Table 22-4 Characteristics of Type I and Type II Endometrial Carcinoma

Characteristics	Type I	Type II
Age	55-65 yr	65-75 yr
Clinical setting	Unopposed estrogen Obesity Hypertension Diabetes	Atrophy Thin physique
Morphology	Endometrioid	Serous Clear cell Mixed müllerian tumor
Precursor	Hyperplasia	Serous endometrial intraepithelial carcinoma
Mutated genes/ genetic abnormalities	*PTEN* *ARID1A* (regulator of chromatin) *PIK3CA* (PI3K) *KRAS* *FGF2* (growth factor) MSI* *CTNNB1* (Wnt signaling) *TP53*	*TP53* Aneuploidy *PIK3CA* (PI3K) *FBXW7* (regulator of MYC, cyclin E) *CHD4* (regulator of chromatin) *PPP2R1A* (PP2A)
Behavior	Indolent Spreads via lymphatics	Aggressive Intraperitoneal and lymphatic spread

*MSI, Microsatellite instability; CTNNB1, beta-catenin gene

are somewhat unique in that individual tumors may harbor multiple mutations that increase PI3K/AKT signaling, suggesting that tumor development and progression is fostered by successive increases in signal strength. Among the mutations that impact the PI3K/AKT pathway in endometrial carcinomas are the following:

- Mutations in the *PTEN* tumor suppressor gene have been identified in 30% to 80% of endometrioid carcinomas.
- *PIK3CA*, an oncogene that encodes the catalytic subunit of PI3K, harbors activating mutations in approximately 40% of endometrioid carcinomas. *PIK3CA* mutations rarely occur in atypical hyperplasias, suggesting that mutations in *PIK3CA* play a role in invasion.
- Mutations that activate *KRAS*, which also stimulates PI3K/AKT signaling, are found in approximately 25% of cases.
- Loss-of-function mutations in *ARID1A*, a regulator of chromatin structure, occur in approximately one-third of tumors. Of interest, *ARID1A* is also frequently mutated in ovarian endometrioid and clear cell carcinomas, tumors that arise within endometriosis. Although the mechanisms are not yet clear, loss of ARID1A function also enhances PI3K/AKT signaling.

Defects involving *DNA mismatch repair genes* are found in about 20% of sporadic tumors and are particularly prevalent in endometrial carcinomas arising in women from

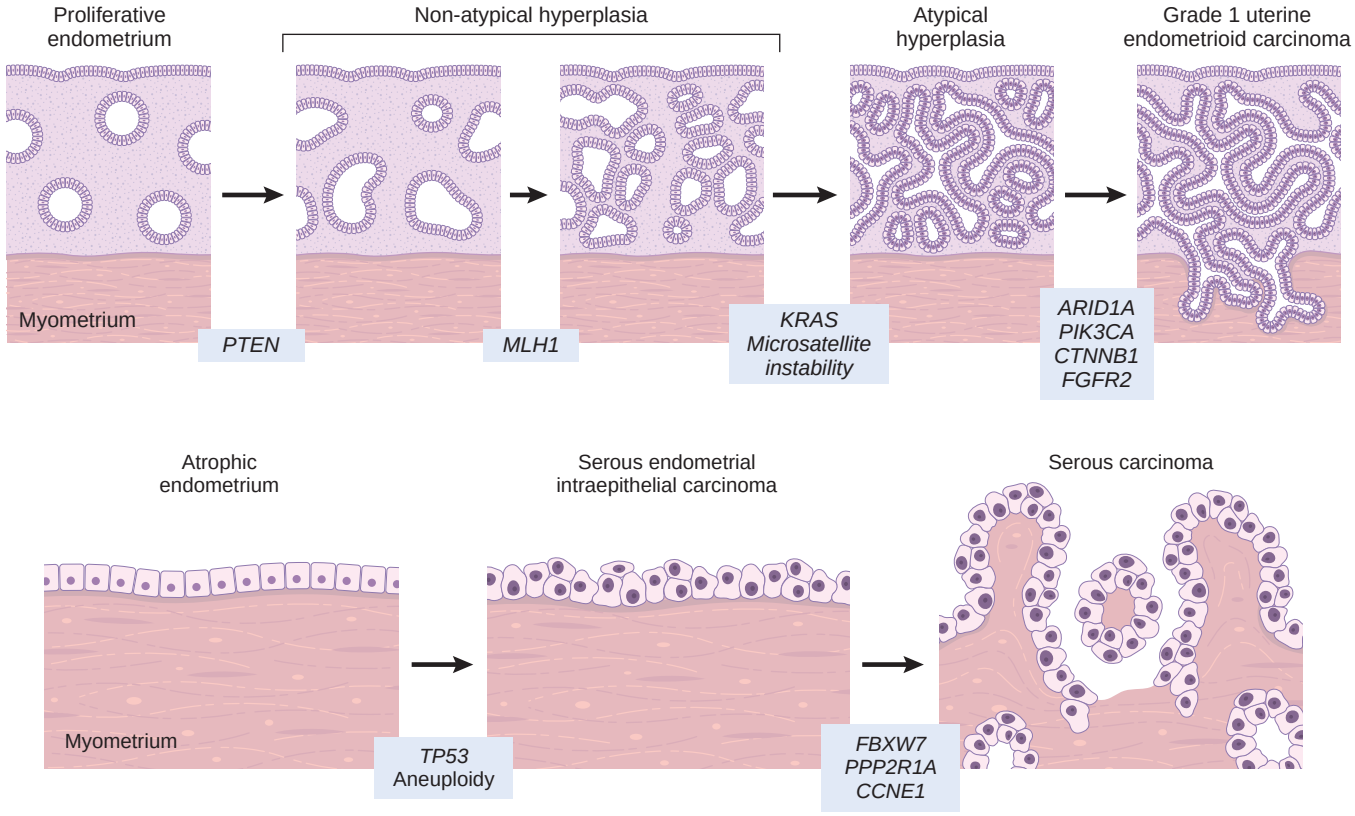

Figure 22-24 **A,** Schematic depicting the development of type I endometrial carcinoma arising in the setting of hyperplasia. **B,** Schematic diagram of the development of type II endometrial carcinoma. The most common molecular genetic alterations are shown at the time they are most likely to occur during the progression of the disease. *MI, Microsatellite instability. *CTNNB1*, beta-catenin gene; *PPP2R1A*, PP2A gene; *CCNE1*, cyclin E gene.