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Staying a Step Ahead of Cancer

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1. Introduction

Despite decades of research, cancer continues to affect millions of people each year. However, the more we discover about cancer, the more we realize that no single therapeutic strategy can effectively treat it. As we learn about the aberrant signals and pathways which lead to cancer, prevention may be a more feasible strategy. Vaccines, chemo preventive compounds, and healthier lifestyle choices are our arms in the battle against this deadly disease. In this chapter we discuss the importance of cancer prevention, how chemoprevention can be our first line of defense, and consider the role of small molecules and vaccines in cancer prevention and therapy. Deciphering the role of early disease detection and understanding how biomarkers and epigenetics can be a tool against cancer is vital. Finally, tackling the causes of cancer is critical for eradicating this malignancy.

The process of carcinogenesis is extremely slow, offering ample opportunity for intervention and prevention. A mutation in the genome may lead to transformation to a precancerous lesion and eventually to cancer with unchecked cell growth. An untold number of genetic changes can trigger cells to become cancerous. Predicting the changes and the susceptible population is even more daunting.

Mutations, whether acquired or inherited and caused by endogenous and exogenous agents, result in oncogenic transformation. In the human genome, there are many different types of genes that control cell growth in a very systematic, precise way. Error in these genes leads to further alterations or mutations. An accumulation of many mutations in different genes occurring in a specific group of cells over time is required to cause malignancy. In general, mutations in two classes of genes, proto-oncogenes and tumor suppressor genes, lead to cancer.

1.1 Proto-oncogenes

Proto-oncogenes are typically responsible for promoting cell growth but alterations lead to transformation into oncogenes and promotion of tumor growth. Mutations in these genes are typically dominant in nature. Often, proto-oncogenes encode proteins that function to stimulate cell division, inhibit cell differentiation, and halt cell death. Oncogenes, however, typically exhibit increased production of these proteins, thus leading to increased cell division, decreased cell differentiation, and inhibition of cell death. These phenotypes typify cancer cells. Underlying genetic mechanisms associated with oncogene activation include point mutations, deletions, or insertions that lead to a hyperactive gene product. Other examples include alterations in the promoter region of a proto-oncogene that lead to

increased transcription. Gene amplification events leading to extra chromosomal copies of a proto-oncogene may also lead to oncogenesis. Chromosomal translocation events that relocate a proto-oncogene to a new chromosomal site that leads to higher expression or lead to a fusion between a proto-oncogene and a second gene, which produces a fusion protein with oncogenic activity may lead to cancer as well.

1.2 Tumor suppressors

Tumor suppressor genes are also present in our cells to control cell growth and apoptosis. Exquisite control over these processes suppresses tumor development. Mutations in tumor suppressors, as mentioned above, can lead to carcinogenesis. Tumor suppressors are in place to oppose threats to the genome. p53, the guardian of the genome, is one of the most commonly mutated tumor suppressor genes in human cancer. p53, a transcription factor, plays a critical role in numerous signaling pathways, from development to maintaining genomic stability and cell death (Brosh and Rotter 2009). Mutant p53 has been shown to exhibit gain-of-function properties that drive tumor progression and metastasis (Brosh and Rotter 2009). p53 is a stress response protein that functions primarily as a tetrameric transcription factor which regulates a large number of genes in response to a variety of cellular insults, including oncogene activation and DNA damage. These signals activate p53 primarily through post-translational modifications that result in augmented p53 protein level and transactivation activity. Activated p53 suppresses cellular transformation mainly by inducing growth arrest, apoptosis, DNA repair and differentiation in damaged cells (Oren 2003). Not surprisingly, p53 function is almost always compromised in tumor cells. Mutations in p53, usually due to somatic mutations, are observed in approximately half of all human cancers and constitute a cornerstone in tumorigenesis (Hollstein et al. 1991, Vogelstein, Lane and Levine 2000).

1.3 Models of carcinogenesis

There are several models of carcinogenesis. One of the models proposed by Dr. Bert Vogelstein proposes the loss of function of tumor suppressors such as p53 which paves the way for genomic instability, changes in metabolism, insensitivity to apoptotic signals, invasiveness and motility. However, the nature of the causal link between early tumorigenic events and the induction of the p53-mediated checkpoints that constitute a barrier to tumor progression remains uncertain. Loss of p53 function occurs during the development of most, if not all, tumor types. The cascade of events starts with a mutation that inactivates tumor suppressor gene leading to hyper-proliferation of epithelial cells. The mutation may also inactivate DNA repair genes while mutation of proto-oncogene creates an oncogene. The same mutation may lead to a cascade of inactivation of several more tumor suppressor genes before resulting in cancer. For example in colon carcinogenesis, loss or mutation of APC gene leads to overexpression on cyclooxygenase (COX) genes, transforming the normal tissue to hyperproliferative epithelium, and resulting in early adenoma. Subsequent DNA hypomethylation leads to mutations such as in k-ras gene, and results in intermediate adenoma. Another mutation following this, such as loss or mutation of DCC or SMAD 4, results in late adenoma. Subsequent mutation in p53 leads to carcinogenesis. Further mutations result in metastasis and greater genomic instability. It is thus quite apparent that the perturbations necessary to form cancer are numerous and complex. **Figure 1** gives an overview of this model of carcinogenesis.

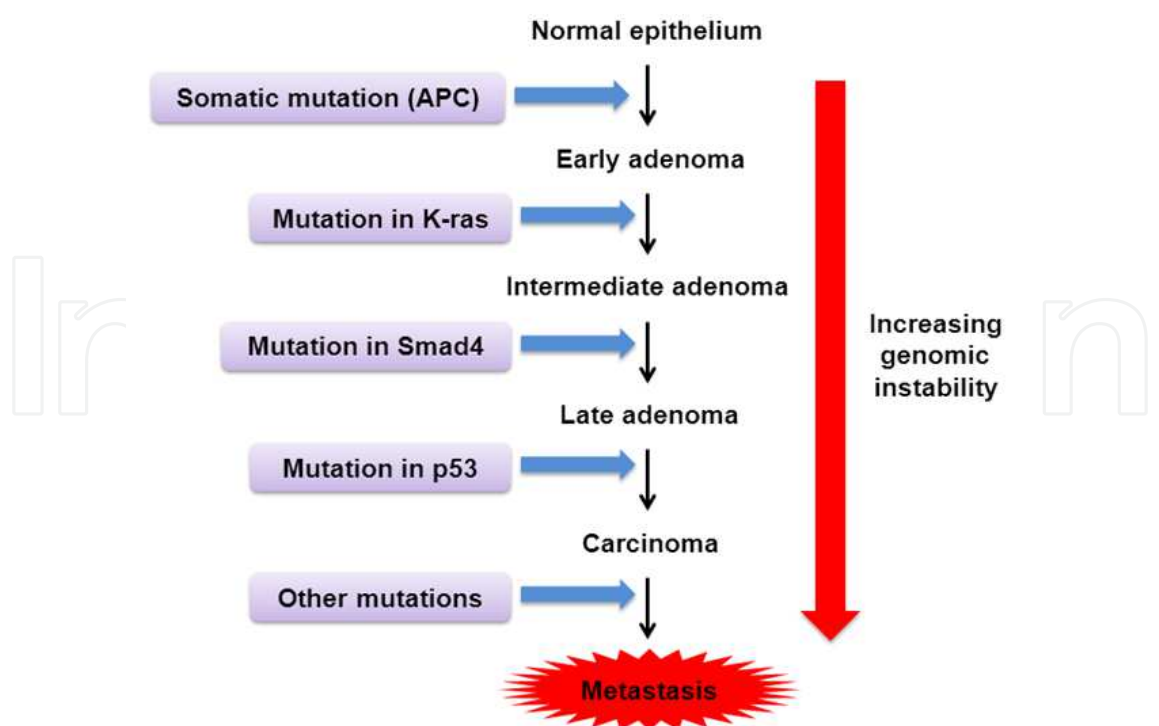


Fig. 1. The cascade of events that leads to colon carcinogenesis.

An alternate theory is Dr. Alfred Knudson’s two-hit theory of cancer causation. This model accounts for both hereditary and non-hereditary cancer. Normal cells have two undamaged chromosomes, one from each parent, containing thousands of genes. People with a hereditary susceptibility to cancer inherit a damaged gene on one of the chromosomes. Thus, their first hit or mutation occurs at conception. Others receive the first hit in their lifetime. A subsequent damage to the same gene on the second chromosome may lead to cancer. Therefore, people with a hereditary susceptibility to cancer just need one hit during their lifetime to produce cancer. An overview of this model is given in **Figure 2**. This model is applicable for cancer such as retinoblastoma where inheritance of the first hit leads to a far greater chance of developing a second cancer causing mutation.

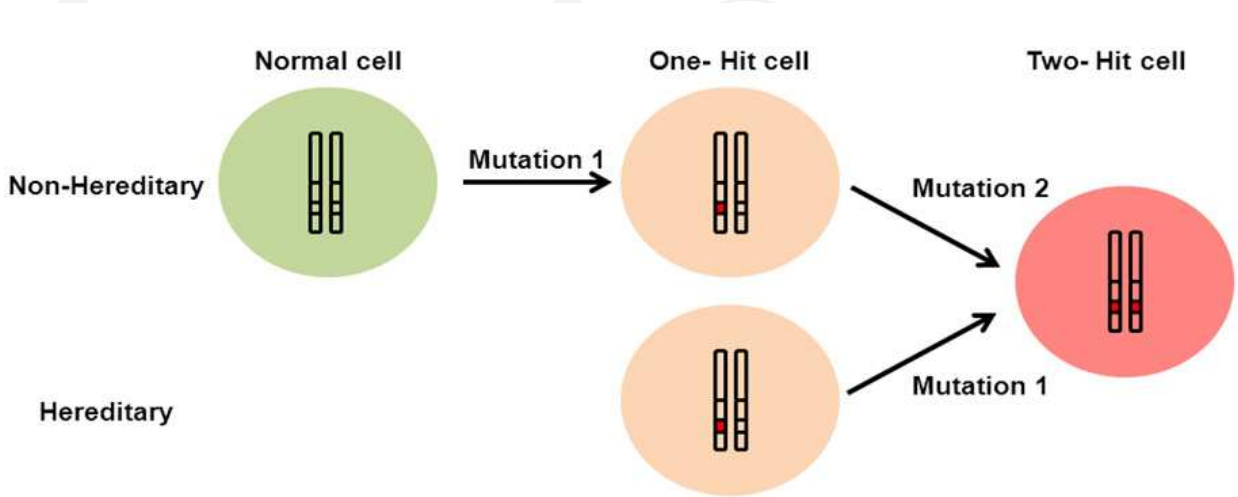


Fig. 2. The two-hit model of carcinogenesis.

2. Genomic instability and cancer

It should be noted that a state of genomic instability prevails in cancer. In certain cases, such as overexpression of licensing factors (hCdt1 and hCdc6), prolonged overexpression of these factors lead to a more aggressive phenotype, bypassing the antitumor barriers of accelerated senescence and apoptosis. The link between activation of DNA-damage response and tumorigenesis implies that continuous DNA damage checkpoint activation could lead to selective suppression of the DNA-damage response-induced antitumor barriers by inactivating mutations resulting in genomic instability and tumor progression (Bartkova et al. 2005, Bartkova et al. 2006, Gorgoulis et al. 2005, Di Micco et al. 2006, Halazonetis, Gorgoulis and Bartek 2008). Cells possessing re-replicated DNA above a critical threshold are typically neutralized by either senescence or apoptosis. However, cells with re-replicated elements below a critical threshold are prone to recombination processes leading to genomic instability. These events favor the selection of resilient cells and lead to therapeutic resistance (Liontos et al. 2007).

Proteins involved in DNA repair pathways have garnered attention because mutations causing dysfunction can lead to increased genetic instability and ultimately to increased cancer risk. Indeed, several studies have demonstrated alterations of these genes are associated with susceptibility to cancer (Berwick and Vineis 2000). Identification of factors associated with prognosis is an ever important process for both an escalation and de-escalation of therapies for appropriately selected patients. Additionally if alterations of these genes impact development of cancer, they are possible targets for therapy.

2.1 DNA damage and repair

The human body is under continuous attack from both external and internal insults which ultimately generates thousands of DNA lesions per day. But it has evolved its own defense mechanism to combat these lesions. The cellular response to DNA damage is critical for maintaining genomic integrity and for preventing carcinogenesis. Since DNA lesions can block genomic replication and transcription and lead to mutations it is imperative that DNA is repaired without any errors. Failure to repair any damage to the nucleic acid results in cell death in the form of apoptosis or necrosis. To combat threats posed by DNA damage, cells have evolved mechanisms, collectively termed the DNA-damage response, to detect DNA lesions, signal their presence, and promote DNA repair. Cells defective in these mechanisms generally display heightened sensitivity towards DNA-damaging agents. While this may be exploited for cancer therapy [e.g. poly ADP-ribose polymerase (PARP) inhibitors in breast cancer susceptibility protein (BRCA) deficient ovarian and breast tumors] it should also be noted that many such defects can lead to human disease, such as cancer.

2.2 DNA repair pathways

In an effort to repair the damaged DNA and avoid passing the damaged DNA onto the progeny cells, the cell has evolved several repair pathways. These repair pathways include base excision repair (BER), nucleotide excision repair (NER), double strand break (DSB) repair via homologous recombination (HR) or non-homologous end joining (NHEJ), and mismatch repair (MMR) (Polo and Jackson 2011, Stratton 2011, Stricker, Catenacci and Seiwert 2011). Though it is not clear what determines the choice of repair pathway, it is an area of active research.

Whereas some lesions are subject to direct protein-mediated reversal, most are repaired by a cascade of catalytic events mediated by multiple proteins. In MMR-mediated repair, detection of mismatches and insertion/deletion loops triggers a single-strand incision that is then worked upon by nuclease, polymerase and ligase enzymes. In BER-mediated repair, a damaged base is often recognized by a DNA glycosylase enzyme that mediates base removal before nuclease, polymerase and ligase proteins complete the repair in processes overlapping with those used in single strand break repair. In contrast, NER-mediated repair recognizes helix-distorting base lesions. It includes two sub-pathways that differ in the mechanism of lesion recognition: transcription-coupled NER, which specifically targets lesions that block transcription, and global-genome NER. A key aspect of NER is that the damage is excised as a 22–30-base oligonucleotide, producing single-stranded DNA that is acted upon by DNA polymerases and associated factors before ligation proceeds.

In NHEJ, DSBs are recognized by the Ku protein that then binds and activates the protein kinase DNA-PKcs, leading to recruitment and activation of end-processing enzymes, polymerases and DNA ligase IV. NHEJ repair, predominantly utilized in the repair of radiation induced DNA damage, is a highly efficient but error-prone process that often results in mutations in the repaired DNA. The NHEJ repair process is dependent on the DNA-dependent protein kinase (DNA-PK) catalytic subunit (DNA-PKcs), the Ku70/Ku80 heterodimer, and the XRCC4–ligase IV complex and ultimately rejoins the ends of DSBs with little or no homology. In response to radiation, DNA-PKcs is autophosphorylated at threonine 2609. This is required for the functional activation of the NHEJ repair pathway. Consistent with the role of NHEJ repair in the repair of radiation-induced DSBs, cells deficient in any NHEJ repair protein have been shown to be hypersensitive to radiation-mediated cytotoxicity (Iliakis et al. 2004, Yang et al. 2009, van Gent, Hoeijmakers and Kanaar 2001). A less-well-characterized Ku-independent NHEJ pathway, called micro-homology-mediated end-joining (MMEJ) or alternative end-joining, results in sequence deletions. Although both NHEJ and MMEJ are error-prone, they can operate in any phase of the cell cycle.

In contrast, HR is generally restricted to S and G2 because it uses sister-chromatid sequences as the template to mediate faithful repair. Although there are several HR sub-pathways, HR is always initiated by single strand DNA generation, which is promoted by various proteins including the MRE11–RAD50–NBS1 (MRN) complex. In events catalyzed by RAD51 and the breast-cancer susceptibility proteins BRCA1 and BRCA2, the single strand DNA then invades the undamaged template and, following the actions of polymerases, nucleases, helicases and other components, DNA ligation and substrate resolution occur. HR is also used to restart stalled replication forks and to repair inter-strand DNA crosslinks, the repair of which also involves the Fanconi anaemia protein complex. This high-fidelity, error-free process is also critical in the repair of lesions resulting from replicative stress (Yang et al. 2009, Jiang et al. 2011, Wang et al. 2010).

2.2.1 Cell cycle checkpoints

Checkpoints are also put in place throughout the cell cycle that halt further progression of DNA replication and cell division upon detection of damaged DNA. This can arrest the cell either transiently or permanently (senescence), as well as activate specific DNA repair pathways in response to certain types of DNA damage. Some of the proteins in these

pathways are mutated or non-functional in human tumors causing cancer cells to be more reliant on an intact DNA repair pathway for survival. Key DNA damage signaling components in mammalian cells are the protein kinases ATM and ATR. ATM is recruited to and activated by DSBs. In contrast, ATR is recruited to and activated by replication protein A-coated double stranded DNA. Two of the best studied ATM/ATR targets are the protein kinases CHK1 and CHK2. Together with ATM and ATR, these proteins reduce cyclin-dependent kinase (CDK) activity by various mechanisms, often mediated by p53. Inhibition of CDKs slows down or arrests cell-cycle progression at the G1-S, intra-S and G2-M cell-cycle checkpoints. This allows more time for DNA repair before replication or mitosis. In parallel, ATM/ATR signaling enhances repair by a variety of methods: inducing DNA-repair proteins transcriptionally or post-transcriptionally, by recruiting repair factors to the damage-site, and by activating DNA-repair proteins by modulating their phosphorylation, acetylation, ubiquitylation or SUMOylation. The aforementioned proteins can be exploited for cancer therapy as well.

2.3 Epigenetic modifications in cancer

Both genotoxic and non-genotoxic mechanisms have been implicated in malignant transformation. Genotoxic mechanisms involve changes in genomic DNA sequences leading to mutations. On the other hand, non-genotoxic mechanisms modulate gene expression directly (Franco et al. 2008). Epigenetic pathway which involves changes in DNA methylation patterns and histone modifications is considered to be a non-genotoxic mechanism capable of modulating gene expression and thus promoting malignant transformation. Thus, it is vital to determine such epigenetic modifications in a way that we can expand on cancer biological marker development with clinical relevance (Franco et al. 2008). Epigenetic molecular marker development has been a hot topic in cancer research because of the ability to contribute to cancer diagnosis and/or prognosis due to their high sensitivity and specificity. A number of epigenetic modifications have been detected in critical genes involved in various cancers that can potentially serve as specific clinical biomarkers.

2.4 DNA hypomethylation and cancer

Promoter DNA hypomethylation modification has been observed for a number of genes including H-ras in prostate and thyroid cancers and cancer-testis antigen gene (CAGE) in prostate, breast, lung and laryngeal cancers. The X-inactive specific transcript (XIST) modification is observed in prostate cancer while erythropoietin (EPO) is found in prostate and breast cancers. Maspin changes are detected in ovarian, pancreatic and lung cancers. Changes in γ -Synuclein are prevalent in ovarian and breast cancers while c-myc modifications are found in breast and lung cancers. Urokinase-type plasminogen activator modification is observed in breast cancer, S100P in pancreatic cancer and Melanoma-associated antigen A (MAGE-A) in lung cancer (Ziech et al. 2010).

2.4.1 DNA hypermethylation and cancer

Promoter DNA hypermethylation modification has been associated with altered expression of critical genes associated with various cancers including BRCA1/BRCA2 in prostate, breast, pancreatic and ovarian cancers, Von Hippel-Lindau tumor suppressor (VHL) and

p53 in breast cancer. A number of changes are observed in lung cancer including P16INK4a, H-cadherin, Death-associated protein kinase 1 (DAPK1), MDM2, and p53. Modification in p14ARF is observed in lung, esophageal and colorectal cancers while changes in hHML1 are seen in colorectal cancer. RASSF1A modification are present in lung and nasopharyngeal cancers (Ziech et al. 2010).

2.4.2 Modifications in chromatin structure in cancer

Besides changes in DNA methylation patterns, the chromatin has also been shown to regulate transcriptional activity. To this end, any modifications in core histone proteins (e.g. H2A, H2B, H3 and H4) can have an impact in the activation and/or repression of transcription. Such modifications can include, among others, methylation, acetylation, deacetylation, phosphorylation, and ubiquitination. Histone acetylation and/or deacetylation are observed in breast, prostate, colon, testicular, renal and pancreatic cancers. Histone demethylation is observed in breast, prostate, colon, testicular and esophageal cancers while histone H3 lysine 27 tri-methylation is observed in breast, ovarian, colon and pancreatic cancers. Histone H3 lysine 9 and/or Histone H4 lysine 20 tri-methylations are present in breast, lung and hepatocellular cancers. Histone H3 lysine 4 methylation is often observed in breast, ovarian, colorectal and hepatocellular cancers (Ziech et al. 2010).

2.5 BRCA1 and cancer

Perhaps, the most noted molecular marker for cancer is mutations in the BRCA family of genes. The BRCA family of proteins is essential for HR-mediated repair of DNA double strand breaks (Jackson and Bartek 2009, Bartek, Lukas and Lukas 2004, Wang et al. 2010, Jiang et al. 2011). As little as one unrepaired DNA double strand break is fatal to the cell (Yang et al. 2009, Aziz, Nowsheen and Georgakilas 2010). Thus, it is not surprising that certain mutations in the BRCA gene lead to an increased risk for breast cancer as part of a hereditary breast-ovarian cancer syndrome. Women with mutated BRCA1 or BRCA2 gene have up to a 60% risk of developing breast cancer (King et al. 2003, Graeser et al. 2009). Similarly, 55% increased risk of developing ovarian cancer is observed with BRCA1 mutations and about 25% for women with BRCA2 mutations (King et al. 2003). Research suggests hypermethylation of the BRCA1 promoter may be an inactivating mechanism for BRCA1 expression not only in breast and ovarian cancer but also lung and oral cancer (Esteller et al. 2000, Marsit et al. 2003). Due to the lack of reliable biomarkers, many women with breast cancer end up being over-treated or under-treated for the disease. Epigenetic modifications have been detected in critical genes involved in breast cancer that could potentially serve as specific clinical molecular markers. These include promoter DNA hypomethylation in c-myc, CAGE, Urokinase-type plasminogen activator, EPO and γ -Synuclein genes and promoter DNA hypermethylation in BRCA1, BRCA2, Von Hippel-Lindau tumor suppressor (VHL) and p53 genes (Ziech et al. 2010).

In addition to breast cancer, mutations in the BRCA1 gene also increase the risk of developing ovarian, fallopian tube, and prostate cancers (Brose et al. 2002, Thompson, Easton and the Breast Cancer Linkage 2002). Mutations in BRCA also increase the risk for a subset of leukemia and lymphoma (Friedenson 2007). Women having inherited a defective BRCA1 or BRCA2 gene have risks for breast and ovarian cancer that are so high

and seem so selective that many mutation carriers choose to have prophylactic surgery. Promoter DNA hypomethylation in *Maspin* and γ -Synuclein genes and promoter DNA hypermethylation in *BRCA1* and *BRCA2* genes have been reported in ovarian cancer (Ziech et al. 2010). A number of epigenetic modifications have been detected in critical genes involved in pancreatic cancer that could potentially serve as specific clinical biomarkers including promoter DNA hypermethylation in *BRCA1* and *BRCA2* genes (Ziech et al. 2010). Thus, the tumor suppressor genes *BRCA1* and *BRCA2* are critical for the maintenance of our genome.

2.6 Mutations in DNA repair genes and cancer

Patients with underlying cellular defects in the response to DNA DSBs often exhibit genomic instability, increased cancer predisposition and radiation sensitivity. There are a number of other genetic disorders that predisposes an individual to cancer via defects in DNA repair pathways. For example, mutations in Ataxia telangiectasia mutated (*ATM*), a critical DNA repair protein, leads to Ataxia Telangiectasia (AT). *ATM* is a serine/threonine protein kinase that is recruited and activated by DNA DSB. It phosphorylates several key proteins that initiate activation of the DNA damage checkpoint, leading to cell cycle arrest, DNA repair or apoptosis. Several of these targets, including *p53*, *CHK2* and *H2AX* are tumor suppressors (Shiloh 2003). Thus AT sufferers are predisposed to lymphoma, breast, brain, stomach, bladder, pancreas, lung, ovaries, T cell prolymphocytic leukemia, B cell chronic lymphocytic leukemia and sporadic colon cancers (Aziz et al. 2010). They are also extremely sensitive to radiation, a source of DNA damage (Alderton 2007).

Nijmegen breakage syndrome (NBS) is a rare autosomal recessive congenital disorder causing chromosomal instability and DNA repair deficiency. *NBS1* codes for a protein that stops cell cycle progression following DNA damage and interacts with *FANCD2* that can activate the *BRCA1/BRCA2* pathway of DNA repair (Stavridi and Halazonetis 2005). Thus, mutations in the *NBS1* gene lead to higher levels of cancer, primarily lymphoma (Aziz et al. 2010). Similarly, Lynch syndrome is marked by defects in MMR genes such as *MSH1*, *MSH2*, *MSH6*, and *PMS2* (Vasen and de Vos tot Nederveen Cappel 2011). This leads to increased incidence of colorectal cancer, cancers of the stomach, small intestine, liver, gallbladder ducts, upper urinary tract, brain, skin, prostate, endometrium and ovary (Aziz et al. 2010). Li-Fraumeni patients demonstrate mutations in *Chk2* and *p53* and defects in MMR. They have a higher incidence of osteosarcoma (Aziz et al. 2010). Werner syndrome, on the other hand, is marked by mutations in *WRN* and *Rad51* genes leading to deficiency in HR- and NHEJ mediated DSB repair. This syndrome leads to a number of cancers including osteosarcoma, colon, rectal, lung, stomach, prostate, breast, thyroid and soft tissue sarcomas (Aziz et al. 2010). Xeroderma Pigmentosum is marked by mutations in *XPD* gene, defects in NER-mediated repair and higher incidence of skin cancer (Aziz et al. 2010). Bloom is caused by mutations in *Blm* gene and leads to leukemia, lymphoma, melanoma, and bladder cancer due to defects in HR-mediated repair (Aziz et al. 2010). Mutations in *RECQL4*, a key BER and HR-repair protein, leads to Rothmund Thompson, Baller Gerold and Rapadilino syndromes which are marked by predisposition to osteosarcoma (Aziz et al.

2010). Mutations in the FANC gene, a marker of Fanconi anemia, leads to deficient DNA crosslink repair and subsequent increased risk of acute myeloid leukemia, head and neck cancer, gynecological malignancies, and gastrointestinal squamous cell carcinoma (Aziz et al. 2010). DNA Lig4 deficiency, a mutation in a key NHEJ repair protein, leads to pancreatic and lung cancers (Aziz et al. 2010). Other defects in NHEJ mediated repair pathways, e.g. Rag1 and Rag2 or Artemis, lead to an increased incidence of lymphoma. XCIND and RS-SCID syndromes are characterized by the aforementioned defects (Aziz et al. 2010). Mutations in XLF, a marker of Cernunnos deficiency and a key NHEJ-mediated repair protein, lead lymphoma while defects in ATR, a key DSB repair protein, lead to ATR-Seckel syndrome which predisposes the individual to leukemia (Aziz et al. 2010).

Another protein, OGG1, an enzyme involved in DNA repair, has been shown to have predictive value for lung cancer (Hatt et al. 2008). OGG1 levels can be easily assayed in blood samples and low levels correlate with higher chance of developing lung cancer. In a recent study, 40% of people with lung cancer had low levels of the enzyme compared to 4% of healthy individuals (Paz-Elizur et al. 2003).

2.7 Other modifications in cancer

Progression of any cancer is accompanied by genetic alteration(s) which leads to altered protein structure and function. In the last several years, the association between human papilloma virus (HPV) and head and neck cancer has been solidified (Wansom et al. 2010, Albers et al. 2005, Sirianni et al. 2004, Sirianni, Wang and Ferris 2005, Kumar et al. 2007, Kumar et al. 2008, Sisk et al. 2002). Interestingly, HPV associated head and neck cancers exhibit better prognosis and appear to respond better to chemo-radiation. Saliva or serum of head and neck cancer patients can be analyzed for p53, EGFR, and HPV status and microsatellite alterations. In addition, a number of epigenetic modifications have been detected in critical genes involved in this particular cancer type that could potentially serve as specific clinical biological markers. These include promoter DNA hypomethylation in H-ras and CAGE genes in thyroid and laryngeal cancers respectively and promoter DNA hypermethylation in p14ARF and RASSF1A genes in esophageal and nasopharyngeal cancers respectively (Ziech et al. 2010).

3. The role of lifestyle choices in cancer

Billions of dollars are spent each year to research new therapeutic strategies against cancer. Still, millions of people die from the disease each year. Thus, successful prevention appears to be the better option and requires attacking the root causes of the disease. The best way to control cancer is to prevent it from happening in the first place. Geographic and economic differences in cancer incidence and mortality are striking. The types of cancer vary greatly between the developed and developing countries. Lung, prostate, breast and colorectal cancer are common in the developed countries like the US while ovarian, cervical, hepatocellular, and head and neck cancer are wide-spread in the poorer nations (Ott et al. 2011). **Table 1** lists the common cancers and their associated risk factors which can be avoided to prevent these malignancies.

Risk factor	Cancer
Tobacco	<ul style="list-style-type: none">• Bladder• Head and neck• Lung
Human papillomavirus	<ul style="list-style-type: none">• Cervical• Head and neck
Hepatitis	<ul style="list-style-type: none">• Hepatocellular
Weight/ Diet	<ul style="list-style-type: none">• Breast• Cervix• Colon• Esophagus• Gall-bladder• Kidney• Liver• Ovary• Pancreas• Prostate• Stomach• Uterus
Alcohol	<ul style="list-style-type: none">• Breast• Colorectal• Esophageal• Liver• Lung• Melanoma• Oral• Pharyngeal• Stomach

Table 1. Preventable cancers and their risk factors.

3.1 HPV

Of note, persistent HPV infections are now recognized as one of the causes of cancer. HPV is the cause of essentially all cervical cancers, as well as most cases of anal cancer. Genital HPV infection also causes some cancers of the vulva, vagina, and penis. In addition, oral HPV infection causes some cancers of the oropharynx and head and neck (Lowy and Munger 2010). HPV-induced cancers often have viral sequences integrated into the cellular DNA. Some of the HPV genes, such as E6 and E7, act as oncogenes that promote tumor growth and malignant transformation. E6/E7 proteins inactivate two tumor suppressor proteins, p53 (inactivated by E6) and retinoblastoma (RB) (inactivated by E7) (Dyson et al. 1989, Sherr and McCormick 2002, Storey et al. 1998, Werness, Levine and Howley 1990). As mentioned before, p53 is a tumor suppressor gene that arrests the cell cycle, prevents cell growth and stimulates apoptosis in the presence of DNA damage (Vogelstein et al. 2000). p53 also upregulates p21 which blocks the formation of the Cyclin D/Cdk4 complex, thereby preventing the phosphorylation of RB and, in turn, halting cell cycle progression by preventing the activation of E2F (Sherr and McCormick 2002). E6 has a close relationship

with E6-associated protein (E6-AP) which is involved in the ubiquitin ligase pathway. E6-AP binds ubiquitin to p53, thereby flagging it for proteosomal degradation (Werness et al. 1990). In contrast, E7 competes for RB binding, freeing the transcription factor E2F to transactivate its targets, thus pushing the cell cycle forward (Dyson et al. 1989). Most HPV infections are cleared rapidly by the immune system and do not progress to cancer. Since the process of transforming normal cells into cancerous ones is slow, cancer occurs in people with persistent HPV infection.

3.2 Alcohol

Alcohol, a carcinogen, also causes a plethora of cancers (Wang et al. 2011, Chang, Straif and Guha 2011, Land et al. 2011, Pelucchi et al. 2008, Thomas 1995). Increased alcohol consumption has been linked to breast, liver, stomach, colorectal, melanoma, lung, and other cancers. Alcohol is thought to stimulate tumor growth by fuelling the production of growth factors that stimulate angiogenesis (Pelucchi et al. 2011). In addition, alcohol suppresses immune activity. Thus, alcohol should only be consumed in moderation.

3.3 Smoking

Cigarette smoking leads to lung cancer since smoking exposes the individual to multiple DNA-damaging carcinogens and mutagens that result in mutations in critical genes that control cellular growth (Gonzalez et al. 2011, Hymowitz 2011, Lam and Minna 2011, Pesch et al. 2011, Proctor et al. 2011, Shields 2011). Moreover, smokers are exposed to multiple tumor promoting substances and inflammatory agents that exacerbate the process. Effective tobacco control led by clean air legislation, taxation, and anti-tobacco advertising is gradually contributing to decreased lung cancer incidence ((CDC) 2011, Bajoga et al. 2011, Ballbe et al. 2011, Kasza et al. 2011, King et al. 2011a, King et al. 2011b, Mage et al. 2011, Walsh et al. 2011). Thorough understanding of the biochemical, genetic and behavioral mechanisms of smoking can help us identify people who have a particularly high susceptibility to tobacco promoted cancers. These individuals can then be targeted for novel prevention measures, such as a nicotine vaccination and chemoprevention. Other simple individual steps that can help against developing cancer include vaccination (discussed in detail in a subsequent section) and screening for cervical cancer and hepatitis B, avoidance of excessive sun exposure for skin cancer, and limiting alcohol consumption for head and neck cancer and liver cancer (Pelucchi et al. 2008, Thomas 1995, Herrero et al. 2011, Chang et al. 2011, Pelucchi et al. 2011, No et al. 2011). Education and public outreach are immensely critical in this field. To this end, as research resources are allocated on cancer prevention, simultaneously there is a need to support scientific research to better understand the specific causes and mechanisms of cancers. Effort to identify susceptible individuals and target them for preventive interventions is necessary.

3.4 Diet

A number of studies have examined the impact of diet on cancer risk. Both the quantity and quality of food plays a role in cancer, with the former thought to be more critical. Some foods do contain anticancer compounds. Phytonutrients, often found in pungent and bitter vegetables, include resveratrol in grapes and curcumin in turmeric (Azari et al. 2009, Feeney 2004, Greenlee, Hershman and Jacobson 2009, Holst and Williamson 2008, Kale, Gawande and

Kotwal 2008, Kaur, Agarwal and Agarwal 2009, Lanzotti 2006, Mates et al. 2011, Mattoo et al. 2010, McGrath and Spigelman 2008, Neto 2007, Surh 2008, Wahlqvist and Lee 2007, Wenefrida et al. 2009). Other molecules, including sulforaphane and genistein, an isoflavone found in soybeans, are currently being tested as pharmaceutical agents in cancer prevention (Ali et al. 2005, Caetano et al. 2006, Takahashi et al. 2006, Shenouda et al. 2004). A healthy balanced diet with these nutrients can help prevent cancer. The barriers to the effectiveness of these phytonutrients lie in the genome and microbiomes. For instance, consumption of a known amount of the phytonutrient sulforaphane does not guarantee absorption of a predicted amount of anti-cancer molecule since differences in the glutathione S transferase M1 gene influences the metabolic rate of sulforaphane, a phytonutrient present in broccoli. The faster it is metabolized, the faster it is expelled from the body (Chung et al. 2000, Gasper et al. 2005, Gross-Steinmeyer et al. 2010, Joseph et al. 2004, Lampe 2007, Lampe 2009, McWalter et al. 2004, Riedl, Saxon and Diaz-Sanchez 2009, Ritz, Wan and Diaz-Sanchez 2007, Traka et al. 2008, Wan and Diaz-Sanchez 2007). Similarly, a number of the nutrients, e.g. isoflavones from soy, cannot be absorbed without the aid of microbes in the intestine (Di Cagno et al. 2010, Ding and Shah 2010, Rekha and Vijayalakshmi 2010, Szliszka et al. 2011, Szliszka and Krol 2011). Nonetheless, a healthy diet can reduce the chances of developing cancer.

Diet plays a vital role in the promotion of prostate cancer (Nelson, De Marzo and Isaacs 2003). Increased total fat intake, animal fat intake, and consumption of red meat have been associated with an increased risk of developing prostate cancer. In addition, the level of consumption of red meat correlates with the risk of prostate cancer (Giovannucci et al. 1993). Cooking meat at high temperatures or broiling on charcoal grills causes heterocyclic aromatic amine and polycyclic aromatic hydrocarbon carcinogens to form (Gross et al. 1993). Substantiating the claim, one such heterocyclic amine carcinogen, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, causes prostate cancer when fed to rats (Shirai et al. 1997). On the other hand, antioxidant carotenoid lycopene found in tomatoes, isothiocyanate sulforaphane found in cruciferous vegetables, as well as other micronutrients may protect against prostate cancer by reducing oxidative genomic damage (Chan and Giovannucci 2001, Cohen, Kristal and Stanford 2000). Other antioxidants, such as vitamin E, isothiocyanate sulforaphane and selenium, may also reduce the risk of prostate cancer (Nelson et al. 2003, Hoque et al. 2001, Cohen et al. 2000, Heinonen et al. 1998). Factors involved in inflammation and angiogenesis, such as NF κ B and vascular endothelial growth factor (VEGF) pathways, have been reported to be critical regulators in prostate carcinogenesis (Heymach et al. 2011).

The association between diet and breast cancer risk has been investigated extensively and has led to some recommendations for cancer prevention. Maintaining a healthy weight reduces the risk for breast cancer. Excess weight and weight gain in adult life are related to higher risk of postmenopausal breast cancer, and weight loss after menopause is associated with substantially reduced risk. Moderate levels of alcohol consumption increase the risk for breast cancer. Interestingly, this effect can be mitigated by adequate folate intake (Kim et al. 2011, Linos, Holmes and Willett 2007, Linos and Willett 2009, Linos and Willett 2007). Emerging research suggests that dietary intake of fiber and nuts during adolescence influences subsequent risk of breast disease and may suggest a viable means for breast cancer prevention (Lin et al. 2010, Su et al. 2010, Holmes et al. 2009). Since breast cancer is a heterogeneous disease and dietary factors may differentially affect certain breast cancer

subtypes future studies should therefore attempt to characterize associations according to tumor characteristics.

A significant association between body mass index and higher cancer-induced mortality has been reported (**Table 1**) (Lampe 2007, Teucher, Rohrmann and Kaaks 2009, Boniol and Autier 2010, Gotay 2010, Khan, Afaq and Mukhtar 2010, Land et al. 2011, Lanzotti 2006, Li et al. 2011a). Specifically, a correlation between being overweight (excess body fat) and cancers of the esophagus, colon, liver, gall-bladder, pancreas, kidney, breast, uterus, cervix, ovary, prostate and stomach has been observed. But researchers have yet to fully decipher the link between being overweight and cancer. The mechanism likely depends on the type of malignancy. For instance, abdominal fat pressing on the stomach causes acid to splash up into the esophagus leading to tissue damage, which can ultimately result in esophageal cancer (Etemadi et al. 2011, Hall and Crowe 2011, Kong et al. 2011, Lagergren 2011, Li et al. 2011b, Olsen et al. 2011, Rutegard et al. 2011, Ryan et al. 2011). Estrogen, produced by fat cells, appears to play a role in endometrial cancer and breast cancer in postmenopausal women since it fuels cellular growth of estrogen receptor positive cancers (Bradlow et al. 2011, Colonna, Douglas Case and Lawrence 2011, Creighton et al. 2011, Perks and Holly 2011, Rondini et al. 2011, Sikalidis and Varamini 2011, Subbaramaiah et al. 2011, Willyard 2011, Yang et al. 2010). Androgen promotes some forms of prostate cancer as well (Aggarwal, Ryan and Chan 2011, Capitanio et al. 2011, Hoda et al. 2010, Ribeiro et al. 2010). Similarly, obesity promotes production of excess insulin which can promote growth of cancer. Interestingly, blockade of these receptors using antibodies and small molecular inhibitors have been shown to stop cancer cell proliferation. For example, Tamoxifen, an antagonist of the estrogen receptor, is currently used for the treatment of both early and advanced estrogen receptor positive breast cancer (University 2011, Amir et al. 2011, Braems et al. 2011, Cuzick et al. 2011, Doughty 2011, Fleeman et al. 2011, Gandhi and Verma 2011, Garrido et al. 2011, Goetz et al. 2011, Kilic et al. 2011, Kiyotani et al. 2011, Lin, Zhang and Manson 2011, Obiorah and Jordan 2011, Teunissen et al. 2011). Furthermore, it has also been approved by the FDA as a chemo preventative agent in women adjudged to be at high-risk of developing breast cancer (University 2011, Amir et al. 2011, Cuzick et al. 2011, Goetz et al. 2011). Similarly, people on metformin treatment to control their insulin level appear to have a lower risk of developing breast and pancreatic cancer (Papanas, Maltezos and Mikhailidis 2010, Rozengurt, Sinnott-Smith and Kisfalvi 2010, Suh and Kim 2011, Vigneri et al. 2009).

Regular physical activity cuts down on the risk of cancer as well. One proposed theory is that active people tend to digest their food faster, decreasing the chance of absorption of any carcinogenic products that happen to be going through the colon to be in contact with the mucosal lining (Azcárate-Peril, Sikes and Bruno-Bárcena 2011). In the same way, improved lung function limits exposure to airborne carcinogens, decreasing the risk of cancer. Interestingly, physically active individuals had lower estrogen levels compared to sedentary women, reducing their chance of developing the disease (Eliassen et al. 2010, Kossman et al. 2011, Lynch, Neilson and Friedenreich 2010, Phipps et al. 2011, Suzuki et al. 2011, Winzer et al. 2011). Thus, it is clear that simple healthy lifestyle choices can help reduce the chances of developing cancer.

3.5 Prophylactic surgery

A more drastic measure to prevent cancer is prophylactic surgery. It involves removal of as much of the at-risk tissue as possible in order to reduce the chance of developing cancer.

Bilateral prophylactic mastectomy (removal of healthy breasts) and prophylactic salpingo-oophorectomy (removal of healthy fallopian tubes and ovaries) do not, however, offer a guarantee against developing cancer. Because not all at-risk tissue can be removed by these procedures, some women have developed breast cancer, ovarian cancer, or primary peritoneal carcinomatosis even after prophylactic surgery.

Additionally, there are instances where despite strict lifestyles, cancer unfortunately will still develop. In these situations where prevention has failed, the next effective strategy is early detection of disease, which can improve the chance of beating cancer. Regular screening for cancer increases the chance of catching the disease early, while it is still treatable. Screening does not, however, change the risk of developing cancer. For example, breast cancer can be screened by mammography and clinical breast exams. Studies are currently under way to test the effectiveness of other breast cancer screening methods, such as magnetic resonance imaging (MRI), in women with BRCA1 or BRCA2 mutations. For ovarian cancer, surveillance methods include transvaginal ultrasound, blood tests for CA-125 antigen, and clinical exams. Similarly, prostate cancer screening includes assaying prostate specific antigen (PSA) levels and digital rectal exam for lumps in the prostate. High PSA levels and lumps may be indicative of cancer but infection and inflammation may falsely elevate PSA levels as well. Routine colonoscopy to look for early signs of cancer is recommended at age 50 or earlier if there is a family history of colorectal cancer, a personal history of inflammatory bowel disease, or other risk factors. These strategies help in diagnosing cancer at its early stages.

The most effective steps to curb cancer are low-cost and low-tech. For example, giving up smoking and losing weight can drastically reduce the chances of developing cancer. Smoking has long been known to be a risk factor while obesity has more recently been recognized as one. Together they account for roughly half of all cancer cases (Ott et al. 2011, Brand et al. 2011, Land et al. 2011, Li et al. 2011a, Boniol and Autier 2010, Giovannucci et al. 2010, Gotay 2010, Khan et al. 2010, Teucher et al. 2009). Since these habits are easier said than done, policies that make unhealthy lifestyle choices difficult and expensive while making healthier ones easier and cheaper will be a step in the right direction. In addition, a number of clinical compounds have also been proposed to reduce the risk of carcinogenesis. These are discussed in detail below.

4. Chemo preventative strategies against cancer

A number of chemo preventative compounds have been proposed to reduce the risk of tumorigenesis (Table 2). A chemoprevention agent that blocks the very first step of tumorigenesis would be best. The next sections will discuss various pathways which can be targeted to potentially prevent cancer.

4.1 Inflammation

Dysregulation of cell proliferation and apoptosis evasion are major determinants of the evolution of neoplasia and tumor growth, the hallmarks of cancer (Hanahan and Weinberg 2000). As tumors move to a progressed state and possibly metastasis, it is generally accepted that there is further induction of genetic and genomic alterations which has been synonymous with an increase in DNA mutations and further loss of homeostasis primarily

Cancer	Drug	Notes	Reference
Breast	Tamoxifen	<ul style="list-style-type: none">• Selective estrogen receptor modulator	(Vogel et al. 2006)
	Raloxifene	<ul style="list-style-type: none">• Selective estrogen receptor modulator	(Vogel et al. 2006)
Cervical/vulvar/anal	HPV vaccine	<ul style="list-style-type: none">• Promotes immune response to prevent HPV infection	(Einstein et al. 2009, Heard 2011, Saslow et al. 2007, Wheeler et al. 2011)
Esophageal	Porfimer sodium and photodynamic therapy with omeprazole	<ul style="list-style-type: none">• Lodges in precancerous cells and upon exposure to light produces reactive species of oxygen• Kills surrounding cancer cells	(Overholt, Panjehpour and Haydek 1999, Overholt et al. 2007, Panjehpour and Overholt 2006)
Skin	Fluorouracil	<ul style="list-style-type: none">• Interferes with DNA synthesis• Results in cell death	(Madan, Lear and Szeimies 2010)
	5-aminolevulinic acid in combination with Porfimer sodium and photodynamic therapy	<ul style="list-style-type: none">• Lodges in precancerous cells and upon exposure to light produces reactive species of oxygen• Kills surrounding cancer cells	(Madan et al. 2010)
	Imiquimod	<ul style="list-style-type: none">• Enhances immune response• Promotes apoptosis	(Madan et al. 2010)
Prostate	Finasteride	<ul style="list-style-type: none">• An inhibitor of 5α-reductase• Inhibits the conversion of testosterone to dihydrotestosterone• Prevents or delays the appearance of prostate cancer• Possible benefit and a reduced risk of urinary problems must be weighed against sexual side effects and the increased risk of high-grade prostate cancer.	(Thompson et al. 2003)

Table 2. Chemo preventative drugs currently approved by the FDA.

via inflammation-based pathways (Colotta et al. 2009, Solinas et al. 2010, Klein and Glazer 2010). Inflammatory chemokines and cytokines such as *CCL2*, *CCL18*, and others have been implicated in such processes (Chen et al. 2011, Bonecchi, Locati and Mantovani 2011, Redon et al. 2010). It has been suggested that the tumor surrounding may contribute to tumor proliferation. Tumors have the ability to alter their stroma and support the development of both tumor cells and non-malignant cells (Polyak, Haviv and Campbell 2009). The tumor eventually escapes from the host immune system via activation of one or several molecular mechanisms that lead to inhibition of immune cell functions or to apoptosis of anti-tumor effector cells (Schreiber, Old and Smyth 2011). The ability to block tumor escape hinges on a better understanding of cellular and molecular pathways operating in the tumor microenvironment. Monitoring the change(s) in the tumor stroma such as those occurring in the mesenchymal stem cells within tumor stroma via molecular and cellular profiles as the tumor progresses allows for identification of cell or protein targets for cancer prevention and therapy (Karnoub et al. 2007). Increasingly, cancer treatments are being modified to include tumor surrounding as a therapeutic target, since the non-malignant cells are more genetically stable and less likely to evolve into drug resistant phenotypes. For example, aspirin inhibits COX-1, while Celebrex inhibits COX-2 (Chan, Ogino and Fuchs 2007, Harris et al. 2005, Cooper et al. 2010, Ghosh et al. 2010, Harris 2007, Koehne and Dubois 2004, Reddy 2007, Reddy and Rao 2005, Smith et al. 1998). COX-1 is produced in tissues throughout the body, and is known to mediate the production of prostaglandins, chemical messengers that control a number of physiological functions, such as lowering blood pressure, regulating body temperature and controlling inflammation (Kundu and Fulton 2002, Smith et al. 1998, Pereira, Medeiros and Dinis-Ribeiro 2009). COX-2, on the other hand, is strictly regulated and tends to spike during inflammation and other stress (Cesario, Rocca and Rutella 2011). Abundance of COX-2 has been linked to the growth and proliferation of cancerous and pre-cancerous cells (Cesario et al. 2011, Khan et al. 2011). Inhibiting the COX pathways can alter cancerous and precancerous cells by decreasing angiogenesis and cell growth (Banu et al. 2007, Half, Sun and Sinicrope 2007, Ishizaki et al. 2006, Sheng et al. 1997, Suh et al. 2009, Tuynman et al. 2008, Zhang et al. 2009). In addition, COX inhibition enhances apoptosis and enables the immune system to recognize and target the cells for destruction (Hida et al. 2000, Ding, Tong and Adrian 2000, Hsu et al. 2000, Souza et al. 2000). While COX-2 inhibitors are still a promising drug for chemoprevention, they have not been approved as a standard chemo preventative agent yet. This is, in part, due to increased risk of stroke, gastrointestinal bleeding, and heart attack following administration of these agents (Marnett 2009, Menter, Schilsky and DuBois 2010, Psaty and Furberg 2005). Nevertheless, a number of clinical trials evaluating the clinical efficacy of aspirin in decreasing the risk of colon, lung, prostate and brain cancer are currently in progress (Rothwell et al. 2011). Five year follow up data suggests that aspirin dramatically reduces the risk of death from solid tumors and gastrointestinal cancers. The latent period before an effect on deaths was about 5 years for esophageal, pancreatic, brain, and lung cancer, but was more delayed for stomach, colorectal, and prostate cancer. For lung and esophageal cancer, benefit was confined to adenocarcinomas. Benefit was unrelated to aspirin dose as long as the administered dose was 75 mg or upwards. Benefit was unrelated to sex or smoking, but increased with age (Rothwell et al. 2011).

Emerging research suggests that other systemic anti-inflammatory drugs may have anti-tumorigenic potential as well. For example, statins, which were initially developed for

cholesterol management, has been shown to disrupt the growth and proliferation of cancer cells such as prostate cancer (Kochuparambil et al. 2011). This has been verified in clinical trials as well where the use of statin drugs was linked with a reduced risk of advanced, especially metastatic or fatal, prostate cancer (Platz et al. 2006).

4.2 Estrogen signaling

Other small molecules, such as metformin and tamoxifen, demonstrate anti-tumor activity against breast cancer (Goodwin, Ligibel and Stambolic 2009, Jiralerspong et al. 2009, Osborne 1998). Raloxifene and tamoxifen have been shown to cut down the risk of estrogen-receptor positive breast cancers by as much as 50% (Vogel et al. 2006). Tamoxifen, a selective estrogen receptor modulator, has demonstrated benefit when used alone as well as in combination with chemotherapy to treat advanced breast cancer. It reduces circulating insulin-like growth factor-1, inhibits angiogenesis, and induces apoptosis (Li et al. 2009). It is also efficacious in reducing tumor recurrence and prolonging survival when administered as postoperative adjuvant therapy in stages I and II disease. In a randomized breast cancer prevention clinical trial to evaluate the worth of taking tamoxifen for the prevention of breast cancer in women considered to be at increased risk for the disease, tamoxifen prevented the appearance of a substantial number of breast cancers (Fisher et al. 1998). Tamoxifen administered daily for at least 5 years prevented invasive breast cancer in women at increased risk (Fisher et al. 1998). Women who took tamoxifen also had fewer diagnoses of noninvasive breast tumors, such as lobular carcinoma in situ. The study found that though tamoxifen reduced the occurrence of estrogen receptor-positive tumors, it had no effect on the occurrence of estrogen receptor-negative tumors (Fisher et al. 2005). Tamoxifen is available in the United States for the reduction of breast cancer incidence in high-risk premenopausal and postmenopausal women.

Raloxifene, another selective estrogen receptor modulator, has successfully been tested for the treatment and prevention of osteoporosis. Raloxifene hydrochloride is a selective estrogen receptor modulator that binds to estrogen receptors to competitively block estrogen-induced DNA transcription (Grese et al. 1997, Brzozowski et al. 1997). An evaluation of breast cancer incidence in women treated with raloxifene for the prevention of osteoporosis showed a 75% decrease in invasive breast cancer, and, as with tamoxifen, only the estrogen receptor positive disease is reduced (Martino et al. 2004, Cummings et al. 1999). These data emphasize the fact that these drugs target the estrogen receptor-mediated growth mechanism. These data validate the original hypothesis that a non-steroidal anti-estrogen in the same class as tamoxifen could be used not only to prevent osteoporosis but also to prevent breast cancer as a beneficial side effect.

4.3 Androgen signaling

Similar to other cancers, prostate cancer chemoprevention involves the use of natural and synthetic agents that inhibit or reverse the development of precancerous lesions or delay progression of these lesions to invasive disease. Since androgens are involved in the development of prostate cancer, they are an obvious chemotherapeutic target. Finasteride, an inhibitor of 5 α -reductase, inhibits the conversion of testosterone to dihydrotestosterone, the primary androgen in the prostate (Thompson et al. 2003). A phase III trial for prostate cancer prevention, the Prostate Cancer Prevention Trial using the drug finasteride,

suggested that this chemopreventive agent can reduce the risk of developing prostate cancer (Thompson et al. 2003). In this clinical trial, 18,882 men 55 years of age or older with a normal digital rectal examination and a prostate-specific antigen level of 3.0 ng per milliliter or lower were randomly assigned to treatment with Finasteride (5 mg per day) or placebo for seven years. The primary end point was the prevalence of prostate cancer during the seven years of the study and a 24% reduction in incidence of prostate cancer was observed in the treatment arm. However, the incidence of high-grade tumors was higher in men receiving finasteride compared to those on placebo (Thompson et al. 2003).

4.4 Vitamin D

Another molecule that has shown great chemopreventive potential is vitamin D. Vitamin D promotes the differentiation and apoptosis of cancer cells, slowing down their proliferation. It has been previously reported that Vitamin D has anti-proliferative effects in prostate cancer and mechanism of action involves nuclear exclusion of cyclin dependent kinase 2 (CDK2) and increase in p27 levels, an inhibitor of CDK2. This results in G1 cell cycle arrest of tumor cells (Yang and Burnstein 2003, Yang et al. 2002). Supplemental vitamin D intake or synthesis of vitamin D has the potential to reduce the incidence and death rates of colon, breast, prostate, and ovarian cancers (Manson, Mayne and Clinton 2011). A number of studies have established the association between vitamin D and its metabolites and cancer. It has long been observed that cancer rates were lower among people living in southern latitudes compared to similar groups in northern latitudes. Long-term studies have confirmed the efficacy of moderate intake of vitamin D in reducing cancer risk and, when administered with calcium, in reducing the incidence of fractures. Calcitriol, the hormonally active form of vitamin D, is being actively evaluated in clinical trials as an anti-cancer agent (Crescioli et al. 2004, Scher et al. 2011). Besides anti-proliferative, pro-apoptotic, and pro-differentiating actions on various malignant cells and decreasing tumor growth in vivo, calcitriol also exhibits several anti-inflammatory effects including suppression of prostaglandin action, inhibition of p38 stress kinase signaling, and the subsequent production of pro-inflammatory cytokines and inhibition of NF- κ B signaling (Krishnan et al. 2011). Calcitriol also decreases the expression of aromatase, the enzyme that catalyzes estrogen synthesis in breast cancer, both by a direct transcriptional repression and indirectly by reducing prostaglandins, which are major stimulators of aromatase transcription (Diaz et al. 2009, Swami et al. 2011, Zanatta et al. 2011, Krishnan et al. 2009). Other important effects include the suppression of tumor angiogenesis, invasion, and metastasis (Krishnan and Feldman 2010, Krishnan and Feldman 2009, So et al. 2010, Krishnan et al. 2010, Chung et al. 2009, Ma, Trump and Johnson 2010). These calcitriol actions provide a basis for its potential use in cancer therapy and chemoprevention.

As mentioned above, calcium supplementation has great anti-tumorigenic potential as well (Lappe et al. 2007). Multiple theories exist on the mechanism of anti-tumor activity of calcium. Calcium binds to bile acids and fatty acids in the gastrointestinal tract to form insoluble complexes known as calcium soaps. This reduces the ability of the acids to damage cells in the lining of the colon and stimulate cell proliferation to repair the damage (Newmark, Wargovich and Bruce 1984, Pence 1993, Suzuki and Mitsuoka 1992, Wargovich, Lynch and Levin 1991). Calcium may also act directly to reduce cell proliferation in the lining of the colon or cause proliferating colon cells to undergo differentiation, which, in turn, leads to a reduction in cell proliferation (Boyce and Ham 1983, Hennings et al. 1980).

Finally, calcium may also improve signaling within cells and cause tumor cells to differentiate and undergo cell death (Varani 2011, Roberts-Thomson, Curry and Monteith 2011, Fedirko et al. 2009, Peterlik, Grant and Cross 2009).

4.5 Retinoids

Retinoids such as all-trans retinoic acid and 9-cis retinoic acid are derivatives of vitamin A that play a pivotal role in a diverse group of biologic processes including cellular proliferation, differentiation, apoptosis, and development (Sporn and Roberts 1983). Retinoic acids have been studied intensively for their anticancer effects, which are exerted through a wide range of mechanisms. All-trans-retinoic acid-based differentiation therapy which slows proliferation and induces differentiation is utilized in acute promyelocytic leukemia (Reichman et al. 1997). Relapse of this subtype of leukemia is often associated with acquired resistance to retinoid maturation induction. In addition to leukemia, retinoids have been shown to be efficacious in the prevention of breast, cervical, neural, and hematological cancers (Casillas et al. 2003, Choi et al. 2000, Ding et al. 2002, Sanborn et al. 2000).

hTERT up-regulation has long been known as a key element in tumorigenesis, vital to the immortality of cancer cells. Treatment with the retinoid 9cUAB30, a synthetic analog of 9-cis-retinoic acid, leads to downregulation of hTERT expression, decrease in telomerase activity, and induction of apoptosis of leukemic cells (Love et al. 2008). The compound has also demonstrated beneficial effects against breast cancer (Hansen et al. 2007). These findings strongly support the use of 9cUAB30 as a chemo preventative agent. A first in human pharmacokinetic study with this compound was recently completed and further research is currently underway.

4.6 Potential chemo preventative agents

A number of other compounds have shown promise based on anti-cancer effects and low toxicity. With most solid-tumor cancers, the biggest threat is not the tumor itself but its ability to metastasize. Genistein, a soy isoflavone has been promising in preventing metastasis of prostate cancer by preventing the activation of the focal adhesion kinase and decreasing the levels of matrix metalloproteinase-2 (MMP-2) (Li et al. 2006, Huang et al. 2005, Kumi-Diaka et al. 2010, El Touny and Banerjee 2009, Xu et al. 2009).

Curcumin, a molecule derived from turmeric, has potential anti-cancer activity as well (Wilken et al. 2011). Curcumin inhibits proliferation and induces apoptosis in cancer cells via suppression of the AKT pathway (Wong et al. 2011, Sun et al. 2010, Duarte et al. 2010, Saini et al. 2011, Prakobwong et al. 2011, Zannotto-Filho et al. 2011, Sreekanth et al. 2011). Moreover, it decreases cell growth via inactivation of NF- κ B, preventing DNA binding, nuclear translocation, and p65 phosphorylation. Curcumin also suppresses activation of STAT-3 as indicated by decreased phosphorylation and inhibition of JAK1 phosphorylation (Rajasingh et al. 2006, Zhang et al. 2010, Saydmohammed, Joseph and Syed 2010, Bill et al. 2010). Moreover, curcumin induces expression of peroxisome proliferator activated receptor gamma and upregulates death receptors, DR4 and DR5. Curcumin also inhibits expression of cell survival proteins such as Bcl-2, Bcl-xl, XIAP, cFLIP, cIAP-1, cIAP-2, and survivin, and proteins linked to cell proliferation, such as cyclin D1 and c-Myc (Bava et al. 2010, Glienke et al. 2010, Prakobwong et al. 2011, Watson et al. 2009, Fossey et al. 2011). The growth

inhibitory effects of curcumin are enhanced in the IKK deficient cells, the enzyme required for NF- κ B activation (Prakobwong et al. 2011). Thus, curcumin mediates its anti-proliferative and apoptotic effects through activation of multiple cell signaling pathways, and thus its anti-tumor activity is under active research. Curcumin blocks a number of targets involved in tumor initiation, promotion, and progression, and is considered a promising chemopreventive agent. Thus, among others, a phase II trial of curcuminoids' effect on cellular proliferation, apoptosis and COX-2 expression in the colorectal mucosa of subjects with recently resected sporadic adenomatous polyps is currently ongoing. Further research is warranted to evaluate the efficacy of curcumin in other cancers.

5. Vaccines for cancer prevention

Cancer vaccines have been developed to boost the immune system to fend off cancer. These vaccines or biological response modifiers work by stimulating or restoring the immune system's ability to fight infections and disease. There are two broad types of cancer vaccines: preventive (or prophylactic) vaccines, which are intended to prevent cancer from developing in healthy people; and treatment (or therapeutic) vaccines, which are intended to treat an existing cancer by strengthening the body's natural defenses against the cancer. The FDA has approved two types of vaccines to prevent cancer: vaccines against the hepatitis B virus, which can cause liver cancer, and vaccines against human papillomavirus types 16 and 18, which are responsible for more than 50% of cervical cancer cases (Lehtinen et al. 2011, Wheeler et al. 2011, El-Serag 2011). Furthermore, researchers are developing treatment vaccines against many types of cancer and testing them in clinical trials.

Table 3 lists the current anti-cancer vaccines either in clinical trial or approved for clinical use. HPV types 16 and/or 18 also cause some vaginal, vulvar, anal, penile, and oropharyngeal cancers (D'Souza et al. 2007, Heard 2011, Wattleworth 2011). The FDA approved vaccines Gardasil and Cervarix protect against HPV 16 and 18 infections which cause cervical cancer (Roden and Wu 2006, Einstein et al. 2009, Saslow et al. 2007). Gardasil is approved for use in females to prevent cervical cancer and some vulvar and vaginal cancers caused by HPV types 16 and 18. It is also approved for use in males and females to prevent anal cancer and precancerous anal lesions caused by these HPV types. Cervarix is approved for use in females ages 10 to 25 to prevent cervical cancer caused by HPV types 16 and 18. All prophylactic vaccines work through the induction of virus-neutralizing antibodies and reduction of the number of cells that are infected after viral infection. This prevents the clinical disease associated with infection. Successful vaccines immunologically mimic the infections they prevent. This primes the adaptive immune system to recall specific effector functions on interaction with the infectious agent in the future. This restimulation process boosts immunity and induces protection against future viral infection. These vaccines are considered to be molecularly targeted because they generate immune responses against specific proteins; that is, the L1 HPV viral capsid protein (for Cervarix and Gardasil) and the hepatitis B surface antigen (for hepatitis B vaccine) (Frederick and Huh 2008, Herzog et al. 2008, Huh, Kendrick and Alvarez 2007, Huh and Roden 2008, Kendrick, Huh and Alvarez 2006, Kirby, Huh and Alvarez 2002, Myers et al. 2008). The HPV vaccines are manufactured from purified L1 structural proteins by recombinant technology. L1 viral capsid proteins are the same protein against which antibodies are made in the natural immune response to HPV. These proteins self-assemble spontaneously to form

Type	Cancer	Vaccine
Therapeutic	Kidney	<ul style="list-style-type: none">• Oncophage
	Prostate	<ul style="list-style-type: none">• Provenge• DC-Vax Prostate• Onyvax-P
	Melanoma	<ul style="list-style-type: none">• Oncophage• M-vax• Uvidem• M3TK• CYT004-MelQbG10• MAGE-A3 antigen-specific cancer immunotherapeutic
	Leukemia	<ul style="list-style-type: none">• GRNVAC1• GVAX leukemia
	Bladder	<ul style="list-style-type: none">• Bexidem
	Colorectal	<ul style="list-style-type: none">• Collidem• IMA901IMA910
	Breast	<ul style="list-style-type: none">• INGN 225• NeuVax• li-Key/HER2/neu cancer vaccine
	Lung	<ul style="list-style-type: none">• INGN 225• Lucanix• IDM-2101• Stimuvax• GV1001
	Brain	<ul style="list-style-type: none">• Oncophage• DC-Vax Brain• HSPPC-96 Oncophage• CDX-110
	Ovarian	<ul style="list-style-type: none">• CVac
	Pancreatic	<ul style="list-style-type: none">• GVAX pancreatic• GV1001
	Lymphoma	<ul style="list-style-type: none">• Biovax ID
	Renal	<ul style="list-style-type: none">• IMA901IMA910
	Liver	<ul style="list-style-type: none">• GV1001
Preventive	Cervical	<ul style="list-style-type: none">• HPV vaccine (Gardasil and Cervarix)
	Vaginal	<ul style="list-style-type: none">• HPV vaccine (Gardasil and Cervarix)
	Vulvar	<ul style="list-style-type: none">• HPV vaccine (Gardasil and Cervarix)
	Anal	<ul style="list-style-type: none">• HPV vaccine (Gardasil and Cervarix)
	Penile	<ul style="list-style-type: none">• HPV vaccine (Gardasil and Cervarix)
	Oropharyngeal	<ul style="list-style-type: none">• HPV vaccine (Gardasil and Cervarix)
	Liver	<ul style="list-style-type: none">• Hepatitis B
	Colorectal	<ul style="list-style-type: none">• MUC1 - poly-ICLC

Table 3. Preventive and therapeutic cancer vaccines either in clinical trial or approved for clinical use.

noninfectious virus-like particles that induce a protective host immune response. Because the virus-like particles contain the same epitopes as naturally occurring HPV, the immune system mounts a primary immune response to the vaccine, enabling a stronger and faster secondary immune response if naturally exposed to the same HPV types (Huh et al. 2007). The difference in the immune response generated by vaccination and natural infection is attributable to high immunogenicity of virus like particles inducing much higher concentrations of neutralizing antibodies to L1. In addition, higher antigen dose in the virus like particles and direct exposure of capsids to systemic immune responses are also observed. One of the challenges in vaccine formulation is balancing immunogenicity and toxicity. Addition of aluminum adjuvants to these vaccines helped to stimulate an immune response by acting as vehicles or immunomodulators. These vehicles transport antigen to lymphoid tissues or cause formation of an antigen depot at the site of injection. Immunomodulators help activate innate and adaptive immunity and increased immunogenicity of the vaccine (Huh et al. 2007, Huh and Roden 2008). The mechanisms by which these vaccines induce protection have not been fully defined but involve cellular immunity and neutralizing immunoglobulin G antibodies. HPV vaccines are designed for prophylactic use only; they do not clear existing HPV infection or treat HPV-related disease. Data from clinical trials utilizing these vaccines suggest that molecular targeting through immunization against infectious agents related to neoplasia is a successful way to prevent or treat early steps of host cell damage that can otherwise lead to cancer.

The FDA has also approved a cancer preventive vaccine that protects against HBV infection. Chronic HBV infection can lead to liver cancer. The original HBV vaccine was approved in 1981, making it the first cancer preventive vaccine to be successfully developed and marketed (Poland and Jacobson 2004). Today, most children in the United States are vaccinated against HBV shortly after birth.

6. Conclusion

With more and more people being diagnosed with cancer every day, undoubtedly, more effort needs to be vested in cancer prevention and therapy. Research organizations are starting to infuse a prevention ethos into their medical approach. Prevention messages are being added to the patient consultation process. A crosstalk between multiple disciplines such as psychology, molecular genetics, epidemiology, and medicine is needed for progressing cancer prevention and therapy.

7. References

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Cancer Prevention - From Mechanisms to Translational Benefits

Edited by Dr. Alexandros G. Georgakilas

ISBN 978-953-51-0547-3

Hard cover, 476 pages

Publisher InTech

Published online 20, April, 2012

Published in print edition April, 2012

This unique synthesis of chapters from top experts in their fields targets the unique and significant area of cancer prevention for different types of cancers. Perspective readers are invited to go through novel ideas and current developments in the field of molecular mechanisms for cancer prevention, epidemiological studies, antioxidant therapies and diets, as well as clinical aspects and new advances in prognosis and avoidance of cancer. The primary target audience for the book includes PhD students, researchers, biologists, medical doctors and professionals who are interested in mechanistic studies on cancer prevention and translational benefits for optimized cancer treatment.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Somaira Nowsheen, Alexandros G. Georgakilas and Eddy S. Yang (2012). Staying a Step Ahead of Cancer, Cancer Prevention - From Mechanisms to Translational Benefits, Dr. Alexandros G. Georgakilas (Ed.), ISBN: 978-953-51-0547-3, InTech, Available from: <http://www.intechopen.com/books/cancer-prevention-from-mechanisms-to-translational-benefits/staying-a-step-ahead-of-cancer>

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