

Chapter 1 Introduction

1.1 Background

- The way life evolved on our planet and the successful evolution of multicellular organisms has a lot to do with cancer. The smallest unit of life, the cell, contains all the components required and adequate for life, with viruses holding a particular position. The term "cellular pathology" was first used in 1863 by the German pathologist Rudolf Virchow, who claimed that diseases result from cellular-level pathological processes. This is particularly true of cancer, which is unquestionably a disease of a cell within a multicellular organism (*Oxford Textbook of Cancer Biology*, 2019).

1.2 Cancer

- Cancer is a disease brought on by a breakdown in the biological processes required for the development and upkeep of multicellular organisms as well as cell growth. Large multicellular animals are complicated, and as a result, a wide range of mistakes and harms can result in malignant lesions with a complex range of biology and clinical behavior, which is what is known as cancer. Cancer must be regarded practically as many different diseases, each to be individually unraveled to understand it and produce an effective treatment fully (*Oxford Textbook of Cancer Biology*, 2019).
- In India, cancer is quickly becoming a leading cause of illness and mortality. Young age (often one decade younger than the Western population), advanced disease, poor performance status, and maybe a more aggressive phenotype is some of the distinguishing characteristics. While many hospitals and regional cancer centers in smaller towns have state-of-the-art diagnostic procedures and treatment plans, this is not yet true of many tertiary cancer centers. It may be possible to improve outcomes by concentrating on epidemiological studies, screening for specific malignancies, and treatment trials for prevalent cancers in India. The key to success is probably an organized, team-based approach at the institutional level and cooperation with other research teams (M. Singh, Prasad, Singh, & Kumar, 2018).
- Cancer is the term used to describe any disease that can affect any part of the body. Other terms used are malignant tumors and neoplasms. The rapid growth of abnormal cells that spread beyond their natural boundaries, invade other bodily parts, and ultimately spread

to other organs is one feature of cancer. We call this process metastasis. Widespread metastases are the primary cause of cancer patients' deaths ("WHO REPORT ON CANCER,").

- Regardless of wealth or social standing, cancer is a major health issue that affects all communities. Cancer has had an unequal and inequitable reaction worldwide. After making the difficult decision to focus their limited resources on the massive burden of infectious diseases, the majority of low- and middle-income countries (LMIC) only recently began to confront the cancer burden (M. Singh et al., 2018).

1.2.1 Types of Cancer

- Cancer can occur in every part of the body and it may create a life-threatening situation. Basic types of cancer are only five. 1. Carcinoma, 2. Sarcoma, 3. Melanoma, 4. Lymphoma and 5. Leukemia. Later on, it is described by which part of the body is affected. Figure 1.1 shows the most common type of cancer in men and women.

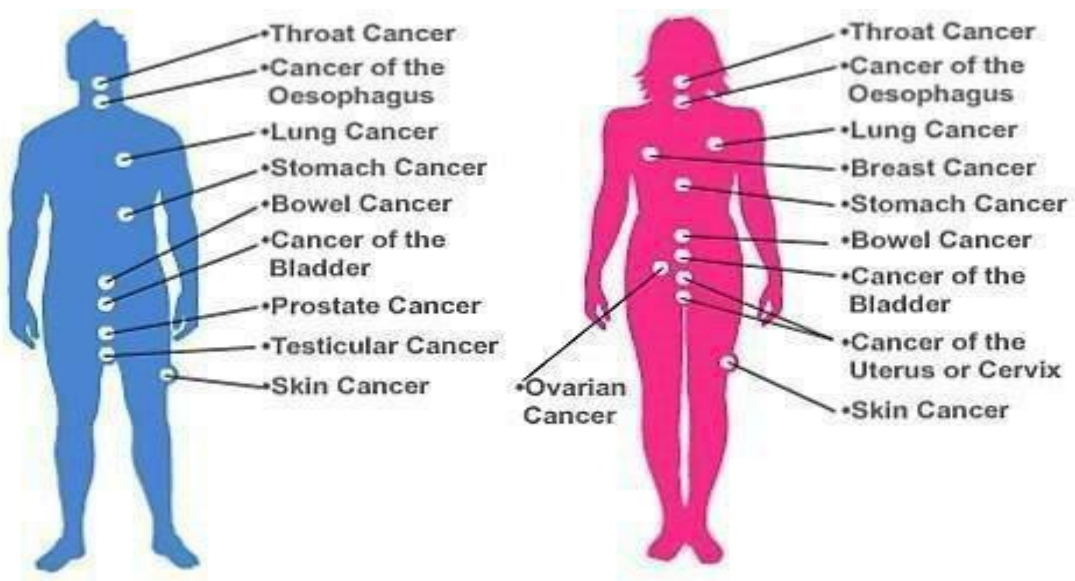


Figure 1.1: The most common types of cancers in various organs (Mncwabe, 2017)

1.3 Cervical Cancer

- Cervical cancer originates in the cells lining the cervix, or lower part of the uterus. The body of the uterus, which is where a fetus develops, is joined to the vagina (the birth canal) by the cervix as given in Figure 1.2. The cervix is divided into two sections and has two different types of cells covering it (DeVita, 2020).

- The opening of the cervix that enters the uterus is known as the endocervix. There are glandular cells throughout it. During a speculum exam, the doctor can see the exocervix also known as the ectocervix), which is the exterior portion of the cervix. It has squamous cells all over it (DeVita, 2020).

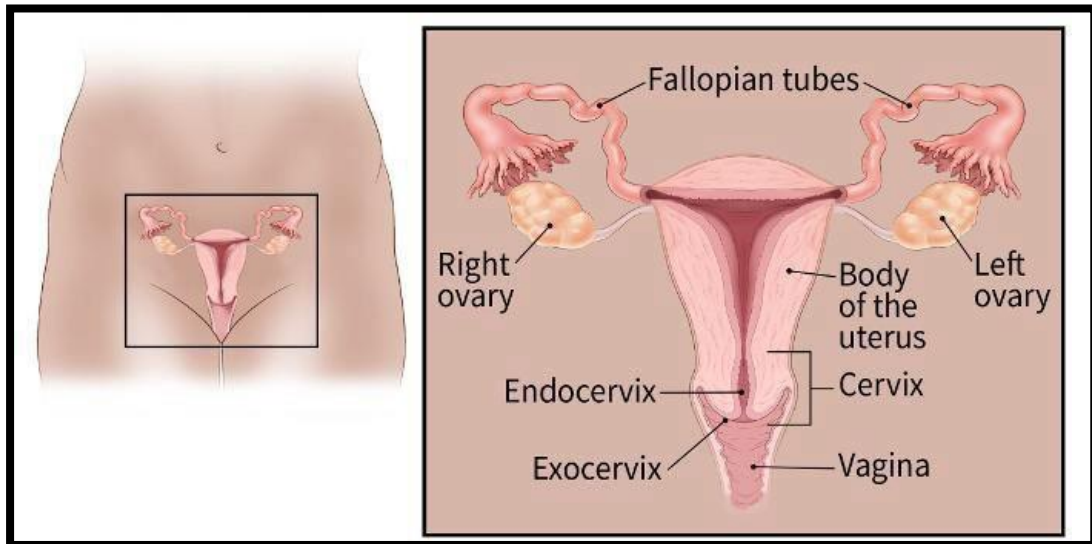


Figure 1.2: Female reproductive system (DeVita, 2020)

- The area of the cervix where these two cell types combine is known as the transition zone. With age and pregnancy, the precise location of the transformation zone shifts. The cells in the transformation zone are where the majority of cervical malignancies start (Jhingran et al., 2020).
- Cancer does not appear out of nowhere in cells in the transformation zone. Instead, the cervix's healthy cells gradually experience aberrant changes before becoming cancerous. These cell alterations are referred to by several medical terminologies, such as dysplasia, cervical intraepithelial neoplasia (CIN), and squamous intraepithelial lesion (SIL). Pre-cancers or pre-cancer changes are possible names for these aberrant alterations (Fontham et al., 2020).
- Based on how much of the cervical tissue seems abnormal, these abnormal alterations in the cervix are evaluated on a scale of 1 to 3 when they are discovered. Only a small portion of the tissue displays abnormality in CIN1 (also known as mild dysplasia or low-grade SIL). These cells will typically transform back into normal cells. More tissue displays abnormality in CIN2 or CIN3 (also known as moderate/severe dysplasia or high-grade SIL). These cell alterations increase the likelihood that the cells will develop into

cancer cells and require close monitoring or removal (Khieu & Butler, 2022).

- Only some women with these cervix abnormalities will acquire cancer, despite the fact that cervical malignancies originate from cells with aberrant modifications. These aberrant cells will typically disappear on their own in most female patients. These aberrant cells, however, can develop into real (invasive) malignancies in some women. Treating abnormal changes in cervical cells can prevent almost all cases of cervical cancer (Khieu & Butler, 2022).

1.3.1 Cancer Screening

- Finding abnormal cells in the cervix or cervical cancer early, when it is more curable and treatable, is the aim of cervical cancer screening. Cervical cancer can be prevented and lives saved by routine screening. The HPV test and the Pap test are the procedures used for cervical cancer screening. The Pap test can identify pre-cancerous abnormalities that can be treated to stop cancer from growing. The HPV test looks for infections brought on by high-risk HPV strains, which increase the risk of cervical cancer and premalignancies. Vaccination can help prevent HPV infection even if there is no known cure for it.

1.3.2 Types of Cancer

- Cervical tumors and pre-cancers are categorized based on how they appear under a microscope in the laboratory. The two most prevalent kinds of cervical cancer are adenocarcinoma and squamous cell carcinoma (Cervical Cancer Treatment – Health Professional Version. 2019; Petignat & Roy, 2007).
- Squamous cell carcinomas make up the majority of cervical malignancies (up to 9 out of 10). Exocervical cells give rise to these malignancies. The transformation zone (where the exocervix and the endocervix unite) is where squamous cell carcinomas most frequently start (Cervical Cancer Treatment – Health Professional Version. 2019).
- Adenocarcinomas make up the majority of the other cervical malignancies. The malignancies known as adenocarcinomas originate from glandular cells. The endocervical mucus-producing gland cells give rise to cervical cancer. Less frequently, cervical malignancies resemble squamous cell carcinomas and adenocarcinomas in their characteristics. Adenosquamous carcinomas or mixed carcinomas are the names given to these (Cervical Cancer Treatment – Health Professional Version. 2019).

- Other cancers can form in the cervix, while most cervical malignancies are adenocarcinomas and squamous cell carcinomas. These other kinds, like lymphoma, melanoma, and sarcoma, are more typical in various areas of the body (Cervical Cancer Treatment – Health Professional Version. 2019).

1.3.3 Diagnosis

- Human papillomavirus infections with high-risk strains are the primary cause of cervical cancer. Both primary prevention (vaccination) and secondary prevention (screening) of this disease are clearly affected by this (Harsha Kumar & Tanya, 2014).
- Main three approaches are there for cervical cancer detection which are given below in the table 1.1.

Molecular	Cytologic	Visual Inspection
Nucleic Acid Amplification test High risk HPV DNA/NAAT mRNA	Conventional Pap smear	Visual inspection with acetic acid or with Lugol's Iodine (VIA/VIU) - naked eyes - magnified by Colposcopy or camera
DNA methylation	Liquid-based cytology (LBC)	Automated visual evaluation of digital images
Protein biomarkers HPV antibodies Oncoproteins	Dual staining to Identify p53 and ki-67	

Table 1.1: Main approaches to diagnose Cervical cancer (Janicek & Averette, 2001)

- The transformation zone of the cervix is where cervical cancer typically develops, and it then spreads to nearby lymph nodes. Invasion of the parametrium is also typical. The location and severity of the disease have a major impact on the clinical presentation. A cervical smear can detect precancerous alterations or very early-stage illness that are

typically asymptomatic. When the tumor results in spontaneous or contact bleeding, or pain if lymph nodes are affected, symptoms typically start to show. Backache and serosanguineous, foul-smelling vaginal discharge are other symptoms. V-DNA at age 25 and every 3-5 years thereafter (Harsha Kumar & Tanya, 2014).

- Conization is not advised when a lesion is apparent to the unaided eye; a cervical biopsy will typically reveal the lesion's identity. Conization is recommended when a colposcopically guided biopsy cannot rule out frank invasion or when colposcopy is poor and a smear test reveals a high-grade lesion. Squamous cell carcinomas account for approximately two thirds of all cervical cancers. There are several different histological abnormalities associated with adenocarcinoma, which is found in 15–25% of cases. Unusual histological changes include adenosquamous carcinoma, neuroendocrine carcinoma, and clear cell carcinoma. Tumor grade (well, moderately, and poorly differentiated), invasion width and depth, and presence (or lack) of lymphovascular space invasion are among the prognostic factors that need to be appropriately taken into account (Petignat & Roy, 2007).
- Before delving into the various molecular markers for triage alternatives and the corresponding test technologies, it is crucial to describe the various sample types that could be employed. Conventional scrapes are still commonly used; they are performed at the outside of the cervix to look for malignant cells (PAP test) in the transformation zone. Samples can be used because they are well preserved against the degradation of DNA, RNA, and proteins by being suspended right away in a methanol-based fixation solution. for (i) PAP/LBC cytology, (ii) hrHPV testing, (iii) HPV16/18 genotyping, and (iv) p16/Ki-67 dual-staining (Janicek & Averette, 2001).
- A biopsy is collected from the problematic areas outside or inside the cervix for microscopic inspection if a woman is sent to a Gynaecologist. In The Netherlands, simultaneous blood draws are typical at the first doctor's appointment, before surgery, during additional treatment sessions, and during the course of therapy follow-up. In the event that an examination indicates an advanced stage of CIN, the level of SCCA in serum or plasma can be utilized to track the disease's course. It would be highly beneficial to identify reliable molecular markers that provides sufficient levels of specificity and sensitivity could be attained. Specifically, a promising strategy for test development is

the translation of molecular markers originally found in tissue or cells to blood or other (Janicek & Averette, 2001).

1.3.4 Treatment

- In general, when non-invasive intraepithelial lesions are identified only microscopically, they are treated with superficial ablative procedures such as cryotherapy or laser therapy. These are outpatient office procedures that do not affect fertility. With cryotherapy, abnormal tissue and the surrounding 5 mm is frozen with a supercooled probe. A single freeze may not be adequate to induce necrosis, so the area is allowed to thaw and is frozen again. Ablation of tissue with a carbon dioxide laser beam is as effective as cryotherapy, and the tissue heals faster with less distortion, but it is a more expensive procedure (KIRWAN, NAFTALIN, & Gynaecology, 1985).
- The development and testing of treatments for healthcare delivery that are effective, safe, timely, efficient, equitable, and patient-centred can be a complex process. It involves understanding and considering the interplay of multiple factors that impact the treatment. In order to gain a comprehensive understanding of how these factors affect healthcare delivery, it is necessary to consult with various stakeholders, including patients, healthcare providers, and policymakers, and employ a variety of study techniques such as data analysis, surveys, and clinical trials. By doing so, we can ensure that treatment is optimized and meets the diverse needs of patients (Taplin et al., 2012).

1.3.5 Challenges in prevention of cervical cancer

- With 6,04,000 new cases expected in 2020, cervical cancer ranks fourth among cancers that affect women worldwide. In low- and middle-income nations, 342 000 cervical cancer-related fatalities occurred, accounting for around 90% of the deaths. Sub-Saharan Africa (SSA), Central America, and South-East Asia have the highest incidence and fatality rates of cervical cancer. The disparities in access to immunisation, screening, and treatment facilities, risk factors like HIV prevalence, and social and economic determinants including sex, gender bias, and poverty are all linked to regional variations in the incidence of cervical cancer (WHO).
- 511.4 million women in India who are 15 years of age or older are at risk of getting cervical cancer. Based on current figures, 123907 women are diagnosed with cervical cancer annually, and 77348 of them pass away from the illness. In India, cervical cancer

is the second most common disease among women and the second most common cancer among women aged 15 to 44. It is estimated that 5.0% of women in the general population are infected with HPV-16/18 at any given moment, and HPVs 16 or 18 are responsible for 83.2% of invasive cervical cancer cases (Bruni L, 2023).

- It is alarming to note that many people lack awareness and have a negative attitude towards preventing cervical cancer. This underscores the need for public health services to take urgent and intensive measures to increase awareness and implement interventions aimed at eliminating this highly preventable cancer (Dhillon et al., 2018).
- Reducing the worldwide burden of cervical cancer will be greatly aided by successful cervical cancer prevention in India. It is essential to educate the general population about cervical cancer, including its risk factors and preventive measures. This education should aim to reduce psychosocial barriers and misconceptions about cervical cancer and its prevention. For instance, it is crucial to dispel the misconception that screening is unnecessary in the absence of symptoms or required only for women with multiple sexual partners (Veerakumar, Kar, & promotion, 2017).
- Educational programs should also consider the role of socioeconomic status in the progression of cervical cancer. Empowering women to find resources and make informed decisions to access healthcare services is vital. As more people become aware of cervical cancer, they are likely to seek preventive measures and facilities for early detection. This demand for prevention would force the public health system to improve facilities for prevention and early detection (J. V. Thulaseedharan, Frie, & Sankaranarayanan, 2019).
- The possibility of eliminating cervical cancer is a powerful concept that can inspire investments in effective cervical cancer prevention in public health services (Nigam, Saxena, Acharya, Mishra, & Batra, 2014).