



RISK FACTORS OF FEMALE REPRODUCTIVE CANCERS IN INDIAN INHABITANTS.

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ABSTRACT

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Cancers of the female reproductive system are a major cause of mortality in females especially among rural areas where lack of awareness, poverty, and illiteracy still exist. Even though treatments are available, not every individual is capable of bearing expenses. A few preventive measures can be taken against risk factors that have suspect to cause female reproductive cancer in the future. These risk factors include early menarche, child marriages, early pregnancy, age at first childbirth, late menopause, alcohol consumption, obesity, occupational exposure to pesticides, smoking, use of oral contraceptive pills, and cumulative menstrual cycle lifetime. Preventive measures can be taken to avoid risk factors causing female reproductive cancers. Utmost efforts should be made to teach women in early cancer detection by creating awareness of risk factors and symptoms. Gynecological cancer screening helps in early identification and therefore improves the overall outcomes.

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INTRODUCTION

Abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases to metastasis is termed as cancer. Cancer can be caused by any tissue of the body. Cancers of the female reproductive system namely cervical cancer, ovarian cancer, endometrial cancer, vaginal cancer, vulvar cancer, fallopian tube cancers are an important cause of cancer morbidity and mortality among women. Common sites of tumors in the female genital tract are cervix, ovary, and endometrium [1]. Ovarian and cervical cancers are identified to be the most common

gynecological cancers affecting women worldwide. There is an alarming rise in cervical cancer second only to breast cancer. A survey shows that every year in India, more than 120,000 women are diagnosed with cervical cancer and 67,477 die from this disease [2]. So it's always better to prevent from suspected risk factors causing female reproductive cancers.

AIM OF THE STUDY: To enlighten the risk factors causing female reproductive cancers, its possible mechanism, and prevention.

EPIDEMIOLOGY: Cervical Cancer: The third most common cancer in women

worldwide, behind breast and colorectal cancers. The overall mortality: incidence ratio of cervical cancer is 52%, it was responsible for 275,000 deaths in 2008, about 88% of which occurred in less developed regions [3].

Endometrial cancer: The sixth most common cancer in women worldwide, with an estimated 288,387 new cases in 2008, and a standardized incidence rate of 8.2 per 100,000 women [4].

Ovarian Cancer and Fallopian tube cancer: The eighth most common cancers among women worldwide, with 224,747 incident cases (standardized incidence rate 6.3 per 100,000 women); 140,163 deaths are estimated to have occurred in 2008[3,4].

Vulvar Cancer: Incidence rates worldwide are estimated to vary between 0.5 and 1.5 per 100,000, without a clear geographical pattern.

Vaginal Cancer: Incidence rates are estimated to be between 0.3 and 0.7 per 100,000 in most countries [5,6].

RISK FACTORS

Age at early menarche, early marriages, early pregnancy, age at first childbirth, late menopause, alcohol, obesity, smoking, use of oral contraceptive pills, and cumulative menstrual cycle lifetime is possible risk factors. Epidemiological studies have shown an increased risk for cervical cancer attributable to sexual and reproductive behavior [7]. Some of the important epidemiological risk factors have been identified which include early age at marriage, coitus before the age of 18 years, first child delivery before the age of 20 years, multiple sexual partners multiparity with poor birth spacing between pregnancies, and poor personal hygiene [8]. Women with sexually transmitted diseases (STDs) like HIV infection, Herpes Simplex Virus, and Human Papilloma Virus (HPV) infection [8,9]. Smoking, Oral Contraceptives (OCs), and lack of some nutritional factors like beta-carotene, vitamin C, and low intake of fruits are other factors associated with increased risk [10].

Early marriage and polygamy play an important role in developing cervical cancer [11]. Common risks for cervical cancer and child marriage are low socioeconomic status, poor access to health care, and husbands who had multiple sex partners [12]. Although cervical cancer has a multifactorial risk, infection with human papillomavirus (HPV) and lack of effective screening have been identified as major components in the development of pre-invasive and invasive types of this disease [13].

Cigarette smoking is considered a causative factor in a variety of cancers. The role of smoking in cervical cancer is sometimes denied, because women who smoke may have other risk factors for cervical cancer, particularly HPV infection. It appears that smoking may play a prominent role in cervical cancer in developing countries, but less of a role in other countries [14]. Ovulations in the age group 20 to 29 years were associated with the greatest risk, with a 20% increase in risk associated with each year of ovulation during this age period [15].

Age at early menarche, especially among premenopausal women, and later menopausal age were associated with an elevated risk of endometrial cancer. Compared to null gravity (women ever having a pregnancy) and nulliparity (women ever having had a live birth), were both associated with a more than the one-fold increased risk of endometrial cancer [16].

Postmenopausal women have a greater risk of developing the disease as compared with premenopausal women, younger age at menarche and late age at menopause, infertility, null parity, increased obesity rates, age of the first child, and long-term use of unopposed estrogens for hormone replacement therapy [17]. Prevention against endometrial cancer has been detected with increasing parity, the use of combined oral contraceptives, and increased age of women at last delivery.

Ever use of talcum powder was associated with a 21% increase in the risk of endometrial cancer, while regular use (\geq once/week) was associated with a 24% increase in risk [18]. Pesticides (Triazine, organochlorines) [33,34] are used widely in

the agriculture environment which can lead to health hazards. It should be noted, however, that there are lower cancer rates among farmers than the overall population for a few cancers, especially those cancers associated with the use of tobacco and alcohol [23].

Table 1: Risk Factors and Their Mechanisms in Female Reproductive Cancers.

Risk Factors	Possible Mechanism
Early menarche	Longer lifetime exposure to endogenous estrogen and progesterone deficiency associated with anovulatory cycles [25].
Early childbirth	Physiological activity in the cervical cell is at a maximal level during adolescence. More susceptible to carcinogenic transformation by early coital experience and secondly the multiplicity of sexual partners [26].
Smoking	Exposure of the deoxyribonucleic acid (DNA) in cervical epithelial cells to nicotine directly, and another mechanism involves long-time exposure to metabolic products of other components of cigarettes such as aromatic polycyclic hydrocarbons and aromatic amines which are resulted from reaction [27].
Obesity	Abnormal endogenous hormone metabolism. Production of estrogen by adipose tissues [28].
Talcum Powder	Exposure to talcum causes inflammation. The existence of leukocytes in cancer tissues and suggested a possible connection between inflammation and cancer. (Insulin, Insulin-like growth factor 1, sex steroids) [29].
Pesticides	It affects genetic material directly via induction of structural and functional damage to chromosomes DNA and histone proteins or indirectly disrupting the profile of gene expression through impairment of cellular organelles like mitochondria and endoplasmic reticulum, nuclear receptors and other factors involved in maintenance in cell hemostasis [30].
Early Marriage	Sexual activity and persistent infection with human papillomavirus (HPV) [31].
Late menopause	Estrogen exposure to tissues for a longer time.
Oral contraceptives	The association between long-term OC use and increased risk of cervical cancer. Women using OC are more likely to be exposed to HPV than are those using barrier contraceptive methods or not having sexual intercourse [32].

POSSIBLE CAUSES FOR FEMALE REPRODUCTIVE CANCERS IN INDIAN POPULATION.

In a developing country like India of the 21st century still, the incidence and mortality rate of female reproductive cancers is high due to poor awareness, illiteracy,

poverty, and exposed risk factors. Even though targeted therapies are available with fewer side effects but cannot be afforded by poor people. Hence preventive measures and increasing awareness can contribute to decreasing reproductive cancers in the female.

Table 2: Symptoms and Diagnosis of types of female reproductive cancers.

Type of cancer	Symptoms	Diagnosis
Cervical Cancer	Abnormal uterine bleeding – Intermenstrual bleeding, post-menopausal bleeding, post-coital bleeding, continuous bleeding, and uncontrolled profuse bleeding and vaginal discharge which is foul-smelling or blood-stained, Pain – pelvic pain, low back pain and pain radiating down to the posterior thighs, Pedal edema, haematuria, urinary incontinence and fecal incontinence [19].	<ul style="list-style-type: none"> •Papanicolaou (Pap) test •Biopsy •Clinical staging is usually done by biopsy, pelvic examination, and chest X-ray.
Ovarian Cancer	The symptoms include abdominal pain, abdominal distention, postmenopausal bleeding (PMB), fatigue, nausea, vomiting, alteration in the bowel, and urinary function, loss of appetite [24].	<ul style="list-style-type: none"> •Ultrasonography is done for suspected early cancers or CT or MRI for suspected advanced cancers. •Tumor markers (eg, cancer antigen [CA 125]) •Surgical staging
Endometrium Cancer	Abnormal vaginal bleeding which is an early symptom associated with endometrial cancer is the most common symptom in women. Serosanguinous vaginal discharge; pyometra: haematometra; irregular or heavy bleeding; abdominal distention and lumbosacral, hypogastric, and pelvic pain are less frequently noted symptoms [21].	<ul style="list-style-type: none"> •Endometrial biopsy •Surgical staging
Vaginal Cancer	Abnormal vaginal bleeding – post-coital, pre-pubertal or post-menopausal, intermenstrual are common symptoms. Other symptoms include dyspareunia and pain in the pelvic area, difficult/painful urination. Advanced tumors affect the rectum/bladder or extending to the pelvic wall cause pain/leg edema.	<ul style="list-style-type: none"> •Biopsy •Clinical staging
Vulvar Cancer	Long-standing pruritus, discharge, pain, bleeding, non-healing ulcer, warty growth, inguinal mass, dysuria, and discharge. Lesions can be fleshy warty growth, unilateral/bilateral, ulcer, red/white color and tender/painless. The most generally described side effect of vulvar cancer is a long history of pruritus. The most evident indication of vulvar malignant growth is a vulvar irregularity or mass, which may present ulcerated, leukoplakic, plump, or warty [20].	<ul style="list-style-type: none"> •Biopsy •Surgical staging

PREVENTION

Cervical Cancer

Screening tests

There are two types of screening tests for cervical abnormalities:

- Pap test
- HPV test

Routine cervical cancer screening tests are recommended as follows: [22]

- From 21 to 29 years of age: Usually pap test for every 3 years. (HPV testing is not generally recommended)
- From 30 to 65 years of age: Every 3 years if only a Pap test is done or every 5 years if only an HPV test is done or if both tests are performed (periodically in women at high risk of cervical cancer)
- After age 65: No more testing is required if the test results have been normal in the preceding 10 years.

Preventive HPV vaccines include:

- A bivalent vaccine that protects against subtypes 16 and 18 (which causes most of the cervical cancers).
- A quadrivalent vaccine that prevents against subtypes 16 and 18 plus 6 and 11
- A 9-valent vaccine that protects against the same subtypes as the quadrivalent plus subtypes 31, 33, 45, 52, and 58 (which causes about 15% of cervical cancers).

Subtypes 6 and 11 cause more than 90% of visible genital warts.

The vaccines do not treat cancer but aim to prevent cervical cancer.

For patients, more than or equal to 15 years, three doses are given over 6 months (at 0, 1 to 2, and 6 months). For patients less than 15 years, two doses are given 6 to 12 months apart.

The HPV vaccine is recommended for both boys and girls, ideally before they become sexually active. The standard recommendation is to vaccinate boys and girls at age 11 to 12 years, but vaccination can begin at age 9.

Ovarian Cancer: Risk of ovarian and, to a lesser degree, breast cancer is reduced in

patients with BRCA1 or BRCA2 gene mutations if prophylactic bilateral salpingo-oophorectomy is done after childbearing is completed. Cancer risk appears to be lower with this approach than with care. Patients with BRCA1 or BRCA2 gene mutations should be referred to a gynecologic oncologist for counseling.

Endometrial Cancer: Because obesity and hypertension increase the risk of endometrial cancer and because evidence suggests that certain lifestyle choices may help prevent endometrial cancer, patients should be counseled about the importance of exercise, weight loss, and an adequate diet.

RECOMMENDATIONS

Further statistical research can be performed to get a positive association between risk factors and female reproductive cancer.

- A free full-body screening for post-menopausal women can be a preventive measure.
- Awareness programs about prevention and risk factors involved in female reproductive cancer among the public and in schools to avoid from a very early age.
- Leaflets, newspapers, and social media can be used in enlightening the women's health issues and its consequences.
- The government should implement schemes for lessening the treatment expenses.

CONCLUSION

Increasing incidence of gynecological cancers has indicated the need for early identification and treatment to promote well-being in women of all ages. Utmost efforts should be made to teach women in early cancer detection by creating awareness of risk factors and symptoms. Gynecological cancer screening helps in early identification and therefore improves the overall outcomes.

REFERENCES

1. Ramesh N, Anjana A, Kusum N, Kiran A, Ashok A, Somdutt S. Overview of benign and malignant tumors of the female genital

- tract. *Journal of Applied Pharmaceutical Science*. 2013;3(01):140-9.
2. Bruni L, Barrionuevo-Rosas L, Albero G, Serrano B, Mena M, Gomez D. Human papillomavirus and related diseases report. HPV Information Centre. 2017.
 3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1. 2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. International Agency for Research on Cancer, Lyon, France. Lyon (France). 2010.
 4. Merritt MA, Cramer DW. Molecular pathogenesis of endometrial and ovarian cancer. *Cancer Biomarkers*. 2011 (1-6):287-305.
 5. Parkin DM, Bray F. Chapter 2: the burden of HPV-related cancers. *Vaccine* 24 (Suppl 3): S3/11–25.
 6. Bosch FX, Cardis E. Cancer incidence correlations: Genital, urinary, and some tobacco-related cancers. *International journal of cancer*. 1990:178-84.
 7. Irimie S, Mariana VL, Mirestean IM, Balacescu O, Meda RU, Balacescu L, Berindan-Neagoe I, Buiga R, Ordeanu C, Viorica NA, Irimie A. Risk factors in a sample of patients with advanced cervical cancer. *Applied Medical Informatics*. 2011:1-0.
 8. World Health Organization, Programme on Cancer Control (World Health Organization), the World Health Organization. Reproductive Health. Cervical cancer screening in developing countries: report of a WHO consultation. World Health Organization; 2002.
 9. Kjaer SK, de Villiers EM, Haugaard BJ, Christensen RB, Teisen C, Møller KA, Poll P, Jensen H, Vestergaard BF, Lynge E, Jensen OM. Human papillomavirus, herpes simplex virus, and cervical cancer incidence in Greenland and Denmark. A population-based cross-sectional study. *International journal of cancer*. 1988:518-24.
 10. Schottenfeld D, Fraumeni Jr JF, editors. *Cancer epidemiology and prevention*. Oxford University Press.
 11. Sreedevi A, Javed R, Dinesh A. Epidemiology of cervical cancer with special focus on India. *International journal of women's health*. 2015;7:405.
 12. Thakur A, Gupta B, Gupta A, Chauhan R. Risk factors for cancer cervix among rural women of a hilly state: a case-control study. *Indian journal of public health*. 2015:45.
 13. Goodman A. HPV testing as a screen for cervical cancer. *BMJ*. 2015 350:h2372.
 14. Steckley SL, Pickworth WB, Haverkos HW. Cigarette smoking and cervical cancer: Part II: a geographic variability study. *Biomedicine & pharmacotherapy*. 2003:78-83.
 15. Purdie DM, Bain CJ, Siskind V, Webb PM, Green AC. Ovulation and risk of epithelial ovarian cancer. *International journal of cancer*. 2003:228-32.
 16. Xu WH, Xiang YB, Ruan ZX, Zheng W, Cheng JR, Dai Q, Gao YT, Shu XO. Menstrual and reproductive factors and endometrial cancer risk: Results from a population-based case-control study in urban Shanghai. *International journal of cancer*. 2004:613-9.
 17. Ali AT. Reproductive factors and the risk of endometrial cancer. *International Journal of Gynecologic Cancer*. 2014:384-93.
 18. Karageorgi S, Gates MA, Hankinson SE, De Vivo I. Perineal use of talcum powder and endometrial cancer risk. *Cancer Epidemiology and Prevention Biomarkers*. 2010:1269-75.
 19. Yarbro CH, Wujcik D, Gobel BH. *Cancer nursing: principles and practice*. Jones & Bartlett Publishers; 2010.
 20. Alkatout I, Schubert M, Garbrecht N, Weigel MT, Jonat W, Mundhenke C, Günther V. Vulvar cancer: epidemiology, clinical presentation, and management

- options. *International journal of women's health*. 2015;7:305.
21. Dinkelspiel HE, Wright JD, Lewin SN, Herzog TJ. Contemporary clinical management of endometrial cancer. *Obstetrics and gynecology international*. 2013;2013.
 22. Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW, Doubeni CA, Epling JW, Kemper AR, Kubik M, Landefeld CS. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. *Jama*. 2018;320(7):674-86.
 23. Blair A, Zahm SH. Agricultural exposures and cancer. *Environmental health perspectives*. 1995;103(suppl 8):205-8.
 24. Bankhead CR, Collins C, Stokes-Lampard H, Rose P, Wilson S, Clements A, Mant D, Kehoe ST, Austoker J. Identifying symptoms of ovarian cancer: a qualitative and quantitative study. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2008;115(8):1008-14.
 25. Gong TT, Wang YL, Ma XX. Age at menarche and endometrial cancer risk: a dose-response meta-analysis of prospective studies. *Scientific reports*. 2015 Sep 11;5:14051.
 26. El-Moselhy EA, Borg HM, Atlam SA. Cervical Cancer: sociodemographic and clinical risk factors among adult Egyptian females. *Adv Oncol Res Treat*. 2016;1(1):106.
 27. Fonseca-Moutinho JA. Smoking and cervical cancer. *ISRN obstetrics and gynecology*. 2011;2011.
 28. Gu W, Chen C, Zhao KN. Obesity-associated endometrial and cervical cancers. *Front Biosci (Elite Ed)*. 2013;5(1):109-8.
 29. Merritt MA, Green AC, Nagle CM, Webb PM, Australian Cancer Study (Ovarian Cancer), and Australian Ovarian Cancer Study Group. Talcum powder, chronic pelvic inflammation, and NSAIDs about the risk of epithelial ovarian cancer. *International Journal of Cancer*. 2008 1;122(1):170-6.
 30. Mostafalou S, Abdollahi M. Pesticides, and human chronic diseases: evidence, mechanisms, and perspectives. *Toxicology and Applied Pharmacology*. 2013 15;268(2):157-77.
 31. Weiderpass E, Labrèche F. Malignant tumors of the female reproductive system. In *Occupational Cancers 2014* (pp. 409-422). Springer, London.
 32. Cibula D, Gompel A, Mueck AO, La Vecchia C, Hannaford PC, Skouby SO, Zikan M, Dusek L. Hormonal contraception and risk of cancer. *Human reproduction update*. 2010;16(6):631-50.
 33. Rodríguez ÁG, López MI, Casillas TÁ, León JA, Mahjoub O, Prusty AK. Monitoring of organochlorine pesticides in blood of women with uterine cervix cancer. *Environmental Pollution*. 2017;220:853-62.
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