Medullary Thyroid Cancer Risk and Mortality in Carriers of Incidentally Identified MEN2A RET Variants, West et al (2025). *JAMA Network Open,* 8 (6), doi: 10.1001/jamanetworkopen.2025.17937.

Background:

- RET germline pathogenic variants are linked to multiple endocrine neoplasia type 2 (MEN2), which is associated with medullary thyroid cancer. With increasing incidental identification of these variants in asymptomatic individuals outside family screening, these individuals' risk of medullary thyroid cancer and all-cause mortality without intervention remain unknown in this context.

Aim:

To evaluate the risk of medullary thyroid cancer and all-cause mortality in clinically unselected individuals with incidentally identified RET variants and assess whether the risk of medullary thyroid cancer differs from those with clinically ascertained RET variants.

Method:

- This prospective cohort study of 383 914 unrelated individuals from the clinically unselected UK population (UK Biobank, recruited in 2006-2010, with follow-up to June 2023) and 122 640 unrelated individuals from a US health system (Geisinger MyCode cohort, recruited 2004-2020, with follow-up to October 2023) compared medullary thyroid cancer risk in these cohorts with 1078 individuals who were clinically ascertained with suspicion of MEN2 from a UK routine practice.

Results:

- In the UK Biobank cohort, 169 individuals had a pathogenic RET variant (prevalence 0.04%).
- In the US health system-based cohort, 77 individuals had a pathogenic RET variant (prevalence 0.06%).
- The variants were predominantly from the moderate-risk category (per American Thyroid Association guidelines) - 99.4% and 94.8%, respectively.
- P.Val804Met was the predominant moderate-risk variant in both cohorts. The Kaplan-Meier estimated medullary thyroid cancer risk by age 75 in variant carriers in the UK cohort was 2.2% and it was 19.3% in the US health system cohort. In the UK Biobank cohort, most variant carriers (98.2%) did not undergo thyroidectomy and their all-cause mortality by age 75 years was similar to non-carriers (6.1% vs 5.7%), with consistent findings in the US health system cohort.

Conclusions:

- In this cohort study, moderate-risk RET variants were most common in incidental cases. The variants were associated with a substantially lower medullary thyroid cancer risk than clinically ascertained cases. This evidence addresses a current knowledge gap, enabling more informed clinical decision-making.

Reflections for practice:

Here we have further evidence that moderate-risk RET variants identified outside the context of a family history of MEN2 phenotype, increasingly as a result of whole genome sequencing screening programmes or large cancer predisposition gene panels, are associated with a relatively low risk of medullary thyroid cancer compared with clinically-ascertained variants. This should inform how carriers of RET variants, identified incidentally, are managed in the multidisciplinary team clinic setting. This study supports the case for management to be surveillance-led and for thyroidectomy surgery to be secondary to this approach. Furthermore, the late-onset presentation identified in this study means that the addition of RET to any new-born screening gene panels requires careful consideration.

Precision risk stratification of primary gastric cancer after eradication of *H. pylori* by a DNA methylation marker: a multicentre prospective study, Yamada et al (2025). *Gut,* 0, 1-9, doi:10.1136/gutjnl-2025-335039

Background:

- While *Helicobacter pylori* eradication has been effective in reducing the incidence of gastric cancer, a significant residual risk remains—particularly in individuals with persistent mucosal damage, such as open-type atrophic gastritis.
- Current surveillance guidelines, such as biennial endoscopy in Japan, are broadly applied but do not differentiate between individuals with varying levels of risk, leading to a "one-size-fits-all" approach.
- There is growing interest in leveraging molecular and epigenetic changes—especially DNA methylation—as biomarkers of cancer risk. These epigenetic field defects in non-neoplastic tissues can serve as a molecular memory of chronic inflammation and environmental insult.
- The RIMS1 gene, previously identified as a candidate marker of accumulated epigenetic damage, showed promising associations with gastric cancer risk in retrospective analyses. However, prospective validation of such markers in a well-characterized, at-risk cohort had not yet been undertaken.
- This study aimed to determine whether DNA methylation levels at a specific CpG site in the RIMS1 gene could prospectively stratify the risk of primary gastric cancer in individuals post-*H. pylori* eradication, all of whom had endoscopically confirmed open-type gastric atrophy.

Method:

- This was a multicentre, prospective cohort study conducted across 24 hospitals in Japan. Participants were selected based on two key inclusion criteria: prior successful *H. pylori* eradication and the presence of open-type gastric atrophy as assessed by endoscopy.
- A total of 1,624 individuals were enrolled and had available baseline DNA methylation measurements from non-cancerous gastric mucosa biopsies, taken from both the antrum and corpus.
- DNA methylation levels were assessed using bisulphite pyrosequencing, specifically targeting a CpG site in the RIMS1 gene, previously validated as a robust epigenetic risk marker.
- Participants were followed longitudinally for a median duration of 4.05 years, during which they underwent periodic endoscopic surveillance. The primary endpoint was the development of primary gastric cancer.
- For risk stratification, participants were divided into quartiles based on their RIMS1 methylation levels, and incidence rates were compared using Cox proportional hazards models.
- An additional objective was to establish a quantitative methylation threshold that could identify a super-high-risk group warranting more intensive screening. This was defined pragmatically as the group for which the number-needed-to-screen (NNS) to detect one cancer was ≤1,000.

- Multivariable models were adjusted for potential confounders, including age, sex, smoking status, and time since eradication therapy.

Result:

- Over the course of follow-up, 27 individuals (1.7%) developed primary gastric cancer, all confirmed histologically.
- There was a strong, dose-dependent association between RIMS1 methylation levels and gastric cancer incidence.
- Participants in the highest quartile (Q4) of methylation had a gastric cancer incidence rate of 972.8 per 100,000 person-years, compared to 127.1 per 100,000 person-years in the lowest quartile (Q1).
- The unadjusted hazard ratio (HR) for gastric cancer in Q4 vs Q1 was 7.7 (95% CI: 1.8–33.7), indicating a substantial increase in risk.
- After adjustment for age and sex, the HR remained statistically significant at 5.7 (95% CI: 1.3–25.5), supporting the biomarker's predictive value independent of baseline demographic factors.
- An optimal methylation cut-off point of 25.7% was identified as defining a super-high-risk subgroup, meeting the pre-specified NNS threshold. Individuals above this cut-off had significantly higher cancer incidence and may warrant annual (rather than biennial) endoscopic surveillance.
- Importantly, the RIMS1 methylation marker provided meaningful stratification within a clinically homogeneous high-risk population, all of whom had open-type atrophy and eradicated *H. pylori*. This highlights its potential to refine current risk models and tailor clinical follow-up strategies more precisely.

Conclusion:

- This study offers the first prospective validation of an epigenetic biomarker—RIMS1 DNA methylation—for gastric cancer risk stratification following *H. pylori* eradication.
- The findings confirm that elevated DNA methylation levels in non-cancerous gastric mucosa can serve as a molecular surrogate for cumulative environmental damage and inflammation, translating into higher cancer risk.
- A key strength of the study lies in its prospective, multicentre design, large sample size, and clear clinical relevance, particularly in the context of screening programs in countries with high gastric cancer incidence.
- The identification of a quantitative methylation threshold (25.7%) enables the development of practical, risk-based surveillance pathways, potentially moving toward personalized endoscopic screening intervals.
- These results support the incorporation of epigenetic biomarkers into post-*H. pylori* surveillance algorithms, offering an additional layer of risk stratification beyond traditional endoscopic and histological assessment.

Association between risk-reducing surgeries and survival in young BRCA carriers with breast cancer: an international cohort study, Blondeaux et al. (2025), *Lancet Oncology,* https://doi.org/10.1016/S1470-2045(25)00152-4

Introduction

- This retrospective study investigates the association between RRM or RRSO and survival outcomes in young *BRCA* carriers with previously early-onset breast cancer diagnosis at ≤40 years old

Methods

- 5290 eligible patients based on below criteria were included in the analysis.
  - 5,290 patients were included in the RRM analysis and 5,290 in the RRSO analysis
  - 2910/5290 patients underwent RRM, following breast cancer dx
  - 2782/5290 patients underwent RRSO, following breast cancer dx
  - 1804/5290 patients underwent both procedures, following breast cancer dx
- Inclusion criteria
  - Female participants with a diagnosis of invasive breast cancer at 40 years or younger
  - Heterozygotes for pathogenic or likely pathogenic variants in *BRCA1, BRCA2,* or both
- Data was collected from medical records or questionnaires including; breast cancer history and treatment, type of *BRCA* PV or likely pathogenic variant, recurrence data, survival and risk reducing surgeries
- *BRCA* testing, diagnostic and staging, treatment and follow-up were carried out
- For primary breast cancer treatment, patients could have either undergone breast-conserving surgery or mastectomy as the primary surgery.
- The primary objective was to measure the overall survival (length of time from breast cancer diagnosis to death from any cause)
- Secondary objectives
  - Disease free survival (length of time from breast cancer dx to development of an event such as; locoregional or distant recurrence, second primary breast cancer, second primary malignancy or death from any cause)
  - Breast cancer free interval (time from breast cancer dx to one of the events listed above)
  - Incidence of second primary breast cancer
  - Incidence of ovarian or fallopian tube cancer

Results

- RRM
  - Median age at RRM was 36.6 years
  - Median age from BC dx to RRM was 0.8 years
  - Median follow-up after RRM was 5.1 years
  - RRM was associated with better overall survival (17.89 years with RRM vs 16.65 years without RRM). This was irrespective of the specific *BRCA* gene, age at breast cancer dx, tumour subtype, nodal status, chemotherapy use and timing of *BRCA* testing

- Patients undergoing RRM experienced lower incidence of a second primary breast cancer (2.57 events per 100 person-years for no RRM vs 0.32 events for RRM)
- RRM was associated with improved disease free survival

❖ RRSO
- Median age at RRSO was 39.7 years
- Median time from BC dx to RRSO was 3 years
- Median follow up after RRSO was 4.9 years
- RRSO was associated with significantly better overall survival (17.73 years with RRSO vs 16.67 years without RRSO). This association was observed irrespective of age at breast cancer diagnosis, tumour size, nodal status, chemotherapy use, and timing of BRCA testing
- Significant link was observed according to specific BRCA gene and tumour subtype (protective effect of RRSO was more pronounced in *BRCA1* carriers)
- Patients undergoing RRSO experiences lower risk of developing ovarian or fallopian tube cancers (0.37 events per 100 person-year for no RRSO vs 0.05 events for RRSO).
- Fewer second primary breast cancers when patient underwent RRSO and RRSO was associated with improved disease-free survival

❖ Overall (5290 participants)
- At median follow-up of 8.2 years; 13% had died, 36.4% had experienced disease-free survival and 33.1% experienced breast cancer
- No significant interaction between RRSO and RRM on overall survival suggesting that they have independent effects. However, a significant interaction was seen in breast cancer-free interval.

Discussion

- The greater benefit of RRSO in *BRCA1* patients could be explained by lower risk of ovarian cancer among *BRCA2* carriers, the young age of the cohort and the short follow-up
- The interaction between tumour subtypes and survival as different risks of developing subtypes in *BRCA1* and *BRCA2* patients. In patients with hormone receptor positive disease receive endocrine therapy which is known to also reduce risk of secondary breast cancers.

Conclusion

In this cohort of *BRCA* patients with previous breast cancer diagnosis at a young age, RRM and RRSO were both associated with a significant improvement in survival outcomes. This provides evidence for tailored counselling.

Recurrent posterior fossa group A (PFA) ependymoma in a young child with constitutional mismatch repair deficiency (CMMRD), Briggs et al. (2022), *Neuropathology and Applied Neurobiology,* 49(1), https://doi.org/10.1111/nan.12862

- CMMRD is a hereditary cancer syndrome associated with biallelic pathogenic variants in one of four DNA mismatch repair genes, specifically MSH2, MSH6, MLH1, or PMS2. Individuals with CMMRD are at a high risk of multiple malignancies in the CNS, hematological, and gastrointestinal systems.
- These cancers usually have cutaneous features similar to NF1 and are generally early onset, aggressive and rapidly fatal after failing chemotherapy and radiotherapy. However, they respond well to PD1 immune checkpoint inhibition and therefore early diagnosis has a significant impact on clinical management.
- This paper describes a case of a 17-year-old female who was undergoing evaluation for cafe au lait macules, but no pathogenic variants had been identified in NF1 or SPERD1. She presented with vomiting and lethargy, and her head MRI showed a cystic mass in the fourth ventricle. Molecular subgrouping of the tumour tissue suggested it was PFA ependymoma. The presence of cafe au lait macules with ependymoma raised the possibility of NF2 or CMMRD.
- Further investigation of the MMR genes through IHC analysis showed a loss of PMS2 in the tumour and normal tissues. Functional testing performed using low-pass genome sequencing showed high genomic MSI and targeted testing revealed two germline pathogenic PMS2 variants in the patient, a maternally inherited frameshift mutation and a paternally inherited exon 12 deletion. These biallelic mutations confirmed the diagnosis of CMMRD.
- Whole genome sequencing was performed after the second relapse following chemotherapy and radiotherapy, which revealed a higher tumor mutation burden as compared to previously recorded in ependymoma in published literature. Genomic comparison between the primary and recurrent tumours revealed minimal overlap in variants and additional mutations in genes like ARID1A, ASXL1, and CIC.
- Despite absent PD-L1 expression, the tumour microenvironment showed high CD8+ T-cell infiltration, plausibly caused by the high TMB and MSI. Based on the elevated TMB, MSI and presence of T-cells in the microenvironment, the patient was started on an immune checkpoint inhibition treatment and remains clinically well on immunotherapy.

Conclusion

- This was an unusual case as ependymoma has not been previously described in CMMRD. Timely diagnosis is crucial for patients, but the lack of awareness and diagnostic difficulties often lead to delays.
- Therefore, the paper advocates for screening of MMR-deficiency using inexpensive tools like IHC in all pediatric brain tumour cases, followed by genetic and functional testing as required. This is especially important as early diagnosis would have implications for the patient's clinical management and would allow for considerations for immunotherapy instead of conventional therapies.

Monthly Journal Round-Up brought to you by:

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