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Cancer and Tumor Biology Research Literatures

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Abstract: Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent research reports as references in the related studies.
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Key words: cancer; tumor; life; research; literature; cell

1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent research reports as references in the related studies.

The following introduces recent reports as references in the related studies.

Aaltonen, L. A., et al. (1994). "Replication errors in benign and malignant tumors from hereditary nonpolyposis colorectal cancer patients." Cancer Res **54**(7): 1645-1648.

A replication error (RER) phenotype has been documented both in sporadic colorectal tumors and in tumors from patients with hereditary nonpolyposis colorectal cancer (HNPCC). In the current study 8 of 49 (16%) sporadic colorectal cancers (CRCs) and 25 of 29 (86%) CRCs from HNPCC patients were found to be RER+. All 9 (100%) CRCs from HNPCC patients with germline mutations of the mismatch repair gene MSH2 were found to be RER+, while 16 of 20 CRCs from HNPCC kindreds unlinked or not studied for linkage to MSH2 were RER+. Corresponding analysis in colorectal adenomas revealed that only 1 of 33 (3%) sporadic tumors but 8 of 14 (57%) HNPCC tumors were RER+. Moreover, RER was found in all 6 extracolonic cancers (endometrium, 2; kidney, 1; stomach, 1; duodenum, 1; and ovary, 1) derived from members of HNPCC families. These data suggest the involvement of mismatch repair deficiency in the premalignant stage of tumorigenesis in HNPCC cases, and suggest that mismatch repair genes (MSH2 or others) are defective in the germline of nearly all these patients.

Aburjania, Z., et al. (2017). "Encapsulated follicular variant of papillary thyroid cancer: are these tumors really benign?" J Surg Res **216**: 138-142.

BACKGROUND: Recent studies suggest that the encapsulated form of follicular variant of papillary thyroid cancer (eFVPTC) behaves more similarly to benign lesions and can be treated with thyroid lobectomy alone instead of total thyroidectomy. To distinguish aggressive cancers from more benign lesions more clearly, the objective of this study was to determine if the eFVPTC behaves less aggressively than the nonencapsulated variant (neFVPTC). METHODS: A prospectively collected endocrine surgery database in our institution was reviewed for all patients with FVPTC on surgical pathology from 1999 to 2012. Samples were rereviewed to determine if the tumor was eFVPTC or neFVPTC, which were correlated with patient outcomes. RESULTS: Of the 68 patients, 59 (87%) had eFVPTC and 9 (13%) had neFVPTC. The mean age was 48 y and 63% were female. Fifty-four of 64 patients (84%) who had a total thyroidectomy received radioactive iodine. The eFVPTC group had lower rates of cervical LN involvement (5% versus 22%, P = 0.2504). The median follow-up time was 3 y (0-13 y) and only two patients

had recurrence, one with eFVPTC and one with neFVPTC. None of the patients had distant metastasis or died of their disease. CONCLUSIONS: eFVPTCs appear to have a lower rate of cervical lymph node metastases compared with neFVPTCs, but recurrent disease may be seen in both subtypes. These findings suggest eFVPTC can be managed more conservatively.

Alfano, R. R., et al. (1991). "Light sheds light on cancer--distinguishing malignant tumors from benign tissues and tumors." Bull N Y Acad Med **67**(2): 143-150.

Difference in fluorescence spectra from human malignant and benign tumors, benign and normal breast tissues were measured. Spectral histograms from 40 samples show the diagnostic possibilities of this optical technology. Fluorescence from model fluorophores (nucleotides, amino acids, and proteins) were used to speculate on the sources of marked features of the tissue fluorescence.

Beger, H. G., et al. (2016). "Parenchyma-Sparing, Limited Pancreatic Head Resection for Benign Tumors and Low-Risk Periampullary Cancer--a Systematic Review." J Gastrointest Surg **20**(1): 206-217.

BACKGROUND: Parenchyma-sparing local extirpation of benign tumors of the pancreatic head provides the potential benefits of preservation of functional tissue and low postoperative morbidity. METHODS: Medline/PubMed, Embase, and Cochrane library databases were surveyed for studies performing limited resection of the pancreatic head and resection of a segment of the duodenum and common bile duct or preservation of the duodenum and common bile duct (CBD). The systematic analysis included 27 cohort studies that reported on limited pancreatic head resections for benign tumors. In a subgroup analysis, 12 of the cohort studies were additionally evaluated to compare the postoperative morbidity after total head resection including duodenal segment resection (DPPHR-S) and total head resection conserving duodenum and CBD (DPPHR-T). RESULTS: Three hundred thirty-nine of a total of 503 patients (67.4%) underwent total head resections. One hundred forty-seven patients (29.2%) of them underwent segmental resection of the duodenum and CBD (DPPHR-S) and 192 patients (38.2%) underwent preservation of duodenum and CBD. One hundred sixty-four patients experienced partial head resection (32.6%). The final histological diagnosis revealed in 338 of 503 patients (67.2%) cystic neoplasms, 53 patients (10.3%) neuroendocrine tumors, and 20 patients (4.0%) low-risk periampullary carcinomas. Severe postoperative complications occurred in 62 of 490 patients (12.7%), pancreatic fistula B + C in 40 of 295 patients (13.6%), resurgery was experienced in 2.7%, and delayed gastric emptying in 12.3%. The 90-day mortality was 0.4%. The subgroup analysis comparing 143 DPPHR-S patients with 95 DPPHR-T patients showed that the respective rates of procedure-related biliary complications were 0.7% (1 of 143 patients) versus 8.4% (8 of 95 patients) (p </= 0.0032), and rates of duodenal complications were 0 versus 6.3% (6 of 95 patients) (p </= 0.0037). DPPHR-S was associated with a higher rate of delay of gastric emptying compared to DPPHR-T (18.9 vs. 2.1%, p </= 0.0001). CONCLUSION: Parenchyma-sparing, limited head resection for benign tumors preserves functional pancreatic and duodenal tissue and carries in terms of fistula B + C rate, resurgery, rehospitalization, and 90-day mortality a low risk of postoperative complications. A subgroup analysis exhibited after total pancreatic head resection that preserves the duodenum and CBD an association with a significant increase in procedure-related biliary and duodenal complications compared to total head resection combined with resection of the periampullary segment of the duodenum and resection of the intrapancreatic CBD.

Chan, H. and C. B. Pratt (1977). "A new familial cancer syndrome? A spectrum of malignant and benign tumors including retinoblastoma, carcinoma of the bladder and other genitourinary tumors, thyroid adenoma, and a probable case of multifocal osteosarcoma." J Natl Cancer Inst **58**(2): 205-207.

An 11-year-old Caucasian girl who had been cured of bilateral retinoblastoma developed non-radiation-induced osteosarcoma in multiple sites of the extremities. Investigation of the medical histories of 36 of her family members through six generations revealed that 8 relatives on the maternal side (22%) had malignant tumors, predominately genitourinary carcinomas, 2(6%) had benign tumors only, and 2(6%) had both benign and malignant neoplasms. The histologic variety of these tumors, the predominance of genitourinary carcinoma, the higher than expected frequency of tumor appearance over six generations, and the occurrence of malignant tumors in direct lineage suggest that the case of retinoblastoma followed by osteosarcoma is part of a familial cancer syndrome.

Chang, U. K., et al. (2011). "Radiosurgery using the Cyberknife for benign spinal tumors: Korea Cancer Center Hospital experience." J Neurooncol **101**(1): 91-99.

This study evaluated clinical outcome and safety of radiosurgery using the Cyberknife for treatment of benign spinal tumors. The authors treated 30 benign spinal tumors in 20 patients with the Cyberknife (Accuray, Inc., Sunnyvale, CA, USA) from 2002 to 2008. Among these there were 20 neurogenic

tumors, eight hemangioblastomas, and two meningiomas. Four patients with neurofibromatosis (NF) type 2 and four patients with Von Hippel Lindau disease were also included. Radiosurgery was done as primary treatment for 22 lesions, for postoperative residual tumor control for four lesions, and for the remaining four lesions with image-based progression after initial subtotal resection. The distribution of lesions was cervical (18 tumors), thoracic (six), and cauda equina level (six). Follow-up data included imaging studies, clinical findings, and radiotherapy data. Tumor volume ranged from 0.04 to 33.65 cm(3) (mean, 4.52 cm(3)). A 14-33 Gy marginal dose was delivered in 1-5 fractions. The mean follow-up period was 35.6 months (range, 12-84 months). On follow-up, most lesions decreased in size (57%) or remained unchanged (33%). Two lesions initially decreased, then increased later. One lesion increased without response. With regard to clinical aspects, radicular pain and myelopathic pain improved after radiosurgery in most cases (94%). Motor weakness recovered in two out of five patients and recovery of sensory change occurred in four out of ten patients. In two patients, symptoms were aggravated by tumor enlargement and the occurrence of new lesion. Mean spinal cord volumes receiving more than 10 and 8 Gy were 0.40 +/- 0.4 and 0.81 +/- 0.7 cm(3), respectively. Stereotactic radiosurgery (SRS) using the Cyberknife showed the ability to control benign spinal tumors without complication in most cases.

Cohen, I., et al. (1998). "Estrogen and progesterone receptors in benign ovarian tumors of menopausal breast cancer patients treated with tamoxifen." Gynecol Obstet Invest **46**(2): 116-122.

In order to assess possible ovarian cell potential for interaction with tamoxifen, thus demonstrating possible effects of this agent on the development of ovarian pathologies through growth stimulation and cell proliferation, we measured estrogen receptors (ER) and progesterone receptors (PR) by immunohistochemical method in 16 benign ovarian tumors removed from 11 postmenopausal breast cancer patients treated with tamoxifen (study group). The results were compared with those measured in 7 similar ovarian tumors obtained from 5 similar patients without tamoxifen treatment (control group I), and in 9 similar tumors removed from 9 age-matched postmenopausal women (control group II). There were no significant differences with regard to ER or PR expression between the study group and control group I and II (ER = 18.75, 0.0 and 11%, respectively; PR = 43.75, 28.5 and 44%, respectively; p = NS). There were also no significant statistical differences between the three groups when subdividing the ovarian pathologies according to different histological types. From the results obtained in this study, it seems that tamoxifen probably does not have any direct influence on the ovaries of menopausal breast cancer patients.

Cuevas-Antonio, R., et al. (2010). "Expression of progranulin (Acrogranin/PCDGF/Granulin-Epithelin Precursor) in benign and malignant ovarian tumors and activation of MAPK signaling in ovarian cancer cell line." Cancer Invest **28**(5): 452-458.

It has been recently demonstrated that progranulin is overexpressed in ovarian cancer and that this protein is involved in the stimulation of cell proliferation, malignancy, and chemoresistance in ovarian cancer. The goal of the present study was to establish the differences in progranulin expression among normal, benign, and malignant ovarian tissues and to identify the signal transduction pathways activated by progranulin in an ovarian cancer cell line. Compared with benign tumors and normal ovarian tissue, progranulin mRNA and protein were overexpressed in malignant tumors. Survival analysis by the Kaplan-Meier method showed a correlation between high mRNA expression levels with poor survival outcome. Progranulin activated the MAPK-signaling pathway in NIH-OVCAR-3 cells. Progranulin expression may be potentially involved in the pathogenesis and malignant progression of ovarian cancer, and thus may represent a therapeutic target for this particular malignancy.

De Bree, E., et al. (2013). "Adipose tissue fatty acid composition in Greek patients with breast cancer versus those with benign breast tumors." Anticancer Res **33**(4): 1667-1672.

BACKGROUND: Fatty acid composition of adipose tissue is a most reliable biomarker of long-term dietary fatty acid intake. Few studies have implemented biomarkers of fatty acid intake in relation to breast cancer. In this study the relation between adipose tissue composition and breast cancer was investigated. PATIENTS AND METHODS: Fatty acid composition in breast and buttock adipose tissue from 94 Greek women with breast cancer and 57 with benign breast tumors was determined. Multivariate analysis was performed to determine the association between fatty acid groups and breast cancer risk. RESULTS: In pre-menopausal women, elevated total polyunsaturated fatty acids (PUFA) in breast adipose tissue and N-3 PUFA in buttock adipose tissue were associated with reduced odds of breast cancer (odds ratio, OR=0.19; 95% confidence interval, CI=0.05-0.76, $p<0.02$ and OR=0.02; 95% CI=0.0009-0.36, $p<0.009$). CONCLUSION: Adipose total PUFA and N-3 PUFA were inversely-related to breast cancer risk in Greek pre-menopausal women. These results may have specific impact on habitual fat intake recommendations.

Geshelin, S. A., et al. (1989). "[Contact thermography in the differential diagnosis of benign tumors and cancer of the breast]." Vrach Delo(8): 103-105.

Contact thermography was performed in 87 patients with benign and in 75 with cancerous tumours of the breast. Hyperthermia over the tumour is characterized by a 2.2 degrees C and higher increase of the temperature and was registered only in cancer of the breast. Anisothermy of the breast was characterized by a +/- 0.5 degrees C and higher and may be considered as a supplementary diagnostic sign distinguishing cancer of the breast from benign tumours.

Gonzalez-Palomares, B., et al. (2017). "Vascular Endothelial Growth Factor (VEGF) Polymorphisms and Serum VEGF Levels in Women With Epithelial Ovarian Cancer, Benign Tumors, and Healthy Ovaries." Int J Gynecol Cancer **27**(6): 1088-1095.

OBJECTIVE: This study analyzed the relation of 5 single-nucleotide polymorphisms (SNPs) in the VEGF (vascular endothelial growth factor) gene in patients with epithelial ovarian cancer (EOC), compared with patients carrying benign tumors or healthy ovaries. We studied serum VEGF levels and the relation with SNPs and association between VEGF SNPs and haplotypes with progression-free survival (PFS) in patients with cancer. METHODS: The genotyping of VEGF gene polymorphisms (-2578 C/A, -1154 G/A, -460 T/C, +405 G/C, +936 C/T) was performed in DNA isolated from blood samples of 100 women. The different genotypes were evaluated by quantitative real-time polymerase chain reaction. Vascular endothelial growth factor protein concentration was assessed in serum using solid-phase sandwich enzyme-linked immunosorbent assay. RESULTS: We found statistically significant differences in the distribution of VEGF genotypes among the 3 groups of patients: -2578 C/A between those with EOC and healthy ovary (P = 0.04), -460 T/C between those with EOC and healthy ovary (P = 0.03), and -460 T/C between those with benign tumors and healthy ovary (P = 0.02). Vascular endothelial growth factor serum levels were analyzed in patients with EOC. Higher levels were found in patients with clear cell carcinoma compared with those with serous, mucinous, or endometrioid tumors (P < 0.05). No clear association was observed between VEGF SNPs and serum VEGF levels. There was no significant correlation between VEGF SNPs and PFS. In haplotype analysis, CGTCT and CGTGT showed worse prognosis without reaching the statistical significance. CGCGC and AGTGC haplotypes had statistically significant differences among patients with EOC, benign tumors, and healthy ovaries (Ps = 0.046 and 0.041, respectively). CONCLUSIONS: The distribution of VEGF genotypes was different in patients with EOC, compared with those with benign tumors or women with healthy ovaries. Vascular endothelial growth factor serum levels were higher in patients with clear cell carcinoma. No correlation was found with improved PFS, but CGTCT and CGTGT haplotypes showed worse prognosis.

Guelstein, V. I., et al. (1988). "Monoclonal antibody mapping of keratins 8 and 17 and of vimentin in normal human mammary gland, benign tumors, dysplasias and breast cancer." Int J Cancer **42**(2): 147-153.

The distribution of keratins 8 and 17 and of vimentin in 28 normal human mammary tissue samples, 16 benign tumors, 26 fibrocystic diseases and 52 malignant breast tumors have been studied using monoclonal antibodies HI, E3 and NT30, respectively. Three cell populations in normal mammary epithelium have been identified: luminal epithelium containing keratin 8, myoepithelium of the lobular structures positive for vimentin, and myoepithelium of extralobular ducts positive for keratin 17. In different kinds of benign tumor and dysplastic proliferation a mosaic of cells with all normal phenotypes has been observed. The majority of cells co-expressed keratins 8 and 17 or vimentin. In the overwhelming majority of carcinomas, cells did not contain myoepithelial markers (keratin 17 and vimentin) but expressed only keratin 8 specific to normal luminal epithelium.

Guo, C., et al. (2017). "Age-related terminal duct lobular unit involution in benign tissues from Chinese breast cancer patients with luminal and triple-negative tumors." Breast Cancer Res **19**(1): 61.

BACKGROUND: Terminal duct lobular unit (TDLU) involution is a physiological process of breast tissue aging characterized by a reduction in the epithelial component. In studies of women with benign breast disease, researchers have found that age-matched women with lower levels of TDLU involution are at increased risk of developing breast cancer. We previously showed that breast cancer cases with core basal phenotype (CBP; estrogen receptor negative [ER(-)], progesterone receptor-negative [PR(-)], human epidermal growth factor receptor 2-negative [HER2(-)], cytokeratins (CK 5 or CK5/6)-positive [CK5/6(+)] and/or epidermal growth factor receptor-positive [EGFR(+)]) tumors had significantly reduced TDLU involution compared with cases with luminal A (ER(+) and/or PR(+), HER2(-), CK5/6(-), EGFR(-)) tumors from a population-based case-control study in Poland. We evaluated the association of TDLU involution with tumor subtypes in an independent population of women in China, where the breast cancer incidence rate,

prevalence of known risk factors, and mammographic breast density are thought to be markedly different from those of Polish women. METHODS: We performed morphometric assessment of TDLUs by using three reproducible semiquantitative measures that inversely correlate with TDLU involution (TDLU count/100 mm(2), TDLU span in micrometer, and acini count/TDLU) by examining benign tissue blocks from 254 age-matched luminal A and 250 triple-negative (TN; ER(-), PR(-), HER2(-), including 125 CBP) breast cancer cases treated in a tertiary hospital in Beijing, China. RESULTS: Overall, we found that TN and particularly CBP cases tended to have greater TDLU measures (less involution) than luminal A cases in logistic regression models accounting for age, body mass index, parity, and tumor grade. The strongest association was observed for tertiles of acini count among younger women (aged <50 years) (CBP vs. luminal A; ORtrend 2.11, 95% CI 1.22-3.67, P = 0.008). CONCLUSIONS: These data extend previous findings that TN/CBP breast cancers are associated with reduced TDLU involution in surrounding breast parenchyma compared with luminal A cases among Chinese women, providing further support for differences in the pathogenesis of these tumor subtypes.

Hiyama, E., et al. (1997). "Telomerase activity is detected in pancreatic cancer but not in benign tumors." Cancer Res **57**(2): 326-331.

Activation of telomerase and stabilization of telomeres are considered to be necessary for immortalization of human tumor cells. In the present study, telomerase activity was detected in 41 (95%) of 43 pancreatic cancer specimens but was detectable in none of 11 benign pancreatic tumors and only one of 3 pancreatitis samples. Low levels of telomerase activity were detected in 5 (14%) of 36 adjacent "normal" pancreatic tissues. These five telomerase-positive "normal" specimens were obtained from patients that also had pancreatic cancer and may reflect occult microinvasion. Telomerase activity was examined in 12 ex vivo brushing samples of the pancreatic duct, and 8 of 8 with pancreatic cancer had detectable telomerase activity, whereas 0 of 4 of benign lesions (cystadenoma and pancreatitis) did. These findings suggest that telomerase activity in cells derived from pancreatic ducts may be useful in the diagnosis of cancer and that telomerase activity may be a critical or rate-limiting step in pancreatic carcinogenesis.

Hsia, C. C., et al. (2004). "Nivalenol, a main Fusarium toxin in dietary foods from high-risk areas of cancer of esophagus and gastric cardia in China, induced benign and malignant tumors in mice." Oncol Rep **12**(2): 449-456.

This is the first report that a Fusarium toxin nivalenol (NIV) naturally existing at high levels in dietary food in high-risk areas of cancer of esophagus and gastric cardia in China induced benign and malignant tumors in mice. The levels of two Fusarium toxins, nivalenol and deoxynivalenol (DON) were quantitated using high performance liquid chromatography (HPLC) in a total of 97 samples of dietary wheat flour, barley and corn collected from families in two areas with high mortality rate of cancer of esophagus and gastric cardia (132/100,000), Linxian, Henan province and Cixiang, Hepei province, China. The mean level of NIV and DON in three dietary foods was 830+/-927 microg/kg (range 584-1,780 microg/kg) and 4,281+/-6,114 microg/kg (range 732-10,980 microg/kg) respectively. The highest mean level of NIV was 1,780+/-1,705 microg/kg found in barley from Linxian, that of DON was 10,980+/-10,139 microg/kg found in corn from Cixiang. NIV was undetectable in 2 samples of rice from USA. The mean levels of NIV in three main dietary foods in those two high-risk areas were estimated at 400 to 800-fold higher than that in the USA, where NIV was undetectable in dietary food, and the mortality rate of esophageal cancer is <5/100,000 in white Caucasians in the USA, (odds ratio was estimated at 17-34, p<0.000005). These data suggest that Linxian and Cixiang peasants who consumed a diet with high NIV had significantly higher risk for developing esophageal cancer than the US residents who consumed food without or with negligible amounts of NIV. Three repeated experiments were performed using Balb/C mice with inter-mittent application of NIV, alternate with 12-Tetradeconoyl-phorbol-13-acetate (TPA) application on skin. Papillomas and carcinomas developed in a total of 23/49 (47%) mice that survived 11-60 weeks of experiments. Among all the tumors, 4 carcinomas in 3 mice were identified. No tumors were found in the 60 control mice applying either TPA or acetone (solvent) only on skin.

Inoue, M., et al. (1992). "Sialyl-Tn, sialyl-Lewis Xi, CA 19-9, CA 125, carcinoembryonic antigen, and tissue polypeptide antigen in differentiating ovarian cancer from benign tumors." Obstet Gynecol **79**(3): 434-440.

Serum sialyl-Tn, sialyl-Lewis Xi, CA 19-9, CA 125, carcinoembryonic antigen (CEA), and tissue polypeptide antigen were measured in 65 women with early-stage ovarian cancer (45 stage I and 20 stage II cases) and 317 with benign pelvic masses. As a single assay, sialyl-Tn showed the best sensitivity and specificity, 46 and 92%, respectively. CA 19-9 detected the greatest number of cancer patients but had the lowest specificity. The combination of sialyl-Tn, CA 125, tissue polypeptide antigen, and CEA seemed to

perform the best, with a sensitivity and specificity of 71 and 76%, respectively. The combination of sialyl-Tn, CA 125, and tissue polypeptide antigen gave similar results and may be more cost-effective. However, one-fifth of the patients with early-stage cancer still showed up as false negatives even with use of the six markers in combination. Approaches other than serum assay alone will be needed to detect all malignant pelvic masses at an early stage.

Kutsenko, A., et al. (2014). "Risk of second benign brain tumors among cancer survivors in the surveillance, epidemiology, and end results program." Cancer Causes Control **25**(6): 659-668.

PURPOSE: To assess risk of developing a second benign brain tumor in a nationwide population of cancer survivors. METHODS: We evaluated the risk of developing second benign brain tumors among 2,038,074 1-year minimum cancer survivors compared to expected risk in the general population between 1973 and 2007 in nine population-based cancer registries in the NCI's surveillance, epidemiology, and end results program. Excess risk was estimated using standardized incidence ratios (SIRs) for all second benign brain tumors and specifically for second meningiomas and acoustic neuromas diagnosed during 2004-2008. RESULTS: 1,025 patients were diagnosed with a second primary benign brain tumor, of which second meningiomas composed the majority (n = 745). Statistically significant increases in risk of developing a second meningioma compared to the general population were observed following first cancers of the brain [SIR = 19.82; 95 % confidence interval (CI) 13.88-27.44], other central nervous system (CNS) (SIR = 9.54; CI 3.10-22.27), thyroid (SIR = 2.05; CI 1.47-2.79), prostate (SIR = 1.21; CI 1.02-1.43), and acute lymphocytic leukemia (ALL) (SIR = 42.4; CI 23.18-71.13). Statistically significant decreases in risk were observed following first cancers of the uterine corpus (SIR = 0.63; CI 0.42-0.91) and colon (SIR = 0.56; CI 0.37-0.82). Differences in risk between patients initially treated with radiotherapy versus non-irradiated patients were statistically significant for second meningioma after primary cancers of the brain (p Het < 0.001) and ALL (p Het = 0.02). No statistically significant increased risks were detected for second acoustic neuromas (n = 114) following any first primary tumor. CONCLUSIONS: Risk of second benign brain tumors, particularly meningioma, is increased following first primary cancers of the brain/CNS, thyroid, prostate, and ALL. Radiation exposure likely contributes to these excess risks.

Lawicki, S., et al. (2008). "Comparative evaluation of plasma levels and diagnostic values of macrophage-colony stimulating factor in patients with breast cancer and benign tumors." Pol Arch Med Wewn **118**(9): 464-469.

INTRODUCTION: Macrophage-colony stimulating factor (M-CSF) is one of the glycoproteins called hematopoetic growth factors. The direct production of this cytokine has been reported in tumor cell lines in vitro and in solid tumors in vivo. OBJECTIVES: In the present study, the levels of M-CSF in patients with breast cancer and in those with a benign breast tumor were evaluated. Moreover, diagnostic values were determined through assessing diagnostic sensitivity and specificity as well as predictive value of positive (PV(+xe)) and negative (PV(-ve)) results. The results obtained were compared to the CA 15-3 and a control group. PATIENTS AND METHODS: The study group was made up of 70 patients with breast cancer and 20 patients with benign tumors and the control group of 30 healthy women. M-CSF was assayed using an ELISA method. CA 15-3 was measured by means of an immunoenzymatic method (MEIA) from ABBOT. RESULTS: Statistically higher levels of M-CSF and CA 15-3 were found in breast cancer patients as compared to the benign tumor and control groups. These levels were also significantly higher in patients with more advanced stages of cancer. A positive correlation between M-CSF and CA 15-3 levels was observed. The diagnostic sensitivity of M-CSF (58%), a specificity (93%), PV(+ve) (94%) and PV(-ve) (43%) were higher or equal to the values obtained for CA 15-3 (49%, 93%, 93% and 40%, respectively). When both parameters studied were determined jointly, sensitivity increased to 72%. CONCLUSIONS: The above data suggests that M-CSF might be useful in both diagnostics and differential diagnosis of benign tumors and breast cancer (except for the lowest degree of the clinical progression).

Mavridis, K., et al. (2013). "Quantified KLK15 gene expression levels discriminate prostate cancer from benign tumors and constitute a novel independent predictor of disease progression." Prostate **73**(11): 1191-1201.

BACKGROUND: Several transcript variants of the kallikrein-related peptidase 15 gene (KLK15) have been identified up to now. The classical KLK15 mRNA isoform encodes for a non-truncated, functional protein. Aberrant KLK15 expression is found in breast, ovarian, and prostate cancers. Our aim in this present study was the specific quantitative expression analysis of the classical KLK15 mRNA transcript in prostate tumors and the examination of its clinical significance in prostate cancer. METHODS: We isolated total RNA from 150 prostate tissue specimens and, following cDNA synthesis, the expression of KLK15 classical mRNA transcript was measured via quantitative Real-

Time PCR using the TaqMan(R) chemistry. HPRT1 was used as a reference gene, and the absolute quantification approach, through the incorporation of standard curves, was applied for the calculation of normalized KLK15 expression. RESULTS: KLK15 expression levels were significantly upregulated in malignant compared to benign samples (P < 0.001). The discriminatory value of KLK15 was confirmed by ROC curve and logistic regression analysis (both P < 0.001). KLK15 was also associated with advanced pathological stage (P = 0.023). KLK15-positive prostate cancer patients presented significantly shorter progression-free survival intervals, determined by biochemical relapse (P = 0.006), compared to KLK15-negative ones. Multivariate Cox regression analysis revealed that KLK15 expression is an independent predictor of biochemical recurrence (HR = 3.36, P = 0.038). CONCLUSIONS: The present study unravels the important role of quantified KLK15 classical mRNA expression levels as a novel biomarker helpful for the differential diagnosis and prognosis of prostate cancer patients.

Merlich, K. I., et al. (1993). "[The subfractional composition of the blood plasma in benign tumors and cancer of the breast based on the data from laser correlational spectroscopy]." Biull Eksp Biol Med **116**(8): 193-195.

LCS was performed in 35 patients with mammary cancer, 59 patients with benign breast tumours and 35 healthy people. 39 samples were taken from inhabitants of Odessa, 89 from St.-Petersburg. Differences were discovered between blood plasma spectra of Odessa and St.-Petersburg residents. Spectra of blood plasma in patients with mammary tumours differed from those of healthy people. LCS may be used for screening, for forming the groups of risk and for diagnosis of mammary gland tumours.

Moody-Ayers, S. Y., et al. (2000). ""Benign" tumors and "early detection" in mammography-screened patients of a natural cohort with breast cancer." Arch Intern Med **160**(8): 1109-1115.

BACKGROUND: Although the cure of breast cancer by "early detection" and prompt treatment rests on the belief that all breast cancers grow at the same rate, many cancers have been shown to grow rapidly and others slowly. In particular, mammography screening may often detect the slow-growing, nonaggressive tumors that might not be found until much later, if at all. METHODS: We reviewed the medical records of a natural cohort of 233 patients. The cohort comprised all women who received their first antineoplastic treatment for breast cancer at Yale-New Haven Hospital during the period from January 1 through December 31, 1988, and had a median follow-up thereafter of 82.4 months. RESULTS: The mammography screen-detected group (MSDG) contained 97 (42%) of the 233 breast cancers. The rates of subsequent freedom from cancer deaths or recurrences were 95% (92 patients) in the MSDG and 79% (107 patients) in all other patients (log-rank 2P<.001). This superiority occurred partly because 90 (93%) of the MSDG were in the good prognosis TNM stages 0, I, and IIA, compared with 92 (68%) of the non-MSDG (chi2 2P = .001). Of the 31 patients with stage 0 (carcinoma in situ), all of whom had disease-free survival, 24 (77%) were found by mammography screening. Even within similar TNM stages, however, the MSDG had distinctly better disease-free survival results than the non-MSDG. For patients in TNM stages I and IIA, the "failure events" had respective rates of 2% and 13% (log-rank 2P = .02). CONCLUSIONS: The results suggest that many of the breast cancers found by mammography screening have excellent prognosis not just because of early detection, but also because many of the cancers are relatively benign, requiring minimal therapy.

Nowak, M., et al. (2010). "Proinflammatory and immunosuppressive serum, ascites and cyst fluid cytokines in patients with early and advanced ovarian cancer and benign ovarian tumors." Neuro Endocrinol Lett **31**(3): 375-383.

OBJECTIVE: To analyze the profiles of interleukin-2 (IL-2), IL-6, IL-8, IL-10, tumor necrosis factor-alpha (TNF-alpha), transforming growth factor-beta1 (TGF-beta1) and interferon-gamma (IFN-gamma) in serum and the tumor microenvironment (cyst fluid, ascites) in women with ovarian cancer or benign ovarian tumors to find the differences in their immunological status. We also estimated serum cytokines as biomarkers to distinguish preoperatively between malignant or benign character of tumors. DESIGN: Prospective study. SETTING: Tertiary referral hospital. POPULATION: 51 women with epithelial ovarian cancer, 26 with benign ovarian tumors of epithelial origin and 21 healthy controls. METHODS: The levels of cytokines were measured using ELISA sets. RESULTS: We did not found differences in the levels of IFN-gamma, TNF-alpha and IL-2 in all fluids isolated from patients with malignant or benign tumors. Women with advanced cancer had significantly higher serum IL-6, IL-10 and TGF-beta1 levels than women with early stages or benign tumors. Moreover, women with very advanced cancer in whom the optimal cytoreduction was disabled had the highest serum levels of IL-10, TGF-beta1 and IL-8. The concentrations of IL-6 and IL-8 were higher in ascites of cancer patients than in ascites of women with benign tumors. The areas under curves constructed for the selected cutoff serum cytokines levels (AUC-ROC)

showed good predictive values for IL-6 (0.87), IL-10 (0.836) and IL-8 (0.797). CONCLUSIONS: Our results indicate on intensified inflammatory process in women with ovarian cancer (accompanied by their immunosuppression). Preoperative analysis of serum IL-6, IL-10 and IL-8 may improve the differential diagnosis of ovarian tumors.

Qin, Y. Y., et al. (2018). "Single and combined use of red cell distribution width, mean platelet volume, and cancer antigen 125 for differential diagnosis of ovarian cancer and benign ovarian tumors." J Ovarian Res **11**(1): 10.

BACKGROUND: Cancer is widely believed to result from chronic inflammation, and red cell distribution width (RDW) and mean platelet volume (MPV) are considered as inflammatory markers for cancer. We investigated the values of RDW, MPV, and cancer antigen 125 (CA125), alone or in combination, for distinguishing between ovarian cancer and benign ovarian tumors. METHODS: The study included 326 patients with ovarian cancer, 290 patients with benign ovarian tumors, and 162 control subjects. Hematologic tests were performed at initial diagnosis. RESULTS: RDW was increased and MPV was decreased in the ovarian cancer group compared with the control and benign ovarian tumor groups. RDW was positively correlated and MPV was negatively correlated with cancer stage. Area under the curve (AUC) analysis for ovarian cancer versus benign ovarian tumors revealed that the specificity and sensitivity were increased for the combination of MPV and CA125 compared with either marker alone, and the specificity was increased for the combination of RDW and CA125, compared with either alone. The AUCs for RDW plus CA125 and MPV plus CA125 were significantly larger than for any of the markers alone. CONCLUSIONS: In conclusion, combinations of the markers RDW, MPV, and CA125 may improve the differential diagnosis of ovarian cancer and benign ovarian tumors.

Roujun, C., et al. (2016). "High prevalence of diabetes mellitus and impaired glucose tolerance in liver cancer patients: A hospital based study of 4610 patients with benign tumors or specific cancers." F1000Res **5**: 1397.

OBJECTIVE: The prevalence of diabetes mellitus (DM), impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) were hypothesised to be different among different tumor patients. This study aimed to study the association between the prevalence of DM, IGT and IFG and liver cancer, colorectal cancer, breast cancer, cervical cancer, nasopharyngeal cancer and benign tumor. METHODS: A hospital based retrospective study was conducted on 4610 patients admitted to the Internal Medical Department of the Affiliated Tumor Hospital of Guangxi Medical University, China. Logistic regression was used to examine the association between gender, age group, ethnicity , cancer types or benign tumors and prevalence of DM, IFG, IGT. RESULTS: Among 4610 patients, there were 1000 liver cancer patients, 373 breast cancer patients, 415 nasopharyngeal cancer patients, 230 cervical cancer patients, 405 colorectal cancer patients, and 2187 benign tumor patients. The prevalence of DM and IGT in liver cancer patients was 14.7% and 22.1%, respectively. The prevalence of DM and IGT was 13.8% and 20%, respectively, in colorectal cancer patients, significantly higher than that of benign cancers. After adjusting for gender, age group, and ethnicity, the prevalence of DM and IGT in liver cancers patients was 1.29 times (CI :1.12-1.66) and 1.49 times (CI :1.20-1.86) higher than that of benign tumors, respectively. CONCLUSION: There was a high prevalence of DM and IGT in liver cancer patients.

Shilov, N. I. (1979). "[Hemostasis system in lung cancer, benign tumors and chronic nonspecific pneumonias]." Vopr Onkol **25**(4): 21-25.

A comparative study, condicted on the coagulation status, indicated that tumor and chronic inflammatory processes in the lung as associated with high blood content of fibrinogen and fibrinogen B, the increased plasma tolerance to heparin and degree of thrombotest with a compensatory increase of the heparin content and antithrombin activity. Lung tumor patients contrary to patients with pneumonias showed a high thromboplastin activity and reduced fibrinolysis indices. The activation of euglobulin fibrinolysis is characteristic of the hemostasis system in patients with chronic pneumonias. The revealed alterations may be used both for timely prophylaxis of coagulopathy and as an adjuvant method in the differential diagnosis.

Spanu, A., et al. (2005). "99mTc labelled cationic lipophilic complexes in malignant and benign tumors: the role of SPET and pinhole-SPET in breast cancer, differentiated thyroid carcinoma and hyperparathyroidism." Q J Nucl Med Mol Imaging **49**(2): 145-169.

Single photon emission tomography (SPET) represents an indispensable diagnostic tool in nuclear medicine. Due to better contrast resolution, cross sectional and 3D images, SPET plays a useful complementary tool to bidimensional planar scintigraphy in certain clinical conditions, while representing the procedure of choice in others. However, high resolution SPET with pinhole collimator (P-SPET) can improve conventional SPET sensitivity with parallel hole collimators. This review summarizes data on the employment of conventional SPET and P-SPET in breast cancer, differentiated

thyroid cancer (DTC) and hyperparathyroidism patients, using the cationic lipophilic complexes [(99m)Tc]metoxy isobutyl isonitrile (sestaMIBI) and [(99m)Tc]tetrofosmin as oncotropic radiotracers. In breast cancer patients, SPET with these radiotracers can play an important complementary role to planar scintimammography in detecting primary tumors, especially when non palpable and small in size, whereas SPET and particularly P-SPET represents the procedure of choice in preoperative axillary lymph node status evaluation in which planar is almost always irrelevant. In DTC follow-up patients, SPET and P-SPET with cationic lipophilic radiotracers are indicated in both locoregional and distant metastasis detection, especially in patients with high Tg serum levels and negative radioiodine scanning in whom these procedures represent a reliable alternative to diagnostic (131)I scanning. Moreover, the combined use of [(99m)Tc]tetrofosmin P-SPET and US can identify recurrences and lymph node metastases in the neck, both fixing and non fixing iodine, downstaged or negative at (131)I scanning. SPET can also be a useful complementary tool to planar parathyroid scintigraphy in the detection and localization of small and ectopic parathyroid adenomas in the neck or mediastinum, while neck P-SPET seems to also significantly increase planar sensitivity in hyperplastic glands. SPET and P-SPET are indicated in persistent and recurrent hyperparathyroidism including from carcinoma.

Tahiri, A., et al. (2014). "Deregulation of cancer-related miRNAs is a common event in both benign and malignant human breast tumors." Carcinogenesis **35**(1): 76-85.

MicroRNAs (miRNAs) are endogenous non-coding RNAs, which play an essential role in the regulation of gene expression during carcinogenesis. The role of miRNAs in breast cancer has been thoroughly investigated, and although many miRNAs are identified as cancer related, little is known about their involvement in benign tumors. In this study, we investigated miRNA expression profiles in the two most common types of human benign tumors (fibroadenoma/fibroadenomatosis) and in malignant breast tumors and explored their role as oncomirs and tumor suppressor miRNAs. Here, we identified 33 miRNAs with similar deregulated expression in both benign and malignant tumors compared with the expression levels of those in normal tissue, including breast cancer-related miRNAs such as let-7, miR-21 and miR-155. Additionally, messenger RNA (mRNA) expression profiles were obtained for some of the same samples. Using integrated mRNA/miRNA expression analysis, we observed that overexpression of certain miRNAs co-occurred with a significant downregulation of their candidate target mRNAs in both benign and malignant tumors. In support of these findings, in vitro functional screening of the downregulated miRNAs in non-malignant and breast cancer cell lines identified several possible tumor suppressor miRNAs, including miR-193b, miR-193a-3p, miR-126, miR-134, miR-132, miR-486-5p, miR-886-3p, miR-195 and miR-497, showing reduced growth when re-expressed in cancer cells. The finding of deregulated expression of oncomirs and tumor suppressor miRNAs in benign breast tumors is intriguing, indicating that they may play a role in proliferation. A role of cancer-related miRNAs in the early phases of carcinogenesis and malignant transformation can, therefore, not be ruled out.

Ulaner, G., et al. (2013). "Musculoskeletal tumors and tumor-like conditions: common and avoidable pitfalls at imaging in patients with known or suspected cancer: Part A: benign conditions that may mimic malignancy." Int Orthop **37**(5): 871-876.

A wide range of musculoskeletal tumors and tumor-like conditions may be encountered when patients undergo radiological examinations. The imaging features of certain normal, reactive, benign neoplastic, inflammatory, traumatic, and degenerative processes in the musculoskeletal system may mimic malignant tumor; misinterpretation of the imaging findings can lead to inappropriate clinical management of the patient. This review describes and illustrates a number of such mimics that we have commonly encountered in our oncological imaging practice, and provides suggestions for avoiding each of these pitfalls. Because many orthopaedic surgeons interpret radiological images themselves, they need to be as aware as radiologists about these issues.

Vysotskii, M. M., et al. (2009). "Serum sFas, leptin, and VEGF in patients with ovarian cancer and benign tumors." Bull Exp Biol Med **148**(5): 810-814.

The initial levels of soluble Fas antigen (sFas), leptin, and vascular endothelium growth factor (VEGF) were measured in the sera of 100 patients with ovarian cancer and benign tumors and in 60 healthy women aged 28-65 years. Serum levels of sFas and VEGF were elevated in the total group of patients with ovarian tumors, while leptin levels were the same as in healthy women. The studied parameters did not depend on the age of patients and healthy women. The levels of sFas and leptin were virtually the same in benign and malignant ovarian tumors, while VEGF concentration was higher in patients with ovarian cancer. The mean serum levels of sFas, VEGF, and leptin in patients with poorly and moderately differentiated serous ovarian cancer were 2-fold higher than in well-differentiated tumors ($p<0.05$), while serum concentrations of sFas and leptin increased with

the disease stage progress in patients with ovarian cancer ($p<0.05$). According to the data of unifactorial analysis, the increase in serum levels of sFas and VEGF in ovarian cancer patients correlated with short duration of the relapse-free period. Multifactorial analysis showed that the disease stage ($p=0.006$), presence of ascites ($p=0.03$), VEGF concentration ($p=0.02$), and the sFas/leptin coefficient ($p=0.045$) are highly significant independent factors for predicting the relapse-free survival of patients with serous ovarian cancer.

Yazici, H., et al. (1996). "Amplification in tumors and benign tissue of breast cancer patients." Cancer Lett **107**(2): 235-239.

Inappropriate expression of the c-erb B2 gene has been associated with aggressive tumor behavior in breast cancer. In this study the c-erb B2 amplification was investigated both in the tumors and benign breast tissue of the patients by competitive PCR. The technique combines the sensitivity and speed of PCR with coamplification of a single copy reference gene to achieve quantitative results. Gene copy numbers in excess of 3 copies were observed in tumors of 7 patients but not in the normal tissue samples. We conclude that the increase in the gene copy numbers is a result of the tumorigenic changes occurring in the cancer cell.

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