The genetic influence on premenopausal and menopausal health: Implications for aging and disease risk



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Abstract
Menopause timing is influenced by genetic, environmental, and lifestyle factors, with significant implications for aging and risk for disease. Genome-wide association studies (GWAS) have identified genetic variants affecting age at natural menopause (ANM), highlighting pathways related to DNA repair, immune function, and ovarian aging. Rare genetic variants in genes like BRCA1, BRCA2, and PALB2 are linked to earlier menopause and increased cancer risks. Additionally, earlier menopause is associated with osteoporosis and cardiovascular disease, while later menopause raises risks for breast and endometrial cancers. Epigenetic studies suggest menopause timing correlates with biological aging. Understanding genetic determinants of menopause offers insights into aging mechanisms and potential interventions for disease prevention. Future research integrating genetics, epigenetics, and environmental factors may lead to personalized approaches for promoting women's health during aging.

Keywords: Epigenetics, menopause, ovarian aging, genetic determinants

1. Introduction
Menopause is a significant biological transition marking the end of a woman's reproductive years. It usually happens between the ages of 45 and 55, although variances exist due to genetic, environmental, and lifestyle factors. This phase is characterized by a reduction in ovarian function, which leads to declined levels of estrogen and other reproductive hormones. The onset of menopause is not merely a reproductive event; it is a complex process that has profound implications for overall health, including cardiovascular function, bone density, and cognitive well-being. The timing of menopause varies widely among women, with some experiencing it earlier than expected, known as premature or early menopause, while others undergo menopause later in life. Understanding the genetic basis of menopause timing is essential, as it provides insight into broader health implications, including aging and disease susceptibility.

Recent research has identified key genetic factors that regulate ovarian function and influence the timing of menopause. These genetic determinants are associated with risks for age-related illnesses such as cardiovascular disease, osteoporosis, and various cancers. Studies have shown that menopause timing is influenced by multiple genetic loci, particularly those involved in DNA repair and cellular aging. By examining the interplay between genetic factors and menopause, researchers can uncover critical pathways involved in aging and develop strategies for disease prevention and management. As research in genetics advances, personalized medicine approaches may offer new avenues for predicting menopause onset and tailoring interventions to reduce health risks associated with early or late menopause (1,2).

2. Genetic determinants of menopause timing

Recent research has identified numerous genetic variants associated with the age at natural menopause (ANM). A meta-analysis of genome-wide association studies (GWAS) involving 3,493 early menopause cases and 13,598 controls revealed that early menopause shares a genetic etiology with normal menopause timing (3,4). The study found that 17 variants previously linked to ANM were also associated with early menopause and primary ovarian insufficiency, suggesting a shared genetic basis. Notably, the combined effect of these common variants accounted for approximately 30% of the variance in early menopause, highlighting the significant role of genetics in determining menopause timing (5).

Further research has uncovered rare genetic variants with substantial impacts on menopause timing. An analysis of genetic sequencing data from over 106,000 post-menopausal women identified rare variants in nine genes associated with ANM. Four of these genes (ETAA1, ZNF518A, PNPLA8, PALB2) were newly implicated and found to influence menopause timing by two to five-and-a-half years earlier than average. These results offer more understanding of the molecular processes behind ovarian ageing and point to possible intervention avenues (6).

3. Genetic links between menopause timing and disease risk

Menopause timing is strongly linked to various health outcomes, with early and late menopause carrying different risks. Research suggests that genetic variants affecting menopause timing also influence the risk of developing age-related diseases. Figure 1 indicates the genetic linkup between perimenopausal and menopausal health and possible interventions.

3.1. Cancer risk

Women experiencing early menopause have a reduced risk of estrogen-sensitive cancers such as breast and endometrial cancer due to lower lifetime estrogen exposure. However, they face an increased risk of other conditions such as osteoporosis and cardiovascular disease. Conversely, late menopause extends estrogen exposure, elevating the risk of hormone-related cancers. Genetic studies indicate that BRCA1 and BRCA2 mutations not only increase cancer risk but also contribute to earlier menopause onset (7). These insights highlight the complex relationship between menopause timing and cancer susceptibility (8).

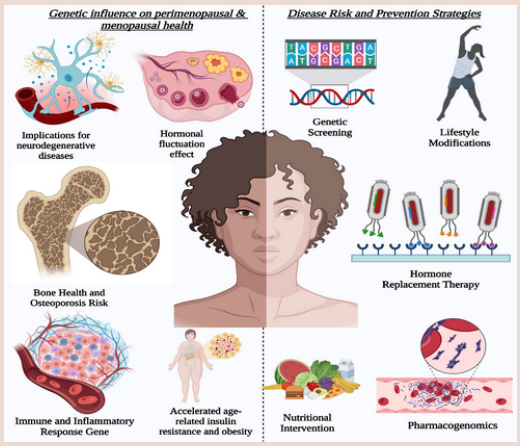

Figure 1. Genetic link between perimenopausal and menopausal health and possible interventions

3.2. Cardiovascular disease and osteoporosis

Early menopause has been associated with a heightened risk of cardiovascular disease. The preventive function of estrogen in preserving vascular health, and its decline during menopause can lead to increased arterial stiffness, hypertension, and lipid imbalances. Genetic studies have linked menopause timing to cardiovascular health, with certain genetic markers predicting a higher predisposition to heart disease in women who undergo menopause earlier than average. Similarly, osteoporosis is a major concern for postmenopausal women, as estrogen deficiency accelerates bone loss. Genetic variants influencing menopause timing, such as those in the LRP5 and ESR1 genes, have been implicated in bone mineral density regulation. Women with earlier menopause are at greater risk for fractures and osteoporosis-related complications, making genetic research crucial for developing targeted prevention strategies (9).

3.3. Immune and inflammatory response gene

The immune system undergoes significant changes during the transition from the perimenopause to menopause including significant hormonal changes influencing the immune system by modulation through estrogen receptor genes like ESR1 and ESR2. Estrogen plays a major role into the modulation of the immune function and its decline during menopause results in enhanced systemic inflammation, immune dysregulation, and high risk of inflammatory diseases. Other key immune and inflammatory genes like tumor necrosis factor alpha gene, interleukin -6 gene, interleukin 1- beta gene, C reactive protein gene are involved in the regulation of inflammatory response and chronic inflammation in menopause (10). The human leukocyte antigen genes, transforming growth factor beta gene, Nod like Receptor Pyrin Domain Containing 3 gene is responsible for autoimmune diseases, immune suppression, regulation of tissue remodelling and inflammasome activation (11).

3.4. Implications for neurogenerative diseases

Neurodegenerative disorders, including Alzheimer's disease (AD), often exhibit sex-specific differences in incidence and progression. Research indicates that aging and the female sex are strongly associated with a higher prevalence of AD. Current literature suggests that decline in progesterone, estrogen and insulin-like growth factor 1 (IGF-1) contribute to neurodegenerative processes in AD. These hormonal changes are linked to increased neuroinflammation, impaired amyloid-beta (Aβ) clearance, and reduced neuroprotection, exacerbating disease progression (12). Estrogen and IGF-1 enhance Aβ clearance by upregulating the expression of Aβ-degrading enzymes such as neprilysin and insulin-degrading enzyme. IGF-1 also promotes microglial phagocytosis of Aβ. These hormones support neuronal survival, synaptic plasticity, and mitochondrial function. Declining levels of these hormones during menopause reduce Aβ clearance, leading to its accumulation and may accelerate neurodegeneration and cognitive decline (13).

4. Genetic makeup, aging, environmental, lifestyle, and disease risk

Reproductive aging is closely intertwined with overall biological aging, with menopause serving as a key indicator of an individual's aging trajectory. Genetic factors influencing menopause also impact aging processes at the cellular level (14).

4.1. DNA repair mechanisms and aging

Several genes involved in menopause timing are also crucial for DNA damage response and repair. The gradual accumulation of DNA damage contributes to aging, and compromised DNA repair mechanisms can accelerate ovarian aging (15). For example, mutations in genes such as CHEK2, ATM, and XRCC1, which regulate DNA damage repair pathways, have been associated with early menopause and increased susceptibility to age-related diseases (16,17)

4.2. Epigenetics and menopause

Epigenetic modifications, such as DNA methylation and histone modifications, influence gene expression and play a role in reproductive aging. Studies have shown that early menopause is associated with specific DNA methylation patterns linked to accelerated biological aging (18). This suggests that genetic and epigenetic factors collectively contribute to menopause timing and its effects on aging-related diseases. Recent findings indicate that specific lifestyle elements, including stress reduction, exercise, and nutrition, can influence epigenetic regulation of genes involved in menopause. Understanding these interactions could open new avenues for personalized health strategies aimed at delaying menopause and reducing disease risks associated with aging (19).

4.3. Environmental and lifestyle influences on disease risk

Lifestyle and environmental factors also play a role in menopausal transition through epigenetic modifications. Chronic stress is another environmental factor that can alter epigenetic regulation,

particularly through modifications in glucocorticoid receptor genes. Persistent exposure to high levels of cortisol has been shown to induce hypermethylation of the NR3C1 gene, which encodes the glucocorticoid receptor. Furthermore, exposure to endocrine-disrupting chemicals (EDCs), such as bisphenol A (BPA) and phthalates, can lead to epigenetic changes that accelerate ovarian aging. Studies have shown that BPA exposure can induce hypomethylation of genes regulating estrogen signaling, potentially leading to an earlier onset of menopause and increased risk of hormone-related cancers (20).

5. Future directions and implications

Ongoing research in genetics and menopause is paving the way for potential interventions to modulate menopause timing and mitigate health risks. Advances in precision medicine and genetic testing may allow for early identification of women at risk for early or late menopause, enabling proactive healthcare measures. Hormone replacement therapy (HRT) tailored to an individual's genetic profile may also provide safer and more effective treatment options (21-23). For example, genetic variations in estrogen metabolism genes such as CYP1A1, CYP1B1, and COMT influence how a woman processes and responds to estrogen therapy (23-26). Women with certain CYP1B1 variants may metabolize estrogen more slowly, increasing their risk of hormone-related cancers if given standard HRT. In contrast, those with efficient estrogen metabolism may benefit from a customized dosage that optimizes efficacy while minimizing side effects. By incorporating genetic screening into treatment plans, healthcare providers can personalize HRT to maximize benefits and reduce potential risks, ensuring a safer approach for menopausal symptom management. As precision medicine continues to evolve, integrating genetic, epigenetic, and lifestyle factors will be essential in promoting healthy aging and reducing disease burden in menopausal and postmenopausal women (27).

5.1. Potential interventions

Targeted therapies based on genetic insights could help manage menopause-related health issues. For instance, hormone replacement therapy (HRT) tailored to an individual's genetic profile may offer more effective and personalized treatment options while minimizing risks. Additionally, emerging research on ovarian tissue preservation and regenerative medicine holds promise for extending the reproductive lifespan in women with early menopause predisposition (28). While lifestyle changes may not significantly alter the timing of menopause itself, they can positively impact overall health and potentially mitigate some of the risks associated with earlier menopause (29). Chronic stress can exacerbate menopausal symptoms (30). Techniques like yoga, meditation, and deep breathing can be beneficial. A healthy diet high in calcium, whole grains, fruits, and vegetables can lower cardiovascular risk and promote bone health. Exercise is crucial for maintaining bone density, cardiovascular health, and overall well-being (31).

5.2. Personalized healthcare strategies

With increasing access to genetic screening, women can gain a better understanding of their reproductive health risks and make informed decisions regarding family planning and disease prevention. Integrating genetic data with lifestyle and environmental factors will be crucial in developing comprehensive health management strategies tailored to individual needs.

6. Conclusion

Genetic research has significantly enhanced our understanding of menopause timing and its implications for aging and disease risk. Identifying key genetic variants associated with menopause has provided critical insights into reproductive aging mechanisms and their connections to overall health. Menopause timing is influenced by a complex interplay of genetic, epigenetic, environmental, and lifestyle factors, making it a crucial area of study for developing targeted interventions and personalized healthcare strategies.

Early menopause is linked to an increased risk of cardiovascular diseases and osteoporosis, whereas late menopause is associated with a heightened risk of hormone-related cancers.

Understanding these genetic associations helps anticipate potential health concerns and implement prophylactic measures. Advancements in genome-wide association studies (GWAS) and epigenetics have paved the way for improved predictions regarding menopause onset, enabling healthcare providers to offer better guidance and treatments to women approaching this life stage.

Moreover, emerging research in regenerative medicine and ovarian tissue preservation presents promising avenues for extending reproductive lifespan and mitigating adverse health effects. Hormone replacement therapy (HRT) tailored to an individual's genetic profile may also provide safer and more effective treatment options. Future research should focus on expanding genetic databases, exploring novel gene-environment interactions, and developing comprehensive health strategies to improve quality of life. By leveraging these scientific advancements, we can enhance reproductive health, ensure better disease management, and contribute to the longevity and well-being of aging populations. Identifying key genetic variants associated with menopause has provided insights into reproductive aging mechanisms and their connections to overall health. As scientific advancements continue, integrating genetic, epigenetic, and environmental data will be essential in developing personalized strategies to promote healthy aging and reduce disease burden in menopausal and postmenopausal women. By leveraging genetic insights, researchers and healthcare professionals can work toward optimizing reproductive health and enhancing longevity in aging populations.

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