

BÖLÜM 36

HEREDİTER KANSER SENDROMLARI

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GİRİŞ

Hereditör kanser sendromları, kansere sebep olabileceği bilinen mutasyonların kalıtımına bağlı gelişir. Genellikle erken yaşta ortaya çıkmaları, aile öyküsünün olması, çoklu primer veya bilateral tümörler şeklinde görülmeleri karakteristik özellikleridir.

Sıklıkla tümör süpresör genlerinin mutasyonlarına bağlı gelişirler. DNA tamir genlerinde, anjiyogeneze ilişkili genlerde ve onkogenlerde ortaya çıkan mutasyonlara bağlı da gelişebildikleri bilinmektedir. En sık görülen hereditör kanser sendromlarına meme-over kanseri sendromu ve hereditör nonpolipozis kolorektal kanserleri (Lynch sendromu) örnek verilebilir.

Bazı nadir görülen kanser durumlarında hereditör kanser sendromları özellikle akla gelmelidir. Adrenokortikal kanserler, karsinoid tümörler, difüz gastrik kanser, fallop tüp/primer periton kanserleri, leiomyosar-

kom, medüller tiroid kanseri, paraganglioma, feokromasitoma, kromofob tip renal hücreli kanser, onkositoma, bazı seks kort tümörleri ve sebase karsinomlar bu tip tümörlere örnek verilebilir.

BRCA1 ve BRCA2 Mutasyonları İle İlişkili Meme ve Over Kanserleri

Hereditör meme ve over kanserlerinin %80 den fazlası BRCA 1 ve BRCA 2 mutasyonlarına bağlı gelişir. Otozomal dominant kalıtım gösterirler ve penetransları yaklaşık %85 tir. Tüm meme ve over kanseri tanısı alan hastalar içinde hereditör meme ve over kanseri sıklığı %7-14 arası değişmektedir.

BRCA1 ve BRCA2, DNA hasar tamiri için önemli olan tümör süpresör genlerdir. Mutasyonları sonucunda DNA tamir mekanizmaları bozulur ve kanser riski belirgin artar. Bu mutasyonların toplumda görülme sıklığı 1/300 ile 1/800 arası değişmektedir. Bazı etnik gruplar da (Askenazi Yahudileri, İzlandalılar)

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Monoallelik mutasyon taşıyıcılarında kanser gelişme riski düşük olduğu için tarama önerileri birinci derece akrabalarında kolon kanseri olan kişilere benzerdir. İlk kanser tanısı almış aile bireyinin tanı yaşından 10 yıl geriye gidilerek veya 40 yaşından itibaren her 5 yılda bir kolonoskopi ile tarama önerilir.

Kemoprevansiyon

MAP ta kemoprevansiyon için yapılmış bir çalışma yoktur.

KAYNAKLAR

- Berger AH, Pandolfi PP. Cancer susceptibility syndromes. In: DeVita Jr. VT, Lawrence TS, Rosenberg SA, editors. DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology. 11th ed. Wolters Kluwer; 2019
- Robson ME, Bradbury AR, Arun B, et al American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. J Clin Oncol. 2015 Nov 1;33(31):3660-7. doi: 10.1200/JCO.2015.63.0996. Epub 2015 Aug 31. PMID: 26324357
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 1.2022. www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf (Accessed on August 16, 2021).
- LaDuca H, Polley EC, Yussuf A, et al. A clinical guide to hereditary cancer panel testing: evaluation of gene-specific cancer associations and sensitivity of genetic testing criteria in a cohort of 165,000 high-risk patients. Genet Med 2020; 22:407.
- Peshkin, BN., Isaacs, C. Overview of hereditary breast and ovarian cancer syndromes associated with genes other than BRCA1/2. Available <https://www.uptodate.com/contents/overview-of-hereditary-breast-and-ovarian-cancer-syndromes-associated-with-genes-other-than-brca1-2>. Last updated Sep29, 2021.
- Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. J Clin Oncol. 2004 Feb 15;22(4):735-42. doi: 10.1200/JCO.2004.05.055. PMID: 14966099.
- Couch FJ, Johnson MR, Rabe KG, et al. The prevalence of BRCA2 mutations in familial pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2007 Feb;16(2):342-6. doi: 10.1158/1055-9965.EPI-06-0783. PMID: 17301269.
- Beiner ME, Finch A, Rosen B, et al Hereditary Ovarian Cancer Clinical Study Group. The risk of endometrial cancer in women with BRCA1 and BRCA2 mutations. A prospective study. Gynecol Oncol. 2007 Jan;104(1):7-10. doi: 10.1016/j.ygyno.2006.08.004. Epub 2006 Sep 8. PMID: 16962648.
- BRCA1 and BRCA2 Gene Mutations and Colorectal Cancer Risk: Systematic Review and Meta-analysis. J Natl Cancer Inst. 2018 Nov 1;110(11):1178-1189. doi: 10.1093/jnci/djy148. PMID: 30380096.
- Evans DG, Moran A, Hartley R, et al. Long-term outcomes of breast cancer in women aged 30 years or younger, based on family history, pathology and BRCA1/BRCA2/TP53 status. Br J Cancer 2010; 102:1091.
- Metcalfe K, Lynch HT, Foulkes WD, et al. Effect of Oophorectomy on Survival After Breast Cancer in BRCA1 and BRCA2 Mutation Carriers. JAMA Oncol. 2015 Jun;1(3):306-13. doi: 10.1001/jamaoncol.2015.0658. PMID: 26181175.
- Isaacs C, Peshkin BN. Cancer risks and management of BRCA1/2 carriers without cancer. Available at https://www.uptodate.com/contents/Cancer_risks_and_management_of_BRCA1/2_carriers_without_cancer. Last updated: Jun 02, 2021.
- NCCN Clinical Practice Guidelines in Oncology. Breast cancer risk reduction. Version 1.2020. www.nccn.org/professionals/physician_gls/ (Accessed on November 11, 2020).
- Paluch-Shimon S, Cardoso F, et al. ESMO Guidelines Committee. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. Ann Oncol. 2016 Sep;27(suppl 5):v103-v110. doi: 10.1093/annonc/mdw327. Erratum in: Ann Oncol. 2017 Jul 1;28(suppl 4):iv167-iv168. PMID: 27664246.
- American Cancer Society Breast Cancer Advisory Group. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2007 Mar-Apr;57(2):75-89. doi: 10.3322/canjclin.57.2.75. Erratum in: CA Cancer J Clin. 2007 May-Jun;57(3):185. PMID: 17392385.
- Moran A, O'Hara C, Khan S, Passaperuma K, Warner E, Causer PA, et al Long-term results of screening with magnetic resonance imaging in women with BRCA mutations. Br J Cancer. 2012 Jun 26;107(1):24-30. doi: 10.1038/bjc.2012.204. Epub 2012 May 15. PMID: 22588560; PMCID: PMC3389408.
- Ciatto S, Houssami N, Bernardi D, et al Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. Lancet Oncol. 2013 Jun;14(7):583-9. doi: 10.1016/S1470-2045(13)70134-7. Epub 2013 Apr 25. PMID: 23623721
- Rebeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol. 2004 May 15;22(6):1055-62. doi: 10.1200/JCO.2004.04.188. Epub 2004 Feb 23. PMID: 14981104.



19. Jakub JW, Peled AW, Gray RJ, et al. Oncologic Safety of Prophylactic Nipple-Sparing Mastectomy in a Population With BRCA Mutations: A Multi-institutional Study. *JAMA Surg.* 2018 Feb 1;153(2):123-129. doi: 10.1001/jamasurg.2017.3422. PMID: 28903167; PMCID: PMC5838709.
20. Xiao YL, Wang K, Liu Q, et al. Risk Reduction and Survival Benefit of Risk-Reducing Salpingo-oophorectomy in Hereditary Breast Cancer: Meta-analysis and Systematic Review. *Clin Breast Cancer.* 2019 Feb;19(1):e48-e65. doi: 10.1016/j.clbc.2018.09.011. Epub 2018 Oct 4. PMID: 30470623.
21. Hunt KK, Euhus DM, Boughey JC, et al. Society of Surgical Oncology Breast Disease Working Group Statement on Prophylactic (Risk-Reducing) Mastectomy. *Ann Surg Oncol* 2017; 24:375.
22. Hartmann LC, Lindor NM. The Role of Risk-Reducing Surgery in Hereditary Breast and Ovarian Cancer. *N Engl J Med* 2016; 374:454.
23. Kurian AW, Sigal BM, Plevritis SK. Survival analysis of cancer risk reduction strategies for BRCA1/2 mutation carriers. *J Clin Oncol* 2010; 28:222.
24. Michaelson-Cohen R, Gabizon-Peretz S, Armon S, et al. Breast cancer risk and hormone replacement therapy among BRCA carriers after risk-reducing salpingo-oophorectomy. *Eur J Cancer* 2021; 148:95.
25. Holmberg L, Iversen OE, Rudenstam CM, et al. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. *J Natl Cancer Inst* 2008; 100:475.
26. Evans DG. Li-Fraumeni Syndrome. Available at <https://www.uptodate.com/contents/li-fraumeni-syndrome>. Last accessed Feb 25, 2021.
27. Stjepanovic N, Moreira L, Carneiro F, Balaguer F, Cervantes A, Balmaña J, Martinelli E; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Hereditary gastrointestinal cancers: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol.* 2019 Oct 1;30(10):1558-1571. doi: 10.1093/annonc/mdz233. PMID: 31378807.
28. Stoffel EM, Mangu PB, Gruber SB, et al. American Society of Clinical Oncology; European Society of Clinical Oncology. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines. *J Clin Oncol.* 2015 Jan 10;33(2):209-17. doi: 10.1200/JCO.2014.58.1322. Epub 2014 Dec 1. PMID: 25452455; PMCID: PMC5321096.
29. Libé R, Bertherat J. Molecular genetics of adrenocortical tumours, from familial to sporadic diseases. *Eur J Endocrinol* 2005; 153:477.
30. Chompret A, Abel A, Stoppa-Lyonnet D, et al. Sensitivity and predictive value of criteria for p53 germline mutation screening. *J Med Genet* 2001; 38:43.
31. Kratz CP, Achatz MI, Brugières L, et al. Cancer Screening Recommendations for Individuals with Li-Fraumeni Syndrome. *Clin Cancer Res* 2017; 23:e38.
32. van Lier MG, Wagner A, Mathus-Vliegen EM, et al. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. *Am J Gastroenterol* 2010; 105:1258.
33. Lim W, Hearle N, Shah B, et al. Further observations on LKB1/STK11 status and cancer risk in Peutz-Jeghers syndrome. *Br J Cancer* 2003; 89:308.
34. Sansal I, Sellers WR. The biology and clinical relevance of the PTEN tumor suppressor pathway. *J Clin Oncol* 2004; 22:2954.
35. Pilarski R. Cowden syndrome: a critical review of the clinical literature. *J Genet Couns.* 2009 Feb;18(1):13-27. doi: 10.1007/s10897-008-9187-7. Epub 2008 Oct 30. PMID: 18972196.
36. Fitzgerald RC, Hardwick R, Huntsman D, et al. Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. *J Med Genet* 2010; 47:436.
37. Hansford S, Kaurah P, Li-Chang H, et al. Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. *JAMA Oncol* 2015; 1:23.
38. Southey MC, Goldgar DE, Winqvist R, et al. PALB2, CHEK2 and ATM rare variants and cancer risk: data from COGS. *J Med Genet* 2016; 53:800.
39. Antoniou AC, Casadei S, Heikkinen T, et al. Breast-cancer risk in families with mutations in PALB2. *N Engl J Med* 2014; 371:497.
40. Hofstadter EW, Domchek SM, Miron A, et al. PALB2 mutations in familial breast and pancreatic cancer. *Fam Cancer* 2011; 10:225.
41. Wong MW, Nordfors C, Mossman D, et al. BRIP1, PALB2, and RAD51C mutation analysis reveals their relative importance as genetic susceptibility factors for breast cancer. *Breast Cancer Res Treat* 2011; 127:853.
42. Vahteristo P, Bartkova J, Eerola H, et al. A CHEK2 genetic variant contributing to a substantial fraction of familial breast cancer. *Am J Hum Genet* 2002; 71:432.
43. Renwick A, Thompson D, Seal S, et al. ATM mutations that cause ataxia-telangiectasia are breast cancer susceptibility alleles. *Nat Genet* 2006; 38:873.
44. Thompson D, Duedal S, Kirner J, et al. Cancer risks and mortality in heterozygous ATM mutation carriers. *J Natl Cancer Inst* 2005; 97:813.
45. Ratajska M, Antoszewska E, Piskorz A, et al. Cancer predisposing BARD1 mutations in breast-ovarian cancer families. *Breast Cancer Res Treat* 2012; 131:89.
46. Song H, Dicks E, Ramus SJ, et al. Contribution of Germline Mutations in the RAD51B, RAD51C, and RAD51D Genes to Ovarian Cancer in the Population. *J Clin Oncol* 2015; 33:2901.
47. Feldkamp MM, Gutmann DH, Guha A. Neurofibromatosis type 1: piecing the puzzle together. *Can J Neurol Sci* 1998; 25:181.
48. Ramus SJ, Song H, Dicks E, et al. Germline Mutations in the BRIP1, BARD1, PALB2, and NBN Genes in Women With Ovarian Cancer. *J Natl Cancer Inst* 2015; 107.

49. Hall MJ, Neuman CC. Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis Available at <https://www.uptodate.com/contents/lynch-syndrome-hereditary-nonpolyposis-colorectal-cancer-clinical-manifestations-and-diagnosis>. Last updated Nov 20, 2020.
50. Hall MJ. Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management. Available at <https://www.uptodate.com/contents/lynch-syndrome-hereditary-nonpolyposis-colorectal-cancer-cancer-screening-and-management>. Last updated Nov 20, 2020.
51. Samadder NJ, Smith KR, Wong J, et al. Cancer Risk in Families Fulfilling the Amsterdam Criteria for Lynch Syndrome. *JAMA Oncol* 2017; 3:1697.
52. Yurgelun MB, Kulke MH, Fuchs CS, et al. Cancer Susceptibility Gene Mutations in Individuals With Colorectal Cancer. *J Clin Oncol* 2017; 35:1086.
53. Bonadona V, Bonaïti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA* 2011; 305:2304.
54. Grindedal EM, Møller P, Eeles R, et al. Germ-line mutations in mismatch repair genes associated with prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2009; 18:2460.
55. Koornstra JJ, Mourits MJ, Sijmons RH, et al. Management of extracolonic tumours in patients with Lynch syndrome. *Lancet Oncol* 2009; 10:400.
56. Parry S, Win AK, Parry B, et al. Metachronous colorectal cancer risk for mismatch repair gene mutation carriers: the advantage of more extensive colon surgery. *Gut* 2011; 60:950.
57. Giardiello FM, Allen JJ, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on colorectal cancer. *Gastroenterology* 2014; 147:502.
58. Dominguez-Valentin M, Sampson JR, Møller P, et al. Analysis in the Prospective Lynch Syndrome Database identifies sarcoma as part of the Lynch syndrome tumor spectrum. *Int J Cancer* 2021; 148:512.
59. Ponti G, Ponz de Leon M. Muir-Torre syndrome. *Lancet Oncol* 2005; 6:980.
60. Chen S, Wang W, Lee S, et al. Prediction of germline mutations and cancer risk in the Lynch syndrome. *JAMA* 2006; 296:1479.
61. Engel C, Rahner N, Schulmann K, et al. Efficacy of annual colonoscopic surveillance in individuals with hereditary nonpolyposis colorectal cancer. *Clin Gastroenterol Hepatol* 2010; 8:174.
62. de Jong AE, Hendriks YM, Kleibeuker JH, et al. Decrease in mortality in Lynch syndrome families because of surveillance. *Gastroenterology* 2006; 130:665.
63. Dominguez-Valentin M, Crosbie EJ, Engel C, et al. Risk-reducing hysterectomy and bilateral salpingo-oophorectomy in female heterozygotes of pathogenic mismatch repair variants: a Prospective Lynch Syndrome Database report. *Genet Med* 2021; 23:705.
64. Chung DC. Clinical manifestations and diagnosis of familial adenomatous polyposis. Available at <https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-familial-adenomatous-polypsis>. Last updated Jul 21, 2020.
65. Moisio AL, Järvinen H, Peltomäki P. Genetic and clinical characterisation of familial adenomatous polyposis: a population based study. *Gut* 2002; 50:845.
66. Heinen CD. Genotype to phenotype: analyzing the effects of inherited mutations in colorectal cancer families. *Mutat Res* 2010; 693:32.
67. Saurin JC, Ligneau B, Ponchon T, et al. The influence of mutation site and age on the severity of duodenal polyposis in patients with familial adenomatous polyposis. *Gastrointest Endosc* 2002; 55:342.
68. Lynch HT, Smyrk T, McGinn T, et al. Attenuated familial adenomatous polyposis (AFAP). A phenotypically and genotypically distinctive variant of FAP. *Cancer* 1995; 76:2427.
69. Sieber OM, Segditsas S, Knudsen AL, et al. Disease severity and genetic pathways in attenuated familial adenomatous polyposis vary greatly but depend on the site of the germline mutation. *Gut* 2006; 55:1440.
70. Groen EJ, Roos A, Muntinghe FL, et al. Extra-intestinal manifestations of familial adenomatous polyposis. *Ann Surg Oncol* 2008; 15:2439.
71. Grover S, Stoffel E. MUTYH-associated polyposis. Available at <https://www.uptodate.com/contents/Mutyh-associated-polyposis>. Last updated Jul 14, 2020.
72. Sieber OM, Lipton L, Crabtree M, et al. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. *N Engl J Med* 2003; 348:791.
73. Theodoratou E, Campbell H, Tenesa A, et al. A large-scale meta-analysis to refine colorectal cancer risk estimates associated with MUTYH variants. *Br J Cancer* 2010; 103:1875.
74. Win AK, Cleary SP, Dowty JG, et al. Cancer risks for monoallelic MUTYH mutation carriers with a family history of colorectal cancer. *Int J Cancer* 2011; 129:2256.
75. Win AK, Dowty JG, Cleary SP, et al. Risk of colorectal cancer for carriers of mutations in MUTYH, with and without a family history of cancer. *Gastroenterology* 2014; 146:1208.
76. Jenkins MA, Croitoru ME, Monga N, et al. Risk of colorectal cancer in monoallelic and biallelic carriers of MYH mutations: a population-based case-family study. *Cancer Epidemiol Biomarkers Prev* 2006; 15:312.
77. Lubbe SJ, Di Bernardo MC, Chandler IP, Houlston RS. Clinical implications of the colorectal cancer risk associated with MUTYH mutation. *J Clin Oncol* 2009; 27:3975.
78. Win AK, Reece JC, Dowty JG, et al. Risk of extracolonic cancers for people with biallelic and monoallelic mutations in MUTYH. *Int J Cancer* 2016; 139:1557.