Articles – Titles, References, and Abstracts about Mind on Cancer

Please read this blog about Mind on Cancer, from which this pdf is linked and in which the results are further described.

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9. Powell ND, Tarr AJ, Sheridan JF. Psychosocial stress and inflammation in cancer. Brain Behav Immun. 2013 Mar;30 Suppl:S41-7. doi: 10.1016/j.bbi.2012.06.015. Epub 2012 Jul 9. PMID: 22790082. 13

10. Mravec B, Tibensky M, Horvathova L. Stress and cancer. Part I: Mechanisms mediating the effect of stressors on cancer. J Neuroimmunol. 2020 Jul 3;346:577311. doi: 10.1016/j.jneuroim.2020.577311. Epub ahead of print. PMID: 32652365. 13

11. Mravec B, Tibensky M, Horvathova L. Stress and cancer. Part II: Therapeutic implications for oncology. J Neuroimmunol. 2020 Jul 3;346:577312. doi: 10.1016/j.jneuroim.2020.577312. Epub ahead of print. PMID: 32652364. 14

12. Panisch LS, Currin-McCulloch J, Covington E. Dissociation among individuals receiving cancer care: A scoping review. J Psychosoc Oncol. 2022;40(5):541-560. doi: 10.1080/07347332.2021.1930324. Epub 2021 Jun 30. PMID: 34190678. 14

13. Zhu J, Liu Q, Nie S, Huang Y, Zhao L, Mo F. LEPR/FOS/JUNB signaling pathway contributes to chronic restraint stress-induced tumor proliferation. Biochem Biophys Res Commun. 2024 Jul 30;719:150042. doi: 10.1016/j.bbrc.2024.150042. Epub 2024 May 6. PMID: 3761633. 15

14. Lawrence WR, McDonald JA, Williams F, Shiels MS, Freedman ND, Lin Z, Magnani JW. Stressful Life Events, Social Support, and Incident Breast Cancer by Estrogen Receptor Status. Cancer Prev Res (Phila). 2023 May 1;16(5):259-267. doi: 10.1158/1940-6207.CAPR22-0472. PMID: 37067915; PMCID: PMC10159918. 16

15. Reznik E, Torjani A. Mechanisms of stress-attributed breast cancer incidence and progression. Cancer Causes Control. 2024 Jul 16. doi: 10.1007/s10552-024-01884-2. Epub ahead of print. PMID: 39012513. 17

16. Ochoa-Arnedo C, Prats C, Travier N, Marques-Feixa L, Flix-Valle A, de Frutos ML, Domingo-Gil E, Medina JC, Serra-Blasco M. Stressful Life Events and Distress in Breast Cancer: A 5-Years Follow-Up. Int J Clin Health Psychol. 2022 May-Aug;22(2):100303. doi 10.1016/j.ijchp.2022.100303. Epub 2022 Apr 1. PMID: 35572072; PMCID: PMC9055056. 17

17. Singh AK, Chatterjee U, MacDonald CR, Repasky EA, Halbreich U. Psychosocial stress and immunosuppression in cancer: what can we learn from new research? BJPsych Adv. 2021 May;27(3):187-197. doi: 10.1192/bja.2021.9. Epub 2021 Apr 23. PMID: 34295535; PMCID PMC8294471.....18

18. Schuller HM, Al-Wadei HA, Ullah MF, Plummer HK 3rd. Regulation of pancreatic cancer by neuropsychological stress responses: a novel target for intervention. Carcinogenesis. 2012 Jan;33(1):191-6. doi: 10.1093/carcin/bgr251. Epub 2011 Nov 9. PMID: 22072614; PMCID: PMC3276326.....19

19. Hasen NS, O'Leary KA, Auger AP, Schuler LA. Social isolation reduces mammary development, tumor incidence, and expression of epigenetic regulators in wild-type and p53-heterozygotic mice. Cancer Prev Res (Phila). 2010 May;3(5):620-9. doi: 10.1158/1940-627.CAPR-09-0225. Epub 2010 Apr 27. PMID: 20424136; PMCID: PMC2865567. 19

20. Hassan S, Pullikuth A, Nelson KC, Flores A, Karpova Y, Baiz D, Zhu S, Sui G, Huang Y, Choi YA, D'Agostino R Jr, Hemal A, von Holzen U, Debinski W, Kulik G. β2-adrenoreceptor Signaling Increases Therapy Resistance in Prostate Cancer by Upregulating MCL1. ol Cancer Res. 2020 Dec;18(12):1839-1848. doi: 10.1158/1541-7786.MCR-19-1037. Epub 2020 Sep 14. PMID: 32928910; PMCID: PMC8080265. 20

21. Priyanka HP, Pratap UP, Nair RS, Vasantharekha R, ThyagaRajan S. Estrogen-receptor status determines differential regulation of α1- and α2-adrenoceptor-mediated cell survival, angiogenesis, and intracellular signaling responses in breast cancer cell line. Med Oncol. 2024 Mar 25;41(5):92. doi: 10.1007/s12032-024-02322-8. PMID: 38526769. 21

22. Fuemmeler BF, Shen J, Zhao H, Winn R. Neighborhood deprivation, racial segregation and associations with cancer risk and outcomes across the cancer-control continuum. Mol Psychiatry. 2023 Apr;28(4):1494-1501. doi: 10.1038/s41380-023-02006-1. Epub 2023 Ma 3. PMID: 36869227. 21

23. Woods-Burnham L, Stiel L, Martinez SR, Sanchez-Hernandez ES, Ruckle HC, Almaguel FG, Stern MC, Roberts LR, Williams DR, Montgomery S, Casiano CA. Psychosocial Stress, Glucocorticoid Signaling, and Prostate Cancer Health Disparities in African American Me. Cancer Health Disparities. 2020;4:https://companyofscientists.com/index.php/chd/article/view/169/188. PMID: 35252767; PMCID: PMC8896511. 22

24. Basten M, Pan KY, van Tuijl LA, de Graeff A, Dekker J, Hoogendoorn AW, Lamers F, Ranchor AV, Vermeulen R, Portengen L, Voogd AC, Abell J, Awadalla P, Beekman ATF, Bjerkeset O, Boyd A, Cui Y, Frank P, Galenkamp H, Garssen B, Hellingman S, Huisman M, Huss , Keats MR, Kok AAL, Krokstad S, van Leeuwen FE, Luik AI, Noisel N, Payette Y, Penninx BWJH, Rissanen I, Roest AM, Rosmalen JGM, Ruiter R, Schoevers RA, Soave D, Spaan M, Steptoe A, Stronks K, Sund ER, Sweeney E, Twait EL, Teyhan A, Verschuren WMM, van der Willik KD, Geerlings MI. Psychosocial factors, health behaviors and risk of cancer incidence: Testing interaction and effect modification in an individual participant data meta-analysis. Int J Cancer. 2024 May 15;154(10):1745-1759. doi: 10.1002/ijc.34852. Epub 2024 Jan 30. PMID: 38289012. 23

25. Cathomas F, Lin HY, Chan KL, Li L, Durand-de Cuttoli R, Parise LF, Aubry AV, Muhareb S, Desland F, Shimo Y, Ramakrishnan A, Estill M, Ferrer-Pérez C, Parise EM, Wang J, Sowa A, Janssen WG, Costi S, Rahman A, Fernandez N, Swirski FK, Nestler EJ, Shen L, Mrad M, Murrough JW, Russo SJ. Peripheral immune-derived matrix metalloproteinase promotes stress susceptibility. Res Sq [Preprint]. 2023 Jan 30:rs.3.rs-1647827. doi: 10.21203/rs.3.rs-1647827/v1. Update in: Nature. 2024 Feb;626(8001):1108-1115. doi: 10.1038/s41586-023-07015-2. PMID: 36778505; PMCID: PMC9915787. 24

26. Johnson MB, Hoffmann JN, You HM, Lastra RR, Fernandez S, Strober JW, Allaw AB, Brady MJ, Conzen SD, McClintock MK. Psychosocial Stress Exposure Disrupts Mammary Gland Development. J Mammary Gland Biol Neoplasia. 2018 Jun;23(1-2):59-73. doi: 10.1007/s1091-018-9392-4. Epub 2018 Apr 23. PMID: 29687293; PMCID: PMC6207373. 25

27. Joshi S, Garlapati C, Aneja R. Epigenetic Determinants of Racial Disparity in Breast Cancer: Looking beyond Genetic Alterations. Cancers (Basel). 2022 Apr 9;14(8):1903. doi: 10.3390/cancers14081903. PMID: 35454810; PMCID: PMC9025441. 26

28. Sotelo JL, Musselman D, Nemeroff C. The biology of depression in cancer and the relationship between depression and cancer progression. Int Rev Psychiatry. 2014 Feb;26(1):16-30. doi: 10.3109/09540261.2013.875891. PMID: 24716498. 26

29. Hsiao FH, Jow GM, Kuo WH, Chang KJ, Liu YF, Ho RT, Ng SM, Chan CL, Lai YM, Chen YT. The effects of psychotherapy on psychological well-being and diurnal cortisol patterns in breast cancer survivors. Psychother Psychosom. 2012;81(3):173-82. doi: 10.1159/000329178. Epub 2012 Mar 3. PMID: 22399076.....27

30. Geyer S. The role of social and psychosocial factors in the development and course of cancer. Wien Klin Wochenschr. 2000 Dec 7;112(23):986-94. PMID: 11190714.....28

31. Draeger DL, Sievert KD, Hakenberg OW. Psychosocial Distress in Bladder Cancer Stratified by Gender, Age, Treatment, and Tumour Stage. Urol Int. 2018;101(1):31-37. doi: 10.1159/000489502. Epub 2018 May 14. PMID: 29758554. 28

32. Liu HM, Ma LL, Li C, Cao B, Jiang Y, Han L, Xu R, Lin J, Zhang D. The molecular mechanism of chronic stress affecting the occurrence and development of breast cancer and potential drug therapy. Transl Oncol. 2022 Jan;15(1):101281. doi: 10.1016/j.tranon.221.101281. Epub 2021 Dec 4. PMID: 34875482; PMCID: PMC8652015.$ 29

33. Sánchez-Díaz CT, Strayhorn S, Tejeda S, Vijayasiri G, Rauscher GH, Molina Y. What mediates the racial/ethnic disparity in psychosocial stress among breast cancer patients? Cancer Causes Control. 2021 Apr;32(4):357-367. doi: 10.1007/s10552-021-01392-7. Epb 2021 Feb 9. PMID: 33559770; PMCID: PMC7946668.....30

34. Magnon C. Cancer Builds a Noxious Partnership with Psychologic Stress. Cancer Res. 2024 Apr 1;84(7):956-957. doi: 10.1158/0008-5472.CAN-24-0628. PMID: 38558129. 30

35. Muscatell KA, Eisenberger NI, Dutcher JM, Cole SW, Bower JE. Links between inflammation, amygdala reactivity, and social support in breast cancer survivors. Brain Behav Immun. 2016 Mar;53:34-38. doi: 10.1016/j.bbi.2015.09.008. Epub 2015 Sep 15. PMID: 2634778; PMCID: PMC5784760.....31

36. Leschak CJ, Dutcher JM, Haltom KEB, Breen EC, Bower JE, Eisenberger NI. Associations between amygdala reactivity to social threat, perceived stress and C-reactive protein in breast cancer survivors. Soc Cogn Affect Neurosci. 2020 Nov 10;15(10):1056-1063. doi: 10.1093/scan/nsz103. PMID: 32039441; PMCID: PMC7657448.....32

37. Bellinger DL, Dulcich MS, Molinaro C, Gifford P, Lorton D, Gridley DS, Hartman RE. Psychosocial Stress and Age Influence Depression and Anxiety-Related Behavior, Drive Tumor Inflammatory Cytokines and Accelerate Prostate Cancer Growth in Mice. Front Onco. 2021 Sep 16;11:703848. doi: 10.3389/fonc.2021.703848. PMID: 34604038; PMCID: PMC8481826.....32

38. Zhang J, Deng YT, Liu J, Gan L, Jiang Y. Role of transforming growth factor-β1 pathway in angiogenesis induced by chronic stress in colorectal cancer. Cancer Biol Ther. 2024 Dec 31;25(1):2366451. doi: 10.1080/15384047.2024.2366451. Epub 2024 Jun 10. PMID: 38857055; PMCID: PMC11168221. 33

39. Ma W, Liu P, Zheng J, Lü J, Zhao Q, Li D, Guo Y, Qian L, Wang Q, Miao X, Yu Z. Immune and nonimmune mechanisms mediate the mental stress-induced tumor growth in a xenograft model of breast cancer. Cell Death Dis. 2021 Oct 23;12(11):987. doi: 10.1038/s4149-021-04280-9. PMID: 34689156; PMCID: PMC8542049. 34

40. Zainal NZ, Ng CG, Wong A, Andrew B, Mohd Taib NA, Low SY. Prevalence of depression, trait anxiety, and social support during the diagnostic phases of breast cancer. J Taibah Univ Med Sci. 2021 Mar 17;16(4):497-503. doi: 10.1016/j.jtumed.2021.01.013. PMID 34408606; PMCID: PMC8348272.....35

41. Barrera I, Spiegel D. Review of psychotherapeutic interventions on depression in cancer patients and their impact on disease progression. Int Rev Psychiatry. 2014 Feb;26(1):31-43. doi: 10.3109/09540261.2013.864259. PMID: 24716499. 36

42. Pudrovska T, Carr D, McFarland M, Collins C. Higher-status occupations and breast cancer: a life-course stress approach. Soc Sci Med. 2013 Jul;89:53-61. doi: 10.1016/j.socscimed.2013.04.013. Epub 2013 Apr 24. PMID: 23726216; PMCID: PMC3982384.....36

43. Oliveira ML, Biggers A, Oddo VM, Yanez B, Booms E, Sharp L, Naylor K, Wolf PG, Tussing-Humphreys L. A Perspective Review on Diet Quality, Excess Adiposity, and Chronic Psychosocial Stress and Implications for Early-Onset Colorectal Cancer. J Nutr. 2024 Ar;154(4):1069-1079. doi: 10.1016/j.tjnut.2024.03.002. Epub 2024 Mar 6. PMID: 38453027; PMCID: PMC11007745. 37

44. Özkan M, Yıldırım N, Dişçi R, İlgün AS, Sarsenov D, Alço G, Aktepe F, Kalyoncu N, İzci F, Selamoğlu D, Ordu Ç, Pilancı KN, Erdoğan Zİ, Eralp Y, Özmen V. Roles of Biopsychosocial Factors in the Development of Breast Cancer. Eur J Breast Health. 2017 Oct 113(4):206-212. doi: 10.5152/ejbh.2017.3519. PMID: 29082379; PMCID: PMC5648278. 38

45. Dye CK, Wu H, VanNoy B, Calluori S, Marfori CQ, Baccarelli AA, Zota AR. Psychosocial Stress and MicroRNA Expression Profiles in Myometrial Tissue of Women Undergoing Surgical Treatment for Uterine Fibroids. Reprod Sci. 2024 Jun;31(6):1651-1661. doi: 10.107/s43032-024-01482-2. Epub 2024 Feb 20. PMID: 38379067. 38

46. Richtig E, Trapp EM, Avian A, Brezinsek HP, Trapp M, Egger JW, Kapfhammer HP, Rohrer PM, Berghold A, Curiel-Lewandrowski C, Demel U. Psychological Stress and Immunological Modulations in Early-stage Melanoma Patients. Acta Derm Venereol. 2015 Jul;95(6):61-5. doi: 10.2340/00015555-2045. PMID: 25587794. 39

47. Surtees PG, Wainwright NW, Luben RN, Khaw KT, Bingham SA. No evidence that social stress is associated with breast cancer incidence. Breast Cancer Res Treat. 2010 Feb;120(1):169-74. doi: 10.1007/s10549-009-0454-6. Epub 2009 Jul 2. PMID: 19572196.

48. Coker AL, Sanderson M, Ellison GL, Fadden MK. Stress, coping, social support, and prostate cancer risk among older African American and Caucasian men. Ethn Dis. 2006 Autumn;16(4):978-87. PMID: 17061756. 40

49. Almeida SS, Oliveira MA, Medeiros R, Guerra MP, Pariante CM, Fernandes L. Emotional, inflammatory, and genetic factors of resilience and vulnerability to depression in patients with premenopausal breast cancer: A longitudinal study protocol. PLoS One. 203 Feb 14;18(2):e0279344. doi: 10.1371/journal.pone.0279344. PMID: 36787313; PMCID: PMC9928105.....41

50. Niebauer E, Fry N, Auster-Gussman LA, Wahbeh H. Patient perspectives on the causes of breast cancer: a qualitative study on the relationship between stress, trauma, and breast cancer development. Int J Qual Stud Health Well-being. 2021 Dec;16(1):1983949.doi: 10.1080/17482631.2021.1983949. PMID: 34694978; PMCID: PMC8547822.....42

51. Nagano J, Nagase S, Sudo N, Kubo C. Psychosocial stress, personality, and the severity of chronic hepatitis C. Psychosomatics. 2004 Mar-Apr;45(2):100-6. doi: 10.1176/appi.psy.45.2.100. PMID: 15016922. 43

52. Barber LE, Zirpoli GR, Cozier YC, Rosenberg L, Petrick JL, Bertrand KA, Palmer JR. Neighborhood disadvantage and individual-level life stressors in relation to breast cancer incidence in US Black women. Breast Cancer Res. 2021 Nov 22;23(1):108. doi: 10.186/s13058-021-01483-y. PMID: 34809694; PMCID: PMC8609879. 43

53. Lutgendorf SK, Sood AK, Anderson B, McGinn S, Maiseri H, Dao M, Sorosky JI, De Geest K, Ritchie J, Lubaroff DM. Social support, psychological distress, and natural killer cell activity in ovarian cancer. J Clin Oncol. 2005 Oct 1;23(28):7105-13. doi: 10.100/JCO.2005.10.015. PMID: 16192594.....44

54. Al-Wadei HA, Plummer HK 3rd, Ullah MF, Unger B, Brody JR, Schuller HM. Social stress promotes and γ-aminobutyric acid inhibits tumor growth in mouse models of non-small cell lung cancer. Cancer Prev Res (Phila). 2012 Feb;5(2):189-96. doi: 10.1158/1940-627.CAPR-11-0177. Epub 2011 Sep 28. PMID: 21955519; PMCID: PMC3320046. 45

55. Trudel-Fitzgerald C, Poole EM, Idahl A, Lundin E, Sood AK, Kawachi I, Kubzansky LD, Tworoger SS. The Association of Work Characteristics With Ovarian Cancer Risk and Mortality. Psychosom Med. 2017 Nov/Dec;79(9):1059-1067. doi: 10.1097/PSY.000000000000046. PMID: 28306624; PMCID: PMC5601015. 45

56. Schuler LA, Auger AP. Psychosocially influenced cancer: diverse early-life stress experiences and links to breast cancer. Cancer Prev Res (Phila). 2010 Nov;3(11):1365-70. doi: 10.1158/1940-6207.CAPR-10-0238. Epub 2010 Nov 7. PMID: 21084258; PMCID: PMC305374.....46

57. Duijts SF, Zeegers MP, Borne BV. The association between stressful life events and breast cancer risk: a meta-analysis. Int J Cancer. 2003 Dec 20;107(6):1023-9. doi: 10.1002/ijc.11504. PMID: 14601065. 46

58. Chida Y, Hamer M, Wardle J, Steptoe A. Do stress-related psychosocial factors contribute to cancer incidence and survival? Nat Clin Pract Oncol. 2008 Aug;5(8):466-75. doi: 10.1038/ncponc1134. Epub 2008 May 20. PMID: 18493231.....47

59. Antoni MH, Lutgendorf SK, Cole SW, Dhabhar FS, Sephton SE, McDonald PG, Stefanek M, Sood AK. The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. Nat Rev Cancer. 2006 Mar;6(3):240-8. doi: 10.1038/nrc1820. PMID: 16498446; PCID: PMC3146042. 48

60. Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. Biol Psychiatry. 2003 Aug 1;54(3):269-82. doi: 10.1016/s0006-3223(03)00566-3. PMID: 12893103. 48

61. Lempesis IG, Georgakopoulou VE, Papalexis P, Chrousos GP, Spandidos DA. Role of stress in the pathogenesis of cancer (Review). Int J Oncol. 2023 Nov;63(5):124. doi: 10.3892/ijo.2023.5572. Epub 2023 Sep 15. PMID: 37711028; PMCID: PMC10552722.....49

62. Ma Y, Kroemer G. The cancer-immune dialogue in the context of stress. Nat Rev Immunol. 2024 Apr;24(4):264-281. doi: 10.1038/s41577-023-00949-8. Epub 2023 Oct 13. PMID: 37833492. 49

63. Barnard ME, Poole EM, Huang T, Sood AK, Kubzansky LD, Tworoger SS. Caregiver burden and risk of epithelial ovarian cancer in the Nurses' Health Studies. Am J Epidemiol. 2024 Jul 5:kwae185. doi: 10.1093/aje/kwae185. Epub ahead of print. PMID: 38973733. .50

64. Geng QS, Shen ZB, Zheng YY, Xue WH, Li LF, Zhao J. Precise medication for tumor patients in the context of mental stress. Cell Transplant. 2021 Jan-Dec;30:9636897211049813. doi: 10.1177/09636897211049813. PMID: 34719974; PMCID: PMC8564128.....50

65. Madden KS, Szpunar MJ, Brown EB. Early impact of social isolation and breast tumor progression in mice. Brain Behav Immun. 2013 Mar;30 Suppl(Suppl):S135-41. doi: 10.1016/j.bbi.2012.05.003. Epub 2012 May 17. PMID: 22610067; PMCID: PMC3431437.51

66. Ellison GL, Coker AL, Hebert JR, Sanderson SM, Royal CD, Weinrich SP. Psychosocial stress and prostate cancer: a theoretical model. Ethn Dis. 2001 Autumn;11(3):484-95. PMID: 11572415. 52

67. Li C, Andrzejak SE, Jones SR, Williams BM, Moore JX. Investigating the association between educational attainment and allostatic load with risk of cancer mortality among African American women. BMC Womens Health. 2023 Aug 24;23(1):448. doi: 10.1186/s1290-023-02529-3. PMID: 37620873; PMCID: PMC10463695. 52

68. Li G, Gan Y, Fan Y, Wu Y, Lin H, Song Y, Cai X, Yu X, Pan W, Yao M, Gu J, Tu H. Enriched environment inhibits mouse pancreatic cancer growth and down-regulates the expression of mitochondria-related genes in cancer cells. Sci Rep. 2015 Jan 19;5:7856. doi 10.1038/srep07856. PMID: 25598223; PMCID: PMC4297951. 53

69. Ma Y, Yang H, Kroemer G. Endogenous and exogenous glucocorticoids abolish the efficacy of immune-dependent cancer therapies. Oncoimmunology. 2019 Oct

11;9(1):1673635. doi: 10.1080/2162402X.2019.1673635. PMID: 32002285; PMCID: PMC6959448.....54

70. Poole EM, Kubzansky LD, Sood AK, Okereke OI, Tworoger SS. A prospective study of phobic anxiety, risk of ovarian cancer, and survival among patients. Cancer Causes Control. 2016 May;27(5):661-8. doi: 10.1007/s10552-016-0739-0. Epub 2016 Mar 29. PMID: 2703470; PMCID: PMC4840033. 54

71. Wang R, Yu S, Yu L, Wang Q, Wu Y. Riddle of the Sphinx: facts and evidence regarding the link between mental stress and tumor occurrence and development. Chin Med J (Engl). 2022 Dec 20;135(24):2998-3000. doi: 10.1097/CM9.0000000000002129. PMID: 36580651;PMCID: PMC10106126. 55

72. Trainor BC, Sweeney C, Cardiff R. Isolating the effects of social interactions on cancer biology. Cancer Prev Res (Phila). 2009 Oct;2(10):843-6. doi: 10.1158/1940-6207.CAPR-09-0167. Epub 2009 Sep 29. PMID: 19789296. 55

73. Moore JX, Andrzejak SE, Bevel MS, Jones SR, Tingen MS. Exploring racial disparities on the association between allostatic load and cancer mortality: A retrospective cohort analysis of NHANES, 1988 through 2019. SSM Popul Health. 2022 Jul 31;19:101185. doi: 10.1016/j.ssmph.2022.101185. PMID: 35990411; PMCID: PMC9382324. 56

74. Hasegawa H, Saiki I. Psychosocial stress augments tumor development through beta-adrenergic activation in mice. Jpn J Cancer Res. 2002 Jul;93(7):729-35. doi: 10.1111/j.1349-7006.2002.tb01313.x. PMID: 12149137; PMCID: PMC5927068. 57

75. Spiegel D, Giese-Davis J, Taylor CB, Kraemer H. Stress sensitivity in metastatic breast cancer: analysis of hypothalamic-pituitary-adrenal axis function. Psychoneuroendocrinology. 2006 Nov;31(10):1231-44. doi: 10.1016/j.psyneuen.2006.09.004. Epub 2006 No 1. PMID: 17081700; PMCID: PMC1790857.....57

76. Imai K, Nakachi K. Personality types, lifestyle, and sensitivity to mental stress in association with NK activity. Int J Hyg Environ Health. 2001 Oct;204(1):67-73. doi: 10.1078/1438-4639-00075. PMID: 11725349. 58

77. Peters S, Grunwald N, Rümmele P, Endlicher E, Lechner A, Neumann ID, Obermeier F, Reber SO. Chronic psychosocial stress increases the risk for inflammation-related colon carcinogenesis in male mice. Stress. 2012 Jul;15(4):403-15. doi: 10.3109/10253890.201.631232. Epub 2011 Dec 20. PMID: 22044139. 59

78. Al-Wadei HA, Al-Wadei MH, Ullah MF, Schuller HM. Celecoxib and GABA cooperatively prevent the progression of pancreatic cancer in vitro and in xenograft models of stress-free and stress-exposed mice. PLoS One. 2012;7(8):e43376. doi: 10.1371/journal.pone.0043376. Epub 2012 Aug 16. PMID: 22916251; PMCID: PMC3420877.....60

79. Ollonen P, Lehtonen J, Eskelinen M. Stressful and adverse life experiences in patients with breast symptoms; a prospective case-control study in Kuopio, Finland. Anticancer Res. 2005 Jan-Feb;25(1B):531-6. PMID: 15816624. 61

80. Irie M, Asami S, Nagata S, Ikeda M, Miyata M, Kasai H. Psychosocial factors as a potential trigger of oxidative DNA damage in human leukocytes. Jpn J Cancer Res. 2001 Mar;92(3):367-76. doi: 10.1111/j.1349-7006.2001.tb01104.x. PMID: 11267949; PMCID: PMC596712.....62

1. Antoni MH, Dhabhar FS. The impact of psychosocial stress and stress management on immune responses in patients with cancer. Cancer. 2019 May 1;125(9):1417-1431. doi: 10.1002/cncr.31943. Epub 2019 Feb 15. PMID: 30768779; PMCID: PMC6467795.

The range of psychosocial stress factors/processes (eg, chronic stress, distress states, coping, social adversity) were reviewed as they relate to immune variables in cancer along with studies of psychosocial interventions on these stress processes and immune measures in cancer populations. The review includes molecular, cellular, and clinical research specifically examining the effects of stress processes and stress-management interventions on immune variables (eg, cellular immune function, inflammation), which may or may not be changing directly in response to the cancer or its treatment. Basic psychoneuroimmunologic research on stress processes (using animal or cellular/tumor models) provides leads for investigating biobehavioral processes that may underlie the associations reported to date. The development of theoretically driven and empirically supported stress-management interventions may provide important adjuncts to clinical cancer care going forward.

2. Wackerhage H, Christensen JF, Ilmer M, von Luettichau I, Renz BW, Schönfelder M. Cancer catecholamine conundrum. Trends Cancer. 2022 Feb;8(2):110-122. doi: 10.1016/j.trecan.2021.10.005. Epub 2021 Nov 12. PMID: 34776398.

Exercise, psychosocial stress, and drugs such as adrenergic agonists and antagonists increase the concentrations of catecholamines and/or alter adrenergic signaling. Intriguingly, exercise studies universally suggest that catecholamines are cancer-inhibiting whereas cancer stress studies typically report the opposite, whereas β-blocker studies show variable effects. Here, we term variable effects of catecholamines in cancer the cancer catecholamine conundrum. Variable effects of catecholamines can potentially be explained by variable expression of nine adrenergic receptor isoforms and by other factors including catecholamine effects on cancer versus immune or endothelial cells. Future studies on catecholamines and cancer should seek to understand the mechanisms that explain variable effects of catecholamines in cancer to utilize beneficial or block detrimental effects of catecholamines in cancer patients.

3. Noverati N, Bashir-Hamidu R, Halegoua-DeMarzio D, Hann HW. Hepatitis B Virus-Associated Hepatocellular Carcinoma and Chronic Stress. Int J Mol Sci. 2022 Apr 1;23(7):3917. doi: 10.3390/ijms23073917. PMID: 35409275; PMCID: PMC8999024.

The Hepatitis B virus is one of the most significant hepatocarcinogens globally. The carcinogenic mechanisms of this virus are complex, and may include interactions with the host's immune system. Certain factors, such as stress on the body, can also potentiate these mechanisms. Stress, although adaptive in an acute form, is deleterious to health when chronic and can both suppress and activate the host's defense system. In hepatocellular carcinoma, this can lead to tumor initiation and progression. Those that are more prone to stress, or exposed to situations that incite stress, may be at higher risk of developing cancer. Racial disparities, for example, are a source of chronic psychosocial stress in America and predispose minorities to poorer outcomes. As it remains perplexing why some individuals with chronic hepatitis B develop feared complications while others do not, it is important to recognize as many risk factors as possible, including those often overlooked such as chronic stress.

4. Liu C, Yang Y, Chen C, Li L, Li J, Wang X, Chu Q, Qiu L, Ba Q, Li X, Wang H. Environmental eustress modulates β-ARs/CCL2 axis to induce anti-tumor immunity and sensitize immunotherapy against liver cancer in mice. Nat Commun. 2021 Sep 30;12(1):5725. doi: 10.1038/s41467-021-25967-9. Erratum in: Nat Commun. 2021 Oct 14;12(1):6100. doi: 10.1038/s41467-021-26376-8. PMID: 34593796; PMCID: PMC8484272.

Although psycho-social stress is a well-known factor that contributes to the development of cancer, it remains largely unclear whether and how environmental eustress influences malignant diseases and regulates cancer-related therapeutic responses. Using an established eustress model, we demonstrate that mice living in an enriched environment (EE) are protected from carcinogen-induced liver neoplasia and transplantable syngeneic liver tumors, owning to a $CD8^+$ T cell-dependent tumor control. We identify a peripheral Neuro-Endocrine-Immune pathway in eustress, including Sympathetic nervous system (SNS)/β-adrenergic receptors (β-ARs)/CCL2 that relieves tumor immunosuppression and overcomes PD-L1 resistance to immunotherapy. Notably, EE activates peripheral SNS and β-ARs signaling in tumor cells and tumor infiltrated myeloid cells, leading to suppression of CCL2 expression and activation of anti-tumor immunity. Either blockade of CCL2/CCR2 or β-AR signaling in EE mice lose the tumor protection capability. Our study reveales that environmental eustress via EE stimulates anti-tumor immunity, resulting in more efficient tumor control and a better outcome of immunotherapy.

5. Barnard ME, Wang X, Petrick JL, Zirpoli GR, Jones D, Johnson WE, Palmer JR. Psychosocial stressors and breast cancer gene expression in the Black Women's Health Study. Breast Cancer Res Treat. 2024 Apr;204(2):327-340. doi: 10.1007/s10549-023-07182-w. Epub 2023 Dec 21. PMID: 38127176; PMCID: PMC11232497.

Purpose: Prior studies indicate that the physiologic response to stress can affect gene expression. We evaluated differential gene expression in breast cancers collected from Black women with high versus low exposure to psychosocial stressors.

Methods: We analyzed tumor RNA sequencing data from 417 Black Women's Health Study breast cancer cases with data on early life trauma and neighborhood disadvantage. We conducted age-adjusted differential gene expression analyses and pathway analyses. We also evaluated Conserved Transcriptional Response to Adversity (CTRA) contrast scores, relative fractions of immune cell types, T cell exhaustion, and adrenergic signaling. Analyses were run separately for estrogen receptor positive (ER+; n = 299) and ER- (n = 118) cases.

Results: Among ER+ cases, the top differentially expressed pathways by stress exposure were related to RNA and protein metabolism. Among ER- cases, they were related to developmental biology, signal transduction, metabolism, and the immune system. Targeted analyses indicated greater immune pathway enrichment with stress exposure for ER- cases, and possible relevance of adrenergic signaling for ER+ cases. CTRA contrast scores did not differ by stress exposure, but in analyses of the CTRA components, ER- breast cancer cases with high neighborhood disadvantage had higher pro-inflammatory gene expression ($p = 0.039$) and higher antibody gene expression ($p = 0.006$) compared to those with low neighborhood disadvantage.

Conclusion: There are multiple pathways through which psychosocial stress exposure may influence breast tumor biology. Given the present findings on inflammation and immune response in ER- tumors, further research to identify stress-induced changes in the etiology and progression of ER- breast cancer is warranted.

6. Mohan A, Huybrechts I, Michels N. Psychosocial stress and cancer risk: a narrative review. Eur J Cancer Prev. 2022 Nov 1;31(6):585-599. doi: 10.1097/CEJ.0000000000000752. Epub 2022 Mar 29. PMID: 35352705.

Background: It is unclear which psychological factors (stressors, emotional correlates, and psychophysiological markers) induce cancer risk. This currently limits the potential for prevention strategies.

Purpose: The aim of this review is to bring forth evidence of stress as a determinant of cancer risk from a public health perspective, written for a broad public of practitioners and scientists.

Methods: Based on a semisystematic literature search, the impact of different aspects/types of stress and the potential physiological and behavioral pathways are summarized, while highlighting further research, public health and clinical implications.

Results: Between 2007 and 2020, 65 case-control or cohort studies have been identified. Apart from overall cancer (N = 24), 12 cancer types have been associated with psychological stress with most for breast (N = 21), colorectal (N = 11) and lung/prostate/pancreas cancer (N = 8 each). Although the evidence regarding the mechanisms is still scarce, cancer development in relation to stress might be due to interacting and combined effects of different stress(or) types, but such interaction has not really been tested yet. The path from stress towards cancer incidence consists of a biological pathway with endocrinology and immunology as well as stress-induced behavioral pathways, including smoking, alcoholism, sleep disruption, an unhealthy diet, and low physical activity together with the related phenomenon of obesity.

Conclusion: Not only the stress but also the stress-induced lifestyle should be targeted for cancer prevention and treatment. Future research should include a more diverse spectrum of cancer types (not only hormonal related like breast cancer) and of stress measures while also considering behavioral covariates.

7. Galluzzi L, Kroemer G. Cancer Cells Thrive on Stress. Trends Cell Biol. 2019 Jun;29(6):447-449. doi: 10.1016/j.tcb.2019.03.005. Epub 2019 Apr 5. PMID: 30962044.

Glucocorticoids (GCs) are widely used for the management of disease- or therapy-related complications in cancer patients. Recent data indicate that activation of GC receptors (GRs) precipitates breast cancer progression by favoring metastatic dissemination and cell survival at distant sites. These findings call for the re-evaluation of GC usage in patients with cancer.

8. Moore JX, Andrzejak SE, Casanova T, Langston ME, Estvold S, Adsul P. Investigating the Joint Effect of Allostatic Load among Lesbian, Gay, and Bisexual Adults with Risk of Cancer Mortality. Int J Environ Res Public Health. 2023 Jun 13;20(12):6120. doi: 10.3390/ijerph20126120. PMID: 37372707; PMCID: PMC10298095.

Sexual minorities (SM) have higher chronic physiologic stress as indicated by allostatic load (AL), which may be explained in part by consistent experiences of discriminatory practices. This is one of the first studies to examine the joint effects of SM status and AL on the association with long-term risk for cancer death. Retrospective analyses were conducted on 12,470 participants using National Health and Nutrition Examination Survey (NHANES) from

years 2001 through 2010 linked with the National Death Index through December 31, 2019. Cox proportional hazards models estimated adjusted hazard ratios (aHRs) of cancer deaths between groups of SM (those reporting as gay, lesbian, bisexual, or having same-sex sexual partners) status and AL. SM adults living with high AL (*n* = 326) had a 2-fold increased risk of cancer death (aHR: 2.55, 95% CI: 1.40-4.65) when compared to straight/heterosexual adults living with low AL (*n* = 6674). Among those living with high AL, SM (*n* = 326) had a 2-fold increased risk of cancer death (aHR: 2.26, 95% CI: 1.33-3.84) when compared to straight/heterosexual adults with high AL (*n* = 4957). SM with high AL have an increased risk of cancer mortality. These findings highlight important implications for promoting a focused agenda on cancer prevention with strategies that reduce chronic stress for SM adults.

9. Powell ND, Tarr AJ, Sheridan JF. Psychosocial stress and inflammation in cancer. Brain Behav Immun. 2013 Mar;30 Suppl:S41-7. doi: 10.1016/j.bbi.2012.06.015. Epub 2012 Jul 9. PMID: 22790082.

Stress-induced immune dysregulation results in significant health consequences for immune related disorders including viral infections, chronic autoimmune disease, and tumor growth and metastasis. In this mini-review we discuss the sympathetic, neuroendocrine and immunologic mechanisms by which psychosocial stress can impact cancer biology. Both human and animal studies have shown the sympathetic and neuroendocrine responses to psychosocial stress significantly impacts cancer, in part, through regulation of inflammatory mediators. Psychosocial stressors stimulate neuroendocrine, sympathetic, and immune responses that result in the activation of the hypothalamic-pituitary-adrenal (HPA)-axis, sympathetic nervous system (SNS), and the subsequent regulation of inflammatory responses by immune cells. Social disruption (SDR) stress, a murine model of psychosocial stress and repeated social defeat, provides a novel and powerful tool to probe the mechanisms leading to stress-induced alterations in inflammation, tumor growth, progression, and metastasis. In this review, we will focus on SDR as an important model of psychosocial stress in understanding neural-immune mechanisms in cancer.

10. Mravec B, Tibensky M, Horvathova L. Stress and cancer. Part I: Mechanisms mediating the effect of stressors on cancer. J Neuroimmunol. 2020 Jul 3;346:577311. doi: 10.1016/j.jneuroim.2020.577311. Epub ahead of print. PMID: 32652365.

Observations indicating a link between psychosocial stress and cancer can be traced back almost 2 millennia. However, the pathways and mechanisms interconnecting them has only been elucidated in more detail since the end of the 20th century. Importantly, recently accumulated evidences have confirmed the ability of stress to promote the induction and progression of cancer. The main aim of this review is to describe the pathways and

mechanisms mediating the stimulatory effects of the neuroendocrine stress response on the induction of cancer, potentiation of cancer growth, and the development of metastases.

11. Mravec B, Tibensky M, Horvathova L. Stress and cancer. Part II: Therapeutic implications for oncology. J Neuroimmunol. 2020 Jul 3;346:577312. doi: 10.1016/j.jneuroim.2020.577312. Epub ahead of print. PMID: 32652364.

Accumulated evidence has confirmed the ability of stress to promote the induction and progression of cancer (for review see Stress and cancer. Part I: Mechanisms mediating the effect of stressors on cancer). In support of this, data from clinical trials utilizing approaches that reduce stress-related signaling have shown prolonged survival of cancer patients. Therefore, the question has arisen as to how we can utilize this knowledge in the daily treatment of cancer patients. The main aim of this review is to critically analyze data from studies utilizing psychotherapy or treatment by β-blockers on the survival of cancer patients. Because these approaches, especially treatment by β-blockers, have been routinely used in clinical practice for decades in the treatment of non-cancer patients, their wider introduction into oncology might be realized in the near future.

12. Panisch LS, Currin-McCulloch J, Covington E. Dissociation among individuals receiving cancer care: A scoping review. J Psychosoc Oncol. 2022;40(5):541-560. doi: 10.1080/07347332.2021.1930324. Epub 2021 Jun 30. PMID: 34190678.

Problem identification: Dissociation is a common presentation of trauma, distinguishable from classic post-traumatic stress disorder (PTSD) symptoms. While pre-cancer and cancer-related traumatic experiences are prevalent among cancer-affected individuals, the specific impact of traumatic dissociation is unclear.

Literature search: This scoping review includes a search of English articles published between 1980 and 2019 referencing dissociation in the context of cancer-affected adults.

Data evaluation/synthesis: Articles assessed how dissociation was addressed in relation to pre-cancer and cancer-related trauma exposure and treatment. Out of 1,265 articles, 71 met inclusion criteria, and 15 underwent a full review. Two studies addressed dissociation related to pre-cancer trauma, nine in regard to cancer-related trauma only, and four in relation to both trauma types. No studies included experimental designs or described interventions.

Conclusions: Despite high rates of trauma exposure among cancer-affected adults, limited studies specifically address the impact of dissociation. Further inquiry on this topic is needed, especially on treatment implications.

13. Zhu J, Liu Q, Nie S, Huang Y, Zhao L, Mo F. LEPR/FOS/JUNB signaling pathway contributes to chronic restraint stress-induced tumor proliferation. Biochem Biophys Res Commun. 2024 Jul 30;719:150042. doi: 10.1016/j.bbrc.2024.150042. Epub 2024 May 6. PMID: 38761633.

Background & aims: Psychosocial stress has become an unavoidable part of life, which was reported to promote tumor development. Chronic stress significantly promotes the norepinephrine (NE) secretion and the expression of leptin receptor (LEPR), leading to tumor invasion, metastasis, and proliferation. However, the mechanism of chronic stress-induced tumor proliferation remains unclear.

Methods: To reveal the effect of chronic stress on tumor proliferation, subcutaneous tumor models combined with chronic restraint stress (CRS) were established. Combined with the transcript omics database of liver cancer patients, the target pathways were screened and further verified by in vitro experiments.

Results: The results showed that the CRS with subcutaneous tumor transplantation (CRS + tumor) group exhibited significantly larger tumor sizes than the subcutaneous tumor transplantation (tumor) group. Compared with the tumor group, CRS obviously increased the mRNA levels of LEPR, FOS, and JUNB of tumor tissues in the CRS + tumor group. Furthermore, the treatment with norepinephrine (NE) significantly elevated the survival rate of H22 cells and enhanced the expression of LEPR, FOS, and JUNB in vitro. Silencing LEPR significantly reduced the expression of FOS and JUNB, accompanied by a decrease in H22 cell viability.

Conclusions: Our study demonstrated that CRS activates the LEPR-FOS-JUNB signaling pathway by NE, aggravating tumor development. These findings might provide a scientific foundation for investigating the underlying pathological mechanisms of tumors in response to chronic stress.

Takagi C, Nakagawa S, Hirata N, Ohta S, Shimoeda S. Evaluating the effect of aromatherapy on a stress marker in healthy subjects. J Pharm Health Care Sci. 2019 Aug 14;5:18. doi: 10.1186/s40780-019-0148-0. PMID: 31428439; PMCID: PMC6693249.

Background/purpose: Chemotherapy is important for cancer treatment, but patients' physical and mental stress may lead to unfavorable pain control, an increase in the risk of relapse, and a reduction in the quality of life (QOL). Recently, aromatherapy has been performed in addition to palliative care in many countries, such as Japan and the United States, but scientific evidence remains insufficient. To

investigate the usefulness of aromatherapy as complementary and alternative medicine, we evaluated its influence on the immune and autonomic nervous systems.

Methods: We instructed healthy volunteers to inhale aroma oil at bedtime for 6 weeks, and measured changes in the salivary level of secretory immunoglobulin A (s-IgA). Furthermore, blood was collected in addition to saliva in some healthy volunteers, and the blood level of noradrenaline (NA) was measured to examine its relationship to changes in the salivary s-IgA level.

Results: Aromatherapy with lavender and grapefruit oils significantly increased the salivary s-IgA level: lavender oil increased 3.5-fold (p = 0.03), and grapefruit oil increased 2.55-fold (p = 0.04). On lavender oil inhalation, there was a weak, positive correlation between changes in the salivary s-IgA level and those in the blood NA level (R^2 = 0.24).

Conclusion: The results showed that aromatherapy with lavender and grapefruit oils reduced stress by acting on the immune and autonomic nervous systems in healthy volunteers. In the future, its clinical usefulness must be investigated through similar examination in patients in whom the stress level may be high.

14. Lawrence WR, McDonald JA, Williams F, Shiels MS, Freedman ND, Lin Z, Magnani JW. Stressful Life Events, Social Support, and Incident Breast Cancer by Estrogen Receptor Status. Cancer Prev Res (Phila). 2023 May 1;16(5):259-267. doi: 10.1158/1940-6207.CAPR-22-0472. PMID: 37067915; PMCID: PMC10159918.

Chronic stress affects immune function and hormonal signaling and has been hypothesized to be associated with breast cancer, although results from the few prior studies are mixed and have not examined potential differences by estrogen receptor (ER) status. Using the Women's Health Initiative study, we included 76,951 postmenopausal women followed for events for a median of 16.7 years to investigate the association between baseline self-reported stressful life events and incident breast cancer by ER status and whether the association was modified by social support. We generated Cox proportional hazards models adjusting for demographic, clinical, lifestyle/behavioral, and social factors to estimate HRs and 95% confidence intervals (95%CI). The mean age was 63 (SD, 7.3), and majority of participants were White race (83.5%) and married or in a marriage-like relationship (63.0%). In analyses stratified by ER status, there was no relationship between stressful life events and ER-positive breast cancer. In contrast, compared with women in the lowest quartile, those in higher quartiles had an increased risk of ER-negative breast cancer, where those in quartile 4 had the highest risk (Quartile 4 vs. Quartile 1; HR = 1.30; 95%CI,

1.01-1.68; Ptrend = 0.050). Moreover, associations were stronger for the highest versus lowest quartile of stressful life events among widowed women (HR = 2.39; 95%CI, 1.29-4.44; Pinteraction<0.001). Association between stressful life events and ER-negative breast cancer was not modified by social support. In this cohort of postmenopausal women, higher experiences of prediagnostic stressful life events were associated with increased risk of ER-negative breast cancer.

15. Reznik E, Torjani A. Mechanisms of stress-attributed breast cancer incidence and progression. Cancer Causes Control. 2024 Jul 16. doi: 10.1007/s10552-024-01884-2. Epub ahead of print. PMID: 39012513.

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer deaths in women, with psychosocial stress commonly cited by patients as one of its causes. While there is conflicting epidemiological evidence investigating the association between psychosocial stress and breast cancer incidence and progression, there is reason to believe that interventions aimed at reducing stress pharmacologically or psychologically may improve breast cancer outcomes. The aim of this review is to discuss the molecular and biological mechanisms of stress-attributed breast cancer incidence and progression, including the induction of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), as well as decreased immune function and stress hormone-induced resistance to chemotherapy. Moreover, these mechanisms have been cited as potential therapeutic targets of pharmacologic and psychological interventions that may improve the care, well-being and survival of breast cancer patients. Further research is recommended to investigate whether interventions in the primary care setting for women with risk factors for breast cancer development may lead to a decreased incidence of invasive breast tumors.

16. Ochoa-Arnedo C, Prats C, Travier N, Marques-Feixa L, Flix-Valle A, de Frutos ML, Domingo-Gil E, Medina JC, Serra-Blasco M. Stressful Life Events and Distress in Breast Cancer: A 5-Years Follow-Up. Int J Clin Health Psychol. 2022 May-Aug;22(2):100303. doi: 10.1016/j.ijchp.2022.100303. Epub 2022 Apr 1. PMID: 35572072; PMCID: PMC9055056.

Background/objective: Environmental factors such as psychosocial stress have demonstrated to have an impact on the breast cancer (BC) course. This study aims to explore the impact of psychotherapy and stressful life events (SLE) on BC survivors' illness trajectories.

Method: 68 women with BC underwent Positive Psychotherapy or Cognitive-Behavioral Stress Management and 37 patients were included as a control group. The effects of distress reduction and SLE on their 5-year recurrence were investigated. Additional analyses examined the effect of receiving vs. not receiving psychotherapy and of the type of therapy on survival and disease-free interval, DFI.

Results: A one-point decrease of the Hospital Anxiety and Depression Scale (HADS) after psychotherapy predicted a lower risk of 5-year recurrence, *OR* = 0.84, *p* = .037, 95% *CI* = 0.71-0.99). Also, a one point-increase in the number threatening SLE (*OR* = 1.92; *p* = .028, 95% *CI* = 1.07-3.43) was related to higher 5-year recurrence.

Conclusions: The findings highlight the necessity of studying not only a given situation (i.e., psychotherapy, SLE) but its specific impact on individuals.

17. Singh AK, Chatterjee U, MacDonald CR, Repasky EA, Halbreich U. Psychosocial stress and immunosuppression in cancer: what can we learn from new research? BJPsych Adv. 2021 May;27(3):187-197. doi: 10.1192/bja.2021.9. Epub 2021 Apr 23. PMID: 34295535; PMCID: PMC8294471.

It is generally believed that the physiological consequences of stress could contribute to poor outcomes for patients being treated for cancer. However, despite preclinical and clinical evidence suggesting that stress promotes increased cancer-related mortality, a comprehensive understanding of the mechanisms involved in mediating these effects does not yet exist. We reviewed 47 clinical studies published between 2007 and 2020 to determine whether psychosocial stress affects clinical outcomes in cancer: 6.4% of studies showed a protective effect; 44.6% showed a harmful effect; 48.9% showed no association. These data suggest that psychosocial stress could affect cancer incidence and/or mortality, but the association is unclear. To shed light on this potentially important relationship, objective biomarkers of stress are needed to more accurately evaluate levels of stress and its downstream effects. As a potential candidate, the neuroendocrine signalling pathways initiated by stress are known to affect anti-tumour immune cells, and here we summarise how this may promote an immunosuppressive, pro-tumour microenvironment. Further research must be done to understand the relationships between stress and immunity to more accurately measure how stress affects cancer progression and outcome.

18. Schuller HM, Al-Wadei HA, Ullah MF, Plummer HK 3rd. Regulation of pancreatic cancer by neuropsychological stress responses: a novel target for intervention. Carcinogenesis. 2012 Jan;33(1):191-6. doi: 10.1093/carcin/bgr251. Epub 2011 Nov 9. PMID: 22072614; PMCID: PMC3276326.

Pancreatic cancer has a poor prognosis and is associated with high levels of psychological stress that may adversely affect clinical outcomes. However, the potential influence of neuropsychological factors on pancreatic cancer has not been investigated to date. Using a mouse model of social stress, we have tested the hypothesis that psychological stress promotes the progression of pancreatic cancer xenografts via neurotransmitter-induced activation of multiple pathways and that the inhibitory neurotransmitter γ-aminobutiric acid (GABA) inhibits these responses. Sytemic and xenograft levels of noradrenalin, adrenalin, GABA, cortisol, vascular endothelial growth factor (VEGF) and cyclic adenosine 3', 5'-monophosphate (cAMP) were measured by immunoassays. Xenograft expression of nicotinic acetylcholine receptors (nAChRs) α3, α4, α5, α6 and α7 and β-adrenergic receptors 1 and 2 were assessed by real-time PCR and western blots. Expression of glutamate decarboxylases GAD65 and GAD67 and phosphorylated and unphosphorylated signaling proteins of relevance to pancreatic cancer were determined in tumor tissue by western blots. Psychological stress significantly promoted xenograft growth and increased systemic and tumor levels of noradrenalin, adrenalin, cortisol, VEGF and cAMP while GABA and GAD were suppressed. Stress upregulated nAChR proteins but not RNAs and induced phosphorylated ERK, CREB, Src and AKT in xenografts. Reduction of cAMP by treatment with GABA prevented tumor progression and activation of signaling proteins. Our findings suggest that neurotransmitter responses to psychological stress negatively impact clinical outcomes of pancreatic cancer via the activation of multiple pathways and that replacement of the suppressed inhibitory neurotransmitter GABA prevents these effects.

19. Hasen NS, O'Leary KA, Auger AP, Schuler LA. Social isolation reduces mammary development, tumor incidence, and expression of epigenetic regulators in wild-type and p53-heterozygotic mice. Cancer Prev Res (Phila). 2010 May;3(5):620-9. doi: 10.1158/1940-6207.CAPR-09-0225. Epub 2010 Apr 27. PMID: 20424136; PMCID: PMC2865567.

Chronic stress is associated with more rapid tumor progression, and recent evidence suggests that stress may contribute to social and ethnic disparities in the incidence and mortality of breast cancer. We evaluated the p53(+/-) FVB/N mouse as a model

to investigate effects of chronic social stress on mammary gland development, gene expression, and tumorigenesis. We individually housed (IH) wild-type and p53(+/-) female FVB/N mice, starting at weaning. At 14 weeks of age, both wild-type and p53(+/-) IH mice showed strikingly reduced mammary development compared with group-housed (GH) controls, with IH mice having significantly fewer preterminal end buds. This morphologic difference was not reflected in levels of mammary transcripts for estrogen receptor-alpha or progestin receptor. However, IH increased levels of mRNA for the kisspeptin receptor in the medial preoptic area of the hypothalamus, associated with reduced duration of estrous cycles. Furthermore, IH altered mammary transcripts of genes associated with DNA methylation; transcripts for methyl-binding protein 2 and DNA methyltransferase 3b (DNMT3b), but not DNMT1 and DNMT3a, were reduced in IH compared with GH females. Interestingly, the glands of p53(+/-) females showed reduced expression of all these mediators compared with wild-type females. However, contrary to our initial hypothesis, IH did not increase mammary tumorigenesis. Rather, p53(+/-) GH females developed significantly more mammary tumors than IH mice. Together, these data suggest that social isolation initiated at puberty might confound studies of tumorigenesis by altering mammary development in mouse models.

20. Hassan S, Pullikuth A, Nelson KC, Flores A, Karpova Y, Baiz D, Zhu S, Sui G, Huang Y, Choi YA, D'Agostino R Jr, Hemal A, von Holzen U, Debinski W, Kulik G. β2-adrenoreceptor Signaling Increases Therapy Resistance in Prostate Cancer by Upregulating MCL1. Mol Cancer Res. 2020 Dec;18(12):1839-1848. doi: 10.1158/1541-7786.MCR-19-1037. Epub 2020 Sep 14. PMID: 32928910; PMCID: PMC8080265.

There is accumulating evidence that continuous activation of the sympathetic nervous system due to psychosocial stress increases resistance to therapy and accelerates tumor growth via β2-adrenoreceptor signaling (ADRB2). However, the effector mechanisms appear to be specific to tumor type. Here we show that activation of ADRB2 by epinephrine, increased in response to immobilization stress, delays the loss of MCL1 apoptosis regulator (MCL1) protein expression induced by cytotoxic drugs in prostate cancer cells; and thus, increases resistance of prostate cancer xenografts to cytotoxic therapies. The effect of epinephrine on MCL1 protein depended on protein kinase A (PKA) activity, but was independent from androgen receptor expression. Furthermore, elevated blood epinephrine levels correlated positively with an increased MCL1 protein expression in human prostate biopsies. In summary, we demonstrate that stress triggers an androgen-independent antiapoptotic signaling via the ADRB2/PKA/MCL1 pathway in prostate cancer cells. IMPLICATIONS: Presented results justify clinical studies of ADRB2 blockers as

therapeutics and of MCL1 protein expression as potential biomarker predicting efficacy of apoptosis-targeting drugs in prostate cancer.

21. Priyanka HP, Pratap UP, Nair RS, Vasantharekha R, ThyagaRajan S. Estrogen-receptor status determines differential regulation of α1- and α2-adrenoceptor-mediated cell survival, angiogenesis, and intracellular signaling responses in breast cancer cell lines. Med Oncol. 2024 Mar 25;41(5):92. doi: 10.1007/s12032-024-02322-8. PMID: 38526769.

Psychosocial stress promotes cancer pathogenesis involving angiogenesis through alterations in neuroendocrine-immune functions that may involve adrenoceptor (AR)-dependent signaling mechanisms in the brain, lymphoid organs, and cancerous cells. Various concentrations of α_1- and α_2- AR-specific agonists and antagonists were incubated in vitro with estrogen receptor-positive (ER +) MCF-7, and ER (-) MDA MB-231 cells to examine the secretions of VEGF-A, VEGF-C, and nitric oxide (NO), and expression of signaling molecules- p-ERK, p-CREB, and p-Akt on the proliferation of breast cancer cell lines. Cellular proliferation, VEGF-A and NO secretion, expression of p-ERK, p-CREB, and p-Akt were enhanced in MCF-7 cells treated with α_1-AR agonist while VEGF-C secretion alone was enhanced in MDA MB-231 cells. Treatment of MCF-7 and MDA MB-231 cells with α_2- AR agonist similarly enhanced proliferation and decreased NO production and p-CREB expression while VEGF-C secretion was decreased in MCF-7 cells and p-Akt expression was decreased in MDA MB-231 cells. α_1-AR inhibition reversed cellular proliferation and VEGF-A secretion by MCF-7 cells while α_2-AR inhibition reversed the proliferation of MCF-7 and MDA MB-231 cells and VEGF-C secretion by MCF-7 cells. Taken together, breast cancer pathogenesis may be influenced by distinct α-AR-mediated signaling mechanisms on angiogenesis and lymphangiogenesis that are dependent on estrogen receptor status.

22. Fuemmeler BF, Shen J, Zhao H, Winn R. Neighborhood deprivation, racial segregation and associations with cancer risk and outcomes across the cancer-control continuum. Mol Psychiatry. 2023 Apr;28(4):1494-1501. doi: 10.1038/s41380-023-02006-1. Epub 2023 Mar 3. PMID: 36869227.

The racial/ethnic disparities in cancer incidence and outcome are partially due to the inequities in neighborhood advantage. Mounting evidences supported a link between neighborhood deprivation and cancer outcomes including higher mortality. In this review, we discuss some of the findings related to work on area-level

neighborhood variables and cancer outcomes, and the potential biological and built/natural environmental mechanisms that might explain this link. Studies have also shown that residents of deprived neighborhoods or of racially or economically segregated neighborhoods have worse health outcomes than residents of more affluent neighborhoods and/or less racially or economically segregated neighborhoods, even after adjusting for the individual-level socioeconomic status. To date, little research has been conducted investigating the biological mediators that may play roles in the associations of neighborhood deprivation and segregation with cancer outcomes. The psychophysiological stress induced by neighborhood disadvantage among people living in these neighborhoods could be a potential underlying biological mechanism. We examined a number of chronic stress-related pathways that may potentially mediate the relationship between area-level neighborhood factors and cancer outcomes, including higher allostatic load, stress hormones, altered epigenome and telomere maintenance and biological aging. In conclusion, the extant evidence supports the notion that neighborhood deprivation and racial segregation have unfavorable impacts on cancer. Understanding how neighborhood factors influence the biological stress response has the potential to inform where and what types of resources are needed within the community to improve cancer outcomes and reduce disparities. More studies are warranted to directly assess the role of biological and social mechanisms in mediating the relationship between neighborhood factors and cancer outcomes.

23. Woods-Burnham L, Stiel L, Martinez SR, Sanchez-Hernandez ES, Ruckle HC, Almaguel FG, Stern MC, Roberts LR, Williams DR, Montgomery S, Casiano CA. Psychosocial Stress, Glucocorticoid Signaling, and Prostate Cancer Health Disparities in African American Men. Cancer Health Disparities. 2020;4:https://companyofscientists.com/index.php/chd/article/view/169/188. PMID: 35252767; PMCID: PMC8896511.

Recent advances in our understanding of racial disparities in prostate cancer (PCa) incidence and mortality that disproportionately affect African American (AA) men have provided important insights into the psychosocial, socioeconomic, environmental, and molecular contributors. There is, however, limited mechanistic knowledge of how the interplay between these determinants influences prostate tumor aggressiveness in AA men and other men of African ancestry. Growing evidence indicates that chronic psychosocial stress in AA populations leads to sustained glucocorticoid signaling through the glucocorticoid receptor (GR), with negative physiological and pathological consequences. Compelling evidence indicates that treatment of castration-resistant prostate cancer (CRPC) with anti-androgen therapy activates GR signaling. This enhanced GR signaling bypasses

androgen receptor (AR) signaling and transcriptionally activates both AR-target genes and GR-target genes, resulting in increased prostate tumor resistance to anti-androgen therapy, chemotherapy, and radiotherapy. Given its enhanced signaling in AA men, GR-together with specific genetic drivers-may promote CRPC progression and exacerbate tumor aggressiveness in this population, potentially contributing to PCa mortality disparities. Ongoing and future CRPC clinical trials that combine standard of care therapies with GR modulators should assess racial differences in therapy response and clinical outcomes in order to improve PCa health disparities that continue to exist for AA men.

24. Basten M, Pan KY, van Tuijl LA, de Graeff A, Dekker J, Hoogendoorn AW, Lamers F, Ranchor AV, Vermeulen R, Portengen L, Voogd AC, Abell J, Awadalla P, Beekman ATF, Bjerkeset O, Boyd A, Cui Y, Frank P, Galenkamp H, Garssen B, Hellingman S, Huisman M, Huss A, Keats MR, Kok AAL, Krokstad S, van Leeuwen FE, Luik AI, Noisel N, Payette Y, Penninx BWJH, Rissanen I, Roest AM, Rosmalen JGM, Ruiter R, Schoevers RA, Soave D, Spaan M, Steptoe A, Stronks K, Sund ER, Sweeney E, Twait EL, Teyhan A, Verschuren WMM, van der Willik KD, Geerlings MI. Psychosocial factors, health behaviors and risk of cancer incidence: Testing interaction and effect modification in an individual participant data meta-analysis. Int J Cancer. 2024 May 15;154(10):1745-1759. doi: 10.1002/ijc.34852. Epub 2024 Jan 30. PMID: 38289012.

Depression, anxiety and other psychosocial factors are hypothesized to be involved in cancer development. We examined whether psychosocial factors interact with or modify the effects of health behaviors, such as smoking and alcohol use, in relation to cancer incidence. Two-stage individual participant data meta-analyses were performed based on 22 cohorts of the PSYchosocial factors and CAncer (PSY-CA) study. We examined nine psychosocial factors (depression diagnosis, depression symptoms, anxiety diagnosis, anxiety symptoms, perceived social support, loss events, general distress, neuroticism, relationship status), seven health behaviors/behavior-related factors (smoking, alcohol use, physical activity, body mass index, sedentary behavior, sleep quality, sleep duration) and seven cancer outcomes (overall cancer, smoking-related, alcohol-related, breast, lung, prostate, colorectal). Effects of the psychosocial factor, health behavior and their product term on cancer incidence were estimated using Cox regression. We pooled cohort-specific estimates using multivariate random-effects meta-analyses. Additive and

multiplicative interaction/effect modification was examined. This study involved 437,827 participants, 36,961 incident cancer diagnoses, and 4,749,481 person years of follow-up. Out of 744 combinations of psychosocial factors, health behaviors, and cancer outcomes, we found no evidence of interaction. Effect modification was found for some combinations, but there were no clear patterns for any particular factors or outcomes involved. In this first large study to systematically examine potential interaction and effect modification, we found no evidence for psychosocial factors to interact with or modify health behaviors in relation to cancer incidence. The behavioral risk profile for cancer incidence is similar in people with and without psychosocial stress.

25. Cathomas F, Lin HY, Chan KL, Li L, Durand-de Cuttoli R, Parise LF, Aubry AV, Muhareb S, Desland F, Shimo Y, Ramakrishnan A, Estill M, Ferrer-Pérez C, Parise EM, Wang J, Sowa A, Janssen WG, Costi S, Rahman A, Fernandez N, Swirski FK, Nestler EJ, Shen L, Merad M, Murrough JW, Russo SJ. Peripheral immune-derived matrix metalloproteinase promotes stress susceptibility. Res Sq [Preprint]. 2023 Jan 30:rs.3.rs-1647827. doi: 10.21203/rs.3.rs-1647827/v1. Update in: Nature. 2024 Feb;626(8001):1108-1115. doi: 10.1038/s41586-023-07015-2. PMID: 36778505; PMCID: PMC9915787.

Psychosocial stress has profound effects on the body, including the peripheral immune system and the brain[1,2]. Although a large number of pre-clinical and clinical studies have linked peripheral immune system alterations to stress-related disorders such as major depressive disorder (MDD)[3,4,5], the underlying mechanisms are not well understood. Here we show that a peripheral myeloid cell-specific proteinase, matrix metalloproteinase 8 (MMP8), is elevated in serum of subjects with MDD as well as in stress-susceptible (SUS) mice following chronic social defeat stress (CSDS). In mice, we show that this increase leads to alterations in extracellular space and neurophysiological changes in the nucleus accumbens (NAc), thereby altering social behaviour. Using a combination of mass cytometry and single-cell RNA-sequencing, we performed high-dimensional phenotyping of immune cells in circulation and brain and demonstrate that peripheral monocytes are strongly affected by stress. Both peripheral and brain-infiltrating monocytes of SUS mice showed increased **Mmp8** expression following CSDS. We further demonstrate that peripheral MMP8 directly infiltrates the NAc parenchyma to control the ultrastructure of the extracellular space. Depleting MMP8 prevented stress-induced social avoidance behaviour and alterations in NAc neurophysiology and extracellular space. Collectively, these data establish a novel mechanism by which peripheral immune

factors can affect central nervous system function and behaviour in the context of stress. Targeting specific peripheral immune cell-derived matrix metalloproteinases could constitute novel therapeutic targets for stress-related neuropsychiatric disorders.

26. Johnson MB, Hoffmann JN, You HM, Lastra RR, Fernandez S, Strober JW, Allaw AB, Brady MJ, Conzen SD, McClintock MK. Psychosocial Stress Exposure Disrupts Mammary Gland Development. J Mammary Gland Biol Neoplasia. 2018 Jun;23(1-2):59-73. doi: 10.1007/s10911-018-9392-4. Epub 2018 Apr 23. PMID: 29687293; PMCID: PMC6207373.

Exposure to psychosocial stressors and ensuing stress physiology have been associated with spontaneous invasive mammary tumors in the Sprague-Dawley rat model of human breast cancer. Mammary gland (MG) development is a time when physiologic and environmental exposures influence breast cancer risk. However, the effect of psychosocial stress exposure on MG development remains unknown. Here, in the first comprehensive longitudinal study of MG development in nulliparous female rats (from puberty through young adulthood; 8-25 wks of age), we quantify the spatial gradient of differentiation within the MG of socially stressed (isolated) and control (grouped) rats. We then demonstrate that social isolation increased stress reactivity to everyday stressors, resulting in downregulation of glucocorticoid receptor (GR) expression in the MG epithelium. Surprisingly, given that chemical carcinogens increase MG cancer risk by preventing normal terminal end bud (TEB) differentiation, chronic isolation stress did not alter TEBs. Instead, isolation blunted MG growth and alveolobular differentiation and reduced epithelial cell proliferation in these structures. Social isolation also enhanced corpora luteal progesterone at all ages but reduced estrogenization only in early adulthood, a pattern that precludes modulated ovarian function as a sufficient mechanism for the effects of isolation on MG development. This longitudinal study of natural variation provides an integrated view of MG development and the importance of increased GR activation in nulliparous ductal growth and alveolobular differentiation. Thus, social isolation and its physiological sequelae disrupt MG growth and differentiation and suggest a contribution of stress exposure during puberty and young adulthood to the previously observed increase in invasive MG cancer observed in chronically socially-isolated adult Sprague-Dawley rats.

27. Joshi S, Garlapati C, Aneja R. Epigenetic Determinants of Racial Disparity in Breast Cancer: Looking beyond Genetic Alterations. Cancers (Basel). 2022 Apr 9;14(8):1903. doi: 10.3390/cancers14081903. PMID: 35454810; PMCID: PMC9025441.

Breast cancer (BC) is the most commonly diagnosed cancer in women. Despite advancements in BC screening, prevention, and treatment, BC incidence and mortality remain high among African American (AA) women. Compared with European American (EA) women, AA women tend to be diagnosed with more advanced and aggressive tumors and exhibit worse survival outcomes. Most studies investigating the determinants of racial disparities in BC have focused on genetic factors associated with African ancestry. However, various environmental and social stressors over an individual's life course can also shape racial stratification in BC. These social and environmental exposures result in long-term changes in gene expression mediated by epigenetic mechanisms. Epigenetics is often portrayed as an intersection of socially patterned stress and genetic expression. The enduring nature of epigenetic changes makes them suitable for studying the effects of different environmental exposures over an individual's life course on gene expression. The role of differential social and environmental exposures in racial disparities in BC suggests varied epigenetic profiles or signatures associated with specific BC subtypes in AA and EA women. These epigenetic profiles in EA and AA women could be used as biomarkers for early BC diagnosis and disease prognosis and may prove valuable for the development of targeted therapies for BC. This review article discusses the current state of knowledge regarding epigenetic differences between AA and EA women with BC. We also discuss the role of socio-environmental factors, including psychosocial stress, environmental toxicants, and dietary factors, in delineating the different epigenetic profiles in AA and EA patients with BC.

28. Sotelo JL, Musselman D, Nemeroff C. The biology of depression in cancer and the relationship between depression and cancer progression. Int Rev Psychiatry. 2014 Feb;26(1):16-30. doi: 10.3109/09540261.2013.875891. PMID: 24716498.

The prevalence of depressive symptoms in patients with cancer exceeds that observed in the general population and depression is associated with a poorer prognosis in cancer patients. The increased prevalence is not solely explained by the psychosocial stress associated with the diagnosis. Pro-inflammatory cytokines, which induce sickness behaviour with symptoms overlapping those of clinical depression, are validated biomarkers of increased inflammation in patients with cancer. A

growing literature reveals that chronic inflammatory processes associated with stress may also underlie depression symptoms in general, and in patients with cancer in particular. Therapeutic modalities, which are frequently poorly tolerated, are used in the treatment of cancer. These interventions are associated with inflammatory reactions, which may help to explain their toxicity. There is evidence that antidepressants can effectively treat symptoms of depression in cancer patients though the database is meager. Novel agents with anti-inflammatory properties may be effective alternatives for patients with treatment-resistant depression who exhibit evidence of increased inflammation.

29. Hsiao FH, Jow GM, Kuo WH, Chang KJ, Liu YF, Ho RT, Ng SM, Chan CL, Lai YM, Chen YT. The effects of psychotherapy on psychological well-being and diurnal cortisol patterns in breast cancer survivors. Psychother Psychosom. 2012;81(3):173-82. doi: 10.1159/000329178. Epub 2012 Mar 3. PMID: 22399076.

Background: Neuroendocrine dysregulation influenced by psychosocial stress is related to breast cancer recurrence. Very few studies examine the impacts of psychotherapy on diurnal cortisol patterns among breast cancer survivors.

Methods: Forty-eight breast cancer patients who completed active cancer treatment were randomly assigned to receive either 8 weekly body-mind-spirit (BMS) group therapy sessions or 1 educational (EDU) session. Self-report measures included the Beck Depression Inventory-II (BDI-II), and the Meaning in Life questionnaire (MLQ) including two subscales: MLQ-Presence and MLQ-Search. Salivary cortisol levels were collected by the subjects in their homes at the time of awakening, 30 and 45 min after awakening, and at 12.00, 17.00, and 21.00 h. Measurement time points include baseline, the 2nd month (completion of BMS therapy), the 5th month, and the 8th month.

Results: There were no significant differences in BDI-II scores ($p>0.05$) and MLQ-Presence scores ($p >0.05$) between BMS and EDU groups at baseline or across the three follow-ups. Nevertheless, greater MLQ-Search scores were found in the BMS group compared to the EDU group during the 5th month of follow-up ($p <0.01$). The higher level of cortisol at 21.00 h ($p < 0.01$) and a flatter diurnal cortisol pattern were more likely to occur in EDU than in BMS participants ($p < 0.05$) at the 8th month of follow-up.

Conclusion: BMS group therapy likely contributed to enhancing an active search for meaning in life toward more opportunities for personal growth and to maintaining stable cortisol responses to everyday life stress for breast cancer survivors.

30. Geyer S. The role of social and psychosocial factors in the development and course of cancer. Wien Klin Wochenschr. 2000 Dec 7;112(23):986-94. PMID: 11190714.

This paper reviews studies dealing with the influence of social and psychosocial factors on the manifestation and course of cancer with special emphasis on breast cancer. Considerable social gradients are seen in the manifestation of malignant diseases. Most cancers (e.g. cervix, ovarian and lung cancer, malignancies of the upper respiratory and digestive organs) demonstrate a social gradient to the disadvantage of individuals from lower social ranks. In contrast, breast cancer is more prominent in middle and higher social groups. Evidence of the effects of social stress, especially concerning life-changing events, stems from retrospective and so-called limited prospective studies. With some exceptions, all these studies deal with breast cancer. In retrospective studies it was found that cancer patients report significantly more stressful experiences than do controls. In limited prospective studies the results are less straightforward, but suggest that severe loss events may be related to the manifestation of malignancies. Population studies found that patients from a lower social status had poorer chances of survival than did individuals from more privileged groups. This holds for most cancers including breast cancer. The few available studies dealing with stressful experiences and the recurrence of cancers are inconsistent, although sound methods have been applied. Nevertheless, the available evidence is no argument against performing more refined studies concerning the role of social factors in the onset and course of malignant diseases. These should provide an integration of psychological and biological perspectives.

31. Draeger DL, Sievert KD, Hakenberg OW. Psychosocial Distress in Bladder Cancer Stratified by Gender, Age, Treatment, and Tumour Stage. Urol Int. 2018;101(1):31-37. doi: 10.1159/000489502. Epub 2018 May 14. PMID: 29758554.

Objectives: Cancer patients have to cope with anxieties -concerning their prognosis, potential recurrence/progression, and treatment-associated sequelae. Stress-related psychosocial factors influence survival and disease-related mortality in cancer patients. Despite improvements in diagnosis and treatment, bladder cancer (BC) remains characterized by high rates of recurrence and progression. We screened -pre-therapeutically the stress level of BC patients stratified by gender, disease state, treatment, and other factors by -self-administered validated questionnaires to integrate them into psychosocial support as needed.

Methods: A cross-sectional analysis of distress and need of psychosocial care was done in 301 patients undergoing treatment for BC by 2 questionnaires (Distress Thermometer [DT] and Hornheider Screening Instrument).

Results: Of the 301 patients, 230 patients underwent transurethral resection for a first -diagnosis, 63 for recurrent disease, 37 had progressive disease, and 25 had advanced metastatic disease and eventually died of BC. The mean stress level in all patients was 4.6. Twenty-eight percent of the patients expressed a need for psychosocial support. In patients with progressive disease, significantly higher stress scores were seen as well as a higher need of psychosocial care (5.4 and 41%).

Conclusions: The median DT-level of 4.6 indicates moderate psychosocial stress in BC patients. From a stress level of 5, the recommendations of a psycho-oncological supervision are pronounced, so that our study showed that early systematic evaluation of psychosocial needs in BC patients is important.

32. Liu HM, Ma LL, Li C, Cao B, Jiang Y, Han L, Xu R, Lin J, Zhang D. The molecular mechanism of chronic stress affecting the occurrence and development of breast cancer and potential drug therapy. Transl Oncol. 2022 Jan;15(1):101281. doi: 10.1016/j.tranon.2021.101281. Epub 2021 Dec 4. PMID: 34875482; PMCID: PMC8652015.$

According to the 2020 data released by the International Agency for Research on Cancer, breast cancer has surpassed lung cancer as the world's most newly diagnosed first-time cancer. Compared with patients with other types of cancer, those with breast cancer experience greater mental stress and more severe psychological impacts because of the life-threatening diagnosis, physical changes, treatment side effects, and family and social life dysfunctions. These usually manifest as anxiety, depression, nervousness, and insomnia, all of which elicit stress responses. Particularly under chronic stress, the continuous release of neurotransmitters from the neuroendocrine system can have a highly profound impact on the occurrence and prognosis of breast cancer. However, because of the complex mechanisms underlying chronic stress and the variability in individual tolerance, evidence of the role of chronic stress in the occurrence and evolution of breast cancer remains unclear. This article reviewed previous research on the correlation between chronic stress and the occurrence and development of breast cancer, particularly the molecular mechanism through which chronic stress promotes breast cancer via neurotransmitters secreted by the nervous system. We also review the progress in the development of potential drugs or blockers for the treatment of breast cancer by targeting the neuroendocrine system.

33. Sánchez-Díaz CT, Strayhorn S, Tejeda S, Vijayasiri G, Rauscher GH, Molina Y. What mediates the racial/ethnic disparity in psychosocial stress among breast cancer patients? Cancer Causes Control. 2021 Apr;32(4):357-367. doi: 10.1007/s10552-021-01392-7. Epub 2021 Feb 9. PMID: 33559770; PMCID: PMC7946668.

Background: Prior studies have observed greater levels of psychosocial stress (PSS) among non-Hispanic (nH) African American and Hispanic women when compared to nH White patients after a breast cancer diagnosis. We aimed to determine the independent and interdependent roles of socioeconomic position (SEP) and unmet support in the racial disparity in PSS among breast cancer patients.

Methods: Participants were recruited from the Breast Cancer Care in Chicago study (n = 989). For all recently diagnosed breast cancer patients, aged 25-79, income, education, and tract-level disadvantage and affluence were summed to create a standardized socioeconomic position (SEP) score. Three measures of PSS related to loneliness, perceived stress, and psychological consequences of a breast cancer diagnosis were defined based on previously validated scales. Five domains of unmet social support needs (emotional, spiritual, informational, financial, and practical) were defined from interviews. We conducted path models in MPlus to estimate the extent to which PSS disparities were mediated by SEP and unmet social support needs.

Results: Black and Hispanic patients reported greater PSS compared to white patients and greater unmet social support needs ($p = 0.001$ for all domains). Virtually all of the disparity in PSS could be explained by SEP. A substantial portion of the mediating influence of SEP was further transmitted by unmet financial and practical needs among Black patients and by unmet emotional needs for Hispanic patients.

Conclusions: SEP appeared to be a root cause of the racial/ethnic disparities in PSS within our sample. Our findings further suggest that different interventions may be necessary to alleviate the burden of SEP for nH AA (i.e., more financial support) and Hispanic patients (i.e., more emotional support).

34. Magnon C. Cancer Builds a Noxious Partnership with Psychologic Stress. Cancer Res. 2024 Apr 1;84(7):956-957. doi: 10.1158/0008-5472.CAN-24-0628. PMID: 38558129.

I was recently surprised to hear a medical doctor on a TV show refute the role of stress in cancer, assuming that "the whole population would have cancer if this was the case." This statement illustrates a long and winding road since Hippocrates

suggested the potential relationship between cancer and psychologic disturbances. The 20th and 21st centuries have finally witnessed the evidence of how physical or psychosocial stress situations contribute to the development and progression of cancer, and it is now assumed that psychologic stress does affect multiple aspects of cancer such as angiogenesis, immunologic escape, invasion, and metastasis. The 2010 publication by Sloan and colleagues in Cancer Research achieved a mechanistic step toward the understanding of how physical distress enhances metastasis through perturbation of the tumor immune system and paves the way for future cancer research in psychoneuroimmunology. This Landmark commentary places this publication in the historical context of science, discusses major advances in the field, and asks questions to be answered while drawing perspectives on the key role of the peripheral and central nervous systems in cancer. See related article by Sloan and colleagues, Cancer Res 2010;70:7042-52.

35. Muscatell KA, Eisenberger NI, Dutcher JM, Cole SW, Bower JE. Links between inflammation, amygdala reactivity, and social support in breast cancer survivors. Brain Behav Immun. 2016 Mar;53:34-38. doi: 10.1016/j.bbi.2015.09.008. Epub 2015 Sep 15. PMID: 26384778; PMCID: PMC5784760.

Psychosocial stress can affect inflammatory processes that have important consequences for cancer outcomes and the behavioral side effects of cancer treatment. To date, however, little is known about the upstream neural processes that may link psychosocial stressors and inflammation in cancer patients and survivors. To address this issue, 15 women who had been diagnosed with early-stage breast cancer and completed cancer treatment and 15 age- and ethnicity-matched women with no cancer history were recruited for a neuroimaging study. Participants provided a blood sample for levels of circulating inflammatory markers (CRP and IL-6), underwent an fMRI scan in which they completed a threat reactivity task designed to elicit activity in the amygdala, and reported their levels of perceived social attachment/support. There were no significant differences between cancer survivors and controls in levels of CRP or IL-6, in amygdala reactivity to the socially threatening images, or in levels of perceived social support. However, results showed a strong, positive correlation between CRP concentration and left amygdala reactivity in the survivor group that was not apparent in controls. Higher levels of social support in the survivor group were also associated with reduced amygdala reactivity and CRP. These data suggest the possibility of a stronger "neural-immune pipeline" among breast cancer survivors, such that peripheral inflammation is more strongly associated with neural activity in threat-related brain regions.

36. Leschak CJ, Dutcher JM, Haltom KEB, Breen EC, Bower JE, Eisenberger NI. Associations between amygdala reactivity to social threat, perceived stress and C-reactive protein in breast cancer survivors. Soc Cogn Affect Neurosci. 2020 Nov 10;15(10):1056-1063. doi: 10.1093/scan/nsz103. PMID: 32039441; PMCID: PMC7657448.

Chronic inflammation in women diagnosed with breast cancer is critically linked with tumor progression, metastasis and survival. C-reactive protein (CRP)-a circulating marker of inflammation-is an important prognostic marker for cancer-related outcomes in breast cancer survivors (e.g. recurrence, fatigue). Psychological stress, which increases circulating markers of inflammation following sympathetic nervous system (SNS) activation, may modulate tumor-relevant inflammatory processes. However, little is known about neural mechanisms that might link stress and downstream SNS-initiated proinflammatory processes, such as elevated CRP. Past work suggests that threat-related neural regions, such as the amygdala, may be key in translating psychological stress into SNS activity and subsequent peripheral inflammation. Thus, we examined amygdala reactivity to socially threatening stimuli in association with perceived stress and plasma CRP levels to further elucidate neuro-immune pathways of social threat processing within breast cancer survivors (N = 37). Significant positive correlations were found between left amygdala reactivity in response to socially threatening stimuli (e.g. angry/fearful faces vs happy faces) and perceived stress in the previous month ($r = 0.32$, $P = 0.025$) and between left amygdala reactivity and CRP ($r = 0.33$, $P = 0.025$). This work builds on prior research implicating the amygdala as a key structure in crosstalk between threat-related neural circuitries and peripheral inflammation, particularly within cancer survivors.

37. Bellinger DL, Dulcich MS, Molinaro C, Gifford P, Lorton D, Gridley DS, Hartman RE. Psychosocial Stress and Age Influence Depression and Anxiety-Related Behavior, Drive Tumor Inflammatory Cytokines and Accelerate Prostate Cancer Growth in Mice. Front Oncol. 2021 Sep 16;11:703848. doi: 10.3389/fonc.2021.703848. PMID: 34604038; PMCID: PMC8481826.

Prostate cancer (PCa) prevalence is higher in older men and poorer coping with psychosocial stressors effect prognosis. Yet, interactions between age, stress and PCa progression are underexplored. Therefore, we characterized the effects of age and isolation combined with restraint (2 h/day) for 14 days post-tumor inoculation on

behavior, tumor growth and host defense in the immunocompetent, orthotopic RM-9 murine PCa model. All mice were tumor inoculated. Isolation/restraint increased sympathetic and hypothalamic-pituitary-adrenal cortical activation, based on elevated serum 3-methoxy-4-hydroxyphenylglycol/norepinephrine ratios and corticosterone levels, respectively. Elevated zero maze testing revealed age-related differences in naïve C57Bl/6 mice, and increased anxiety-like behavior in tumor-bearing mice. In open field testing, old stressed mice were less active throughout the 30-min test than young non-stressed and stressed, and old non-stressed mice, suggesting greater anxiety in old stressed mice. Old (18 month) mice demonstrated more depression-like behavior than young mice with tail suspension testing, without effects of isolation/restraint stress. Old mice developed larger tumors, despite similar tumor expression of tumor vascular endothelial growth factor or transforming growth factor-beta1 across age. Tumor chemokine/cytokine expression, commonly prognostic for poorer outcomes, were uniquely age- and stress-dependent, underscoring the need for PCa research in old animals. Macrophages predominated in RM-9 tumors. Macrophages, and $CD4^+$ and $CD4^+FoxP3^+$ T-cell tumor infiltration were greater in young mice than in old mice. Stress increased macrophage infiltration in old mice. Conversely, stress reduced intratumoral $CD4^+$ and $CD4^+FoxP3^+$ T-cell numbers in young mice. $CD8^+$ T-cell infiltration was similar across treatment groups. Our findings support that age- and psychological stress interacts to affect PCa outcomes by interfering with neural-immune mechanisms and affecting behavioral responses.

38. Zhang J, Deng YT, Liu J, Gan L, Jiang Y. Role of transforming growth factor-β1 pathway in angiogenesis induced by chronic stress in colorectal cancer. Cancer Biol Ther. 2024 Dec 31;25(1):2366451. doi: 10.1080/15384047.2024.2366451. Epub 2024 Jun 10. PMID: 38857055; PMCID: PMC11168221.

Background: Chronic stress can induce stress-related hormones; norepinephrine (NE) is considered to have the highest potential in cancer. NE can stimulate the expression of hypoxia-inducible factor-1α (HIF-1α), which is associated with vascular endothelial growth factor (VEGF) secretion and tumor angiogenesis. However, the underlying mechanisms are poorly understood.

Methods: Tumor-bearing mice were subjected to chronic restraint stress and treated with normal saline, human monoclonal VEGF-A neutralizing antibody bevacizumab, or β-adrenergic receptor (β-AR) antagonist (propranolol). Tumor growth and vessel density were also evaluated. Human colorectal adenocarcinoma cells were treated with NE, propranolol, or the inhibitor of transforming growth factor-β (TGF-β) receptor Type I kinase (Ly2157299) *in vitro*. TGF-β1 in mouse serum and cell culture

supernatants was quantified using ELISA. The expression of HIF-1α was measured using Real time-PCR and western blotting. Cell migration and invasion were tested.

Results: Chronic restraint stress attenuated the efficacy of bevacizumab and promoted tumor growth and angiogenesis in a colorectal tumor model. Propranolol blocked this effect and inhibited TGF-β1 elevation caused by chronic restraint stress or NE. NE upregulated HIF-1α expression, which was reversed by propranolol or Ly2157299. Propranolol and Ly2157199 blocked NE-stimulated cancer cell migration and invasion.

Conclusions: Our results demonstrate the effect of NE on tumor angiogenesis and the critical role of TGF-β1 signaling during this process. In addition, β-AR/TGF-β1 signaling/HIF-1α/VEGF is a potential signaling pathway. This study also indicates that psychosocial stress might be a risk factor which weakens the efficacy of anti-angiogenic therapy.

39. Ma W, Liu P, Zheng J, Lü J, Zhao Q, Li D, Guo Y, Qian L, Wang Q, Miao X, Yu Z. Immune and nonimmune mechanisms mediate the mental stress-induced tumor growth in a xenograft model of breast cancer. Cell Death Dis. 2021 Oct 23;12(11):987. doi: 10.1038/s41419-021-04280-9. PMID: 34689156; PMCID: PMC8542049.

Excess mental stress may harm health, and even accelerate cancer initiation and progression. One fourth of breast cancer patients suffer mental stress including anxiety, sadness, or depression, which negatively affect prognosis and survival. However, the regulatory mechanism is yet to be determined. Herein, we applied unpredictable stress stimuli to the breast tumor-bearing mice to establish a xenograft model of breast cancer suffering mental stress, followed by behavioral tests, tumor growth tracking, immune analysis, miRNA screening, and tumor cell proliferation analysis as well. As a result, increased stress hormone levels in serum, decreased percentage of T and NK cells in both blood and tumor samples and accelerated tumor growth in vivo were observed in the mice exposed to mental stress. Promoted cell proliferation was observed in both primary tumor cells derived from the stressed mice and 4T1 breast cancer cells treated with stress hormone corticosterone. In addition, a subset of miRNAs including miR-326, 346, 493, 595, 615, and 665 were identified through a miRNA screening with downregulation in tumors of the stressed mice. CCND1 was identified as a common target gene of miR-346 and miR-493, the top two most significantly downregulated miRNAs by stress exposure. The stress-miRNA-CCND1 signaling regulation of the tumor cell proliferation was further validated in 4T1 cells treated with corticosterone in vitro. GO terms and KEGG pathways analyses on the target genes of miR-346 and miR-493

revealed their involvement in the regulation of human cancer and neuron system, indicating the importance of non-coding genome in mediating the mental stress-induced cancer regulation. In conclusion, this study not only explored immune and nonimmune mechanisms through which mental stress exposure contributes to tumor growth in breast cancer, but also suggested a new therapeutic strategy for cancer patients suffering mental stress.

40. Zainal NZ, Ng CG, Wong A, Andrew B, Mohd Taib NA, Low SY. Prevalence of depression, trait anxiety, and social support during the diagnostic phases of breast cancer. J Taibah Univ Med Sci. 2021 Mar 17;16(4):497-503. doi: 10.1016/j.jtumed.2021.01.013. PMID: 34408606; PMCID: PMC8348272.

Objective: This study aims to determine the prevalence of depression, trait anxiety, and social support among women suspected of breast cancer (BC) and to investigate the association of these factors with the diagnosis of BC.

Methods: A cross-sectional study was conducted on 745 women who presented with breast symptoms in a university breast clinic in Malaysia. Participants were instructed to respond to self-report questionnaires on depression, trait anxiety, and social support while they were waiting for assessment of their suspected BC. The final diagnoses of these patients were traced one month after examining their medical records. Descriptive statistics were performed to examine the socio-demographic and clinical characteristics of all participants. A multiple regression analysis was carried out to determine the association of the abovementioned factors with the diagnosis of BC.

Results: The analysis showed that BC was diagnosed in 109 (14.6%), benign breast disease (BBD) in 550 (73.8%), and healthy breast (HB) in 86 (11.5%) women. The prevalence of depression was 53.2% in women with BC, 53.6% in women with BBD, and 60.5% in women with HB prior to diagnosis. The prevalence of trait anxiety was 33%. Mean scores for trait anxiety were 42.2 ± 9.0 and 41.8 ± 9.1 for the BC group and BBD group, respectively. The level of perceived social support was similar in all three groups.

Conclusion: We found no significant difference in depression, trait anxiety, and social support among women with newly diagnosed BC, BBD, and HB in women with breast symptoms while undergoing diagnostic evaluation. A longitudinal study is essential to establish the association between chronic mental stress and BC.

41. Barrera I, Spiegel D. Review of psychotherapeutic interventions on depression in cancer patients and their impact on disease progression. Int Rev Psychiatry. 2014 Feb;26(1):31-43. doi: 10.3109/09540261.2013.864259. PMID: 24716499.

Depression, ranging from mild to severe, is the most frequently found psychological symptom among individuals with cancer. Depression in cancer patients has been known to mitigate emotional distress, quality of life, adherence to medical treatment, and overall health outcomes. Specifically, depression has been associated with impaired immune response and with poorer survival in patients with cancer. Various studies have found that psychotherapeutic interventions are effective in reducing symptoms of depression, which in turn could affect disease progression and mortality. This paper provides updated information on psychotherapeutic interventions geared towards cancer patients suffering from depressive disorders, and its impact on disease progression. PubMed, Cochrane Library database, PsycINFO and PsycARTICLES databases were searched from January 1980 through August 2013 using key words: psychotherapy, treatment, oncology, cancer, psycho-oncology, psychosocial issues, psychosocial stress, depression, mood disorder, and psychoneuroimmunology.

42. Pudrovska T, Carr D, McFarland M, Collins C. Higher-status occupations and breast cancer: a life-course stress approach. Soc Sci Med. 2013 Jul;89:53-61. doi: 10.1016/j.socscimed.2013.04.013. Epub 2013 Apr 24. PMID: 23726216; PMCID: PMC3982384.

Using the 1957-2011 data from 3682 White non-Hispanic women (297 incident breast cancer cases) in the Wisconsin Longitudinal Study, United States, we explore the effect of occupation in 1975 (at age 36) on breast cancer incidence up to age 72. Our study is motivated by the paradoxical association between higher-status occupations and elevated breast cancer risk, which presents a challenge to the consistent health advantage of higher social class. We found that women in professional occupations had 72122% and women in managerial occupations had 57-89% higher risk of a breast cancer diagnosis than housewives and women in lower-status occupations. We explored an estrogen-related pathway (reproductive history, health behaviors, and life-course estrogen cycle) as well as a social stress pathway (occupational experiences) as potential explanations for the effect of higher-status occupations. The elevated risk of breast cancer among professional women was partly explained by estrogen-related variables but remained large and statistically significant. The association between managerial occupations and breast cancer incidence was fully explained by job authority defined as control over others'

work. Exercising job authority was related to higher breast cancer risk (HR = 1.57, 95% CI: 1.12, 2.18), especially with longer duration of holding the professional/managerial job. We suggest that the assertion of job authority by women in the 1970s involved stressful interpersonal experiences that may have promoted breast cancer development via prolonged dysregulation of the glucocorticoid system and exposure of the breast tissue to adverse effects of chronically elevated cortisol. Our study emphasizes complex biosocial pathways through which women's gendered occupational experiences become embodied and drive forward physiological repercussions.

43. Oliveira ML, Biggers A, Oddo VM, Yanez B, Booms E, Sharp L, Naylor K, Wolf PG, Tussing-Humphreys L. A Perspective Review on Diet Quality, Excess Adiposity, and Chronic Psychosocial Stress and Implications for Early-Onset Colorectal Cancer. J Nutr. 2024 Apr;154(4):1069-1079. doi: 10.1016/j.tjnut.2024.03.002. Epub 2024 Mar 6. PMID: 38453027; PMCID: PMC11007745.

Colorectal cancer (CRC) is the third most common cancer worldwide. Although the overall incidence of CRC has been decreasing over the past 40 y, early-onset colorectal cancer (EOCRC), which is defined as a CRC diagnosis in patients aged >50 y has increased. In this Perspective, we highlight and summarize the association between diet quality and excess adiposity, and EOCRC. We also explore chronic psychosocial stress (CPS), a less investigated modifiable risk factor, and EOCRC. We were able to show that a poor-quality diet, characterized by a high intake of sugary beverages and a Western diet pattern (high intake of red and processed meats, refined grains, and foods with added sugars) can promote risk factors associated with EOCRC development, such as an imbalance in the composition and function of the gut microbiome, presence of chronic inflammation, and insulin resistance. Excess adiposity, particularly obesity onset in early adulthood, is a likely contributor of EOCRC. Although the research is sparse examining CPS and CRC/EOCRC, we describe likely pathways linking CPS to tumorigenesis. Although additional research is needed to understand what factors are driving the uptick in EOCRC, managing body weight, improving diet quality, and mitigating psychosocial stress, may play an important role in reducing an individual's risk of EOCRC.

44. Özkan M, Yıldırım N, Dişçi R, İlgün AS, Sarsenov D, Alço G, Aktepe F, Kalyoncu N, İzci F, Selamoğlu D, Ordu Ç, Pilancı KN, Erdoğan Zİ, Eralp Y, Özmen V. Roles of Biopsychosocial Factors in the Development of Breast Cancer. Eur J Breast Health. 2017 Oct 1;13(4):206-212. doi: 10.5152/ejbh.2017.3519. PMID: 29082379; PMCID: PMC5648278.

Objective: The aim of this study was to determine the roles of biopsychosocial risk factors in the development of breast cancer.

Materials and methods: This hospital-based case-control study included 491 women with breast cancer (study group) and 512 women who did not have cancer or other serious diseases (control group). Biological, psychological, and social risk factors were compared between the two groups. Data were collected using the semi-structured interview, the Stress Assessment Form, and the Coping Strategy Indicator to assess these factors.

Results: When the significantly different biopsychosocial variables between the study and the control groups were evaluated together, independent breast cancer risk factors were found as follows: a stressor experienced in the last 5 years, age 40 years and older, inadequate social support perception, use of avoidance coping strategy, being a housewife, having a family history of cancer, and having a body mass index ≥25.

Conclusion: This study showed a relationship between breast cancer risk and manageable variables (obesity, stressor and coping strategy, social support, and employment status), age and family history of cancer, which are biopsychosocial factors. Biopsychosocial aspects are becoming a greater part of many different healthcare systems.

45. Dye CK, Wu H, VanNoy B, Calluori S, Marfori CQ, Baccarelli AA, Zota AR. Psychosocial Stress and MicroRNA Expression Profiles in Myometrial Tissue of Women Undergoing Surgical Treatment for Uterine Fibroids. Reprod Sci. 2024 Jun;31(6):1651-1661. doi: 10.1007/s43032-024-01482-2. Epub 2024 Feb 20. PMID: 38379067.

Uterine leiomyomas (fibroids) are the most common non-cancerous tumors affecting women. Psychosocial stress is associated with fibroid risk and severity. The relationship between psychosocial stress and fibroid pathogenesis may involve

alterations in microRNAs (miRNAs) although this has yet to be examined. We investigated associations between two psychosocial stress measures, a composite measure of recent stressful life events and perceived social status, with expression levels of 401 miRNAs in myometrium (n = 20) and fibroids (n = 44; 20 with paired fibroid and myometrium samples) among pre-menopausal women who underwent surgery for fibroid treatment. We used linear regressions to identify psychosocial stressors associated with miRNAs, adjusting for covariates (age, body mass index, race/ethnicity, and oral contraceptive use). The association between psychosocial stressors and miRNAs was considered statistically significant at an FDR $p < 0.10$ and showed a monotonic response (nominal p-trend < 0.05). In the myometrium, 21 miRNAs were significantly associated with a composite measure of recent stressful events, and two miRNAs were associated with perceived social status. No fibroid miRNAs were associated with either stress measure. Pathway analyses revealed miRNA-mRNA targets were significantly enriched (FDR $p < 0.05$) in pathways relevant to cancer/tumor development. Of the 74 differentially expressed miRNAs between myometrium and fibroids, miR-27a-5p and miR-301b were also associated with stress exposure. Our pilot analysis suggests that psychosocial stress is associated with myometrial miRNA expression and, thus, may have a role in the pathogenesis of fibroids from healthy myometrium.

46. Richtig E, Trapp EM, Avian A, Brezinsek HP, Trapp M, Egger JW, Kapfhammer HP, Rohrer PM, Berghold A, Curiel-Lewandrowski C, Demel U. Psychological Stress and Immunological Modulations in Early-stage Melanoma Patients. Acta Derm Venereol. 2015 Jul;95(6):691-5. doi: 10.2340/00015555-2045. PMID: 25587794.

Mental stress may have a negative impact on the immune state of cancer patients, in whom immunologic surveillance is essential for survival. This study investigated the immunological response of 19 patients with early-stage melanoma and a matched control group undergoing the Determination Stress Test before surgery. Cytokine and chemokine levels and lymphocyte subpopulations were measured at baseline and post-stress test time-points. Following the stress test lower levels of interleukin (IL)-6 were observed in the melanoma group compared with healthy volunteers ($p = 0.044$). IL-10 increased significantly in the control group 30 min after the stress test ($p = 0.002$) in comparison with the melanoma group ($p = 0.407$). CCL5/Rantes decreased significantly in the melanoma group, whereas CD16/CD56+ natural killer cells increased in both groups, with a sharp decrease below baseline after stress in the melanoma group ($p = 0.001$). This pilot study shows an altered immunological response to stressors in melanoma patients.

47. Surtees PG, Wainwright NW, Luben RN, Khaw KT, Bingham SA. No evidence that social stress is associated with breast cancer incidence. Breast Cancer Res Treat. 2010 Feb;120(1):169-74. doi: 10.1007/s10549-009-0454-6. Epub 2009 Jul 2. PMID: 19572196.

Women commonly attribute the experience of stress as a contributory cause of breast cancer. The purpose of this study is to investigate the associations between a history of social stress and breast cancer risk. A total of 11,467 women with no prior history of breast cancer, participants in the European Prospective Investigation into Cancer (EPIC)-Norfolk population-based prospective cohort study, completed a comprehensive assessment of lifetime social adversity exposure. Summary measures of social adversity were defined according to difficult circumstances in childhood, stressful life events and longer-term difficulties in adulthood, derived measures representing the subjective 'impact' of life events and associated 'stress adaptive capacity', and perceived stress over a 10-year period. Incident breast cancers were identified through linkage with cancer registry data. During 102,514 (median 9) person-years of follow-up, 313 incident breast cancers were identified. No associations were observed between any of the summary social adversity measures and subsequent breast cancer risk, with or without adjustment for age, menopausal status, parity, use of menopausal hormones, age at menarche, age at first birth, family history of breast cancer, physical activity, social class, body mass index, height, and alcohol intake. This study found no evidence that social stress exposure or individual differences in its experience are associated with the development of breast cancer. These findings may aid strategies designed to meet the psychosocial and emotional needs of breast cancer survivors and may be interpreted in a positive way in the context of commonly voiced beliefs that the experience of stress is a contributory cause of their disease.

48. Coker AL, Sanderson M, Ellison GL, Fadden MK. Stress, coping, social support, and prostate cancer risk among older African American and Caucasian men. Ethn Dis. 2006 Autumn;16(4):978-87. PMID: 17061756.

Objectives: While psychosocial stress and high effort coping have been associated with reduced immune function, no epidemiologic study has addressed psychological stress and risk of prostate cancer. The purpose of this analysis was to investigate the association between stress, coping, social support, and risk of prostate cancer among older men (age 65-79 years).

Design: Population-based case-control study in South Carolina.

Participants: Cases were 400 incident, histologically confirmed prostate cancer cases identified through the South Carolina Central Cancer Registry between 1999 and 2001 (70.6% response rate). Controls were 385 men identified through the 1999 Health Care Financing Administration Medicare beneficiary file for South Carolina (63.8% response rate).

Main outcome measures: Consenting participants completed telephone interviews addressing demographics (age, race, income, education, marital status, body mass index), medical and prostate cancer screening history, stress (Global Perceived Stress), coping (John Henryism Scale), and social support.

Results: After adjusting for age, race, and South Carolina region, higher John Henryism scores (>24) were modestly associated with prostate cancer risk relative to lower scores (<24) (adjusted odds ratio 1.63, 95% confidence interval 1.11-2.40). This effect is somewhat more pronounced among those perceiving some stress, yet the effect of John Henryism on prostate cancer risk was reduced among those with high levels of social support. Neither higher stress nor social support alone was associated with prostate cancer risk.

Conclusions: Higher John Henryism scores indicating high-effort coping may be associated with an increase in prostate cancer risk.

49. Almeida SS, Oliveira MA, Medeiros R, Guerra MP, Pariante CM, Fernandes L. Emotional, inflammatory, and genetic factors of resilience and vulnerability to depression in patients with premenopausal breast cancer: A longitudinal study protocol. PLoS One. 2023 Feb 14;18(2):e0279344. doi: 10.1371/journal.pone.0279344. PMID: 36787313; PMCID: PMC9928105.

Background: Psychosocial stress and depressive disorder have been associated with cancer as putative contributors to worse prognosis. On the other hand, cancer diagnosis is a recognised life event that can contribute to distress and depressive states. Humoral and cellular inflammation can promote depressive disorder by means of decreased monoamine synthesis, glutamate neurotoxicity, neurogenesis and neuroplasticity, dysregulated hypothalamic-pituitary-adrenal axis, and glucocorticoid resistance. This protocol objectives are to observe the interactions between psychosocial variables and biochemical and immunological biomarkers in a longitudinal, prospective design; to identify inflammation-related depression endophenotypes in breast cancer patients and to understand if early diagnosed and treated depression in this population will translate in better inflammation status and better global prognosis.

Methods: Prospective observational cohort, composed by 100 consecutive premenopausal patients, diagnosed with non-distant metastatic breast carcinoma and with no history of major psychopathology or other organic illness. The participants will have an in-person assessment in three different moments, along illness treatment and follow-up, with respect to cytometric, immunologic, and psychosocial parameters and will be tested for depression vulnerability and resilience inflammation-related functional genetic polymorphisms. Additionally, at years 5 and 10 post enrollment, patients`medical records will be assessed. As a control cohort, all patients excluded due to psychiatric history or past psychiatric treatments will have their clinical records assessed at years 5 and 10 after admission. All the data will be managed with the SPSS® software.

Discussion and conclusion: This study is an original longitudinal cohort of breast cancer premenopausal patients, with a comprehensive approach to psychosocial, clinical, inflammatory, and genetic variables. It expects to provide evidence regarding the links between genetic, cytometric, immunologic, and psychosocial factors, their potential contribution to the pathophysiology of depressive disorder, breast cancer course, progression, and prognosis. It may further contribute with data to better efficacy of the psycho-oncological interventions.

50. Niebauer E, Fry N, Auster-Gussman LA, Wahbeh H. Patient perspectives on the causes of breast cancer: a qualitative study on the relationship between stress, trauma, and breast cancer development. Int J Qual Stud Health Well-being. 2021 Dec;16(1):1983949. doi: 10.1080/17482631.2021.1983949. PMID: 34694978; PMCID: PMC8547822.

Purpose: We qualitatively evaluated breast cancer survivors' perception of the relation between breast cancer development and both childhood trauma and stressful life events in adulthood.**Methods**: Women (N = 50) who have or had a positive breast cancer diagnosis completed a close-ended survey, a timeline of significant life events, and an in-depth interview. All interviews were transcribed and inductively coded using thematic analysis with an emphasis on patient perspectives of illness.**Results**: Participants reported a perceived connection between breast cancer development and stressful life events, and four themes were identified: 1) experiencing major interpersonal stress in both childhood and adulthood, 2) ideas about the relationship between emotional stress and physical disease, 3) ideas about how different types of stress contribute to developing breast cancer, 4) post-treatment post-traumatic growth and meaning-making.**Conclusions**: Our findings suggest that of the participants who felt something could be causally attributed to their developing breast cancer, most of them made causal attributions between social, personal, and physical stress and trauma across the lifetime to the aetiology of their breast cancer. We suggest that breast cancer patients and survivors may benefit from additional psycho-social, stress-reducing, and/or somatic-based trauma-informed therapies to address stress and trauma.

51. Nagano J, Nagase S, Sudo N, Kubo C. Psychosocial stress, personality, and the severity of chronic hepatitis C. Psychosomatics. 2004 Mar-Apr;45(2):100-6. doi: 10.1176/appi.psy.45.2.100. PMID: 15016922.

This cross-sectional study examined the association between the severity of chronic hepatitis C and the type 1 personality, which has been shown by Grossarth-Maticek to be strongly related to the incidence of cancer and mortality. Sixty-nine patients with chronic hepatitis C completed the Stress Inventory, a self-report questionnaire to measure psychosocial stress and personality, and were classified into three groups according to hepatitis severity: group A, chronic hepatitis C with a normal serum alanine aminotransferase level; group B, chronic hepatitis C with an elevated alanine aminotransferase level; and group C, liver cirrhosis. Each of four scales related to the type 1 personality--low sense of control, object dependence of loss, unfulfilled need for acceptance, and altruism--was significantly and positively associated with hepatitis severity. The type 1 score, calculated as the average of these scales, was also strongly related to hepatitis severity ($p<0.0001$), and adjustment for age, sex, education level, smoking, drinking, and duration brought no attenuation into the association. Chronic psychosocial stress relevant to the type 1 personality may also influence the course of chronic hepatitis C.

52. Barber LE, Zirpoli GR, Cozier YC, Rosenberg L, Petrick JL, Bertrand KA, Palmer JR. Neighborhood disadvantage and individual-level life stressors in relation to breast cancer incidence in US Black women. Breast Cancer Res. 2021 Nov 22;23(1):108. doi: 10.1186/s13058-021-01483-y. PMID: 34809694; PMCID: PMC8609879.

Background: Research on psychosocial stress and risk of breast cancer has produced conflicting results. Few studies have assessed this relation by breast cancer subtype or specifically among Black women, who experience unique chronic stressors.

Methods: We used prospective data from the Black Women's Health Study, an ongoing cohort study of 59,000 US Black women, to assess neighborhood- and individual-level psychosocial factors in relation to risk of breast cancer. We used factor analysis to derive two neighborhood score variables after linking participant addresses to US Census data (2000 and 2010) on education, employment, income and poverty, female-headed households, and Black race for all households in each residential block group. We used Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) adjusted for established breast cancer risk factors.

Results: During follow-up from 1995 to 2017, there were 2167 incident invasive breast cancer cases (1259 estrogen receptor positive (ER +); 687 ER negative (ER-)). For ER- breast cancer, HRs were 1.26 (95% CI 1.00-1.58) for women living in the highest quartile of

neighborhood disadvantage relative to women in the lowest quartile, and 1.24 (95% CI 0.98-1.57) for lowest versus highest quartile of neighborhood socioeconomic status (SES). For ER+ breast cancer, living in the lowest quartile of neighborhood SES was associated with a reduced risk of ER+ breast cancer (HR = 0.83, 95% CI 0.70-0.98). With respect to individual-level factors, childhood sexual abuse (sexual assault ≥ 4 times vs. no abuse: HR = 1.35, 95% CI 1.01-1.79) and marital status (married/living together vs. single: HR = 1.29, 95% CI 1.08-1.53) were associated with higher risk of ER+, but not ER- breast cancer.

Conclusion: Neighborhood disadvantage and lower neighborhood SES were associated with an approximately 25% increased risk of ER- breast cancer in this large cohort of Black women, even after control for multiple behaviors and lifestyle factors. Further research is need to understand the underlying reasons for these associations. Possible contributing factors are biologic responses to the chronic stress/distress experienced by individuals who reside in neighborhoods characterized by high levels of noise, crime and unemployment or the direct effects of environmental toxins.

53. Lutgendorf SK, Sood AK, Anderson B, McGinn S, Maiseri H, Dao M, Sorosky JI, De Geest K, Ritchie J, Lubaroff DM. Social support, psychological distress, and natural killer cell activity in ovarian cancer. J Clin Oncol. 2005 Oct 1;23(28):7105-13. doi: 10.1200/JCO.2005.10.015. PMID: 16192594.

Purpose: Psychosocial stress has been related to impaired immunity in cancer patients. However, the extent to which these relationships exist in immune cells in the tumor microenvironment in humans has not been explored. We examined relationships among distress, social support, and natural killer (NK) cell activity in ovarian cancer patients in peripheral-blood mononuclear cells (PBMC), ascitic fluid, and tumor-infiltrating lymphocytes (TIL).

Patients and methods: Patients awaiting surgery for a pelvic mass suspected of being ovarian cancer completed psychological questionnaires and gave a presurgical sample of peripheral blood. Samples of tumor and ascites were taken during surgery, lymphocytes were then isolated, and NK cytotoxicity and percentage were determined. The final sample, which was confirmed by surgical diagnosis, included 42 patients with epithelial ovarian cancer and 23 patients with benign masses.

Results: Peripheral NK cell activity was significantly lower among ovarian cancer patients than in patients with benign masses. Among ovarian cancer patients, NK cytotoxicity in TIL was significantly lower than in PBMC or ascitic fluid. Social support was related to higher NK cytotoxicity in PBMC and TIL, adjusting for stage. Distress was related to lower NK cytotoxicity in TIL. A multivariate model indicated independent associations of both distress and social support with NK cell activity in TIL.

Conclusion: Psychosocial factors, such as social support and distress, are associated with changes in the cellular immune response, not only in peripheral blood, but also at the tumor

level. These relationships were more robust in TIL. These findings support the presence of stress influences in the tumor microenvironment.

54. Al-Wadei HA, Plummer HK 3rd, Ullah MF, Unger B, Brody JR, Schuller HM. Social stress promotes and γ-aminobutyric acid inhibits tumor growth in mouse models of non-small cell lung cancer. Cancer Prev Res (Phila). 2012 Feb;5(2):189-96. doi: 10.1158/1940-6207.CAPR-11-0177. Epub 2011 Sep 28. PMID: 21955519; PMCID: PMC3320046.

Psychologic distress is associated with increased lung cancer incidence and mortality. We have shown that non-small cell lung cancer (NSCLC) cells in vitro are stimulated by the cyclic AMP (cAMP)-dependent activation of cAMP-responsive element binding protein (CREB) and extracellular signal-regulated kinase (ERK) downstream of β-adrenergic receptors and that this pathway is inhibited by the neurotransmitter γ-aminobutyric acid (GABA). Because the stress neurotransmitters noradrenalin and adrenalin are β-adrenergic agonists, the current study has tested the hypothesis that social stress stimulates NSCLC growth in vivo and that GABA inhibits this effect. Social stress was induced in mice carrying xenografts from two NSCLC cell lines in the presence and absence of treatment with GABA. Xenograft sizes were measured after 30 days. Noradrenalin, adrenalin, cortisol, GABA, and cAMP were measured in blood and tumor tissues by immunoassays. Expression of nicotinic receptors in the xenografts was assessed by real-time PCR and Western blotting. Protein expression of phospho (p)-CREB, CREB, phospho (p)-ERK, ERK, and glutamate decarboxylase (GAD) 65 and 67 were determined by Western blotting. Xenograft sizes in stress-exposed mice were significantly increased. Nicotinic acetylcholine receptor (nAChR) subunits α3, α4, α5, and α7 in xenograft tissues showed posttranscriptional induction. Noradrenalin, adrenalin, and cortisol were elevated in serum and xenograft tissue whereas GABA was suppressed. Levels of cAMP, p-CREB, and p-ERK were increased whereas GAD65 and GAD67 were suppressed in tumor tissue. Treatment with GABA reversed the effects of stress. Our findings suggest that social stress stimulates NSCLC by increasing nAChR-mediated stress neurotransmitter signaling and that GABA is a promising novel agent for NSCLC intervention.

55. Trudel-Fitzgerald C, Poole EM, Idahl A, Lundin E, Sood AK, Kawachi I, Kubzansky LD, Tworoger SS. The Association of Work Characteristics With Ovarian Cancer Risk and Mortality. Psychosom Med. 2017 Nov/Dec;79(9):1059-1067. doi: 10.1097/PSY.0000000000000464. PMID: 28306624; PMCID: PMC5601015.

Objective: Ovarian cancer (OvCA) is a leading cause of cancer death for women. Depression and social isolation have been associated with a higher OvCA risk and poorer survival, but

other forms of chronic psychosocial stress, including work-related characteristics, remain understudied.

Methods: Women from three prospective cohorts (Nurses' Health Study: n = 31,754; Nurses' Health Study II: n = 74,260; Northern Sweden Health and Disease Study: nnested case-control study = 196) completed a job questionnaire, assessing demand and control at work, social support provided by coworkers and supervisor, and job security. Multivariate Cox and conditional logistic regression models estimated hazard ratios (Nurses' Health Study/Nurses' Health Study II) and odd ratios (Northern Sweden Health and Disease Study) of OvCA risk and mortality among cases. Random coefficient models were used for meta-analyses.

Results: There were 396 OvCA cases and 186 deaths during follow-up. Overall, job strain, strain chronicity, social support, and job security were not significantly associated with OvCA risk (e.g., pooled relative risk [RR]high demand/low control = 1.06, confidence interval [CI] = 0.72-1.55) or mortality (e.g., pooled RRhigh demand/low control = 1.08, CI = 0.64-1.82). When considered individually, compared with low levels, only moderate levels of demand were associated with a reduced OvCA risk (pooled RR = 0.66, CI = 0.49-0.90). Social support provided by the coworker or the supervisor did not moderate the association of job strain with either OvCA risk or overall mortality.

Conclusions: We did not observe clear associations between work characteristics and OvCA incidence or mortality, but further research with diverse populations is warranted.

56. Schuler LA, Auger AP. Psychosocially influenced cancer: diverse early-life stress experiences and links to breast cancer. Cancer Prev Res (Phila). 2010 Nov;3(11):1365-70. doi: 10.1158/1940-6207.CAPR-10-0238. Epub 2010 Nov 7. PMID: 21084258; PMCID: PMC3058374.

This perspective on Boyd et al. (beginning on page 1398 in this issue of the journal) discusses recent published research examining the interplay between social stress and breast cancer. Cross-disciplinary studies using genetically defined mouse models and established neonatal and peripubertal paradigms of social stress are illuminating biological programming by diverse early-life experiences for the risk of breast cancer. Understanding the mechanisms underlying this programming can lead to the identification of risk factors and sensitive developmental windows, enabling improved prevention and treatment strategies for this devastating disease.

57. Duijts SF, Zeegers MP, Borne BV. The association between stressful life events and breast cancer risk: a meta-analysis. Int J Cancer. 2003 Dec 20;107(6):1023-9. doi: 10.1002/ijc.11504. PMID: 14601065.

Breast cancer is the most prevalent cancer in women in Western societies. Studies examining the relationship between stressful life events and breast cancer risk have

produced conflicting results. The purpose of this meta-analysis was to identify studies on this relationship, between 1966 and December 2002, to summarize and quantify the association and to explain the inconsistency in previous results. Summary odds ratios and standard errors were calculated, using random effect meta-regression analyses, for the following categories: stressful life events, death of spouse, death of relative or friend, personal health difficulties, nonpersonal health difficulties, change in marital status, change in financial status and change in environmental status. The presence of publication bias has been explored, and sensitivity analyses were performed to identify heterogeneity, using calculation of the percentage of variability due to heterogeneity, meta-regression analyses and stratification. Only the categories stressful life events (OR = 1.77, 95% CI 1.31-2.40), death of spouse (OR = 1.37, 95% CI 1.10-1.71) and death of relative or friend (OR = 1.35, 95% CI 1.09-1.68) showed a statistically significant effect. Publication bias was identified in both stressful life events (p = 0.00) and death of relative or friend (p = 0.02). Sensitivity analyses resulted in the identification of heterogeneity in all categories, except death of spouse. The results of this meta-analysis do not support an overall association between stressful life events and breast cancer risk. Only a modest association could be identified between death of spouse and breast cancer risk.

58. Chida Y, Hamer M, Wardle J, Steptoe A. Do stress-related psychosocial factors contribute to cancer incidence and survival? Nat Clin Pract Oncol. 2008 Aug;5(8):466-75. doi: 10.1038/ncponc1134. Epub 2008 May 20. PMID: 18493231.

A substantial body of research has investigated the associations between stress-related psychosocial factors and cancer outcomes. Previous narrative reviews have been inconclusive. In this Review, we evaluated longitudinal associations between stress and cancer using meta-analytic methods. The results of 165 studies indicate that stress-related psychosocial factors are associated with higher cancer incidence in initially healthy populations (P = 0.005); in addition, poorer survival in patients with diagnosed cancer was noted in 330 studies (P <0.001), and higher cancer mortality was seen in 53 studies (P <0.001). Subgroup meta-analyses demonstrate that stressful life experiences are related to poorer cancer survival and higher mortality but not to an increased incidence. Stress-prone personality or unfavorable coping styles and negative emotional responses or poor quality of life were related to higher cancer incidence, poorer cancer survival and higher cancer mortality. Site-specific analyses indicate that psychosocial factors are associated with a higher incidence of lung cancer and poorer survival in patients with breast, lung, head and neck, hepatobiliary, and lymphoid or hematopoietic cancers. These analyses suggest that stress-related psychosocial factors have an adverse effect on cancer incidence and survival, although there is evidence of publication bias and results should be interpreted with caution.

59. Antoni MH, Lutgendorf SK, Cole SW, Dhabhar FS, Sephton SE, McDonald PG, Stefanek M, Sood AK. The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. Nat Rev Cancer. 2006 Mar;6(3):240-8. doi: 10.1038/nrc1820. PMID: 16498446; PMCID: PMC3146042.

Epidemiological studies indicate that stress, chronic depression and lack of social support might serve as risk factors for cancer development and progression. Recent cellular and molecular studies have identified biological processes that could potentially mediate such effects. This review integrates clinical, cellular and molecular studies to provide a mechanistic understanding of the interface between biological and behavioural influences in cancer, and identifies novel behavioural or pharmacological interventions that might help improve cancer outcomes.

60. Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. Biol Psychiatry. 2003 Aug 1;54(3):269-82. doi: 10.1016/s0006-3223(03)00566-3. PMID: 12893103.

Depression and cancer commonly co-occur. The prevalence of depression among cancer patients increases with disease severity and symptoms such as pain and fatigue. The literature on depression as a predictor of cancer incidence is mixed, although chronic and severe depression may be associated with elevated cancer risk. There is divided but stronger evidence that depression predicts cancer progression and mortality, although disentangling the deleterious effects of disease progression on mood complicates this research, as does the fact that some symptoms of cancer and its treatment mimic depression. There is evidence that providing psychosocial support reduces depression, anxiety, and pain, and may increase survival time with cancer, although studies in this latter area are also divided. Psychophysiological mechanisms linking depression and cancer progression include dysregulation of the hypothalamic-pituitary-adrenal axis, especially diurnal variation in cortisol and melatonin. Depression also affects components of immune function that may affect cancer surveillance. Thus, there is evidence of a bidirectional relationship between cancer and depression, offering new opportunities for therapeutic intervention.

61. Lempesis IG, Georgakopoulou VE, Papalexis P, Chrousos GP, Spandidos DA. Role of stress in the pathogenesis of cancer (Review). Int J Oncol. 2023 Nov;63(5):124. doi: 10.3892/ijo.2023.5572. Epub 2023 Sep 15. PMID: 37711028; PMCID: PMC10552722.

Stress is a state of disrupted homeostasis, triggered by intrinsic or extrinsic factors, the stressors, which are counteracted by various physiological and behavioural adaptive responses. Stress has been linked to cancer development and incidence for decades; however, epidemiological studies and clinical trials have yielded contradictory results. The present review discusses the effects of stress on cancer development and the various underlying mechanisms. Animal studies have revealed a clear link between stress and cancer progression, revealing molecular, cellular and endocrine processes that are implicated in these effects. Thus, stress hormones, their receptor systems and their intracellular molecular pathways mediate the effects of stress on cancer initiation, progression and the development of metastases. The mechanisms linking stress and cancer progression can either be indirect, mediated by changes in the cancer microenvironment or immune system dysregulation, or direct, through the binding of neuroendocrine stress-related signalling molecules to cancer cell receptors. Stress affects numerous anti- and pro-cancer immune system components, including host resistance to metastasis, tumour retention and/or immune suppression. Chronic psychological stress through the elevation of catecholamine levels may increase cancer cell death resistance. On the whole, stress is linked to cancer development and incidence, with psychological stressors playing a crucial role. Animal studies have revealed a better link than human ones, with stress-related hormones influencing tumour development, migration, invasion and cell proliferation. Randomized controlled trials are required to further evaluate the long-term cancer outcomes of stress and its management.

62. Ma Y, Kroemer G. The cancer-immune dialogue in the context of stress. Nat Rev Immunol. 2024 Apr;24(4):264-281. doi: 10.1038/s41577-023-00949-8. Epub 2023 Oct 13. PMID: 37833492.

Although there is little direct evidence supporting that stress affects cancer incidence, it does influence the evolution, dissemination and therapeutic outcomes of neoplasia, as shown in human epidemiological analyses and mouse models. The experience of and response to physiological and psychological stressors can trigger neurological and endocrine alterations, which subsequently influence malignant (stem) cells, stromal cells and immune cells in the tumour microenvironment, as well as systemic factors in the tumour macroenvironment. Importantly, stress-induced neuroendocrine changes that can regulate immune responses have been gradually uncovered. Numerous stress-associated immunomodulatory molecules (SAIMs) can reshape natural or therapy-induced antitumour responses by engaging their corresponding receptors on immune cells. Moreover, stress can

cause systemic or local metabolic reprogramming and change the composition of the gastrointestinal microbiota which can indirectly modulate antitumour immunity. Here, we explore the complex circuitries that link stress to perturbations in the cancer-immune dialogue and their implications for therapeutic approaches to cancer.

63. Barnard ME, Poole EM, Huang T, Sood AK, Kubzansky LD, Tworoger SS. Caregiver burden and risk of epithelial ovarian cancer in the Nurses' Health Studies. Am J Epidemiol. 2024 Jul 5:kwae185. doi: 10.1093/aje/kwae185. Epub ahead of print. PMID: 38973733.

Psychosocial stress may increase ovarian cancer risk and accelerate disease progression. We examined the association between caregiver burden, a common stressor, and risk of epithelial ovarian cancer. We prospectively followed 67,724 women in the Nurses' Health Study (NHS; 1992-2012) and 70,720 women in the NHSII (2001-2009) who answered questions on informal caregiving (i.e., caregiving outside of work). Women who reported no informal caregiving were considered non-caregivers while, among women who provided care outside of work, caregiver burden was categorized by time spent caregiving and perceived stress from caregiving. For the 34% of women who provided informal care for ≥15 hours per week, 42% described caregiving as moderately to extremely stressful. Pooled multivariate analyses indicated no difference in ovarian cancer risk for women providing ≥15 hours of care per week compared to non-caregivers (hazard ratio (HR)=0.96; 95% confidence interval (CI): 0.79-1.18), and no association was evident for women who reported moderate or extreme stress from caregiving compared to non-caregivers (HR=0.96; 95% CI: 0.75-1.22). Together with prior work evaluating job strain and ovarian cancer risk, our findings suggest that, when evaluating a stressor's role in cancer risk, it is critical to consider how the stressor contributes to the overall experience of distress.

64. Geng QS, Shen ZB, Zheng YY, Xue WH, Li LF, Zhao J. Precise medication for tumor patients in the context of mental stress. Cell Transplant. 2021 Jan-Dec;30:9636897211049813. doi: 10.1177/09636897211049813. PMID: 34719974; PMCID: PMC8564128.

Cancer is the leading cause of disease-related death worldwide due to its late diagnosis and poor outcomes. Precision medicine plays an important role in the treatment of tumors. As found for many types of tumors, mental stress plays a vital role in the promotion and progression of tumors. In this paper, we briefly introduce the manifestation and effects of mental symptoms in tumor patients. We next

specifically discuss the multiple roles of precision medicine in the tumor therapy. Finally, we also highlight the precision medicine strategy for psychiatric symptoms in tumor patients, which promises to enhance the efficacy of tumor therapy.

65. Madden KS, Szpunar MJ, Brown EB. Early impact of social isolation and breast tumor progression in mice. Brain Behav Immun. 2013 Mar;30 Suppl(Suppl):S135-41. doi: 10.1016/j.bbi.2012.05.003. Epub 2012 May 17. PMID: 22610067; PMCID: PMC3431437.

Evidence from cancer patients and animal models of cancer indicates that exposure to psychosocial stress can promote tumor growth and metastasis, but the pathways underlying stress-induced cancer pathogenesis are not fully understood. Social isolation has been shown to promote tumor progression. We examined the impact of social isolation on breast cancer pathogenesis in adult female severe combined immunodeficiency (SCID) mice using the human breast cancer cell line, MDA-MB-231, a high β-adrenergic receptor (AR) expressing line. When group-adapted mice were transferred into single housing (social isolation) one week prior to MB-231 tumor cell injection into a mammary fat pad (orthotopic), no alterations in tumor growth or metastasis were detected compared to group-housed mice. When social isolation was delayed until tumors were palpable, tumor growth was transiently increased in singly-housed mice. To determine if sympathetic nervous system activation was associated with increased tumor growth, spleen and tumor norepinephrine (NE) was measured after social isolation, in conjunction with tumor-promoting macrophage populations. Three days after transfer to single housing, spleen weight was transiently increased in tumor-bearing and non-tumor-bearing mice in conjunction with reduced splenic NE concentration and elevated CD11b+Gr-1+ macrophages. At day 10 after social isolation, no changes in spleen CD11b+ populations or NE were detected in singly-housed mice. In the tumors, social isolation increased CD11b+Gr-1+, CD11b+Gr-1-, and F4/80+ macrophage populations, with no change in tumor NE. The results indicate that a psychological stressor, social isolation, elicits dynamic but transient effects on macrophage populations that may facilitate tumor growth. The transiency of the changes in peripheral NE suggest that homeostatic mechanisms may mitigate the impact of social isolation over time. Studies are underway to define the neuroendocrine mechanisms underlying the tumor-promoting effects of social isolation, and to determine the contributions of increased tumor macrophages to tumor pathogenesis.

66. Ellison GL, Coker AL, Hebert JR, Sanderson SM, Royal CD, Weinrich SP. Psychosocial stress and prostate cancer: a theoretical model. Ethn Dis. 2001 Autumn;11(3):484-95. PMID: 11572415.

African-American men are more likely to develop and die from prostate cancer than are European-American men; yet, factors responsible for the racial disparity in incidence and mortality have not been elucidated. Socioeconomic disadvantage is more prevalent among African-American than among European-American men. Socioeconomic disadvantage can lead to psychosocial stress and may be linked to negative lifestyle behaviors. Regardless of socioeconomic position, African-American men routinely experience racism-induced stress. We propose a theoretical framework for an association between psychosocial stress and prostate cancer. Within the context of history and culture, we further propose that psychosocial stress may partially explain the variable incidence of prostate cancer between these diverse groups. Psychosocial stress may negatively impact the immune system leaving the individual susceptible to malignancies. Behavioral responses to psychosocial stress are amenable to change. If psychosocial stress is found to negatively impact prostate cancer risk, interventions may be designed to modify reactions to environmental demands.

67. Li C, Andrzejak SE, Jones SR, Williams BM, Moore JX. Investigating the association between educational attainment and allostatic load with risk of cancer mortality among African American women. BMC Womens Health. 2023 Aug 24;23(1):448. doi: 10.1186/s12905-023-02529-3. PMID: 37620873; PMCID: PMC10463695.

Background: African American (AA) women navigate the world with multiple intersecting marginalized identities. Accordingly, AA women have higher cumulative stress burden or allostatic load (AL) compared to other women. Studies suggest that AA women with a college degree or higher have lower AL than AA women with less than a high school diploma. We examined the joint effect of educational attainment and AL status with long-term risk of cancer mortality, and whether education moderated the association between AL and cancer mortality.

Methods: We performed a retrospective analysis among 4,677 AA women within the National Health and Nutrition Examination Survey (NHANES) from 1988 to 2010 with follow-up data through December 31, 2019. We fit weighted Cox proportional hazards models to estimate adjusted hazard ratios (aHRs) of cancer death between educational attainment/AL (adjusted for age, income, and smoking status).

Results: AA women with less than a high school diploma living with high AL had nearly a 3-fold increased risk (unadjusted HR: 2.98; 95%C CI: 1.24-7.15) of cancer death compared to AA college graduates living with low AL. However, after adjusting for age, this effect attenuated (age-adjusted HR: 1.11; 95% CI: 0.45-2.74). AA women with high AL had 2.3-fold increased risk of cancer death (fully adjusted HR: 2.26; 95% CI: 1.10-4.57) when compared to AA with low AL, specifically among women with high school diploma or equivalent and without history of cancer.

Conclusions: Our findings suggest that high allostatic load is associated with a higher risk of cancer mortality among AA women with lower educational attainment, while no such association was observed among AA women with higher educational attainment. Thus, educational attainment plays a modifying role in the relationship between allostatic load and the risk of cancer death for AA women. Higher education can bring several benefits, including improved access to medical care and enhanced medical literacy, which in turn may help mitigate the adverse impact of AL and the heightened risk of cancer mortality among AA women.

68. Li G, Gan Y, Fan Y, Wu Y, Lin H, Song Y, Cai X, Yu X, Pan W, Yao M, Gu J, Tu H. Enriched environment inhibits mouse pancreatic cancer growth and down-regulates the expression of mitochondria-related genes in cancer cells. Sci Rep. 2015 Jan 19;5:7856. doi: 10.1038/srep07856. PMID: 25598223; PMCID: PMC4297951.

Psycho-social stress has been suggested to influence the development of cancer, but it remains poorly defined with regard to pancreatic cancer, a lethal malignancy with few effective treatment modalities. In this study, we sought to investigate the impacts of enriched environment (EE) housing, a rodent model of "eustress", on the growth of mouse pancreatic cancer, and to explore the potential underlying mechanisms through gene expression profiling. The EE mice showed significantly reduced tumor weights in both subcutaneous (53%) and orthotopic (41%) models, while each single component of EE (inanimate stimulation, social stimulation or physical exercise) was not profound enough to achieve comparative anti-tumor effects as EE. The integrative transcriptomic and proteomic analysis revealed that in response to EE, a total of 129 genes in the tumors showed differential expression at both the mRNA and protein levels. The differentially expressed genes were mostly localized to the mitochondria and enriched in the citrate cycle and oxidative phosphorylation pathways. Interestingly, nearly all of the mitochondria-related genes were down-regulated by EE. Our data have provided experimental evidence in favor of the application of positive stress or of benign environmental stimulation in pancreatic cancer therapy.

69. Ma Y, Yang H, Kroemer G. Endogenous and exogenous glucocorticoids abolish the efficacy of immune-dependent cancer therapies. Oncoimmunology. 2019 Oct 11;9(1):1673635. doi: 10.1080/2162402X.2019.1673635. PMID: 32002285; PMCID: PMC6959448.

Glucocorticoids mediate potent anti-inflammatory and immunosuppressive effects. A chronic elevation of the endogenous glucocorticoid tonus subsequent to mental stress, as well as continuous treatment with exogenous glucocorticoids, activate an immunosuppressive transcription factor, TSC22D3, in dendritic cells, causing the subversion of cancer therapy-elicited antineoplastic immune responses and subsequent therapeutic failure.

70. Poole EM, Kubzansky LD, Sood AK, Okereke OI, Tworoger SS. A prospective study of phobic anxiety, risk of ovarian cancer, and survival among patients. Cancer Causes Control. 2016 May;27(5):661-8. doi: 10.1007/s10552-016-0739-0. Epub 2016 Mar 29. PMID: 27023470; PMCID: PMC4840033.

Purpose: In ovarian cancer patients and mouse models, psychosocial stress is associated with higher circulating markers of angiogenesis and cell migration, impaired immune response, and increasing tumor burden and aggressiveness. In the Nurses' Health Studies (NHS/NHSII), we assessed whether phobic anxiety, a marker of chronic distress, was associated with risk of incident ovarian cancer as well as survival among ovarian cancer patients.

Methods: We used Cox proportional hazards regression to model the relative risks (RRs) and 95 % confidence intervals (CI) of ovarian cancer incidence and survival by categories of the Crown-Crisp phobic anxiety index (CCI).

Results: We identified 779 cases of ovarian cancer during 2,497,892 person-years of follow-up. For baseline CCI (NHS: 1988; NHSII: 1993), we observed a statistically nonsignificant increased risk of epithelial ovarian cancer (RR for CCI ≥ 4 vs. 0 or 1: 1.14; 95 % CI 0.96-1.36). However, when we updated CCI (NHS: 2004; NHSII: 2005), the associations were attenuated. Pre-diagnosis CCI was not associated with ovarian cancer survival (RR for ≥4 vs. 0 or 1: 1.00; 95 % CI 0.77-1.31); results were similar for post-diagnosis CCI.

Conclusions: Distress, as measured by phobic anxiety symptoms, was not associated with ovarian cancer risk, although we cannot rule out a modest association. Future

research should explore the role of phobic anxiety and other forms of psychological distress and ovarian cancer risk and survival.

71. Wang R, Yu S, Yu L, Wang Q, Wu Y. Riddle of the Sphinx: facts and evidence regarding the link between mental stress and tumor occurrence and development. Chin Med J (Engl). 2022 Dec 20;135(24):2998-3000. doi: 10.1097/CM9.0000000000002129. PMID: 36580651; PMCID: PMC10106126.

To the Editor: The answer to the “Riddle of Sphinx” is “human”, whose image is both negative and positive. It is often used as a metaphor for complex, mysterious, and incomprehensible problems. With the deterioration of modern living environment and the aggravation of stress, the incidence of the tumor is on the rise. Excessive or prolonged stress can lead to acute or chronic organ dysfunction and metabolic disorders. Studies have shown that tumor patients are often under long-term adverse stress states. Chronic mental stress alters tumor cell survival, proliferation and metastasis by activating stressrelated transcriptional regulators and signaling pathways in the body. With the demonstration of their important role in tumor development under stress, related pathways or cytokines could be antagonized or inhibited to change the trajectory of the tumor development. This article explores how chronic mental stress affects the presence of tumor cells by influencing the expression of brain-derived neurotrophic factor (BDNF), insulin-like growth factor 2/insulin-like growth factor 1 receptor (IGF2/IGF1R), C-reactive protein (CRP) and other possible pathways in cancer patients.

72. Trainor BC, Sweeney C, Cardiff R. Isolating the effects of social interactions on cancer biology. Cancer Prev Res (Phila). 2009 Oct;2(10):843-6. doi: 10.1158/1940-6207.CAPR-09-0167. Epub 2009 Sep 29. PMID: 19789296.

This perspective on Williams et al. (beginning on p. 850 in this issue of the journal) examines the connections between biological responses activated during psychosocial stress and mammary tumorigenesis. Experiments in mouse models of cancer are identifying aspects of tumor biology that may be regulated by hormones such as glucocorticoids released during psychosocial stress. Our growing understanding of the actions of glucocorticoids on breast tumors could lead to important changes in cancer treatment.

73. Moore JX, Andrzejak SE, Bevel MS, Jones SR, Tingen MS. Exploring racial disparities on the association between allostatic load and cancer mortality: A retrospective cohort analysis of NHANES, 1988 through 2019. SSM Popul Health. 2022 Jul 31;19:101185. doi: 10.1016/j.ssmph.2022.101185. PMID: 35990411; PMCID: PMC9382324.

Background: Several studies suggest that chronic stress may be associated with increased risk of cancer mortality. Our study sought to determine the association between allostatic load (AL), a measure of cumulative stress, and risk of cancer death; and whether these associations varied by race/ethnicity.

Methods: We performed retrospective analysis using National Health and Nutrition Examination Survey (NHANES) years 1988 through 2010 linked with the National Death Index through December 31, 2019. We fit Fine & Gray Cox proportional hazards models to estimate sub-distribution hazard ratios (SHRs) of cancer death between high and low AL status (models adjusted for age, sociodemographics, and comorbidities).

Results: In fully adjusted models, high AL was associated with a 14% increased risk of cancer death (adjusted (SHR): 1.14, 95% CI: 1.04-1.26) among all participants and a 18% increased risk of cancer death (SHR:1.18, 95% CI: 1.03-1.34) among Non-Hispanic White (NH-White) adults. When further stratified by age (participants aged <40 years), high AL was associated with a 80% increased risk (SHR: 1.80, 95% CI: 1.35-2.41) among all participants; a 95% increased risk (SHR: 1.95, 95% CI: 1.22-3.12) among NH-White adults; a 2-fold (SHR: 2.06, 95% CI: 1.27-3.34) increased risk among Non-Hispanic Black (NH-Black) adults; and a 36% increased risk among Hispanic adults (SHR: 1.36, 95% CI: 0.70-2.62).

Conclusions: Overall, the risk of cancer death was associated with high AL; however, when stratified among NH-Black and Hispanic adults this association was slightly attenuated.

Impact: High AL is associated with increased risk of overall cancer death, and future studies should delineate the association between AL and cancer-specific mortality to better understand the causal mechanisms between cumulative stress and cancer.

74. Hasegawa H, Saiki I. Psychosocial stress augments tumor development through beta-adrenergic activation in mice. Jpn J Cancer Res. 2002 Jul;93(7):729-35. doi: 10.1111/j.1349-7006.2002.tb01313.x. PMID: 12149137; PMCID: PMC5927068.

Housing conditions affect behavioral and biological responses of animals. We investigated the effect of same-sex-grouped (G), crowded (GC) and isolated (I) conditions on the growth of B16 melanoma or Meth A fibrosarcoma implanted in the footpad of syngeneic male C57BL / 6 or BALB / c mice. Differential housing altered host resistance to tumor growth. The host responses to stress were reflected in thymic atrophy, which was lowest in the G mice, highest in the GC mice and intermediate in the I mice. The GC condition was a more stressful social environment than the I condition in both male C57BL / 6 and BALB / c mice. Reflecting the extent of psychosocial stress, tumor growth was augmented in the order of GC, I and G condition, and a negative mass correlation between tumor and thymus was observed, thus clearly indicating that the host resistance to tumors was attenuated by psychosocial stress. Furthermore, the stress-enhanced tumor growth and thymus atrophy were completely abrogated by the oral administration of the non-selective beta-adrenergic antagonist, propranolol. On the contrary, the chronic administration of corticosterone significantly induced the atrophy of thymus and spleen without affecting tumor growth. These results suggest an interrelationship among psychosocial stress, tumor growth and beta-adrenergic activation.

75. Spiegel D, Giese-Davis J, Taylor CB, Kraemer H. Stress sensitivity in metastatic breast cancer: analysis of hypothalamic-pituitary-adrenal axis function. Psychoneuroendocrinology. 2006 Nov;31(10):1231-44. doi: 10.1016/j.psyneuen.2006.09.004. Epub 2006 Nov 1. PMID: 17081700; PMCID: PMC1790857.

The normal diurnal cortisol cycle has a peak in the morning, decreasing rapidly over the day, with low levels during the night, then rising rapidly again to the morning peak. A pattern of flatter daytime slopes has been associated with more rapid cancer progression in both animals and humans. We studied the relationship between the daytime slopes and other daytime cortisol responses to both pharmacological and psychosocial challenges of hypothalamic-pituitary-adrenal (HPA) axis function as well as DHEA in a sample of 99 women with metastatic breast cancer, in hopes of elucidating the dysregulatory process. We found that the different components of HPA regulation: the daytime cortisol slope, the rise in cortisol from waking to 30 min later, and cortisol response to various challenges, including dexamethasone (DEX) suppression, corticotrophin releasing factor (CRF) activation, and the Trier Social Stress Task, were at best modestly associated. Escape from suppression stimulated by

1mg of DEX administered the night before was moderately but significantly associated with flatter daytime cortisol slopes (r=0.28 to .30 at different times of the post DEX administration day, all p<.01). Daytime cortisol slopes were also moderately but significant associated with the rise in cortisol from waking to 30 min after awakening (r=.29, p=.004, N=96), but not with waking cortisol level (r=-0.13, p=.19). However, we could not detect any association between daytime cortisol slope and activation of cortisol secretion by either CRF infusion or the Trier Social Stress Task. The CRF activation test (following 1.5mg of DEX to assure that the effect was due to exogenous CRF) produced ACTH levels that were correlated (r=0.66, p<.0001, N=74) with serum cortisol levels, indicating adrenal responsiveness to ACTH stimulation. Daytime cortisol slopes were significantly correlated with the slope of DHEA (r=.21, p=.04, N=95). Our general findings suggest that flatter daytime cortisol slopes among metastatic breast cancer patients may be related to disrupted feedback inhibition rather than hypersensitivity in response to stimulation.

76. Imai K, Nakachi K. Personality types, lifestyle, and sensitivity to mental stress in association with NK activity. Int J Hyg Environ Health. 2001 Oct;204(1):67-73. doi: 10.1078/1438-4639-00075. PMID: 11725349.

We conducted a cross-sectional study among 302 healthy Japanese male workers to make a mechanistic approach to the association between personality types and cancer; two types of personality, the emotionally unstable-introvert and the emotionally stable-extravert, were compared with each other in lifestyle, mental stress status, and biological markers such as plasma levels of neurotransmitters and NK activity of peripheral lymphocytes. We first found that emotionally unstable-introverts have a more unhealthy lifestyle associated with low NK activity than among stable-extraverts, along with higher sensitivity to mental stress (also known to suppress NK activity) than stable-extraverts. Second, emotionally unstable-introverts were found to have in fact decreased NK activity along with higher plasma levels of noradrenaline, when compared with stable-extraverts. Our results thus demonstrate that emotionally unstable-introverts have a decreased capacity of immunological host defense against cancer, which is possibly due to two factors, unhealthy lifestyle and high sensitivity to mental stress.

77. Peters S, Grunwald N, Rümmele P, Endlicher E, Lechner A, Neumann ID, Obermeier F, Reber SO. Chronic psychosocial stress increases the risk for inflammation-related colon carcinogenesis in male mice. Stress. 2012 Jul;15(4):403-15. doi: 10.3109/10253890.2011.631232. Epub 2011 Dec 20. PMID: 22044139.

Patients with inflammatory bowel diseases (IBDs) have a higher risk of developing colorectal cancer (CRC) than the general population. Furthermore, chronic psychosocial stress increases the likelihood of developing IBD and multiple types of malignant neoplasms, including CRC. Here, for the first time, we investigate the effects of chronic psychosocial stress in male mice on an artificially induced CRC, by employing the chronic subordinate colony (CSC) housing paradigm in combination with the reliable azoxymethane (AOM)/dextran sodium sulfate (DSS) CRC model. Colonoscopy revealed that CSC mice showed accelerated macroscopic suspect lesions. In addition, more CSC mice developed low-grade dysplasia (LGD) and/or high-grade dysplasia (HGD) in the colonic tissue compared to the single-housed control mice (SHC). CSC mice showed an increased number of Ki67+ and a decreased number of terminal deoxynucleotidyl transferase dUTP nick end labeling epithelial cells in colonic tissue. Colonic liver receptor homolog-1 (LRH-1), cyclooxygenase II (COXII), tumor necrosis factor, forkhead box P3 (FoxP3) mRNA as well as colonic ß-catenin, COXII, and LRH-1 protein expression were also increased in CSC compared with SHC mice. Although the number of CD4+ Th cells was increased, a tendency toward a decreased colonic interferon-γ (IFN-γ) mRNA expression was observed. Furthermore, despite an increased percentage of CD3+ cells and CD3+/FoxP3+ double-positive cells within mesenteric lymph node cells of CSC mice, IFN-γ secretion from these cells was unaffected. Altogether, our results suggest that chronic psychosocial stress increases the risk for AOM/DSS-induced and, thus, inflammation-related CRC. Finally, assessment of additional time points may test whether the shift from tumor-protective Th1 cell to regulatory T-cell immunity represents a consequence of increased carcinogenesis or a causal factor involved in its development.

78. Al-Wadei HA, Al-Wadei MH, Ullah MF, Schuller HM. Celecoxib and GABA cooperatively prevent the progression of pancreatic cancer in vitro and in xenograft models of stress-free and stress-exposed mice. PLoS One. 2012;7(8):e43376. doi: 10.1371/journal.pone.0043376. Epub 2012 Aug 16. PMID: 22916251; PMCID: PMC3420877.

Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis and is associated with high levels of psychological distress. We have shown that beta-adrenergic receptors (β-ARs), which are activated by stress neurotransmitters, regulate PDAC cells via cyclic AMP (cAMP)-dependent signaling in vitro, that social stress promotes PDAC progression in mouse xenografts and that γ-aminobutyric acid (GABA) inhibits these responses in vitro and in vivo. The targeted inhibition of stress-induced regulatory pathways may abolish the potentially negative impact of psychological stress on clinical outcomes. Our current data show that chronic exposure of PDAC cell lines Panc-1 (activating point mutations in K-ras) and BXPC-3 (no mutations in K-ras) in vitro to the stress neurotransmitter epinephrine at the concentration (15 nM) previously measured in the serum of mice exposed to social stress significantly increased proliferation and migration. These responses were inhibited in a concentration-dependent manner by celecoxib. The effects of celecoxib alone and in combination with γ-aminobutyric acid (GABA) on the progression of subcutaneous mouse xenografts from the cell line (BXPC-3) most responsive to epinephrine were then investigated in the presence and absence of social stress. Cancer-stimulating factors (VEGF & prostaglandin E(2) [PGE(2)]) and levels of cAMP were measured by immunoassays in blood and xenograft tissue. Phosphorylation of the signaling proteins ERK, CREB, Src, and AKT was assessed by ELISA assays and Western blotting. Expression of COX-2, 5-lipoxygenase, and p-5-LOX were determined by semi-quantitative Western blotting. Celecoxib alone significantly inhibited xenograft progression and decreased systemic and tumor VEGF, PGE2, and cAMP as well as phosphorylated signaling proteins in stress-exposed and stress-free mice. These responses were significantly enhanced by co-treatment with GABA. The celecoxib-induced downregulation of COX-2 protein and p-5-LOX was also significantly enhanced by GABA under both experimental conditions. Our findings identify the targeted inhibition of stress-induced pathways as a promising area for more effective cancer intervention in pancreatic cancer.

79. Ollonen P, Lehtonen J, Eskelinen M. Stressful and adverse life experiences in patients with breast symptoms; a prospective case-control study in Kuopio, Finland. Anticancer Res. 2005 Jan-Feb;25(1B):531-6. PMID: 15816624.

Background: Psychosocial stress is widely thought to play a role in the aetiology of cancer in general and breast cancer in particular. Many studies have investigated the association between stressful life events and risk of breast cancer. However, the field of psychosocial cancer research is often problematic and findings have been contradictory, varying from no association to strong association. This inconsistency in results may be explained by the fact that most of the epidemiological data available come from retrospective case-control studies. We have conducted this case-control study with a so called "limited prospective study design"to reduce the potential for recall bias.

Materials and methods: This study is an extension of the Kuopio Breast Cancer Study. Women with breast symptoms were referred by physicians to the Kuopio University Hospital (Finland) and were asked to participate in this study. The women were interviewed and reports on adverse and stressful life events were obtained before any diagnostic procedures were done, so neither the investigator nor the subject knew the final diagnosis of breast symptoms at the time of the interview. The research method used was the semi-structured in-depth interview method. All study subjects were also asked to complete standardised questionnaires (Beck Depression Inventory, Spielberger Trait Inventory).

Results: The clinical examination and biopsy showed breast cancer (BC) in 34 patients, benign breast disease (BBD) in 53 patients, while 28 study subjects showed to be healthy (HSS). The results indicated that BC patients had had significantly ($p=0.02$) more very severe (Gr IV) and severe (Gr III) stress in the previous 10 years preceding the investigation than the BBD and HSS groups. The BC group also reported significantly more moderate or severe losses than the BBD or the HSS groups ($p=0.0009$).

Conclusion: The results of this study support an overall association between stressful life events and breast cancer risk. The biological explanation of the overall association might be that stress disturbs various areas of the immune systems predisposing to neoplasia.

80. Irie M, Asami S, Nagata S, Ikeda M, Miyata M, Kasai H. Psychosocial factors as a potential trigger of oxidative DNA damage in human leukocytes. Jpn J Cancer Res. 2001 Mar;92(3):367-76. doi: 10.1111/j.1349-7006.2001.tb01104.x. PMID: 11267949; PMCID: PMC5926712.

Although numerous studies have been carried out on the stress-cancer linkage, the results are still inconclusive. One of the useful, but rarely applied, methods to assess this linkage is to examine the relationship between psychosocial stress and cancer-predisposing genetic alterations simultaneously. We investigated whether various psychosocial factors can be associated with the levels of 8-hydroxydeoxyguanosine (8-OH-dG), a biomarker of cancer-related oxidative DNA damage, in peripheral blood leukocytes in 362 healthy workers (276 males and 86 females). After adjustments for age, body mass index, cigarette smoking, and alcohol use, female subjects showed positive relationships between the amount of 8-OH-dG and the Tension-Anxiety, Depression-Rejection, Anger-Hostility, Fatigue, and Confusion scores of the Profile of Mood States, respectively. The levels of 8-OH-dG also increased reliably in the female subjects who had poor stress-coping behaviors, particularly wishful thinking strategy, in the NIOSH general job stress instrument. There were positive relationships of the 8-OH-dG levels to average working hours, a self-blame coping strategy, and recent loss of a close family member in male subjects. These findings in a nonclinical sample of healthy adults not only provide evidence of a stress-cancer linkage, but also suggest possible sex differences in the mechanisms of stress-related cancer initiation.