Total DNA methylation as an epigenetic malignancy biomarker of human brain tumors

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Background:
Human brain tumors remain to be a diagnostic and therapeutic challenge for modern medicine. Despite many advanced tools and drugs used, their detection is too late and the treatment ineffective. We describe a simple and reliable method for diagnosis of brain gliomas. It is based on thin layer chromatography quantitative determination of 5-methylcytosine (m^5C) in relation to some of damage products of DNA from tumour tissue and peripheral blood from brain tumor patients.
DNA methylation (m^5C) is a central mechanism of epigenetic inheritance, a unique way to encode information and control cellular differentiation and development processes. Currently there is much evidence that oxidative stress through reactive oxygen species (ROS) play an important role in the etiology and progression of a number of human diseases. m^5C along with other basic components of DNA are the targets for ROS what results in the appearance of modified nucleic acid bases. Therefore the analysis of total m^5C amount in DNA, can put a new light on neoplasia.

Materials and Methods:
We have applied DNA postlabelling method to the samples taken from brain tumour (gliomas, meningiomas, metastases) tissues combined with peripheral whole blood samples from the same patients. DNA was isolated, hydrolysed into nucleotides and separated on thin layer chromatography after labelling with [γ^{32}P]ATP. Chromatograms were evaluated using phosphoimager and the amount of m^5C was calculated as spot intensities ratio of $[m^5C/(m^5C+C+T)] \times 100$ and expressed as R coefficient.

Results:
The level of m^5C shown as R value was decreasing as the tumor malignancy was increasing. There was also a clear difference observed between grade II and III astrocytomas. Grade III produced almost constant level of total m^5C with R value of 1, but WHO II was higher. Glioblastomas (grade IV) presented R values below 0.6. The results obtained from peripheral blood samples DNA were concordant with that relation (higher tumor malignancy – lower R value). 5-methylcytosine level in DNA from intracranial meningiomas was also changing depending on the malignancy grade. Total DNA methylation in brain metastases showed broad diversity, but also negatively correlated with the increasing primary tumor grade. Moreover, R values for blood samples correlated with those obtained from tumor tissues of the same patients.

Conclusions:

The R value can not only be a good diagnostic marker for brain tumors, indicating their malignancy, and also a factor differentiating low-grade and high-grade gliomas. Therefore, DNA methylation pattern may be a useful tool to give a primary diagnosis of a brain tumor or as a marker for early detection of relapse of disease, especially because the R values for the same patients are similar in their blood and brain tumour tissues. The method described is simple, reliable and easy to apply. It enables the analysis with a limited amount of the starting material, what is a common issue in biological sampling.

Pre-surgery immune profile of adult glioma patients

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Background: Changes in glioma patients' immune profiles over the course of disease may predict outcomes. DNA based immunomethylomics quantifies blood immune cells based on cell specific DNA methylation signatures. To assess changes in immune profiles, we are longitudinally collecting blood samples from glioma patients pre-surgery and at other clinically relevant time points. Here we report patients' pre-surgery immune profiles.
Materials and Methods: All patients underwent biopsy or resection of a presumed new glioma or recurrent lower grade glioma. Blood DNA methylation was assessed with Illumina EPIC methylation arrays. Relative cell fractions of CD4, CD8, B-cells, natural killer cells, monocytes, and neutrophils, were estimated via our validated deconvolution algorithm. Total nucleated cell counts from Nexcelom cytometry were used to compute absolute cell counts. Other measures include total lymphocytes, CD4/CD8 ratio, neutrophil to lymphocyte ratio (NLR), and lymphocyte to monocyte ratio (LMR)).
Results: The first 125 participants include 56 newly diagnosed glioblastomas (GBM), 28 newly diagnosed grade II-III gliomas, and 41 recurrent grade II-III gliomas. Median patient age is 49 years. 53 (43%) had recent dexamethasone exposure. In overall non-parametric analyses, most cell subsets, especially CD4, differed across grade, diagnosis group, WHO classification and dexamethasone exposure. In post-hoc pairwise analyses, immune profiles of IDH wildtype GBM patients who had taken dexamethasone differed from patients with GBM or grade II-III glioma who had not taken dexamethasone; they had clinically relevant and statistically significantly lower absolute CD4 counts, total white cell counts, and percent of total lymphocytes, and higher absolute neutrophil counts, NLR and LMR. However, some dexamethasone naïve GBM patients also had altered immune profiles.
Conclusions: Comparisons of relative immune cell fractions with those from 454 non-glioma controls from the UCSF Adult Glioma Study showed that across grade and WHO classification, for the most part, immune profiles of glioma patients not exposed to dexamethasone did not differ from controls.

Importance of the intersection of age and sex to understand variation in incidence and survival for primary malignant gliomas

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Background:

Gliomas are the most common type of primary, malignant brain and other CNS tumors, accounting for approximately 25.1% of all primary brain and other CNS tumors and 80.8% of malignant tumors. They cause significant morbidity and mortality. This study investigates the intersection between age and sex to better understand variation of incidence and survival for glioma in the United States.

Materials and Methods:

Incidence data from 2000-2017 were obtained from the Central Brain Tumor Registry of the United States which obtains data from the Center for Disease Control's (CDC) National Program of Cancer Registries (NPCR) and National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, and survival data from the CDC's NPCR SEER*Stat Database: NPCR Survival Analytic file for 2001-2016. Age-adjusted incidence rates and rate ratios (IRR) per 100,000 were generated to compare male-to-female incidence by age group. Cox proportional hazard models stratified by age group were performed, generating hazard ratios (HR) to assess male-to-female differences in overall survival. All analyses were performed overall for all gliomas and by glioma subtype.

Results:

Overall, glioma incidence was higher in males than females. Male-to-female IRR was lowest in ages 0-9 years (IRR: 1.04, 95% CI:1.01 - 1.07, p=0.003), steadily increasing with age, peaking at 50-59 years (IRR:1.56, 95% CI: 1.53 - 1.59, p<0.001). Females had worse survival than males for ages 0-9 (HR:0.93, 95% CI:0.87 - 0.99), though male survival was worse for all other age groups, with the difference highest in those 20-29 years (HR:1.36, 95% CI:1.28-1.44). Incidence and survival differences by age and sex also varied by histological subtype of glioma.

Conclusions:

The impact of age or sex difference in incidence and survival for primary malignant gliomas have been described. However, in order to better understand this variation, the intersection of these important variables is key. The current work shows that the combined impact of age and sex dependency is dependent on glioma subtype. These results contribute to the growing understanding of the impact sex and age differences have on cancer incidence and survival.

Circulating cholesterol and glioma risk: results from the UK Biobank, Nurses' Health Study, and Health Professionals Follow-Up Study

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Background: Evidence is mixed on whether cholesterol plays a role in the pathogenesis of glioma. We explored the association between cholesterol levels and glioma risk in three prospective cohorts.

Materials and Methods: Using prospective data from the UK Biobank, we examined the association of total cholesterol (TC), high- and low-density lipoprotein cholesterol (HDL-C, LDL-C), and triglycerides (TG) with glioma risk in multivariable (MV)-adjusted Cox proportional hazards models. Within the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS), we carried out a matched, nested case-control pilot study to examine the association between cholesterol and glioma risk.

Results: In the UK Biobank, 490 gliomas accrued over 2,358,964 person-years. TC was not significantly associated with glioma risk (MV HR=1.20, 95%CI: 0.89-1.61 for highest quartile vs. lowest, p-trend=0.24). In four-year lagged analyses (n=229), higher TC was associated with significantly higher risk of glioma in men (MV HR =2.26, 95%CI: 1.32-3.89, p-trend=0.002) but not women (MV HR =1.28, 95%CI: 0.61-2.68, p-trend=0.72); similar findings emerged for HDL-C and LDL-C. In the NHS/HPFS, no significant associations were found between cholesterol and glioma risk.
Conclusions: In the UKB, higher prediagnostic TC and LDL-C levels were associated with higher risk of glioma in four-year lagged analyses, but not in non-lagged analyses. For both exposures, significant associations were only shown in men. A similar pattern was shown for HDL-C. In a separate nested case-control analysis with modest power, cholesterol levels were not associated with glioma.

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Conflicts of Interest: Nothing to disclose.

Neurocutaneous syndromes, perinatal factors, and the risk of brain tumors— a cohort study among 4 million children

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Background: Neurocutaneous syndromes, or phakomatoses, constitute a genetically and clinically diverse group of congenital disorders with distinctive cutaneous, ocular, and neurologic manifestations. These syndromes are associated with cancer predisposition, particularly for brain tumors, and have also been linked to certain birth characteristics. Since several birth characteristics have been associated with childhood cancer as well, the question arises whether this association might be partly explained by neurocutaneous syndromes. Elucidating these relationships is of value both for the understanding of childhood cancer etiology and for identifying children at increased risk. Thus, our aim was to quantify the risk of brain tumors in children with different neurocutaneous syndromes and to assess to what extent the previously reported associations between perinatal factors and brain tumors could be explained by neurocutaneous syndromes.

Materials and Methods: This population-based cohort study included children registered in the Swedish Medical Birth Register (MBR) between 1973 and 2014, for whom information on both biological parents and main covariates was available (n=4,178,722). Neurocutaneous syndromes diagnoses (n=2,800) were retrieved from the MBR, National Patient Register, and Cause of Death Register, whereas diagnoses of brain tumors were retrieved from the Swedish Cancer Register; these nationwide population and health data registers were linked through the unique personal identity number assigned to all Swedish residents. The association between neurocutaneous syndromes, birth characteristics, and brain tumors (<20 years at diagnosis) was evaluated using Cox proportional hazards regression models.

Results: We observed an increased risk of brain tumors among children with any neurocutaneous syndrome (HR 73.2, 95% CI 60.6–88.5), neurofibromatosis type 1 (HR 52.3, 95% CI 39.7–68.8), tuberous sclerosis complex (HR 121.0, 95% CI 84.9–172.5), and Sturge-Weber syndrome (HR 49.6, 95% CI 12.4–198.4), whereas no children with ataxia-telangiectasia or von Hippel-Lindau disease were diagnosed with a brain tumor during follow-up. Several perinatal factors, including high birth weight, being born large for gestational age, low 5-minute Apgar score, and large head circumference were weakly associated with the risk of childhood brain tumors; associations were stronger among those diagnosed with a brain tumor within the first 2 years of life. Adjusting for neurocutaneous syndromes did not affect these associations.

Conclusions: Children with neurocutaneous syndromes were at considerably increased risk of brain tumors. Moreover, several perinatal factors were associated with elevated brain tumor risks, although these associations were often weak; we have previously shown that these perinatal characteristics are more common among children with neurocutaneous syndromes. Yet, regardless of the strong association between neurocutaneous syndromes and risk for childhood brain tumors, adjusting for the former did not explain the observed associations between perinatal factors and brain tumor risk. Thus, it stands to reason that other syndromes or biological mechanisms underlie the relationship between specific birth characteristics and childhood brain tumors.

The immuno-genetics of viral antigen response influence glioma susceptibility and survival in a subtype-specific manner

Authors: Geno Guerra, Linda Kachuri, George Wendt, Helen Hansen, Steven J. Mack, Annette Molinaro, Paige Bracci, John K. Wiencke, Jeanette Eckel Passow, Robert B. Jenkins, Margaret Wrensch, Stephen S. Francis

Background: Infections and genetic variants in the human leucocyte antigen (HLA) have been independently linked to glioma risk. More recently, several clinical trials have suggested a prognostic benefit to antiviral medications in glioma treatment. In this study we assess the relationship between genetic predictors of viral antigen response to 7 viral infections and glioma risk and survival that is robust against reverse causation.

Materials and Methods: We constructed polygenic risk scores (PRS) for each antigen using genome-wide significant ($p<5\times10^{-8}$) independent variants (linkage disequilibrium $r^2<0.01$) previously identified in the UK Biobank cohort. Classical HLA alleles were imputed to two-field resolution. Associations with glioma risk and survival were estimated in 2632 cases and 2445 controls from the UCSF Adult Glioma Study and the Mayo clinic and 786 cases from The Cancer Genome Atlas and 5711 cancer-free controls from the Wellcome Trust Case Control Consortium.

Results: Genetically predicted stronger antigen responses to Epstein-Barr virus (EBV) ZEBRA antigen and Merkel cell polyomavirus (MCV) L1 antigen were associated in opposite directions with glioma risk overall (odds ratio (OR_{ZEBRA})=0.94, p=0.022 / OR_{MCV}=1.05, p=0.040) and with IDH-wild type (OR_{ZEBRA}=0.91, p=0.008 / OR_{MCV}=1.09, p=0.011) and TERT-only (OR_{ZEBRA}=0.89, p=0.011/ OR_{MCV}=1.11, p=0.018) subtypes. Correlation between PRS_{ZEBRA} and PRS_{MCV} (Pearson's r =-0.354, $p=3.8\times10^{-14}$) also suggests a shared underlying germline mechanism. In line with these findings, HLA-DQA1*03:01, which influences response to EBV ZEBRA ($p=1.3\times10^{-16}$), was associated with glioma overall (OR =1.18, $p=3.9\times10^{-4}$), IDH-wild type (OR=1.22, p=0.0014), and TERT-only (OR=1.21, p=0.034) subtypes. PRS associations for EBV EBNA antigen were restricted to IDH-mutated (OR=1.08, p=0.045) subtypes, with the largest effect in IDH-mutated/1p19q co-deleted (OR=1.13, p=0.028) group. Considering clinical outcomes, we detected an association between predicted antigen responses to three EBV antigens (ZEBRA, EBNA and EAD) and survival in patients with IDH-mutated tumours (HR_{ZEBRA}=0.85, p=0.012 / HR_{EBNA}=1.21, p=0.005 / HR_{EAD}=1.17, p=0.015/ 923 patients, 251 events), and in IDH-mutated/1p19q co-deleted tumours (HR_{ZEBRA}=0.76, p=0.019/ HR_{EBNA}=1.39, p=0.019/ HR_{EAD}=1.32, p=0.03/ 372 patients, 77 events). PRS_{EBNA} and PRS_{EAD} were also associated with survival in IDH-mutated/1p19q non-co-deleted tumours (HR_{EBNA}=1.26, p=0.019/ HR_{EAD}=1.21, p=0.03/ 496 patients, 153 events).

Conclusions: Our study is the first to associate genetically predicted immune response to viral antigens and glioma risk. We demonstrate that HLA-DQA1*03:01 influences glioma risk in the same glioma subtypes, potentially suggesting shared genetic architecture represented by the classical HLA allele. We also provide preliminary evidence of a prognostic value for genetically programmed reactivity to several EBV antigens for patients with IDH-mutated gliomas. Further studies are required to disentangle the complex interactions between the HLA, infections and glioma risk and survival.

Parental migraine and risk of pediatric central nervous system cancers

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Background: Migraine is a common disorder among parents of childbearing age, affecting 10-20% of Danish adults. Migraine impacts pregnancy, as it has been associated with preeclampsia and adverse birth outcomes including low birth weight and preterm birth.

To the best of our knowledge, there are no previous studies examining whether a family history of migraine is related to pediatric central nervous system (CNS) tumors. However, two studies (one underpowered) suggested possible increases in brain tumors in adult patients with a history of migraine, associations that persisted after a 3-year lagging analysis (e.g. to account for headache due to the tumor). Migraine is also reported in children with neurofibromatosis 1. The goal of this analysis was to determine associations between a family history of migraine and pediatric brain tumor.

Methods: In a population-based study in Denmark, we utilized data from national registries to investigate this hypothesis. Cancer cases were taken from the Cancer Registry and family history of migraine was taken from the National Patient Register. Migraine-specific medications (triptans, ergotamines) were identified and patients with these prescriptions were ascertained from the Prescription Register. Covariates were taken from the Medical Births Registry. Controls were matched by birth date and sex and selected at random from the Central Population Registry. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI), with adjustment for confounders.

Results: Maternal diagnosis of migraine prior to the child's cancer diagnosis was related to an increased risk of central nervous system tumors (OR=1.31, 95% CI 1.02, 1.68), particularly glioma (OR=1.64, 95% CI 1.12, 2.40). Paternal diagnosis of migraine prior to the child's cancer diagnosis was associated with intracranial and intraspinal embryonal tumors (OR=1.64, 95% CI 0.97, 2.78).

Conclusions: This study raises questions about possible shared genetic, other endogenous, or exogenous risk factors for both migraine

Distance from reporting hospital and survival among adolescents and young adults diagnosed with CNS tumors

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Background: There is evidence that longer travel is associated with improved short-term surgical outcomes for glioblastoma in adults. However, no studies have specifically focused on whether travel distance impacts long-term brain tumor outcomes overall and by type in adolescents and young adults (AYA). Our objective was to determine the association between travel distance and survival in AYAs diagnosed with brain tumors overall and by type.

Materials and Methods: National Cancer Database data on AYA 15-39 years old diagnosed with CNS and Other Intracranial and Intraspinal Neoplasms (referred to as CNS tumors) from 2010-2014 were obtained. Distance between the case's residence and the reporting hospital was classified as short ($\leq$12.5 miles), intermediate (>12.5 and <50 miles), and long ($\geq$50 miles). Facility CNS tumor volume was categorized into quartiles according to the number of CNS tumor cases reported by the facility during the study period. Cox proportional hazards regression models were used for analyses.

Results: The analysis included 9406 AYA diagnosed with CNS tumors. The hazard of death was 1.06 (95% CI 0.96-1.17) and 0.82 (95% CI 0.73-0.93) for those travelling intermediate and long vs. short distances, respectively, after adjusting for age, sex, race, zipcode level education, and zipcode level income. After adjusting for the facility CNS tumor volume quartile, the association was attenuated for long vs. short distance travelled (HR 0.92, 95% CI 0.81-1.04). There was effect modification by tumor type with significantly lower hazards of death for those traveling long vs. short distances specifically for low grade astrocytic tumors (HR 0.38, 95% CI 0.20-0.75) and ependymomas (HR 0.30, 95% CI 0.10-0.88), but not for other brain tumor types.

Conclusions: Travelling long distances for brain tumor care may be associated with better survival in AYA patients for some CNS tumor types. This may be explained by travel to facilities with more experience treating CNS tumors. Further research is needed to understand reasons underlying these associations.

Genetic determinants of systemic inflammatory markers influence glioma risk

Authors: Linda Kachuri, Geno Guerra, George A. Wendt, Helen Hansen, Annette Molinaro, Paige Bracci, John K. Wiencke, Jeanette Eckel Passow, Robert B. Jenkins, Margaret Wrensch, Stephen S. Francis

Background: Peripheral white blood cell and platelet counts, and their ratios, are commonly used markers of systemic inflammation. While there is accumulating evidence for their prognostic utility in glioma, the etiologic relevance of blood cell counts is unclear. We investigated this question in a Mendelian randomization study, which uses genetic predictors of blood cell indices as instrumental variables to distinguish disease correlates from putative glioma risk factors.

Materials and Methods: Genetic predictors of blood cell traits were identified in 335,191 individuals in the UK Biobank cohort, without cancer or autoimmune conditions that could influence blood cell profiles. Genome-wide association studies (GWAS) of 9 hematologic phenotypes discovered 3000 independent variants with $P<5\times10^{-8}$, explaining between 4.0% (basophils) and 23.9% (platelets) of trait variation. To evaluate associations with glioma risk, these genetic instruments were applied to a GWAS meta-analysis of 3418 cases and 8156 controls, comprised of 2632 patients and 2445 controls from the UCSF Adult Glioma Study and the Mayo clinic, and 786 cases from The Cancer Genome Atlas with 5711 cancer-free controls from the Wellcome Trust Case Control Consortium. All analyses were restricted to individuals of predominantly European ancestry.

Results: Genetically predicted increase in the platelet to lymphocyte ratio (PLR) was associated with glioma overall (odds ratio (OR) per 1 unit =1.25, 95% confidence intervals: 1.10–1.43, $p=9.1\times10^{-4}$), but the magnitude of this effect was larger for IDH-mutated (OR=1.39, 1.13–1.71, p=0.0017) and IDH-mutated/1p19q non-deleted (OR=1.54, 1.19–1.98, $p=9.4\times10^{-4}$) tumours, compared to IDH-mutated 1p19q co-deleted (OR=1.15, p=0.37) or IDH wild type (OR=1.23, p=0.017). There was further evidence of effect modification by IDH mutation status for other blood cell markers. Genetically predicted increase in lymphocyte counts was inversely associated only with IDH-mutated 1p19q non-deleted tumours (OR=0.71, 0.55–0.91, p=0.0065; 615 cases). Higher neutrophil counts conferred a lower risk of IDH-mutated (OR=0.69, 0.52–0.90, p=0.0075) and IDH-mutated 1p19q non-deleted (OR=0.60, 0.43–0.85, p=0.0039) subtypes. There was no evidence of directional pleiotropy and these findings remained robust in sensitivity analyses accounting for heterogeneity.

Conclusions: Our study points to a shared genetic basis between blood cell variation and glioma susceptibility, with evidence of germline-somatic interaction. Genetic predisposition to higher PLR, indicating a pro-inflammatory shift towards elevated platelet counts and/or lymphopenia, appears to be a risk factor for multiple glioma subtypes. This effect was most pronounced for IDH-mutated 1p19q non-deleted tumours, consistent with an inverse effect of increased lymphocyte counts in the same subtype. The associations with glioma risk observed for inherited differences in white blood cell counts and PLR suggest the possibility of novel, immune-mediated susceptibility mechanisms for glioma that could have potential disease management implications

A genome-wide association analysis of childhood glioma and assessment of the contribution of enhanced European genetic risk via admixture analysis

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Background:
Glioma is the most common brain tumor in children, comprising almost half of all pediatric central nervous system tumors. The biologic and histologic heterogeneity of pediatric glioma makes its treatment highly challenging. The incidence of glioma varies significantly by ethnicity, with higher rates observed in European populations, suggestive of genetic contributions. While the majority of gliomas are curable, high-grade malignant cases have poor survival rates, underscoring the importance of research in this common tumor affecting children. We aimed to identify genetic variants that are associated with childhood glioma and determine whether European genetic ancestry contributes to enhanced childhood glioma risk.

Materials and Methods:
We conducted a genome-wide association study (GWAS) to identify genetic variants that are significantly associated with childhood glioma risk in a multi-ethnic California birth cohort (1982-2011). Study subjects included 3141 glioma cases (age 0-14 at diagnosis) and 3167 cancer-free controls matched by birth year, with additional 2913 controls from the 1000 Genomes Project and Human Genome Diversity Project. In subjects with pilocytic glioma, we also estimated the proportions of European, African and Native American ancestry proportions among admixed Hispanic subjects and tested whether genome wide European ancestry proportion is associated with risk. Regional admixture mapping and conditional analyses were performed to identify associations with local ancestral haplotypes.

Results:

Meta-analysis of GWAS in all ethnicities identified strong and significant hits in a specific noncoding RNA in chromosome 10. Global ancestry analysis demonstrated that a higher European ancestral background contributes to elevated childhood pilocytic astrocytoma risk (Wilcoxon rank sum test, P value = 0.003475). Regional admixture mapping revealed a locus in chromosome 6 (P value = 4.70×10^{-6}) as the most significant regional ancestry loci associated with pilocytic glioma risk, with additional contributions from other loci around the genome.

Conclusions:

We discover for the first time the genetic variants that are associated with childhood glioma risk, and captured the ancestral difference in glioma risk both globally and regionally. This latter analysis partly explains the demonstrated higher incidence and familial relative risk of low grade glioma in Europeans when compared to groups of other ancestral origins.

Targeted Gene-Expression analysis during malignant transformation in primary and secondary malignant meningioma

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Background: Malignant meningiomas comprise 2-5% of all meningiomas. The process of malignant transformation when benign meningiomas (WHO grade I-II) become malignant (WHO grade III) has not previously been investigated in sequential tumour surgeries. Upregulation of FOXM1 expression and DREAM-complex repression have shown phenotypical subgroups correlating with WHO grade and aggressiveness. We investigated the RNA expression of 30 genes central to meningioma biology and 770 genes involved in neuroinflammatory pathways in primary and secondary malignant meningioma patients who underwent one to several operations.

Materials and Methods: We identified a cohort of consecutive malignant meningioma patients treated at Rigshospitalet, Copenhagen from 2000-2020 (n=51) and gathered their malignant tumours and previous WHO grade I/II tumours. The malignant cohort (MC) was counter matched with a benign cohort (BC) where patients had no recurrences during follow-up. RNA expression signatures from 140 samples from the MC and 51 samples from the BC were analysed with the Nanostring Neuroinflammation panel customized with 30 genes known to be relevant in meningioma phenotypes.

Results: 49% of MC patients had a previous grade I/II meningioma making them secondary malignant meningioma patients. Progression-free survival calculated from first malignant surgery to first recurrence or death showed no significant difference in the primary vs. secondary patients. Preliminary results of single-gene analysis of MC tumours showed FOXM1, MYBL2, TOP2A, BIRC5 expression was higher in WHO grade III samples. Gene-expression signatures in the individual patients and gene ontology enrichment analyses are in process.

Conclusions: FOXM1, MYBL2, TOP2A, BIRC5 RNA expression levels seem to rise during malignant progression across patients. Gene-expression analysis using the Nanostring technology is feasible and a potentially powerful tool to distinguish meningiomas prone to malignant transformation from truly benign meningiomas.

Poor prognosis associated with *TERT* gene alterations in meningioma is independent of the WHO classification: a meta-analysis of individual patient data

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Background: *TERT* gene alterations (*TERT*-alt) have been linked to increased risk of recurrence in meningiomas, whereas the association to mortality largely remain incompletely investigated. As incongruence between clinical course and WHO grade exists, reliable biomarkers have been sought.

Materials and Methods: We performed an individual patient data meta-analysis including all hitherto published *TERT*-alt meningioma patients. We adhered to the PRISMA-IPD Statement. We stratified for WHO grades and compared *TERT*-alt patients to their *TERT* promoter wild-type (*TERT*p-wt) counterpart as: incidence rates, survival probabilities and cumulative recurrences. We estimated the effects of *TERT*-alt, WHO grade, age at diagnosis and sex as hazard ratios.

Results: After screening 163 papers, we identified eight eligible papers and contacted the authors. The response and contribution rate were 100%, thus we compiled raw data from all eight studies. We allocated patients to either *TERT*-alt (n=59) or *TERT*p-wt (n=618). *TERT*-alt occurred in 4.7%, 7.9% and 15.4% of WHO-I, -II and -III meningiomas, respectively.

The median recurrence-free survival was 14 months for all *TERT*-alt patients versus 101 months for all *TERT*p-wt patients. For recurrence, the hazard ratio for *TERT*-alt was 3.74 in reference to *TERT*p-wt in the multivariate analysis.

For all *TERT*-alt patients versus all *TERT*p-wt patients, the median overall survival was 58 and 160 months, respectively. For death, the hazard ratio for *TERT*-alt was 2.77 compared to *TERT*p-wt in the multivariate analysis.

TERT-alt affected prognosis independent of WHO grades. Particularly, the recurrence rate was 4.8 times higher in WHO-I & -II *TERT*-alt patients compared to WHO-III *TERT*p-wt patients. The

mortality rate was 2.7 times higher in the WHO-I & -II *TERT*-alt patients compared to WHO-III *TERT*p-wt patients.
Conclusions: *TERT*-alt is an important biomarker for significantly higher risk of recurrence and death in meningiomas independent of WHO grade.
TERT-alt should be managed and surveilled aggressively. We propose that *TERT*-alt analysis should be implemented as a routine diagnostic test in meningioma and integrated into the WHO classification.

A Systematic Review and Meta-analysis of Sex-Hormone Receptors in Meningioma

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ABSTRACT

OBJECTIVE
Clinical observation suggests meningiomas are sex-hormone sensitive tumors; however, the specific relationships between progesterone (PGR) and estrogen (ER) receptors with patient characteristics remain poorly defined.

METHODS
Publications indexed in Pubmed for the terms "Hormone Receptor Meningioma" (n = 393), "Progesterone Receptor Meningioma" (n = 416) and "Estrogen Receptor Meningioma" (n = 259) were reviewed from the database's inception to December 31st 2020. Among the 634 unduplicated articles screened, 80 English-language publications met criteria of unaggregated patient data with receptor status determined by estradiol or progesterone-ligand-binding(LB), protein immunohistochemistry(IHC), or mRNA expression. We examine associations between patient characteristics with receptor status by method of receptor detection.

RESULTS
The data include 1563 patients (66% female, mean age = 52.5 years) with meningioma. $PGR^{(+)}$ positivity rate did not vary by detection method (75.8% LB vs 73.4% IHC, p=0.39).$PGR^{(+)}$ is associated with female sex (OR = 2.03, $CI_{95\%}$[1.57, 2.62]), skull-base location (OR = 1.8, $CI_{95\%}$[1.23, 2.62]), WHO Grade I (OR = 2.60, $CI_{95\%}$ [1.73, 3.89]), initial diagnosis (OR = 2.38, $CI_{95\%}$ [1.51, 3.75] , and meningothelial histology (OR = 2.47, $CI_{95\%}$ [1.63, 3.74]). $ER^{(+)}$ positivity rate did differ by detection method and was lower for IHC vs LB (28.6% LB vs 10.1% IHC) OR = 0.28, $CI_{95\%}$ [0.20, 0.39]) likely due to the fact that IHC detects only $ER\alpha^{+}$ while estradiol LB detects all ER^{+}. No significant associations with ER^{+} status were appreciated when IHC was used, but was significantly associated with grade when LB was used (p=0.002).

CONCLUSION
The importance of uniform receptor detection methods in assessing hormone receptors for meningioma is elucidated and may explain variation between results across studies and the association between hormonal variables and receptor status. Further understanding about the receptor status in meningioma has implications for the targeted use of Selective-Estrogen Receptor Modulators.

Educational achievements among survivors of a central nervous system tumour during childhood — findings from the SALiCCS research program

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Background:

Survivors of childhood cancer may experience somatic late effects and also socioeconomic consequences of the disease in their young adulthood. Educational achievements, such as attaining upper secondary education, is an important milestone for future career. Previous research suggests survivors of tumours of the central nervous system (CNS) to be of particular risk of lower educational achievements, but methodological drawbacks are present. Further, a better understanding of survivors being at higher risk of lower education or delay in education is needed. In this large multinational population-based study, we aimed to describe educational achievements among survivors of CNS-tumours, in comparison to the general population and the survivors' siblings.

Materials and Methods:
This study is part of the SALiCCS (Socioeconomic Consequences in Adult Life after Childhood Cancer in Scandinavia) research program, a register-based matched cohort study including Denmark, Finland and Sweden. All children diagnosed with cancer age 0-19 are identified from the national cancer registers. For each cancer survivor, five matched population comparisons are selected from the population registers, and all siblings to the survivors are included as a second comparison group.

In the current study, we included all survivors born 1960-1990, diagnosed with a CNS-tumour between 1971-2009, alive and living in the respective country the year they turn 25. We excluded children diagnosed with cancer predisposing syndromes and siblings born more than 5 years apart from their corresponding survivor. This resulted in a study population including 3,007 survivors (Ependymoma 8%; Astrocytoma and other gliomas 49%; Embryonal CNS tumours 10%; Other specified and unspecified CNS tumours 32%), 14,066 population comparisons and 2,557 siblings. Annual individual information on highest achieved education was retrieved from national registers and binary categorized by upper secondary educational level (ISCED level 3) versus not. Using log-binomial regression we estimated the relative risk (RR) with 95% confidence intervals (CI) of failing to achieve

upper secondary education at age 25, comparing survivors and comparisons. We furthermore examined the risk of educational delay.

Results: At age 25, 74% of the survivors of CNS-tumours had achieved upper secondary education, while 83% of the population comparisons and siblings had done so. This resulted in a RR (95% CI) of failing to achieve upper secondary school at age 25 of 1.55 (1.45-1.66), comparing survivors of CNS tumours with population comparisons. The RR was most pronounced among children diagnosed before school start (at ages 0-6) and those diagnosed in the earlier time period (1971-1989). Children of parents with high educational level was more likely to achieve a higher education themselves, overall and among survivors of CNS-tumours. However, the risk difference of failing was similar when stratifying by parental education.

Conclusions: In this Nordic register-based study we demonstrate that survivors of CNS-tumours experience difficulties in educational achievements, in line with previous research. Compared to the general population, fewer survivors had achieved upper secondary education at age 25. Survivors with parents having low education had worse outcomes, but higher parental education did not compensate the educational disadvantage seen among survivors of CNS-tumours.

Interactions of age and blood immune factors provide non-invasive predictors of glioma survival

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Background: Lineage-specific DNA methylation marks differentiate leukocyte cell types while individual biological aging mechanisms impact other methylation alterations. Human glioma incidence and survival times have been shown to be associated with aberrant immune profiles and have a strong dependency on age. In addition to well-established prognostic patient characteristics, this study incorporates blood leukocyte-based DNA methylation markers of immune cells and epigenetic and chronologic age in glioma survival models along with other known risk factors. This work aims to assess whether blood-based biomarkers provide important prognostic information that generalizes across disparate glioma subtypes.

Materials and Methods: We evaluated immune-cell fractions and epigenetic age in archived blood from the UCSF Adult Glioma Study (AGS), including a training set of 197 *IDH*-wildtype, 1p19q intact, *TERT* wildtype (*IDH*/1p19q/*TERT*-WT) glioma patients, an evaluation set of 350 patients with other subtypes of glioma, and 454 subjects without glioma.

Results: Significant differences were observed with IDH/1p19q/TERT-WT patients having lower CD4 and CD8 T cell, natural killer, and B cell fractions, and higher neutrophil fractions than subjects without glioma. Two of three epigenetic age estimates indicated that *IDH*/1p19q/*TERT*-WT patients were significantly older than subjects without glioma, despite them not differing by chronologic age due to partial matching. Recursive partitioning analysis (RPA) delineated four statistically significantly different survival groups for *IDH*/1p19q/*TERT*-WT patients based on an interaction between chronological age and two blood immune factors, CD4 T cells and neutrophils. The same RPA also significantly delineated four survival risk groups in the 350 patients with other glioma subtypes.

Conclusions: Delineation of different survival groups in the training and evaluation sets based on an interaction between chronological age and blood immune characteristics suggests that common host immune factors among different glioma types may impact glioma survival. The capacity of immunomethylomics to capture diverse, clinically relevant information and the simplicity of its implementation make this a powerful tool for non-invasive personalized patient evaluation in the neuro-oncology clinic.

Hormonal contraceptives and risk of meningioma: results from a Swedish register-based case-control study

Authors: Giorgio Tettamanti, Judith Schwartzbaum, Xiaochen Shu, Hanna Mogensen, Tiit Mathiesen, Maria Feychting

Background: Studies regarding the effect of hormonal contraceptives on the risk of meningioma in women are conflicting. Some previous studies on hormonal contraceptives and meningioma reported positive associations, although sometimes only modest, while others reported no association. Moreover, the majority of previous studies focused only on oral contraceptives and relied on self-reported information. The aim of the current study is to evaluate the effect of hormonal contraceptives on the risk of meningioma among young and middle-aged women using data from the nationwide Swedish healthcare registers, including the Prescribed Drug Register.
Materials and Methods: All women born 1955-1995 who had a diagnosis of a meningioma, after age 20, in the Swedish Cancer Register between 2007 and 2015 were included in the study (n = 1055). For each case, 20 controls were individually matched by year of birth and county of residence at date of diagnosis. Information regarding prescriptions of hormonal contraceptives was retrieved from the Prescribed Drug Register: hormonal contraceptives were classified as progestogens, medroxyprogesterone, estrogens and progestogens in combination, and estrogens and levonorgestrel in combination. Women were defined as exposed if they had at least one prescription of any hormonal contraceptive at least one year before the index date: different exposure definitions have been used in sensitivity analyses (longer induction time and higher number of prescriptions). Conditional logistic regression models were used to evaluate the association between hormonal contraceptives and meningioma occurrence. Analyses were adjusted for marital status, educational level, income, parity, country of birth, history of diseases of the circulatory system, and family history of breast cancer and central nervous system tumors.
Results: Women who were prescribed any hormonal contraceptives at least one year before the index date had a two times increased odds of meningioma (OR = 2.08, 95% CI 1.81-2.40). While a five-fold increased odds of meningioma was associated with contraceptives containing medroxyprogesterone (OR = 5.45, 95% CI 4.52-6.58), only a weak association for other progesterone contraceptives (i.e. excluding medroxyprogesterone contraceptives) was found (OR = 1.34, 95% CI 1.10-1.64), indicating that the overall association was in large part explained by medroxyprogesterone contraceptives. Weak associations were also observed for estrogens and progestogens in combination and estrogens and levonorgestrel in combination contraceptives. Similar results were found when using different exposure definitions.
Conclusions: Results from this large register-based case-control study show a strong association between prescriptions of hormonal contraceptives containing medroxyprogesterone (long-acting hormonal contraceptives administered through injections) and risk of meningioma: only weak associations were observed for other hormonal contraceptives. Our findings are consistent with the observation of progesterone receptors in a substantial proportion of meningiomas and the recent findings of a progestin-dependent subgroup of meningiomas.

Central Nervous System (CNS) Tumour incidence rates (2013-2017) and mortality rates (2014-2018) in Canada

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Background: Established in 2016, the goal of our BTRC Surveillance Research Collaboration is to address the lack of detailed data on Central Nervous System (CNS) tumours in Canada. Using the most recent available data, we present the first comprehensive report on all primary CNS tumours incidence (excluding Quebec) and mortality among Canadians.

Materials and Methods: Data on all primary CNS tumours diagnosed between 2013-2017 were obtained from the Canadian Cancer Registry. International Classification of Diseases for Oncology (3rd edition) site/histology codes were grouped into histological categories according to the schema developed by the Central Brain Tumor Registry of the United States (U.S). Data on deaths from primary CNS tumours between 2014-2018 were obtained using Statistics Canada's Vital Statistics Death Database, an administrative survey collecting demographic and cause of death information on all deaths in Canada. All deaths were classified according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). Age-standardized incidence rates (ASIR) and age-standardized mortality rates (ASMR) and corresponding 95%CI were calculated per 100,000 person-years, using direct standardization with the 2011 Canadian and 2000 U.S population standards.

Results: The average annual ASIR for malignant CNS tumours was 7.93 per 100,000 (95%CI: 7.78-8.08) while the ASIR for non-malignant CNS tumours was 13.12 per 100,000 (95%CI: 12.93-13.31). Compared to the large variation in ASIR for non-malignant tumours among provinces that ranged from 5.26 per 100,000 (95% CI: 4.46-6.18) for Newfoundland and Labrador to 16.56 per 100,000 (95% CI: 16.27-16.87) for Ontario, the ASIR for malignant tumours were relatively stable (from 5.43 per 100,000 (95% CI: 3.52-8.86) for the territories to 8.16 per 100,000 (95% CI: 7.95-8.37) for Ontario). The ASMR for malignant CNS tumours was 5.79 per 100,000 (95% CI: 5.69-5.90) while ASIR for non-malignant CNS tumours was 0.94 per 100,000 (95% CI: 0.89-0.98). When standardized to the 2000 US standard population and compared to the US rates, ASIR rates were similar for primary malignant CNS tumours (7.13 per 100,000 vs. 7.08 per 100,000) but the Canadian rate for all primary non-malignant CNS tumours is only 70% of the U.S. rate (11.70 per 100,000 vs 16.71 per 100,000), and the Canadian ASMR rate was slightly higher for primary malignant CNS tumours (4.99 per 100,000 vs. 4.42 per 100,000).

Conclusions: We present the most comprehensive and up-to-date data on primary CNS tumour diagnoses and deaths among Canadians. Findings indicate underestimation of non-malignant CNS tumours during the study period. Incomplete case capture contributes to underestimates of the burden of primary CNS tumours in Canada and compromises the accurate interpretation of surveillance statistics, particularly for non-malignant primary CNS tumours.