu B, Chen Q, Zhang X, Cheng L (2016) Serous carcinoma arising from uterine adenomyosis/adenomyotic cyst of the cervical stump: a report of 3 cases. Diagn Pathol 11:46 **(Published online EpubJun 04 (10.1186/s13000-016-0496-0))**
15. Izadi-Mood N, Samadi N, Sarmadi S, Eftekhar Z (2007) Papillary serous carcinoma arising from adenomyosis presenting as intramural leiomyoma. Arch Iran Med 10:258–260 **(Published online EpubApr (07102/aim.0026))**
16. Matsuo K, Cahoon SS, Gualtieri M, Scannell CA, Jung CE, Takano T, Paulson RJ, Muderspach LI, Roman LD (2014) Significance of adenomyosis on tumor progression and survival outcome of endometrial cancer. Ann Surg Oncol 21:4246–4255 **(Published online EpubDec (10.1245/s10434-014-3880-6))**
17. Goumenou AG, Arvanitis DA, Matalliotakis IM, Koumantakis EE, Spandidos DA (2000) Loss of heterozygosity in adenomyosis on hMSH2, hMLH1, p16Ink4 and GALT loci. International journal of molecular medicine 6:667–671 **(Published online EpubDec)**
18. Jones RK, Searle RF, Bulmer JN (1998) Apoptosis and bcl-2 expression in normal human endometrium, endometriosis and adenomyosis. Hum Reprod (Oxford, England) 13:3496–3502 **(Published online EpubDec)**
19. Jichan N, Xishi L, Guo SW (2010) Promoter hypermethylation of progesterone receptor isoform B (PR-B) in adenomyosis and its rectification by a histone deacetylase inhibitor and a demethylation agent. Reprod Sci 17:995–1005 **(Published online EpubNov (10.1177/1933719110377118))**
20. Sampson JA (1925) Endometrial carcinoma of the ovary arising in endometrial tissue of that organ. Arch Surg 10:1–72
21. Colman HI, Rosenthal AH (1959) Carcinoma developing in areas of adenomyosis. Obset Gynecol 14:342–348
22. Gizzo S, Patrelli TS, Dall'asta A, DI Gangi S, Giordano G, Migliavacca C, Monica M, Merisio C, Nardelli GB, Quaranta M, Noventa M, Berretta R (2016) Coexistence of adenomyosis and endometrioid endometrial cancer: role in surgical guidance and prognosis estimation. Oncol Lett 11(2):1213–1219 **(Epub 2015 Dec 15)**