

THE **DRA** PROJECT
Accelerating Disparity
Reducing Advances

THE **BFP** Project
Biomonitoring Futures



Cancer 2015

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Cancer 2015

A forecast of likely incidence and treatment advances for breast, colon and lung cancers

Introduction

The Biomonitoring Futures Project (BFP) is exploring how biomonitoring related to diabetes and cancer might evolve over the next decade and its potential to reduce health disparities. The BFP, funded by the Robert Wood Johnson Foundation, is a component of IAF's larger effort to identify and accelerate the most significant disparity reducing advances – the DRA Project. This document summarizes recent forecasts for three common cancers (breast, colon and lung) and then explores likely developments in the treatment of cancer. A separate report will provide more detailed forecasts for developments in biomarkers and biomonitoring for cancer and pre-cancer. There is great potential for reducing cancer related health disparities and enhancing health gains through the use of low cost, culturally appropriate and clinically efficient biomonitoring.

The Cancer Burden

Cancer has become the leading cause of death for those less than 85 years of age. One half of men and one third of women will develop a cancer during their lifetimes. While the death rate has dropped by 60% (age-adjusted per 100,000) for heart disease and 70% for stroke between 1950 and 2002, cancer is essentially unchanged.¹ Since 1993 the death rates from the four most common cancers – breast, colon, lung and prostate – have been declining about 1% per year, but for other cancers the decline has been minimal.² About 570,300 people will die from cancer this year. Overall, cancer incidence rates have been dropping about 0.5% per year for the past 15 years, but still 1,373,000 new cases of cancer will be diagnosed this year.

Breast Cancer

Breast cancer is the most common type in women representing 32% of all cancers (excluding skin cancers). About 211,000 new cases of invasive breast cancer will be diagnosed in 2006 (58,500 additional cases of in situ cancer) with the incidence increasing 0.3% per year. With an estimated 40,400 deaths in 2006, breast cancer is the second leading cause of cancer deaths in women (behind lung cancer), representing 15% of all cancer deaths. The death rate has been declining about 2.3% per year since 1990 due to earlier diagnosis and more effective treatment.³

Colon Cancer

Colorectal cancer is the third most common cancer with about 145,300 new cases per year, and the second most common cause of cancer death with 56,300 expected to die in 2006. Seventy two percent of the cases arise in the colon with the rest originating in the rectum. The incidence has been declining since 1998, probably due to better detection and removal of precancerous polyps. The death rate has been steadily declining for many years (from 35 per 100,000 men in 1975 down to 24 in 2000). This likewise has been due to earlier and more effective treatment.⁴

Lung Cancer

Lung cancer is the biggest cancer killer with 163,500 deaths expected in 2006. The incidence has been declining since the early 1990s in men and is just coming off its peak in women due to the decline in smoking several years earlier. However, because most diagnoses are made late, the five year survival is still only 15% overall. Lung cancer is the second leading cause of cancer (behind prostate in men and breast in women) with 172,500 new cases being diagnosed this year. Advances in targeted therapy are just becoming available for lung cancer.⁵

By 2015 there should be at least a 23% reduction in breast cancer and an 18% reduction in colon cancer and men's lung cancer mortality rates from 2005. Women's lung cancer mortality will be dropping. Elevated mortality rates for Blacks will continue to drop so that the disparity will be reduced by more than half.⁶

Advances in the Prevention and Management of Cancer

Prevention

Two of the three cancers being considered are preventable – lung and colon cancer. It is estimated that 87% of **lung cancers** are the result of smoking or passive exposure to tobacco smoke (spouses of smokers have a 30% greater risk). Ten years after a person quits smoking his risk drops to 1/3 what it would have been with continued smoking. Other risk factors are exposure to asbestos, radon, radioactive ore dust, inhaled chemicals, minerals and fuels, radiation therapy to the chest and recurring inflammation such as tuberculosis.⁷ Essentially all these exposures are avoidable.

Obesity, eating more than 7 servings of red meat per week, cigarette smoking, and having more than 4 alcoholic drinks a week have been shown to increase the relative risk of **colorectal cancer**, while more

than 3 hours of physical activity a week and consumption of 5 or more servings of fruits or vegetables a day seem to reduce the risk.⁸ More importantly, appropriate screening for fecal occult blood and colonoscopy will detect most premalignant polyps in time for removal to prevent cancer from developing.

A healthy lifestyle with regular physical activity, healthy weight, minimal use of alcohol, and avoidance of hormone replacement therapy appear to have a modest benefit in preventing **breast cancer**. The use of tamoxifen (antiestrogen drug) for 5-6 years in high risk women reduces the risk of cancer by 32% - 49% in two clinical trials. Bilateral mastectomies in high risk patients also prevent most cancers (but cancer can form in residual breast tissue).⁹

An exciting example of a major advance in chemoprevention is the human papilloma virus vaccine to prevent most cases of cervical cancer. After successful clinical trials the FDA is using “fast track status” review for likely approval of the first product in 2006.¹⁰

Advances in biotechnology are leading to increased understanding of the underlying causes of cancers at the genetic and molecular levels. Genetic variations associated with increased risk for specific cancers are being discovered. By 2015 there may be simple tests to determine those predisposed to developing breast and other cancers. Attention can then be focused on behavior change, possible chemopreventive therapies and close monitoring to either prevent the cancer or to detect it early for successful treatment.

Screening

As alluded to above, screening for **colorectal cancer** starting at age 50 (earlier for high risk individuals) will result in the discovery of most adenomatous polyps for removal before they progress to cancer. Current guidelines recommend various combinations of annual fecal occult blood testing (FOBT) or fecal immunochemical testing every year, a flexible sigmoidoscopy or double-contrast barium enema every 5 years and colonoscopy every 10 years. The National Polyp Study suggested that periodic colonoscopy could prevent 76% - 90% of colon cancers.¹¹ Sadly, only 19% of those 50 and older had FOBT in the past year and 46% had either flexible sigmoidoscopy or colonoscopy in the past 5 years. The numbers are dramatically less for those without health insurance.¹²

Breast cancer is usually asymptomatic until late in the course, and when a lump can be felt in the breast the cancer has frequently spread. Therefore, besides monthly self-examinations and physician examinations it is important for women aged 40 and older to have annual mammograms (younger for high risk patients). Mammograms will detect 80% - 90% of the cancers in asymptomatic women. Unfortunately only 61.5% of all Americans over 40 years old received a mammogram in the past year, and the number tested drops to 43.7% for women with 11 or fewer years of education and 28.9% for those without insurance coverage. Racial disparities for having a mammogram have been dramatically reduced, but there are still a couple percentage points of difference.¹³ There is also a problem of inadequate number of radiologists trained in reading mammograms.

Unfortunately there are no effective screening tests for **lung cancer** which detect the disease early enough to prevent death. Routine chest x-rays are now uncommon unless the patient has symptoms or is at high risk for cancer. There is growing evidence that spiral or helical low dose CT scanning can pick up smaller lesions and it is frequently used for concerned smokers. The National Lung Screening Test (NLST) study is evaluating whether CT scanning is justified as a screening test, with results expected in 2009.

By 2015 well over 90% of Americans could receive timely screening for breast and colon cancer if there is the politicoeconomic will to make it happen. Public awareness and aggressive health system support are essential. Hopefully there will be an effective biomarker or imaging test for screening lung cancer by that time.

Effective Management

Effective cancer management usually requires a collaborative team of providers; ideally tied together by an electronic health record so all participants have complete access to information. An oncologist, surgeon or radiation therapist who has extensive experience in treating the particular type of cancer is the preferred team leader. For complex cases an oncology center is better able to provide the expertise and resources for comprehensive treatment. It is also the portal for access to most clinical trials of potential new therapies. Besides treating the malignancy it is important to address the emotional, economic and other quality of life factors that these patients and their families struggle with.

Advances in Biomonitoring

a. Biomarkers

- **Blood biomarkers for proteins**

It is hoped that simple blood tests will predict the risk of future cancers, diagnose early, asymptomatic (even precancerous) disease and identify subtypes for deciding appropriate therapy. Single protein markers such as prostate-specific antigen (PSA), carcinoembryonic antigen (CEA) for colon cancer and CA125 for ovarian cancer are not specific enough for screening, but help in disease management. Platelets contain proteins that regulate angiogenesis, and these protein levels change with the development of cancer and onset of metastatic disease. This might lead to a test indicating that cancer is developing or spreading somewhere, calling for further evaluation. More specific markers may be discovered over the next few years.

Cancer cells overproduce some proteins; so profiling dozens to hundreds of proteins may elucidate specific patterns strongly correlated with a certain cancer. This method might be useful in detecting early asymptomatic ovarian cancer while cure is still possible, or differentiate aggressive from indolent prostate cancers to guide therapy. Intraepithelial Neoplasia (IEN), or precancer, is so small that protein abnormalities are not detected in the blood (must be done on biopsies of the lesion). It would make a significant difference if future ultrasensitive blood biomarker tests could detect this important precancerous process.^{14 15 16 17}

- **Blood biomarkers for genes**

Variations in a single gene can be diagnostic of inherited diseases such as familial adenomatous polyposis. It appears that an abnormality in chromosome 6 leads to increased susceptibility for lung cancer even with a small amount of smoking. Genetic variations, primarily combinations of single nucleotide polymorphisms (SNPs), are associated with higher risk of eventually developing certain cancers. “Genomic fingerprints” are patterns of variations in hundreds of genes that correlate with specific diseases. It is hoped that genetic tests using these principles will be useful in identifying those at higher risk so they can be closely monitored and make appropriate lifestyle changes. Also, genetic tests might indicate that a cancer is developing so then early evaluation can pinpoint the tumor for immediate therapy. Particular patterns might even identify the unique characteristics of the cancer for selecting the right targeted therapies. To date genetic data is useful in the management of some cancers, but it must be extracted from biopsies of the tumor, not peripheral blood.¹⁸

- **Breath and Saliva tests**

Researchers are trying to develop a reliable screening breath test for lung cancer that would analyze the “smellprint” of volatile organic compounds in exhaled breath. Preliminary studies show reasonable negative predictive value, but low positive predictive value. Saliva tests of messenger RNA patterns are 90% accurate for oral cancer in early trials. Other tests for breast and ovarian cancer are still in early stages of investigation.^{19 20 21}

- **Skin testing**

A unique skin test harvests epidermal cells on adhesive tape for analysis of cellular DNA or mRNA that has altered expression due to the influence of substances produced by prostate cancer

cells. Researchers are trying to narrow down the pattern to about 25 genes statistically predictive of the cancer.²²

- **Stool testing**

Besides the standard fecal occult blood testing new methods are looking at abnormal DNA, mRNA and possibly specific proteins from sloughed cancer cells that might have higher predictive value in identifying cancer.²³

Most of these advanced concepts for future biomarkers are in their infancy. Researchers are discovering the vast complexity of nature's networked genetic processes and molecular pathways. Progress is likely to be slower than expected initially until the understanding and tools advance to the point of facilitating the process of discovery and translation into clinically useful tests. The biggest hurdle will be proof of adequate sensitivity and specificity in clinical trials. The final biomarker test must be easy to use, cost effective and accepted by providers and patients for it to be incorporated into clinical practice. It will probably take a combination of biomarkers to effectively identify a particular cancer and determine the most promising therapeutic regimen. It will take a long time to work out and confirm the right guidelines given this complexity. Unfortunately, biomarker tests will likely be expensive early on unless special effort is made to make them accessible to community health centers and the underserved.

By 2015 there will be better screening and treatment biomarkers that are relatively inexpensive and easy to use. It is uncertain which modalities will prove most beneficial – blood, breath, saliva, skin, urine, or something else. It will take some time to design appropriate protocols of how to most effectively utilize them in a community clinic setting.

b. Molecular Imaging

Molecular imaging is a fast growing field which is just coming into widespread clinical use. An imaging probe zeros in on the specific target of interest and because of radioactivity or other characteristics is visualized by an imaging device such as MRI (magnetic resonance imaging), PET (positron emission tomography), or SPECT (single photon emission computed tomography) scanning. These techniques can detect early cancerous changes years before symptoms. They can tell if a lesion is benign or malignant, identify early metastases anywhere in the body, rapidly tell if the tumor is responding to a therapy and help predict prognosis. The molecular imaging probe can be combined with a therapy to specifically deliver it to the cancer cells.^{24 25} In the long run they will save money as promising therapeutic approaches are selected and ineffective therapies are rapidly identified and discontinued.

By 2010 molecular imaging will be commonly used in cancer treatment and hopefully the high expense will be offset by savings in therapy.

Likely Therapeutic Advances

a. Targeted Therapies

Targeted therapies are specifically designed to interfere with a molecular or gene target known to have an important role in cancer growth, progression or destruction. Two recent success stories are the small molecule kinase inhibitor imatinib mesylate (Gleevec) that cures many with chronic myeloid leukemia and trastuzumab (Herceptin), which is an antibody against HER-2/neu overexpressed in many metastatic breast cancers. Just approved sunitinib malate (Sutent) is a once-a-day-pill containing four tyrosine kinase inhibitors that starve tumors of nutrients and directly kill cancer cells. It is approved for advanced kidney cancer and gastrointestinal stromal tumors (GIST). Biomarkers are being developed with many of these new therapies to determine before treatment whether they will likely be beneficial. There are many types of targets to pursue such as: specific critical signaling pathways for tumor growth and spread (i.e. insulin growth factor pathway), hormonal-based therapies (i.e. tamoxifen), blocking the development of blood vessels into tumors (i.e. vascular endothelial growth factor inhibitors), anticancer antibodies (i.e. anti-epidermal growth factor receptor used for advanced colon cancer) and promoting apoptosis (cell self-destruction). There are well over a dozen approved targeted therapeutic agents with many more in advanced clinical trials.^{26 27 28 29}

By 2015 dozens of targeted therapies will be available. Protocols will evolve determining the optimal combinations and time sequences of chemotherapy and targeted agents to use in specific cancers. Advances in biomarkers will lead to more precise selection based upon unique characteristics of the individual's cancer cells at that point in time. These new therapies will dramatically increase survival, but they will be very expensive (\$10,000 - \$30,000 per course of medication plus drug administration, laboratory and other associated costs). Health plans will struggle to determine under which circumstances to cover a prolonged course of multiple drugs. It will be very difficult to provide these advanced therapies to the uninsured and underserved.

b. Gene Therapy

About 60% of all gene therapy efforts are focused on cancer. The standard approach of trying to insert genes into a critical mass of millions of cancer cells has not been effective. A creative approach is to deliver a gene that encodes for the production of a prodrug converting enzyme into some cancer cells.

When the safe prodrug is given to the patient it accumulates in cancer cells where the converting enzyme changes it into a cytotoxin that kills the cells and their surrounding neighboring cancer cells.

By 2015 gene therapy may be effective for one or a few cancer types.

c. Stem Cell Therapy

Bone marrow transplants after aggressive chemotherapy for leukemias and other cancers are examples of using adult stem cells to repopulate destroyed blood cells. Using the patient's own bone marrow avoids rejection, but likely contains malignant cells. Using another matched person's marrow can cause immune rejection so immunosuppressive drugs are required. Umbilical cord blood contains immature stem cells that are less likely to cause an immune reaction. There is an attempt to create lines of histocompatible stem cells that could be better matched to the patient to avoid the use of strong immunosuppressive drugs. Stem cell research will also yield insights into cellular biology and apoptosis (programmed cell death) that will benefit the development of targeted therapies.

A novel stem cell approach is to use genetically engineered cells from the patient which localize in the cancer and release an anticancer therapy. Mesenchymal progenitor cells (which make connective tissue) can be harvested, grown in the lab, "infected" with a virus inserting a special gene, and then given back to the patient. These cells concentrate in areas of injury (cancer continuously remodels itself like a chronic injury) where the inserted gene is stimulated to produce interferon-beta, that inhibits cancer growth.³⁰

By 2015 stem cells approaches will provide more effective bone marrow transplants and may be used to specifically target and destroy cancer cells.

d. Cancer Vaccines

The goal of a therapeutic cancer vaccine is to stimulate the immune system to recognize and destroy cancer cells without harming normal tissue. Researchers have tried tumor antigens, killed tumor cells, dendritic cells and other approaches to accomplish this. It has been difficult to activate and sustain an immune response powerful enough to make a clinical difference. However, a recent trial of a vaccine against prostate cancer succeeded in prolonging the patient's life by a few months. It used the patient's

dendritic cells altered to express a protein found on the majority of prostate cancer cells.³¹ It is unknown if a universal vaccine can be created that produces a sufficient response, or whether a specific vaccine will be necessary for each unique tumor type.

By 2015 there is a chance that an effective vaccine will be available for use in combination with other therapy for a specific cancer. It will likely take another 10 – 20 years for vaccines to be used as primary therapy.

e. Controlling Cancer by Controlling Gene Expression

Scientists are discovering the details of the complex process of gene expression – how the genes (segments of DNA) within the chromosomes direct the production of specific proteins. Environmental factors influence which specific proteins are produced among several potential choices (phenomenon called epigenetics) and there are mechanisms to turn off the expression of genes (such as RNA interference and antisense). Genetic variations can make an individual more susceptible to developing cancer and other diseases. Normal cells become cancerous as a result of mutations to specific genes. Therefore methods to manipulate gene expression could be used to alter person's genetic susceptibility for developing cancer or to alter genetic expression in cancer cells for cure or long-term control. This is another realm of biotechnology that is in its infancy, but could lead to a preventive or therapeutic measure by 2015.

f. Targeted Drug Delivery

One goal of cancer therapy is to make sure the drug is delivered to malignant cells without harming normal tissue cells. Many ways to accomplish this are available. Toxic drugs can be encapsulated in liposomes, dendrimers or other nano-structures. Tumor-specific antibodies can be associated with drug molecules which cause them to seek out and attach to cancer cells. Genetically-modified viruses can preferentially infect cancer cells and destroy them. Photodynamic therapy is a concept where a photosensitizing drug is preferentially absorbed by fast-growing cancer cells. A laser light is focused on the tumor which activates the incorporated drug resulting in destruction of the cancer cells. Also, as mentioned before, a prodrug enzyme can be administered to tumor cells by gene therapy or stem cells to activate a later administered prodrug into a cytotoxin killing the cells.

By 2015 additional novel ways will be available to specifically target cancer cells for destruction while reducing morbidity and improving quality of life.

Conclusion

Cancer remains one of the biggest challenges in medicine as the second largest cause of death of Americans overall, and the cause of significant fear and disease burden. Advances will lead to earlier diagnoses, and more effective cures. In those individuals where the cancer cannot be eliminated, cancer will be changed from a lethal disease to one, like many chronic diseases where the patient can have a prolonged life of high quality. However, the greatest problems remain getting people to alter lifestyles to prevent cancer and for the health system to proactively monitor patients to ensure that early screening either prevents the cancer or identifies it early enough for cure. We have the knowledge and tools to do this, but society lacks the will.

Medical advances come at a cost and it is not uncommon for treatment of a cancer to exceed \$100,000. The new biomarkers and therapies mentioned in this report are likely to be very expensive. It will take special effort on the part of policy makers, disease groups, the biopharma industry and health providers to find ways to reduce the cost to make them available for the underserved.

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