Study on Breast Cancer Genetic Risk

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Why in News?

Recently, a study conducted and published by IIT-M reported that 1 in 4 Indian breast cancer patients carries inherited genetic risk variants, most of them outside the well-known BRCA1/2 genes.

- **Cancer –** It is a ***disease caused by uncontrolled cell division*** due to genetic mutations that *disrupt normal growth-regulating genes.*
- These mutations may be –
  - **Somatic –** Acquired during lifetime.
  - **Germline –** Inherited and present in all cells (with increase lifetime risk).
- **Breast Cancer –** It is a disease where abnormal cells in the breast grow uncontrollably.

  India reports around 1.9 lakh new breast cancer cases annually, and over 10% of breast cancers are linked to inherited germline mutations.

- **Types –** Most common are
  - Invasive Ductal Carcinoma (starts in ducts) and
  - Invasive Lobular Carcinoma (starts in glands).
- **Other types -** Ductal Carcinoma in Situ (non-invasive) and less common inflammatory or Paget's disease.
- **Key Symptoms –** Includes a new lump in the breast/armpit, skin changes like dimpling (like small pits), or nipple discharge.
- **Key Genetic Risk Factors – BRCA1 and BRCA2 -** They normally help repair serious DNA damage through a process called homologous recombination repair (HRR).
- When these genes are mutated, the body cannot properly fix broken DNA,

leading to unstable cells that can turn cancerous.

- **Other DNA Repair Genes –** Genes like ATM, PALB2 and CHEK2 also help repair damaged DNA.
- If they do not function properly, DNA errors build up over time, increasing cancer risk.
- **Tumour Suppressor and Cell-Control Genes –** Genes such as MLH1, NF1, TP53, and RB1 normally control cell growth, repair DNA mistakes, and remove damaged cells.
- When they're defective and fail to repair DNA properly, they avoid natural cell death, ultimately leading to cancer development.
- **Treatment – Surgery –** Ranges from removing the tumour to removing the entire breast.
- **Radiation Therapy –** High-energy rays are used to kill cancer cells.
- **Systemic Therapy –** Includes chemotherapy, hormone therapy, and targeted therapies (e.g., HER2 inhibitors).

Key Findings of the Study

- **Inherited Risk –** Study found that *about 1 in 4 breast cancer patients (24.6%) carried an inherited genetic change* that increases cancer risk
- **Risks beyond BRCA Genes –** Although BRCA1 and BRCA2 are widely known breast cancer genes, only **8.35%** of patients had mutations in these genes, showing that ***most inherited risk (67%) was due to other genes beyond BRCA.***
- **Important Non-BRCA Genes Were Identified –** Several other genes were found to be commonly affected:
  - MLH1 (3.5%)
  - NF1 (2.7%)
  - TP53 (1.5%)
  - RB1 (1.5%)
- This means breast cancer risk in Indian patients is more genetically complex than previously believed.

*The **Bharat Cancer Genome Atlas (BCGA)**, led by IIT Madras, is an open-access database that maps the unique genetic patterns of cancers in Indians, aims to improve diagnosis and treatment through precision medicine.*

- **Role of DNA Repair Genes –** Many mutations were found in genes involved in the Homologous Recombination Repair (HRR) pathway.

    - HRR normally helps repair damaged DNA. When this repair system fails, cells accumulate damage and can turn cancerous.
- **Unique or Rare Globally –** The study found **31 HRR variants and 41 other variants** that were absent in global databases but present in Indian patients.
- Hence, some genetic risks may be specific or more common in the Indian population.
- **RECQL, an Emerging Risk Gene –** Two RECQL gene variants were found in **1.7%** of patients.
- Some of these showed higher frequency in South Asians, indicating possible population-specific risk patterns.
- **Testing shift –** Need to re-examine current genetic testing strategies in India, which continue to rely heavily on BRCA-only.
    - Shift to broader multi-gene panel or exome-based germline testing.

Reference

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