CGG/ERN GENTURIS/ICARE Monthly Journal Round-Up – April 2024

Translational science

Genomic Profiling Reveals Germline Predisposition and Homologous Recombination Deficiency in Pancreatic Acinar Cell Carcinoma. Mandelker *et al.* 2023. *Journal of Clinical Oncology*. DOI: 10.1200/JCO.23.00561.

- Patients with pancreatic acinar call carcinoma (PACC) have a somewhat better prognosis than patients with pancreatic adenocarcinoma (PDAC), however recurrence rates are high (50-70%) and 5-year survival is low (17%).
- This research carried out somatic and germline analysis of 28,780 patients with cancer, 49 of whom were diagnosed with PACC.
- 36.7% of PACCs had germline pathogenic variants (PVs) in homologous recombination (HR) and DNA damage response (DDR) genes.
    - BRCA1 (n = 1), BRCA2 (n = 12), PALB2 (n = 2), ATM (n = 2), and CHEK2 (n = 1).
- Nearly half (48%) of PACCs with pure acinar cell histology displayed germline pathogenic variants in HR/DDR genes with biallelic loss of the wild type allele in the tumour. The consistent observation of genomic features of HRD in these tumours suggests that these alterations are likely etiologically linked to the development of the cancer.
- Activating BRAF alterations were only detected in patients without germline PVs in HR/DDR genes suggesting two distinct oncogenic driver aetiologies.
- BRCA2 germline pathogenic variants were significantly more frequent in pure PACCs (35%) than in pancreatic adenocarcinoma (3.1%), high-grade serous ovarian carcinoma (5.1%), prostate cancer (3.4%), and breast cancer (2.5%).
- There was no significant differences in age at diagnosis, stage at diagnosis or family history of cancer between patients with or without these germline PVs.
- Patients with HR/DDR PVs had a numerically longer overall survival than patients with wild-type genes (78.2 months v 35.9 months), consistent with previous studies showing improved outcomes for PDAC patients with HR/DDR PVs.

In the clinic

The heterogeneous cancer phenotype of individuals with biallelic germline pathogenic variants in *CHEK2*. Hinić *et al.* 2024. *Genetics in Medicine*. doi: 10.1016/j.gim.2024.101101

- Monoallelic pathogenic variants (PVs) in CHEK2 moderately increase a woman's chance of developing a breast cancer over her lifetime. Frequencies of loss-of-function (LoF) CHEK2 PVs may be as high as 1.5% in the general population, thus occasionally individuals may have biallelic or compound heterozygous CHEK2 PVs.
- Phenotypes were assessed for 294 (210 females, 74 males) individuals with biallelic CHEK2 PVs.

- Most individuals have the two most common founder variants in the Northern- (c.1100del; p.(Thr367MetfsTer15)) and Central- (c.470T>C; p.(Ile157Thr)) European populations.
- 53.4% (157/294) of individuals developed ≥1 (pre)malignancy.
    - 19 with colorectal cancer
    - 19 with thyroid cancer
    - 12 with prostate (pre)malignancies
    - 62.4% of females (131/210) developed ≥1 (pre)malignancy.
    - Median age of onset of first (pre)malignancy was 48 years (46 years for females, 55 years for males).
    - 79.4% of females developed at least one breast (pre)malignancy.
- In line with previous research, differences were observed in cancer risks based on the specific CHEK2 variants.
    - Group 1 = biallelic LoF CHEK2 PVs (such as c.1100del)
    - Group 2 = compound heterozygous CHEK2 PVs
    - Group 3 = biallelic missense CHEK2 PV c.470T>C p.(Ile157Thr)
    - Group 4 = biallelic for other missense CHEK2 PVs
    - Females in group 1 who developed cancer were significantly more likely to be diagnosed with breast cancer, have ≥2 (pre)malignancies and be affected at an earlier age than females in group 3 who developed cancer.
- As one might expect, comparison between individuals with biallelic versus monoallelic LoF CHEK2 PVs showed that homozygous individuals were significantly more likely to develop a non-breast (pre)malignancy such as CRC and ovarian cancer and median age of breast cancer onset was younger.
- Findings suggest that biallelic CHEK2 PVs likely increase the susceptibility to develop multiple malignancies in various tissues, both in females and males.
- The findings are in line with current understanding of the link between CHEK2 PVs and breast cancer, though the findings may be biased as in most cases the development of breast cancer was the likely reason for CHEK2 genetic testing.
- The possible phenotypic differences between LoF PVs and missense PVs may be due to ascertainment bias in genetic testing at various ERN GENTURIS genetic centres e.g. in Poland, where all individuals with cancer are tested for various founder variants in cancer predisposing genes, among which is the CHEK2 c.470T>C p.(Ile157Thr) variant.
- The lack of males identified with biallelic CHEK2 PVs may be due later age of cancer onset and a wide-spectrum of cancer types resulting in lack of diagnostic genetic testing.
- More research is needed to estimate cancer risks for males and females with biallelic CHEK2 PVs and to guide risk management.

Counselling and ethics

MRI Surveillance and Breast Cancer Mortality in Women With BRCA1 and BRCA2 Sequence Variations. Lubinski *et al*. 2024. *JAMA Oncology*. doi:10.1001/jamaoncol.2023.6944

- MRI breast cancer surveillance is used for women with *BRCA1/2* pathogenic variants (PVs) and has been shown to be effective at down-staging breast cancer. This study aimed to understand breast cancer mortality risk in these women.

- Participants completed questionnaires every 2 years to document screening histories, incident cancers and vital status.
    - Data was collected on surgeries (e.g. bilateral oophorectomy), hormone use, and - for those who developed BC – pathology and treatment.
- A total of 2488 women participated in this study: 2004 with BRCA1 sequence variants; 484 with BRCA2 sequence variants
- Among the 1756 women in the MRI surveillance group, there was a mean of 4.7 screening MRI examinations, with 70.6% having had at least 1 MRI examination.
- The majority of women in the no MRI surveillance group (86.7%) had at least 1 screening mammogram.
- During the study follow-up, 13.8% of participants (344 women) developed breast cancer.
    - 148 detected by screening, of which 106 were detected by MRI.
    - 1.4% of participants (35 women) died of breast cancer.
- 364 women opted for risk-reducing mastectomy (RRM) during follow up, 11 of them were diagnosed with BC at the time of surgery but none of the women who underwent RRM during the study died of BC.
- At 20 years, risk of BC mortality was: 3.2% for women in the MRI surveillance group; 14.9% for women who did not undergo MRI surveillance.
- Hazard ratios were used to measure breast cancer mortality associated with MRI surveillance compared with no MRI surveillance.
    - The study found a hazard ratio of 0.23 between groups, which shows that women with MRI surveillance have almost an 80% reduction in mortality compared to women with no MRI surveillance.
    - HRs for breast cancer mortality associated with MRI surveillance were 0.2 for women with BRCA1 and 0.87 for women with BRCA2 PVs.
- The study could therefore conclude that for women with BRCA1 PVs, MRI surveillance was associated with significantly reduced breast cancer mortality compared to no MRI surveillance. Further study is needed to ascertain if MRI surveillance has the same survival benefit for women with BRCA2 PVs.

Bilateral Oophorectomy and All-Cause Mortality in Women With BRCA1 and BRCA2 Sequence Variations. Kotsopoulos *et al*. 2024. *JAMA Oncology*. doi:10.1001/jamaoncol.2023.6937

- This study is an updated and expanded piece of research first reported in 2014 showing oophorectomy reducing all-cause mortality in women with BRCA PVs by 70%.
- 4332 women were enrolled in this international, longitudinal cohort study and completed 2 yearly questionnaires to update exposures and ascertain incident cancers and deaths.
    - Women aged 35-75 with no prior history of cancer, mean age 42.6 years.
    - 67.8% had risk reducing bilateral oophorectomy (at a mean age of 45.4 years).
- 1400 women in the unexposed group (no oophorectomy, oophorectomy performed for ovarian cancer treatment or unilateral oophorectomy) - 8.3% died (116 women) during study follow-up.
- 2932 women in the exposed group (oophorectomy, including where invasive cancer was detected at the time of surgery and where unilateral oophorectomy removed second ovary at a later date than the first) - 3.8% died (112 women) during study follow-up.
- Overall, 851 women developed cancer.

  - 228 women died - 57 of ovarian or fallopian tube cancer, 58 of breast cancer, 16 peritoneal cancer and 97 died of other cancers or causes
- Age-adjusted HR for all-cause mortality was 0.32 (0.28 for BRCA1, 0.43 for BRCA2)
  - This shows that preventative bilateral oophorectomy is associated with around a 70% reduction in all-cause mortality in women with BRCA1 and BRCA2 PVs.

Estimated cumulative all-cause mortality to age 75		
	Oophorectomy at age 35	No oophorectomy
BRCA1	25%	62%
BRCA2	14%	28%

- This study also measured breast cancer-specific mortality.
  - 582 incident cases of breast cancer (BC) during the study period.
- HR for breast cancer incidence associated with oophorectomy was 0.72 – demonstrating about a 30% reduction in BC risk in women with oophorectomy.
  - HRs per gene were 0.79 for BRCA1, 0.55 for BRCA2.
- The overall HR for death from BC with oophorectomy was 0.44 (0.50 for BRCA1 and 0.22 for BRCA2), demonstrating a 55% reduction in breast cancer-specific mortality for women who underwent oophorectomy.

Monthly Journal Round-Up brought to you by:

Izzy Turbin, Principal Genetic Counsellor, Addenbrooke's Hospital, Cambridge
Nancy Whish, STP Trainee Genetic Counsellor, Addenbrooke's Hospital, Cambridge

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