Endometrial Cancer, Endometriosis and Adenomyosis

Subjects: Oncology

Contributor: Marjolein Hermens

Previous research shows that women with endometriosis and adenomyosis have an increased ovarian cancer risk. However, it is unclear whether these women have an increased risk of developing uterine cancer. This information is of key importance to women with endometriosis or adenomyosis. Therefore, this study aims to assess the uterine cancer risk in women with endometriosis or adenomyosis in a large population.

endometrial cancer endometriosis adenomyosis risk

1. Introduction

Endometriosis and adenomyosis are prevalent benign gynecological conditions in which endometrial-like glands and stroma are present outside the uterine cavity or in the myometrium, respectively [1][2][3][4]. Endometriosis and adenomyosis share characteristics with malignant tissue including tissue invasion, increased proliferative capability, induction of angiogenesis, the ability to evade apoptosis, and the ability to develop local and distant foci [5][6].

In 2018, around 380,000 women were diagnosed with endometrial cancer worldwide [7], and it is the most common gynecological cancer in developed countries [8]. Endometrial cancer prognosis is relatively good, as is it often found in the early stage [8]. The five most common histopathological subtypes are endometrioid, clear-cell, serous, mucinous endometrial cancer and adenocarcinoma not otherwise specified (NOS) [8].

Several studies have shown that endometriosis is associated with an increased risk of ovarian cancer, specifically endometrioid and clear cell ovarian subtypes [9][10][11]. However, contradictory evidence exists as to whether endometriosis and adenomyosis are associated with endometrial cancer [11][12][13][14][15]. Additionally, most studies included women with clinical or surgical endometriosis/adenomyosis, whereas histological diagnosis is still considered the gold standard [2]. Furthermore, studies on adenomyosis and endometrial cancer included small samples sizes [13][14][15].

Given the contradictory results and scarce evidence, especially for adenomyosis, larger epidemiological studies are warranted to elucidate the possible association between endometriosis/adenomyosis and endometrial cancer. Therefore, the objective of this study is to assess the incidence of endometrial cancer in women with histologically proven endometriosis or adenomyosis, and to determine whether there is a specific relationship with certain histological endometrial cancer subgroups.

2. Principal Findings

This large nationwide cohort study observed an increased association between endometriosis/adenomyosis and endometrial cancer with an age-adjusted OR of 2.58 (95%CI 2.37–2.81). We found the highest ORs for clear cell endometrial cancer subtype (OR 30.31 95%CI 9.83–93.51) and adenocarcinoma NOS (OR 79.61 95%CI 61.70–102.72). The histological diagnosis of endometriosis/adenomyosis and endometrial cancer was synchronously diagnosed in most women. After excluding the first year of follow-up there was a substantial reduction of endometrial cancer cases in the endometriosis/adenomyosis cohort and as a consequence, the observed ORs for endometrial cancer in the endometriosis/adenomyosis cohort showed no increased association.

3. Results of the Study in the Context of Other Observations

A recent large meta-analysis showed a relative risk of 1.23 (95%CI 0.97–1.57) for endometrial cancer in women with solely endometriosis, whereas we found an age-adjusted OR of 2.63 (95%CI 2.35–2.95) [11]. The studies included in this meta-analysis had a high level of heterogeneity and mostly used self-reported or clinically diagnosed endometriosis instead of histologically diagnosed endometriosis. In addition, two nationwide studies form Finland and Scotland, including women with surgically confirmed endometriosis, found no increased risk of endometrial cancer [16][17]. These studies included women at a younger age compared to our study, but with similar follow-up time, which could possibly explain the lower endometrial cancer incidence in these studies in general. Moreover, our endometriosis cohort with histologically diagnosed endometriosis might have more severe disease with a potentially different risk profile.

In the adenomyosis cohort we found an age-adjusted OR for endometrial cancer of 2.63 (95%CI 2.40–2.87) and an age-adjusted OR of 1.11 (95%CI 0.82–1.50) after excluding the first year of follow-up. Kok et al. [15] found a similar adjusted hazard ratio of 4.38 (95%CI 1.22–15.72) for endometrial cancer in women with mostly surgically diagnosed adenomyosis with preserved uterus and ovaries at time of clinical diagnosis. Similarly, the meta-analysis by Raffone et al. showed that the prevalence of adenomyosis in women with diagnosed endometrial cancer was similar to the prevalence reported in hysterectomies for other gynecological conditions [13]. The included studies, however, did not assess a control group of women without endometrial cancer, and therefore a direct comparison was not possible.

Due to the nature of our study, the women in the endometriosis/adenomyosis cohort more frequently had a hysterectomy as compared to the nevus cohort. We hypothesize that the women who underwent a hysterectomy might have had a higher endometriosis/adenomyosis disease burden or clinically showed no adequate response to hormonal treatment, possibly resulting in a higher risk for endometrial cancer. In contrast, the women with a better response to hormonal treatment might have been on hormonal therapy for longer and therefore might have had a decreased risk of developing endometrial cancer, as in general, the use of oral contraceptives causes a decrease in the risk of endometrial cancer by about 50% [18], and could therefore explain the lower risk found in the endometriosis/adenomyosis cohort with more than a year of follow-up.

Strikingly, of all women with endometrial cancer and a hysterectomy, roughly 20% had no endometrial cancer diagnosis before hysterectomy, and of this group around 35% had no previous endometrial sampling within a year of endometrial cancer diagnosis at all. These women were possibly being treated for benign uterine diseases, but unexpectedly had endometrial cancer diagnosed. We therefore recommend considering endometrial sampling before a hysterectomy, especially in the case of severe endometriosis/adenomyosis complaints, as knowing the malignant status preoperatively will often have consequences for the surgical procedure, i.e., staging.

4. Endometrial Cancer Subtypes

Endometrial cancer subtypes have rarely been evaluated in previous studies. One study showed a stronger association for type I endometrial cancers (endometrioid, mucinous endometrial cancer and adenocarcinoma NOS) [19], which is partially in accordance with our findings. The reason for the high number of adenocarcinoma NOS cases in the endometriosis/adenomyosis cohort is not clear. Most of the adenocarcinoma NOS were low-grade tumors without any specific report of histological subtype. Unfortunately, it was not possible to review the samples, but we hypothesize that these cases were mostly well-differentiated endometrioid endometrial cancers, as clear cell and serous endometrial cancer are per definition classified as high-grade tumors [20].

Type I endometrial cancers are commonly associated with a relatively good prognosis [8]. A recent meta-analysis showed that women with adenomyosis and endometrial cancer had longer overall survival when compared to women with endometrial cancer without adenomyosis [21]. However, in this study it was not possible to calculate multivariate hazard ratios. Our study group recently performed a nationwide cohort study comparing survival in women with endometrial cancer with or without endometriosis/adenomyosis [22]. In this study, we found increased overall survival after endometrial cancer diagnosis in women with endometriosis/adenomyosis. After correction for confounders like age, stage, grade and histological subtype no increased survival was found.

5. Age at Endometrial Cancer Diagnosis and Combined Endometriosis and Adenomyosis

In the metachronous analysis, women in the endometriosis cohort were younger (56 years) at endometrial cancer diagnosis when compared to the adenomyosis cohort (64 years) and the nevus cohort (62 years). The average age at endometrial cancer diagnosis in the Netherlands is 67 years [23]. The lower endometrial cancer age in the endometriosis cohort could be explained by endometriosis being a disease in young fertile women. These women are significantly younger at inclusion (36 years) when compared to the women with adenomyosis (45 years) or a nevus (45 years). The median follow-up in the endometriosis cohort is 12 years, which means that the average woman in the endometriosis cohort is 48 years at end of study follow-up, and therefore, that a large number of women in the endometriosis cohort might not have reached the average Dutch endometrial cancer age.

In our study, 6712 (7.9%) women in the endometriosis cohort had concurrent adenomyosis and in the endometriosis cohort 6026 (11.9%). This is in line with previously reported studies reporting endometriosis

incidences between 3–18% in women with adenomyosis [24]. Excluding the cases with both endometriosis and adenomyosis did not alter the results.

6. Possible Key Factors in the Malignant Transformation of Endometriosis/Adenomyosis

Endometriosis and adenomyosis are both estrogen-dependent entities; additionally, type I endometrial cancers are associated with increased estrogen levels [25][26]. When looking into the hypothesis of the malignant transformation of endometriosis/adenomyosis, there might be a role for the immune system. In both endometriosis and adenomyosis, the immune system seems to be more active [27][28]. As the immune system also plays an important factor in carcinogenesis by tumor initiation, promotion and progression [29], an activated immune system in endometriosis/adenomyosis might play a key role in the malignant transformation of these diseases. However, additional studies are needed to test this hypothesis.

Studies on the possible malignant transition of adenomyosis are scarce. One study on molecular changes in adenomyosis showed upregulated Kirsten rat sarcoma virus (KRAS) genes and reduced Phosphatase and tensin homolog (PTEN) expression in adenomyosis [30]. Furthermore, the process of epithelial-to-mesenchymal transition (EMT) seems to be crucial in the development of adenomyosis but also plays an important role in carcinogenesis [31][32]. Several studies have shown that changes in genes like AT-rich interactive domain-containing protein 1A (ARID1A), PTEN, KRAS, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) and Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A alpha isoform (PPP2R1A) are present in women with endometriosis, but these are also known cancer-driving mutations involved in endometrial cancer carcinogenesis [33][34]. However, cancer-associated mutations were also found in endometriotic lesions without concurrent cancer, in particular in deep infiltrating lesions which are rarely associated with cancer development [35]. It remains unclear whether these mutations are key in malignant transformation of endometriosis/adenomyosis. Nonetheless, identification of possible driver mutations in endometriosis/adenomyosis samples might help in the future to identify women at risk for developing endometrial cancer.

7. Strengths and Limitations

The strength of this study is that it is a large nationwide study in which we only included women with histologically proven endometriosis or adenomyosis, which is still considered the gold standard for these diagnoses. However, using a histological database can also be considered a limitation, as no clinical data were available. As women with endometriosis/adenomyosis often have other known risk factors for cancer development, studies adjusting for these possible confounders are warranted. Due to the nature of our database, it was not possible to correctly differentiate endometriosis subtypes. Furthermore, women in the nevus cohort could have had a clinical diagnosis of endometriosis/adenomyosis without histological confirmation. Another limitation of our study is the high number of hysterectomies in the adenomyosis cohort, and consequently the low number of exposure years. We therefore performed logistic regression analysis to calculate odds ratios. Additionally, it is not known whether the women in

the nevus cohort had had a hysterectomy before start of the study, but since median age at inclusion was 45 years, a high rate of hysterectomies before start of study seems unlikely. Previously, two studies showed a slightly increased incidence (2–3% increase) of benign dermal nevi in women with laparoscopic confirmed endometriosis [36][37]. To our knowledge, no association between ovarian cancer and nevi exists; we therefore believe the effect of this association on our results is limited. Moreover, this study is prone to detection bias, and therefore we performed a second analysis excluding the first year of follow-up. Lastly, PALGA uses identification codes based on the first eight letters of the family name and birth date, therefore results from different women may have been combined. We believe the effect of this is minimized by using a large control cohort with the same risk of merged cases.

References

1. Gordts, S.; Grimbizis, G.; Campo, R. Symptoms and classification of uterine adenomyosis, including the place of hysteroscopy in diagnosis. Fertil. Steril. 2018, 109, 380–388.
2. Dunselman, G.A.; Vermeulen, N.; Becker, C.; Calhaz-Jorge, C.; D'Hooghe, T.; De Bie, B.; Heikinheimo, O.; Horne, A.W.; Kiesel, L.; Nap, A.; et al. ESHRE guideline: Management of women with endometriosis. Hum. Reprod. Oxf. Engl. 2014, 29, 400–412.
3. Eskenazi, B.; Warner, M.L. Epidemiology of endometriosis. Obstet. Gynecol. Clin. N. Am. 1997, 24, 235–258.
4. Adamson, G.D.; Kennedy, S.H.; Hummelshoj, L. Creating Solutions in Endometriosis: Global Collaboration through the World Endometriosis Research Foundation. J. Endometr. 2010, 2, 3–6.
5. Mao, X.; Zheng, W.; Mao, W. Malignant changes in adenomyosis in patients with endometrial adenocarcinoma: A case series. Medicine 2017, 96, e8336.
6. Pollacco, J.; Sacco, K.; Portelli, M.; Schembri-Wismayer, P.; Calleja-Agius, J. Molecular links between endometriosis and cancer. Gynecol. Endocrinol. 2012, 28, 577–581.
7. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2018, 68, 394–424.
8. Amant, F.; Mirza, M.R.; Koskas, M.; Creutzberg, C.L. Cancer of the corpus uteri. Int. J. Gynaecol. Obstet. 2018, 143 (Suppl. 2), 37–50.
9. Hermens, M.; van Altena, A.M.; Nieboer, T.E.; Schoot, B.C.; van Vliet, H.; Siebers, A.G.; Bekkers, R.L.M. Incidence of endometrioid and clear-cell ovarian cancer in histological proven endometriosis: The ENOCA population-based cohort study. Am. J. Obstet. Gynecol. 2020, 223, 107.e1–107.e11.

10. 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.
11. Kvaskoff, M.; Mahamat-Saleh, Y.; Farland, L.V.; Shigesi, 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 2020, 27, 393–420.
12. Kalaitzopoulos, D.R.; Mitsopoulou, A.; Iliopoulou, S.M.; Daniilidis, A.; Samartzis, E.P.; Economopoulos, K.P. Association between endometriosis and gynecological cancers: A critical review of the literature. Arch. Gynecol. Obstet. 2020, 301, 355–367.
13. Raffone, A.; Seracchioli, R.; Raimondo, D.; Maletta, M.; Travaglino, A.; Raimondo, I.; Giaquinto, I.; Orsini, B.; Insabato, L.; Pellicano, M.; et al. Prevalence of adenomyosis in endometrial cancer patients: A systematic review and meta-analysis. Arch. Gynecol. Obstet. 2020, 295, 1459–1468.
14. Shen, F.; Liu, Y.; Lin, L.; Zhao, M.; Chen, Q. Association of benign gynaecological diseases and risk of endometrial and ovarian cancers. J. Cancer 2020, 11, 3186–3191.
15. Kok, V.C.; Tsai, H.J.; Su, C.F.; Lee, C.K. The Risks for Ovarian, Endometrial, Breast, Colorectal, and Other Cancers in Women With Newly Diagnosed Endometriosis or Adenomyosis: A Population-Based Study. Int. J. Gynecol. Cancer 2015, 25, 968–976.
16. Saavalainen, L.; Lassus, H.; But, A.; Tiitinen, A.; Härkki, P.; Gissler, M.; Pukkala, E.; Heikinheimo, O. Risk of Gynecologic Cancer According to the Type of Endometriosis. Obstet. Gynecol. 2018, 131, 1095–1102.
17. Saraswat, L.; Ayansina, D.; Cooper, K.G.; Bhattacharya, S.; Horne, A.W.; Bhattacharya, S. Impact of endometriosis on risk of further gynaecological surgery and cancer: A national cohort study. Bjog 2018, 125, 64–72.
18. Mueck, A.O.; Seeger, H.; Rabe, T. Hormonal contraception and risk of endometrial cancer: A systematic review. Endocr. Relat. Cancer 2010, 17, R263–R271.
19. Mogensen, J.B.; Kjær, S.K.; Mellemkjær, L.; Jensen, A. Endometriosis and risks for ovarian, endometrial and breast cancers: A nationwide cohort study. Gynecol. Oncol. 2016, 143, 87–92.
20. Clement, P.B.; Young, R.H. Non-endometrioid carcinomas of the uterine corpus: A review of their pathology with emphasis on recent advances and problematic aspects. Adv. Anat. Pathol. 2004, 11, 117–142.
21. Raimondo, D.; Raffone, A.; Travaglino, A.; Maletta, M.; Casadio, P.; Ambrosio, M.; Chiara Aru, A.; Santoro, A.; Franco Zannoni, G.; Insabato, L.; et al. Impact of adenomyosis on the prognosis of patients with endometrial cancer. Int. J. Gynaecol. Obstet. 2021.

22. Hermens, M.; van Altena, A.M.; van der Aa, M.; Bulten, J.; van Vliet, H.; Siebers, A.G.; Bekkers, R.L.M. Endometrial cancer prognosis in women with endometriosis and adenomyosis. A retrospective nationwide cohort study of 40,847 women. Unpublished work. 2021.
23. Burg, L.; Timmermans, M.; van der Aa, M.; Boll, D.; Rovers, K.; de Hingh, I.; van Altena, A. Incidence and predictors of peritoneal metastases of gynecological origin: A population-based study in the Netherlands. J. Gynecol. Oncol. 2020, 31, e58.
24. Yu, O.; Schulze-Rath, R.; Grafton, J.; Hansen, K.; Scholes, D.; Reed, S.D. Adenomyosis incidence, prevalence and treatment: United States population-based study 2006–2015. Am. J. Obstet. Gynecol. 2020, 223, 94.e1–94.e10.
25. Ignatov, A.; Ortmann, O. Endocrine Risk Factors of Endometrial Cancer: Polycystic Ovary Syndrome, Oral Contraceptives, Infertility, Tamoxifen. Cancers 2020, 12, 1766.
26. Felix, A.S.; Weissfeld, J.L.; Stone, R.A.; Bowser, R.; Chivukula, M.; Edwards, R.P.; Linkov, F. Factors associated with Type I and Type II endometrial cancer. Cancer Causes Control 2010, 21, 1851–1856.
27. Riccio, L.; Santulli, P.; Marcellin, L.; Abrão, M.S.; Batteux, F.; Chapron, C. Immunology of endometriosis. Best Pract. Res. Clin. Obstet. Gynaecol. 2018, 50, 39–49.
28. Bourdon, M.; Santulli, P.; Jeljeli, M.; Vannuccini, S.; Marcellin, L.; Doridot, L.; Petraglia, F.; Batteux, F.; Chapron, C. Immunological changes associated with adenomyosis: A systematic review. Hum. Reprod. Update 2020.
29. Karin, M.; Greten, F.R. NF-kappaB: Linking inflammation and immunity to cancer development and progression. Nat. Rev. Immunol. 2005, 5, 749–759.
30. Hever, A.; Roth, R.B.; Hevezi, P.A.; Lee, J.; Willhite, D.; White, E.C.; Marin, E.M.; Herrera, R.; Acosta, H.M.; Acosta, A.J.; et al. Molecular characterization of human adenomyosis. Mol. Hum. Reprod. 2006, 12, 737–748.
31. Bilyk, O.; Coatham, M.; Jewer, M.; Postovit, L.M. Epithelial-to-Mesenchymal Transition in the Female Reproductive Tract: From Normal Functioning to Disease Pathology. Front. Oncol. 2017, 7, 145.
32. Vannuccini, S.; Tosti, C.; Carmona, F.; Huang, S.J.; Chapron, C.; Guo, S.W.; Petraglia, F. Pathogenesis of adenomyosis: An update on molecular mechanisms. Reprod. Biomed. Online 2017, 35, 592–601.
33. Toumpeki, C.; Liberis, A.; Tsirkas, I.; Tsirka, T.; Kalagasidou, S.; Inagamova, L.; Anthoulaki, X.; Tsatsaris, G.; Kontomanolis, E.N. The Role of ARID1A in Endometrial Cancer and the Molecular Pathways Associated With Pathogenesis and Cancer Progression. In Vivo 2019, 33, 659–667.

34. Kyo, S.; Sato, S.; Nakayama, K. Cancer-associated mutations in normal human endometrium: Surprise or expected? Cancer Sci. 2020, 111, 3458–3467.
35. Anglesio, M.S.; Papadopoulos, N.; Ayhan, A.; Nazeran, T.M.; Noë, M.; Horlings, H.M.; Lum, A.; Jones, S.; Senz, J.; Seckin, T.; et al. Cancer-Associated Mutations in Endometriosis without Cancer. N. Engl. J. Med. 2017, 376, 1835–1848.
36. Kvaskoff, M.; Han, J.; Qureshi, A.A.; Missmer, S.A. Pigmentary traits, family history of melanoma and the risk of endometriosis: A cohort study of US women. Int. J. Epidemiol. 2014, 43, 255–263.
37. Kvaskoff, M.; Mesrine, S.; Clavel-Chapelon, F.; Boutron-Ruault, M.C. Endometriosis risk in relation to naevi, freckles and skin sensitivity to sun exposure: The French E3N cohort. Int. J. Epidemiol. 2009, 38, 1143–1153.