Study reveals how premature menopause increases risk of cardiovascular disease

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Menopause that occurs before a woman is 40 years old accelerates aging and is a risk factor for cardiovascular disease. New research led by investigators at Massachusetts General Hospital (MGH) reveals women with such premature menopause often exhibit certain blood cell changes that elevate their risk of developing coronary artery disease. The findings, which were published in *Circulation* to coincide with the American Heart Association's Scientific Sessions 2020, uncover the mechanisms behind premature menopause's link to cardiovascular disease and point to a potential blood marker for identifying women at especially high risk.

"We recently found that the presence of chronological-age-associated mutations in blood cells—called clonal hematopoiesis—without overt cancer is a new risk factor for coronary artery disease," says senior author Pradeep Natarajan, MD, who is an investigator in Preventive Cardiology at MGH and an assistant professor of Medicine at Harvard Medical School. "We wondered whether earlier age at menopause independently was associated with clonal hematopoiesis."

To investigate, the team analyzed blood samples from 11,495 postmenopausal women aged 40-70 years from the UK Biobank and 8,111 postmenopausal women aged 50-79 years from the U.S.'s Women's Health Initiative (WHI). A total of 418 women (2.1 percent) had natural premature menopause and 887 (4.5 percent) had surgical premature menopause. Over a median follow-up of 10.0 and 13.1 years in the UK Biobank and the WHI, respectively, there were 473 and 1,146 new cases of coronary artery disease. The team used DNA sequencing of blood cells to identify the presence of clonal hematopoiesis. (Its presence was not detectable by routine clinical laboratory tests, including complete blood counts or C-reactive protein.)

Premature menopause was associated with a 36 percent higher likelihood of exhibiting clonal hematopoiesis in the blood, with a larger association for women with natural premature menopause. Clonal hematopoiesis was in turn associated with a 36 percent higher likelihood of developing coronary artery disease. When there were high levels of clonal hematopoiesis, the risk was 48 percent higher.

Previous research has shown that coronary artery disease that arises following clonal hematopoiesis may involve key inflammatory pathways that are less relevant in the context of other cardiovascular risk factors. Therefore, women with premature menopause and signs of clonal hematopoiesis may benefit from prevention strategies targeting these pathways.

"Our work suggests that women with premature menopause are enriched for clonal hematopoiesis, and screening may facilitate novel precision medicine strategies for coronary artery disease in affected women," says Natarajan.

More information: Michael C. Honigberg et al, Premature Menopause, Clonal Hematopoiesis, and

Coronary Artery Disease in Postmenopausal Women, *Circulation* (2020). DOI: 10.1161/CIRCULATIONAHA.120.051775