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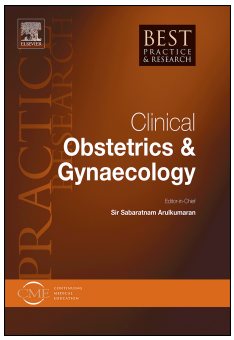

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PERIMENOPAUSAL MANAGEMENT OF OVARIAN ENDOMETRIOSIS AND RELATED CANCER RISK: WHEN IS MEDICAL OR SURGICAL TREATMENT INDICATED?

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ABSTRACT

In women with endometriosis the lifetime risk of ovarian cancer is increased from 1.4% to about 1.9%. The risk of clear cell and endometrioid ovarian cancer is, respectively, tripled and doubled. Atypical endometriosis, observed in 1-3% of endometriomas excised in premenopausal women, is the intermediate precursor lesion linking typical endometriosis and clear cell/endometrioid tumors. Prolonged oral contraceptive use is associated with a major reduction in ovarian cancer risk among women with endometriosis. Surveillance ± progestogen treatment or surgery should be discussed in perimenopausal women with small, typical endometriomas. In most perimenopausal women with a history of endometriosis but without endometriomas, surveillance instead of risk-reducing bilateral salpingo-oophorectomy seems advisable. Risk-reducing salpingo-oophorectomy might benefit patients at particularly increased risk, but the evidence is inconclusive. Risk profiling models and decision aids may assist patients in their choice. Screening of the general perimenopausal population to detect asymptomatic endometriomas is unlikely to reduce disease-specific mortality.

KEYWORDS

Endometriosis; ovarian cancer; risk-reducing salpingo-oophorectomy; endometrioma; medical treatment; screening; early diagnosis.

1. INTRODUCTION

Endometriosis is associated with a moderate increase in ovarian cancer risk. According to large population-based studies and meta-analyses of cohort and case-control studies, the overall relative risk varies from 1.4 to 1.8 [1-3]. The risk of ovarian cancer appears particularly elevated among subjects with a long-standing history of untreated ovarian endometriosis [4-9]. The main objectives of this review are i) to suggest a management plan for perimenopausal patients with ovarian endometriomas, and ii) to clarify whether perimenopausal women with a history of endometriosis but without current endometriomas would benefit from prevention interventions in terms of reduced mortality from endometriosis-associated ovarian cancer (EAOC). To this aim, relevant epidemiological and oncological information has been critically reviewed. In this regard, several excellent articles are available on the pathogenesis and classification of ovarian cancers [10-13].

For the purpose of the present review, some definitions need preliminary clarification. Perimenopause is defined by the World Health Organization and the North American Menopause Society as the two to eight years preceding menopause and one year following final menses [14,15]. The age of 45 years is here considered as the lower limit of the perimenopausal period. Endometriomas are defined as typical or atypical based on published ultrasonographic characteristics [16-18]. In the absence of a precise measure consistently indicated by international gynecological and radiological societies, endometriomas are considered as small or large based on the maximum cut-off diameter of 5 cm suggested by Muzii *et al*. [19]. In addition, the association between endometriosis and specific epithelial ovarian cancer histotypes is assumed to be causal. This view is supported by a large body of evidence and shared by most, albeit not all, authoritative experts in the field [1-3, 10-13].

2. EPIDEMIOLOGICAL AND HISTOPATHOLOGICAL OUTLINE OF THE ASSOCIATION BETWEEN ENDOMETRIOSIS AND OVARIAN CANCER

A woman's lifetime risk of developing ovarian cancer is about 1 in 75 [13]. In western countries ≥ 90% of ovarian malignancies are epithelial in origin. According to the dualistic pathogenic model [11], the main epithelial ovarian cancer histotypes are classified as type I and II. The former group comprises the so-called endometriosis-associated tumors that include endometrioid, clear cell, and seromucinous carcinomas. Type II tumors are mainly composed of high-grade serous carcinomas (HGSOC), which represent almost 70% of ovarian carcinomas [11]. Among the EAOC, the seromucinous histotype is fairly rare. Thus, the endometrioid ovarian carcinomas (ENOC) and the clear cell ovarian carcinomas (CCOC) are the most frequent histotypes associated with endometriosis. In particular, it has been suggested that ENOC derive from cells of the secretory cell lineage, whereas CCOC derive from, or have similarities to, cells of the ciliated cell lineage [20].

Women with endometriosis are at about tripled risk for CCOC and doubled risk for ENOC [1]. The prevalence of CCOC is variable, depending on the geographic area considered. In fact, figures between 1% and 13% have been reported in Europe and North America, and between 15% and 25% in some Asian region, particularly in Japan [21]. The prevalence of ENOC varies between 7% and 13% in surgical series. A synchronous carcinoma of the eutopic endometrium has been reported in 15% to 20% of cases of ENOC, thus suggesting a common origin or common risk factors [22]. Overall, CCOC and ENOC are, respectively, the second and third most common ovarian cancer histotypes. They represent about 20% of all ovarian carcinomas, but account for no more than 10% of the deaths from this disease, whereas HGSOC accounts for about 90% of the deaths [11,13,22]. This seems partly due to the fact that most CCOC and ENOC are detected at early stages, when the 5-year survival rate is around 90%, whereas HGSOC are usually detected at advanced stages, with a 5-year survival rate of about 30% [23,24].

This striking difference in stage at detection between EAOC and HGSOC seems to be related to different biological behaviors, but also to different pathogeneses and the fact that a precursor lesion is identifiable for CCOC and ENOC, but not for HGSOC. In fact, according to the dualistic model, most HGSOC derives from minute and undetectable atypical lesions within the

fimbriated end of the fallopian tube (serous tubal intraepithelial carcinomas, STIC) [25]. When malignant cells exfoliate from STIC, they implant not only on the ovaries, but also on the peritoneum, the omentum, and on abdominopelvic organs. Therefore, most HGSOC develop as late stage cancers from inception. Conversely, most CCOC and ENOC would arise within ovarian endometriotic cysts that are detectable at transvaginal ultrasonography (TVUS), and are confined to the ovary for a variable period of time [11]. Thus, when only one ovary is involved and surgery is promptly undertaken, the disease is usually at stage I.

Based on the lifetime risk of developing ovarian cancer in western countries, i.e., 1/75 (1.33%), the magnitude of the potential effect of untreated ovarian endometriotic cysts can be tentatively calculated. Considering a prevalence of HGSOC, CCOC, ENOC and "other" histotypes of, respectively, 70%, 10%, 10%, and 10% among ovarian cancers arising in the general female population [13,22], and hypothesizing that the relative risk of developing CCOCs, ENOCs and "other" histotypes is, respectively, 3, 2, and 1.5 in women with endometriosis, the lifetime risk of developing an ovarian cancer in this latter sub-population would be 1/56 (1.79%; difference with the general female population = +0.46%). This is in line with literature findings [1-3]. Hypothesizing an overall percent survival for HSGOC, CCOC, ENOC and "other" histotypes of, respectively, 20%, 35%, 55%, and 35%, yields a rough lifetime risk of dying from ovarian cancer of 1/100 (1%) in the general female population [13], and of 1/77 (1.31%) in postmenopausal women with untreated ovarian endometriosis (difference with the general female population = +0.31%). These estimates may vary according to the geographical area considered. They are herein calculated only to provide an approximation of the potential epidemiological burden.

3. MOLECULAR AND GENETIC OUTLINE OF ENDOMETRIOSIS-ASSOCIATED OVARIAN CANCER

Molecular pattern of endometriosis-associated ovarian cancers

It is puzzling how endometriosis can be the precursor tissue of two distinct ovarian cancer histotypes without any recurrent genetic mutation that is unique to either of them (Table 1). The differences in the genomic landscape features between ENOC and CCOC are not absolute. Thus, mutations alone cannot explain their clinical and phenotypic distinctions and the ovarian environment is likely to play a critical role [20].

Ovarian cancer is considered as a hormone-responsive cancer [26]. However, one of the predominant and clinical relevant aspect distinguishing these two histotypes is the differential estrogen receptor expression. The progesterone receptor and estrogen receptor (ER) mediate some effects of female steroid hormones on proliferation and apoptosis of ovarian cancer cells. Actions of estradiol are mediated by two isoforms of ERs: ERα and ERβ that differ not only in their tissue distribution, but also in their ligand binding specificity and affinity [26]. Besides subtypes, the presence of ERβ variants (β1-β5) due to alternative splicing, further complicates the biological significance of ERβ signaling. ERβ1 is the only isoform capable of binding ligands while ERβ2 and ERβ5 can heterodimerize with ERβ1 and induce its transcriptional activity ligand-dependently [27]. Cytoplasmic ERs are also known to exert effects through nongenomic signaling [26,27]. ERα has been shown to represent an independent prognostic marker for ENOC [28] while nuclear ERα was barely detectable in CCOC. Significant loss of cERβ2 and of cERβ5 expression was also observed in CCOC (Table 1). An improved survival in patients with hormone-receptor-positive tumors has been reported, partly explained by increased numbers of patients who respond to endocrine treatments [28].

Although some mutations are present in both histotypes, there are however important molecular differences between CCOC and ENOC:

Inactivating ARID1A mutations are the most common molecular genetic alteration reported thus far in CCOC and ENOC, but a higher frequency of ARID1A mutations has been detected in CCOC (46–57%) compared with ENOC (30%) [29]. These mutations result in loss of expression of the protein encoded by ARID1A (BAF250a) which normally suppresses cellular proliferation

through a p53-dependent transcription regulation of several tumor suppressors including CDKN1A (encoding p21) and SMAD3 [30]. As a matter of fact, loss of protein expression of the ARID1A tumor suppressor gene has been demonstrated in endometriosis adjacent to clear cell tumor samples [31]. According to Yamamoto and coworkers, ARID1A protein immunoreactivity was deficient in 17 (61%) of the 28 CCOC [32]. According to Ayhan *et al.*, loss of ARID1A staining was observed in 75% of the 24 CCOC adjacent to endometriomas [33]. Stamp *et al.* found that the incidence of BAF250a loss was 55% in CCOC and 33% in ENOC [34]. Interestingly, mutations in ARID1A or loss of BAF250a expression have not been shown to be associated with a different cancer phenotype or prognosis in EAOC. No differences in the clinical behavior were observed comparing BAF250a-positive versus BAF250a-negative cancers supporting the idea that ARID1A mutations might represent a marker of genomic instability without driving the phenotype [35].

Overexpression of the transcription factor HNF-1beta and PIK3CA mutations are also common in CCOC [34,35]. Using whole-genome shotgun sequencing of 7 CCOC and targeted sequencing in synchronous endometriosis, 98% of somatic mutations were found in common between carcinomas and endometriotic lesions. ARID1A and PIK3CA mutations appeared consistently in concurrent endometriosis when present in the primary CCOC [24,36]. Importantly, aberrant expression of ARID1A, PIK3CA, and NF-kB genes has been recognized as the major target genes involved in oxidative stress-induced carcinogenesis and, in the context of the malignant transformation of endometriosis, the high oxidative potential of iron has been emphasized [34].

Menstrual red blood cells in the extravascular space tend to lyse quickly and, as a result of hemoglobin oxidization, heme is released. Free heme promotes oxidative damage and formation of reactive oxygen species (ROS), which, in turn, split the heme ring and release redoxactive free iron. Free iron is a strong oxidant and, when present at high levels, contributes to the production of ROS [37-41]. A fine-tuned regulation of lethal and sublethal oxidative stress responses might modulate either cell death or tumor initiation, respectively, due to the iron-induced DNA damage, mutations, and genomic instability. Under the proliferative stress generated by iron and oxidative stress,

endometriotic cells can escape apoptosis under the up-regulation of the transcription factor HNF-1beta expression and subsequently re-enter the cell cycle with genotoxic stress. Mutations in ARID1A gene and subsequent protein alteration may result in a defective repair or replication of damaged DNA. Activating mutations of the PIK3CA gene lead to activation of the AKT pathway resulting in improved cancer cell growth, survival and invasion [34]. AKT phosphorylation is also associated with ARID1A/BAF250a deficient tumors [35]. In line with this hypothesis and with the reduction of the hormone dependency of CCOC, oxidative stress has been shown to act as a physiological regulator of ERs [34].

A more complex scenario may be foreseen for ENOC based on recent molecular, epidemiologic and histopathologic studies [42]. Endometrioid ovarian cancers possess different clinical characteristics when compared to cancers that are not associated with the disease. Patients with ENOC are younger and are more likely to have low grade and early-stage tumors which are more frequently synchronous to endometrial carcinomas. The fact that synchronous endometrial and ovarian tumors are no longer considered the result of two independently occurring, simultaneous tumors, but are rather clonally derived, opens a new scenario on the origin and/or spread of endometriosis-associated tumors. Site of origin and directionality of metastasis, as well as the specific ovarian and endometrial microenvironment features that may influence progression are however yet to be clarified [43].

Major genetic alterations involved in ENOC are represented by PTEN, ARID1A, KRAS and CTNNB1 gene mutations [42]. Mutations in exon 3 of the gene encoding β-catenin (CTNNB1) were identified in 21 (60%) of 35 ENOC, but were not identified in any of the 28 CCOC investigated by Matsumoto and coworkers [44]. Mutations in PTEN gene were identified in 20% of ENOC and in 8.3% of CCOC [45]. KRAS mutations were identified in 12 (29%) of 42 ENOC [46]. Mutations in the KRAS gene lead to constitutive activation of the KRAS-BRAF-MEK-MAPK signaling pathway and the resulting sustained MAPK activity has myriad effects on cell function, including cellular proliferation, apoptosis, adhesion and migratory capacity.

Cancer driver mutations in endometriosis

The transformation of a normal cell into a cancer cell is due to the progressive acquisition of driver mutations. Several studies have evaluated somatic cancer-associated mutations in endometriotic lesions without concurrent cancer in order to assess whether endometriosis might be considered as a precursor of cancer [45]. While TP53 mutations are absent in solitary ovarian endometriotic cysts [45], PTEN mutations were found in 20% and 53% of these lesions in two different studies [47,48]. Loss of ARID1A/BAF250a has been observed quite rarely in non-atypical endometriosis (from 0 to 20% of samples) while atypical endometriosis was found to be ARID1A/BAF250a negative in a variable proportion of cases according to different studies (from 10% to 100%) [23,34,49]. No PIK3CA mutations were observed in 23 endometriotic samples [23]. Interestingly, KRAS and ARID1A mutations have been recently detected in deep infiltrating endometriotic lesions that very rarely undergo malignant transformation [50]. This poses some doubts on the real oncogenic potential of these mutations. As correctly pointed out by Chui and co-workers, the role of cancer driver mutations has still to be elucidated as well as the correlation between the genotype and the clinical outcomes [51].

4. IS OVARIAN ENDOMETRIOSIS A PREMALIGNANT LESION?

As the lifetime risk of developing an adenocarcinoma of the endometrium is about 2% in the general female population, there seems to be no reason to believe that the same type of mucosa should not undergo malignant derailments at a similar rate when displaced at ectopic sites. Indeed, EAOC have been described as endometrial cancers in the wrong place [12]. The chronic inflammatory pelvic environment of women with endometriosis may theoretically even facilitate the transformation of a normal endometrial cell into a malignant cell. However, determining whether the mere presence of endometrium at ectopic sites should be considered *per se* a premalignant condition seems crucial and constitutes the conceptual base of any strategy aimed at reducing EAOC mortality. Lesions are defined “precancerous” based on definite epidemiologic,

morphologic, molecular, and biologic criteria that imply the acquisition of genetic, karyotypic, structural, or functional changes in a cluster of cells that differentiate them from the surrounding normal tissue [52]. In other words, premalignant lesions should reflect an intermediate stage along the pathway leading to cancer. When enough genetic changes have occurred, modifications in appearance and function are observed, but not yet associated with the typical malignant behavior. Examples includes actinic keratosis, Barrett's esophagus, atrophic gastritis, ductal carcinoma in situ, and cervical dysplasia [52].

In 2004 the National Cancer Institute and The George Washington University Cancer Institute convened a conference of expert pathologists with the objective of reaching a consensus on the definition of precancerous lesions. Based on the premise that the identification and elimination of specific cancer precursors would lead to the near-eradication of that type of cancer, it was agreed that the detection of premalignant lesions should not necessarily be based exclusively on histologic criteria. In order to demonstrate the effect of any prevention intervention, it is crucial to appropriately define a precancer independently of detection methods adopted. The five developed defining criteria that must be applied to precancerous lesions are reported in Table 2. According to the authors of the consensus document, "*these five criteria represent the minimal set of conditions for a lesion detected by any method to be considered a precancer. These conditions are necessary and sufficient. All of the criteria must apply, and they all must apply concurrently (i.e. not additive over time)*" [52]. One of the novelties here is that the definition of precancer lesions is not entirely based on specific morphologic features, but also on cytogenetic, molecular, and even behavioral (phenotypic) characteristics.

Although all the criteria must simultaneously apply, the third and the fifth ones seems particularly relevant for the endometriosis population. According to the third criterion, a precancerous lesion must be different from the normal tissue from which it arises. In other words, the "normal", although displaced, endometrium cannot be considered a precancerous lesion. If intrauterine endometrium is the source of the ectopic mucosa, then the usual intermediate steps

leading to endometrial cancer (atypical hyperplasia; endometrial intraepithelial neoplasia) should be expected to occur also when the endometrium is located in the pelvis before an "ovarian" cancer develops. Distinguishing premalignant lesions from normal endometrial tissue, malignant tissue, and other lesions is important. As an example, in ovarian endometriotic cysts it is sometimes cumbersome to discriminate between the true cytological/structural atypia and the benign reactive atypia associated with underlying inflammation (Figure 1) [53,54].

Several authors indicate only atypical endometriosis, and not normal endometrium at ectopic sites, as a premalignant lesion. Kommoss and Gilks [55] maintain that the assumed precursor of ENOC and CCOC is atypical endometriosis resulting from ovarian implantation of endometrial tissue after trans-tubal spread. Anglesio and Wilbur [24,54] specifies that cytologically atypical *ovarian endometriosis* (large nuclei that are either hyperchromatic or pale, have an increased nucleus-to-cytoplasm ratio, cellular crowding, stratification, or tufting) should be considered the direct precursor of CCOC and ENOC, as atypical endometriosis has been identified contiguous with these tumor histotypes [56]. Samartzis *et al*. [23] maintain that atypical endometriosis should be considered the histological precursor lesion of CCOC, as common truncating mutations and loss of protein expression of the ARID1A tumor suppressor gene have been demonstrated in these tumors and in contiguous atypical endometriosis. However, as previously mentioned, these mutations can also be found in deep infiltrating endometriosis that, according to Anglesio *et al*. [50], is not a cancer precursor. Indeed, according to the results two systematic literature reviews, only a few cases of carcinomas arising in rectovaginal endometriotic lesions have been reported [57,58].

Therefore, a specific role seems to be played by the ovarian microenvironment in increasing the risk of malignant derailment [20]. Karnezis concurs that the ovarian microenvironment seems to be essential for the malignant transformation of endometriosis because many endometriotic lesions are located outside the ovary, including the pelvic peritoneum, but carcinomas at such sites are rare [12]. In this regard, Blanco *et al*. observed that the stroma surrounding ovarian epithelial tumors is activated to elaborate steroid hormones which may stimulate further neoplastic growth [59].

Kurman *et al*. [11] defined the eutopic endometrium as the *precursor site of origin* of CCOC and ENOC, endometriosis as the *potential precursor lesion*, and atypical endometriosis as the *immediate precursor lesion*. Karnezis indicates endometriosis as the *tissue of origin* of ENOC and CCOC, endometrial epithelial cells as the *cells of origin*, and endometrioid borderline tumors as the *precursor lesion* [12]. According to these views, ectopic endometrium, similarly to the eutopic counterpart, has the *potential* for malignant derailment, but should not be considered a precancer. In addition, Karnezis [12] categorized endometriosis as "high risk" and "low risk", based on the presence of atypical endometriosis, intended as an intermediate precursor that links typical endometriosis and ovarian cancers.

Therefore, given the current consensus on the very low malignant potential of peritoneal endometriosis, be it "superficial", as in early disease stages, or "deep", as in rectovaginal plaques, efforts should be focused on the identification of those ovarian endometriotic cysts that include atypical epithelial lesions.

Here the fifth criterion for the definition of premalignant lesions states that there must be a method by which the precancer can be diagnosed. According to the authors, "*this requirement is not constrained by the diagnostic method, which today is primarily routine histopathologic examination of excisional biopsies. Any single or combinatorial diagnostic modality with sufficient sensitivity and specificity that is clinically useful may fulfill this requirement. Functional imaging and molecular analysis of biologic samples are examples of emergent technology that might be useful in this regard*" [52]. This is an important area of future endometriosis research, as the possibility of identifying those endometriomas that harbor atypical epithelial foci would allow, on one hand timely surgery with prevention of lesion progression, and on the other hand conservative management with reduction of morbidity and cost in the majority of women in whom premalignant lesions can be reliably ruled out.

5. EARLY DETECTION OF ENDOMETRIOSIS-ASSOCIATED OVARIAN TUMORS

An in-depth description of ultrasonographic characteristics of the spectrum of ovarian lesions ranging from the so-called “typical” benign ovarian endometrioma to overtly suspicious masses originating from endometriotic cysts is beyond the scope of the present review, and the reader may refer to several authoritative articles, including those by Exacoustos *et al*. [16] and Guerriero *et al*. [17,18]. Here only summary information is given regarding some elements that may increase the awareness towards a possible malignant derailment of ovarian endometriosis.

According to Exacoustos *et al*. [16], the ‘typical’ endometrioma is a unilocular or multilocular (one to four locules) cyst, with homogeneous low-level echogenicity (ground glass echogenicity) of the cyst fluid, no solid parts, and no papillations with detectable blood flow, detected in a premenopausal woman. Papillary projections are protrusion of solid tissue into the cyst lumen with a height of 3 mm or more. The ultrasonographic characteristics of endometriomas may differ according to pre- or postmenopausal status. Endometriotic cysts in postmenopausal women are more frequently multilocular, and less likely to exhibit ground glass echogenicity, as anechoic cyst fluid or cyst fluid with mixed echogenicity is often observed [16]. Guerriero *et al*. confirmed that in older women multilocular cysts and cysts with papillations and other solid components become more common whereas ground glass echogenicity of cyst fluid becomes less common compared with endometriomas observed in younger women. Interestingly, the maximal cyst diameter does not seem to vary significantly with age [18].

Nezhat *et al*. warns that an increase in endometrioma size in postmenopause or during hormonal therapy in premenopause, modification of ultrasonographic characteristics, and appearance of mural node formation constitute ominous signs that require surgical excision [10]. Relapsing or worsening pelvic pain symptoms, such as newly developed dysmenorrhea and dyspareunia, should further increase the index of suspicion [23]. Advancing age (≥ 45 years) and the size of endometriomas (≥ 8 cm) were independent predictors of development of ovarian cancer among women with ovarian endometrioma [6,7,60].

At TVUS, borderline tumors and carcinomas arising from endometriotic cysts generally show a vascularized solid component [16]. Tanase *et al*. [61] reported that, whereas in premenopausal women the majority of mural nodular lesions observed within ovarian endometriomas were retracted blood clots, in older women and those with larger cyst diameters, mural nodules were more likely malignant, especially in case of large nodule sizes and taller than wider lesions. Also in the study by Taniguchi *et al*. [62] the rapid growth of an endometrioma and the presence of mural nodules were the most reliable predictors of malignancy.

In the large series of Kuo *et al*. [63], the frequency of unexpected EAOC in presumed ovarian endometriomas was 0.14%. All patients with malignancies were aged ≥ 40 years and almost two thirds of them had vegetations within the ovarian cyst at preoperative ultrasonography.

Evaluation of all suspicious endometriomas by gynecologists or radiologists with specific oncological experience may greatly increase the performance of imaging techniques in the detection of those cysts that requires prompt surgical removal. In this regard, according to the recommendations of the First International Consensus Report on Adnexal Masses, "*despite extensive research into various risk prediction models, subjective assessment in the hands of an expert remains as accurate as any technique for assessment of adnexal masses by sonography. Thus, it is appropriate to consider referral to an expert gynecologic sonologist when faced with a challenging or indeterminate adnexal mass*" [64].

Of relevance here, the debate on ultrasonographic signs of malignancy does not shed light on the possibility of identifying premalignant endometriomas, i.e. endometriomas harboring atypical lesions. Ultrasonographic findings may significantly differ between endometriomas degenerated into cancer and endometriomas with atypical lesions. Specific studies aimed at disentangling this issue are currently lacking and represent a research priority. Noteworthy, this kind of studies should rely on vast series of women, as atypical endometriosis is rare, and should be prospectively undertaken in centers systematically performing a thorough and detailed pre-surgical TVUS evaluation following a standardized methodology [18].

6. MANAGEMENT OF PERIMENOPAUSAL WOMEN WITH OVARIAN ENDOMETRIOMAS

When a typical ovarian endometrioma of < 5 cm is identified in a young woman seeking conception in the future, the risk of iatrogenic ovarian reserve reduction may suggest refraining from surgery [19]. Moreover, when surgery for endometriomas is chosen in women of < 45 years of age, gonadal conservation may be preferable even when pregnancy desire is no longer an issue, as premature hypo-estrogenism may increase the risk of cardiovascular events and all-cause mortality [65]. However, when women approach the menopause, the reproductive and hormonal benefits deriving from surgical abstention or conservative procedures progressively vanish. Therefore, removal of ovaries with endometriotic cysts may be discussed in perimenopausal women.

Unfortunately, no robust information is available on the effect of surveillance compared with that of surgery (unilateral salpingo-oophorectomy or cystectomy/partial ovarian excision) on mortality from EAOC in patients with endometriosis/endometriomas. According to the results of a case-control study conducted by Rossing *et al*. [8], the risk of invasive epithelial ovarian cancer varied according to performance of ovarian surgery after the diagnosis of endometriosis. In fact, with respect to women without a history of endometriosis, the OR of ovarian cancer was 1.6 (95% CI: 1.1–2.3) among women with endometriosis who did not undergo surgery, and 1.2 (95% CI: 0.5–2.5) among those who did. Moreover, only unilateral salpingo-oophorectomy appeared protective (OR, 0.8; 95% CI: 0.3–2.1), whereas cystectomy/partial ovarian excision was not (OR, 3.3; 95% CI: 0.7–15.3). In particular, the OR of ENOC and CCOC was 3.2 (95% CI: 1.9–5.6) among women with a history of endometriosis with no subsequent ovarian surgery, compared with 1.6 (95% CI: 0.4–5.7) among those who underwent ovarian surgery. However, the small number of cases limited the precision of the estimates. In fact, only 94 women with a history of endometriosis were included in this study, and only 20 of them underwent previous ovarian surgery.

In the nested case-control study by Melin *et al*. [9], all women with a first-time discharge diagnosis of endometriosis in the period 1969–2007 were identified using the National Swedish

Patient Register, and all women diagnosed with epithelial ovarian cancer at least one year after the endometriosis diagnosis (cases) were identified by linkage to the National Swedish Cancer Register. Matched controls were randomly selected from the study base. A significant association was observed between unilateral salpingo-oophorectomy, as well as radical excision of all visible endometriosis, and ovarian cancer risk (adjusted OR, 0.19; 95% CI 0.08–0.46 and 0.30; 95% CI 0.12–0.74, respectively). Unfortunately, no information has been provided on ovarian cancer histotype, thus the effect of unilateral salpingo-oophorectomy is expected. Moreover, the categorization of radical versus non-radical endometriosis excision was based on retrospective review of surgical notes.

In case unilateral salpingo-oophorectomy is performed, the risk of overall ovarian cancer mortality is reduced by definition, but this effect may be largely due to a decrease in the risk of death from HGSOC following salpingectomy, rather than from CCOC and ENOC following removal of ovaries with endometriomas. Therefore, the results of the above two studies do not definitively clarify whether surgery specifically aimed at removing ovaries with endometriomas is better than surveillance, in terms of reduced mortality from EAOC, for perimenopausal endometriosis patients.

Consequently, two different clinical approaches may be envisaged in perimenopausal women with small (< 5 cm), typical endometriomas, i.e., i) removal of the affected ovary/ovaries plus bilateral salpingectomy, especially in cases of long-standing endometriomas in women who are not using OC or progestogens, or ii) strict surveillance ± progestogen treatment with immediate surgery in case of modifications of ultrasonographic cyst patterns (e.g., cyst volume increase and appearance of septa, papillary projections, mural nodules, or changes in vascularization), or suspicious rise in serum CA 125 and human epididymis protein 4 (HE4) levels. In theory, surveillance could be justified by the fact that endometriosis-related cancers usually remain intra-cystic for a variable period of time [11,22].

The median age at diagnosis of ENOC and CCOC is, respectively, 47 and 55 years [21,22,23]. Therefore, the effect size of surgery is likely directly related with the age at which the affected ovaries are removed. Surgery should be considered in case of long-standing endometriomas [4-7], especially if they are not being treated with oral contraceptives (OC) or progestogens, but also in case of de-novo detection of an endometrioma during medical treatment, as the risk of malignancy appears here substantially increased [7,61,63]. Moreover, according to Haraguchi *et al*. [66] recurrent endometriomas are at especially augmented risk of malignant transformation, as all EAOC in their series developed in patients who experienced a cyst recurrence.

Not removing the ovary with endometriotic cysts means that perimenopausal women should undergo periodic TVUS and serum marker level measurements for many years. In addition, the variable degree of anxiety caused by knowing of being at increased risk for a dreadful cancer should be carefully weighed. These factors augment the overall burden of treatment, including out-of-pocket costs, and may unfavorably impact on health-related quality of life [67]. On the other hand, the patient medical history must be considered because, especially when multiple and extensive abdominopelvic procedures have been performed, the operative risk may be increased to the point that sometimes the balance may be tipped toward expectant management. Removing the adnexa when previous surgical notes report the presence of extensive and dense pelvic adhesions with difficult visualization of the internal genitalia (frozen pelvis), exposes to an increased risk of bowel and ureteral lesions, as well as of the ovarian remnant syndrome [68]. In case surgical abstention is chosen, progestogens may be used as a therapeutic measure during surveillance, after information is provided on the potential benefits and potential harms of combining periodic assessments with medical therapy in specific clinical conditions. Regrettably, insufficient data are available on variation of EAOC risk when hormonal treatments are started during perimenopause. Suspicious modifications of TVUS appearance or increase in cyst size during suppressive medical therapy requires prompt surgical exploration.

A further aspect to be discussed with the perimenopausal patient with deep lesions in addition to ovarian endometriomas is whether, in case bilateral salpingo-oophorectomy is decided, deep lesions should also be removed. Symptoms must guide the choice, as only persistent pain despite hypo-estrogenizing medical treatment justifies the additional surgical risk of excising lesions that very rarely undergo malignant transformation and that will most likely become quiescent after gonadal removal. In case the ovaries are removed, but deep lesions are left in place, tibolone or combinations including a progestogen should be used in women requesting hormone replacement therapy [69].

All the above information should be provided to perimenopausal patients with endometriomas, and uncertainties should be openly discussed. No robust evidence seems to exist to support either surveillance or surgery in all women with small, typical endometriomas. A commonsense approach may be adopted in these circumstances, that is, suggesting surveillance in patients at high surgical risk, and surgery in those at average surgical risk. If surveillance is chosen in women not using medical therapies, the possibility of starting treatment with progestogens should be discussed. Surgery is obviously the only reasonable choice when large and/or doubtful endometriomas are present.

7. RISK-REDUCING MEDICAL TREATMENT IN PERIMENOPAUSAL WOMEN

Prolonged OC use is associated with a major reduction in the risk of developing an endometrioma [70,71]. This effect seems to be due to ovulation inhibition, as endometriomas have been demonstrated to derive from corpora lutea [72]. Therefore, OC and progestogens should theoretically reduce the risk of both, ENOC and CCOC in women with a history of endometriosis, but without current endometriomas. This risk-reducing effect seems an important added value of OC and progestogens in symptomatic endometriosis patients, even in the late reproductive years.

Moreover, according to Kim [2], the carcinogenic process leading to ENOC is primarily an estrogen-rich, progesterone-poor hormonal environment, whereas persistent oxidative stress

induced by a high intra-cystic level of heme and free iron may result in stress-resistant type such as CCOC. Thus, in theory, OC and progestogens use for prolonged periods of time in women who already have endometriomas may reduce the risk of mainly receptor-positive ENOC to a greater extent with respect to the risk of mainly receptor-negative CCOC. However, there are currently no data to support this hypothesis.

Modugno *et al*. [73], after pooling data from four population-based case-control studies on epithelial ovarian cancer comprising 2098 cases and 2953 control subjects, observed that use of OCs for >10 years was associated with a major reduction in ovarian cancer risk among women with endometriosis (odds ratio, 0.21; 95% CI, 0.08-0.58). Unfortunately, information on the effect of OC specifically on EAOC was not available. Actually, it seems difficult to define differences in the effect of OC on various ovarian cancer histotypes, and it may not be excluded that the results were largely due to a reduction in risk of HGSOC, similarly to what has been observed in the general population [74,75].

Independently of histotypes, the reduction in ovarian cancer risk in endometriosis patients refers to OC use *before* menopause. In premenopausal women with a history of endometriosis and without current endometriomas, prolonged OC and progestogen use should be suggested until the natural menopause is reached, as the reduction in risk is directly related with duration of use. In addition, this protective effect extends for decades after OC use are discontinued [74,76]. In the model developed by Pearce *et al*. [76], OC use was essentially absent among the women at higher (> 4%) lifetime ovarian cancer risk (2015). There is no rationale supporting the use of hormonal treatments *after* menopause, neither as a preventive nor as a therapeutic measure.

8. SURVEILLANCE OR RISK-REDUCING SURGICAL TREATMENT IN PERIMENOPAUSAL WOMEN WITH A HISTORY OF ENDOMETRIOSIS BUT WITHOUT ENDOMETRIOMAS?

i) <u>Surveillance</u>

The potential benefits of surveillance of the population of asymptomatic women with a previous diagnosis of endometriosis but without endometriomas are currently unknown. It is not possible to exclude that periodic assessment in a population at higher risk according to risk profiling models similar to that developed by Pearce *et al*. [76] may result in a reduction in mortality from ENOC and CCOC, also considering the different pathogenesis and natural history with respect to HGSOC. In fact, STIC, the precursor lesion of HGSOC, is so small that TVUS cannot detect it. The situation is different for EAOC, because they usually develop from epithelial atypia within ovarian endometriomas and are initially confined to one ovary. Therefore, in the case of ENOC and CCOC, detecting a de-novo ovarian cyst with TVUS characteristics of an endometrioma in women at increased risk, may allow timely surgery with eradication of stage I disease (or suspicious cysts without overt carcinomas) without extra-ovarian dissemination and with good long-term prognosis. However, given that type I tumors account for only 10% of the deaths from ovarian cancer, it is unclear if a prevention strategy aimed at identifying early EAOC would impact on the overall mortality from ovarian cancer.

The conceptual premise for such a surveillance program in premenopausal endometriosis patients, is that all women with newly detected endometriomas after the age of 45 years should undergo removal of the affected ovary and, when there is no pregnancy desire, also of both fallopian tubes. This would reduce not only the risk of EAOC, but also of HGSOC, thus increasing the benefit of periodic assessment.

ii) <u>Risk-reducing surgical treatment</u>

With “risk-reducing surgical treatment” we here refer to a patient population with a previous diagnosis of endometriosis/endometriomas, but with no current evidence of endometriotic ovarian cysts, and the question to be answered is whether women with a history of endometriosis but without ovarian endometriomas at TVUS should undergo prophylactic salpingo-oophorectomy when approaching the natural menopause.

In the risk profiling model developed by Pearce *et al*. [76], five risk and protective factors were taken into account (i.e., OC use, parity, tubal ligation, endometriosis, and first-degree family history of ovarian cancer in conjunction with a genetic risk score) to define the distribution of lifetime ovarian cancer risk in the general population of up to age 85 for non-Hispanic white women. Risk/protective factor profiles were developed combining the distribution of these variable, considering the relative risks derived from published data, and using control data derived from four representative population-based U.S. studies. The estimated lifetime ovarian cancer risk for 214 combinations of risk/protective factors ranged from 0.35% (95% CI, 0.29–0.42) to 8.78% (95% CI, 7.10–10.9). In the higher quintile genetic risk scores, most women with lifetime risk ranging from 4% to 8% had a self-reported history of endometriosis. As an example, nulliparous endometriosis patients with a negative family history for ovarian cancer and who did not undergo tubal ligation, have a lifetime risk of 4.03% (95% CI, 3.29%-4.94%) if they used OC for 1-4 years, and of 4.40% (95% CI, 3.71%-5.20%) in case they did not use OC. Most other reported combinations of factors are associated with even greater lifetime ovarian cancer risks, with point estimates ranging from 4.81% to 7.99%. However, in routine practice the background genetic risk of endometriosis patients is usually unknown. Moreover, the frequency of women included in subgroups at higher ovarian cancer risk is very low, ranging from 0.02% to 0.11% of the general population [76] (Pearce 2015). Finally, external validation of the model by Pearce *et al*. [76] is lacking.

Manchanda *et al*. [77] conducted a healthcare economy analysis to define risk thresholds at which risk-reducing salpingo-oophorectomy can be cost-effective for the prevention of sporadic ovarian cancer in lower risk (BRCA negative) women aged 51 years. A decision-analytic model was developed to compare the costs and effects of offering risk-reducing salpingo-oophorectomy for 2%, 4%, 5%, 6%, 8% and 10% lifetime ovarian cancer risk thresholds. At the 2% ovarian cancer risk level, routine risk-reducing salpingo-oophorectomy does not save more quality-adjusted life years (QALY) and is not cost-effective. At a 4% ovarian cancer risk level, risk-reducing salpingo-oophorectomy saves more QALYs but is not cost-effective at the incremental cost-effectiveness

ratio = £25,577, which is above the £20,000 U.K. ($ 26,650; €22,605) National Institute for Health and Care Excellence (NICE) threshold. However, at risk thresholds of ≥5%, risk-reducing salpingo-oophorectomy saves more life-years and QALYs and is highly cost-effective. According to this model, and based on the lifetime ovarian cancer risk estimates reported by Pearce *et al*. [76], risk-reducing bilateral salpingo-oophorectomy appears cost-effective only in women with endometriosis considered at high risk.

In the NICE guideline NG73 a suggestion regarding this specific area of endometriosis management was not deemed opportune because, as an absolute risk is difficult to quantify, "*recommendations would not aid decision making, would cause anxiety in women with endometriosis and could be misconstrued, for example women seeking treatments (such as removal of the ovaries) that this small risk increase would not warrant*". Moreover, the Committee also stated "*the potential harms associated with misinterpretation or over-interpretation of any recommendation based on this data would outweigh any benefits conferred by women being specifically informed about this data. This may lead to unnecessary procedures*" [78, pages 116-118]. The above position refers to women with endometriosis in general, and not to those with current ovarian endometriomas.

Overall, no sufficiently robust data are available to justify systematic risk-reducing salpingo-oophorectomy in all women with a previous diagnosis of endometriosis, but without current evidence of endometriomas. Thus, this preventive measure should be discussed only with women at highly increased risk, such as those who report a positive family history of ovarian cancer, of infertility, and who have never used OC.

A special situation is when a histologic diagnosis of cytological and/or structural atypia has been made on a previously excised endometrioma, and the ovary has not been removed because of pregnancy desire. Although cystectomy likely eradicated the lesion, persisting predisposing factors may pose that woman at high risk of developing a EAOC, thus it seems prudent to discuss

prophylactic bilateral salpingo-oophorectomy after the age of 45 years even if the ovaries are normal at TVUS and serum CA 125 and HE4 levels are not increased [24].

According to available studies, atypical endometriosis foci are detected in 1%–3% of ovarian endometriotic cysts [79-81]. However, it is unclear whether those endometriomas were all judged preoperatively as low-risk, or whether also endometriomas with suspicious findings were included. Moreover, frequencies were not reported according to strata of age, and it is not possible to exclude that prevalence rates may be directly related with patient age. In a series of 874 endometriomas without suspicious findings at preoperative TVUS removed in 516 patients, the prevalence of true atypical endometriosis was 1.0% (95% CI, 0.5% to 1.9%) based on the number of cysts, and 1.7% (95% CI, 0.9% to 3.3%) based on the number of women [53].

An additional problem here is defining the rate of progression of atypical endometriosis toward CCOC and ENOC. In fact, it is accepted that only a fraction of precursor lesions progress toward frank malignancy, and this figure would be important in order to plan effective prevention strategies.

9. SCREENING FOR ASYMPTOMATIC ENDOMETRIOMAS BETWEEN PREVENTION AND OVERDIAGNOSIS

Screening has been defined by the UK National Screening Committee as "*the systematic application of a test or enquiry to identify individuals at sufficient risk of a specific disorder to warrant further investigation or direct preventive action, amongst persons who have not sought medical attention on account of symptoms of that disorder*" [82]. The main objective of screening for ovarian cancer is to decrease the number of deaths from this disease. A secondary aim of screening is to increase the life expectancy of women who develop ovarian cancer [83]. The modality through which screening should decrease mortality is mostly by identifying pre-neoplastic lesions before they become overt ovarian cancer; the modality through which screening should

increase life expectancy is by allowing detection of already developed ovarian cancer when it is still confined within the ovary.

Thus, given that superficial and deep peritoneal endometriosis very rarely undergo malignant transformation, any screening program aimed at reducing mortality from EAOC should be targeted at detecting endometriotic cysts with atypical lesions, as well as stage I EAOC, in the general population. Unfortunately, screening programs for ovarian cancer have so far been disappointing. Results from the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) screening trial indicated no mortality benefit and added morbidity due to increased surgical intervention [84]. Extended follow-up (median, 14,7 years) of the PLCO trial did not yielded more favorable results from screening for ovarian cancer with CA-125 and TVUS [85]. Recently, even the results of the UK collaborative trial of ovarian cancer screening (UKCTOCS) [86] have been heavily questioned based on methodological and other aspects [83]. Thus, because a reduction in mortality from ovarian cancer as a result of screening has not been documented, it is not routinely offered in the general population *tout court*, independently of ovarian cancer histotypes [77,83]. Indeed, the PLCO and the UKCTOCS screening trials obviously were not limited to the detection of HGSOC and, within the framework of such strategies, all suspicious ovarian lesions, including endometriosis-related tumors, were surgically removed. Despite this, survival has not changed.

Beyond good intentions, any screening strategy should translate into a demonstrable reduction in disease-specific mortality, although many epidemiologists would argue that the effect of any screening should be reflected in a reduction of all-cause mortality. Importantly, health economy evaluations should be conducted in order to assess the efficiency of any prevention measure, that is, the effect of an intervention in relation to the resources it consumes (is it worth the effort?), before fostering its implementation into clinical practice.

With regard to the possibility of screening for EAOC, the NICE guideline NG73 committee considered "*that there is no national screening available for ovarian cancer and that there is no*

clear management plan that would help to reduce a possible small increased risk [in women with endometriosis]" [78, page 116].

10. THE CENTRAL ROLE OF INFORMED PATIENTS: HOW TO COMMUNICATE THE RISK

Hazel Thornton wrote an enlightening editorial on the practical and ethical implications of different modalities to communicate the benefits, harms, and risks to patients [87]. Physicians must understand statistics and their meaning, know how to access reliable information, and develop the capability of communicating the relevant information in a clear and easily comprehensible manner. Without these premises, patient-centered medicine is simply impracticable. There is no single approach to management of perimenopausal women with small endometriomas, and the pros and cons of surgery and strict surveillance in different clinical conditions should be impartially explained. The temptation for both parties to "do something" and thus chose extirpative surgery is expected, but may not always be the best option in high surgical risk patients at low EAOC risk according to risk profiling models. Uncertainties should be addressed without fear of losing patient trust. Representing evidence as natural frequencies fosters greater insight than percentages or probabilities. Relative risks should never be used as they may convey a distorted information. According to Thornton, worry can be manipulated also by the labelling of outcomes.

The most controversial issue is probably risk-reducing salpingo-oophorectomy in the absence of TVUS detected endometriomas. Patient should know that the increase in risk, in absolute terms, is around half of a point percentage of developing an ovarian cancer and a third of a point percentage of dying from ovarian cancer compared with the general female population without a history of endometriosis. In other words, they should be informed that, rounding up, their lifetime probability of *not* developing an ovarian cancer is about 98% instead of 99%. When counseling women, several variables should be discussed, including factors that may impact on the risk of developing EAOC, such as prolonged use of OC or progestogens, parity, and family history.

Patients should also be invited to consider the additional surgical risk associated with previous surgical procedures, as well as with individual factors such as severe co-morbidities or obesity.

Manchanda *et al*. suggest the development of patient decision aids to facilitate understanding of risk [77]. Specific informed consent forms for different clinical conditions would need to be elaborated as well. According to Pearce *et al*. [76], "*the precise lifetime risk at which a woman would consider a risk-reducing salpingo-oophorectomy is a matter to be decided by the woman in consultation with her physician. For women who are at, for example, three times the average lifetime risk of ovarian cancer (4.11% vs. 1.37%), such a discussion might be warranted*".

However, only a minority of endometriosis patient without endometriomas is at such highly increased risk. Indeed, the NICE Committee maintained "*there needs to be a balance between women being fully informed about their condition (including related risks), with rationales for not encouraging unnecessary treatments*" [78, page 116].

SUMMARY

The lifetime risk of ovarian cancer is increased from 1.4% in the general population to about 1.9% in women with endometriosis. The risk of clear cell and endometrioid ovarian cancer is, respectively, tripled and doubled in women with endometriosis. These histotypes account for approximately 20% of all ovarian cancer and < 10% of deaths from ovarian cancer. Contrarily to clear cell tumors, endometrioid cancers are generally estrogen sensitive and associated with hormonal risk factors. Clear cell ovarian cancers may be caused by the mutagenic content of endometriomas, rich of free heme- and catalytic iron-derived reactive oxygen species. Atypical endometriosis, observed in 1-3% of endometriomas excised in premenopausal women, is the intermediate precursor lesion that links typical endometriosis and clear cell/endometrioid tumors. Oral contraceptive use for >10 years is associated with about 80% reduction in ovarian cancer risk among women with endometriosis. Surveillance ± progestogen treatment or surgery should be discussed in perimenopausal women with small typical endometriomas. If surgery is chosen in women not wishing conception, removal of affected ovaries, rather than cystectomy, together with bilateral salpingectomy should be performed, especially in case of long-standing or recurrent endometriomas. In most perimenopausal women with a history of endometriosis but without endometriomas, surveillance instead of risk-reducing bilateral salpingo-oophorectomy seems advisable. Hypothetically, risk-reducing salpingo-oophorectomy may benefit patients at particularly increased risk, but supporting evidence is limited. Risk profiling models and decision aids may assist patients in their choice. Screening of the general population to detect asymptomatic endometriomas is unlikely to reduce disease-specific mortality.

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Practice Points:

- Endometriosis is associated with a three-fold increase in risk of endometrioid and clear-cell ovarian cancer
- Atypical endometriosis is the precursor lesion of endometriosis-associated ovarian cancers and is observed in 1-3% of ovarian endometriomas removed in premenopausal women
- The lifetime risk of ovarian cancer in women with a history of endometriosis is about 1.9% compared with 1.4% in the general population
- Long periods (≥ 10 years) of oral contraceptive use greatly reduce the risk of ovarian cancer in women with a history of endometriosis
- In most women with a history of endometriosis but without ultrasonographic evidence of endometriomas, surveillance rather than risk-reducing salpingo-oophorectomy seems advisable
- In women with small, long-standing typical endometriomas, removal of the affected ovary/ovaries and bilateral salpingectomy can be considered when approaching the menopause

Research Agenda:

- The potential benefit of risk-reducing salpingo-oophorectomy in women with a history of endometriosis should be better defined according to different risk profiles
- Potential benefits, potential harms, and healthcare economic aspects of prolonged surveillance in asymptomatic women with a history of endometriosis but without current endometriomas should be assessed in a randomized, controlled trial
- Early markers of the malignant potential of endometriomas removed at conservative surgery should be identified
- Surveillance and management strategies for women with a previous histologic diagnosis of atypical endometriomas should be defined

- Patient decision aids should be developed to facilitate women comprehension of actual risks and support shared decision-making in different clinical conditions

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960 TABLE 1. Common molecular patterns in endometriosis-associated carcinomas.

Endometriosis-associated ovarian clear cell carcinoma	**Endometriosis-associated ovarian endometrioid carcinoma**
Mutations in • *ARID1A* • *PIK3CA* • *CTNNB1* • *PTEN* Expression of • HNF-1beta ++ • BAF250a -- • Napsin A ++ • Nuclear ERα -- • Cytoplasmatic ERβ2 -- • Cytoplasmatic ERβ5 --	Mutations in • *PTEN* • *CTNNB1* • *KRAS* • *ARID1A* • *PIK3CA* • *PPP2R1A* Expression of • BAF250a --

961

TABLE 2. A conceptual definition of premalignant lesions based on five diagnostic criteria developed during the National Cancer Institute Consensus Conference on Precancer. November 8–9, 2004, George Washington University Medical Center, Washington, DC.

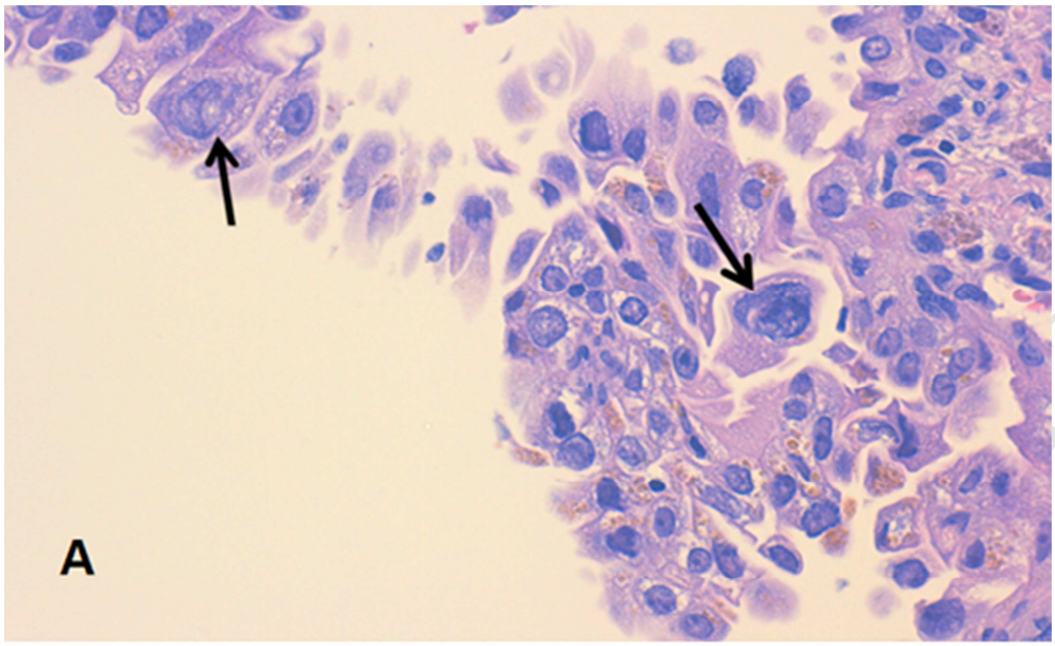
(1)	Evidence exists that the precancer is associated with an increased risk of cancer.
(2)	When a precancer progresses to cancer, the resulting cancer arises from cells within the precancer.
(3)	A precancer is different from the normal tissue from which it arises.
(4)	A precancer is different from the cancer into which it develops, although it has some, but not all, of the molecular and phenotypic properties that characterize the cancer.
(5)	There is a method by which the precancer can be diagnosed.

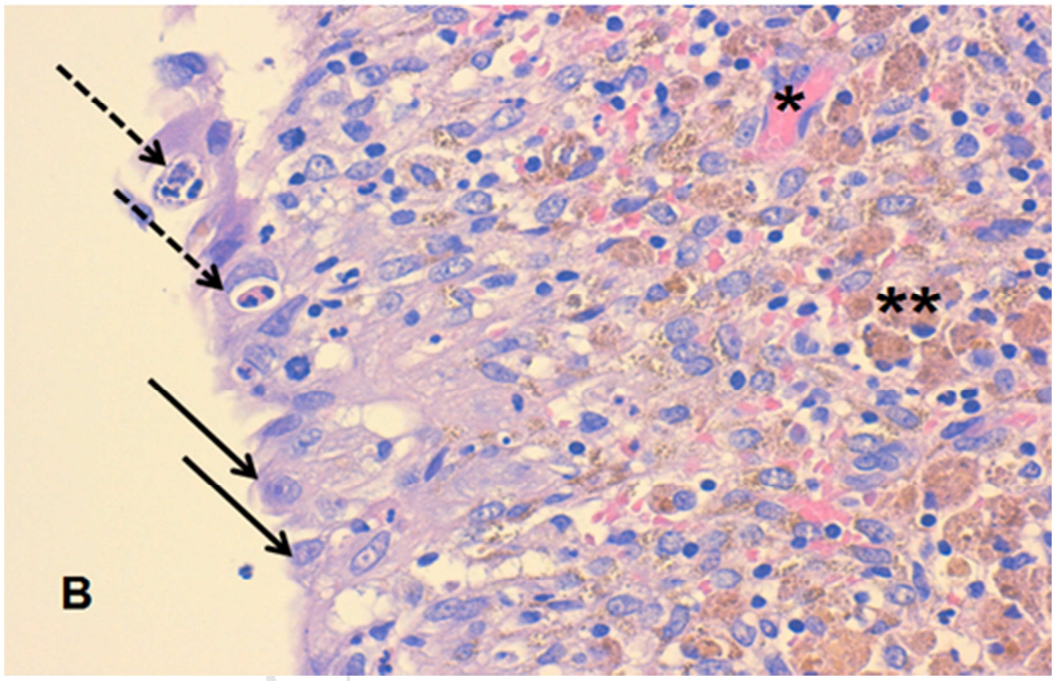
From Berman *et al*. [52]

LEGEND TO FIGURE 1

1A. A high-power image of an endometriotic cyst wall with atypical cells showing eosinophilic cytoplasm, large hyperchromatic (arrows) or pale nuclei with moderate pleomorphism, increased nucleus-to-cytoplasm ratio, mitosis, and cellular crowding, stratification, or tufting. (hematoxylin and eosin, original magnification 40x).

1B. High-power image of an endometriotic cyst wall showing hyperplastic epithelial cells exhibiting uniform reactive atypia with variable nuclear features: increased nucleus-to-cytoplasm ratio, pale nuclei with slight pleomorphism, prominent nucleoli (arrows) and acute inflammatory cells within the epithelium (dotted arrows). The endometriotic stromal cells are admixed with acute and chronic inflammatory cells; * prominent capillaries; ** hemosiderin laden macrophages. (hematoxylin and eosin, original magnification 40x).





HIGHLIGHTS

- Endometriosis is associated with a moderate increase in ovarian cancer risk
- In women with endometriosis the risk of endometrioid ovarian cancer is doubled
- The risk of ovarian cancer is associated with age and endometriotic cyst dimension