CHAPTER – III

Renal Profile, Liver Profile, Oxidative Stress and Antioxidants Status in Breast Cancer, Cervix Cancer and Ovarian Tumour

Introduction:

The present chapter deals with three types of female malignancies—Breast Cancer (IIIA), Cervix Cancer (IIIB) and Ovarian Tumour (IIIC). Various biochemical parameters, the Renal Profile (Blood Urea, Serum Creatinine and Serum Uric Acid), Liver Profile (Serum Bilirubin, Serum Alkaline Phosphatase, Serum Glutamate Oxaloacetate Transaminase SGOT, Serum Glutamate Pyruvate Transaminase SGPT, Serum Total Protein and Serum Albumin) were evaluated in the test groups. Antioxidant Status (Vitamin A, Reduced Glutathione) and oxidative stress indicators Thiobarbituric Acid Reactive Substances (TBARS) or Malondialdehyde (MDA) and Sensitivity of Erythrocytes to Lipid Peroxidase (SEPH) were studied.

PART- III (A) : BREAST CANCER

Biochemical Parameters in Breast Cancer:

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in females worldwide, accounting for 23% (1.38 million) of the total new cancer cases and 14 % (4,58,400) of the total cancer deaths in 2008. About half the breast cancer cases and 60% of the deaths are estimated to occur in economically developing countries. In general, incidence rates are high in Western and Northern Europe, Australia, New Zealand and North America; intermediate in South America, the Caribbean, and Northern Africa, and low in sub Saharan Africa and Asia (4,5). The factors contributing to this variation in incidence rates largely stem from differences in reproductive and hormonal factors
and the availability of early detection services\textsuperscript{(110,111)}. Reproductive factors that increase risk include a long menstrual history, nulliparity, recent use of postmenopausal hormone therapy or oral contraceptives, and late age at first birth\textsuperscript{(112)}. Alcohol consumption also increases the risk of breast cancer\textsuperscript{(113,114)}.

Incidence rates in some of the Western Countries such as United States, United Kingdom, France and Australia sharply decreased from the beginning of the millennium, partly due to lower use of combined postmenopausal hormone therapy\textsuperscript{(116-121)}. On contrast breast cancer death rates have been decreasing in North America and several European Countries over the past 25 years, largely as a result of early detection through mammography and improved treatment,\textsuperscript{(110,115,122)}. In many African and Asian Countries including Uganda, South Korea and India, incidences and mortality rates have been rising,\textsuperscript{(123,124)} with changes in reproductive patterns, physical inactivity and obesity being the main contributory factors;\textsuperscript{(110,125,126)} increases in breast cancer awareness and screening activity may be partially responsible for the rising incidence in these populations.

Maintaining a healthy body weight, increasing physical activity and minimizing alcohol intake are the best available strategies to reduce the risk of developing breast cancer\textsuperscript{(127)}. Early detections through mammography increase treatment option and save lives. Recommended early detection strategies in these countries include the promotion of awareness of early signs and symptoms and screening by clinical breast examination\textsuperscript{(128)}.

**Incidence and Epidemiology:**

Cancer of the female breast is rarely found before the age of 25 years except in certain familial cases. The incidence increases with age from 1 in 232 in the fourth decade to 1 in 29 in the seventh decade. The overall incidence of breast cancer in the population increased steadily upto
1988 but is stable since then. Observations bearing on the incidence of this disease can be summarized as follows:

1. **Genetic Predisposition:**

A family history is a risk factor for the development of breast cancer, and 5% to 10% of breast cancer is attributable to inheritance of an autosomal dominant gene \(^{(129)}\). The probability of genetic inheritance increases if there are multiple affected relatives and the cancers occur at young ages. As said earlier, two genes BRCA1 and BRCA2, account for the majority of hereditary breast cancer \(^{(130)}, (131)\). However, less than 20% of women with a family history of breast cancer will carry these genes \(^{(132)}, (133)\). Genetic susceptibility due to other genes is much less common. Breast Cancer affects the majority of women with the Li-Franmeni syndrome (multiple sarcoma and carcinomas) which is associated with germ line mutations of the tumour suppressor gene p53. Women with Cowden disease have a 30 to 50% risk of breast cancer by age 50 years and heterozygous cancers for ataxia - telangiectasia (ATM gene) have an 11% risk at the same age.

2. **Increasing Age:**

Breast Cancer is uncommon before age 25 years but then there is a steady rise to the time of menopause followed by a slower rise throughout life. The average age at diagnosis is 64 years.

3. **Proliferative Breast Disease:**

It is associated with an increased risk.

1. Carcinoma of the Contralateral Breast or Endometrium shows increased risk.

2. Radiation Exposure

Women exposed to therapeutic radiation or after bomb exposure have a higher rate of breast cancer. Risk increases with a younger age and higher radiation doses.
4. Geographic Influences:

The incidence of breast cancer varies four fold to seven fold when Asian and other countries are compared with the United States and Northern European Countries having the highest rates.

5. Length of Reproductive Life:
Risk increases with near by menarche and late menopause.

6. Parity:
Breast cancer is more frequent in nulliparous than in multiparous women.

7. Age at First Child:
Risk is increased in women older than 30 years at the time of their first child.

8. Obesity:
There is decreased risk in obese women younger than 40 years owing to the association with an ovulatory cycles and lower progesterone levels late in the cycle. There is increased risk in postmenopausal obese women attributed to synthesis of estrogens in fat depots.

9. Exogenous Estrogens:
The role of postmenopausal hormone replacement therapy or oral contraceptives as risk factors for developing breast cancer remains controversial\(^\text{133}\). Any risk if present, is small.

Etiology and Pathogenesis:
The epidemiologic data cited and studies of mammary tumours in vitro and in experimental animals point to three sets of important influences, in breast cancer.

A) Genetic factors
B) Hormonal influences and
C) Environmental factors
A) Genetic factors:

These are discussed earlier in Genetic Predisposition.

B) Hormonal Influences:

Endogenous estrogen, excess or more accurately, hormonal imbalance, clearly plays a significant role. Many of the risk factors mentioned such as long duration of reproductive life, nulliparity and late age at first child - imply increased exposure to estrogen peaks during the menstrual cycle. Functioning ovarian tumours that elaborate estrogens are associated with breast cancer in postmenopausal women. Mildly increased breast cancer risk has been documented in post-menopausal women with high-normal levels of circulating estrogen \(^{(134)}\).

C) Environmental Factors:

Environmental influences are suggested by the variable incidence of breast cancer in genetically homogenous groups and the geographic differences in prevalence. Historically, breast cancer incidence rates in United States and other Western Countries are four to seven times higher than in Non-Western countries. As Japan and Taiwan have adopted westernization, breast cancer incidences have increased.

Studies do suggest that moderate or heavy alcohol consumption is associated with an increased risk of breast cancer. The role of viruses has been pursued since Bitther's discovery in 1936 that a filterable agent, transmitted through the mother's milk, causes breast cancer in suckling mice \(^{(135)}\). This virus was later identified as Retrovirus. Environmental contaminants such as organochlorine, pesticides may have estrogogenic effects on humans.
Cellular Changes in Breast Cancer Progression:

Specific cellular changes occur in the progression of breast cancer and forms the basis of some of our current views on cancer progression\(^{136,137}\). One of the earliest detectable changes is loss of normal regulation of cell number, resulting in epithelial hyperplasia or sclerosing adenosis. Next, genetic instability occurs in multiple small clonal populations of cells recognizable histologically as atypical hyperplasia. After progression to carcinoma, numerous cellular alterations can be identified, including -

- Increased expression of oncogens (e.g. C-erb-B2, Her2/neu, INT\(_2\), c-ras, c-myc).
- Decreased expression or function of tumour suppressor genes (e.g. NM23, p53, RB)
- Alterations in cell structure (e.g. increased expression of vimentin, decreased expression of fodrin)
- Loss of cell adhesion (e.g. loss of E-cadherin in lobular carcinomas, loss of integrins in poorly differentiated carcinomas)
- Increased expression of cell cycle proteins (e.g. cyclins, ki-67, proliferating cell nuclear antigen)
- Increased expression of angiogenic factors (e.g. vascular endothelial growth factor, fibroblast growth factor), and increased expression of proteases (e.g. cathepsin D, stromelysins)

All of these changes occurring in some but not all cancers, suggesting that the malignant phenotype are due to an accumulation of multiple changes rather than an orderly progression.

Classification and Distribution:

Curiously, carcinoma is more common in the left breast than in the right, in a ratio of 110 : 100. The cancers are bilateral or sequential in the same breast in 4% or more of cases. Among the carcinomas small enough
for their general areas of origin to be identified, approximately 50% arise in
the upper outer quadrant, 10% in each of the remaining quadrants and
about 20% in the central or subaereolar region. The site of origin influences
the pattern of nodal metastasis to a considerable degree. Carcinoma is
divided into noninvasive or in situ carcinoma and invasive carcinomas.

**Figure: 3A-1**

*General Areas of Cancer Origin in Breast*

<table>
<thead>
<tr>
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<th>50%</th>
<th>10%</th>
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*20% Central or subareolar region.*

The most common histologic types of invasive breast carcinomas
are listed in following table.
Table 3 (A) 1

Distribution of Histologic Types of Breast Cancer

<table>
<thead>
<tr>
<th>Histologic Types of Breast Cancer</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>In Situ Carcinoma</td>
<td>15% to 30%</td>
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<tr>
<td>Ductal Carcinoma In Situ (DCIS)</td>
<td>80%</td>
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<tr>
<td>Lobular Carcinoma In Situ</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Invasive Carcinoma</strong></td>
<td><strong>70% to 85%</strong></td>
</tr>
<tr>
<td>Ductal carcinoma (no special type)</td>
<td>79%</td>
</tr>
<tr>
<td>Lobular carcinoma</td>
<td>10%</td>
</tr>
<tr>
<td>Tubular / crioriform Carcinoma</td>
<td>6%</td>
</tr>
<tr>
<td>Colloid (mucinous) Carcinoma</td>
<td>2%</td>
</tr>
<tr>
<td>Medullary Carcinoma</td>
<td>2%</td>
</tr>
<tr>
<td>Papillary</td>
<td>1%</td>
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</table>

Features common to all invasive cancers:

There are additional morphologic features common to all invasive breast carcinomas, whatever the histologic type. As focul lesions, they extend progressively in all directions. In the course of time, they may become adherent to the deep fascia of the chest wall and thus become fixed in position. Extension to the skin may cause not only fixation but also retraction and dimpling of the skin, an important characteristic of malignant growth. At the same, the lymphatic's may become so involved as to block the local area of skin drainage and cause lymphedema and thickening of the skin - this change is known as Peau d' orange.
Spread of the tumour eventually occurs through the lymphohematogenous roots. The path ways of lymphatic dissemination are in all possible directions: Lateral to the axilla, superior to the nodes above the clavical and the neck, medial to the other breast, inferior to the abdominal viscera and lymph nodes, and deep to the nodes within the chest, particularly along the internal mammary arteries. The two most favored directions of drainage are the axillary nodes and the nodes along the internal mammary artery.

**Staging and Clinical Course:**

Breast cancer has been divided into smaller groups to standardize comparisons of results of various therapeutic modalities among clinics and guide treatment. The American Joint Committee on Cancer Staging\(^{(138)}\) divides the clinical stages as follows:

- **Stage 0** - DCIS or LCIS (5-year survival rate 92%)
- **Stage I** - Invasive carcinoma 2cm. or less in size (including carcinoma in situ with microinvasion) without nodal involvement and no distant metastases (5-years survival rate 87%)
- **Stage II** - Invasive carcinoma 5cm. or less in size with involvement but movable axillary nodes and no distant metastasis, or a tumour greater than 5cm. without nodal involvement or distant metastases (5 years survival rate 75%)
- **Stage III** - Breast cancers greater than 5cm. in size with nodal involvement; or any breast cancer with fixed axillary nodes; or any breast cancer with involvement of the ipsilateral internal mammary lymph nodes; or any breast cancer with skin involvement, pectoral and chest wall fixation, oedema, or clinical inflammatory carcinoma, if distant metastases are absent (5 years survival rate 46%)

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- Stage IV - any form of breast cancer with distant metastases (including ipsilateral supraclavicular lymph nodes) (5 years survival rate 13%)

**Clinical course:**

A number of factors influence the prognosis of women with breast cancer without distant metastasis (139) -

1. Lymph node metastases
2. Locally advanced disease
3. Tumour size
4. Histologic subtypes
5. Tumour grade
6. Estrogen and progesterone receptors
7. Lymphovascular invasion
8. Proliferative rate
9. DNA content
10. Expression of oncogenes or loss of expression of tumour suppressor genes
11. Angiogenesis
12. Proteases

Although axillary node status is the single most important prognostic factor, 20% to 30% of patients with histologically negative lymph nodes suffer recurrences and die of their disease within 10 years.

Current therapeutic approaches include local and regional control, using combination of surgery (mastectomy or breast conservation) and postoperative irradiation, and systemic control using hormonal treatment or chemotherapy or both. Axillary node dissection is performed for prognostic purposes, but the axilla can also be adequately treated with radiation alone. Newer therapeutic strategies include inhibition (by pharmacologic agents
or specific antibodies) of membrane-bound growth factor receptors (eg. Her 2/Heu), stromal proteases and angiogenesis (140).

Breast cancer (malignant breast neoplasm) is a type of cancer originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk. Cancers originating from ducts are known as ductal carcinomas; those originating from lobules are known as lobular carcinomas. Breast cancer is a disease of humans and other mammals; while the overwhelming majority of cases in humans are women, men can also sometimes develop breast cancer (141).

Worldwide, breast cancer comprises 22.9% of all cancers (excluding non-melanoma skin cancers) in women (142). In 2008, breast cancer caused 4,58,503 deaths worldwide (13.7% of cancer deaths in women) (142). Breast cancer is more than 100 times more common in women than breast cancer in men, although males tend to have poorer outcomes due to delays in diagnosis (143,144).

Prognosis and survival rates vary greatly depending on cancer type, staging and treatment, and geographical location of the patient. Survival rates in the Western World are very good (144). For instance, overall, more than 8 out of 10 women (84%) in England that are diagnosed with the disease survive it for at least 5 years (145). In the developing countries, however, survival rates are much poorer.

The first noticeable symptom of breast cancer is typically a lump that feels different from the rest of the breast tissue. More than 80% of breast cancer cases are discovered when the woman feels a lump (146). The earliest breast cancers are detected by a mammogram (147). Lumps found in lymph nodes located in the armpits (146) can also indicate breast cancer.

Indications of breast cancer other than a lump may include changes in breast size or shape, skin dimpling, nipple inversion, or spontaneous single-nipple discharge. Pain ("mastodynia") is an unreliable tool in
determining the presence or absence of breast cancer, but may be indicative of other breast health issues \(^{(146,147,148)}\).

Inflammatory breast cancer is a particular type of breast cancer which can pose a substantial diagnostic challenge. Symptoms may resemble a breast inflammation and may include itching, pain, swelling, nipple inversion, warmth and redness throughout the breast, as well as an orange-peel texture to the skin referred to as *peau d'orange*; \(^{(149)}\) the absence of discernible lump delays detection dangerously.

Another reported symptom complex of breast cancer is Paget's disease of the breast. This syndrome presents as eczematoid skin changes such as redness and mild flaking of the nipple skin. As Paget's disease advances, symptoms may include tingling, itching, increased sensitivity, burning, and pain. There may also be discharge from the nipple. Approximately half of women diagnosed with Paget's disease also have a lump in the breast \(^{(150)}\).

In rare cases, what initially appears as a fibroadenoma (hard movable lump) could in fact be a phyllodes tumor. Phyllodes tumors are formed within the stroma (connective tissue) of the breast and contain glandular as well as stromal tissue. Phyllodes tumors are not staged in the usual sense; they are classified on the basis of their appearance under the microscope as benign, borderline, or malignant \(^{(151)}\).

Occasionally, breast cancer presents as metastatic disease, that is, cancer that has spread beyond the original organ. Metastatic breast cancer will cause symptoms that depend on the location of metastasis. Common sites of metastasis include bone, liver, lung and brain \(^{(152)}\). Unexplained weight loss can occasionally herald an occult breast cancer, as can show symptoms of fevers or chills. Bone or joint pains can sometimes be manifestations of metastatic breast cancer, as can jaundice or neurological symptoms. These symptoms are called *non-specific*, meaning they could be manifestations of many other illnesses \(^{(153)}\).
Risk factors:

The primary risk factors for breast cancer are female sex, age, lack of childbearing or breastfeeding, higher hormone levels race, economic status and dietary iodine deficiency.

Lifestyle:

Smoking tobacco may increase the risk of breast cancer. With the greater the amount of smoking and the earlier in life smoking begins, the higher the risk.

In a study of attributable risk and epidemiological factors published in 1995, later age at first birth and not having children accounted for 29.5% of U.S. breast cancer cases, family history of breast cancer accounted for 9.1% and factors correlated with higher income contributed 18.9% of cases. Attempts to explain the increased incidence (but lower mortality) correlated with higher income include epidemiologic observations such as lower birth rates correlated with higher income and better education, possible overdiagnosis and overtreatment because of better access to breast cancer screening, and the postulation of as yet unexplained lifestyle and dietary factors correlated with higher income. In more recent years, research has indicated the impact of diet and other behaviors on breast cancer. These additional risk factors include a high-fat diet, alcohol intake, obesity, and environmental factors such as tobacco use, radiation, endocrine disruptors, and shiftwork. Although the radiation from mammography is a low dose, the cumulative effect can cause cancer.

In addition to the risk factors specified above, demographic and medical risk factors include:

- Personal history of breast cancer: A woman who had breast cancer in one breast has an increased risk of getting a second breast cancer.
- Family history: A woman's risk of breast cancer is higher if her mother, sister, or daughter had breast cancer, the risk becomes significant if at least two close relatives had breast or ovarian
cancer. The risk is higher if her family member got breast cancer before age 40. An Australian study found that having other relatives with breast cancer (in either her mother's or father's family) may also increase a woman's risk of breast cancer and other forms of cancer, including brain and lung cancers\(^\text{(172)}\).

- Certain breast changes: Atypical hyperplasia and lobular carcinoma in situ found in benign breast conditions such as fibrocystic breast changes are correlated with an increased breast cancer risk.

Those with a normal body mass index at age 20 who gained weight as they aged had nearly double the risk of developing breast cancer after menopause in comparison to women who maintained their weight. The average 60-year-old woman's risk of developing breast cancer by age 65 is about 2 percent; her lifetime risk is 13 percent\(^\text{(173)}\).

**Genetics:**

The genes associated with hereditary breast-ovarian cancer syndromes usually increase the risk slightly or moderately; the exception is women and men who are carriers of BRCA mutations. These people have a very high lifetime risk for breast and ovarian cancer, depending on the portion of the proteins where the mutation occurs. Instead of a 12 percent lifetime risk of breast cancer, women with one of these genes have a risk of approximately 60 percent\(^\text{(174)}\).

**Medical conditions:**

There is an association between oral contraceptives and the development of premenopausal breast cancer\(^\text{(175)}\). Whether or not this association is causal is debated and if there is indeed a link the absolute effect is small\(^\text{(176)}\). The abortion–breast cancer hypothesis posits that induced abortion increases the risk of developing breast cancer\(^\text{(177)}\). This hypothesis has been the subject of extensive scientific inquiry which has concluded that abortion does not cause breast cancer\(^\text{(178,179,180)}\).
Pathophysiology:

Figure No. 3(A) 2

An overview of signal transduction pathways involved in apoptosis. Mutations leading to loss of apoptosis can lead to tumorigenesis

Carcinogenesis:

Breast cancer, like other cancers, occurs because of an interaction between the environment and a defective gene. Normal cells divide as many times as needed and stop. They attach to other cells and stay in place in tissues. Cells become cancerous when mutations destroy their ability to stop dividing, to attach to other cells and to stay where they belong. Mutations that can lead to breast cancer have been experimentally linked to estrogen exposure. (181)
Failure of immune surveillance, the removal of malignant cells throughout one's life by the immune system (182), abnormal growth factor signaling in the interaction between stromal cells and epithelial cells can facilitate malignant cell growth (183,184). In breast adipose tissue, overexpression of leptin leads to increased cell proliferation and cancer (185).

In the United States, 10 to 20 percent of patients with breast cancer and patients with ovarian cancer have a first- or second-degree relative with one of these diseases. The familial tendency to develop these cancers is called hereditary breast-ovarian cancer syndrome. The best known of these, the BRCA mutations, confer a lifetime risk of breast cancer of between 60 and 85 percent and a lifetime risk of ovarian cancer of between 15 and 40 percent. Some mutations associated with cancer, such as p53, BRCA1 and BRCA2, occur in mechanisms to correct errors in DNA. These mutations are either inherited or acquired after birth. Presumably, they allow further mutations, which allow uncontrolled division, lack of attachment, and metastasis to distant organs (167,186). However there is strong evidence of residual risk variation that goes well beyond hereditary BRCA gene mutations between carrier families. This is caused by unobserved risk factors (187). This implicates environmental and other causes as triggers for breast cancers. The inherited mutation in BRCA1 or BRCA2 genes can interfere with repair of DNA cross links and DNA double strand breaks (known functions of the encoded protein) (188). Because of this repair deficit, risks from carcinogenic chemicals and ionizing radiation can increase (189). These carcinogens cause DNA damage such as DNA cross links and double strand breaks that often require repairs by pathways containing BRCA1 and BRCA2 (190,191). But it is these repair pathways that can be crippled by inherited mutation. There is evidence that cancer risks increase in mutation carriers exposed to such opportunistic carcinogens (192). Thus risks for cancers may be reduced by avoiding or compensating for carcinogens that exploit the inherited BRCA gene deficiency (193).
However, mutations in BRCA genes account for only 2 to 3 percent of all breast cancers (194). About half of hereditary breast–ovarian cancer syndromes involve unknown genes.

**Classification:**

Breast cancers are classified by several grading systems. Each of these influences the prognosis and can affect treatment response. Description of a breast cancer optimally includes all of these factors.

- **Histopathology.** Breast cancer is usually classified primarily by its histological appearance. Most breast cancers are derived from the epithelium lining the ducts or lobules, and these cancers are classified as ductal or lobular carcinoma. *Carcinoma in situ* is growth of low grade cancerous or precancerous cells within a particular tissue compartment such as the mammary duct without invasion of the surrounding tissue. In contrast, *invasive carcinoma* does not confine itself to the initial tissue compartment (195).

- **Grade.** Grading compares the appearance of the breast cancer cells to the appearance of normal breast tissue. Normal cells in an organ like the breast become differentiated, meaning that they take on specific shapes and forms that reflect their function as part of that organ. Cancerous cells lose that differentiation. In cancer, the cells that would normally line up in an orderly way to make up the milk ducts become disorganized. Cell division becomes uncontrolled. Cell nuclei become less uniform. Pathologists describe cells as well differentiated (low grade), moderately differentiated (intermediate grade), and poorly differentiated (high grade) as the cells progressively lose the features seen in normal breast cells. Poorly differentiated cancers have a worse prognosis.

- **Stage.** Breast cancer staging using the TNM system is based on the size of the tumour (T), whether or not the tumor has spread to the lymph nodes (N) in the armpits, and whether the tumor has
metastasized (M) (i.e. spread to a more distant part of the body).
Larger size, nodal spread, and metastasis have a larger stage number and a worse prognosis.

The main stages are:

- Stage 0 is a pre-cancerous or marker condition, either ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS).
- Stages 1–3 are within the breast or regional lymph nodes.
- Stage 4 is 'metastatic' cancer that has a less favorable prognosis.

**Prevention:**

Exercise may decrease breast cancer risk \(^{(196)}\). Also avoiding alcohol and obesity. Prophylactic bilateral mastectomy may be considered in patients with BRCA1 and BRCA2 mutations \(^{(197,198)}\). A 2007 report concluded that women can somewhat reduce their risk by maintaining a healthy weight, drinking less alcohol, being physically active and breastfeeding their children \(^{(199)}\). Some carcinogens are known to take advantage of deficiencies in processes that depend on normal BRCA1 and BRCA2 function. Avoiding these known carcinogens may reduce risks for BRCA1/2 mutation carriers \(^{(200)}\).

The World Cancer Research Fund estimated that 38% of breast cancer cases in the US are preventable through reducing alcohol intake, increasing physical activity levels and maintaining a healthy weight \(^{(201)}\). It also estimated that 42% of breast cancer cases in the UK could be prevented in this way, as well as 28% in Brazil and 20% in China.

**Screening:**

Breast cancer screening refers to testing otherwise-healthy women for breast cancer in an attempt to achieve an earlier diagnosis. The assumption is that early detection will improve outcomes. A number of
screening test have been employed including: clinical and self breast exams, mammography, genetic screening, ultrasound, and magnetic resonance imaging.

A clinical or self breast exam involves feeling the breast for lumps or other abnormalities. Research evidence does not support the effectiveness of either type of breast exam, because by the time a lump is large enough to be found it is likely to have been growing for several years and will soon be large enough to be found without an examination. Mammographic screening for breast cancer uses x-rays to examine the breast for any uncharacteristic masses or lumps. The Cochrane collaboration in 2011 concluded that mammograms reduce mortality from breast cancer by 15 percent but also result in unnecessary surgery and anxiety, resulting in their view that it is not clear whether mammography screening does more good or harm. Many national organizations recommend regular mammography, nevertheless. For the average woman, the U.S. Preventive Services Task Force recommends mammography every two years in women between the ages of 50 and 74. The Task Force points out that in addition to unnecessary surgery and anxiety, the risks of more frequent mammograms include a small but significant increase in breast cancer induced by radiation.

In women at high risk, such as those with a strong family history of cancer, mammography screening is recommended at an earlier age and additional testing may include genetic screening that tests for the BRCA genes and / or magnetic resonance imaging. Molecular breast imaging is currently under study and may also be an alternative.

The stage of the breast cancer is the most important component of traditional classification methods of breast cancer, because it has a greater effect on the prognosis than the other considerations. Staging takes into consideration size, local involvement, lymph node status and whether metastatic disease is present. The higher the stage at diagnosis, the poorer
the prognosis. The stage is raised by the invasiveness of disease to lymph nodes, chest wall, skin or beyond, and the aggressiveness of the cancer cells. The stage is lowered by the presence of cancer-free zones and close-to-normal cell behaviour (grading). Size is not a factor in staging unless the cancer is invasive. For example, Ductal Carcinoma In Situ (DCIS) involving the entire breast will still be stage zero and consequently an excellent prognosis with a 10 year disease free survival of about 98% (207).

The breast cancer grade is assessed by comparison of the breast cancer cells to normal breast cells. The closer to normal the cancer cells are, the slower their growth and the better the prognosis. If cells are not well differentiated, they will appear immature, will divide more rapidly, and will tend to spread. Well differentiated is given a grade of 1, moderate is grade 2, while poor or undifferentiated is given a higher grade of 3 or 4 (depending upon the scale used). The most widely used grading system is the Nottingham scheme (208).

Epidemiology:

Worldwide, breast cancer is the most common invasive cancer in women. (The most common form of cancer is non-invasive non-melanoma skin cancer; non-invasive cancers are generally easily cured, cause very few deaths, and are routinely excluded from cancer statistics.) Breast cancer comprises 22.9% of invasive cancers in women and 16% of all female cancers (209, 210).

In 2008, breast cancer caused 4,58,503 deaths worldwide (13.7% of cancer deaths in women and 6.0% of all cancer deaths for men and women together) (142). Lung cancer, the second most common cause of cancer-related death in women, caused 12.8% of cancer deaths in women (18.2% of all cancer deaths for men and women together) (142).
Role of Antioxidants:

Reactive oxygen metabolites (ROMs), including superoxide anion (O$_2^-$), hydrogen peroxide (H$_2$O$_2$) and hydroxyl radical (OH), play an important role in carcinogenesis. There are some primary antioxidants such as superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) which protect against cellular and molecular damage caused by the ROMs. Some researchers conducted the present study to determine the rate of O$_2^-$ and H$_2$O$_2$ production, and concentration of malondialdehyde (MDA), as an index of lipid peroxidation, along with the SOD, GPx and CAT activities in 54 breast cancer (BC) patients. Forty-two age- and sex-matched patients with minor surgical problems, who had no history of any neoplastic or breast disorders, were taken as controls. The rate of O$_2^-$ production was significantly higher (p<0.001) in BC patients than controls, irrespective of clinical stages and menopausal status. Similarly, H$_2$O$_2$ production was significantly higher in BC patients, especially in stage III and postmenopausal groups, as compared to the respective controls. MDA concentration was also observed significantly elevated in stage II (p<0.001), stage III (p<0.01), postmenopausal (p < 0.005), and premenopausal (p < 0.02) group as compared to their corresponding controls. SOD and GPx activities were found significantly raised in all the groups (p < 0.001), except the GPx activity was found, with a smaller alteration in stage IV (p < 0.02). On the contrary, CAT activity was found significantly depressed in all the study groups. The maximum depression was observed in stage II (-61.8%). Lower CAT activity in this study may be the effect of higher production of ROMs, particularly O$_2^-$ and OH. SOD and GPx, however, were less affected by these higher ROMs production. The results of this study have shown a higher ROMs production and decreased CAT activity, which support the oxidative stress hypothesis in carcinogenesis. The relatively higher SOD and GPx may be due to the response of increased ROMs production in the blood. However, the higher SOD and GPx
activities may be inadequate to detoxify high levels of H$_2$O$_2$ into H$_2$O leading to the formation of the most dangerous OH radical followed by MDA. Vanderhaeghe L R et al concluded that administration of CAT may be helpful in the management of BC patients. However, further elaborate clinical studies are required to evaluate the role of such antioxidant enzymes in BC management (211).

Kao Hsiung et al studied biochemical markers which included the urinary deoxypurinoline (Dpd), bone specific alkaline phosphates (B-ALP), creatinine, total alkaline phosphates (T-ALP) for assessment of bone metastases in patients with breast cancer. Above parameters were determined in 148 patients who suffered from breast cancer the samples from with or without bone metastasis, and 42 healthy women. For comparison, other biochemical markers, like carcinoembryonic antigen (CEA), CA15-3 and tissue polypeptide antigen (TPA) were also studied. The results showed elevated values with significant difference in urinary Dps/Cre ratio between the control group and breast cancer patients with p<0.05. In advanced stage of breast cancer patients they were higher than in early stage (7.45+3.23), p <0.05) was the level of significance. Serum B-ALP activities increased only in stage 1V(p<0.05) i.e. severe metastases. The results showed that the increase of a bone osteolytic activity took place earlier than of a bone osteoblastic activity in the metastasis of breast cancer patients (212).

Shimosumak et al reported that some biochemical markers of bone turnover are expected to reflect the disease activity of metastasis bone tumour. A panel of bone turnover markers was assessed in similar normocalcemic patients with bone metastasis from breast cancer and 19 breast cancer patients without clinical evidence of bone metastasis. Bone formation was investigated by measuring bone alkaline phosphatase, osteocalcium (OC) and carboxy-terminal polypeptide of type I pro collagen (PIPC). Bone resorption parameters were studied. Significant correlations
were observed between each of bone turnover markers. The mean level of the six bone turnover markers were higher in patients with bone metastasis than those without them and significant was observed except for OC. Clinical usefulness of these markers account for the case and cost effectiveness of the measurement (213).

Simboli-Campbell M et al studied that 1,25- Dihydroxyvitamin D3 (1,25(OH)2(D)3), induces morphological and biochemical markers of apoptosis in MCF - 7 breast cancer cells. D3 (1,25(OH)2(D)3), the active metabolite of vitamin D, is a potent inhibitor of breast cancer cell growth both in vivo and in vitro. T-complement data which documents in vitamin D-mediated growth arrest of MCF-7, they assessed the role of apoptosis in vitamin D-mediated growth arrest of MCF-7 cells. There findings indicate that, in addition to its anti-proliferative effects, 1,25(OH)2(D)3 activates the apoptotic cell death pathway in MCF-7 breast cancer cells.(214)

Li F et al studied Biochemical markers of bone turnover in women with surgically treated carcinoma of the breast. They measured biochemical markers of bone turnover in fasting urine and blood samples obtained from 38 women with previous surgical treatment. Significantly elevated urinary pyridinoline as nmol mmol-1, creatinine (47.5 and 42.5 against 26.3 in normal controls, both P < 0.001) were seen. Deoxypyridinoline (11.9 and 10.5 compared with 6.3, P <0.001 and P = 0.002 respectively) were found with unchanged urinary hydroxyproline, serum alkaline phosphatase and procollagen I carboxyterminal peptide (PIPC). These finding suggest enhanced bone resorption resulting from the humoral osteoclast activating effect of the previous breast cancer or underlying carcinoma recurrence (215).

Moro L et al evaluated Biochemical Markers for detecting bone metastasis in patients with breast cancer. Urinary galactosyl - hydroxylysine and serum alkaline phosphatase were used to monitor bone
resorption and deposition, respectively. The markers were able to predict metastases (216).

Duffy MJ studied Biochemical markers as prognostic indices in breast cancer including histological variables such as tumour size, grade, and axillary node status. In recent years some new potential prognostic markers of a biochemical nature have been described: estradiol receptors, progesterone receptors, epidermal growth factor receptors, erbB-2 proto-oncogene, and certain proteolytic enzymes. None of these new markers excels axillary node status as a prognostic marker. Biochemical markers can, however, be evaluated with use of minimal surgery and may help distinguish the minority of aggressive axillary-node-negative breast cancers (217).

Kasapovic J et al when studied antioxidant status and lipid peroxidation in the blood of breast cancer patients of different ages, it was concluded as follows: Oxidative stress is considered to be implicated in the pathophysiology of breast cancers (218).

The level of lipid hydroperoxides (LP) was measured in blood plasma and the activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR) enzymes, as well as the level of total glutathione (GSH) and SOD protein were measured in blood cells of breast cancer patients and age-matched healthy subjects. Their results showed that breast carcinoma is related to increase of lipid peroxidation in plasma with concomitant decrease of AO defense capacity in blood cells, which becomes more pronounced during aging of the patients. Suppression of SOD activity related to breast cancer is most likely caused by decreased de novo synthesis of this enzyme. Similar patterns of suppression in SOD and CAT activities related to aging were recorded both in controls and patients. Age-related decrease in SOD activity seems not to be caused by altered protein levels of this enzyme.
Suppression of AO enzymes associated with breast cancer and aging is most likely the cause of increased levels of reactive oxygen species (ROS). Their results indicate significant role of oxidative-induced injury in the breast carcinogenesis, particularly during the later stages of aging. Overall data support the importance of endogenous AOs in the etiology of breast cancer across all levels of predicted risk (218).

Rajneesh et al presented study on Lipid peroxidation and antioxidant status in patients with breast cancer) to evaluate the status of lipid peroxidation and antioxidants as biomarkers in human plasma. The extent of lipid peroxidation as evidenced by the formation of Thiobarbituric Acid Reactive Substances (TBARS) and conjugated dienes (CD) as well as the status of the antioxidants SOD, CAT, reduced glutathione (GSH), glutathione peroxidase (GPx) and glutathione S-transferase (GST) were studied. The plasma samples of the breast cancer patients showed enhanced level of lipid peroxidation when compared to the corresponding controls. This was accompanied by a significant elevation in both enzymic and non-enzymic antioxidants. These findings indicate the significant increase in lipid peroxidation as evidenced by the level of TBARS and antioxidant status such as elevated SOD, CAT, GPx, GSH and GST in samples from breast cancer patients compared to controls (219).

Manuela Gago-Dominguez et al studied lipid peroxidation, oxidative stress genes and dietary factors in breast cancer protection. They have recently proposed that lipid peroxidation may be a common mechanistic pathway by which obesity and hypertension lead to increased renal cell cancer risk. During this exercise, they noted a risk factor swap between breast and kidney cancer (oophorectomy and increased parity, detrimental for kidney, beneficial for breast; high blood pressure, detrimental for kidney, beneficial for breast when it occurs during pregnancy; alcohol, beneficial for kidney, detrimental for breast, and so on). They have subsequently proposed the hypothesis that lipid
peroxidation represents a protective mechanism in breast cancer, and reviewed the evidence of the role of lipid peroxidation on established hormonal and non-hormonal factors for breast cancer. Here, they reviewed the evidence in support of lipid peroxidation playing a role in the relationships between dietary factors and breast cancer. Available evidence implicates increased lipid peroxidation products in the anti-carcinogenic effect of suspected protective factors for breast cancer, including soy, marine n-3 fatty acids, green tea, isothiocyanates, and vitamin D and calcium. They also reviewed the epidemiological evidence supporting a modifying effect of oxidative stress genes in dietary factor-breast cancer relationships.

Punnonen K et al studied Antioxidant enzyme activities and oxidative stress in human breast cancer. They have analysed products of lipid peroxidation reactions and activities of antioxidant enzymes in cancerous breast tissue and in corresponding reference tissue. In addition, the serum lipid peroxidation and peroxyl-radical-trapping capacity of breast cancer patients were compared to those of healthy subjects. A total of 23 patients with breast cancer participated in this study. In the cancerous tissue, catalase activity was lower than in the reference tissue, while the activities of superoxide dismutase, glutathione peroxidase and the hexose monophosphate shunt were elevated. The content of thiobarbituric-acid-reactive material was slightly lower in the cancerous tissues, but the levels in serum were found to be elevated in patients with breast cancer. The amounts of conjugated diene double bonds were essentially equal both in the cancerous and in the reference tissue. Moreover, in breast cancer patients the serum levels of diene conjugation and the peroxyl-radical-scavenging capacity did not differ from those measured in healthy subjects. This study indicates that the antioxidant defence system is altered in cancerous breast tissues, but does not support the hypothesis suggesting
that formation of lipid peroxides in the tumour tissue itself is of primary importance in the carcinogenesis \(^{(221)}\).

Gago-Dominguez \textit{M et al} studied role of lipid peroxidation in the epidemiology and prevention of breast cancer. They have proposed a common mechanistic pathway by which obesity and hypertension lead to increased renal cell cancer risk. Their hypothesis posits lipid peroxidation, which is a principal mechanism in rodent renal carcinogenesis, as an intermediate step that leads to a final common pathway shared by numerous observed risks (including obesity, hypertension, smoking, hysterectomy, parity, preeclampsia, diabetes, and analgesics) or protective factors (including oral contraceptive use and alcohol) for renal cell cancer. During this exercise, they have noticed how certain risk factors for renal cell carcinoma are protective for breast cancer and how certain protective factors for renal cell carcinoma increase risk for breast cancer. Parity and oophorectomy, for example, are positively associated with renal cell carcinoma but are negatively associated with breast cancer. Similarly, obesity and hypertension are positively associated with renal cell carcinoma, but obesity is negatively associated with breast cancer in premenopausal women and hypertension during pregnancy is negatively associated with breast cancer. Furthermore, alcohol intake, negatively associated with renal cell carcinoma, is also positively associated with breast cancer. They proposed here the possibility that lipid peroxidation may represent a protective mechanism in breast cancer. Although this runs counter to the conventional view that lipid peroxidation is a process that is harmful and carcinogenic, They present here the chemical and biological rationale, based on epidemiologic and biochemical data, which may deserve further consideration and investigation \(^{(222)}\).

Khanzode \textit{SS et al} studied antioxidant enzymes and lipid peroxidation in different stages of breast cancer \(^{(223)}\). Oxidative stress resulting from an imbalance between pro-oxidants and antioxidants seems
to play an important role in human breast carcinogenesis. There are conflicting results regarding the tissue levels of malondialdehyde (MDA), ascorbic acid and superoxide dismutase SOD in breast cancer patients. Changes in above parameters were observed with the stage wise progression of the disease. MDA and SOD levels were found to be increased gradually from stage I to Stage IV as compared to control group (P<0.001) with maximum rise in stage IV patient. In contrast mean plasma ascorbic acid levels were low in all stages. It has been observed that ascorbic acid deficiency results in accumulation of lipid peroxides, which is a resultant product of lipid peroxidation. This study can be useful to established blood based biochemical markers for diagnosis and monitoring the course of breast cancer (223).
Results and Discussion

Breast cancer or malignant breast neoplasm is a type of cancer originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk (1).

In the present study the kidney function profile and liver function profile, oxidative stress indicators along with levels of antioxidants in breast cancer patients was evaluated. The study population consisted of 50 patients. The age of patients was from 35 year to 65 years.

All the selected patients were screened for breast cancer and who did not undergo any treatment for cancer such as the radiotherapy or chemotherapy. Blood samples were analyzed for renal function tests, liver function tests, vitamin A, reduced glutathione and Thiobarbituric Acid Reactive Substances (TBARS).

The results of the statistical analysis of the biochemical parameters in breast cancer and significant/special cases of breast cancer are summarized in Table No. I, II, III, IV, V and VI and Graph No. 1 to 6.

Table No. 1 shows the results of renal function tests i.e. blood urea, serum creatinine and serum uric acid in studied breast cancer patients. The blood urea level was significantly higher (23.58 ± 5.719 mg/dl) in the patients as compared to the control (20.6 ± 3.410 mg/dl). This may be due to the lack of early detection; the progression of the disease leads to metastases (152). The serum creatinine levels in breast cancer patients were also increased significantly (1.17±0.006mg/dl) against (0.77 ± 0.008 mg/dl) in control patients.

Third parameter of renal function tests, the serum uric acid level correlated with blood urea and serum creatinine, showing elevated values. The serum uric acid levels were elevated (7.25±0.27 mg/dl) in cancer patients against (4.47±0.654 mg/dl) in control. The elevated uric acid has been considered as a secondary phenomenon that is either innocuous or perhaps even beneficial, since uric acid can be an antioxidant. A strong relationship between disease progress and antioxidant was observed (223).
Table II shows the levels of liver function test parameters viz serum alkaline phosphatase, serum glutamate oxaloacetate transaminase SGOT and total proteins in breast cancer and control groups. The serum alkaline phosphatase levels were (8.57 ± 2.126 KAU) against (7.99 ± 0.089 KAU) of test and control groups respectively. The levels are towards the upper limits supporting the occurrence of metastasis resulting in bone resorption. The SGOT levels were significantly higher (12.6±0.884 IU/L) as compared to the control group (10.10 ±1.779  IU/L) (212).

The serum protein levels (5.67 ± 0.055 gm/dl) were to the lower side of the normal range as compared to the control group (7.01±0.165 gm/dl). The studied parameter values correlated with the malfunctioning of the liver due to the metastases occurring from the diseased condition.

Table III depicts the correlation of the antioxidants and breast cancer. The antioxidant studied were vitamin A and reduced glutathione. Vitamin A and reduced glutathione levels showed significant decrease in the mean values of test (7.520±20.960 µg/dl) against ( 37.10±3.674 µg/dl) of the control (vitamin A) and test mean value (12.793±1.664 mg/dl) against (30.16±0.493 mg/dl) of control (reduced glutathione). The antioxidant system contributes towards the inhibition of carcinogenesis (218). Glutathione, acts on multiple levels of the defense system. The thiol group of glutathione participates against deleterious effects of reactive O2 species evolved during biological imbalance as well as cancerous conditions. Decreased glutathione level has most likely a consequent of oxidative stress created by carcinogen and free radical scavenging (218).

The oxidative stress parameter- TBARS were elevated (23.500±17.737 nmol/ml) significantly against the control group mean value of (5.405±7.603 nmol/ml). This may be because of the advanced diseased condition.

Kao Hsiung et al (212) studied biochemical markers such as bone specifically alkaline phosphatase (B-ALP), creatinine, total alkaline phosphatase (T-ALP) for assessment of bone metastases in patients with
breast cancer. The results showed that the increase of a bone osteolytic activity took place earlier than that of a bone osteoblastic activity in the metastatic breast cancer patients.

**Special Cases of Breast Cancer**

There were some few cases (n=10) of breast cancer patients in which Kidney Function Test and Liver Function Test were more pronounced and Reduced Glutathione Levels were decreased. In these noteworthy special cases of breast cancers showing elevated antioxidant values were observed. The results of the statistical analysis of the biochemical parameters in these patients are summarized in table **IV, V and VI**. The renal profile (Table IV) mean values were as follows: blood urea (17.70±0.011 mg/dl) against control (19.60±3.579 mg/dl) serum creatinine (0.87±0.011 mg/dl) against control (0.725±0.008 mg/dl) and serum uric acid mean was (5.285±2.408 mg/dl) against control (4.180±0.588 mg/dl). The blood urea and serum uric acid values were highly significant.

**Table V** shows liver profile of these special cases of breast cancer patients. Significant increase in the serum glutamate oxaloacetate transaminase (SGOT) activity was seen. The mean value for SGOT was (12.80±6.596 IU/L) and control mean value was (9.650±1.807 IU/l). The values were on upper limits and statistically significant. This supports the study that common sites of metastasis in breast cancer patients include bone, liver, lung and brain (152). Serum alkaline phosphatase mean was (7.655±1.852 KAU) as compared to control (7.590±0.095 KAU). These readings support that the osteolytic activity took place earlier than that of bone osteoblastic activity (212). Serum proteins showed a mean of (6.575 ± 0.843 gm/dl) and control as (6.655±0.174 gm/dl).

**Table VI** exhibits the level of antioxidant parameters. Vitamin A levels were significantly decreased in the test group (6.160±25.500 µg/dl) when compared to the control group (35.350±3.620 µg/dl). However, the levels of reduced glutathione were significantly increased in the test group (46.509±19.825 mg/dl) as compared to the control (28.711±0.441 mg/dl).
Shah P (224) studied New Findings on the Role of Glutathione in Cancer. Studies showed that tumour cells have elevated levels of glutathione which confer resistance to Chemotherapy drugs. Our observations support this study that tumour cells in breast cancer have elevated levels of GSH which confer resistance to the carcinogenesis and chemotherapy drugs (205,221,223,224).

TBARS values which are bio indicators of lipid peroxidation and oxidative stress were significantly higher in the above studied malignancy, the mean test group being (22.800±11.889 nmol/ml). The control mean value was (5.305±7.347nmol/ml) (223).

Oxidative stress resulting from an imbalance between pro-oxidants and antioxidants seems to play an important role in human breast carcinogenesis. Khanzode SS et al studied antioxidant enzymes and lipid peroxidation in different stages of breast cancer (223). They showed that the MDA which represents membrane changes, its levels increased significantly with clinical progression of breast cancer. Balance between free radical activity and anti-oxidant defense system becomes an important requirement to prevent the damage of cellular membrane. Similar studied were carried out by Yedekar ME and Nargund MP (225) on free radicals in human diseases and the role of antioxidants. Also Djuric Z, et al’s findings co related the results. Thus increased oxidative stress plays an important role in initiation, promotion and metastasis in breast cancer (225,226).

One exclusive case of breast cancer was studied in the patient diagnosed with cancer of breast (right), within right axilla. The renal profile was within normal limits. Liver profile showed highly elevated values of serum alkaline phosphatase (292 IU/L), SGOT (204 IU/L), SGPT (85IU/L) and serum proteins (8.3 gm/dl) with serum albumin (3.3 gm/dl). These values show liver malfunctioning which might be the cause of elevated activity of the enzymes. This supports that progression in disease leads to the metastases of the organ affected (212).
Mahajan M et al (227) studied oxidative stress and its relationship with Adenosine Deaminase (ADA) activity in various stages of breast cancer. Reactive Oxygen Species (ROS) cause damage to the DNA producing mutations and formation of tumours such as carcinoma of breast. Tumour cells are known to produce ROS at a greater pace than the non-transform cells. Results show that SOD and GSH are important components of antioxidant defense system in human body. Serum SOD activity and GSH levels were significantly low in female patients suffering from breast carcinoma as compared to healthy females. This decrease was associated with significant increase in ADA activity indicating the intense cell proliferation in breast tumours. They concluded that increased oxidative stress is responsible for creating a favourable amount for the tumours to develop (227).

When the effect of antioxidants supplementations in breast cancer patients receiving chemotherapy was studied by Dey Sarkar P. et al (228) it was found that there was a significant increase in the levels of MDA and a fall in antioxidant enzymes SOD and Catalase before chemotherapy. After supplementations for three months, significantly low level of lipid peroxidation product, MDA and rise in antioxidant enzymes was seen. The reduced oxidative stress in group of patients taking antioxidant vitamin D supplementations during chemotherapy was observed (228).

The overall results indicated that renal profile, liver profile, oxidative stress and antioxidant status were affected in breast cancer patients. In special cases there was a pronounced increase in alkaline phosphatase, SGOT and as well as serum proteins, suggesting metastases in these patients.
### VARIOUS PARAMETERS IN BREAST CANCER

#### TABLE I
Kidney Function Test in Breast Cancer

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Breast Cancer</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Urea (mg/dl)</td>
<td>23.58 ± 5.719*</td>
<td>20.6 ± 3.410</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dl)</td>
<td>1.17 ± 0.006*</td>
<td>0.77 ± 0.008</td>
</tr>
<tr>
<td>Serum Uric Acid (mg/dl)</td>
<td>7.25 ± 0.27*</td>
<td>4.47 ± 0.654</td>
</tr>
</tbody>
</table>

#### TABLE II
Liver Function Test in Breast Cancer

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Breast Cancer</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline Phosphatase (KAU)</td>
<td>8.57±2.126</td>
<td>7.99±0.089</td>
</tr>
<tr>
<td>SGOT (IU/L)</td>
<td>12.60±0.884*</td>
<td>10.10±1.779</td>
</tr>
<tr>
<td>Serum Proteins (gm/dl)</td>
<td>5.67±0.055*</td>
<td>7.01±0.165</td>
</tr>
</tbody>
</table>

#### TABLE III
Serum Antioxidants and Oxidative Stress Levels in Breast Cancer

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Breast Cancer</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A (µg/dl)</td>
<td>7.520±20.960*</td>
<td>37.100±3.674</td>
</tr>
<tr>
<td>Reduced Glutathione (mg/dl)</td>
<td>12.793±1.664*</td>
<td>30.16±0.493</td>
</tr>
<tr>
<td>TBARS (nmol/ml)</td>
<td>23.500±17.737*</td>
<td>5.405±7.603</td>
</tr>
</tbody>
</table>

All values are mean with ± standard deviation  **p<0.05 *p<0.01
Graph No. 1

Kidney Function Test in Breast Cancer

Graph No. 2 (A)

Serum Alkaline Phosphatase in Breast Cancer
Graph No. 2 (B)

SGOT in Breast Cancer

Graph No. 2 (C)

Serum Protein Levels in Breast Cancer
Graph No. 3 (A)
Serum Vitamin A Levels in Breast Cancer

Graph No. 3 (B)
Serum Reduced Glutathione Levels in Breast Cancer
Graph No. 3 (C)

Serum TBARS Levels in Breast Cancer

![Graph showing serum TBARS levels in breast cancer and control. The graph indicates a significantly higher level of TBARS in breast cancer (23.5 nmol/ml) compared to the control (5.4 nmol/ml).]
VARIOUS PARAMETERS IN BREAST CANCER
(Special Cases)

**TABLE IV**
Kidney Function Test in Breast Cancer

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Breast Cancer</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Urea (mg/dl)</td>
<td>17.70±3.801**</td>
<td>19.60±3.579</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dl)</td>
<td>0.87±0.011*</td>
<td>0.725±0.008</td>
</tr>
<tr>
<td>Serum Uric Acid (mg/dl)</td>
<td>5.285±2.408**</td>
<td>4.180±0.588</td>
</tr>
</tbody>
</table>

**TABLE V**
Liver Function Test in Breast Cancer

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Breast Cancer</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline Phosphatase (KAU)</td>
<td>7.655±1.852</td>
<td>7.590±0.095</td>
</tr>
<tr>
<td>SGOT (IU/L)</td>
<td>12.800±6.596*</td>
<td>9.650±1.807</td>
</tr>
<tr>
<td>Serum Proteins (gm/dl)</td>
<td>6.575±0.843</td>
<td>6.655±0.174</td>
</tr>
</tbody>
</table>

**TABLE VI**
Antioxidants and Oxidative Stress Levels in Breast Cancer

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Breast Cancer</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A (µg/dl)</td>
<td>6.160±25.500*</td>
<td>35.350±3620</td>
</tr>
<tr>
<td>Reduce Glutathione (mg/dl)</td>
<td>46.509±19.825*</td>
<td>28.711±0.441</td>
</tr>
<tr>
<td>TBARS (nmol/ml)</td>
<td>22.800±11.889*</td>
<td>5.305±7.347</td>
</tr>
</tbody>
</table>

All values are mean with ± standard deviation  **p<0.05   *p<0.01
Graph No. 4
Kidney Function Test in Breast Cancer (Special Cases)

Graph No. 5 (A)
Serum Alkaline Phosphatase Level in Breast Cancer (Special Cases)
Graph No. 5 (B)
SGOT in Breast Cancer (Special Cases)

Graph No. 5 (C)
Serum Protein Level in Breast Cancer (Special Cases)
Graph No. 6 (A)
Serum Vitamin A Level in Breast Cancer (Special Cases)

Graph No. 6 (B)
Serum Reduced Glutathione Level in Breast Cancer (Special Cases)
Graph No. 6 (C)

TBARS Levels in Breast Cancer (Special Cases)

TBARS (nmol/ml.)

Parameters

- Breast Cancer
- Control

nmol/ml

22.8

5.3
PART III-B CERVIX CANCER

Biochemical Parameters in Cervix Cancer:

The cervix is both a sentinel for potentially serious upper genital tract infection and a target for viral and other carcinogens which may lead to invasive carcinoma. The potential threat of cancer, however, is central to Papanicolaou smear screening programs and histologic interpretation of biopsy specimens by the pathologist. Worldwide, cervical carcinoma alone is responsible for about 5% of all cancer deaths in women.

Cervical cancer is the term for a malignant neoplasm arising from cells originating in the cervix uteri. One of the most common symptoms of cervical cancer is abnormal vaginal bleeding, but in some cases there may be no obvious symptoms until the cancer has progressed to an advanced stage \(^{(229)}\). Treatment usually consists of surgery (including local excision) in early stages, and chemotherapy and/or radiotherapy in more advanced stages of the disease.

Intraepithelial and Invasive Squamous Neoplasia:

No form of cancer better documents the remarkable effects of prevention, early diagnosis and curative therapy on the mortality rate than does cancer of the cervix. Fifty years ago, carcinoma of the cervix was the leading cause of cancer deaths in women in the United States, but the death rate has declined by two thirds to its present rank as the eight source of cancer mortality, causing about 4500 deaths annually (behind lung, breast, colon, pancreas, ovary, lymph nodes and blood). In sharp contrast to this reduce mortality, the detection frequency of early cancer and a precancerous condition is high. Much credit for these dramatic gains belongs to the effectiveness of Papanicolaou cytologic test in detecting cervical \(^{(230)}\) precancers and to the accessibility of the cervix to be colposcopy and biopsy.
**Pathogenesis:**

To understand the pathogenesis of cervical cancer it is important to understand the components involved in its development, which have been identified from a series of clinical, epidemiologic, pathologic and molecular studies. Epidemiologic data have long implicated a sexually transmitted agent specifically on the basis of the risk factors for cervical cancer, which include:

- Early age at first intercourse
- Multiple sexual partners
- A male partner with multiple previous sexual partners

Potential risk factors that remain poorly understood include oral contraceptive use, cigarette smoking, parity, family history, associated genital infections and lack of circumcision in the male sexual partner. (231,232)

**Figure 3(B)1**

Cervix in relation to upper part of vagina and posterior portion of uterus.
The early stages of cervical cancer may be completely asymptomatic \((229,233)\). Vaginal bleeding, contact bleeding, or (rarely) a vaginal mass may indicate the presence of malignancy. Also, moderate pain during sexual intercourse and vaginal discharge are symptoms of cervical cancer. In advanced disease, metastases may be present in the abdomen, lungs or elsewhere. Symptoms of advanced cervical cancer may include: loss of appetite, weight loss, fatigue, pelvic pain, back pain, leg pain, swollen legs, heavy bleeding from the vagina, bone fractures, and/or (rarely) leakage of urine or faeces from the vagina (rarely)\(^{(234)}\).

Concerning sexually transmitted agents, Human papillomavirus (HPV) is currently considered an important factor in cervical oncogenesis. This virus is known cause of the sexually transmitted vulvar condyloma acuminate and has been isolated from vulvar and vaginal squamous cell carcinomas. Human papillomavirus (HPV) infection appears to be a necessary factor in the development of almost all cases (90\%) of cervical cancer \(\text{\cite{229,235}}\). HPV vaccines effective against the two strains of this large family of viruses that currently cause approximately 70\% of cases of cervical cancer have been licensed in the U.S, Canada, Australia and the Europe \(\text{\cite{236,237}}\). Since the vaccines only cover some of the cancer causing ("high-risk") types of HPV, women should seek regular Pap smear screening, even after vaccination \(\text{\cite{238}}\).

The evidence does not implicate HPV as the only factor. A high percentage of young women are infected with one or more HPV types during their reproductive years, and only a few develop cancer. Other carcinogens, the immune status of the individual, nutrition and many other factors influence whether the HPV infection remains subclinical (latent), turns into precancerous, or eventually progresses to cancer. In addition some cervical cancers are associated with \(p^{\text{53}}\) mutations, implying other modes of cancer development, including host gene mutation \(\text{\cite{239}}\). Following
The figure explains the role of HPV in cervical carcinogenesis and its impact on the population in the United States.

**Cofactors:**

Other risk factors for cervical cancer include: chlamydia infection, stress and stress-related disorders, dietary factors, hormonal contraception, multiple pregnancies, exposure to the hormonal drug diethylstilbestrol, and family history of cervical cancer. Early age at first intercourse and first pregnancy are also considered risk factors, magnified by early use of oral contraceptives.

A postulated steps in the pathogenesis of cervical neoplasia. Conditions influencing progression are listed at the lower enter of the diagram. The intermediate steps include risks of infection with high-risk HPV types, development of advanced cervical intraepithelial neoplasia (CIN), and progression to invasive carcinoma.
Cervical Intraepithelial Neoplasia:

The reason that papanicalaou smear screening is more effective in preventing cervical cancer is that majority of cancers are preceded by a precancerous lesion. This lesion may exist in the non invasive stage for as long as 20 years and shed abnormal cells that can be detected on cytologic examination (242). These precancerous changes should be viewed with the following in mind -
1. they represent a continuum of morphologic change with relatively indistinct boundaries;
2. they will not invariably progress to cancer and may spontaneously regress, with the risk of persisting or progressing to cancer increasing with the severity of the precancerous change;
3. they are associated with papilloma viruses and high risk HPV types are found in increasing frequency in the higher grade precursors (243,244).

**Morphology:**

The cervix is the narrow portion of the uterus where it joins with the top of the vagina. Most cervical cancers are squamous cell carcinomas, arising in the squamous (flattened) epithelial cells that line the cervix. Adenocarcinoma, arising in glandular epithelial cells is the second most common type. Very rarely, cancer can arise in other types of cells in the cervix.

Invasive cervical carcinoma manifests in three somewhat distinctive patterns:

- fungating (of exoplytic)
- ulcerating and
- infiltrative cancer

The most common variant is the fungating tumour, which produces an obviously neoplastic mass that projects above the surrounding mucosa.

**Precancerous lesions:-**

Cervical intraepithelial neoplasia, the potential precursor to cervical cancer, is often diagnosed on examination of cervical biopsies by a pathologist. For premalignant dysplastic changes, the CIN (cervical intraepithelial neoplasia) grading is used.
The naming and histologic classification of cervical carcinoma precursor lesions has changed many times over the twentieth century. The World Health Organization classification\(^{(245,246)}\) system was descriptive of the lesions, naming them mild, moderate or severe dysplasia or carcinoma in situ (CIS). The term, Cervical Intraepithelial Neoplasia (CIN) was developed to place emphasis on the spectrum of abnormality in these lesions, and to help standardise treatment\(^{(245)}\). It classifies mild dysplasia as CIN1, moderate dysplasia as CIN2, and severe dysplasia and CIS as CIN3. More recently, CIN2 and CIN3 have been combined into CIN2/3. These results are what a pathologist might report from a biopsy. Though squamous cell carcinoma is the cervical cancer with the most incidence, the incidence of adenocarcinoma of the cervix has been increasing in recent decades\(^{(229)}\).
Cervical cancer is staged as follows -

**Table 3 (B) 1**

International Federation of Gynecology and Obstetrics Clinical Staging of Cervical Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>Stage I</td>
<td>Carcinoma is confined to the cervix</td>
</tr>
<tr>
<td>Stage IA1</td>
<td>Microscopic lesion; invasion of the stroma $\leq 3.0$ mm in depth and $\leq 7.0$ mm in width</td>
</tr>
<tr>
<td>Stage IA2</td>
<td>Microscopic lesion; invasion of the stroma $&gt; 3.0$ mm and $\leq 5.0$ mm in depth and $&lt; 7.0$ mm in width</td>
</tr>
<tr>
<td>Stage IB1</td>
<td>Clinical (visible) lesion confined to the cervix and not $&gt; 4.0$ cm in size</td>
</tr>
<tr>
<td>Stage IB2</td>
<td>Similar, but clinical lesion $&gt; 4.0$ cm in size</td>
</tr>
<tr>
<td>Stage II</td>
<td>Carcinoma extends beyond the cervix but not to the pelvic sidewall, or carcinoma involves the vagina but not the lower third</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>No obvious parametrial involvement</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>Obvious parametrial involvement</td>
</tr>
<tr>
<td>Stage III</td>
<td>Carcinoma extends to the pelvic sidewall or to the lower third of the vagina. All cases with hydronephrosis or nonfunctioning kidney should be included, unless known to be due to another cause</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>No extension to the pelvic sidewall, but involvement of the lower third of the vagina</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>Extension to the pelvic sidewall and/or hydronephrosis or nonfunctioning kidney</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Carcinoma extends beyond the true pelvis and involves the bladder or rectal mucosa</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>Involves the bladder or rectal mucosa</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>
Clinical Course:

It is apparent from the preceding discussion that cancer of the cervix and its precursors evolve slowly in the course of many years. During this interval, the only sign of disease may be the shedding of abnormal cells from the cervix. For these reasons, periodic PAP smears should be performed on all women after they become sexually active.

Modes of treatment of squamous neoplasia of the cervix depend on the stage of the neoplasm; treatment of precancerous include Papanicolaou smear follow up (for mild lesions), cryotherapy, laser, wire loop excision, and cone biopsy. Invasive cancer usually result in hysterectomy and; for advance lesion, radiation. With current method of treatments, there is a five year survival rate of above 80% to 90% with stage I, 75% with Stage II, 35% with Stage III and 10% to 15% with stage IV disease. Most patients with stage IV cancer die as a consequence of local extension of the tumour (eg into and about the urinary bladder and ureters, leading to urethral obstruction, pylonephritis and uremia) rather than distant metastases (Refer as per table, page 88).

Prevention:

1. Screening:

The widespread introduction of cervical screening by the Papanicolaou test, or Pap smear for cervical cancer screening has been credited with dramatically reducing the incidence and mortality of cervical cancer in developed countries (233). Pap smear screening every 3-5 years with appropriate follow-up can reduce cervical cancer incidence by up to 80% (247). Abnormal results may suggest the presence of pre cancerous changes allowing examination and possible preventive treatment. If premalignant disease or cervical cancer is detected early, it can be
monitored or treated relatively noninvasively, with little impairment of fertility. Liquid-based cytology is another potential screening method (248).

2. Vaccination:

There are two HPV vaccines (Gardasil and Cervarix) which reduce the risk of cancerous or precancerous changes of the cervix and perineum by about 93% (248). HPV vaccines are typically given to women age 9 to 26 as the vaccine is only effective if given before infection occurs. The vaccines have been shown to be effective for at least 4 (238) to 6 (250) years.

3. Nutrition:

Vitamin A is associated with a lower risk (251) as is vitamin B12, vitamin C, vitamin E, and beta-carotene (252).

Prognosis:

Prognosis depends on the stage of the cancer. With treatment, the 5-year relative survival rate for the earliest stage of invasive cervical cancer is 92%, and the overall (all stages combined) 5-year survival rate is about 72%. These statistics may be improved when applied to women newly diagnosed, bearing in mind that these outcomes may be partly based on the state of treatment five years ago when the women studied were first diagnosed (253). With treatment, 80 to 90% of women with stage I cancer and 50 to 65% of those with stage II cancer are alive 5 years after diagnosis. Only 25 to 35% of women with stage III cancer and 15% or fewer of those with stage IV cancer are alive after 5 years (254).
Epidemiology:

Worldwide, cervical cancer is second most common\(^{(255, 256)}\) and the fifth deadliest cancer in women\(^{(257)}\). It affects about 16 per 100,000 women per year and kills about 9 per 100,000 per year\(^{(258)}\). Approximately 80% of cervical cancers occur in developing countries\(^{(259)}\). Worldwide, in 2008, it was estimated that there were 473,000 cases of cervical cancer, and 253,500 deaths per year\(^{(255, 260)}\).

![Micrograph of a (cervical) adenosquamous carcinoma, a type of cervical cancer. H&E stain.](image)

Figure 3(B)

Treatment:

The treatment of cervical cancer varies worldwide, largely due to large variances in disease burden in developed and developing nations, access to surgeons skilled in radical pelvic surgery, and the emergence of "fertility sparing therapy" in developed nations. Because cervical cancers are radiosensitive, radiation may be used in all stages where surgical options do not exist.

Microinvasive cancer (stage IA) may be treated by hysterectomy (removal of the whole uterus including part of the vagina). For stage IA2, the lymph nodes are removed as well. Alternatives include local surgical...
procedures such as a loop electrical excision procedure (LEEP) or cone biopsy \(^{(261)}\). For 1A1 disease, a cone biopsy (aka *cervical conization*) is considered curative.

Besides screening tests carried as described above, biochemical tests on blood are also studied (as tabulated below). They include the liver function tests, renal function tests, calcium, phosphorus, glucose and lactate dehydrogenase. Elevated values of the parameters in these tests shows metastases of that organ due to the disease that is cervix cancer.
<table>
<thead>
<tr>
<th>Component</th>
<th>An increased value may be due to</th>
<th>A decreased value may be due to</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP</td>
<td>primary bone cancer or cancer that has spread to the bone (bone metastasis) primary liver cancer or cancer that has spread to the liver (liver metastasis) lung cancer pancreatic cancer</td>
<td></td>
</tr>
<tr>
<td>ALT and AST</td>
<td>liver disease liver cancer cancer that has spread to the liver (liver metastasis)</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td>inflammation or infection liver disease kidney disease</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>liver disease or blockage (obstruction) within the liver due to tumours blockage of the bile duct (obstruction) by a tumour cancer in the head of the pancreas</td>
<td></td>
</tr>
<tr>
<td>BUN</td>
<td>kidney disease or blockage (obstruction) of the urinary tract by a tumour</td>
<td>liver disease</td>
</tr>
<tr>
<td>Calcium</td>
<td>parathyroid gland tumours that produce parathyroid hormone tumours that produce parathyroid hormone-like substances or cause bone destruction, such as cancer that has spread to the bone (bone metastasis)</td>
<td>pancreatic disease kidney failure</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Kidney disease or blockage (obstruction) of the urinary tract by a tumour. Cancer can cause the body to use and breakdown more protein.</td>
<td>Liver disease</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Conditions such as diabetes, inflammation of the pancreas, and liver disease.</td>
<td>Pancreatic tumours</td>
</tr>
<tr>
<td>Glucose</td>
<td>Many diseases, including liver disease, many cancers, including advanced cancers, leukemia, lymphoma.</td>
<td>Liver disease</td>
</tr>
<tr>
<td>LDH</td>
<td>Kidney disease, liver disease, tumour lysis syndrome, primary bone cancer or cancer that has spread to the bone (bone metastasis)</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Phosphorus (phosphate)</td>
<td>Leukemia, multiple myeloma, lymphoma, excess cell destruction that may follow chemotherapy and radiation therapy (tumour lysis syndrome).</td>
<td>Hodgkin's lymphoma, multiple myeloma</td>
</tr>
<tr>
<td>Uric acid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results and Discussion

Cancer of Cervix is the most common cancer type found in females. In India most of the deaths occur due to it because of the late diagnosis of the disease. By the time it is recognized, the disease progression is seen vastly. This results in hampering the organ functioning, in cancer of cervix it is the kidney functioning.

Singh Neeta et al (262) put forth a study of HPV and Molecular Markers in Cervical Cancer. Infections with high risk type of Human Papilloma Virus (HPV) are etiological agents for cervical cancer. The immunohistochemical analysis showed HPV presence in 90% of cervical tumours. This correlates with our description about cervix cancer. HPV 16 was the most frequent type detected. They concluded that HPV type detected may be important for oncogenesis and for future evaluation as potential prognostic and therapeutic targets in cervical cancer.

In the present study the kidney function test comprising of blood urea, serum creatinine, and serum uric acid were performed on blood and serum samples of patients diagnosed for cancer of cervix. Serum alkaline phosphatase, serum glutamate oxaloacetate transaminase (SGOT) and serum proteins were analyzed in liver profile. Antioxidant parameters studied were Vitamin A and Reduced Glutathione. Thiobarbituric Acid Reactive Substances TBARS (Malondialdehyde) was evaluated as oxidative stress parameter. The results of renal and liver profile are represented in Graph No. 7 and 8, while those related to antioxidant state and oxidative stress are depicted in graph No. 9 (A to D). The results regarding special cases are represented in graph No. 11 and 12.

Table No. VII shows the renal profile of cervix cancer patients. In the test group of the patients, blood urea values were (20.105±7.25mg/dl) not significantly different than in the control (19.650±2.450 mg/dl). Serum creatinine mean level was on the upper side (1.0 ± 0.025 mg/dl) as
compared to the control \((0.755\pm0.008\text{ mg/dl})\). Serum uric acid, recognized as an antioxidant, was significantly elevated \((7.33\pm3.421\text{ mg/dl})\) against the control group mean value \((4.810\pm0.854\text{ mg/dl})\). The relationship between the elevated serum creatinine and serum uric acid can be correlated with the progression and metastasis of the disease towards kidney in these patients with cancer of cervix (Parameters given in reference table- 3 (B)2.

**Table No. VIII** shows the results of liver function in Cervix cancer patients. Serum alkaline phosphatase \((7.855\pm2.55\text{ KAU})\) and serum protein \((5.200\pm0.080\text{ gm/dl})\) levels were on lower side as compared to the controls \((7.525\pm0.086\text{ KAU})\) and \((6.685\pm0.156\text{ gm/dl})\) respectively. The SGOT \((13.80\pm7.80\text{ IU/L})\) levels were significantly on higher side compared to the control \((9.700 \pm 1.620 \text{ IU/L})\).

**Table IX** shows the levels of antioxidants in the cervix cancer patients. Vitamin A and reduced glutathione mean levels were significantly on lower side, the values being \((13.7\pm3.59 \mu g/dl)\) and \((17.75\pm12.322\mu g/dl)\) against the control mean values \((35.35\pm 3.82 \mu g/dl)\) and \((27.981\pm1.181 \mu g/dl)\) respectively. Oxidative stress parameter, TBARS \((10.35\pm35.48 \text{ nmol/ml})\) levels were elevated as compared to the control levels \((5.3\pm 7.34 \text{ nmol/ml})\). SEPH mean levels were significantly increased \((77.84\pm33.73 \%)\) against the mean control value \((5.2\pm1.0\%)\).

**Special cases of Cervix cancer**

Some particular noteworthy cases of cervix cancer were observed. In these cases kidney functions and liver functions were affected to higher degree and glutathione levels were decreased. The patients showed highly elevated values of the kidney profile. This correlates as mentioned earlier that blockage (obstruction) of the urinary tract by a tumour results in elevated urea level in the patient. Cancer can cause the body to use and breakdown more protein which results in elevated / increased serum
creatinine levels. Increase in the serum uric acid levels suggest excess cell destruction.

Table No. X shows results of renal profile parameter among these patients. There was a significant increase in blood urea (47.4±9.154mg/dl) in test group as compared to the control group (21.0±2.550mg.dl). The mean serum creatinine and serum uric acid values in cancer patients of cervix were (1.80±0.071mg/dl) and (8.92±0.045mg/dl) respectively when compared with the control means as (0.82±0.045 mg/dl) and (4.54±0.963mg/dl); thus displaying significantly higher values in the test group.

Many researchers have reported that elevated kidney function test parameter levels were associated with the metastases due to progression of disease. Ghosh N.K (263) studied drug induced markers of cancer in cervical carcinoma cells and reported the elevation of serum level of CEA undergoing treatment with antitumour drugs the peptide and steroid hormones were quantitated by specific radio immunoassays (RIA) in cultured cells, media and homogenates of tumours tissues. It suggested the proximity on DNA strand of several oncofetal and oncoplacental genes depressed by anti neoplastic drugs. The results may be used to recognize the retention by cancer patient of occult malignancy after radiotherapy or surgery.

The antioxidants-Vitamin A (9.140±1.378 µ/dl) and reduced glutathione (7.780±0.626 mg/dl) mean levels were on lower side in these cervix cancer subjects (Table No. XI) as compared to test mean levels. The oxidative stress parameter TBARS levels were significantly high (20.80±7.596 nmol/ml) as compared to control level (4.81±2.678 nmol/ml).

Jain S K studied increased production of oxygen radicals lead to cellular lipid peroxidation. (264) Frietas J P et al showed that the generation of free radicals inhibit the activity of Superoxide dismutase enzyme leading
to accumulation of superoxide radicals which accelerate the lipid peroxidation, which may lead to damage of the erythrocyte membrane resulting in their haemolysis \(^{(265)}\). Arora M et al observed very lower levels of antioxidant enzymes like Superoxide dismutase SOD, Catalase and Glutathione peroxidase (GSH-Px) and increased lipid peroxidation and cell fragility \(^{(266)}\).

Singh Neelima studied Free Radical Induced Damage, a Myth or Reality \(^{(267)}\). The concept of free radicals injury is a very old (1939) so it is reality that free radicals have been implicated in the etiology of large number of major diseases. They can adversely alter many crucial biological molecules leading to loss of form and functions, such undesirable changes in the body can lead to diseased conditions. This study concluded that the rising and decreasing pattern of antioxidant enzymes could help in the diagnosis of disease. Lipid peroxidation product MDA was found to be increased significantly (p<0.001). This conclusion correlates with our results of MDA / TBARS showing elevated mean levels \(^{(262)}\).

Rana S V et al \(^{(268)}\) studied the liver cell damage by free radicals. Oxidative stress due to free radical generation by metabolism and subsequent lipid peroxidation of hepatocyte membrane may be involved in toxic and drug induced liver injury. There was significant decrease in reduced glutathione levels and significant increased in lipid peroxodation. It was concluded from the present study that the changes in liver enzymes, reduced glutathione and lipid peroxidation may be due to free radical induced damage to liver \(^{(268)}\).

Cervical cancer is one of major cause of oncological mortality in India. Although cancer of cervix (CaCx) is mediated Human Papilloma Virus (HPV) infection but Reactive Oxygen Species (ROS) also play an important role in the initiation and progression of the disease. Jain R et al \(^{(269)}\) did the present study to examine the relation between lipid peroxidation
and enzymatic antioxidant status in CaCx patients. A significant higher level of serum lipid peroxide in the form of MDA (p<0.05) was observed. Significantly lowered activity (p<0.05) of SOD, GPx (glutathione peroxidase) and Catalase in CaCx patients were observed compared to normal healthy subjects. There finding showed that the oxidative stress is induced extensively among CaCx patients. It could be concluded that oxidative stress may be associated with the pathophysiology of cervical carcinoma \(^{(269)}\).

\[\textcircled{6} \textcircled{6} \textcircled{6} \textcircled{6} \textcircled{6}\]
### VARIOUS PARAMETERS IN CERVIX CANCER

#### TABLE NO VII
Kidney Function Tests in Cervix Cancer

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood urea (mg/dl)</td>
<td>20.105±7.251</td>
<td>19.650±2.450</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.0±0.025*</td>
<td>0.755±0.008</td>
</tr>
<tr>
<td>Serum uric acid (mg/dl)</td>
<td>7.33±3.421*</td>
<td>4.810±0.854</td>
</tr>
</tbody>
</table>

#### TABLE NO VIII
Liver Function Tests in Cervix Cancer

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline phosphatase (KAU)</td>
<td>7.855±2.55</td>
<td>7.525±0.086</td>
</tr>
<tr>
<td>SGOT (IU/L)</td>
<td>13.800±4.708*</td>
<td>9.700±1.620</td>
</tr>
<tr>
<td>Serum Proteins (gm/dl)</td>
<td>5.200±0.080*</td>
<td>6.685±0.156</td>
</tr>
</tbody>
</table>

#### TABLE NO IX
Antioxidants and Oxidative Stress Levels in Cervix Cancer

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Breast Cancer</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A (µg/dl)</td>
<td>13.7±3.59*</td>
<td>35.35±3.62</td>
</tr>
<tr>
<td>Reduce Glutathione (mg/dl)</td>
<td>17.75±12.322*</td>
<td>27.981±1.181</td>
</tr>
<tr>
<td>TBARS (nmol/ml)</td>
<td>10.35±35.48*</td>
<td>5.30±7.34</td>
</tr>
<tr>
<td>SEPH (%)</td>
<td>77.84±33.73*</td>
<td>5.2±1.0</td>
</tr>
</tbody>
</table>

All values are mean with ± standard deviation  **P<0.05    * P<0.01
Graph No. 7
Kidney Function Test in Cervix Cancer

![Graph No. 7](image)

Graph No. 8 (A)
Serum Alkaline Phosphatase Level in Cervix Cancer

![Graph No. 8 (A)](image)
Graph No. 8 (B)
SGOT Levels in Cervix Cancer

Graph No. 8 (C)
Serum Protein Levels in Cervix Cancer
Graph No. 9 (A)
Vitamin A in Cervix Cancer

Graph No. 9 (B)
Reduced Glutathione in Cervix Cancer
Graph No. 9 (C)
Serum TBARS in Cervix Cancer

Graph No. 9 (D)
SEPH in Cervix Cancer
### VARIOUS PARAMETERS IN CERVIX CANCER

*(Special Cases)*

#### TABLE NO X

Kidney Function Tests in Cervix Cancer

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood urea (mg/dl)</td>
<td>47.4±9.154*</td>
<td>21.0±2.550</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.80±0.071*</td>
<td>0.82±0.045</td>
</tr>
<tr>
<td>Serum uric acid (mg/dl)</td>
<td>8.92±0.779*</td>
<td>4.54±0.963</td>
</tr>
</tbody>
</table>

#### TABLE NO XI

Antioxidants and oxidative stress Levels in Cervix Cancer

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A (µg/dl)</td>
<td>9.140±1.378*</td>
<td>37.4±2.302</td>
</tr>
<tr>
<td>Reduced glutathione (mg/dl)</td>
<td>7.780±0.626*</td>
<td>28.4±1.140</td>
</tr>
<tr>
<td>TBARS (nmol/ml)</td>
<td>20.800±7.596*</td>
<td>4.810±2.678</td>
</tr>
</tbody>
</table>

*All values are mean with ± standard deviation  **P<0.05   * P<0.01*
Graph No. 10
Kidney Function Test in Cervix Cancer (Special Cases)

Graph No. 11 (A)
Serum Vitamin A Levels in Cervix Cancer (Special Cases)
Graph No. 11 (B)
Serum Reduced Glutathione Levels in Cervix Cancer (Special Cases)

![Graph showing serum reduced glutathione levels in cervix cancer and control groups.]

Graph No. 11 (C)
Serum TBARS Levels in Cervix Cancer (Special Cases)

![Graph showing serum TBARS levels in cervix cancer and control groups.]

---

For detailed values:
- Reduced Glutathione (mg/dl) for Cervix Cancer: 7.78
- Reduced Glutathione (mg/dl) for Control: 28.4
- TBARS (nmol/ml) for Cervix Cancer: 20.8
- TBARS (nmol/ml) for Control: 4.81
PART III - C : OVARIAN TUMOUR

Biochemical Parameters in Ovarian Tumour Patients

Ovarian cancer is a cancerous growth arising from the ovary. Symptoms are frequently very subtle early on and may include: bloating, pelvic pain, difficulty in eating and frequent urination, and are easily confused with other illnesses \(^{(270)}\). More than 90% ovarian cancers are classified as "epithelial" and are believed to arise from epithelium of the ovary. However, some evidence suggests that the fallopian tube could also be the source of some ovarian cancers \(^{(271)}\).

Ovarian cancer is the leading cause of death among gynaecologic malignancies. In 1999, there were 25,200 new ovarian cancers diagnosed and 14,000 deaths from this disease. More than 48% of ovarian cancers occur in women over the age of 65. Most cases of ovarian cancers are diagnosed at advanced stage, with extensive intra-abdominal spread present at the time of initial diagnosis.

Many risk factors have been identified for ovarian cancer. The best documented of these is the relationship between the number of lifetime ovulatory cycles and ovarian cancer risk. High dietary fat consumption, has been implicated as factors that elevate ovarian cancer risk. Genetic influences are also important. About 5% of ovarian cancer patients have a family history of significance. Women who fall into these categories often develop ovarian cancer at a younger age than those who develop sporadic tumors. Cancer family syndrome (Lynch type II) is characterized by nonpolyposis colon cancer and either breast, ovarian or endometrial adenocarcinoma. All these syndromes are transmitted in an autosomal dominant pattern with variable degrees of penetrance.

Several pathologic categories of ovarian tumors exist. Epithelial cancer (adenocarcinoma) accounts for more than 80% of ovarian tumors and has an average age of onset over 40. These malignancies arise from coelomic epithelium; histologic subtypes of epithelial tumors include
serous, mucinous, transitional cell, clear cell, and undifferentiated. Epithelial cancers are assigned grades of 1 to 3; the higher the grade, the less well differentiated the tumor.

Sex cord/stromal tumors arise from mesenchymal tissues and account for about 5% of ovarian cancers. These tumors may occur at any age; subtypes consist of granulosa cell, thecoma, fibroma, and Sertoli-Leydig histologies. Germ cell tumors make up another category. They typically afflict children and adolescents and are relatively rare in postmenopausal women. These tumors account for approximately 15% to 20% of ovarian cancers. Ovarian metastases may arise from other primary cancers such as breast, endometrial, lymphoma, colon, and stomach and may present with signs and symptoms similar to de novo ovarian cancer.

Ovarian cancer often has an insidious onset with nonspecific symptoms, which often results in a delay in diagnosis. Gastrointestinal symptoms are common including dyspepsia, nausea, early satiety, altered bowel habits, eructation, abdominal discomfort, pain, and distension.

Spread of ovarian cancer occurs by capsular invasion, peritoneal seeding and lymphatic infiltration. Peritoneal spread is the most common pattern and includes most peritoneal surfaces with frequent involvement of the omentum and diaphragm. Carcinoma of the uterus and cervix usually disseminate through pelvic lymphatics, whereas ovarian cancer drains to the para-aortic nodal tissue. Distant spread to intrathoracic regions or liver parenchyma may occur when malignant cells are transported via hematogenous routes. Extraovarian spread worsens prognosis. Another prognostic factor is tumour grade, which is usually more important than histologic subtype when forecasting outcome for women with early-stage ovarian epithelial cancers.

**Signs and symptoms:-**

Signs and symptoms of ovarian cancer are frequently absent early on and when they exist they may be subtle. Most women with ovarian cancer report one or more symptoms such as abdominal pain or discomfort,
an abdominal mass, bloating, back pain, urinary urgency, constipation, tiredness and a range of other non-specific symptoms, as well as more specific symptoms such as pelvic pain, abnormal vaginal bleeding or involuntary weight loss (273,274,275). There can be a build-up of fluid (ascites) in the abdominal cavity.

**Cause:**

In most cases, the exact cause of ovarian cancer remains unknown. The risk of developing ovarian cancer appears to be affected by several factors (276). Older women, and in those who have a first or second degree relative with the disease, have an increased risk. Hereditary forms of ovarian cancer can be caused by mutations in specific genes (most notably BRCA1 and BRCA2, but also in genes for hereditary nonpolyposis colorectal cancer). Infertile women and those with a condition called endometriosis, and those who use postmenopausal estrogen replacement therapy are at increased risk. Use of combined oral contraceptive pills is a protective factor (276,277). Early age at first pregnancy, older age of final pregnancy and the use of low dose hormonal contraception have also been shown to have a protective effect. The risk is also lower in women who have had their fallopian tubes blocked surgically (tubal ligation) (277,278). Analysis of 489 high-grade serous ovarian adenocarcinomas found that the p53 gene was mutated in 96% of cases (279). Other genes commonly mutated were NF1, BRCA1, BRCA2, RB1 and cyclin-dependent kinase 12 (CDK12).

It is now believed that tumours of the ovary arise ultimately from one of three ovarian components.

1. The surface coelomic epithelium, which embryologically gives rise to the mullerian epithelial, that is the fallopian tubes (ciliated columnar cells), the endometrial lining (nonciliated columnar cells) or the endocervical glands (mucinous nonciliated cells).
2. The germ cells which migrate to the ovary from the yolk sac and are totipotential; and

3. The stroma of the ovary, which includes the sex cords, forerunners of the endocrine apparatus of the postnatal ovary.

Although some of the specific tumours have distinctive features and are hormonally active, most are nonfunctional and tend to produce relatively mild symptoms until they have reached a large size. Malignant tumours have usually spread outside the ovary by the time a definitive diagnosis is made. Some of these tumours, principally epithelial tumours tend to be bilateral.

**Hormones:**

The relationship between use of oral contraceptives and ovarian cancer was shown in a summary of results of 45 case-control and prospective studies. Cumulatively these studies show a protective effect for ovarian cancers. Women who used oral contraceptives for 10 years had about a 60% reduction in risk of ovarian cancer.

**Risk factors:**

Women who have had children are less likely to develop ovarian cancer than women who have not, and breastfeeding may also reduce the risk of certain types of ovarian cancer. Tubal ligation and hysterectomy reduce the risk and removal of both tubes and ovaries (bilateral salpingo-oophorectomy) dramatically reduces the risk of not only ovarian cancer but breast cancer also \(^{280}\). A study in The Lancet suggests that tubal ligation can reduce the risk of hereditary ovarian cancer by 72 per cent in women who carry the BRCA1 gene \(^{281}\). The use of oral contraceptives (birth control pills) for five years or more decreases the risk of ovarian cancer in later life by 50% \(^{282}\).
Figure 3 (C) 1:
A very large ovarian cancer as seen on CT

Figure 3 (C) 2:
A pathological specimen of ovarian carcinoma.

Figure 3 (C) 3:
A benign tumor of the ovary, discovered during a C-section; this is a 4 cm teratoma

Figure 3 (C) 4
Ovarian adenocarcinoma deposit in the mesentry of the small bowel
Classification:

Ovarian cancer is classified according to the histology of the tumor, obtained in a pathology report. Histology dictates many aspects of clinical treatment, management, and prognosis.

- Surface epithelial-stromal tumour, also known as ovarian epithelial carcinoma, is the most common type of ovarian cancer. It includes serous tumour, endometrioid tumor and mucinous cystadenocarcinoma.

- Sex cord-stromal tumor, including estrogen-producing granulosa cell tumor and virilizing Sertoli-Leydig cell tumor or arrhenoblastoma, accounts for 8% of ovarian cancers.

- Germ cell tumor accounts for approximately 30% of ovarian tumors but only 5% of ovarian cancers, because most germ cell tumors are teratomas and most teratomas are benign. Germ cell tumor tends to occur in young women and girls. The prognosis depends on the specific histology of germ cell tumor, but overall is favourable.

- Mixed tumors, containing elements of more than one of the above classes of tumor histology.

Staging:

Ovarian cancer staging is by the FIGO staging system and uses information obtained after surgery, which can include a total abdominal hysterectomy, removal of (usually) both ovaries and fallopian tubes, (usually) the omentum, and pelvic (peritoneal) washings for cytopathology. The AJCC staging is the same as the FIGO staging. The AJCC staging system describes the extent of the primary Tumor (T), the absence or presence of metastasis to nearby lymph Nodes (N), and the absence or presence of distant Metastasis (M) \(^{(283)}\).

- Stage I — limited to one or both ovaries
- IA — involves one ovary; capsule intact; no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings
- IB — involves both ovaries; capsule intact; no tumor on ovarian surface; negative washings
- IC — tumor limited to ovaries with any of the following: capsule ruptured, tumor on ovarian surface, positive washings

- Stage II — pelvic extension or implants
  - IIA — extension or implants onto uterus or fallopian tube; negative washings
  - IIB — extension or implants onto other pelvic structures; negative washings
  - IIC — pelvic extension or implants with positive peritoneal washings

- Stage III — peritoneal implants outside of the pelvis; or limited to the pelvis with extension to the small bowel or omentum
  - IIIA — microscopic peritoneal metastases beyond pelvis
  - IIIB — macroscopic peritoneal metastases beyond pelvis less than 2 cm in size
  - IIIC — peritoneal metastases beyond pelvis > 2 cm or lymph node metastases

- Stage IV — distant metastases to the liver or outside the peritoneal cavity

Para-aortic lymph node metastases are considered regional lymph nodes (Stage IIIC). As there is only one para-aortic lymph node intervening before the thoracic duct on the right side of the body, the ovarian cancer can rapidly spread to distant sites such as the lung.

The AJCC/TNM staging system includes three categories for ovarian cancer, T, N and M. The T category contains three other
subcategories, T1, T2 and T3, each of them being classified according to the place where the tumor has developed (in one or both ovaries, inside or outside the ovary). The T1 category of ovarian cancer describes ovarian tumors that are confined to the ovaries, and which may affect one or both of them. The sub-subcategory T1a is used to stage cancer that is found in only one ovary, which has left the capsule intact and which cannot be found in the fluid taken from the pelvis. Cancer that has not affected the capsule, is confined to the inside of the ovaries and cannot be found in the fluid taken from the pelvis but has affected both ovaries is staged as T1b. T1c category describes a type of tumor that can affect one or both ovaries, and which has grown through the capsule of an ovary or it is present in the fluid taken from the pelvis. T2 is a more advanced stage of cancer. In this case, the tumor has grown in one or both ovaries and is spread to the uterus, fallopian tubes or other pelvic tissues. Stage T2a is used to describe a cancerous tumor that has spread to the uterus or the fallopian tubes (or both) but which is not present in the fluid taken from the pelvis. Stages T2b and T2c indicate cancer that metastasized to other pelvic tissues than the uterus and fallopian tubes and which cannot be seen in the fluid taken from the pelvis, respectively tumors that spread to any of the pelvic tissues (including uterus and fallopian tubes) but which can also be found in the fluid taken from the pelvis. T3 is the stage used to describe cancer that has spread to the peritoneum. This stage provides information on the size of the metastatic tumors (tumors that are located in other areas of the body, but are caused by ovarian cancer). These tumors can be very small, visible only under the microscope (T3a), visible but not larger than 2 centimeters (T3b) and bigger than 2 centimeters (T3c).

This staging system also uses N categories to describe cancers that have or not spread to nearby lymph nodes. There are only two N categories, N0 which indicates that the cancerous tumors have not affected the lymph nodes, and N1 which indicates the involvement of lymph nodes close to the tumor.
The M categories in the AJCC/TNM staging system provide information on whether the ovarian cancer has metastasized to distant organs such as liver or lungs. M0 indicates that the cancer did not spread to distant organs and M1 category is used for cancer that has spread to other organs of the body.

The AJCC/TNM staging system also contains a Tx and a Nx sub-category which indicates that the extent of the tumor cannot be described because of insufficient data, respectively the involvement of the lymph nodes cannot be described because of the same reason.

The ovarian cancer stages are made up by combining the TNM categories in the following manner:

- **Stage I:** T1+N0+M0
  - IA: T1a+N0+M0
  - IB: T1b+N0+M0
  - IC: T1c+N0+M0

- **Stage II:** T2+N0+M0
  - IIa: T2a+N0+M0
  - IIB: T2b+N0+M0
  - IIC: T2c+N0+M0

- **Stage III:** T3+N0+M0
  - IIIA: T3a+ N0+M0
  - IIIB: T3b+ N0+M0
  - IIIC: T3c+ N0+M0 or Any T+N1+M0

- **Stage IV:** Any T+ Any N+M1

Complications arising in ovarian tumour are spread of the cancer to other organs, progressive function loss of various organs, Ascites (fluid in the abdomen) and Intestinal obstructions These cells can implant on other abdominal (peritoneal) structures, including the uterus, urinary bladder,

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bowel, lining of the bowel wall (omentum) and, less frequently, to the lungs.

**Ovarian Tumours:**

Tumours of the ovary are common form of neoplasia in women (284,285) among cancers of the female genital tract, the incidence of ovarian cancer ranks below only carcinoma of the cervix and the endometrium. Ovarian cancer accounts for 6% of all cancer in the female and is the fifth most common form of cancer in women in the United States (excluding skin cancer).

There are numerous types of ovarian tumours, both benign and malignant. About 80% are benign and these occur mostly in young women between the ages 20 and 45 years. The malignant tumours are more common in older women between the ages 40 and 65 years. Risk factors of ovarian cancer are much less clear. There is higher frequency of carcinoma in unmarried women and in married women with low parity. Gonadal dysgenesis in children is associated with a higher risk of ovarian cancer. The risk of developing ovarian cancer in women 40 to 59 years of age who have taken oral contraceptives, is reduced (286). The most intriguing risk factor is genetic and candidate host genes, which may be altered in susceptible families. (i.e. ovarian cancer genes). Mutations in both BRCA1 (287) and BRCA2 (288) increase susceptibility to ovarian cancer.

Recurrence risk is increased with advanced-stage disease, high tumour grade, and large tumour volume. Refractory cancer carries with it a very poor prognosis. Death usually occurs within 18 to 36 months as the cancer propagates and sprawls out on the splanchnic bed, causing bowel obstruction, nausea, and vomiting. Sepsis often follows bowel or ureteral obstruction. Severe electrolyte abnormalities may result from nutritional deficiencies, renal dysfunction following cisplatin treatment and accumulation of massive peritoneal or pleural effusions.
Results and discussion

Renal profile, liver profile, oxidative stress indicators [malondialdehyde (MDA) or Thiobarbituric Acid Reactive Substances (TBARS)] and the antioxidant status (vitamin A, reduced glutathione) were studied in the patients screened for ovarian tumour.

The results are represented in Table No. XII, XIII, IV and Graph No. 12, 13 and 14.

Table No. XII depicts the renal profile results. Blood urea and serum creatinine in these patients were within normal limits, the mean values being (19.2±0.837mg/dl) and (0.9±0.100mg/dl) against the control values (21.0±2.550mg/dl) and (0.82±0.045mg/dl) respectively. The serum uric acid level was decreased (3.32±0.217mg/dl) as compared to the control (4.54±0.963mg/dl).

Liver profile parameters are shown in Table No. XIII. Both the parameters, serum alkaline phosphatase and serum glutamate oxaloacetate transaminase (SGOT) were elevated significantly. The mean levels were (38.4±2.510 KAU) against the control mean (11.0±1.01KAU) of serum alkaline phosphatase. SGOT mean levels in test were (26.4±4.278 IU/L) and (10.4±1.517IU/L) in the control. Serum total proteins and serum albumin mean levels were (7.46±0.152 gm/dl) and (4.44±0.114gm/dl) respectively. The control mean level for proteins was (6.84±0.550 gm/dl) and for albumin it was (3.16±0.089gm/dl).

Antioxidant levels studied in the ovarian tumour patients are shown in Table No. XIV. Vitamin A mean values (24.6±0.894µg/dl) were decreased as compared to the control group mean levels (37.4±2.302µg/dl). The mean level of a non-enzymatic antioxidant, reduced glutathione was (18.472±1.182mg/dl) against the mean control value.
(28.4±1.740mg/dl). This level is also decreased significantly. The TBARS or (MDA), showed significantly increased mean level values being (22.7±0.332 nmol/ml) against the control mean level values (4.81±2.678 nmol/ml).

Surapaneni K M (289) studied the status of lipid peroxidation, reduced GSH, ascorbic acid, vitamin E and antioxidant enzymes in patients to assess the alteration in the oxidant and antioxidant profile in the patients (289). It was observed that the levels of MDA (the lipid peroxidation product was determined as TBARS) were elevated significantly (p<0.001) in patients compared to controls with the increase in severity and duration of the disease. The activities of antioxidant enzymes viz. SOD, GPX, GST were significantly increased as compared to controls with the progression of the disease. The levels of the non-enzymatic antioxidants such as reduced glutathione, ascorbic acid, vitamin E and catalase activity were significantly decreased as compared to the progression of the disease (289). This studies results co-relate with our results of reduced glutathione and TBARS as stated above.

Cancer of the ovary is the commonest cause of death from gynecological neoplasms. As ovarian tumour is relatively inaccessible, there is a great need for methods to improve early diagnosis and to assist with the management of patients with this disease. Haije WG (290) put forth a study, Biochemical markers in ovarian cancer : Possibilities and limitations. In this presentation the state of the art is discussed with regard to the usefulness of the presently recognized tumour antigens and other of the biochemical markers in ovarian tumour/cancer of the oncodevelopmental antigens, only alpha fetoprotein and chorionic gonadotropin are well established as good markers in tumours with, respectively, yolk sac and trophoblastic elements. In epithelial tumours, which constitute majority of the cyst adenocarcinomas, some tumour products have been described, which may have potential as a marker, for
example, ovarian cancer associated antigens, some glycoprotein glycosyltransferases and carcinoplacental alkaline phosphates (CPAP). Inspite of the studies so far, early detection of ovarian cancer is a goal still to be reached by clinical chemistry in the oncology field.

Van Nagell JR. Jr. et al \(^{(291)}\) studied biochemical markers in the plasma and tumours of patients with gynecologic malignancies. Tumour markers in gynecologic malignancies can be classified generally as oncofetal proteins, carcino-placental proteins and more specific tumour associated antigens, Carcino-embryonic antigen (CEA) is most effective as a tumour marker in mucinous adenocarcinomas of the endocervix and ovary and in keratinizing squamous cell carcinomas of the cervix. In contrast the use of alphafetoprotien (AFP) is limited to patients with germ cell tumours of the ovary and specifically endodermal sinus tumours, β-human chorionic gonadotropin (beta-HCG) malignancies and may be useful in some selected cases with epithelial carcinomas of the ovary. Their study concludes potential future uses of biochemical markers radiolabelled antibodies to tumour-associated antigens and antigen directed chemotherapy \(^{(291)}\).

Similar study was done by Donaldson ES et al \(^{(292)}\). They studied the multiple biochemical markers in patients with gynecologic malignancies. Their findings showed that prior to therapy, over 85% of patients with ovarian or cervical cancer had elevated plasma levels of one or more antigens vig CEA, AFP or HCG. The HCG concentrations were seen to be highest in patients with serous cyst adenocarcinomas of the cervix. Plasma antigen levels were directly related to tumour differentiation and stage of disease and generally retuned to normal eight to twelve weds following therapy. They concluded that affective plasma and tumour antigen screening during initial evaluation of patients with gynecologic tumours may be helpful to identity the most appropriate antigen for immune
detection procedure and for serial plasma determination following therapy (292).

Kiricuta I et al (293) measured the glucose and sialic acid in patients with malignant ovarian tumour. Patients with benign tumours and with advanced ovarian cancer were subjected to primary or secondary surgery (optimal tumour debunking). They suggested the possibility to use these parameter as markers in monitory ovarian cancer evaluation and treatment. (293).

Knight JA et al (294) did comparison of biochemical markers between benign and malignant ovarian cysts. To investigate the presumption that earlier diagnosis of ovarian tumours might lead to an improved outcome, they compared several substances in the fluid of benign and malignant ovarian cysts and the results showed the following: 1) Benign cysts were readily separated from malignant cysts, on the basis of total lactate dehydrogenase activity (LD) and except mucinous cysts by their isoenzyme patterns. 2) CEA levels differed greatly between benign and malignant cysts. 3) Prominent quantitative differences between Roche and Abbott CEA activity were present in both benign and malignant cysts (294).
### VARIOUS PARAMETERS IN OVARIAN TUMOUR

#### TABLE NO XII

Kidney Function Tests in Ovarian Tumour

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood urea (mg/dl)</td>
<td>19.2±0.837</td>
<td>21.0±2.550</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.9±0.100</td>
<td>0.82±0.045</td>
</tr>
<tr>
<td>Serum uric acid (mg/dl)</td>
<td>3.32±0.217*</td>
<td>4.54±0.963</td>
</tr>
</tbody>
</table>

#### TABLE NO XIII

Liver Function Tests in Ovarian Tumour

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline phosphatase (KAU)</td>
<td>38.4±2.510*</td>
<td>11.0±1.0</td>
</tr>
<tr>
<td>SGOT (IU/L)</td>
<td>26.4±4.278*</td>
<td>10.4±1.517</td>
</tr>
<tr>
<td>Serum Proteins (gm/dl)</td>
<td>7.46±0.152**</td>
<td>6.84±0.550</td>
</tr>
<tr>
<td>Serum Albumin (gm/dl)</td>
<td>4.44±0.114*</td>
<td>3.16±0.089</td>
</tr>
</tbody>
</table>

Table No XIV

Serum Antioxidants and Oxidative Stress Levels in Ovarian Tumour

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Breast Cancer</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A (µg/dl)</td>
<td>24.6±0.894</td>
<td>37.4±2.302</td>
</tr>
<tr>
<td>Reduced Glutathione (mg/dl)</td>
<td>18.472±1.182</td>
<td>28.4±1.240</td>
</tr>
<tr>
<td>TBARS (nmol/ml)</td>
<td>22.7±0.332*</td>
<td>4.81±2.678</td>
</tr>
</tbody>
</table>

All values are mean with ± standard deviation **P<0.05 * P<0.01
Graph No. 12

Kidney Function Tests in Ovarian Tumour

Graph No. 13 (A)

Serum Alkaline Phosphatase Levels in Ovarian Tumour

**Parameters**
- Blood urea (mg/dl)
- Serum creatinine (mg/dl)
- Serum uric acid (mg/dl)

**Test**
- Blood urea: 19.2
- Serum creatinine: 0.9
- Serum uric acid: 3.32

**Control**
- Blood urea: 21
- Serum creatinine: 0.82
- Serum uric acid: 4.54

**Parameters**
- Alkaline phosphatase (KAU)

**Test**
- Alkaline phosphatase (KAU): 38.4

**Control**
- Alkaline phosphatase (KAU): 11
Graph No. (13B)

SGOT in Ovarian Tumour

Graph No. (13C)

Serum Total Proteins and Albumin Levels in Ovarian Tumour
Graph No. 14 (A)
Serum Vitamin A Levels in Ovarian Tumour

Graph No. (14B)
Serum Reduced Glutathione Levels in Ovarian Tumour
Graph No. (14C)

TBARS Levels in Ovarian Tumour

TBARS (nmol/ml)

Parameters

Test

Control

0

5

10

15

20

25

22.7

4.81

nmol/ml