**Review/Research Article**

Exposure to Water‑Pipe Smoking Dysregulates a Set of Genes Associated with Breast Cancer Development and an Unfavorable Outcome

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| **Abstract**  A concise and factual unstructured abstract is required (150- 250 words). The abstract should state briefly the purpose of the research, the principal results, and major conclusions. (Perpetua-10)  **Keywords:** 4-6 keywords relevant to the article should be listed below the abstract. Separate the keywords with comma. (Perpetua-10)  **Keywords:** *Adenocarcinoma, Cervix, Minimal deviation, Cancer* |

# Introduction

Cervical cancer continues to be a major public health problem affecting middle‑aged women, particularly in the developing countries of the world. Cervical cancer is the fourth most common cancer in women, ranking after breast cancer, colorectal cancer, and lung cancer. Early diagnosis and treatment of cervical cancer can substantially decreases the mortality. However, the minimal deviation adenocarcinoma (MDA) of the cervix mimics benign lesions of the cervix, and the diagnosis is usually missed by the gynecologists, radiologists, and pathologists.

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MDA was first designated as “malignant adenoma of the cervix” by Gusserow.[1] However, Silverberg and Hurt[2] proposed the term “minimal deviation adenocarcinoma” for this tumor due to its deceptively benign microscopic appearance. Since that time, only a few cases of MDA have been reported in the English literature. In 2014, MDA has been reclassified by the WHO as a subcategory of gastric‑type mucinous cervical adenocarcinoma.[3] MDA is a rare variant of cervical adenocarcinoma and accounts for 1%–3% of all cervical adenocarcinoma cases.[4] MDA demonstrates an endophytic and not an exophytic growth pattern. It resembles multiple benign nabothian cysts on transvaginal ultrasonography. Routine screening methods for the uterine cervix including the Papanicolaou (Pap) and the human papillomavirus (HPV) tests.[5] Moreover, even invasive diagnostic tools (e.g., punch biopsy and cervical conization) often misdiagnose MDA before performing definitive surgery. Because of its rarity and perhaps because cytologic change are subtle, the diagnosis is often missed by the pathologists. Differentiating MDA from normal endocervical glands is difficult due biopsies. This could lead to an incidental diagnosis of MDA following a simple hysterectomy for other benign conditions. Although MDA has a benign histological appearance, it is typically aggressive. In addition, MDAs are so rare that their true nature and clinical course has not been fully clarified. This lack of information delays accurate diagnosis and leads to poor patient prognosis. It is very important to diagnose MDA as the prognosis of MDA is known to be relatively poor.[6,7] Early diagnosis is important to manage MDA. Clinicians should consider MDA among the differential diagnoses in patients with a suspicious clinical presentation even with negative cervical screening tests. Since MDA is a tumor with deceptively innocent histologic patterns, it is important for the pathologists to understand the pathology of MDA in great detail, so that early diagnosis is made.

# Materials and Methods

Based on the literature reviews and meta‑analysis of 347 cases of MDA, the mean age at diagnosis is 45 years (range 20–78 years).[4] The symptoms and signs of MDA are not different from those of common cervical adenocarcinoma. Depending upon the size of tumor, the presenting feature may be abnormal vaginal discharge/mucoid or profuse watery vaginal discharge, menometrorrhagia, irregular genital bleeding, and abdominal swelling.[8,9] The most common presenting symptom was watery discharge. More often, patients are asymptomatic and MDA is an incidental finding in cone biopsy or hysterectomy specimen. Uncommonly patient present with abdominal discomfort, barrel‑shaped cervix, cervical mass, and rarely adnexal metastases. It is associated in 10%–15% with Peutz–Jeghers syndrome. It is also frequently associated with lobular endocervical glandular hyperplasia[9] On clinical examination, the cervix is usually firm and indurated.[10]

# Etiopathogenesis and role of human papillomavirus

The etiopathogenesis of MDA remains unclear. Although a significant association is observed between HPV infection and carcinogenesis of the uterine cervix, previous studies have revealed no significant association between MDA and the HPV virus,[11‑14] an important distinguishing feature between MDA and common cervical cancer[15] When sensitive PCR techniques are utilized, MDA are usually found to be negative for HPV.[15]

MDA is more likely to either precede or develop coincidentally with an ovarian carcinoma than other types of cervical adenocarcinomas. The ovarian neoplasms with which MDA are most likely to be associated include mucinous adenocarcinomas and sex cord tumors with annular tubules. Both MDA of the cervix and ovarian sex cord tumors with annular tubules have been strongly associated with Peutz–Jeghers syndrome. In one series, 4 of 27 women with Peutz–Jeghers syndrome developed MDA. Therefore, close surveillance of women with Peutz–Jeghers syndrome is recommended, including careful endocervical cytologic examination and periodic endocervical curettage. A few studies have demonstrated a close link between MDA and gastric metaplasia or endocervical glandular hyperplasia.[15]

# Cervical cytology of minimal deviation adenocarcinoma

Routine screening methods (HPV test and/or cytology) can easily miss MDA due to its HPV negativity and bland cytology. Previous studies have suggested cytology had a low sensitivity to detect MDA, which is attributed to its bland cytologic features, and to their location being more often in the upper endocervical canal. Subtle cytologic features including mono layered and honeycomb sheets with vesicular nuclei, prominent nucleoli, vacuolar or foamy cytoplasm, and intracytoplasmic neutrophil entrapment suggest the diagnosis of MDA on cytology.

Studied cytological findings in a series of patients, and concluded that that even if well sampled, the definitive cytologic diagnosis of MDA in the absence of a more poorly differentiated component may be very difficult if not impossible. Although in five cases they have identified a population of cells which we believe corresponds to the very well differentiated component of MDA, in four of these smears, these cells lacked sufficient nuclear and cytoplasmic abnormalities to allow reliable distinction from reactive endocervical cells. However, if such cells are seen in abundance, especially in large branching sheets, a careful search for more atypical cells on the smear or a recommendation for a biopsy follow‑up might lead to the detection of MDA. Thus, the Pap test used as a diagnostic tool for MDA has shown a limited detection rate (32.7%,).[4]

# Results and Discussion

Results should be clear and concise. This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature. (Perpetua- 10)

Ensure that all figures have a caption. Supply captions separately, not attached to the figure. Please make sure that figure files are in TIFF or JPEG format (300 dpi).

Mention all the tables and figures in the text as follows:

**(Table 1),** **(Figure 1)**

adenoma malignum, is a designation that refers to a well‑differentiated form of GAS. On gross examination, most cases showed a firm, indurated or friable mass, or a “barrel‑shaped” enlarged cervix.

The characteristic histopathological features of MDA are as follows: (1) A well‑differentiated mucinous adenocarcinoma in which most glands are indistinguishable histologically from normal endocervical glands, **(Figure 1)** (2) a lesion showing cytologically bland glands of varying sizes and shapes, (3) a lesion showing increased mitotic activity, (4) a lesion with hyperplastic glands at the surface, and (5) lesions showing an increased number of glands deeper than the lower level in normal endocervical glands.

The characteristic microscopic features of MDA are the presence of architecturally atypical glands that vary in size, shape, and location. In the mucin‑producing forms, the glands are lined by a single layer of tall columnar epithelium that usually has minimal, if any nuclear atypia. The nuclei are bland and are located at the base of epithelium. The glands have bizarre angular outpouchings, which vary greatly in size **(Figure 2)**.

Desmoplasia is frequently present surrounding the angular outpouchings of MDA or in the deep portion of the tumor. Large areas of invasive tumor may be devoid of any stromal reaction. In such areas, the presence of glands adjacent to thick‑walled blood vessels is a helpful finding in determining that stromal invasion is present. The most reliable criterion to assess malignant nature of MDA is the haphazard arrangement of glands that extend beyond the level of normal endocervical glands and presence of occasional mitosis in glandular cells **(Figure 3)**. MDA often involves more than two thirds of the thickness of the cervical stroma and should be regarded as invasive because the normal endocervical crypts and tunnels do not extend beyond 7 mm.

# Differential diagnosis

The differential diagnosis of MDA includes several conditions in which nonneoplastic glands extend beyond 7 mm from the surface. These conditions include endocervical tunnel clusters, deeply situated nabothian cysts, endocervicosis of the cervical wall, and mesonephric hyperplasia. The glands of endocervical tunnel clusters, mesonephric hyperplasia, and deep nabothian cysts are usually much more uniform in size than are the glands of MDA and lack the bizarre branching and irregular outpouchings that are characteristic of the glands of MDA. The benign processes also lack a desmoplastic response. Interestingly, the benign endocervical glandular lesion termed lobular endocervical glandular hyperplasia, which may mimic adenoma malignum, is now also thought to have

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| **Figure 1. Architecturally atypical glands that vary in size, shape, (H and E,×10)** |

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| **Figure 2. The glands have bizarre angular outpouchings, (H and E, ×40)** |

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| **Figure 3. Presence of occasional mitosis in glandular cells (H and E, ×40)** |

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| Table 1. Legalon drug effect on lipids profile | | | | |
|  | **1st Group**  **control** | **2nd Group**  **H2O2 0.5%** | **3rd Group**  **Legalon 6mg/kg + H2O2 0.5%** | **4th Group**  **Legalon 6mg/kg** |
| Cholesterol | 84.88±3.53  a | 177.35±7.14  B | 72.33±4.24  A | 73.01±2.28  A |
| Triglyceride | 80.49±5.39  a | 111.78±1.48  B | 27.80±2.59  C | 75.51±4.16  A |
| HDL-C | 34.45±0.96  a | 25.00±0.95  b,c | 23.72±1.85  C | 50.05±2.79  D |
| LDL-C | 64.24±5.36  a | 174.71±7.87  B | 54.21±3.01  c,a | 38.05±2.49  C |
| VLDL-C | 13.81±2.42  a | 22.36±0.29  B | 5.55±0.52  C | 15.10±0.83  A |
| Risk index | 1.87±0.16  a | 7.05±0.24  B | 2.33±0.24  A | 0.77±0.19  C |

# Conclusion

With large‑scale implementation of HPV vaccine, the incidence of HPV‑associated cervical adenocarcinoma is expected to decrease. The relative proportion of MDA and other rare HPV negative adenocarcinomas would increase. Early diagnosis is important to manage MDA. Clinicians should consider MDA among the differential diagnoses in patients with a suspicious clinical presentation even with negative cervical screening tests. Awareness of the morphologic features and immunohistochemical profile of MDA will allow pathologists to recognize and accurately diagnose this rare and aggressive entity.

Because of the rarity of MDA, future research should be focussed on nationwide studies. Data collection, information sharing, and inter‑institutional consultations are necessary to define the nature of MDA to establish appropriate therapeutic guidelines and provide optimal advanced therapy in the era of precision medicine.

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# Conflict of interest

None. Any interest, financial relationship, personal relationship, religious or political beliefs that might influence the objectivity of the author can be considered as a potential source of conflict of interest. All manuscripts submitted to the journal must include a conflict of the interest disclosure statement or a declaration by the authors that they do not have any conflicts of interest to declare.

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# Ethics statement

None. Studies involving humans and animals must have been performed with the approval of an appropriate ethics committee and provide the reference number.

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