Circulating Inflammatory Proteins Associated with Dementia Risk in Older Adult Cancer Survivors in the Atherosclerosis Risk in Communities (ARIC) Study

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Background Inflammation is linked to cognitive impairment (CI) in cancer survivors. But its role in survivors who develop dementia is unclear. Methods We evaluated dementia risk per log2 increase in 580 inflammatory proteins in 391 dementia-free long-term (>5 yrs) older adult survivors of prostate, breast, colorectal, endometrial and bladder cancers in ARIC. Plasma inflammatory proteins were measured at visit 5 (2011–13) using SomaScan, an aptamer-based assay. Participants were followed through visit 6 (2016–17). We adjusted for age, sex, race, years since cancer diagnosis, ApoE4, renal function, anti-inflammatory drug use and cancer/CVD shared risk factors. We also investigated proteins associated with dementia in 196 prostate and 135 breast cancer survivors, accounting for multiple testing by Bonferroni correction and false discovery rate Q-values. Results Survivors were 20% Black, 54% male, mean age of 76yrs, median time since diagnosis of 12yrs. 67 dementia cases occurred in 1780 person-yrs. After FDR correction, 73 proteins were statistically significantly associated with dementia risk. TMEM87B, CD9, RAF1, IL21sR and FGF7 showed the strongest positive association, with HR:3.4–3.8 per Δlog2. LAIR1, IL36B, FGFR3, FLRT3 and LSAMP showed the strongest inverse association, HR:0.1–0.2. Only syntaxin12 (STX12) was significant after Bonferroni correction, HR:2.2. Associations of some inflammatory proteins with dementia were cancer site-specific. In breast cancer survivors, IL6, HMGA2, IFN-GR1, SAP, TNFRSF1a, TNFRSF14, and TNFAIP3, were associated with dementia. STX12 and RAF1 were significantly associated ($q < 0.05$) with dementia in all, prostate, and breast cancer survivors. Conclusion Inflammatory proteins were associated with dementia in older adult cancer survivors, including STX12 (enriched in brain, linked to WNT signaling loss, exerts CNS effects) and RAF1 (regulates MAPK/ERK pathway, previously identified in dementia etiology). Inflammatory proteins previously associated with CI, including TNF proteins/receptors, were associated with dementia in breast cancer survivors. If confirmed, these proteins may warrant evaluation as potential biomarkers for dementia risk screening, and possibly preventive/therapeutic targets in cancer survivors. Funding: NHLBI, NCI, NPCR

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Early Life Exposure to Tobacco Smoke and Ovarian Cancer Risk in Adulthood

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Background: Ovarian cancer risk in adulthood may be affected by early life exposure to tobacco smoke. We investigated this relationship in two large prospective cohorts, the Nurses' Health Study (NHS) and NHSII. Methods: In total, analyses included 110,305 NHS participants (1976–2016) and 112,859 NHSII participants (1989–2017). Self-reported early life smoking exposures were queried at baseline or follow-up questionnaires. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for risk of ovarian cancer overall and by tumor histotype. Results: Compared with women who never smoked, ovarian cancer risk was similar for women who started to smoke at age <18 (HR = 0.98, 95%CI: 0.86–1.11) or ≥18 (HR = 1.02, 95%CI: 0.93–1.12). Overall, ovarian cancer risk was not different among participants whose mother did versus did not smoke during pregnancy (HR = 1.05, 95%CI: 0.87–1.27); however, an increased risk was observed among women who themselves were never smokers (HR = 1.38, 95%CI: 1.05–1.81) but not ever smokers (HR = 0.86, 95%CI: 0.66–1.14; Pheterogeneity = 0.02). These associations did not differ by histotype (Pheterogeneity≥0.35). Parental smoking in the home during childhood/adolescence was related to a 15% increased risk of ovarian cancer in adulthood (HR = 1.15, 95%CI: 1.04–1.27) and this association was notably stronger among women with non-serous/ low- grade serous tumors (HR = 1.28, 95%CI: 1.02–1.61) versus high-grade serous/ poorly differentiated tumors (HR = 1.09, 95%CI: 0.93–1.28, Pheterogeneity = 0.25). Conclusions: Exposure to parental tobacco smoke, but not early initiation of smoking, was associated with a modest elevated risk of ovarian cancer. Further investigations are required to confirm these findings and elucidate underlying mechanisms.

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Early-life Exposures and Age at Breast Development in the Sister Study Cohort

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Purpose: Early age at breast development (thelarche) has been associated with increased breast cancer risk. Average age at thelarche has declined over time, but there are few established risk factors for early thelarche. We examined associations between pre- and postnatal exposures and age at thelarche in a U.S. cohort of women born between 1928 and 1974. Methods: Breast cancer-free women ages 35–74 years who had a sister diagnosed with breast cancer were enrolled in the Sister Study from 2003–2009 (N = 50,884). At enrollment, participants reported their age at thelarche, which we categorized as early (≤10 years), average (11–13 years), and late (≥14 years), as well as information on early-life exposures. We estimated odds ratios (ORs) and 95% confidence intervals (CIs) for early and late thelarche relative to average age at thelarche using polytomous logistic regression for each early-life exposure, adjusted for birth cohort, race/ethnicity and family income level in childhood. We examined modification by birth cohort, race/ethnicity, family income, relative weight at age 10, and extent of breast cancer family history through stratification. Results: Early thelarche was more common in recent birth cohorts and among non-Hispanic Black and Hispanic women. Early thelarche (≤10 years) was associated with multiple prenatal exposures: gestational hypertensive disorder (OR = 1.25, 95% CI, 1.09–1.43), maternal diethylstilbestrol (DES) use (OR = 1.23, 95% CI, 1.04–1.45), maternal smoking during pregnancy (OR = 1.20, 95% CI, 1.13–1.27), and young maternal age (OR 1.30, 95% CI, 1.16–1.47 for <20 vs 25–29 years). Being firstborn was also associated with early thelarche (OR = 1.25, 95% CI, 1.17–1.33). Low birthweight (<2500 vs 2500–3999g) was suggestively associated with both early (OR = 1.06, 95% CI, 0.96–1.17)