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THE NATIONAL CANCER INSTITUTE EARLY DETECTION RESEARCH NETWORK: TWO DECADES OF PROGRESS IN CANCER BIOMARKERS

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Over the last two decades, substantial progress has been made in the development of cancer biomarkers and their application to unmet needs across the spectrum of cancer care. NCI's Early Detection Research Network (EDRN) has had an important role in facilitating this progress.[1] Having been formally established in 2000, the EDRN now includes more than 300 investigators from academic institutions and the private sectors who have discovered, developed or evaluated more than a thousand cancer biomarkers that have been reported in more than 3,400 peer-reviewed articles, with 20% in high impact journals. Possibly of greater importance, the EDRN has provided support, infrastructure, standards, quality control and a process to evaluate and to validate candidate biomarkers, facilitating "go" or "no go" decisions regarding their further development. Collaborative research has been encouraged with monthly meetings of working groups and semi-annual gatherings of all EDRN investigators. Through the efforts of the EDRN and its investigators, 7 biomarkers and devices have attained full FDA approval and an additional assay has received Breakthrough Device designation.

To recognize the progress that has been made over the last 20 years, as well as the contribution of the EDRN, this issue of *Cancer Epidemiology Biomarkers and Prevention* includes a series of reviews prepared by members of the EDRN that capture the current state and paths to further development of cancer biomarkers which permit not only early detection, but more effective triage, prognostication, and prediction and monitoring of response to treatment across a wide range of cancers from different sites.

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IMPROVING ESTABLISHED SCREENING STRATEGIES

For some sites including lung, colon, prostate, breast, esophagus and liver, screening is already part of clinical practice. Here, biomarkers are being developed to improve specificity, identify individuals who would benefit from screening, decrease overdiagnosis, make screening more convenient, and increase the prevalence of screening. Biomarkers have generally been detected in blood, but have also been measured in more proximate sources, including sputum for lung cancer, stool for colorectal cancer and urine for prostate cancer after digital rectal examination.

Lung Cancer

One of the most important advances of the last two decades has been early detection of lung cancer with spiral “low dose” computerized tomography (LDCT). Screening individuals with a heavy smoking history of 30 pack years has detected enough early stage disease to improve survival among the screened by as much as 20%. LDCT screening, however, has a high false-positive rate and detects large numbers of small indeterminate nodules up to 30 mm in diameter.[2] Indeterminate nodules have also been found in as many as a quarter of chest CT scans performed for other medical indications. To date, screening has been limited to heavy smokers, who represent only 27% of individuals destined to get lung cancer in our country. Discovery and development of biomarkers to estimate lung cancer risk with greater precision, to reduce false positives and to categorize indeterminate pulmonary nodules from CT scans have great potential to improve early detection of lung cancer. A proteomic signature measured by mass spectroscopy (Nodify XL2™)[3] and a panel of 7 autoantibodies (EarlyCDT-Lung™)[4,5] with high negative predictive value are now commercially available to aid in identifying indeterminant lesions with a low risk of malignancy. The Percepta™ gene expression mRNA signature of bronchial epithelial washings has identified patients with suspicious lung lesions and negative bronchoscopy who are unlikely to have cancer and who can be spared additional invasive diagnostic procedures with a >90% negative predictive value.[6]

Other alterations of nucleic acids in blood and sputum have been developed as biomarkers for lung cancer.[7] Liquid biopsy has been used to detect EGFR DNA mutations that predict sensitivity or resistance to different tyrosine kinase inhibitors.[8] Detection of stage I-II lung cancer has been reported by detecting mutations in peripheral blood ctDNA.[9] Profiles of miRNA have been used to identify candidates for LDCT and to stratify risk of indeterminate nodules.[10,11] DNA methylation of CpG islands in the promoter regions of particular genes has been measured in plasma and in sputum. Methylated DNA biomarkers have been used to identify individuals who might benefit from LDCT and to stratify indeterminate nodules. The most impressive results have been obtained with models based on whole methylome sequencing, rather than with panels of individual biomarkers. One methylome-based study yielded 75% sensitivity for stage Ia lung cancer and 86% for stage Ib lung cancer, testing plasma from patients with indeterminate nodules.[12]

Inflammation contributes to the initiation, progression and metastasis of lung cancer.[13] Inflammatory cytokines – including IL-6, IL-8 and C reactive protein (CRP) - are elevated in sera from lung cancer patients, years prior to diagnosis.[14] Development of better risk models

that include inflammatory and non-inflammatory biomarkers and that do not depend solely upon smoking history should extend LDCT to a larger population with a greater impact on lung cancer mortality.

Colorectal Cancer

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States, second only to lung cancer. Despite the availability of multiple screening options, 40% of eligible patients are not screened in our country, necessitating the need for additional accessible, patient-acceptable and cost-effective screening methods. In the United States, optical colonoscopy has been the standard of care, but in other developing and developed countries two stage strategies are in place where stool biomarkers prompt colonoscopy.[15] The fecal immunochemical test (FIT) for blood in stool has generally provided the initial stage. DNA biomarkers, both genetic and epigenetic have been evaluated alone and in combination with FIT.[16] In 2014 the FDA approved the Cologuard™ (FIT-DNA) stool test that measures aberrantly methylated *BMP3* and *NDRG4* DNA, mutant *K-RAS* DNA, beta actin and hemoglobin by FIT. While FIT-DNA detected 92.3% of all CRC and 94% of early stage cancers, FIT detected 73.8% and 70%.[17] With regard to the polyp precursors of CRC that are excised during colonoscopy, FIT-DNA detected 42.4% of advanced precancerous lesions, whereas FIT identified 23.8%. Thus, FIT-DNA offers significantly greater sensitivity as an initial phase of a two-stage strategy where a positive test prompts colonoscopy, but there is still room for improvement in detecting pre-malignant lesions. In addition, a blood test could provide greater convenience and possibly wider adoption by the community. A single blood test has been approved by the FDA for early detection of colorectal carcinoma (Epi proColon™) that detects methylated *SEPT9* DNA in plasma. A meta-analysis of 25 studies indicated that the overall sensitivity for detecting colorectal cancer was 71% at 92% specificity and the sensitivity for detecting adenomas and polyps >1 cm was 23% at 91% specificity.[18] Panels of blood protein biomarkers show greater promise for detecting pre-malignant disease. A combination of galectin-3 ligand, galectin-3, CYFRA21 and carcinoembryonic antigen (CEA) in serum has detected 56% of advanced polyps at 90% specificity.[15] The combination of galectin-3 ligand and CEA had comparable sensitivity and is being tested prospectively in an EDRN-sponsored study.

Prostate Cancer

Since implementing prostate specific antigen (PSA) screening in the early 1990's, prostate cancer mortality has decreased by nearly 50% in the United States.[19] PSA, however, detects both aggressive, lethal cancers and more indolent disease that does not shorten survival. The challenge of overdiagnosis and consequent overtreatment has prompted the United States Preventive Services Task Force to discourage routine screening and to individualize the use of PSA based on discussions between patients and their physicians. Over the last two decades, the EDRN has contributed to the development of tests that distinguish aggressive from indolent disease, reducing the number of unnecessary biopsies in men unlikely to have prostate cancer. The Prostate Health Index (PHI) includes total PSA, free PSA and [−2]pro PSA. The PHI test has been approved by the FDA to identify men with a total PSA between 4 –10 ng/mL who are likely to benefit from biopsies. Elevation of PCA3 long noncoding RNA in urine after prostate examination provides a highly specific biomarker for prostate

cancer. The PROGENSA PCA3 assay has been FDA approved to identify men suspected of having prostate cancer who should have a repeat prostate biopsy. Combining detection of the TMPRSS2:ERG fusion gene and PCA3 in urine provides greater sensitivity than PCA3 alone.[19] EDRN investigators are prospectively evaluating men with low grade prostate cancers who have been followed with active surveillance and ultimately undergo prostatectomy to identify biomarkers that predict upgrading to more aggressive disease that needs treatment. EDRN studies are also underway to integrate changes in Magnetic Resonance Imaging with multiple biomarkers to detect more aggressive disease.

Breast Cancer

Mammography has contributed to the 30% decline in breast cancer mortality observed over the last three decades, but screening has also detected substantial amounts of pre-malignant disease that might never have progressed. Overdiagnosis and consequent overtreatment can be reduced by developing biomarkers to identify indolent disease, incorporating biology and risk assessment in screening strategies, changing the pathology guideline for tumor classification, and refining the classification of precancerous lesions.[20] Improvements in diagnostics and in biomarker-driven classification must be linked to a willingness to avoid unnecessary treatment in well-defined groups of patients.

Despite improvements in breast imaging, around 15–20% of breast cancers still go undetected.[21] Many developing nations cannot afford routine mammography screening. Blood-based assays that detect early stage breast cancers could be quite valuable as a cost-effective alternative to mammography or to detect cases missed by conventional imaging. While small cancers may not shed sufficient protein or DNA to permit detection, tumor-specific autoantibodies could be evoked by very early lesions. Autoantibodies have been detected against TP53, MUC1, HER2 and a variety of other tumor associated antigens. Panels of protein targets have detected autoantibodies with 66–67% sensitivity at 82–84% specificity.[21] The EDRN has encouraged further development of this approach.

Esophageal Cancer

Most esophageal adenocarcinomas originate from metaplastic small intestinal epithelial cells at the gastro-esophageal junction, termed Barrett's esophagus.[22] Detection and monitoring of Barrett's esophagus are generally performed with upper endoscopy. EDRN investigators identified a two-marker panel of methylated *VIM* and methylated *CCNA1* DNA that detected 95% of Barret's esophagus, dysplasia and esophageal adenocarcinoma with 91% specificity in brushings obtained at endoscopy.[23] To make screening more convenient, a swallowable balloon-based device has been developed called EsoCheck™ that can sample cells at the gastro-esophageal junction in 5 minutes without endoscopy. Detection of methylated *VIM* and methylated *CCNA1* DNA in cells sampled with the balloon device detected non-dysplastic Barret's esophagus with a sensitivity of 90% and specificity of 92%.[23] This strategy was approved by the FDA in 2019 and promises to enhance detection of Barret's esophagus and esophageal adenocarcinoma.

Hepatocellular Cancer

Hepatocellular cancer (HCC) is the leading cause of cancer worldwide related to endemic hepatitis B infection.[24] HCC is also the fastest growing cause of cancer mortality in the United States due to increasing prevalence of nonalcoholic fatty liver disease, alcohol-related liver disease, and hepatitis C infection.[24] HCC generally arises in the context of chronic liver disease where screening has been recommended every six months with abdominal ultrasound. With this approach, only 45% of cases are detected in early stage where surgery can be curative. Addition of Alpha-fetoprotein (AFP) increases early detection to 63%.[25] As 40–50% of HCC do not elevate levels of AFP, additional biomarkers are being developed to aid in early detection. The EDRN provided independent validation of des-gamma carboxyprothrombin (DCP), and lectin-bound alpha-fetoprotein (AFPL3) prior to FDA approval in 2011.[26] Using a GALAD score that integrates gender, age, AFP, AFPL3 and DCP, a sensitivity of 80–91% and specificity of 81–90% was achieved for detecting early stage (< 3 cm) disease across several international cohorts,[27] but in a German study of patients with nonalcoholic fatty liver disease sensitivity was only 68% at 95% specificity.[28] EDRN investigators are currently evaluating more than a dozen protein, glycomic and nucleic acid biomarkers that could further improve sensitivity for early detection of HCC.

DEVELOPING NEW SCREENING STRATEGIES

Effective screening strategies have not yet been established for several malignancies, including ovarian cancer, pancreatic cancer and mesothelioma.

Ovarian Cancer

Over the last three decades, 5-year survival for ovarian cancer has improved from 37% to 46% through more widespread use of cytoreductive surgery and combination chemotherapy, but the cure rate of <40% has changed little due, in part, to detection at a late stage (III-IV) in 75–80% of cases. At present, there is no established screening test for ovarian cancer, but a two-stage strategy where rising serum CA125 triggers transvaginal sonography shows promise.[29] In the United Kingdom Collaborative Trial for Ovarian Cancer Screening (UKCTOCS) that included some 200,000 postmenopausal women, a pre-specified subset of patients with prevalent disease had a 20% reduction in ovarian cancer mortality.[30] Statistical bounds around this estimate are broad and re-analysis will be required later this year before it can be accepted. Whatever the outcome, there is room for improvement in the sensitivity for both stages of the strategy. The EDRN has supported studies of biomarker panels that can detect early stage (I-II) disease at 98% specificity. A four institution EDRN collaboration is studying different autoantibodies and antigen-autoantibody complexes. Notably, anti-TP53 autoantibodies are associated with 22% of ovarian cancers and can be elevated 8 months prior to CA125 and 22 months prior to clinical diagnosis in patients who do not experience a rise in CA125.[31] Multiple autoantibodies are being evaluated with standard panels of sera from patients with early stage ovarian cancer and from control to identify biomarkers that detect cases missed by CA125.

At present only about half of women with ovarian cancer in the United States are referred at diagnosis to gynecologic oncologists who are specially trained to perform complete excision

of all visible cancer, improving overall survival. Most generally present with a pelvic mass that can either be malignant or benign. The EDRN has supported development of 3 FDA approved biomarker panels [ROMA™ (CA125, HE4),[32] OVA1™ (CA125, transferrin, transthyretin, apolipoprotein AI, beta 2 microglobulin),[33] and OVERA™ (CA125, HE4, FSH, transferrin, apolipoprotein A1, transferrin, HE4, FSH)[34]] that identify women with pelvic masses who are most likely to have ovarian cancer, rather than benign disease, and who would benefit from referral to a specially trained surgeon.

Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) is another malignancy with poor prognosis that is diagnosed in late stage in 85% of cases.[35] For the 15% of patients with disease limited to the pancreas, approximately 50% will survive 4.5 years, compared to 5% at 5 years with metastatic disease. PDAC is generally detected with imaging, but image-based screening is recommended only for individuals with a strong family history and/or predisposing germ line mutation (*ATM, BRCA2, BRCA1, PALB2, p16/CDKN2A, hMLH1, hMSH2 and hPMS6)*. Blood biomarkers are required to identify individuals at average genetic risk who would benefit from imaging. Other risk factors include recent onset of diabetes and the presence of intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) that can progress to PDAC in 3–6% of cases. As the mortality of pancreatic surgery can be as high as 2–4% in some centers, biomarkers in cyst fluid that can distinguish pre-malignant from benign lesions would aid in appropriate management.

Consortia of EDRN investigators have established reference sets of sera from early stage (I-II) patients and fluids from pancreatic cysts to evaluate conventional and novel biomarkers. A panel of serum CA19–9, sTRA, thrombospondin, DCD, TIMP1, MUC4, angiostatin and PMS2 detected 79% of early stage PDAC patients at 95% specificity.[35] Abnormalities in cyst fluids are being evaluated with next generation sequencing of DNA, assays for methylated DNA and measurement of telomerase, mucins and DAS-1. Several other candidate biomarkers are being evaluated for biomarkers in blood and cyst fluids.

Mesothelioma

Malignant pleural mesothelioma (MPM) is a rare disease that occurs in asbestos-exposed individuals after 20–40 years.[36] Less than 5% of patients are detected in stage I. Soluble mesothelin related peptide (SMRP) is the one FDA approved biomarker for aiding in diagnosis of MPM. EDRN resources and investigators had contributed to the validation of the MESOMARK™ assay for diagnosing and monitoring mesothelioma. In different meta-analyses, MPM exhibited a sensitivity of 32–64% at 89–95% specificity.[37,38] In longitudinal screening studies MPM could be elevated up to a year before diagnosis. Other biomarkers are being evaluated including proteins (osteopontin, fibulin-3, IL-6, vimentin, HMGB1, calretinin, ENOX-2, thioredoxin-1, VEGF) SOMAmers, glycopeptide signatures, miRNA, ctDNA and methylated DNA. Promising panels will need to be validated.[39]

Universal Screening Strategies

Five EDRN investigators have helped to develop CancerSEEK that has attempted to detect eight types of cancer in stage I-III by assaying 61 mutations/amplicons in 16 genes and 8

protein biomarkers.[16] A case-control study was performed with 1,005 cancer patients (ovary, liver, stomach, pancreas, esophagus, colorectal, lung, and breast cancer) and 812 controls.[40] The median sensitivity across the eight cancer types was 70% at >99% specificity. A machine-learning algorithm was able to localize the source of the cancer to one of two anatomic sites in a median of 83% of patients.[40] In the DETECT-A study of 10,006 women not previously known to have cancer, DNA mutations and protein biomarkers detected 26 cancers and 15 were confirmed and localized by PET-CT.[41] While this is a work in progress, there is great potential to detect cancer from multiple organs.

NOVEL TYPES OF BIOMARKERS AND METHODS OF ANALYSIS

With EDRN support, new types of biomarkers have been developed over the last two decades, including circular RNA. Artificial intelligence has been applied to the analysis of imaging data.

Circular RNA

Circular RNA (circRNA) constitutes a class of single stranded RNAs that are covalently closed in a loop structure without polarity or polyadenylated tails.[42] circRNAs are abundant and resist degradation by exoribonucleases, providing stability in blood and body fluids. Both cancer-associated and tissue associated circRNAs have been described. Expression of different circRNAs has been linked to prognosis across at least a dozen different cancer types. circRNAs can predict response or toxicity after radiation therapy, cytotoxic and targeted drugs, endocrine treatment and immunotherapy. Studies in patients with non-small cell lung, breast, colorectal, gastric, pancreatic, HCC, GU and head and neck cancers suggest that circRNAs also have potential for early detection.

Radiomics

Early detection of cancers utilizes not only biomarkers, but imaging techniques, including low dose CT for lung cancer, x-ray mammography, ultrasound for HCC or optical imaging for esophageal and colorectal cancers.[43] Traditionally, imaging information has been assessed qualitatively, but over the last decade, use of computerized tools has permitted conversion of images into quantitative data (radiomics), with subsequent analysis of these data using artificial intelligence, including convolutional neural networks and generative adversarial networks. This type of analysis requires large amounts of well annotated data. Radiomics is improving diagnostic accuracy of early lesions, defining risk and distinguishing malignant or aggressive cancers from benign disease. These techniques have been used to evaluate dysplastic nevi, malignant melanomas, indeterminate pulmonary nodules, malignant breast lesions, pancreatic IPMNs, prostate cancers during active surveillance and liver stiffness in patients at risk for HCC.

PRINCIPLES OF BIOMARKER DEVELOPMENT MOVING FORWARD

Pitfalls

The number of useful new biomarkers introduced into the clinic remains limited. Despite hundreds of candidates, few maintain their sensitivity, specificity and predictive values when

tested in the clinic.[44] False discovery relates to limited data sets, reproducibility and tumor heterogeneity. Each of these challenges is addressed by the EDRN. Circulating tumor DNA (ctDNA) is a recent example with limitation in specificity, sensitivity, fragmentation, lead time, mutant allele fraction and clinical relevance. Even when ctDNA is analyze in 10 ml of blood, it will be difficult to detect cancers l< 1 cm in diameter. Analysis of ctDNA with artificial intelligence algorithms may improve sensitivity.

Rigor

Since 2000, the EDRN has introduced rigor into biomarker development with guidelines, study design standards, biomarker reference sets and the most rigorous blinding policy in the biomarker field.[45] Importantly, the EDRN has developed an array of statistical and computational tools for early detection biomarker evaluation and developed a multi-disciplinary team-science approach. Moving forward, the EDRN can strengthen its discovery pipeline, conduct better and more efficient validation studies, and develop even more effective statistical and computational tools.

CONCLUSION

This edition of *Cancer Epidemiology Biomarkers and Prevention* should provide a useful assessment of the current contribution of biomarkers to early detection and the unmet needs that still must be addressed. We are grateful to all members of the EDRN who have contributed to this issue and the many achievements of the Network.

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