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Cell-free DNA methylation patterns for early detection and management of ovarian and breast cancers

Despite a myriad of attempts in the last three decades to diagnose ovarian cancer (OC) and breast cancer (BC) earlier, this clinical aim remains a significant challenge. Aberrant methylation patterns of linked CpGs analyzed in DNA fragments shed by cancers into the bloodstream (i.e. cell-free DNA) can provide highly specific signals indicating cancer presence.We analyzed cancerous and non-cancerous tissues using a methylation array or reduced representation bisulfite sequencing to discover the most specific OC and BC methylation patterns. A DNA-methylation-serum-marker panel was developed using targeted ultra-high coverage bisulfite sequencing in 151 women and validated in 250 women with various conditions, particularly those associated with high CA125 levels (endometriosis and other benign pelvic masses), serial samples from 25 patients undergoing neoadjuvant chemotherapy and a nested case control study of 172 UKCTOCS control arm participants which included serum samples up to two years prior to OC diagnosis. In addition, we analysed 419 BC patients (in both pre- and post-adjuvant chemotherapy samples) from SUCCESS (Simultaneous Study of Gemcitabine-Docetaxel Combination adjuvant treatment, as well as Extended Bisphosphonate and Surveillance-Trial) and 925 women (pre-diagnosis) from the UKCTOCS (UK Collaborative Trial of Ovarian Cancer Screening) population cohort, with overall survival and occurrence of incident BC (that may or may not lead to death), respectively, as primary endpoints. The cell-free DNA amount and average fragment size in the serum samples was up to 10 times higher than average published values (based on samples that were immediately processed) due to leakage of DNA from white blood cells as a result of the delay in time with respect to serum separation..For BC, one specific marker was an independent poor prognostic marker in pre-diagnosed with a fatal BC within 3-6 and 6-12 months of sample donation, respectively, with a specificity of 88%. The sensitivity with respect to detecting fatal BC was ~4-fold higher when compared to non-fatal BC.Our data suggests that DNA methylation (DNAme) patterns in cell-free DNA have the potential to detect a proportion of OCs and BCs up to two years in advance of diagnosis and may potentially guide personalized treatment. The prospective use of novel collection vials which stabilize blood cells and reduce background DNA contamination in serum/plasma samples will facilitate clinical implementation of liquid biopsy analyses.

Speaker Biography

Martin Widschwendter is Professor in Women's Cancer, Head of the Department of Women's Cancer, University College London (UCL), and a Consultant Gynaecological Oncology Surgeon at University College London Hospital (UCLH). In 2001, having completed his training in Gynaecology and Obstetrics in Austria, Martin worked at the Norris Comprehensive Cancer Centre in Los Angeles (USA) and spent three years as the lead clinician and surgeon of a large breast cancer centre before embarking on a career at UCL/UCLH from 2005 where he undertook sub-speciality training in gynaecological oncology. As the Head of Department of Women's Cancer at UCL, he established a research group focusing on the role of early detection, risk prediction and prevention of breast and gynaecological cancers with major research programmes. With respect to his clinical work as a Consultant Gynaecological Oncologist, Martin's interest is in complex radical laparoscopic and open surgery.

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