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Molecular epidemiology approach: Nested Case-Control Studies in Glioma and Lymphoid Malignancies

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Akademisk avhandling

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Avhandlingen kommer att försvaras på engelska.

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Abstract

Background: Nested case-control studies aim to link molecular markers with a certain outcome. Repeated prediagnostic samples may improve the evaluation of marker-disease associations. However, data regarding the benefit of repeated samples in such studies are sparse. We aimed to assess the relationship between blood levels of various proteins and risk of glioma, B cell lymphoma, and multiple myeloma to gain further understanding of disease etiology and to evaluate the clinical relevance of the studied markers. To this end, marker-disease associations were evaluated considering the natural history of the studied disease and the time between blood sample collection and diagnosis using both single (I-II) and repeated prediagnostic blood samples (III-IV).

Patients and methods: We conducted four nested case-control studies and one meta-analysis using samples from three prospective cohorts: the Janus Serum Bank, the Northern Sweden Health and Disease study, and the European Prospective Investigation into Cancer and Nutrition study. The following studied endpoints and relationships were included: I) glioma risk and the association with the receptor tyrosine kinases (soluble) sEGFR and sERBB2; II) B cell lymphoma risk and the association with the immune markers sCD27 and sCD30; III) B cell lymphoma risk and the association with immune markers (CXCL13, sTNF-R1, sCD23, sCD27, and sCD30) and their trends over time; and IV) multiple myeloma risk and the association with 10 immune markers and growth factors (MCP-3, MIP-1α, MIP-1β, VEGF, FGF-2, fractalkine, TGF-α, IL-13, TNF-α, and IL-10) and their trends over time.

Results: Risk of developing **I) glioma** was weakly associated with high blood levels of sERBB2. In addition, high levels of both sEGFR and sERBB2 assessed 15 years before diagnosis were associated with glioblastoma risk. Risk of **II) B cell lymphoma** was associated with high levels of sCD30, whereas high levels of sCD27 were associated with risk of chronic lymphocytic leukemia. Meta-analyses showed consistent results for sCD30 across cohorts and lymphoma subtypes, whereas results for sCD27 were less consistent across cohorts and subtypes. In addition, **III) B cell lymphoma** risk was associated with levels of CXCL13, sCD23, sCD27, and sCD30 assessed in samples collected 17 years pre-diagnosis. Marker levels increased in cases closer to diagnosis, particularly for indolent lymphoma with a marked association for chronic lymphocytic leukemia and sCD23. Increasing levels closer to diagnosis were also observed for diffuse large B cell lymphoma and CXCL13. Risk of **IV) multiple myeloma** was associated with low levels of MCP-3, VEGF, FGF-2, fractalkine, and TGF-α. Levels of these markers decreased in myeloma cases over time, especially for TGF-α. TGF-α concentration assessed at time of the prediagnostic repeated sample seemed to help predict progression to multiple myeloma.

Conclusions: Both the natural history of the studied disease and the time between sample collection and diagnosis are crucial for the evaluation of marker-disease associations. Using repeated prediagnostic blood samples improves the understanding of marker-disease associations and might help to identify useful biomarker candidates.

Keywords
Glioma, B cell lymphoma, multiple myeloma, risk, repeated samples, prospective longitudinal study, nested case-control study, circulating sEGFR and sERBB2, circulating immune markers and growth factors, marker-disease association, disease progression, NSHDS, Janus, linear mixed modeling.

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