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A CASE-CASE APPROACH TO THE STUDY OF CUTANEOUS MELANOMA. *M Kvaskoff, N Pandeya, D C Whiteman (Queensland Institute of Medical Research, Herston, QLD 4006, Australia)

Recent research suggests a causal heterogeneity for several cancers, such as melanoma and breast and colon cancers. Melanoma has been hypothesized to arise through 2 different pathways according to phenotype, body site, and sun exposure. To test this hypothesis, we explored etiologic differences by anatomic site of melanoma using a case-case comparative approach. This design maximises response rates and minimises differential recall bias. 808 melanoma patients aged 18-79 years and diagnosed in 2007-2011 were sampled from pathology laboratories in Queensland, Australia. A research nurse counted melanocytic nevi and solar keratoses (SKs) and recorded phenotypic factors in all participants. We compared counts for nevi and SKs between melanomas arising on the head and neck (MHN, n = 130) and those arising on the trunk (MT, n = 572, the reference group). Odds-ratios (ORs) and 95% confidence intervals were computed using logistic regression models. MHN patients were significantly less likely to have high nevi counts compared with MT patients (OR = 0.19 for $\geq$ 130 nevi compared with $<$ 30, ptrend $<$ 0.0001). The strongest associations were observed for counts for nevi on the trunk, where melanocytic proliferation is the largest. MHN patients were also more likely than MT patients to have high numbers of SKs (OR = 2.79 for $\geq$ 8 SKs compared with 0, ptrend = 0.002). In summary, compared with MT, MHN is inversely associated with number of nevi at all body sites (especially the trunk), but positively associated with number of SKs, a marker of chronic sun exposure. Our findings accord with the hypothesis of causal heterogeneity for melanoma, with one pathway associated with nevus propensity, and one pathway associated with cumulated sun exposure.

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DIFFERENCES IN RISK FACTORS FOR SERRATED COLORECTAL POLYPS ACCORDING TO CPG ISLAND METHYLATOR PHENOTYPE (CIMP) STATUS. *A N Burnett-Hartman, P N Newcomb, M T Mandelson, M A Wurscher, K W Makar (Fred Hutchinson Cancer Research Center, Seattle, WA 98109)

Colorectal cancers (CRC) with a CpG Island Methylator Phenotype (CIMP) are hypothesized to have serrated polyp precursors; serrated polyps include hyperplastic polyps (HP), traditional serrated adenomas (TSA), and sessile serrated polyps (SSP). We conducted a case-control study of CIMP-positive and negative serrated polyps among participants, aged 24-79, evaluated via colonoscopy. Cases had HPs, SSPs, or TSAs (n = 261); controls had no colorectal pathologies (n = 1037). Methylation of polyp tissue DNA was quantified by MethyLight PCR using a validated CIMP panel (*CACNA1G*, *IGF2*, *NEUROG1*, *RUNX3*, and *SOCS1*). Polytomous regression was used to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between sex, race, age, smoking history, body mass index (BMI), alcohol consumption, physical activity, family history of CRC, non-steroidal anti-inflammatory drug (NSAID) use, and hormone therapy and CIMP-positive and CIMP-negative serrated polyps, separately. Of 261 cases, 76 were CIMP-positive (3 or more markers positive). For CIMP-negative serrated polyps, there was an inverse association with age (OR = 0.97; 95% CI: 0.95-0.99), and there were positive associations with smoking (0 pack-years vs. $>$ 22) (OR = 4.25; 95% CI: 2.73-6.62) and BMI (18.5-25 kg/m^2 vs. $\geq$ 30) (OR = 1.65; 95% CI: 1.05-2.56). For CIMP-positive serrated polyps, only Caucasian race (OR = 2.58; 95% CI: 1.01-6.58) was significant. Our study suggests CIMP-positive and CIMP-negative serrated polyps have different risk-factors; the association between CIMP-positive polyps and Caucasian race may be a clue for the role of genetics in the initiation of CIMP-positive CRC.

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AN ASSESSMENT OF NECESSARY CONDITIONS FOR THE HEALTHY WORKER SURVIVOR EFFECT. *A I Naimi, S R Cole, D B Richardson (University of North Carolina, Chapel Hill, NC 27599)

The healthy worker survivor effect (HWSE) is recognized as a potential source of bias in occupational exposure-disease associations. The necessary conditions for bias are associations between: (1) work status and subsequent outcome; (2) exposure and subsequent work status; and (3) work status and subsequent exposure. Here, we present an analysis of the component associations of the HWSE in a study of the association of asbestos exposure and lung cancer mortality. Data were obtained on 3,072 workers in an asbestos textile plant between 1 Jan 1940 and 31 Dec 1965, followed through 31 Dec 2001 for vital status and cause of death. Annual asbestos exposure levels were estimated using job-specific ambient asbestos concentration measurements and job history information. During 118,519 person-years of follow up, 198 lung cancer deaths occurred. Cox proportional hazards models, adjusted for gender, age, birth year, and race, were used to estimate the magnitude of the association between (1) work status and lung cancer mortality, and (2) asbestos exposure and subsequent work status. By design association (3) is infinite: people who leave work have no chance of incurring subsequent work-based exposure. The covariate-adjusted hazard for lung cancer mortality was 3.2 times larger after leaving the workplace (95% confidence limits [CL]: 1.0, 10.2). The covariate-adjusted hazard for leaving the workplace was 0.01 times smaller for every 100 fiber-years/mL of cumulative asbestos exposure (95% CL: 0.01, 0.02). Based on prior simulation work, these associations imply that HWSE is an important source of bias in these data, and that standard adjustment for work status may induce appreciable bias.

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COMPARISON OF STANDARD METHODS WITH G-ESTIMATION OF ACCELERATED FAILURE-TIME MODELS TO ADDRESS THE HEALTHY WORKER SURVIVOR EFFECT. *J Chevrier, S Picciotto, E A Eisen (University of California, Berkeley, CA 94720)

Background: Studies of autoworkers report associations between exposure to straight metalworking fluids (MWF) and cancer mortality. Previous studies, however, have not addressed the healthy worker survivor effect (HWSE). Several methods have been proposed but none consider that this bias may be caused by time-varying confounders affected by prior exposure. G-estimation of accelerated failure-time models was developed to address this issue but was never applied to account for the HWSE. Methods: We apply g-estimation of accelerated failure time models to estimate hazard ratios for chronic obstructive pulmonary disease (COPD), heart disease, and selected cancers in relation to straight MWF exposure in 38,747 autoworkers. We compare results with those from standard Cox-based methods previously proposed to address the HWSE. We expand our analysis by using a series of binary variables to capture the change in effect with increasing exposure concentration. Results: Standard methods suggest that exposure to straight MWF has a null or protective effect for mortality from all causes combined, all cancers combined, COPD, and heart disease. In contrast, results using g-estimation suggest that exposure may be causally related to these outcomes. Analysis of specific cancer sites by g-estimation also suggested increased mortality risk for lung cancer. Conclusion: Bias may arise because health status is associated with mortality, determines future exposure and is predicted by past exposure. G-estimation accounts for health status being both a confounder and possibly an intermediate variable between exposure and disease. This method may thus provide a better control for the HWSE than standard methods.