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Transforming Cancer Prevention through Precision Medicine and Immune-oncology

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Abstract

We have entered a transformative period in the history of cancer prevention. Recent remarkable advances in sequencing technology and computational biology have now provided us with unprecedented opportunities to study the biology of premalignancy, including deep genomic characterization of these lesions, and a detailed assessment of the tumor immune microenvironment. This extraordinary technology has enabled development of novel genomic biomarkers to personalize cancer detection, identified driver mutations in circulating DNA from patients with premalignant lesions, and defined immune gene signatures that are predictive of progression to invasive malignancy. More recently, we have witnessed the remarkable realization of the early promise of immunotherapy which has emanated from a deep understanding of the complexities of the immune system. Just as precision therapy and immunotherapy are transforming cancer treatment, precision medicine and immunoprevention approaches are being translated to the clinic and showing great promise. Here, we set out a brief agenda for the immediate future of cancer prevention, which will involve precision medicine and immunoprevention – pivotal elements of a broader domain of personalized public health.

A Time of Transformation

We have entered a transformative period in cancer prevention. Immense breakthroughs in our understanding of the pathogenesis of multiple cancer types and the rapid advent of new technologies to further our knowledge are providing unprecedented opportunities to make a

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major impact on the natural history of cancer. Although there are clearly contrasting opinions about the current state of cancer prevention science (1, 2), we stand on the cusp of a revolution (3, 4). Just as precision therapy and immunotherapy are transforming cancer treatment, precision medicine and immunoprevention are now moving to the clinic with the same great promise. Additional gains, such as identification of tractable molecular targets, more sophisticated risk stratification strategies and algorithms, better preclinical models, earlier detection of premalignant lesions and early stage cancers, new agents, rational development of combinatorial chemopreventive interventions, and current availability of 14 FDA-approved drugs for application to cancer prevention (3), all point to a strong possibility to reduce cancer incidence, morbidity, and mortality in the near future. Given that the global burden of cancer is enormous and increasing (the number of diagnosed cases is expected to grow worldwide from 13.3 million in 2010 to 20 million by 2030; ref. 5), cancer prevention and early detection are essential to our ability to lessen the burden of cancer in our lifetime. The optimism surrounding progress in cancer therapeutics should propel investigation into applications of enabling technologies and extrapolation of effective interventions in established disease to the more difficult challenges of cancer prevention or interception (6). Here, we set out a brief agenda for the immediate future of this exciting field, which will include both precision medicine (impacting early cancer detection and prevention) and immunoprevention – elements of a broader domain of personalized public health.

Precision Medicine

Premalignancy and Early Cancer Detection

In contrast to studies in malignancy (7, 8), genome-wide analyses of premalignancy have been extremely rare. Remarkable technological advances in next-generation sequencing (NGS; requiring only nanograms of starting DNA/RNA from minute biopsies down to single cells), computational biology, and high-throughput functional screening have now provided us with very real possibilities to deeply probe the biology of premalignancy. Recent studies in lung squamous premalignancy of single-nucleotide polymorphism (SNP) arrays identified losses of tumor suppressors *RNF20* and *SSBP2* and amplification of the *RASGRP3* oncogene (9) and RNA-seq analyses identifying 3q26.33-3q29 (including *SOX2*) amplification/overexpression (10). Driver mutations have even been detected in circulating cell-free DNA in patients with atypical adenomatous hyperplasia, preinvasive (premalignant) lesions of the lung, which could be used for early detection and to follow the effects of preventive interventions (11). Studies of the airway field of injury have detected *EGFR* mutations in adjacent histologically normal epithelium of *EGFR* mutant lung adenocarcinoma (12) and whole-genome expression profiling has identified other activated oncogenic signaling pathways (e.g., PI3K/AKT) in the airway of smokers with lung cancer (13) and in the cytologically normal bronchial airway of smokers with premalignant lesions, potentially enabling genomic approaches to monitoring the preventive effects of PI3K inhibitors (14). This precision genomics approach is currently being tested in a Phase-IIb prevention trial of myo-inositol among high-risk smokers with premalignant lesions. These genomic markers within the airway field of injury are also emerging as key tools to aid in early detection, with recent clinical validation of a bronchial airway gene-expression classifier as a highly sensitive tool for lung cancer detection in two prospective multicenter

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trials of current and former smokers with pulmonary lesions (15). This paradigm to personalize early detection of cancer among those at high risk has extended into other tumor settings including a highly sensitive stool DNA test (for *KRAS* mutations, aberrant *NDRG4* and *BMP3* methylation) for colorectal-cancer screening (16).

Emerging studies support the model that a specific sequence of acquired genomic events over many years characterize the transition from normal epithelium to invasive carcinoma and that specific “driver” events, acquired in a particular order, enable cells to progress from benign growth to an invasive phenotype. A recent study sequenced 293 cancer-relevant genes in primary melanomas and their adjacent precursor lesions to study the succession of genetic alterations during melanoma progression (17). Whereas benign nevi harbored *BRAF* V600E mutations exclusively, this study identified an intermediate (premalignant) category of melanocytic neoplasia characterized by additional mutations, including *TERT* promoter mutations and *NRAS* mutations, and found a mutational signature implicating ultraviolet radiation as a major driver of melanocytic neoplasia progression. Ultra-deep sequencing of 74 cancer genes in 234 biopsies of sun-exposed eyelid epidermis revealed mutations similar to that seen in many malignancies, including *NOTCH1/2* and *FAT1* genes (18). *NOTCH1* driver mutations have also been detected in oral premalignancy (19). Other recent genomics studies in lobular carcinoma in situ of the breast and small precursor lesions in the pancreas have identified driver-gene mutations suggesting that some early lesions may be more easily targetable to prevent progression (20, 21). Some data suggest that driver mutations in early neoplasia can differ from those in frank cancer. A critical next step for this field will be developing systematic approaches for whole-genome profiling of premalignant lesions followed longitudinally as they progress toward cancer--the recently proposed initiative “Pre-Cancer Genome Atlas” or “PCGA” (22). This initiative will provide critical insights into the molecular events (and possible sequence) in premalignant cells and their microenvironment that drive progression to invasive cancer (Figure 1), enabling precision approaches to cancer prevention and early detection.

As described above, the PCGA currently focuses on solid tumors of epithelial origin; however, it does apply to and could include hematological neoplasia. The TCGA did include one blood cancer (AML). Very recent studies have applied genomics to hematologic premalignant disease. Somatic mutations in genes such as *DNMT3A* and *TET2*, typically associated with hematologic malignancies, have been identified in the blood of people without a known hematologic disorder. The prevalence of people with these mutations, termed clonal hematopoiesis of indeterminate potential or CHIP, increases with age (reaching nearly 15% in people over the age of 70; 23) and is associated with an increased risk (0.5–1.0% per year) of progression to a blood cancer (24). Another recent study found somatic mutations typical of myelodysplastic syndrome (MDS; and AML) in as many as 40% of patients with idiopathic cytopenias of undetermined significance or ICUS (25). This subset of patients with clonal ICUS is described as having clonal cytopenias of undetermined significance (CCUS) and may be at greatest risk of progressing to a frank malignancy. Several prospective studies of ICUS and CCUS have been initiated to identify patients with preclinical MDS (26) most likely to progress and therefore, potential candidates for early treatment or prevention. Related hematologic malignancy work is studying the monoclonal gammopathy of undetermined significance (MGUS)-multiple

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myeloma sequence, including smoldering myeloma, which has an overall risk of progression to malignancy (multiple myeloma) of 10% per year (compared with 1% per year for MGUS). Current genomic work is aimed at risk stratification of MGUS and smoldering myeloma to identify patients with biological premalignancy (27).

Prevention Trials

The first precision medicine trial design for cancer prevention (EPOC) was reported just two months ago (28), beginning a new era of molecular selection in prevention trials (29). Perhaps the most promising current precision medicine approach to change standard of care in cancer prevention involves aspirin in colorectal cancer (CRC) prevention. In September 2015, the US Preventive Services Task Force (USPSTF) recommended low-dose aspirin for CRC prevention based on age and risk (30), a major milestone for the field of cancer prevention. Given aspirin's potential adverse effects (e.g., bleeding), further tailoring aspirin use is a high priority. A series of recent reports based on studies of colorectal neoplasia, prostaglandins, and aspirin mechanism support a precision medicine approach in this setting: (a) high urinary PGE-M levels were prognostic (associated with advanced adenomas risk) and predictive for aspirin and/or NSAID preventive activity (31); (b) aspirin reduced CRC risk in patients with high 15-hydroxyprostaglandin dehydrogenase mRNA expression in the normal mucosa adjacent to cancer (32); and (c) aspirin, NSAIDs, or both were associated with reduced CRC risk and the association of these agents with risk differed based on a SNP at chromosome 12 that could potentially affect prostaglandin synthesis (33). A related study reported that SLCO2A1 mutation carriers develop early-onset CRC neoplasia and are NSAID-resistant suggesting for the first time that disordered prostaglandin catabolism can mediate inherited susceptibility to colorectal neoplasia in humans, mimicking the phenotype of the related HPGD-null mouse (34). SLCO2A1 encodes the prostaglandin transporter, shown to play a critical role in colorectal neoplasia (35). Combined, these studies make a compelling case for a precision medicine trial design based on biomarkers associated with this pathway for precision risk stratification and aspirin prevention.

Precision prevention may also involve risk stratification, early detection, and risk-reduction in patients carrying cancer predisposition genes, including both rare high penetrance and more common less powerful genes. Surgical prevention by removal of at-risk tissues is effective but may come at a high cost in quality of life, such as prophylactic premenopausal oophorectomies. Many hereditary syndromes feature predisposition to tumors of multiple sites or include prominent involvement of sites not amenable to surgical risk reduction (e.g., Li Fraumeni, Cowden's, VHL or RASopathies; ref. 36). Strategies exploiting specific molecular defects in malignancies developing in the setting of predisposition genes are now being examined as therapies. For example, *BRCA1/2* mutations induce defects in DNA repair that have been shown to confer sensitivity to PARP inhibitors across associated tumor types, including breast, ovary, prostate, and pancreas (37, 38). The possibility of specific therapies for BRCA mutation carriers has led to incorporation of *BRCA* germline characterization for all ovarian and triple-negative breast cancers into NCCN guidelines. Opportunities for medical risk reduction for *BRCA*-mutation carriers may target DNA-repair defects and/or capitalize on other site-specific data, such as tamoxifen in breast cancer prevention (39).

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Screening all newly diagnosed CRC patients for Lynch syndrome, characterized by microsatellite instability (40), helps identify patients eligible for immunotherapy (anti-PD1; ref. 41). In addition, identification of the proband will enable the definition of those more likely to have a hereditary cancer susceptibility syndrome so they and their at-risk family members can benefit from intensive cancer surveillance and consideration of risk-reducing interventions (42–44). Colorectal cancer survivors with Lynch syndrome require intensified surveillance for additional primary tumors and perhaps secondary prevention interventions. Somatic genomic markers are emerging as key tools to aid in the early detection in this setting, e.g., oral cancer in Fanconi anemia (45) based on one of the very few established molecular risk markers in premalignancy (46). Study of the biology of tumors that develop in individuals carrying predisposing mutations has led to novel vaccine prevention strategies in Lynch Syndrome and *BRCA1/2* carriers (see below in *Immunoprevention*). The application of genome-wide association study (GWAS) data as modifiers of high-penetrance genes or more complex risk models of common less-penetrance genes offers other promise going forward (33, 47).

Immunoprevention

A successful example of immunoprevention is the nationwide hepatitis B virus (HBV) vaccination program in Taiwan that began in 1984 and produced an 80% reduction in the incidence of hepatocellular carcinoma (48). Expanding worldwide access to HBV vaccination is a harbinger of benefits to come. Recent work suggests that specific HBV mutations can predict antiviral preventive efficacy bringing precision medicine into this field (49). Global perspectives on the patterns of HPV-related cancers (e.g., oropharyngeal) and preventing virally related cancers with vaccines, including efforts to make these vaccines available to countries experiencing financial hardships, highlight the burden and challenges of these viral diseases (50, 51). A study in Haiti found that cervical intraepithelial neoplasia COX2 levels were higher in dual HIV/HPV-infected women than in women infected with HIV alone (52), suggesting that drugs such as aspirin which can enhance immunosurveillance and inhibit synthesis of PGE_2, an immunosuppressive bioactive lipid (53), may reduce the risk of cervical cancer in HIV-infected women.

HPV vaccination uptake remains uneven in parts of the US and world (54). An RCT in Costa Rica showed that even a single HPV16/18 vaccine dose could induce a sustained antibody response (55). Subsequent larger compelling papers confirmed this observation and planning is now underway for an RCT to evaluate the protection of one versus two doses in Costa Rica (56). A US immune-bridging study (including males) done in parallel would be of great public health significance. A single vaccine dose, providing strong and sustained protection against HPV infection would produce dramatic advantages of cost and logistics and be the best way to overcome the barriers to vaccine uptake globally. Another preventive vaccine approach is to eradicate existing premalignant lesions where the pathway to transformation is known. The first vaccine tested clinically in premalignant HPV disease (vulvar intraepithelial neoplasia) was composed of long peptides derived from HPV16 E6 and E7 oncoproteins and produced major activity and strong T-cell responses (57). This therapeutic vaccine approach has produced positive results in an RCT in cervical intraepithelial neoplasia [58]).

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A number of prevention studies have focused on the growing public health epidemic of HPV-associated oropharyngeal cancer, including two early detection research studies: oropharyngeal “PAP” smears (59) and influence of childhood tonsillectomy effect on subsequent oropharyngeal cancer (60). The dramatic cancer disparity of blacks versus whites in HPV-positive oropharyngeal cancer (61) is well established; updated data suggest that these patterns may be changing over time (62). A recent report on the long-term persistence of oral HPV16 infection in men (63) adds important new data to the scarce information currently available regarding the natural history of oral HPV in light of the rising incidence of oropharyngeal cancer among men. Current work is moving genomics to this prevention and early detection setting to identify molecular risk groups in the setting of oral HPV16 infection.

Although more complex and recent than the development of vaccines against foreign pathogen-associated targets (e.g., hepatitis B), vaccines against the less-immunogenic genetic drivers and other tumor antigens are showing promise in preclinical prevention models (e.g., KRAS in pancreas models; activating EGFR mutations in lung adenocarcinoma [64, 65]) and have now entered early phase clinical trials (e.g., HER2, MUC1). This focus is very timely, as evidenced by a major new initiative by Cancer Research UK, which recently issued a £20M Grand Challenge that includes a charge to develop vaccines to prevent non-viral cancers (66). The first clinical trial of a preventive vaccine based on a tumor antigen tested in premalignant disease (advanced adenoma) was recently reported (67). The vaccine consisted of the 100-mer peptide derived from the tandem repeat region in the MUC1 extracellular domain and adjuvant, TLR3-agonist Poly-LCIC. It elicited both humoral and cellular MUC1-specific immunity and increased IgG levels after a booster injection at one year, demonstrating induction of immune memory. The vaccine was well tolerated without any toxicity or evidence of autoimmunity. Currently this vaccine is being tested for efficacy (prevention of adenoma recurrence) in a multi-center RCT (NCT02134925; personal communication OJ Finn).

Advanced genomic technology is also allowing study of the immune microenvironment in premalignancy, which may indicate immunity-driven elimination of lesions, evidence of immune surveillance, and signatures of immune escape. Preclinical studies demonstrate that multi-antigen vaccines are more effective than single antigen vaccines by inducing immunity to more antigens, generating more activated T-cells homing to the premalignant lesion (68). A multi-antigen vaccine for colon cancer, targeting several immunogenic proteins that are upregulated in adenomas and conserved through carcinoma [69], is moving towards the clinic. Preliminary studies of single antigen vaccines are encouraging in reducing polyp formation in AOM-treated mice and APC min-mice (personal communication ML Disis). Of potentially great importance to CRC prevention is the finding that aspirin (recently recommended for CRC prevention by the USPTF; see above) can increase tumor-trafficking CD8 T-cells to enhance immunosurveillance and reverse immune escape in premalignant lesions, suggesting the significant potential of combining aspirin with CRC vaccines (70).

Gene amplification resulting in abnormal overexpression of non-mutated self-antigens is an early event in the malignant transformation of many solid tumors. A three-antigen vaccine (targeting IGFBP2, IGF-1R, and HER2—all upregulated in high-risk breast lesions from

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DCIS to atypical hyperplasia) was shown to be safe and effective in transgenic mice (68) and will start phase-I clinical trials in Q1 2016. A five-antigen vaccine targeting breast cancer stem cells (immunizing against CD105/Yb-1/SOX2/CDH3/ and MDM2) called STEMVAC is currently in clinical trials (NCT02157051). Further clinical development of these vaccines will be based on immunogenicity in the phase I trials. A prophylactic lung cancer vaccine, using the same approach in terms of genomic screening and then functional screening to identify candidate proteins upregulated in dysplasia and conserved in stage I/II disease, is in development.

Immunoprevention may also involve patients carrying cancer predisposition genes. A novel example of this approach involves a vaccine targeting hTERT under development by Vonderheide (71) and colleagues for *BRCA* carriers. This vaccine is being tested clinically now in the adjuvant setting with plans to move to *BRCA1/2* healthy carriers initially in a window trial before prophylactic surgery. A vaccine targeting mutations that define Lynch syndrome to prevent the development of cancer is under development (72) and is extremely exciting and promising given the striking efficacy of immunotherapy approaches in the treatment of CRC in this context (41).

Conclusion

Recent remarkable advances in sequencing technology, computational biology, and high-throughput functional screening are transforming cancer prevention through precision medicine and immune-oncology. These extraordinary tools provide unprecedented opportunity to interrogate the biology of premalignancy, and identify novel genomic biomarkers to personalize cancer detection and prevention, driver mutations in circulating DNA, and gene signatures, which define a neoplastic immune environment predictive of progression to invasive malignancy. Just as precision therapy and immunotherapy are transforming cancer treatment, precision medicine and immunoprevention approaches are being translated to the clinic and showing great promise. We stand at the edge of new a frontier that will include comprehensively characterizing the molecular and cellular events that drive premalignant progression. The technology and science are evolving rapidly and herald a new era of precision medicine and immunoprevention in cancer prevention that will require new paradigms for implementation into clinical practice.

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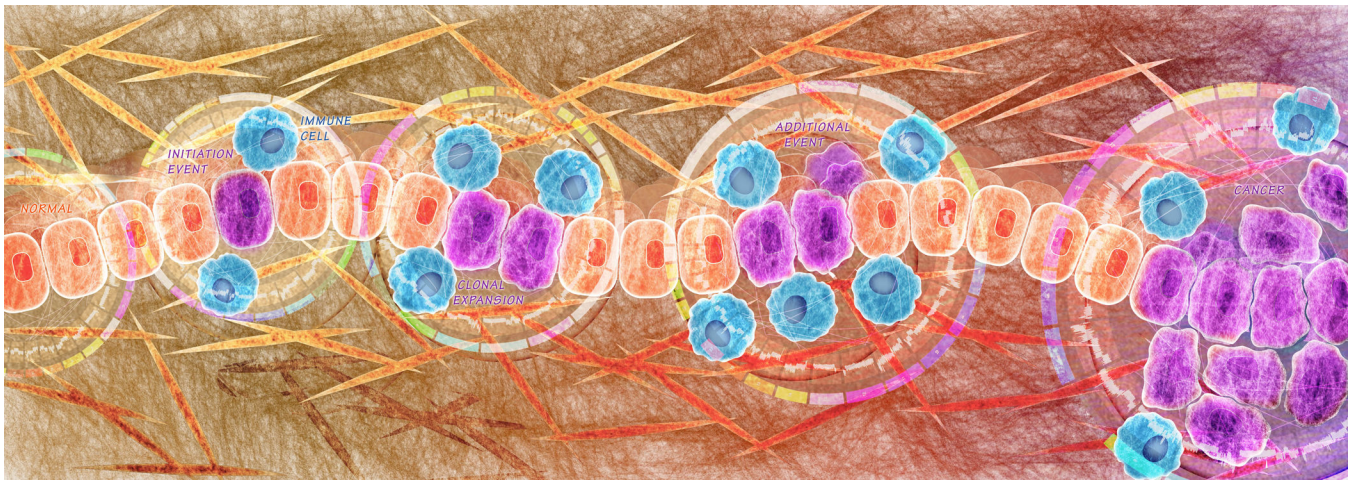

Figure 1.

The molecular alterations associated with earliest pathological steps preceding the development of invasive carcinoma have not been well characterized. A Premalignant Cancer Genome Atlas (PCGA) is needed to both support the collection and molecular profiling (circus plot) of premalignant lesions (purple cells) to identify the sequence of initial driver events that cause normal cells (orange cells) to acquire cancer hallmarks such as uncontrolled growth that enable lesions (purple cells) to progress to fully invasive carcinoma, including the critical “additional genomic events” (e.g., checkpoint/tumor suppressor loss or other co-activating event) that transform a premalignant lesions (purple cells in the 4th circle to the right) to frank cancer (far right). In addition to the sequence of driving events, characterizing the premalignant microenvironment, including the contribution of the stroma and the immune system particularly T-cell (blue cells) regulation that will allow for a better understanding of the selective forces that determine which molecular drivers give an evolutionary advantage to drive premalignant lesions to become invasive cancer. This figure is modified in part from Campbell et al. (21).