



BÖLÜM 5

JİNEKOLOJİK KANSERLERDE GENETİK RİSK VE TESTLER

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İnsan genom projesinin 2003 yılında tamamlanmasıyla birlikte kadın sağlığında da çok sayıda yenilik ve gelişme kaydedilmiştir. Özellikle kişiselleştirilmiş kanser riskini öngörmede kalıtsal kanser testlerine dayanan önemli adımlar atılmıştır. Ailesel kanser sendromlarının tespiti ile kişiselleştirilmiş kalifiye bir değerlendirme sağlanarak, gerekli bilgilendirilmelerin yapılması doğrultusunda kanser taramasının erken dönemlerde başlaması ve kanser gelişimini önleyici metotlarla morbidite ve mortalitenin azaltılması sağlanır.

Esasen kadınlar için en yaygın sağlık hizmeti veren birinci basamak aile hekimlerinin ve jinekologların, hasta ve yakınlarına kanıtlanmış tarama ve risk azaltma önlemlerini uygulayabilmeleri için, kansere genetik yatkınlık barındırabilecek kadınları tanıabilmeleri gerekmektedir. Daha yeni kemoterapötik ajanların, hedefe yönelik tedavilerin ve immünoterapilerin ortaya çıkmasıyla birlikte kanser tedavisinde olağanüstü ilerleme kaydedilmiş olsa da, malignitelerin tedavisi hala kesin olarak garanti edilememektedir. Bu nedenle, kanserlerin tedaviden ziyade birincil önlenmesi altın standart olarak kabul edilmelidir.

Jinekolojik kanserlerde moleküller ve genetik olaylarla ilgili bilgimizin giderek artmasına rağmen halen buz dağının tepesini görmekteyiz. Her yeni bilgi ile birlikte daha fazlasını öğrenmeye devam ediyoruz.

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kanser genetiği uzmanlarından ziyade, hastaların en sık ziyaret ettiği birinci basamak hekimlerinin sorumluluğundadır. Bu nedenle, tüm hekimler potansiyel bir kalıtsal sendromun uyarı işaretlerini belirleyebilmek için iyi bir kanser öyküsü almak ve bu bireyleri (ve ailelerini) kansersiz ve sağlıklı kalma şanslarını önemli ölçüde artırabilecek kaynaklara yönlendirmekle yükümlüdür.

KAYNAKLAR

1. Bokhman JV. Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol.* 1983;15(1):10-17. doi:10.1016/0090-8258(83)90111-7
2. Walsh T, Casadei S, Lee MK, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proc Natl Acad Sci U S A.* 2011;108(44):18032-18037. doi:10.1073/pnas.1115052108
3. King MC, Marks JH, Mandell JB; New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science.* 2003;302(5645):643-646. doi:10.1126/science.1088759
4. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies [published correction appears in *Am J Hum Genet.* 2003 Sep;73(3):709]. *Am J Hum Genet.* 2003;72(5):1117-1130. doi:10.1086/375033
5. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet.* 1998;62(3):676-689. doi:10.1086/301749
6. Lancaster JM, Powell CB, Chen LM, Richardson DL; SGO Clinical Practice Committee. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions [published correction appears in *Gynecol Oncol.* 2015 Sep;138(3):765]. *Gynecol Oncol.* 2015;136(1):3-7. doi:10.1016/j.ygyno.2014.09.009
7. Daly MB, Pilarski R, Berry M, et al. NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2017. *J Natl Compr Canc Netw.* 2017;15(1):9-20. doi:10.6004/jnccn.2017.0003
8. Stadler ZK, Salo-Mullen E, Patil SM, et al. Prevalence of BRCA1 and BRCA2 mutations in Ashkenazi Jewish families with breast and pancreatic cancer. *Cancer.* 2012;118(2):493-499. doi:10.1002/cncr.26191
9. Mersch J, Jackson MA, Park M, et al. Cancers associated with BRCA1 and BRCA2 mutations other than breast and ovarian [published correction appears in *Cancer.* 2015 Jul 15;121(14):2474-5]. *Cancer.* 2015;121(2):269-275. doi:10.1002/cncr.29041
10. Shu CA, Pike MC, Jotwani AR, et al. Uterine Cancer After Risk-Reducing Salpingo-oophorectomy Without Hysterectomy in Women With BRCA Mutations. *JAMA Oncol.* 2016;2(11):1434-1440. doi:10.1001/jamaoncol.2016.1820

11. Tiwari AK, Roy HK, Lynch HT. Lynch syndrome in the 21st century: clinical perspectives. *QJM*. 2016;109(3):151-158. doi:10.1093/qjmed/hcv137
12. Provenzale D, Gupta S, Ahnen DJ, et al. Genetic/Familial High-Risk Assessment: Colorectal Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2016;14(8):1010-1030. doi:10.6004/jnccn.2016.0108
13. Barrow E, Hill J, Evans DG. Cancer risk in Lynch Syndrome. *Fam Cancer*. 2013;12(2):229-240. doi:10.1007/s10689-013-9615-1
14. Chui MH, Gilks CB, Cooper K, Clarke BA. Identifying Lynch syndrome in patients with ovarian carcinoma: the significance of tumor subtype. *Adv Anat Pathol*. 2013;20(6):378-386. doi:10.1097/PAP.0b013e3182a92cf8
15. Chui MH, Ryan P, Radigan J, et al. The histomorphology of Lynch syndrome-associated ovarian carcinomas: toward a subtype-specific screening strategy. *Am J Surg Pathol*. 2014;38(9):1173-1181. doi:10.1097/PAS.0000000000000298
16. Palles C, Cazier JB, Howarth KM, et al. Germline mutations affecting the proof-reading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas [published correction appears in *Nat Genet*. 2013 Jun;45(6):713. Guarino Almeida, Estrella [corrected to Guarino, Estrella]]. *Nat Genet*. 2013;45(2):136-144. doi:10.1038/ng.2503
17. Briggs S, Tomlinson I. Germline and somatic polymerase ϵ and δ mutations define a new class of hypermutated colorectal and endometrial cancers. *J Pathol*. 2013;230(2):148-153. doi:10.1002/path.4185
18. Bellido F, Pineda M, Aiza G, et al. POLE and POLD1 mutations in 529 kindred with familial colorectal cancer and/or polyposis: review of reported cases and recommendations for genetic testing and surveillance. *Genet Med*. 2016;18(4):325-332. doi:10.1038/gim.2015.75
19. Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C. Lifetime cancer risks in individuals with germline PTEN mutations. *Clin Cancer Res*. 2012;18(2):400-407. doi:10.1158/1078-0432.CCR-11-2283
20. van Lier MG, Wagner A, Mathus-Vliegen EM, Kuipers EJ, Steyerberg EW, van Leerdam ME. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. *Am J Gastroenterol*. 2010;105(6):1258-1265. doi:10.1038/ajg.2009.725
21. Resta N, Pierannunzio D, Lenato GM, et al. Cancer risk associated with STK11/LKB1 germline mutations in Peutz-Jeghers syndrome patients: results of an Italian multicenter study. *Dig Liver Dis*. 2013;45(7):606-611. doi:10.1016/j.dld.2012.12.018
22. McGarry TJ, Kulin HE, Zaino RJ. Peutz-Jeghers syndrome. *Am J Gastroenterol*. 2000;95(3):596-604. doi:10.1111/j.1572-0241.2000.01831.x
23. Villani A, Tabori U, Schiffman J, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study. *Lancet Oncol*. 2011;12(6):559-567. doi:10.1016/S1470-2045(11)70119-X
24. Kratz CP, Achatz MI, Brugières L, et al. Cancer Screening Recommendations for Individuals with Li-Fraumeni Syndrome. *Clin Cancer Res*. 2017;23(11):e38-e45. doi:10.1158/1078-0432.CCR-17-0408

25. Villani A, Shore A, Wasserman JD, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. *Lancet Oncol.* 2016;17(9):1295-1305. doi:10.1016/S1470-2045(16)30249-2
26. Olivier M, Goldgar DE, Sodha N, et al. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. *Cancer Res.* 2003;63(20):6643-6650.
27. Cobain EF, Milliron KJ, Merajver SD. Updates on breast cancer genetics: Clinical implications of detecting syndromes of inherited increased susceptibility to breast cancer. *Semin Oncol.* 2016;43(5):528-535. doi:10.1053/j.seminoncol.2016.10.001
28. Fernandez AF, Esteller M. Viral epigenomes in human tumorigenesis. *Oncogene.* 2010;29(10):1405-1420. doi:10.1038/onc.2009.517
29. Saavedra KP, Brebi PM, Roa JC. Epigenetic alterations in preneoplastic and neoplastic lesions of the cervix. *Clin Epigenetics.* 2012;4(1):13. Published 2012 Aug 31. doi:10.1186/1868-7083-4-13
30. Moody CA, Laimins LA. Human papillomavirus oncoproteins: pathways to transformation. *Nat Rev Cancer.* 2010;10(8):550-560. doi:10.1038/nrc2886
31. Carreras R, Alameda F, Mancebo G, et al. A study of Ki-67, c-erbB2 and cyclin D-1 expression in CIN-I, CIN-III and squamous cell carcinoma of the cervix. *Histol Histopathol.* 2007;22(6):587-592. doi:10.14670/HH-22.587
32. Ngan HY, Cheung AN, Liu SS, Yip PS, Tsao SW. Abnormal expression or mutation of TP53 and HPV in vulvar cancer. *Eur J Cancer.* 1999;35(3):481-484. doi:10.1016/s0959-8049(98)00407-9
33. Soliman PT, Oh JC, Schmeler KM, et al. Risk factors for young premenopausal women with endometrial cancer. *Obstet Gynecol.* 2005;105(3):575-580. doi:10.1097/01.AOG.0000154151.14516.f7
34. Daniels MS. Genetic testing by cancer site: uterus. *Cancer J.* 2012;18(4):338-342. doi:10.1097/PPO.0b013e3182610cc2
35. Ring KL, Bruegl AS, Allen BA, et al. Germline multi-gene hereditary cancer panel testing in an unselected endometrial cancer cohort. *Mod Pathol.* 2016;29(11):1381-1389. doi:10.1038/modpathol.2016.135
36. Win AK, Reece JC, Ryan S. Family history and risk of endometrial cancer: a systematic review and meta-analysis. *Obstet Gynecol.* 2015;125(1):89-98. doi:10.1097/AOG.0000000000000563
37. Bansal N, Yendluri V, Wenham RM. The molecular biology of endometrial cancers and the implications for pathogenesis, classification, and targeted therapies. *Cancer Control.* 2009;16(1):8-13. doi:10.1177/107327480901600102
38. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, et al. Integrated genomic characterization of endometrial carcinoma [published correction appears in Nature. 2013 Aug 8;500(7461):242]. *Nature.* 2013;497(7447):67-73. doi:10.1038/nature12113
39. Byron SA, Pollock PM. FGFR2 as a molecular target in endometrial cancer. *Future Oncol.* 2009;5(1):27-32. doi:10.2217/14796694.5.1.27

40. Mutter GL, Lin MC, Fitzgerald JT, et al. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. *J Natl Cancer Inst.* 2000;92(11):924-930. doi:10.1093/jnci/92.11.924
41. Tamura M, Gu J, Matsumoto K, Aota S, Parsons R, Yamada KM. Inhibition of cell migration, spreading, and focal adhesions by tumor suppressor PTEN. *Science.* 1998 Jun 5;280(5369):1614-7. doi: 10.1126/science.280.5369.1614. PMID: 9616126.
42. Bilbao C, Rodríguez G, Ramírez R, et al. The relationship between microsatellite instability and PTEN gene mutations in endometrial cancer. *Int J Cancer.* 2006;119(3):563-570. doi:10.1002/ijc.21862
43. Koh WJ, Abu-Rustum NR, Bean S, et al. Uterine Neoplasms, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2018;16(2):170-199. doi:10.6004/jnccn.2018.0006
44. Lax SF, Kendall B, Tashiro H, Slebos RJ, Hedrick L. The frequency of p53, K-ras mutations, and microsatellite instability differs in uterine endometrioid and serous carcinoma: evidence of distinct molecular genetic pathways. *Cancer.* 2000;88(4):814-824.
45. Doll A, Abal M, Rigau M, et al. Novel molecular profiles of endometrial cancer-new light through old windows. *J Steroid Biochem Mol Biol.* 2008;108(3-5):221-229. doi:10.1016/j.jsbmb.2007.09.020
46. Luchini C, Veronese N, Solmi M, et al. Prognostic role and implications of mutation status of tumor suppressor gene ARID1A in cancer: a systematic review and meta-analysis. *Oncotarget.* 2015;6(36):39088-39097. doi:10.18632/oncotarget.5142
47. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [published correction appears in CA Cancer J Clin. 2020 Jul;70(4):313]. *CA Cancer J Clin.* 2018;68(6):394-424. doi:10.3322/caac.21492
48. Kurman RJ, Shih IeM. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer--shifting the paradigm. *Hum Pathol.* 2011;42(7):918-931. doi:10.1016/j.humpath.2011.03.003
49. Kurman RJ, Shih IeM. Pathogenesis of ovarian cancer: lessons from morphology and molecular biology and their clinical implications. *Int J Gynecol Pathol.* 2008;27(2):151-160. doi:10.1097/PGP.0b013e318161e4f5
50. Pennington KP, Walsh T, Harrell MI, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. *Clin Cancer Res.* 2014;20(3):764-775. doi:10.1158/1078-0432.CCR-13-2287
51. Jasin M. Homologous repair of DNA damage and tumorigenesis: the BRCA connection. *Oncogene.* 2002;21(58):8981-8993. doi:10.1038/sj.onc.1206176
52. O'Quinn C, Steele P, Ludman MD, Kieser K. Hereditary breast ovarian cancer syndromes in the Maritimes. *J Obstet Gynaecol Can.* 2010;32(2):155-159. doi:10.1016/S1701-2163(16)34430-9
53. Ramus SJ, Gayther SA. The contribution of BRCA1 and BRCA2 to ovarian cancer. *Mol Oncol.* 2009;3(2):138-150. doi:10.1016/j.molonc.2009.02.001

54. Neri A, Rabinerson D, Kaplan B, Levavi H. Hereditary ovarian cancer. *Isr J Med Sci.* 1995 Feb-Mar;31(2-3):172-5. PMID: 7744589.
55. Fishman DA, Cohen L, Blank SV, et al. The role of ultrasound evaluation in the detection of early-stage epithelial ovarian cancer. *Am J Obstet Gynecol.* 2005;192(4):1214-1222. doi:10.1016/j.ajog.2005.01.041
56. Johnson CC, Kessel B, Riley TL, et al. The epidemiology of CA-125 in women without evidence of ovarian cancer in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial. *Gynecol Oncol.* 2008;110(3):383-389. doi:10.1016/j.ygyno.2008.05.006
57. Skates SJ, Greene MH, Buys SS, et al. Early Detection of Ovarian Cancer using the Risk of Ovarian Cancer Algorithm with Frequent CA125 Testing in Women at Increased Familial Risk - Combined Results from Two Screening Trials. *Clin Cancer Res.* 2017;23(14):3628-3637. doi:10.1158/1078-0432.CCR-15-2750
58. Renkonen-Sinisalo L, Bützow R, Leminen A, Lehtovirta P, Mecklin JP, Järvinen HJ. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. *Int J Cancer.* 2007;120(4):821-824. doi:10.1002/ijc.22446
59. Gerritzen LH, Hoogerbrugge N, Oei AL, et al. Improvement of endometrial biopsy over transvaginal ultrasound alone for endometrial surveillance in women with Lynch syndrome. *Fam Cancer.* 2009;8(4):391-397. doi:10.1007/s10689-009-9252-x