# Cancer and Evolution 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. This article introduces recent research reports as references in the cancer and evolution related studies.
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**Key words:** cancer; evolution; life; research; literature

## 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.

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

Ashcroft, P., F. Michor, et al. "Stochastic tunneling and metastable states during the somatic evolution of cancer." Genetics. 2015 Apr;199(4):1213-28. doi: 10.1534/genetics.114.171553. Epub 2015 Jan 26.

Tumors initiate when a population of proliferating cells accumulates a certain number and type of genetic and/or epigenetic alterations. The population dynamics of such sequential acquisition of (epi)genetic alterations has been the topic of much investigation. The phenomenon of stochastic tunneling, where an intermediate mutant in a sequence does not reach fixation in a population before generating a double mutant, has been studied using a variety of computational and mathematical methods. However, the field still lacks a comprehensive analytical description since theoretical predictions of fixation times are available only for cases in which the second mutant is advantageous. Here, we study stochastic tunneling in a Moran model. Analyzing the deterministic dynamics of large populations we systematically identify the parameter regimes captured by existing approaches. Our analysis also reveals fitness landscapes and mutation rates for which finite populations are found in long-lived metastable states. These are landscapes in which the final mutant is not the most advantageous in the sequence, and resulting metastable states are a consequence of a mutation-selection balance. The escape from these states is driven by intrinsic noise, and their location affects the probability of tunneling. Existing methods no longer apply. In these regimes it is the escape from the metastable states that is the key bottleneck; fixation is no longer limited by the emergence of a successful mutant lineage. We used the so-called Wentzel-Kramers-Brillouin method to compute fixation times in these parameter regimes, successfully validated by stochastic simulations. Our work fills a gap left by previous approaches and provides a more comprehensive description of the acquisition of multiple mutations in populations of somatic cells.

Ayadi, M., A. Bouygues, et al. "Chronic chemotherapeutic stress promotes evolution of stemness and WNT/beta-catenin signaling in colorectal cancer cells: implications for clinical use of WNT-signaling inhibitors." Oncotarget. 2015 May 11.

Most solid tumors contain a subfraction of cells with stem/progenitor cell features. Stem cells are naturally chemoresistant suggesting that chronic chemotherapeutic stress may select for cells with increased "stemness". We carried out a comprehensive molecular and functional analysis of six independently selected colorectal cancer (CRC) cell lines with acquired resistance to three different chemotherapeutic agents derived from two distinct parental cell lines. Chronic drug exposure resulted in complex alterations of stem cell markers that could be classified into three categories: 1) one cell line, HT-29/5-FU, showed

increased "stemness" and WNT-signaling, 2) three cell lines showed decreased expression of stem cell markers, decreased aldehyde dehydrogenase activity, attenuated WNT-signaling and lost the capacity to form colonospheres and 3) two cell lines displayed prominent expression of ABC transporters with a heterogeneous response for stem cell markers. While WNT-signaling could be attenuated in the HT-29/5-FU cells by the WNT-signaling inhibitors ICG-001 and PKF-118, this was not accompanied by any selective growth inhibitory effect suggesting that the cytotoxic activity of these compounds is not directly linked to WNT-signaling inhibition. We conclude that classical WNT-signaling inhibitors have toxic off-target activities that need to be addressed for clinical development.

Boddy, A. M., H. Kokko, et al. "Cancer susceptibility and reproductive trade-offs: a model of the evolution of cancer defences." Philos Trans R Soc Lond B Biol Sci. 2015 Jul 19;370(1673). pii: 20140220. doi: 10.1098/rstb.2014.0220.

The factors influencing cancer susceptibility and why it varies across species are major open questions in the field of cancer biology. One underexplored source of variation in cancer susceptibility may arise from trade-offs between reproductive competitiveness (e.g. sexually selected traits, earlier reproduction and higher fertility) and cancer defence. We build a model that contrasts the probabilistic onset of cancer with other, extrinsic causes of mortality and use it to predict that intense reproductive competition will lower cancer defences and increase cancer incidence. We explore the trade-off between cancer defences and intraspecific competition across different extrinsic mortality conditions and different levels of trade-off intensity, and find the largest effect of competition on cancer in species where low extrinsic mortality combines with strong trade-offs. In such species, selection to delay cancer and selection to outcompete conspecifics are both strong, and the latter conflicts with the former. We discuss evidence for the assumed trade-off between reproductive competitiveness and cancer susceptibility. Sexually selected traits such as ornaments or large body size require high levels of cell proliferation and appear to be associated with greater cancer susceptibility. Similar associations exist for female traits such as continuous egg-laying in domestic hens and earlier reproductive maturity. Trade-offs between reproduction and cancer defences may be instantiated by a variety of mechanisms, including higher levels of growth factors and hormones, less efficient cell-cycle control and less DNA repair, or simply a larger number of cell divisions (relevant when reproductive success requires large body size or rapid reproductive cycles). These mechanisms can affect intra- and interspecific variation in cancer susceptibility arising from rapid cell proliferation during reproductive maturation, intrasexual competition and reproduction.

Bravo, I. G. and M. Felez-Sanchez "Papillomaviruses: Viral evolution, cancer and evolutionary medicine." Evol Med Public Health. 2015 Jan 28;2015(1):32-51. doi: 10.1093/emph/eov003.

Papillomaviruses (PVs) are a numerous family of small dsDNA viruses infecting virtually all mammals. PVs cause infections without triggering a strong immune response, and natural infection provides only limited protection against reinfection. Most PVs are part and parcel of the skin microbiota. In some cases, infections by certain PVs take diverse clinical presentations from highly productive self-limited warts to invasive cancers. We propose PVs as an excellent model system to study the evolutionary interactions between the immune system and pathogens causing chronic infections: genotypically, PVs are very diverse, with hundreds of different genotypes infecting skin and mucosa; phenotypically, they display extremely broad gradients and trade-offs between key phenotypic traits, namely productivity, immunogenicity, prevalence, oncogenicity and clinical presentation. Public health interventions have been launched to decrease the burden of PV-associated cancers, including massive vaccination against the most oncogenic human PVs, as well as systematic screening for PV chronic anogenital infections. Anti-PVs vaccines elicit protection against infection, induce cross-protection against closely related viruses and result in herd immunity. However, our knowledge on the ecological and intrapatient dynamics of PV infections remains fragmentary. We still need to understand how the novel anthropogenic selection pressures posed by vaccination and screening will affect viral circulation and epidemiology. We present here an overview of PV evolution and the connection between PV genotypes and the phenotypic, clinical manifestations of the diseases they cause. This differential link between viral evolution and the gradient cancer-warts-asymptomatic infections makes PVs a privileged playground for evolutionary medicine research.

Brown, J. S., J. J. Cunningham, et al. "The multiple facets of Peto's paradox: a life-history model for the evolution of cancer suppression." Philos Trans R Soc Lond B Biol Sci. 2015 Jul 19;370(1673). pii: 20140221. doi: 10.1098/rstb.2014.0221.

Large animals should have higher lifetime probabilities of cancer than small animals because each cell division carries an attendant risk of mutating

towards a tumour lineage. However, this is not observed-a (Peto's) paradox that suggests large and/or long-lived species have evolved effective cancer suppression mechanisms. Using the Euler-Lotka population model, we demonstrate the evolutionary value of cancer suppression as determined by the 'cost' (decreased fecundity) of suppression verses the 'cost' of cancer (reduced survivorship). Body size per se will not select for sufficient cancer suppression to explain the paradox. Rather, cancer suppression should be most extreme when the probability of non-cancer death decreases with age (e.g. alligators), maturation is delayed, fecundity rates are low and fecundity increases with age. Thus, the value of cancer suppression is predicted to be lowest in the vole (short lifespan, high fecundity) and highest in the naked mole rat (long lived with late female sexual maturity). The life history of pre-industrial humans likely selected for quite low levels of cancer suppression. In modern humans that live much longer, this level results in unusually high lifetime cancer risks. The model predicts a lifetime risk of 49% compared with the current empirical value of 43%.

Carvalho, J. and C. Oliveira "Extracellular Vesicles - Powerful Markers of Cancer EVolution." Front Immunol. 2015 Jan 12;5:685. doi: 10.3389/fimmu.2014.00685. eCollection 2014.

Castellanos-Martin, A., S. Castillo-Lluva, et al. "Unraveling heterogeneous susceptibility and the evolution of breast cancer using a systems biology approach." Genome Biol. 2015 Feb 21;16:40. doi: 10.1186/s13059-015-0599-z.

BACKGROUND: An essential question in cancer is why individuals with the same disease have different clinical outcomes. Progress toward a more personalized medicine in cancer patients requires taking into account the underlying heterogeneity at different molecular levels. RESULTS: Here, we present a model in which there are complex interactions at different cellular and systemic levels that account for the heterogeneity of susceptibility to and evolution of ERBB2-positive breast cancers. Our model is based on our analyses of a cohort of mice that are characterized by heterogeneous susceptibility to ERBB2-positive breast cancers. Our analysis reveals that there are similarities between ERBB2 tumors in humans and those of backcross mice at clinical, genomic, expression, and signaling levels. We also show that mice that have tumors with intrinsically high levels of active AKT and ERK are more resistant to tumor metastasis. Our findings suggest for the first time that a site-specific phosphorylation at the serine 473 residue of AKT1 modifies the capacity for tumors to disseminate. Finally, we present two predictive models that can explain the heterogeneous behavior of the disease in the mouse population when we consider simultaneously certain genetic markers, liver cell signaling and serum biomarkers that are identified before the onset of the disease. CONCLUSIONS: Considering simultaneously tumor pathophenotypes and several molecular levels, we show the heterogeneous behavior of ERBB2-positive breast cancer in terms of disease progression. This and similar studies should help to better understand disease variability in patient populations.

Csendes, J. A., A. Munoz Ch, et al. "Blood count and C-reactive protein evolution in gastric cancer patients with total gastrectomy surgery." Arq Bras Cir Dig. 2014 Nov-Dec;27(4):234-6. doi: 10.1590/S0102-67202014000400002.

BACKGROUND: The complete blood count (CBC) and C-reactive protein (CRP) are useful inflammatory parameters for ruling out acute postoperative inflammatory complications. AIM: To determine their changes in gastric cancer patients submitted to total gastrectomy. METHODS: This is a prospective study, with 36 patients with gastric cancer who were submitted to elective total gastrectomy. On the first, third and fifth postoperative day (POD), blood count and CRP changes were assessed. Patients with postoperative complications were excluded. RESULTS: Twenty-one (58%) were men and 15 (42%) women. The mean age was 65 years. The leukocytes peaked on the 1st POD with a mean of 13,826 u/mm(3), and decreased to 8,266 u/mm(3) by the 5th POD. The bacilliforms peaked on the 1st POD with a maximum value of 1.48%. CRP reached its maximum level on the 3rd POD with a mean of 144.64 mg/l+/-44.84. Preoperative hematocrit (HCT) was 35% and 33.67% by the 5th POD. Hemoglobin, showed similar values. CONCLUSIONS: Leukocytes increased during the 1st POD but reached normal values by the 5th POD. CRP peaked on the 3rd POD but did not reach normal values by the 5th POD.

Engelen, T., B. M. Winkel, et al. "The next evolution in radioguided surgery: breast cancer related sentinel node localization using a freehandSPECT-mobile gamma camera combination." Am J Nucl Med Mol Imaging. 2015 Feb 15;5(3):233-45. eCollection 2015.

Accurate pre- and intraoperative identification of the sentinel node (SN) forms the basis of the SN biopsy procedure. Gamma tracing technologies such as a gamma probe (GP), a 2D mobile gamma camera (MGC) or 3D freehandSPECT (FHS) can be used to provide the surgeon with radioguidance to the SN(s). We reasoned that integrated use of these technologies results in the generation of a "hybrid" modality that combines the

best that the individual radioguidance technologies have to offer. The sensitivity and resolvability of both 2D-MGC and 3D-FHS-MGC were studied in a phantom setup (at various source-detector depths and using varying injection site-to-SN distances), and in ten breast cancer patients scheduled for SN biopsy. Acquired 3D-FHS-MGC images were overlaid with the position of the phantom/patient. This augmented-reality overview image was then used for navigation to the hotspot/SN in virtual-reality using the GP. Obtained results were compared to conventional gamma camera lymphoscintigrams. Resolution of 3D-FHS-MGC allowed identification of the SNs at a minimum injection site (100 MBq)-to-node (1 MBq; 1%) distance of 20 mm, up to a source-detector depth of 36 mm in 2D-MGC and up to 24 mm in 3D-FHS-MGC. A clinically relevant dose of approximately 1 MBq was clearly detectable up to a depth of 60 mm in 2D-MGC and 48 mm in 3D-FHS-MGC. In all ten patients at least one SN was visualized on the lymphoscintigrams with a total of 12 SNs visualized. 3D-FHS-MGC identified 11 of 12 SNs and allowed navigation to all these visualized SNs; in one patient with two axillary SNs located closely to each other (11 mm), 3D-FHS-MGC was not able to distinguish the two SNs. In conclusion, high sensitivity detection of SNs at an injection site-to-node distance of 20 mm-and-up was possible using 3D-FHS-MGC. In patients, 3D-FHS-MGC showed highly reproducible images as compared to the conventional lymphoscintigrams.

Faulkes, C. G., K. T. Davies, et al. "Molecular evolution of the hyaluronan synthase 2 gene in mammals: implications for adaptations to the subterranean niche and cancer resistance." Biol Lett. 2015 May;11(5). pii: 20150185. doi: 10.1098/rsbl.2015.0185.

The naked mole-rat (NMR) Heterocephalus glaber is a unique and fascinating mammal exhibiting many unusual adaptations to a subterranean lifestyle. The recent discovery of their resistance to cancer and exceptional longevity has opened up new and important avenues of research. Part of this resistance to cancer has been attributed to the fact that NMRs produce a modified form of hyaluronan-a key constituent of the extracellular matrix-that is thought to confer increased elasticity of the skin as an adaptation for living in narrow tunnels. This so-called high molecular mass hyaluronan (HMM-HA) stems from two apparently unique substitutions in the hyaluronan synthase 2 enzyme (HAS2). To test whether other subterranean mammals with similar selection pressures also show molecular adaptation in their HAS2 gene, we sequenced the HAS2 gene for 11 subterranean mammals and closely related species, and combined these with data from 57 other mammals. Comparative screening revealed that one of the two putatively important HAS2 substitutions in the NMR predicted to have a significant effect on hyaluronan synthase function was uniquely shared by all African mole-rats. Interestingly, we also identified multiple other amino acid substitutions in key domains of the HAS2 molecule, although the biological consequences of these for hyaluronan synthesis remain to be determined. Despite these results, we found evidence of strong purifying selection acting on the HAS2 gene across all mammals, and the NMR remains unique in its particular HAS2 sequence. Our results indicate that more work is needed to determine whether the apparent cancer resistance seen in NMR is shared by other members of the African mole-rat clade.

Gillies, R. J. and R. A. Gatenby "Metabolism and its sequelae in cancer evolution and therapy." Cancer J. 2015 Mar-Apr;21(2):88-96. doi: 10.1097/PPO.0000000000000102.

Cancers progress through a series of events that can be characterized as "somatic evolution." A central premise of Darwinian evolutionary theory is that the environment imparts pressure to select for species that are most fit within that particular microenvironmental context. Furthermore, the rate of evolution is proportional to both (1) the strength of the environmental selection and (2) the phenotypic variance of the selected population. It is notable that, during the progression of cancers from carcinogenesis to local invasion to metastasis, the selective landscape continuously changes, and throughout this process, there is increased selection for cells that have altered metabolic phenotypes: implying that these phenotypes impart a selective advantage during the process of environmental selection. One of the most prevalent selected phenotypes is that of aerobic glycolysis, that is, the continued fermentation of glucose even in the presence of adequate oxygen. The mechanisms of this so-called "Warburg effect" have been well studied, and there are multiple models to explain how this occurs at the molecular level. Herein, we propose that unifying insights can be gained by evaluating the environmental context within which this phenotype arises. In other words, we focus not on the "how" but the "why" do cancer cells exhibit high aerobic glycolysis. This is best approached by examining the sequelae of aerobic glycolysis that may impart a selective advantage. Many of these have been considered, including generation of anabolic substrates, response rates of glycolysis vis-a-vis respiration, and generation of antioxidants. A further sequeala considered here is that aerobic glycolysis results in a high rate of lactic acid production; resulting in acidification of the extracellular space. Indeed, it has been shown that a low extracellular pH promotes local invasion,

promotes metastasis, and inhibits antitumor immunity. In naturally occurring cancers, low extracellular pH is a strong negative prognostic indicator of metastasis-free survival. Furthermore, it has been shown that inhibition of extracellular acidosis can inhibit metastasis and promote antitumor immunity. Hence, we propose that excess acid production confers a selective advantage for cells during the somatic evolution of cancers.

Hayashida, M. Z., V. M. Fernandes, et al. "Epidemiology and clinical evolution of non-melanoma skin cancer in renal transplant recipients: a single-center experience in Sao Paulo, Brazil." Int J Dermatol. 2015 May 13. doi: 10.1111/ijd.12632.

BACKGROUND: Non-melanoma skin cancer (NMSC) is very common among renal transplant recipients (RTRs) as a result of the immunosuppressed status of these patients and other factors. Few studies have examined the clinical characteristics and evolution of NMSC in RTRs in tropical countries. OBJECTIVES: The aim of this study was to characterize the epidemiology and clinical evolution of NMSC in RTRs. METHODS: We conducted a retrospective study including 68 RTRs with NMSC diagnosed from July 2004 to December 2009 with a minimum follow-up of three years. We analyzed demographic and transplant- and NMSC-related data. RESULTS: The mean age of patients at the first diagnosis of NMSC was 51 years (range: 29-71 years). Most first diagnoses occurred within nine years post-transplant. The majority of patients (n = 48) had Fitzpatrick skin phototype II, although NMSC was also observed in those with skin phototypes III and IV. Forty-six (67.6%) RTRs had received a kidney from a living donor. Fifty-five (80.9%) RTRs had received cytotoxic immunosuppressives, 51 (75.0%) had received calcineurin inhibitors, and two (2.9%) had received mTOR inhibitors. Most of the RTRs developed about eight NMSC lesions, but up to 25 NMSC lesions were diagnosed in one patient. Most lesions (67.6%) were located on sun-exposed areas. Squamous cell carcinoma (SCC) represented the predominant tumor type, accounting for 70.6% of all tumors, whereas basal cell carcinoma accounted for 29.4% of all tumors. Invasive SCC predominated over in situ SCC. Finally, 48.5% of patients had a previous history of viral warts. CONCLUSIONS: Long-term use of immunosuppressive therapy increases the risk for tumor occurrence. Multiple NMSC tumors can develop in patients in tropical countries, even in patients with a high skin phototype. Therefore, RTRs should understand the high risk for the development of malignant tumors and should be properly informed about the prevention and treatment of NMSC.

Kanu, N., E. Gronroos, et al. "SETD2 loss-of-function promotes renal cancer branched evolution through replication stress and impaired DNA repair." Oncogene. 2015 Mar 2. doi: 10.1038/onc.2015.24.

Defining mechanisms that generate intratumour heterogeneity and branched evolution may inspire novel therapeutic approaches to limit tumour diversity and adaptation. SETD2 (Su(var), Enhancer of zeste, Trithorax-domain containing 2) trimethylates histone-3 lysine-36 (H3K36me3) at sites of active transcription and is mutated in diverse tumour types, including clear cell renal carcinomas (ccRCCs). Distinct SETD2 mutations have been identified in spatially separated regions in ccRCC, indicative of intratumour heterogeneity. In this study, we have addressed the consequences of SETD2 loss-of-function through an integrated bioinformatics and functional genomics approach. We find that bi-allelic SETD2 aberrations are not associated with microsatellite instability in ccRCC. SETD2 depletion in ccRCC cells revealed aberrant and reduced nucleosome compaction and chromatin association of the key replication proteins minichromosome maintenance complex component (MCM7) and DNA polymerase delta hindering replication fork progression, and failure to load lens epithelium-derived growth factor and the Rad51 homologous recombination repair factor at DNA breaks. Consistent with these data, we observe chromosomal breakpoint locations are biased away from H3K36me3 sites in SETD2 wild-type ccRCCs relative to tumours with bi-allelic SETD2 aberrations and that H3K36me3-negative ccRCCs display elevated DNA damage in vivo. These data suggest a role for SETD2 in maintaining genome integrity through nucleosome stabilization, suppression of replication stress and the coordination of DNA repair.Oncogene advance online publication, 2 March 2015; doi:10.1038/onc.2015.24.

Kovac, M., C. Navas, et al. "Recurrent chromosomal gains and heterogeneous driver mutations characterise papillary renal cancer evolution." Nat Commun. 2015 Mar 19;6:6336. doi: 10.1038/ncomms7336.

Papillary renal cell carcinoma (pRCC) is an important subtype of kidney cancer with a problematic pathological classification and highly variable clinical behaviour. Here we sequence the genomes or exomes of 31 pRCCs, and in four tumours, multi-region sequencing is undertaken. We identify BAP1, SETD2, ARID2 and Nrf2 pathway genes (KEAP1, NHE2L2 and CUL3) as probable drivers, together with at least eight other possible drivers. However, only ~10% of tumours harbour detectable pathogenic changes in any one driver gene, and where present, the mutations are often predicted to be present within cancer sub-clones. We specifically detect parallel evolution of multiple

SETD2 mutations within different sub-regions of the same tumour. By contrast, large copy number gains of chromosomes 7, 12, 16 and 17 are usually early, monoclonal changes in pRCC evolution. The predominance of large copy number variants as the major drivers for pRCC highlights an unusual mode of tumorigenesis that may challenge precision medicine approaches.

Kroigard, A. B., M. J. Larsen, et al. "Clonal expansion and linear genome evolution through breast cancer progression from pre-invasive stages to asynchronous metastasis." Oncotarget. 2015 Mar 20;6(8):5634-49.

Evolution of the breast cancer genome from pre-invasive stages to asynchronous metastasis is complex and mostly unexplored, but highly demanded as it may provide novel markers for and mechanistic insights in cancer progression. The increasing use of personalized therapy of breast cancer necessitates knowledge of the degree of genomic concordance between different steps of malignant progression as primary tumors often are used as surrogates of systemic disease. Based on exome sequencing we performed copy number profiling and point mutation detection on successive steps of breast cancer progression from one breast cancer patient, including two different regions of Ductal Carcinoma In Situ (DCIS), primary tumor and an asynchronous metastasis. We identify a remarkable landscape of somatic mutations, retained throughout breast cancer progression and with new mutational events emerging at each step. Our data, contrary to the proposed model of early dissemination of metastatic cells and parallel progression of primary tumors and metastases, provide evidence of linear progression of breast cancer with relatively late dissemination from the primary tumor. The genomic discordance between the different stages of tumor evolution in this patient emphasizes the importance of molecular profiling of metastatic tissue directing molecularly targeted therapy at recurrence.

Lam, T. K., C. Q. Chang, et al. "Evolution of the "drivers" of translational cancer epidemiology: analysis of funded grants and the literature." Am J Epidemiol. 2015 Apr 1;181(7):451-8. doi: 10.1093/aje/kwu479. Epub 2015 Mar 11.

Concurrently with a workshop sponsored by the National Cancer Institute, we identified key "drivers" for accelerating cancer epidemiology across the translational research continuum in the 21st century: emerging technologies, a multilevel approach, knowledge integration, and team science. To map the evolution of these "drivers" and translational phases (T0-T4) in the past decade, we analyzed cancer epidemiology grants funded by the National Cancer Institute and published literature for 2000, 2005, and 2010. For each year, we evaluated the aims of all new/competing grants and abstracts of randomly selected PubMed articles. Compared with grants based on a single institution, consortium-based grants were more likely to incorporate contemporary technologies (P = 0.012), engage in multilevel analyses (P = 0.010), and incorporate elements of knowledge integration (P = 0.036). Approximately 74% of analyzed grants and publications involved discovery (T0) or characterization (T1) research, suggesting a need for more translational (T2-T4) research. Our evaluation indicated limited research in 1) a multilevel approach that incorporates molecular, individual, social, and environmental determinants and 2) knowledge integration that evaluates the robustness of scientific evidence. Cancer epidemiology is at the cusp of a paradigm shift, and the field will need to accelerate the pace of translating scientific discoveries in order to impart population health benefits. While multi-institutional and technology-driven collaboration is happening, concerted efforts to incorporate other key elements are warranted for the discipline to meet future challenges.

Le Pennec, S., T. Konopka, et al. "Intratumor heterogeneity and clonal evolution in an aggressive papillary thyroid cancer and matched metastases." Endocr Relat Cancer. 2015 Apr;22(2):205-16. doi: 10.1530/ERC-14-0351. Epub 2015 Feb 17.

The contribution of intratumor heterogeneity to thyroid metastatic cancers is still unknown. The clonal relationships between the primary thyroid tumors and lymph nodes (LN) or distant metastases are also poorly understood. The objective of this study was to determine the phylogenetic relationships between matched primary thyroid tumors and metastases. We searched for non-synonymous single-nucleotide variants (nsSNVs), gene fusions, alternative transcripts, and loss of heterozygosity (LOH) by paired-end massively parallel sequencing of cDNA (RNA-Seq) in a patient diagnosed with an aggressive papillary thyroid cancer (PTC). Seven tumor samples from a stage IVc PTC patient were analyzed by RNA-Seq: two areas from the primary tumor, four areas from two LN metastases, and one area from a pleural metastasis (PLM). A large panel of other thyroid tumors was used for Sanger sequencing screening. We identified seven new nsSNVs. Some of these were early events clonally present in both the primary PTC and the three matched metastases. Other nsSNVs were private to the primary tumor, the LN metastases and/or the PLM. Three new gene fusions were identified. A novel cancer-specific KAZN alternative transcript was detected in this aggressive PTC and in dozens of additional thyroid tumors. The PLM harbored an exclusive whole-chromosome 19 LOH. We have

presented the first, to our knowledge, deep sequencing study comparing the mutational spectra in a PTC and both LN and distant metastases. This study has yielded novel findings concerning intra-tumor heterogeneity, clonal evolution and metastases dissemination in thyroid cancer.

McGranahan, N., F. Favero, et al. "Clonal status of actionable driver events and the timing of mutational processes in cancer evolution." Sci Transl Med. 2015 Apr 15;7(283):283ra54. doi: 10.1126/scitranslmed.aaa1408.

Deciphering whether actionable driver mutations are found in all or a subset of tumor cells will likely be required to improve drug development and precision medicine strategies. We analyzed nine cancer types to determine the subclonal frequencies of driver events, to time mutational processes during cancer evolution, and to identify drivers of subclonal expansions. Although mutations in known driver genes typically occurred early in cancer evolution, we also identified later subclonal "actionable" mutations, including BRAF (V600E), IDH1 (R132H), PIK3CA (E545K), EGFR (L858R), and KRAS (G12D), which may compromise the efficacy of targeted therapy approaches. More than 20% of IDH1 mutations in glioblastomas, and 15% of mutations in genes in the PI3K (phosphatidylinositol 3-kinase)-AKT-mTOR (mammalian target of rapamycin) signaling axis across all tumor types were subclonal. Mutations in the RAS-MEK (mitogen-activated protein kinase kinase) signaling axis were less likely to be subclonal than mutations in genes associated with PI3K-AKT-mTOR signaling. Analysis of late mutations revealed a link between APOBEC-mediated mutagenesis and the acquisition of subclonal driver mutations and uncovered putative cancer genes involved in subclonal expansions, including CTNNA2 and ATXN1. Our results provide a pan-cancer census of driver events within the context of intratumor heterogeneity and reveal patterns of tumor evolution across cancers. The frequent presence of subclonal driver mutations suggests the need to stratify targeted therapy response according to the proportion of tumor cells in which the driver is identified.

Mukhtar, R. A., J. M. Wong, et al. "Preventing Overdiagnosis and Overtreatment: Just the Next Step in the Evolution of Breast Cancer Care." J Natl Compr Canc Netw. 2015 Jun;13(6):737-43.

The problem of overdiagnosis and overtreatment has been highlighted in breast cancer and many other cancer types, most notably prostate cancer. Addressing this problem presents an opportunity to continue the evolution of breast cancer care. Advances in technology, such as molecular subtyping, have increased the understanding of breast cancer biology and the range of associated behavior, and have provided tools that allow greater personalization of treatment. This article identifies 3 areas of breast cancer care where opportunity currently exists to refine management strategies and help decrease overtreatment and overdiagnosis: the use of adjuvant-external beam radiation in invasive breast cancer, the application of aggressive treatment for all ductal carcinoma in situ, and the authors' approach to breast cancer screening. Personalizing treatment based on patient and tumor characteristics holds promise for minimizing harms and maximizing benefits. This approach will allow continual improvement and ultimately result in providing the right treatment for each patient.

Nagayasu, T., N. Yamasaki, et al. "The evolution of bronchoplasty and broncho-angioplasty as treatments for lung cancer: evaluation of 30 years of data from a single institution." Eur J Cardiothorac Surg. 2015 Feb 26. pii: ezv065.

OBJECTIVES: The purpose of this study was to evaluate the factors contributing to the outcomes of bronchoplasty for lung cancer by analysing a single institution's data for a 30-year period. METHODS: A retrospective review of 213 patients who underwent bronchoplasty for lung cancer between 1980 and 2010 was undertaken. The patients were divided into two groups by the date of surgery: the first period was 1980-95, and the second period was 1996-2010. RESULTS: Bronchoplasty and broncho-angioplasty were performed in 100 (75.8%) and 32 (24.2%) patients, respectively, in the first period and 61 (75.3%) and 20 (24.7%) patients, respectively, in the second period. Overall 90-day operative morbidity and mortality rates were 25.8 and 9.8%, respectively, in the first period and 45.7 and 2.5%, respectively, in the second period. Thirty-day mortality rates were 6.8% in the first period and 0% in the second period. Five-year survival was 41.1% (n = 132) in the first period and 61.5% (n = 81) in the second period (P = 0.0003). Comparing bronchoplasty and broncho-angioplasty, the 5-year survival was 45.6 and 26.5%, respectively, in the first period (P = 0.0048) and 60.9 and 62.1%, respectively, in the second period (P = 0. 8131). Using multivariate analysis to identify potential prognostic factors, the type of operation (broncho-angioplasty), postoperative complications and histology (non-squamous cell carcinoma) were significant factors affecting survival in the first period, but none of the factors significantly affected survival in the second period. When the rates of pN2 or N3 histological type disease were compared in each period, the rate of pN2 or N3 disease in non-squamous cell carcinoma was 51.4% in the first period and 45.5% in the second

period; both were significantly higher than in squamous cell carcinoma (31.6 and 16.9%, respectively; P = 0. 0365 and 0.0073). CONCLUSIONS: The present study suggests that progress in the preoperative staging system and perioperative medical management, as well as surgery, has contributed to current improvements in patients undergoing bronchoplasty and broncho-angioplasty. However, since nodal status in non-squamous cell carcinoma is not precisely evaluated before the operation, the indication for bronchoplasty should be considered carefully.

Natrajan, R. C. "Breast cancer heterogeneity: parallel evolution or conscious uncoupling?" J Pathol. 2015 May 7. doi: 10.1002/path.4557.

Breast cancer is known to display considerable inter- and intra-tumour genetic heterogeneity. It is now widely accepted that no two breast cancers harbour the same complement of genomic alterations, and that both primary and metastatic breast cancers are composed of multiple genetically diverse subclones that evolve under different selective pressures. Recent work published in the Journal of Pathology by Desmedt and colleagues questions the evolutionary dynamics of multi-focal breast cancer with similar pathological features by studying the mutational repertoire of different lesions. Whilst the majority of the lesions showed some common driver alterations, one-third lacked any common mutations, suggesting very early clonal divergence. These and other recent observations underscore the need for a fundamental understanding of the rules governing breast cancer evolution, and highlight the need for in-depth assessment of driver alterations for appropriate patient management and selective treatment. Copyright (c) 2015 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd.

Poleszczuk, J., P. Hahnfeldt, et al. "Evolution and phenotypic selection of cancer stem cells." PLoS Comput Biol. 2015 Mar 5;11(3):e1004025. doi: 10.1371/journal.pcbi.1004025. eCollection 2015 Mar.

Cells of different organs at different ages have an intrinsic set of kinetics that dictates their behavior. Transformation into cancer cells will inherit these kinetics that determine initial cell and tumor population progression dynamics. Subject to genetic mutation and epigenetic alterations, cancer cell kinetics can change, and favorable alterations that increase cellular fitness will manifest themselves and accelerate tumor progression. We set out to investigate the emerging intratumoral heterogeneity and to determine the evolutionary trajectories of the combination of cell-intrinsic kinetics that yield aggressive tumor growth. We develop a cellular automaton model that tracks the temporal evolution of the malignant subpopulation of so-called cancer stem cells(CSC), as these cells are exclusively able to initiate and sustain tumors. We explore orthogonal cell traits, including cell migration to facilitate invasion, spontaneous cell death due to genetic drift after accumulation of irreversible deleterious mutations, symmetric cancer stem cell division that increases the cancer stem cell pool, and telomere length and erosion as a mitotic counter for inherited non-stem cancer cell proliferation potential. Our study suggests that cell proliferation potential is the strongest modulator of tumor growth. Early increase in proliferation potential yields larger populations of non-stem cancer cells(CC) that compete with CSC and thus inhibit CSC division while a reduction in proliferation potential loosens such inhibition and facilitates frequent CSC division. The sub-population of cancer stem cells in itself becomes highly heterogeneous dictating population level dynamics that vary from long-term dormancy to aggressive progression. Our study suggests that the clonal diversity that is captured in single tumor biopsy samples represents only a small proportion of the total number of phenotypes.

Raman, S. P., Y. Chen, et al. "Evolution of imaging in rectal cancer: multimodality imaging with MDCT, MRI, and PET." J Gastrointest Oncol. 2015 Apr;6(2):172-84. doi: 10.3978/j.issn.2078-6891.2014.108.

Magnetic resonance imaging (MRI), multidetector computed tomography (MDCT), and positron emission tomography (PET) are complementary imaging modalities in the preoperative staging of patients with rectal cancer, and each offers their own individual strengths and weaknesses. MRI is the best available radiologic modality for the local staging of rectal cancers, and can play an important role in accurately distinguishing which patients should receive preoperative chemoradiation prior to total mesorectal excision. Alternatively, both MDCT and PET are considered primary modalities when performing preoperative distant staging, but are limited in their ability to locally stage rectal malignancies. This review details the role of each of these three modalities in rectal cancer staging, and how the three imaging modalities can be used in conjunction.

Roche, B., B. Ujvari, et al. "Bad luck and cancer: Does evolution spin the wheel of fortune?" Bioessays. 2015 Jun;37(6):586-7. doi: 10.1002/bies.201500012. Epub 2015 Mar 20.

Cancer is a complex disease, with sophisticated cellular mechanisms as the targets of

evolutionary processes driven by random genetic and epigenetic mutations. Oncogenesis is evolutionarily linked to stem cell numbers/mutations and organ/body size; therefore, inter-disciplinary frameworks across different scales (cellular, tissue, organs and species) are necessary to decipher cancer progression.

Sato, F., S. Saji, et al. "Genomic tumor evolution of breast cancer." Breast Cancer. 2015 May 22.

Owing to recent technical development of comprehensive genome-wide analysis such as next generation sequencing, deep biological insights of breast cancer have been revealed. Information of genomic mutations and rearrangements in patients' tumors is indispensable to understand the mechanism in carcinogenesis, progression, metastasis, and resistance to systemic treatment of breast cancer. To date, comprehensive genomic analyses illustrate not only base substitution patterns and lists of driver mutations and key rearrangements, but also a manner of tumor evolution. Breast cancer genome is dynamically changing and evolving during cancer development course from non-invasive disease via invasive primary tumor to metastatic tumor, and during treatment exposure. The accumulation pattern of base substitution and genomic rearrangement looks gradual and punctuated, respectively, in analogy with contrasting theories for evolution manner of species, Darwin's phyletic gradualism, and Eldredge and Gould's "punctuated equilibrium". Liquid biopsy is a non-invasive method to detect the genomic evolution of breast cancer. Genomic mutation patterns in circulating tumor cells and circulating cell-free tumor DNA represent those of tumors existing in patient body. Liquid biopsy methods are now under development for future application to clinical practice of cancer treatment. In this article, latest knowledge regarding breast cancer genome, especially in terms of 'tumor evolution', is summarized.

Shin, D. S. and A. Ribas "The evolution of checkpoint blockade as a cancer therapy: what's here, what's next?" Curr Opin Immunol. 2015 Apr;33:23-35. doi: 10.1016/j.coi.2015.01.006. Epub 2015 Jan 23.

Unleashing the immune system to fight cancer has become one of the main treatment modalities since the anti-CTLA-4 antibody, ipilimumab was approved for patients with advanced melanoma in 2011. Pembrolizumab and nivolumab, two anti-PD-1 antibodies recently approved for the treatment of patients with metastatic melanoma, are being actively investigated for the treatment of multiple caners including lung, breast, bladder and renal cancers along with other anti-PD-1/L1 antibodies. Early results of combining of anti-CTLA-4 antibody and anti-PD-1 antibody treatment for advanced melanoma patients are showing impressive response rates with manageable toxicity profiles. There are several other checkpoint molecules that are likely potential inhibitory targets. The outcome of blocking some of these negative immune regulators, such as LAG-3 or TIM-3, is being pursued in the clinic or about to enter clinical development. Blockade of these molecules is demonstrating promising preclinical activity alone or when combined with anti-PD-1/L1. Future studies will define bio-markers of these therapies and how to target them alone or in combination with other immunotherapies, chemotherapy, radiotherapy and small molecule inhibitors.

Siravegna, G., B. Mussolin, et al. "Clonal evolution and resistance to EGFR blockade in the blood of colorectal cancer patients." Nat Med. 2015 Jun 1. doi: 10.1038/nm.3870.

Colorectal cancers (CRCs) evolve by a reiterative process of genetic diversification and clonal evolution. The molecular profile of CRC is routinely assessed in surgical or bioptic samples. Genotyping of CRC tissue has inherent limitations; a tissue sample represents a single snapshot in time, and it is subjected to spatial selection bias owing to tumor heterogeneity. Repeated tissue samples are difficult to obtain and cannot be used for dynamic monitoring of disease progression and response to therapy. We exploited circulating tumor DNA (ctDNA) to genotype colorectal tumors and track clonal evolution during treatment with the epidermal growth factor receptor (EGFR)-specific antibodies cetuximab or panitumumab. We identified alterations in ctDNA of patients with primary or acquired resistance to EGFR blockade in the following genes: KRAS, NRAS, MET, ERBB2, FLT3, EGFR and MAP2K1. Mutated KRAS clones, which emerge in blood during EGFR blockade, decline upon withdrawal of EGFR-specific antibodies, indicating that clonal evolution continues beyond clinical progression. Pharmacogenomic analysis of CRC cells that had acquired resistance to cetuximab reveals that upon antibody withdrawal KRAS clones decay, whereas the population regains drug sensitivity. ctDNA profiles of individuals who benefit from multiple challenges with anti-EGFR antibodies exhibit pulsatile levels of mutant KRAS. These results indicate that the CRC genome adapts dynamically to intermittent drug schedules and provide a molecular explanation for the efficacy of rechallenge therapies based on EGFR blockade.

Stepanenko, A. A. and V. V. Dmitrenko HEK293 in cell biology and cancer research: phenotype, karyotype, tumorigenicity, and stress-induced genome-

phenotype evolution, Gene. 2015 May 27. pii: S0378-1119(15)00650-2. doi: 10.1016/j.gene.2015.05.065.

293 cell line (widely known as the Human Embryonic Kidney 293 cells) and its derivatives were the most used cells after HeLa in cell biology studies and after CHO in biotechnology as a vehicle for the production of adenoviral vaccines and recombinant proteins, for analysis of the neuronal synapse formation, in electrophysiology and neuropharmacology. Despite the historically long-term productive exploitation, the origin, phenotype, karyotype, and tumorigenicity of 293 cells are still debated. 293 cells were considered the kidney epithelial cells or even fibroblasts. However, 293 cells demonstrate no evident tissue-specific gene expression signature and express the markers of renal progenitor cells, neuronal cells and adrenal gland. This complicates efforts to reveal the authentic cell type/tissue of origin. On the other hand, the potential to propagate the highly neurotropic viruses, inducible synaptogenesis, functionality of the endogenous neuron-specific voltage-gated channels, and response to the diverse agonists implicated in neuronal signaling give credibility to consider 293 cells of neuronal lineage phenotype. The compound phenotype of 293 cells can be due to heterogeneous, unstable karyotype. The mean chromosome number and chromosome aberrations differ between 293 cells and derivatives as well as between 293 cells from the different cell banks/labs. 293 cells are tumorigenic, whereas acute changes of expression of the cancer-associated genes aggravate tumorigenicity by promoting chromosome instability. Importantly, the procedure of a stable empty vector transfection can also impact karyotype and phenotype. The discussed issues caution against misinterpretations and pitfalls during the different experimental manipulations with 293 cells.

Swanton, C., N. McGranahan, et al. APOBEC Enzymes: Mutagenic Fuel for Cancer Evolution and Heterogeneity, Cancer Discov. 2015 Jun 19.

Deep sequencing technologies are revealing the complexities of cancer evolution, casting light on mutational processes fueling tumor adaptation, immune escape, and treatment resistance. Understanding mechanisms driving cancer diversity is a critical step toward developing strategies to attenuate tumor evolution and adaptation. One emerging mechanism fueling tumor diversity and subclonal evolution is genomic DNA cytosine deamination catalyzed by APOBEC3B and at least one other APOBEC family member. Deregulation of APOBEC3 enzymes causes a general mutator phenotype that manifests as diverse and heterogeneous tumor subclones. Here, we summarize knowledge of the APOBEC DNA deaminase family in cancer, and their role as driving forces for intratumor heterogeneity and a therapeutic target to limit tumor adaptation. SIGNIFICANCE: APOBEC mutational signatures may be enriched in tumor subclones, suggesting APOBEC cytosine deaminases fuel subclonal expansions and intratumor heterogeneity. APOBEC family members might represent a new class of drug target aimed at limiting tumor evolution, adaptation, and drug resistance. Cancer Discov; 5(7); 1-9. (c)2015 AACR.

Ugarte, M. D., A. Adin, et al. "Analyzing the evolution of young people's brain cancer mortality in Spanish provinces." Cancer Epidemiol. 2015 Jun;39(3):480-5. doi: 10.1016/j.canep.2015.03.013. Epub 2015 Apr 20.

OBJECTIVES: To analyze the spatio-temporal evolution of brain cancer relative mortality risks in young population (under 20 years of age) in Spanish provinces during the period 1986-2010. METHODS: A new and flexible conditional autoregressive spatio-temporal model with two levels of spatial aggregation was used. RESULTS: Brain cancer relative mortality risks in young population in Spanish provinces decreased during the last years, although a clear increase was observed during the 1990s. The global geographical pattern emphasized a high relative mortality risk in Navarre and a low relative mortality risk in Madrid. Although there is a specific Autonomous Region-time interaction effect on the relative mortality risks this effect is weak in the final estimates when compared to the global spatial and temporal effects. CONCLUSIONS: Differences in mortality between regions and over time may be caused by the increase in survival rates, the differences in treatment or the availability of diagnostic tools. The increase in relative risks observed in the 1990s was probably due to improved diagnostics with computerized axial tomography and magnetic resonance imaging techniques.

Vandenhende, M. A., C. Roussillon, et al. "Cancer-Related Causes of Death among HIV-Infected Patients in France in 2010: Evolution since 2000." PLoS One. 2015 Jun 17;10(6):e0129550. doi: 10.1371/journal.pone.0129550. eCollection 2015.

OBJECTIVES: The current study aimed at describing the distribution and characteristics of malignancy related deaths in human immunodeficiency virus (HIV) infected patients in 2010 and at comparing them to those obtained in 2000 and 2005. METHODS: Data were obtained from three national surveys conducted in France in 2010, 2005 and 2000. The underlying cause of death was documented using a standardized questionnaire fulfilled in French hospital wards involved in the management of HIV infection. RESULTS: Among the

728 deaths reported in 2010, 262 were cancer-related (36%). After a significant increase from 28% in 2000 to 33% in 2005 and 36% in 2010, cancers represent the leading cause of mortality in HIV infected patients. The proportion of deaths attributed to non-AIDS/non-hepatitis-related cancers significantly increased from 2000 to 2010 (11% of the deaths in 2000, 17% in 2005 and 22% in 2010, p<0.001), while those attributed to AIDS-defining cancers decreased during the same period (16% in 2000, 13% in 2005 and 9% in 2010, p = 0.024). Particularly, the proportion of respiratory cancers significantly increased from 5% in 2000 to 6% in 2005 and 11% in 2010 (p = 0.004). Lung cancer was the most common cancer-related cause of death in 2010 (instead of non-Hodgkin lymphoma so far) and represented the leading cause of death in people living with HIV overall. CONCLUSIONS: Cancer prevention (especially smoking cessation), screening strategies and therapeutic management need to be optimized in HIV-infected patients in order to reduce mortality, particularly in the field of respiratory cancers.

Velasquez, J. O., S. E. Bohorquez, et al. "Geometrical nuclear diagnosis and total paths of cervical cell evolution from normality to cancer." J Cancer Res Ther. 2015 Jan-Mar;11(1):98-104. doi: 10.4103/0973-1482.148704.

BACKGROUND: The diagnosis of cervix cytology has problems of inter-observer reproducibility. Methodologies based on fractal geometry objectively differentiated normal, low-grade squamous intraepithelial lesion (L-SIL) and high-grade squamous intraepithelial lesion (H-SIL) states. AIMS: The aim was to develop a mathematical-physical diagnosis and a theoretical generalization of the evolution paths of cervical cells from normal to carcinoma based on their occupation in the box-counting space. SUBJECTS AND METHODS: Overlaying a grid of 8 x 8 pixels, the a number of squares occupying the nucleus surface and cytoplasm of 5 normal cells, 5 ASCUS, 5 L-SIL and 5 H-SIL were evaluated, as well as the ratio C/N, establishing differences between states. Sensitivity, specificity, negative likelihood ratio, and Kappa coefficient over the gold standard were calculated. Also was developed a generalization of all possible paths from normality to carcinoma. RESULTS: The occupancy spaces of the nuclear surface allow differentiating normal L-SIL and H-SIL thus avoiding the indeterminacy of ASCUS cells. Compared to the Gold Standard, this method has sensitivity and specificity of 100%, negative likelihood ratio of 0, and Kappa coefficient of 1. 62,900 possible routes of evolution were determined between normal and H-SIL, states, based on the structural basis of the cells. CONCLUSIONS: it was obtained an objective and reproducible diagnostic methodology of the development of preneoplastic and neoplastic cervical cells for clinical application. Additionally were developed all possible paths of preneoplastic cellular alteration to carcinoma which facilitates the tracking of patients over time to clinical level, warning of alterations that lead to malignancy, based on the spatial occupation measurements of the nucleus in fractal space regardless of causes or risk factors.

Wellisch, D. K., S. R. Ormseth, et al. "Evolution of Emotional Symptoms Over Time Among Daughters of Patients With Breast Cancer." Psychosomatics. 2014 Jul 2. pii: S0033-3182(14)00123-6. doi: 10.1016/j.psym.2014.07.001.

OBJECTIVE: This study longitudinally profiled anxiety and depressive symptoms of daughters of patients with breast cancer and examined the mothers survival status, the daughters age at the time of mothers diagnosis, and the style of family communication about breast cancer as moderators of change in symptomatology across participants first 3 appointments at the University of California, Los Angeles Revlon Breast Center High Risk Clinic. METHODS: We evaluated the effects of hypothesized predictors on change in anxiety and depressive symptoms, 3 (symptomatology at first, second, and third clinic visits) x 2 (mother survived or died) x 2 (<20 or >/=20y old at diagnosis) x 2 (open or closed family communication) repeated-measures analyses of variance were employed. RESULTS: There was a main effect for time of diagnosis on state anxiety, demonstrating a significant reduction in anxiety across clinic visits overall (p < 0.001). There were also significant 3-way interactions. For state anxiety, mothers survival status moderated the time of diagnosis x age at diagnosis and time of diagnosis x family communication interaction effects. For daughters whose mothers died, decreased anxiety was observed in those who were younger at the time of diagnosis (p = 0.001). For daughters whose mothers survived, anxiety was decreased for those with closed family communication styles (p = 0.001). The time of diagnosis x mothers survival x age at diagnosis interaction was also significant for depressive symptoms (p = 0.001). Among daughters whose mothers died, those who were younger showed decreases in symptoms (p = 0.004). CONCLUSION: These daughters appeared to benefit from the high-risk program as demonstrated by decreased symptomatology, particularly daughters whose mothers died who were younger at the time of diagnosis.

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