Prostate Cancer – a genetic puzzle.

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What are genes?

• Genes carry information in the form of DNA within each cell of the human body.
• Researchers estimate that there are 30,000 different genes in each cell.
• Genes are packaged onto chromosomes. There are 23 pairs of chromosomes in each cell.
• One chromosome of each pair is inherited from the person's father and one from the person's mother.
Male Karyotype (organized profile of a person's chromosomes) 46 XY
The Function of Genes

• Genes control how a cell functions, including how quickly it grows, how often it divides, and how long it lives.
• To control these functions, genes produce proteins that perform specific tasks and act as messengers for the cell.
• Therefore, it is essential that each gene have the correct instructions or "code" for making its protein so that the protein can perform the proper function for the cell.
• The code for these instructions is found in the DNA – the DNA makes us unique.
What role do genes play in cancer?

• Many cancers begin when one or more genes in a cell are mutated (changed), creating an abnormal protein or no protein at all. The information provided by an abnormal protein is different from that of a normal protein, which can cause cells to multiply uncontrollably and become cancerous.
DNA and proteins
Genetic Inheritance

• A person may either be born with a genetic mutation in all of their cells inherited (germline mutation) or acquire a genetic mutation in a single cell during his or her lifetime.

• An acquired mutation is passed on to all cells that develop from that single cell (called a somatic mutation).

• Most prostate cancers (about 75%) are considered sporadic, meaning that the damage to the genes occurs by chance after a person is born and during their lifetime.
• Diseases Arise From Gene Mutations/Damage

**Germline mutations**

- Present in egg or sperm
- Are inheritable
- Cause cancer family syndromes

**Somatic mutations**

- Occur in non-germline tissues
- Are non-heritable and cause sporadic cancers
Genes and prostate cancer

• Prostate cancer that runs in a family, called familial prostate cancer, is less common (about 20%) and occurs because of a combination of shared genes and shared environmental or lifestyle factors. Described as **Acquired or Multifactoral**

• **Hereditary (inherited)** prostate cancer is rare (about 5%) and occurs when gene mutations are passed within a family from one generation to the next.
The Cancer Family History is the Key to risk calculation.

Hereditary cancers account for only a small proportion (approx 5%) of all cancer.
When to Suspect a Hereditary Cancer Syndrome

- Cancer in 2 or more close relatives (on same side of family)
- Early age at diagnosis
- Multiple primary tumours
- Bilateral or multiple rare cancers
- Constellation of tumours consistent with specific cancer syndrome (eg, breast and ovary)
- Evidence of autosomal dominant transmission
What are the chances a mutated gene is inherited?

• Every cell usually has two copies of each gene: one inherited from a person’s mother and one inherited from a person’s father.

• Hereditary prostate cancer appears to follow an **autosomal dominant inheritance** pattern, in which a mutation needs to happen in only one copy of the gene for the person to have an increased risk of getting the disease.

• This means that a parent with a gene mutation may pass on a copy of the normal gene or a copy of the gene with a mutation.
Autosomal dominant inheritance:
In this example a man has two children carrying the affected gene and two unaffected children.

Therefore, a child who has a parent with a mutation has a 50% chance of inheriting that mutation. A brother, sister, or parent of a person who has a gene mutation also has a 50% chance of having the same mutation.
How might a man think prostate cancer runs in his family?

• A man may have an increased risk of developing prostate cancer if two or more close relatives have prostate cancer.

• **Familial** prostate cancer is when two or more first-degree relatives (father, brother, son) are diagnosed with prostate cancer.

• **Inherited** prostate cancer is when a family has any of the following characteristics:
  – Three or more first-degree relatives with prostate cancer
  – Prostate cancer in three generations on the same side of the family
  – Two or more close relatives (father, brother, son, grandfather, uncle, nephew) on the same side of the family diagnosed with prostate cancer before age 55
What is a man's risk if prostate cancer runs in his family?

- If a man has a first-degree relative with prostate cancer, his risk of developing prostate cancer is two to three times higher than the average risk. (Average Risk is 1 in 6 = 15% chance)
- The risk increases as more relatives are diagnosed with prostate cancer.
- African/American men are at 250% more at risk than other men possible reasons include culture, environment, and differences in the biology of the disease
Which inherited genetic mutations raise the risk of prostate cancer?

- There is no one gene that definitively causes prostate cancer, although some genes or gene mutations have been shown to be more common for men with prostate cancer.
- One gene known to increase the risk of prostate cancer, by as much as three times the average risk, is located on chromosome 17. What this gene does when it is not mutated is not known, but men who inherit the mutated version of the gene have a 44% higher prostate-specific antigen (PSA) level.
Hereditary Breast and Ovarian Cancer

• HBOC is associated with mutations in the \textit{BRCA1} and/or \textit{BRCA2} (BRCA stands for BReast CAncer). HBOC is most commonly associated with an increased risk of breast and ovarian cancer in women.
• Men with HBOC also have an increased risk of breast cancer and prostate cancer.
• Mutations in \textit{BRCA1} and \textit{BRCA2} are thought to cause only a small percentage of familial prostate cancers.
• Genetic testing may only be appropriate for families with prostate cancer that may also have HBOC.
Other potential genes

- Other genes that may cause an increased risk of developing prostate cancer include *HPC1*, *HPC2*, *HPCX*, and *CAPB*.
- HPC1 on chromosome 1q24-q25 was first proposed in 1996. Mutations in this locus are noted in some patients with hereditary (families with multiple cases of early-onset) prostate cancer.
- HPC1 revealed the following characteristics:
  - Younger age at diagnosis.
  - Higher tumour grade (Gleason score).
  - More advanced stage at diagnosis.
And more...

- 2003 – The **HPC2/ELAC2 gene** on chromosome 17p11 was identified as a candidate **gene** for hereditary and sporadic prostate cancer (HPC) susceptibility. Ashkenazi Jewish populations

- Hereditary prostate cancer, X-linked **HPCX1** 2000 Icelandic studies

- **Research on these genes is new and it is not clear that they definitely cause prostate cancer.**
The UK Genetic Prostate Cancer Study (UKGPCS) established in 1993 is the largest prostate cancer study of its kind in the UK, involving nearly 170 hospitals, 417 Consultants and 324 research nurses. Based at The Institute of Cancer Research in Surrey, and collaborates with the Royal Marsden NHS Trust.

This was a genome wide association study (a type of case control study of people with or without a specific disease) that aimed to identify variations within the DNA that could be associated with susceptibility to prostate cancer.
The aim is to find genetic changes which are associated with prostate cancer risk.

If they can find alterations in genes that increase the chances of getting prostate cancer, it may be possible in the future to use this knowledge:

To screen other family members to see if they are also at a higher risk of developing prostate cancer.

To develop new prostate cancer treatments for the future.
How the study was done...

• The researchers took blood samples from 1,854 white men in the UK who had prostate cancer showing clinical symptoms. All the men had either been diagnosed by 60 or had a family history of prostate cancer as this meant that they were more likely to have a genetic component to their cancer than men diagnosed later or who had no family history.

• The researchers also obtained blood samples from 1,894 white men aged 50 or over from the UK who did not have prostate cancer. All the men in this control group had low levels of prostate-specific antigen (PSA) and these men were chosen as men with low PSA levels are unlikely to develop prostate cancer.
DNA Analysis

• The DNA was extracted from these blood samples and the researchers looked at 541,129 points in the DNA that were known to have variations to see whether they could find genetic variants that were more or less common in cases than in controls.
• To confirm these results the researchers repeated the tests on DNA from another 3,268 men with prostate cancer and 3,366 controls from the UK and Australia.
• The researchers then looked at the genes near the identified variants and suggested some effects the variants might have.
In the first stage of the study, the researchers found that variants in regions on chromosomes 8 and 17 were associated with risk of prostate cancer, confirming previous findings from other studies.

They also found eight other variants associated with an increased risk of developing prostate cancer, and three variants associated with a reduced risk. Eight of these variants, located in seven different areas, were confirmed by the tests on the second set of cases and controls.
The decision not to introduce prostate cancer screening for all men was partly based on the knowledge that this research was taking place that could identify men at higher risk; this does indicate that there may be a place for a focussed screening programme. Research to assess the effectiveness of any screening programme is now needed.

Conclusion

The genetics of prostate cancer is complex, and there will be many genetic and environmental factors playing a role. Further studies are needed before large-scale genetic screening programmes for susceptibility to prostate cancer become a reality.

Thank you.
Diolch yn fawr.

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