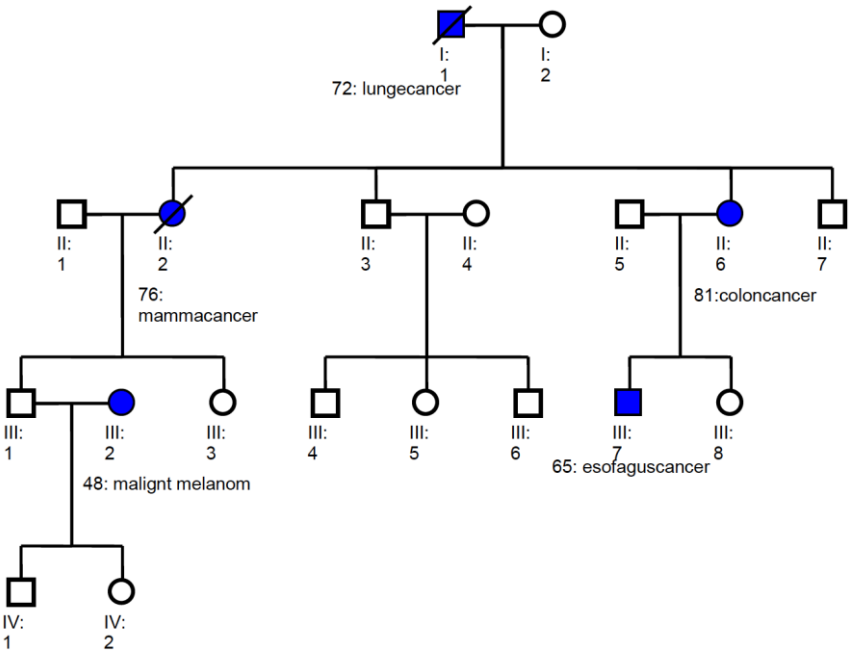
**Exercise 1**

A. Nearly 10% of all cancers are inherited, the majority in an autosomal dominant manner with incomplete penetrance. List what you should look for to Identify this type of Inherited cancer in a pedigree.

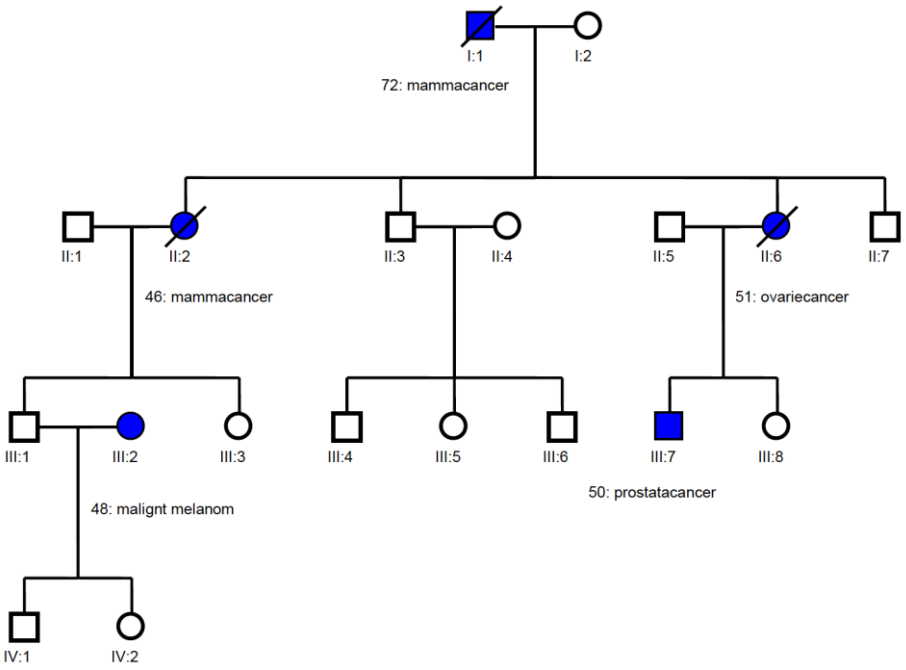
B. Do you think that the cancer cases in Pedigree A are inherited in an autosomal dominant manner with incomplete penetrance or sporadic? Why?

Pedigree A




C. Do you think that the cancer cases in Pedigree B are inherited in an autosomal dominant manner with incomplete penetrance or sporadic? Why?

Pedigree B

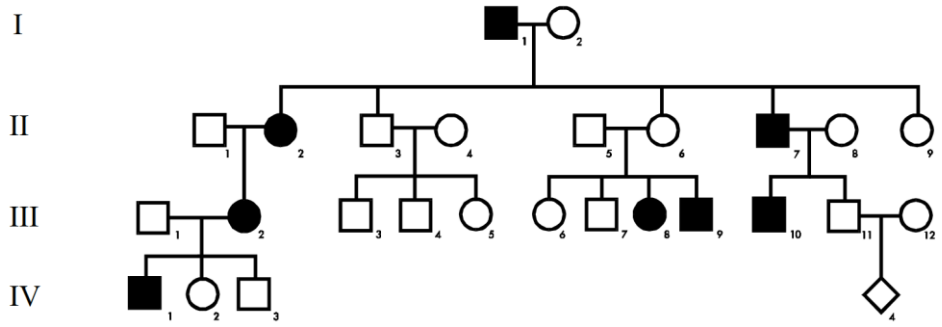



D. How would a pedigree look if the autosomal dominant mutation were of low penetrance and not high?

## Exercise 2

In the following family, a rare monogenic cancer with a penetrance of 85 % is inherited.

A. What is the mode of inheritance of this cancer? Substantiate your answer.




B. What is the probability that IV-3 gets the cancer inherited in this family?

C. Give a probable molecular explanation for the fact that II-6 is healthy, but III-8 has got the cancer.

D. Further analyses in the family have shown that disease phenotype is due to loss of heterozygosity (LOH). What does this tell you about the disease-causing mutation inherited in this family?

## Exercise 3

For today you were assigned to read the article *"Pan-cancer study detects genetic risk variants and shared genetic basis in two large cohorts"*. Please answer the following questions:

A. This study is a meta-analysis of two large cohorts, and Table 1 describes previously unreported genome-wide significant loci from this meta-analysis. Explain what each column means.

B. What do odds ratios (OR) of 0.5, 1, 1.2, and 2 mean?

C. What is the range (min and max) of the OR values?

D. Table 2 lists SNP-based heritability and twin/family-based heritability estimates for each cancer. Do you observe a difference between these estimates?

E. Explain why there might be a difference between SNP-based and twin/family-based heritability estimates.

F. What are the limitations of the study?

## Exercise 4

For today you were assigned to read the article "*The role of polygenic risk and susceptibility genes in breast cancer over the course of life*". Please answer the following questions:

A. They used three different methods to estimate PRS (see Table 1). Which method did they choose, and why? what are the limitations of this type of methods?
B. Using Figure 3, explain how the PRS modifies the risk conferred by having a positive first-degree family history.
C. Explain the association between PRS and contralateral breast cancer.
D. What are the limitations of the study?

## Exercise 5

1) To date 50 to 60 oncogenes have been recognized. HER2 Is an oncogene. Answer the following questions:

A. Describe Its normal function as a pronto-oncogene?
B. What happens when it turns into an oncogene?
C. Describe how the anti-HER2 treatment work?

2) More than 1,000 tumor suppressor genes have been Identified. BRCA1/BRCA2 are tumor suppressor genes. Answer the following questions:

A. Describe their normal function?
B. Describe what can happen if these genes are mutated?
C. Describe how PARP inhibitor treatment work?

3) TP53 is a tumor suppressor gene and the most frequently mutated gene found

A. Describe Its normal function?
B. Describe what can happen if this gene is mutated?

## Exercise 6

Breast cancer is a relatively frequent disease with 3,500 new cases each year in Denmark. 5 - 10% of patients with breast cancer have abnormalities in either the gene *BRCA1* or the gene *BRCA2. BRCA1* and *BRCA2* are located on chromosome 17q21 and 13q12.3, respectively.

A woman with mutation in *BRCA1* has a 40% risk of developing ovarian cancer. Mutations in *BRCA2* increase the risk of breast cancer in men.

If a woman is carrier of a mutation in either *BRCA1* or *BRCA2* she will have a lifetime risk of approximately 80 % for developing breast cancer. Disease debut is often early ( <45 years).

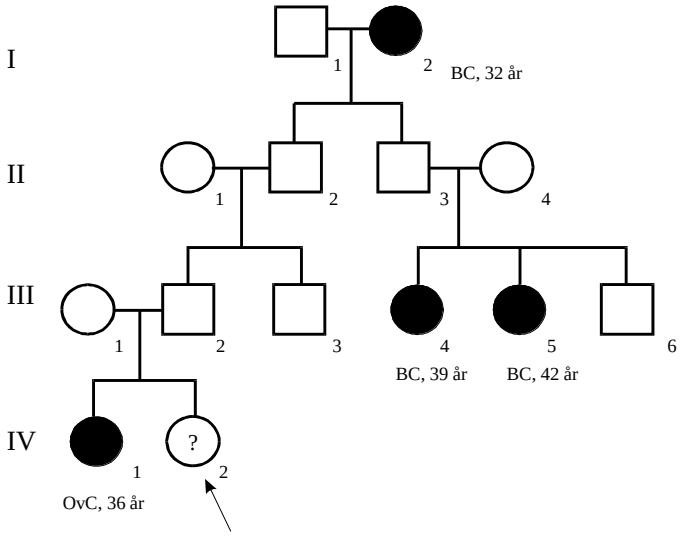
A. What type of cancer-causing gene Is BRCA1 and BRCA2? and what type of Inherence does they follow?

B. A 35-year-old woman (IV-2 in the pedigree shown below) seeks genetic counselling since several family members have breast cancer.
Assess on the basis of the pedigree shown below if the cancer cases in her family may be due to the inheritance of either a *BRCA1* or *BRCA2* mutation, or the cancer cases are caused solely by somatic mutations.

   Note: The person's ages on time of cancer diagnosis are indicated in the figure.

   BC = breast cancer

   OvC = ovarian cancer.



C. A 28-year-old woman (III-2 in the pedigree shown below) seeks medical advice from her GP. She is worried that she may be carrier of a mutation in either the *BRCA1* or *BRCA2* genes, and that the mutation might have been inherited by her now 8-year-old daughter (IV-1). The woman is referred to genetic counselling, where the family's pedigree is constructed (cf. below).

In this family, is it an inherited *BRCA1* or *BRCA2* mutation, or random accumulation of somatic mutations that most likely cause breast cancer?