

Chromosomal Mosaicism Associated With Increased Risk of Hematologic Cancer

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Previous studies have suggested that chromosomal mosaicism (CM; chromosomal differences across cells in the same person) in white blood cells is a risk factor for hematologic cancer, including leukemia, lymphoma, multiple myeloma, or myelodysplastic syndrome, though the studies were relatively small. CM has also been linked to spontaneous abortions, birth defects, cognitive defects, and some cancers. CM includes duplications and deletions of chromosomal sections, as well as loss of heterozygosity within chromosomal regions. (This can be problematic if, for example, the loss of heterozygosity results in 2 identical copies of a deleterious allele, such as a non-functional version of a DNA repair gene.)

Ursula Schick, Andrew McDavid, Dr. Chris Carlson, and colleagues in Public Health Sciences undertook a recent study to further investigate the association between CM and hematologic cancers, using genotyped samples from 2 previous studies: the Electronic Medical Records and Genomics study (eMERGE), and the Women's Health Initiative (WHI). They originally planned to monitor chromosomal abnormalities just as a data quality precaution in a separate study of the genetics of dementia, and they were surprised to find that subjects with CM had an increased risk of developing cancer. As Andrew McDavid notes, "scientific inquiry is not just about starting with some hypothesis and testing it, but about being open to changing your hypothesis altogether."

In this most recent study, the investigators included CM cases in which at least 5-10% of cells had the same chromosomal abnormality. Mosaic anomalies included losses, gains, and copy-neutral loss of heterozygosity (i.e. no change in the number of chromosomal sections, but a change from a heterozygous to a homozygous pair of alleles). 12,176 individuals were genotyped, ranging in age from 50 to 79 years. Most (60%) had at least 10 years of follow-up, with a required minimum of 1 year. Participants were also required to be free of a hematologic cancer diagnosis before, and for a full year after, entry into the study.

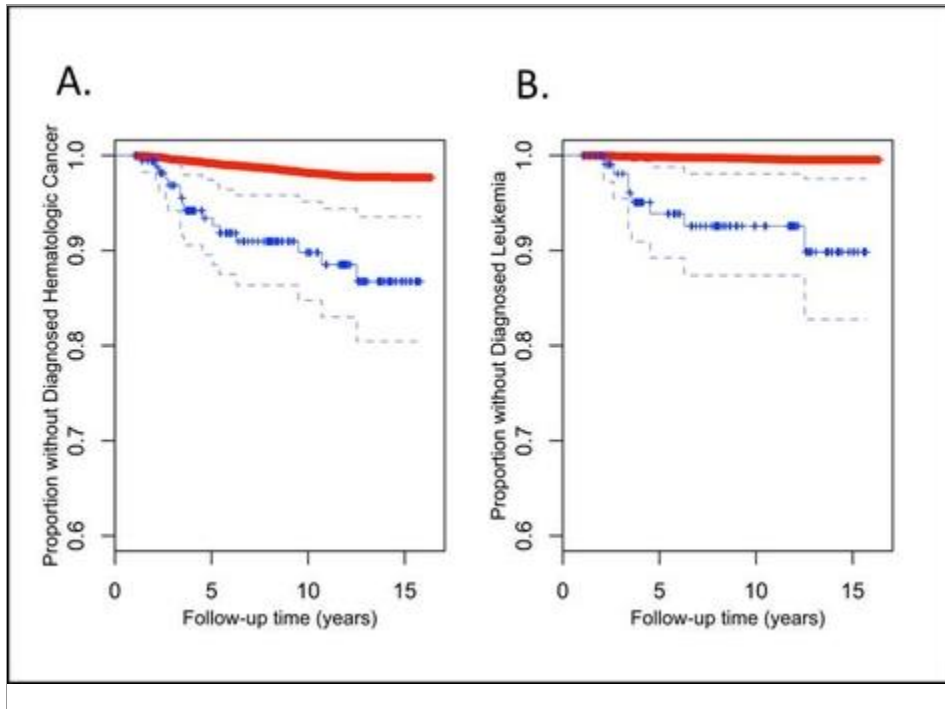
The authors detected CM in 1.4% of participants overall, and in 7% of the participants who later developed a hematologic cancer (n=229). CM was particularly common in those who went on to

develop leukemia (17.6% of cases), compared to other hematologic cancers (3.9%). Older patients were more likely to have CM (2.7% of persons aged \geq 80 years, versus 0.9% of people <60 years). The presence of a mosaic anomaly was associated with a 5-fold greater risk of developing a hematologic cancer (95% CI: 3.3-9.3). Leukemia risk was highest, with an almost 20-fold increase (95% CI 8.9-41.6) associated with CM, versus a 3-fold higher risk of non-leukemic cancers (95% CI 1.5-6.8).

The findings of Schick *et al.* support evidence from previous studies that CM in white blood cells is a risk factor for hematologic cancers, particularly leukemia, and that CM is more frequent in older individuals. This may be due to the accumulation of mutations over time and with increasing age, and/or a reduced capacity for DNA repair with older age. It is not entirely clear biologically why CM would be associated with hematologic cancers, but tumor suppressor genes, which play a regulatory role in cell division, may be involved in the development of both CM and hematologic cancers.

Questions for future research include how mosaic anomalies change over time in an individual, and whether individuals with CM in white blood cells also have chromosomal anomalies in other tissues. Another aspect of these findings which deserves attention in future studies is the question of screening. "The most interesting piece of this study is actually ... that the hazard ratio for a subsequent leukemia diagnosis is large enough that it might warrant returning these incidental results to study participants. [Our study]... was retrospective, with the DNA collected at least a decade previously, so the question isn't whether we should return results to our participants, but rather whether prospective studies using similar GWAS genotyping platforms could or should screen for somatic anomalies," Dr. Carlson noted.

[Schick UM, McDavid A, Crane PK, Weston N, Ehrlich K, Newton KM, Wallace R, Bookman E, Harrison T, Aragaki A, Crosslin DR, Wang SS, Reiner AP, Jackson RD, Peters U, Larson EB, Jarvik GP, Carlson CS](#). 2013. Confirmation of the reported association of clonal chromosomal mosaicism with an increased risk of incident hematologic cancer. PLoS One 8(3):e59823. doi: 10.1371/journal.pone.0059823.



Dr. Chris Carlson

The proportion of subjects remaining free of (A) hematologic cancer and (B) leukemia, stratified by presence (blue) or absence (red) of a mosaic anomaly (>2 mb).