The Role of Surgery in Cancer Prevention

For individuals at increased risk for certain cancers, surgery is a potential means of reducing that risk. Many of these individuals have a hereditary predisposition for specific cancers, and since the advent of genetic testing, surgery has been increasingly used as a cancer prevention tool. In this monograph, we discuss the management of individuals at increased risk for breast, gastric, thyroid, and colorectal cancers. We begin this monograph with a broad overview of cancer genetics and then discuss the role of surgery in cancer prevention among individuals with hereditary cancer syndromes. It should be emphasized that the overall impact of surgery in cancer prevention has not been fully elucidated, and surgeons should inform patients not only about the potential for benefit, but also the potential for harm.

Cancer Genetics

Cancer is essentially a genetic disease that results from a series of stochastic genetic changes. This acquisition of genetic aberrations by cancer cells confers a selective growth advantage, which is a prerequisite for assumption of a malignant phenotype.[1] The incidence of many common cancers increases with age with kinetics dependent on the fourth or fifth power of elapsed time. It has therefore been proposed that a minimum of 4 to 7 mutations in critical genes must occur for transformation of a normal cell into its malignant counterpart (Fig 1).[2] This multistage process of genetic alteration, which forms the basis of malignant transformation, can result from either inherited (germ line) or acquired (somatic) mutations in cellular genes.[3] Germ line mutations are present within all cells, whereas somatic mutations affect individual cells within a particular tissue.

Hereditary cancers are attributable to inherited or germ line mutations and have yielded important information on key genes involved in tumor formation. Studies of affected patients and their families have provided a unique understanding of genes mutated in the context of hereditary

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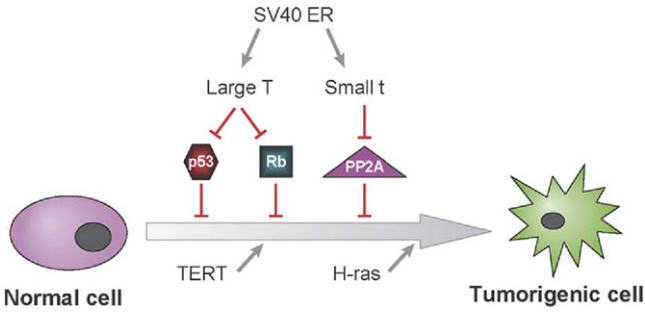

FIG 1. At least 4 events are required to convert a normal human cell into a cancer cell in vitro. Introduction of clones specifying the SV40 large T antigen and small t antigens functionally disrupts the Rb and p53 protein pathways (events 1 and 2), while hTERT prevents telomere shortening (event 3). Finally, oncogenic H-ras results in malignant transformation (event 4). (Reprinted with permission from Stewart and Weinberg.[2]) (Color version of figure is available online.)

predisposition and provided insight into the genetic initiation process. These self-same genes are often also involved in the pathogenesis of the sporadic forms of cancer, which are dependent on 2 separate rather than a single somatic mutation. Thus, according to Knudson's "two-hit" hypothesis, individuals with an inherited predisposition already possess a mutation in 1 allele and thus require only 1 further somatic mutation for tumor formation (Fig 2).[4,5] Most human cancers are a consequence of somatic mutations, with only 1% being due to preexistent germ line mutations. Acquisition of such mutations can result from a background error rate in DNA synthesis, or the baseline rate of spontaneous mutation can be augmented by environmental factors interacting with cellular DNA either directly or indirectly. Exogenous exposure to DNA-damaging agents can arise from either radiation or genotoxic chemicals, whereas endogenous sources of genomic insult can be inflicted from processes such as oxidative stress due to an excess of cellular free radicals. The chances of 2 somatic mutations occurring within the same cell are correspondingly smaller than for a single event for any equivalent mutation rate. Nonetheless, once acquired, these somatic mutations can be passed on to progeny cells during the replicative process.

Heterogeneity of Cancer

One of the most challenging features of cancer is tumor heterogeneity, with much variation not only between individuals with respect to a designated tumor type, but also among cells of any single tumor. Furthermore, this cellular heterogeneity is expressed at both the genomic

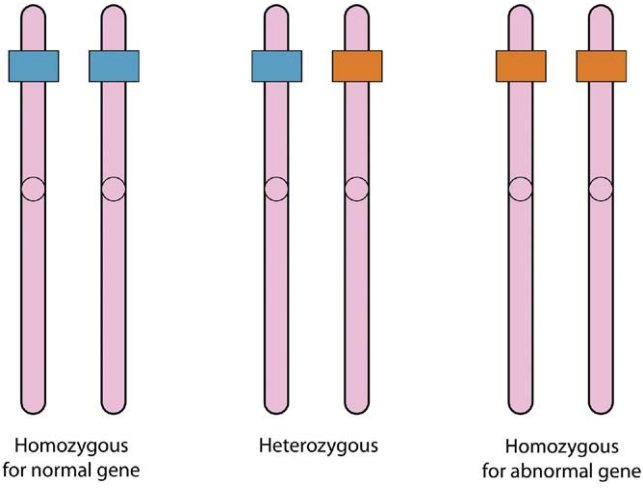

FIG 2. According to Knudson's "two-hit" hypothesis, mutations in both alleles of a normal gene pair (shown in blue) are a prerequisite for cancer development (shown in orange). Individuals with an inherited predisposition already possess a mutation in 1 allele (heterozygous) and only 1 further mutation is necessary for tumor formation. (Color version of figure is available online.)

and the phenotypic levels, despite the assumption that most cancers have been derived from a single normal cell. This latter cell is considered to have acquired a state of "immortalization," whereby a limited number of mutations lead to a growth advantage relative to neighboring cells. These preliminary changes are a precursor to frank malignant transformation, which is conditional on further transforming mutations. Comprehensive expression of the malignant phenotype mandates further genetic changes specific to processes of angiogenesis, invasion, and metastasis. Thus, the sequential acquisition of DNA mutations allows cells to display features that include the following: 1) independence from stimulatory growth signals, 2) insensitivity to growth inhibitory signals, 3) ability to evade apoptosis, 4) unlimited replicative potential, 5) ability to promote or sustain angiogenesis, and 6) invasive and metastatic capabilities. These characteristics collectively result in the invasive phenotype that is manifest clinically at a local and subsequently systemic level with widespread metastases at distant sites such as lung, bone, liver, and brain.

The last few decades have witnessed the ongoing elucidation of the genetic aberrations and disruption of pathways of communication that characterize cancer. Concepts of carcinogenesis have been dominated by the paradigm of oncogenes and more recently tumor suppressor genes.[6] Mutations within these 2 operational classes of genes accumulate either

randomly or sequentially and are the underlying cause for cellular transformation. In the context of oncogenes, activating mutations often result in a positive or "gain-of-function" change, which leads to an alteration in protein products encoded, such as polypeptide growth factors and their receptors, key components of signal transduction, and nuclear regulators of the cell cycle. By contrast, tumor suppressor genes are associated with mutations that lead to "loss-of-function" through inactivation or deletion of natural elements of the cellular genome. This class of genes encode for products that exert a negative influence on cellular proliferation but promote pathways involved in DNA repair mechanisms and apoptosis, leading to programmed cell death.

Increasingly, it is appreciated that cancer cells have inherent genetic instability, which encourages further accumulation of mutations. Although the predisposing mechanisms remain unclear, mutations in genes involved in repair of damaged DNA and maintenance of genomic integrity likely play a vital role in generation of genetic instability.[7] A more recent theory proposes that carcinogenesis is predicated on cancer stem cells, which represent the "cell of origin" of most common tumors.[8] Cancer cells resemble normal cells of their parent tissue and remain functionally part of a regulatory network, which allows variable levels of intercellular communication. The cancer stem cell hypothesis envisages cancer as an "aberrancy in normal self" and therapies are aimed at reasserting normal regulation of cellular growth patterns. Cancer is a consequence of perturbations in the complex network of intercellular communication.[9] Understanding the essence of disruption in this molecular circuitry has permitted the rational development of targeted therapies, which has now translated into effective treatments with improvements in disease-free and overall survival for several cancer types.

Origin of Cancer Cells

It has long been acknowledged that tumors in vivo are 3-dimensional structures consisting of a heterogenous group of cells that represent a caricature of normal tissue. A tumor is composed of several cells types in addition to neoplastic epithelium. These include various mesenchymal derivatives such as fibroblasts and endothelial cells, which have important interactions with epithelial cells in both topographic and functional contexts. The epithelial component of a tumor is not merely a rapidly proliferating homogenous clone. For most cancers, the target cell for initial malignant transformation is unknown. Currently, there are 2 models for the origin of cancer cells: "clonal evolution" and "cancer stem cell" theories. These 2 theories can both account for the cellular

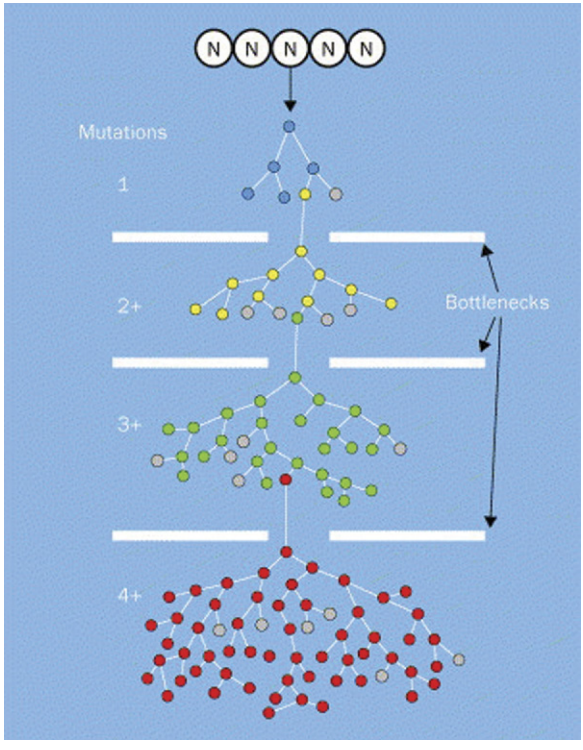

FIG 3. Clonal evolution of a cancer. Sequential mutations result in successive descendent clones possessing a selective growth advantage, which enables them to overcome "bottlenecks" imposed by restrictions of space, nutrients, and oxygen. First subclone is shown in yellow; second in green and third in red. Gray represents dying cells. N = normal stem cells. (Reprinted with permission from Greaves.[10] (Color version of figure is available online.)

heterogeneity of cancer and are not mutually exclusive; elements of each theory are probably a variable approximation to the truth.

Monoclonal Theory

Traditionally, a cancer is presumed to be monoclonal in origin and to arise from a process of "clonal evolution." According to this theory, a single cell undergoes malignant transformation and forms a primary clone from which further subclones are derived and culminate in a multiclonal, heterogenous tumor. There is progressive and divergent accumulation of genetic and epigenetic mutations that provides a selective growth advantage for mutated cells and permits them to bridge "bottlenecks" imposed by restrictions of space, nutrients, and oxygen (Fig 3).[10] Acquisition of

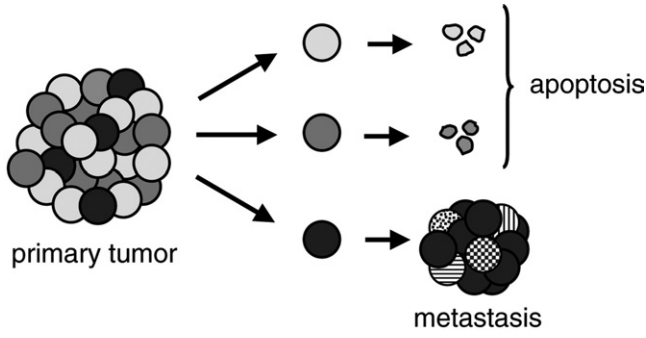

FIG 4. The mature tumor contains cells of monoclonal origin but forming a heterogeneous mixture of independent clones. These display phenotypic and genetic diversity and only a fraction of these will have the potential to migrate and form distant metastases (dark gray cells). Further mutations within this subclone will occur, yielding metastases containing cells with diverse properties (striped and variously patterned cells). (Reprinted with permission from Dalerba P, Cho RW, Clarke MF. Cancer stem cells: models and concepts. Annu Rev Med 2007;58:267-84.)

mutations provides a positive selection pressure but also generates a degree of instability within the genome, which leads to further mutations and ultimately phenotypic and genetic diversity (Fig 4).

A new paradigm has been introduced for the origin and development of cancer with the emergence of the cancer stem cell hypothesis. Stem cells are multi-potent and possess the ability to differentiate into multiple lineages and can proliferate indefinitely. In particular, stem cells have greater longevity than normal cells and exist long enough within tissues to accumulate the requisite number of mutations for malignant transformation. Stem cells have the capacity for self-renewal and undergo asymmetrical divisions to give rise to a pool of identical progenitor cells/transit amplifying cells that differentiate into cellular type appropriate for the tissue location. Stem cells reside in their stem cell niches and represent a continuous source of cellular regeneration and differentiation within the tissues of various organs.[11] A finite population of cells known as the cancer stem cells has been identified in several cancer types including those of the breast and nervous system. Normal stem cells are hypothesized to be the target for carcinogenesis and not mature somatic cells (Fig 5).[8] Tumors arise from differentiation of rapidly proliferating, undifferentiated stem cells and contain varying proportions of undifferentiated and differentiated malignant stem cells. Both cell types are essential for the continued propagation and expansion of a tumor. According to this hypothesis, a cell can possess the typical features of a malignant phenotype yet still have gone through a sequential process of

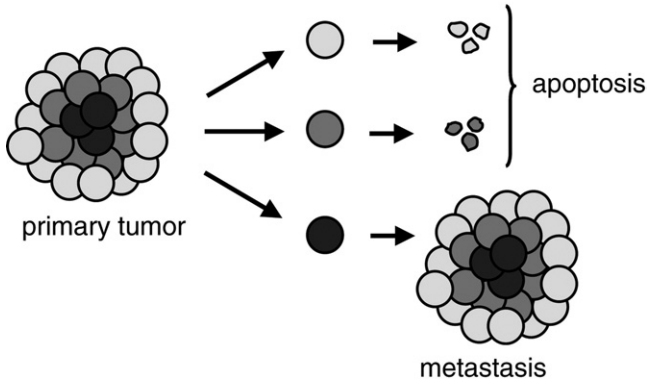

FIG 5. According to the cancer stem cell hypothesis, intratumoral heterogeneity arises from cell differentiation and only cancer stem cells (dark gray cells) have the capacity to migrate and form distant metastases with differentiated cancer cells undergoing apoptosis. The proportion of differentiated/apoptotic malignant stem cells (light gray cells) relative to those that continue to proliferate determines tumor grade. (Reprinted with permission from Dalerba P, Cho RW, Clarke MF. Cancer stem cells: models and concepts. Annu Rev Med 2007;58:267-84.)

differentiation to a comparable point as the normal cell lineage.[11] Alternatively, a more differentiated progeny may revert back to stem cell status because of mutations causing reactivation of primordial genetic programs within a stem cell. There are several observations that support the cancer stem cell hypothesis. First, carcinogenesis is a multi-stage process and tissue stem cells have a prolonged lifespan that allows for the accumulation of serial mutations that would be less probable in a differentiated cell. Second, the capacity of cancer stem cells to self-renew may reflect their being a mutant version of normal stem cells. Finally, cancer stem cells have the same immunophenotype antigen profile as their normal cellular counterparts.

The concept of cancer stem cells has been well-established in teratocarcinomas and hematological malignancies,[12,13] although the possibility that these cells might be derived from more committed progenitor cells with acquired capability of self-renewal cannot be excluded. It should be noted that the term "cancer stem cell" is used to functionally define a subset of cells that initiate carcinogenesis and can "differentiate" into a heterogenous progeny that regenerates the cancer. Furthermore, the precise relationship between normal stem cells and their malignant counterparts (ie, cancer stem cells) remains unclear. Nevertheless, there is proof of concept that cancer stem cells provide a hierarchical lineage for the origin and development of cancer.[8]

According to this concept, cancer can be viewed as an "aberrant organ"

that has "differentiated" from cancer stem cells. A small population of relatively quiescent and slowly dividing cancer stem cells are responsible for continued expansion of a tumor by generation of more "differentiated" cancer cells with short-term proliferative capacity that constitutes much of the tumor bulk (epithelial component). Cancer stem cells develop when normal stem cells become "activated" following acquisition of transforming mutations. Within tumorous tissue, differentiation is not completely abrogated, with cancer cells retaining morphologic and immunophenotypic features of the original tissue type. Cancer stem cells undergo cellular differentiation to a variable degree, which determines histologic grade and other phenotypic features while contributing to tumor heterogeneity.

Types of Mutational Change

In recent years there has been major progress in elucidating the genetic alterations that lead to disruption and dislocation of molecular and biochemical pathways. Although no single genetic change has been identified that causes cancer, it is now appreciated that cancer cells display a finite number of aberrant pathways and the defective portion of the DNA is relatively small in proportion to overall genome size. Exogenous agents such as chemicals and irradiation induce direct DNA damage, but a background mutation rate occurs from the hydrolytic interaction of water itself with DNA. This results in the cleavage of glycosidic bonds that can depurinate or depyrimidate nucleotide bases or cause strand breaks. Genetic alterations associated with malignant change can be broadly divided into the following 5 categories:

1. Nucleotide sequence changes because of nucleotide substitutions, deletions, or insertions of few nucleotides (eg, missense mutations in the K-ras gene are present in up to 90% of pancreatic adenocarcinomas).
2. Chromosome number changes due to losses or gains in whole chromosomes resulting in aneuploidy.
3. Chromosomal translocations can occur due to fusions of different chromosomes or segments of a single chromosome that are noncontiguous. This interchange of chromosomal material can result in an oncogene being positioned next to transcription regulatory sequences, leading to overexpression. Alternatively, a fusion gene may be formed with a resultant tumorigenic gene product. One classic example of this is the formation of Philadelphia chromosome in chronic myelogenous leukemias. This results in fusion of the carboxy terminus of c-able

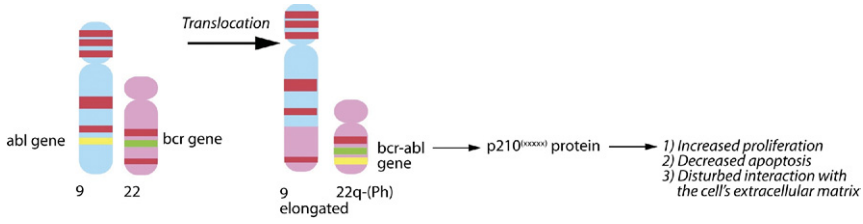

FIG 6. CML is characterized by a reciprocal translocation (t[9;22] [q34;q11]), which generates a small 22q chromosome referred to as the Philadelphia chromosome. This translocation results in the oncogene c-abl being transferred from chromosome 9 (band 9q34) to the *bcr* gene (band 22q11). Breakpoints can occur over variable distances on each chromosome to form the Philadelphia chromosome. This yields a fusion *bcr-abl* gene product, which is thought to lead to constitutive activation of a mitogenic growth factor receptor. (Color version of figure is available online.)

gene on chromosome 9 and the amino terminus of the BCR gene on chromosome 22 (Fig 6).[14]

4. Gene amplifications occur as a result of multiple copies of an "amplicon" containing 0.5-10 megabases of DNA. This represents a phenomenon that occurs late in the pathogenesis of cancer. If such an "amplicon" encodes an oncoprotein, the result will be oncoprotein overexpression that promotes tumorigenesis. This is a mechanism through which cancer cells overexpress a large number of oncogenes. Overexpression of these oncogenes leads to the aggressive phenotype of some of these cancers. For instance, amplification of the N-myc gene is commonly found in neuroblastomas (Fig 7).[15]
5. Epigenetic changes such as gene silencing by DNA methylation (eg, breast cancer susceptibility gene 1 [BRCA1 gene] is inactivated in sporadic breast cancers by promoter methylation).[16]

Genetic Instability

Accumulation of genetic mutations is the underlying mechanism for carcinogenesis and the process of clonal selection amplifies the rate of spontaneous mutation. Current evidence suggests that genetic instability is an inherent property of many cancers and further enhances the frequency of mutational events. Genetic instability therefore provides the opportunity for multiple spontaneous mutational events, which can eventually affect oncogenes and tumor suppressor genes with induction of tumor formation. Genetic instability can occur at 2 levels: nucleotide and chromosomal. Instability occurring at the nucleotide level can result from substitution, deletion, or insertions of several nucleotides. At the chro-

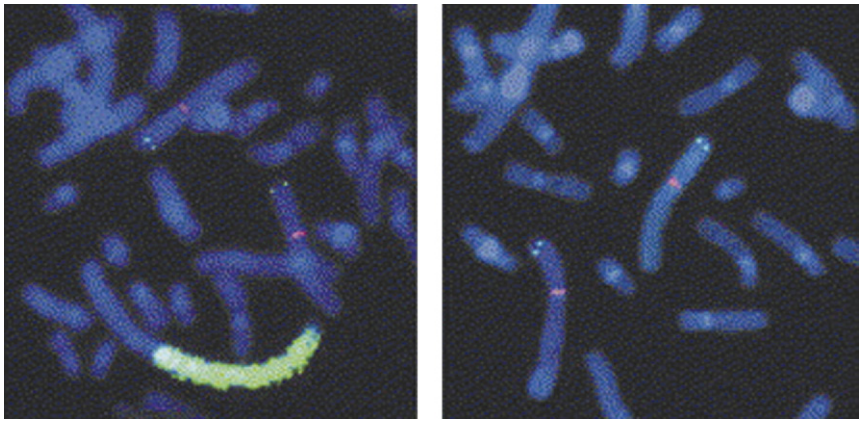

FIG 7. Amplification is a principal mechanism for activation of oncogenes. Cytogenetic analysis reveals homogeneous staining of a chromosomal region in neuroblastoma indicates 150-fold amplification of the N-myc gene (right panel) compared with a normal cell (left panel). (Reprinted with permission from Schwab M, Westermann F, Hero B, Berthold F. Neuroblastoma: biology and molecular and chromosomal pathology. Lancet Oncol 2003;4:472-80.) (Color version of figure is available online.)

mosomal level, instability occurs due to losses or gains in whole or large segments of chromosomes.

Chromosomal Instability

Chromosomal instability is characterized by gains or losses of chromosomal segments and occurs commonly in cancer cells. Karyotypic analyses indicate that most epithelial cancers display aneuploidy, which is attributable to inappropriate chromosomal segregation during mitosis.[17] The frequency of this phenomenon in human cancers implies that mutations in many genes can lead to genetic instability, which is at least 10-fold higher in aneuploid compared with diploid tumors. Mutations in more than 100 genes are predicted to cause chromosomal instability; aberrant genes that potentially can lead to chromosomal instability include those involved in chromosome condensation, sister chromatid cohesion, kinetochore assembly, and centrosome duplication. Mutations leading to specific checkpoint defects including spindle checkpoint disruption and aberrant DNA-damage checkpoints will promote chromosomal instability.[18] "Spindle checkpoint" genes that ensure error-free segregation of chromosomes on the mitotic spindle are frequently disrupted in these circumstances[19] with mutations in human spindle checkpoint genes commonly detected in human cancers. The main genes

involved in spindle checkpoint response include DH1, DH2, DH3/BUBR1, BUB1, BUB3, MPS1, and CDC20. The human BUB1 gene has been found to be mutated in colorectal cancer, which has a phenotype characterized by massive chromosomal instability. Mutations in BUB1 can act in a dominant-negative manner by causing aberrant spindle checkpoint in both mouse and human cells when expressed exogenously. Furthermore, DH2 gene expression appears to be repressed in several solid epithelial tumors, including breast cancers. The DNA-damage checkpoint prevents cells with DNA damage from entering mitosis. Such DNA damage can result from endogenous causes such as dysfunctional polymerases during normal DNA replication, genotoxins (eg, reactive oxygen species), or incomplete DNA repair. Alternatively, exogenous DNA damage may be induced by chemical carcinogens or ionizing radiation. If a cell enters the mitotic cycle in possession of damaged DNA before replication, inappropriate chromosomal segregation and mitotic recombination can result. DNA-damage checkpoint genes that are known to be involved in human cancers include ATM, ATR, BRCA1, breast cancer susceptibility gene 2 (BRCA2), and p53.[20]

A further mechanism for chromosomal instability is abnormal number and function of centrosomes.[21] In a normal cell, centrosomes nucleate the ends of the microtubule spindle along which sister chromosomes separate during mitosis. In cancer cells, additional copies of centrosomes encourage formation of multipolar spindles, which disrupt chromosome segregation.

Aneuploidy within cancers can result from telomere dysfunction and this is a final mechanism for chromosomal instability.[22] Telomeres are ribonuclear protein complexes located at the end of all functional eukaryotic chromosomes. Telomeres contain a high proportion of hexanucleotide repeat sequences TTAGGG spanning 4-15 kilo base pairs in length and are capped by associated proteins. Dysfunctional telomeres at chromosomal termini promote end-to-end fusions and fusion-bridge-breakage cycles, resulting in gross structural chromosomal abnormalities. When inappropriate chromosomal segregation occurs in normal cells during mitosis, functional p53 protein will cause such cells to arrest in the G1 phase of the cell cycle. By contrast, if the p53 product is defective, cell cycling may progress with entry of cells into S-phase. This will eventually lead to aneuploidy in the daughter cells. The presence of unbalanced translocations leads to induction of apoptosis when p53 is functional, but an ineffective protein product will permit propagation of these chromosomal abnormalities and formation of tumors with unbalanced translocations.

Chromosome Translocations. There are 2 main types of chromosome translocations in human cancers: complex and simple patterns.

Complex translocations are common in human cancers and appear to be a stochastic event with no fixed pattern to their occurrence, even within tumors of the same histopathological subtype. The molecular basis for these complex translocations is unknown, but may be a consequence of cells entering mitosis before double-strand breaks are repaired. This will favor random union of free DNA ends through nonhomologous recombinations.

Simple translocations appear to be a nonstochastic event characterized by distinctive patterns of breakpoints and chromosomal rearrangements in specific cancers (namely leukemias, lymphomas, and sarcomas). These simple types of translocation are less likely to be due to any underlying genetic instability but instead may reflect low frequency aberrations in normal physiological recombination events. This is most evident for lymphoid malignancies where DNA strand breaks are generated in lymphoid cells as part of the normal recombination process. This generates the great diversity in immunoglobulin and T-cell receptor genes. It is possible that translocation patterns of lymphoid malignancies could be a reflection of the low-frequency aberrations in the physiological recombination process. Whatever the mechanism, such translocations result in fusion of 2 disparate coding regions and tend to place an oncogene under the influence of a strong promoter.

Nucleotide Excision Repair

Instability at the nucleotide level is uncommon in cancer and is usually attributable to defects in the 2 main cellular DNA repair systems: nucleotide-excision repair and mismatch repair. Nucleotide-excision repair is a versatile DNA repair mechanism that detects and repairs bulky DNA lesions induced by exogenous mutagens, in particular, ultraviolet-induced DNA lesions such as cyclobutane pyrimidine dimers and pyrimidine 6-4 pyrimidone photoproducts.[23] The importance of nucleotide-excision repair was first recognized in the study of xeroderma pigmentosum, an autosomal-recessive disease characterized by severe ultraviolet photosensitivity and predisposition to skin tumors.[24]

DNA Mismatch Repair

The DNA mismatch repair system is responsible for correction of DNA replication errors, especially elimination of base-base mismatches and abnormal nucleotide loops resulting from insertions/deletions of DNA

TABLE 1. Examples of genes containing microsatellite sequences, and neoplasms in which the gene has been demonstrated to contain mutations within its microsatellite sequence

Gene	Microsatellite sequence	Neoplasms
TGF-β1 Type II receptor	AAAAAAAA	Gastrointestinal (HNPCC, colorectal, gastric and ampullary adenocarcinoma and Barrett's esophagus), glioma, endometrial
IGFIIR	GGGGGGGG	Gastrointestinal (HNPCC and Barrett's esophagus)
BAX	GGGGGGGG	Gastrointestinal (HNPCC and colorectal)

HPNCC, hereditary nonpolyposis colon cancer.

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and incorporated during defective DNA replication. Base-base mismatches typically affect nonrepetitive DNA sequences, whereas insertion/deletion loops occur at sites of repetitive DNA sequences leading to gains or losses of short mono- or dinucleotide repeat units [eg, poly(A) or poly(CA) repeats] within microsatellite regions. Microsatellite repeat sequences are characterized by identical nucleotide repeats and reside in many coding regions of genes. A hallmark of defective DNA mismatch repair genes are alterations within microsatellite regions, a phenomenon known as "microsatellite instability (MSI)." Mutations within these microsatellite sequences have been demonstrated in many cancers (Table 1) and have been identified in most tumors arising in patients with hereditary nonpolyposis colon cancer, (HNPCC) or Lynch syndrome, which is a disease caused by mutations in genes required for DNA mismatch repair.[25,26] The identity of these mismatch genes was first investigated in bacteria in which defects in mismatch-repair genes *mut S* or *mut L* result in MSI. Similar defects were discovered in yeast homologues of either *mut S* or *mut L* and subsequently a human homologue of *mut S*, named MSH2, has been located on chromosome 2 and is inactivated in kindreds of HNPCC patients with colon cancer. Furthermore, the human homologue of *mut L* named MLH1 has been traced to chromosome 3 of HNPCC kindreds. It is now known that most HNPCC cases (>95%) arise from mutations in these MLH1 and MSH2 genes.[27] A correspondingly lower proportion (15%) of sporadic colorectal cancers exhibit MSI and this often results from a nonmutational event such as epigenetic inactivation of MLH1 gene.[26] Currently, at least 7 human homologues of *mut S* (ie, MSH2, MSH3, MSH6) and *mut L* (MLH1, MLH3, PMS1, PMS2) have been identified.

Cancer Cell Cycle Checkpoints

Cell cycle checkpoints refer to specific processes through which the cell actively monitors the integrity and replication status of DNA. Progression through the cell cycle can be halted until the fidelity of DNA replication and repair is confirmed. DNA damage from both endogenous or exogenous sources is a major contributor to the development of human cancers. These checkpoints exert a restraining influence on cell cycling and represent an important strategy developed to ensure that repair of damaged DNA is not compromised by time limitation. These control mechanisms minimize propagation of heritable mutations and reduce the risk of cancer development.

The stimulus of DNA damage initiates a sequence of events that eventually halts cell cycle progression. Activation of the genes for ATM (ataxia telangiectasia mutated) and ATR (ATM- and Rad3-related) kinases is the key initial step.[20] ATM kinase is primarily activated in the context of double-stranded DNA breaks, whereas ATR kinase is critical in the response to arrest of DNA replication forks—the DNA structures formed during cellular replication. ATM and ATR are protein kinases with high molecular weight (over 300 kDa, respectively) that mediate their function by phosphorylating downstream substrates. In the presence of double-strand breaks, ATM becomes activated through dissociation from a homodimeric to monomeric form. This is associated with autophosphorylation, which triggers a rapid conformational change. Activated ATM orchestrates the function of a series of proteins involved in DNA repair, cell cycle arrest, and apoptosis. The phosphorylation targets for this kinase include p53, NBS1 (Nijmegen Breakage Syndrome), BRCA1, SMC1, and CHK2. By contrast, ATR is a constitutively active kinase whose function is regulated by subcellular localization. Thus, when ATR is situated close to an abnormal stretch of single-stranded DNA such as occurs at sites of replication fork arrest, it will phosphorylate critical substrates, which include RAD17 and CHK1. The proximal checkpoint kinases ATM and ATR are themselves controlled by the effector kinases CHK2 and CHK1, respectively.

G1/S Checkpoint

The G1/S checkpoint is the dominant pathway through which DNA strand breaks influence cell cycle progression. The molecular basis for this gatekeeper function has recently been clarified from studies on individuals with inherited cancer predisposition syndromes. The kinases ATM and ATR can directly activate the tumor suppressor gene p53 by

phosphorylation or indirectly modulate activity levels via phosphorylation of CHK2/CHK1. The p53 protein product is of paramount importance in DNA repair mechanisms throughout all cells and defective p53 function occurs in approximately one half of all human cancers. Levels of this nuclear phosphoprotein increase rapidly within cells in response to damage from ultraviolet light or cytotoxic drugs due to stabilization of the protein, which can act in a dominant-negative manner. It is indeed deserving of the title "guardian of the genome" and appears to have a universal and overarching role in maintenance of genomic integrity. Activation of p53 through any of the aforementioned pathways increases expression of p53 regulated genes, which have critical caretaker and gatekeeper functions. One consequence of p53 activation is transcriptional activation of p21C1P1/WAF1, which inhibits another important cyclin-dependent kinase cyclin E/CDK2. The latter mediates arrest of cell growth in mink lung epithelial cells in response to negative growth factors. When cells are thus arrested in G1, DNA synthesis cannot be initiated. The p21 protein acts in a similar manner to p16 and inhibits Rb kinase. This maintains the Rb protein in an inactive, unphosphorylated state, which prevents E2F activation (blockade of cells in G1). In addition to repair of damaged cellular DNA, p53 can induce apoptosis in the presence of a severe genetic insult. Thus, mutations of p53 create a state of "double jeopardy" by allowing cells to continue replication with persistent strand breaks and failure of cell death in response to widespread irreparable DNA damage.

G2/M Checkpoint

Cells will usually arrest in G2 in the presence of DNA damage. A specific checkpoint prevents the onset of mitosis and cells with mutant p53 can enter mitosis in the presence of DNA strand breaks and other forms of chromosomal abnormalities. This p53 dependent G2 arrest is mediated through upregulation of the CDK inhibitor p21, GADD45a (growth arrest and DNA-damage inducible 45alpha), and 14-3-3 sigma proteins. The latter is an inhibitor of the cyclin B/cyclin-dependent protein kinase 2 complex required for initiation of mitosis. Perhaps the dominant pathway for halting all cell cycle progression does not directly involve p53; ATM and ATR can inhibit the cyclin B/cyclin-dependent kinase 1 through modulation of CDC25 phosphatases, which normally activate CDK1 at the G2/M boundary. Drugs that selectively disrupt the G2/M checkpoint can potentially render cancer cells more susceptible to the genotoxic effects of chemotherapy and radiotherapy. This strategy

would be especially pertinent to cancer cells containing abnormal p53, which will also have defective control of the G1/S checkpoint.

Oncogenes

From a historical perspective, the revolution in understanding carcinogenesis at the molecular level originated from work on RNA tumor viruses, which can rapidly induce tumors after inoculation into animal cells.[28,29] These viruses contain reverse transcriptase and can synthesize DNA with a complementary base pair sequence to viral RNA. This DNA can then be incorporated into host DNA and cause malignant transformation. Both normal and malignant cells contain DNA sequences that are homologous or identical to the oncogenic segments of these so-called retroviruses. These are termed cellular proto-oncogenes and correspond to viral (v-onc) oncogenes. These have probably arisen during evolution from incorporation of the cellular counterparts into viral structures. There is a remarkable level of conservation of these "ancestral" oncogenes. Seminal work by Peyton Rous on avian sarcomas led to isolation of the Rous sarcoma virus (RSV), which contains a gene (v-src) that alone is capable of transforming fibroblasts in cell culture and forming tumors (sarcomas) in chickens. RSV is 1 of several "acutely transforming" retroviruses that can induce tumors in animal systems after a short-term latency period. Interestingly, RSV is the only retrovirus to contain both oncogenic and replicative sequences. Most of the RNA tumor viruses have lost some of the genetic information coding for replication because of incorporation of oncogenic sequences.

It may be surmised that cellular proto-oncogenes become activated either by overexpression of the normal gene product (quantitative change) or by alteration of the proto-oncogene to yield an abnormal product with oncogenic activity (qualitative change).[30] The aforementioned types of genetic alterations (point mutations, gene amplification, chromosomal translocation) can lead to either type of inappropriate expression of a proto-oncogene.

Most oncogenes code for protein products that form components of mitogenic growth signaling pathways. Stimulation of these pathways leads to increased rates of proliferation and promotes tumor formation. One of the earliest oncogene products to be characterized was from the src gene.[31] Antisera raised against the src gene product revealed a phosphorylated protein with a molecular weight of approximately 60,000 Da (pp60 v-src). The protein product of the cellular homologue was similar (pp60 c-src) and located mainly on the cytoplasmic side of the plasma membrane. Furthermore, this protein was capable of "autophosphoryla-

tion" as well as phosphorylation of other proteins.[32] Phosphorylation occurred on tyrosine residues and therefore the protein was known as a tyrosine protein kinase (as opposed to serine or threonine protein kinases).

There are several potential mechanisms for activation of an oncogene, including point mutations, gene amplification, and chromosomal translocation. The latter can lead to formation of chimeric proteins with aberrant function and can result in disruption of normal intracellular signaling pathways. As an example, the bcr-abl fusion protein in chronic myelogenous leukemia is the result of reciprocal chromosomal translocation t(9;22) that forms the Philadelphia chromosome. The translocation fuses the N-terminal region of Bcr protein to the C-terminal sequence of the Abl cytoplasmic tyrosine kinase, resulting in a chimeric protein that is constitutively active. The downstream signaling pathways activated by bcr-abl include the ras-Raf-ERK, JAK-STAT, and PI-3K pathways (Fig 6).

Receptor Protein Tyrosine Kinases as Oncogenes

Receptor protein tyrosine kinases are growth factor receptors that have extracellular, transmembrane, and intracellular domains. Binding of the cognate ligand to the extracellular binding site causes dimerization of receptors that lead to autophosphorylation of a tyrosine residue on the intracellular domain (which has intrinsic tyrosine kinase activity) (Fig 8). This is turn triggers a cascade of events that involves formation of a membrane complex with binding of cytoplasmic signaling proteins containing Src homology-2 (SH-2) and protein tyrosine binding domains (PTB). Amplification of the genes controlling receptor protein-tyrosine kinase is common in human cancers, resulting in overexpression and enhanced responsiveness to positive growth factor signals. This overexpression of receptors tends to promote ligand-independent dimerization with constitutive activation of the receptor, which can lead to stimulation of downstream mitogenic pathways in the absence of any external stimulus.[33] Epidermal growth factor receptor (EGFR) and HER2/neu are otherwise known as ErbB1 and erbB2, respectively, and belong to a family of receptor protein tyrosine kinases (erbB 1-4), so-called because of their homology to the erythroblastoma viral gene product v-erbB.[34] Genes for both of these growth factor receptors are frequently amplified in breast, pancreas, and lung cancers. Furthermore, EGFR/ErbB1 is overexpressed in up to 80% of head and neck cancers with levels of expression correlating inversely with survival (ie, an adverse prognostic indicator).[35] Ligand binding to receptor protein-tyrosine kinase usually leads to downstream activation of ras and the mitogen-activated protein

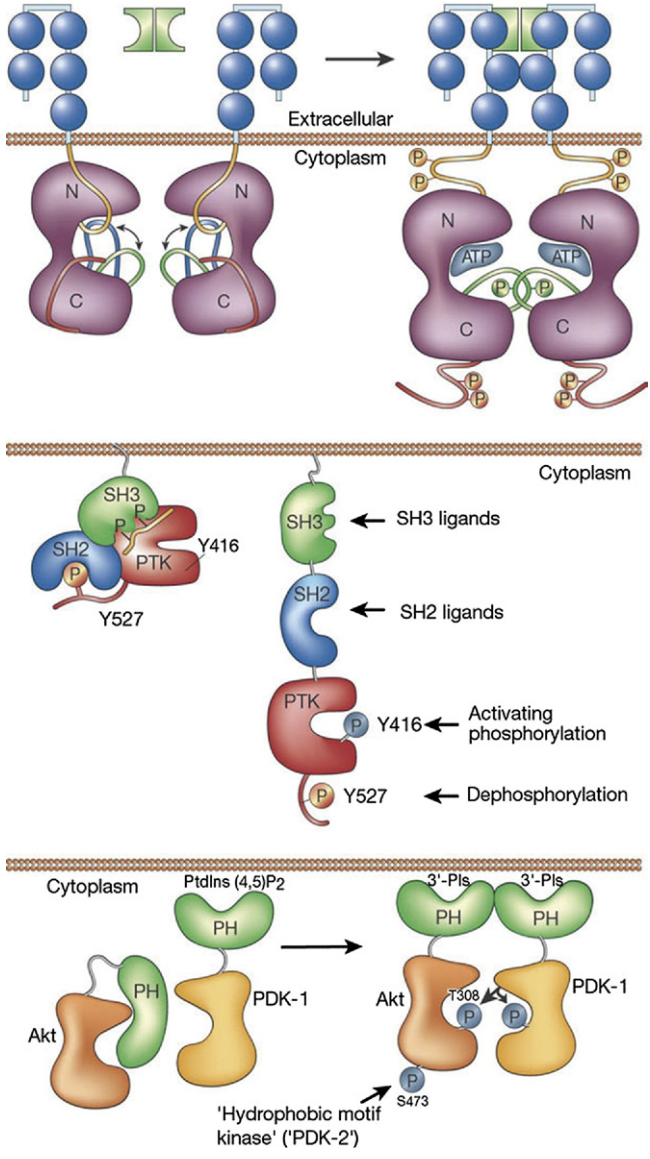

FIG 8. A typical growth factor receptor is composed of extracellular, transmembrane, and intracellular domains. The latter may possess intrinsic tyrosine kinase activity, which permits autophosphorylation. Some growth factor receptors do not have a cognate ligand. (Color version of figure is available online.)

kinase cascades. The binding of EGF and similar ligands (TGFα) to the EGFR is a classic example of this.[36] Interestingly, HER2/neu (erbB2) has no natural ligand and functions as an amplifier by forming heterodimers with other members of the erbB family. Overexpression results in formation of homodimers of erbB2, which have constitutively active tyrosine kinase activity. In contrast to EGFR, this activated HER2/neu has a much broader range of potential downstream substrates that can transduce mitogenic, growth stimulatory signals.[37]

Mutations in the c-ret and c-met receptor protein-tyrosine kinase oncogenes are found in some familial cancer syndromes such as multiple endocrine neoplasia (MEN) 2A and 2B and familial forms of medullary thyroid cancer (c-ret).[38] Papillary renal carcinoma can be associated with mutations of c-met. Both of these oncogenes are activated by missense mutations leading to abnormal distribution of cysteine residues in the extracellular domain of the receptor. Inappropriate intermolecular disulfide bond formation encourages dimerization, constitutive tyrosine kinase activation, and enhanced mitogenic signaling.

Cytoplasmic Protein Tyrosine Kinases as Oncogenes

The existence of a cytoplasmic portion of the receptor tyrosine kinase molecule with intrinsic tyrosine kinase activity modifies the nature of the "second messenger" system, whereby an extracellular signal is translated into an internal cellular response. Receptor protein-tyrosine kinase can directly phosphorylate a range of intracellular proteins leading to activation. Lay membrane bound receptors that do not possess tyrosine kinase activity must first bind a signal transducing or G protein, which then binds other molecules (guanine nucleotides), which will directly activate second messengers.

The cytoplasmic portion of receptor protein tyrosine kinases converges on a common second messenger system called ras proteins. The primary role of these proteins is to act as "shuttling" molecules that couple receptor activation to downstream effector pathways involved in regulation of cellular proliferation, differentiation, and survival. Ras proteins are small GTPases that oscillate between inactive guanosine diphosphate (GDP)—bound and active guanosine triphosphate (GTP)—bound forms. Following ligand growth factor binding and dimerization, the receptor is autophosphorylated and forms an activated complex with recruitment of intracellular proteins to docking sites on the inner surface of the plasma membrane. The so-called "docking proteins" form a scaffold structure, which facilitates aggregation and interaction with downstream signaling components including the ras family of proteins. This complex also binds

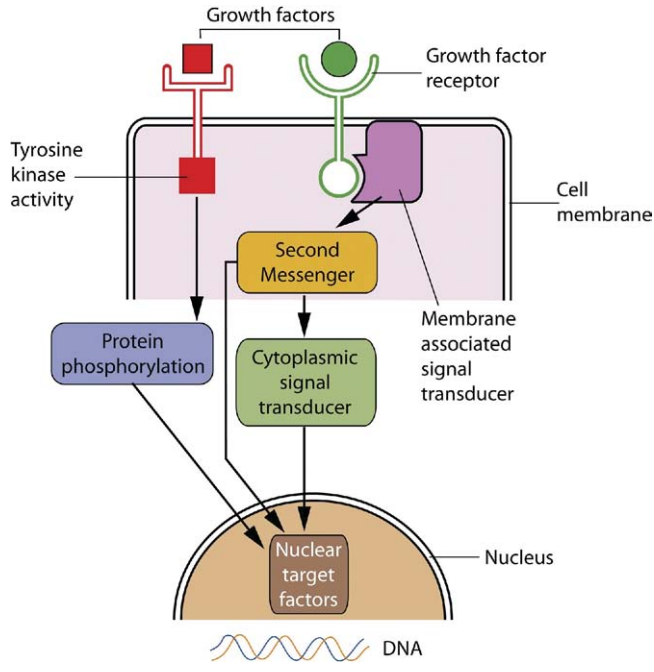

FIG 9. Ligand binding to the extracellular domain of receptor tyrosine kinases triggers dimerization and receptor activation with autophosphorylation of specific tyrosine residues in the cytosolic domain. This leads to recruitment of intracellular proteins (GRB2), which bind to phosphotyrosine residues, which constitute "docking sites." This activated complex also binds a protein called SOS, which catalyses activation of ras proteins by exchange of GDP for GTP. Active ras binds to Raf, which in turn phosphorylates the kinase MEK. This phosphorylates MAP kinase, which stimulates several potentially mitogenic pathways. (Color version of figure is available online.)

a series of adapter molecules together with a protein termed SOS, which catalyses the activation of ras proteins by exchange of GDP for GTP. This activated form of GTP-bound ras can interact with multiple downstream effectors to influence a spectrum of cellular processes varying from DNA synthesis to cell morphology and adhesion (Fig 9). The system is switched off by GTPase activating proteins (GAPs), which hydrolyze GTP-bound ras to its GDP-bound form. Activating mutations of ras are found in approximately 30% of human cancers and permit cells to partially bypass receptor protein-tyrosine kinase signaling pathways.[39] The ras oncogene was originally discovered in 2 retroviruses, which gave rise to sarcomas in mice. The 2 oncogenes H-ras and K-ras were found to yield almost identical gene products, which resembled that of a further oncogene derived from neuroblastoma DNA-N-ras. These 3 genes together with several other ras-related genes constitute the "ras multigene

family." Oncogenic sequences usually result from a missense point mutation and the ras protein is maintained in the activated GTP bound state. A single amino-acid substitution can render the GTP-bound form resistant to hydrolysis by GAPs. Generation of a continuous mitogenic signal provides a powerful driver for tumorigenesis. K-ras mutations are common in solid tumors: pancreatic (>90%), colorectal, endometrial, biliary tract, lung, and cervical. They occur together with H-ras mutations in approximately one third of leukemias and other myeloid malignancies, whereas H-ras mutations alone are found in bladder tumors. Downstream targets regulated by ras proteins include Raf, which is a serine/threonine kinase that coordinates with ras to phosphorylate the kinase MEK, which in turn phosphorylates MAP kinase.[40] Ras also controls the rate of breakdown of inositol phospholipids (PI3-k/Akt/mTOR pathway).

Nuclear Proteins as Oncogenes

Oncogene products that reside within the nucleus itself can exert a more direct influence on gene expression through binding to segments of DNA that contain gene regulatory elements. The myc oncogene is well characterized as a nuclear oncogene with growth stimulatory properties. The latter were first identified in avian retroviruses, which transformed myeloid cell lines—hence the term myc (myelomonocytic). These retroviruses also induced sarcomas and adenocarcinomas and were of interest because they lacked oncogenes. However, the myc gene is a member of a multigene family and a viral form v-myc corresponds to the cellular homologue. Distinct forms of the gene exist in neuroblastoma/retinoblastoma (N-myc) and small cell lung carcinomas (L-myc) and all 3 forms of the gene have been implicated in human malignancy.[41] The myc gene is universally expressed in cells and participates in a highly conserved pathway, which is shared by most cells. Levels of the myc product are generally increased in actively dividing cells and the myc gene encodes transcriptional factors controlling proliferation, differentiation, and apoptosis. Abnormal expression within tumor cells may result from breakdown of a negative feedback loop whereby the myc product fails to appropriately regulate activity of the gene. Oncogenic forms of myc may result from a variety of changes including point mutation, amplification, and translocation. An example of the latter is Burkitt lymphoma, where translocation places the myc gene in proximity to an immunoglobulin enhancer region. This results in augmented rates of transcription and overexpression of myc protein.

Tumor Suppressor Genes

Tumor suppressor gene products are integral components of cell cyle regulatory pathways and have both "gatekeeper" and "caretaker" functions. Some tumor suppressor genes possess functional duality and inactivation leads to major disruption of cell cycle regulation. Thus, it is the absence of a normal gene function rather than the presence of an abnormal gene per se that characterizes tumor suppressor gene disorders. A significant advance in the understanding of multistep carcinogenesis and in particular the concept of tumor suppressor genes came from studies into the genetic basis of retinoblastomas.[42] Familial cases with bilateral tumors were noted to have lost a part of chromosome 13 (13q14). Sporadic cases with unilateral tumors also showed a similar chromosomal loss and Knudson proposed his famous "two-hit" hypothesis (Fig 3)[4,5,43]; in familial cases of the disease, 1 "hit" is inherited as a germ line mutation and the second "hit" is acquired early in life (perhaps in utero). It is now known that these 2 "hits" each correspond to allelic loss of a tumor suppressor gene—the retinoblastoma gene Rb-1. This gene was mapped to the chromosomal region 13q14 and its normal product is present in all cells except those of retinoblastoma tissue. Thus, tumor formation is related to absence of the retinoblastoma gene product.

Transcriptional Factors as Oncosuppressor Genes

The Rb gene product is a universally expressed nuclear protein that has a fundamental role in controlling progression of cells through the G1 checkpoint at the transition from G1 to S-phase entry.[44] Levels of the Rb protein are critical determinants of overall functional status and when the amount of protein falls below a threshold value, "suppressor" activity is lost and the cell acquires an oncogenic phenotype. Transfection of the Rb gene into tumor cells lacking Rb expression reasserts normal features and cell behavior.

Like the Rb protein, the p53 gene product is present in a wide variety of normal cells and levels of expression are increased in up to one half of all cancers. Moreover, the protein product appears to be more stable with a longer half-life in transformed cells. As previously discussed, p53 is often referred to as the "guardian" of the genome. It has an important cell cycle checkpoint function and protects cells from genotoxic damage. p53 causes cells to arrest in the G1 phase of the cell cycle and can act as a homotetrameric transcriptional factor, which is activated in response to cellular insults such as irradiation, hypoxia, and drug-induced DNA damage. Although levels of p53 are increased in some tumors, the protein

product is abnormal and p53 mutations are usually inactivating and associated with loss of gene function. Moreover, the p53 gene can act in a dominant negative manner, whereby the presence of any abnormal protein product can impair function of normally expressed protein. Defective p53 introduced into the germ line of transgenic mice leads to augmented tumorigenesis in the offspring of these p53 deficient mice.[45] Therefore, p53 functions as a tumor suppressor gene at the transcriptional level rather like the Rb gene. Indeed, the 2 proteins form part of a signaling network that regulates progression through the cell cycle and exerts a restraint on inappropriate growth promoting signals. Mutations of the p53 gene occur in the Li–Fraumeni syndrome, which is associated with breast cancer, sarcomas, and adrenocortical tumors.[46] Two further key components of this network include $p16^{ink4a}$ and $p14^{ARF}$. These are both encoded from a common locus on chromosome 9p21 called INK4a-ARF (alternate reading frame protein), which possesses 2 open reading frames. $p16^{ink4a}$ binds and inhibits the cyclin D-dependent kinases CDK4 and CDK6 and thereby induces Rb dependent G1 arrest.[47,48] Mutations of this gene are commonly found in familial and sporadic forms of melanoma, pancreatic, lung, and bladder cancers. $p14^{ARF}$ is also a potent tumor suppressor capable of activating p53 by binding directly to the p53 inhibitor MDM2. Mutations within this gene frequently occur in T-cell leukemias.

Receptor Tumor Suppressor Genes

The hedgehog pathway is a signaling cascade with important roles in directing patterning and organ specificity during development and embryogenesis. Stimulation of this pathway can promote either proliferation or differentiation, depending on cell type. Derangement of Hh signaling has provided valuable insight into mechanisms of cancer progression. The Hh pathway is activated by binding of ligand to a transmembrane receptor called patched-1 (ptch-1).[49] Three mammalian Hh proteins have been identified (Sonic Hh, Indian Hh, and Desert Hh); these are secreted by cells following autoprocessing and can act in either an autocrine or a paracrine manner on adjacent cells. Unbound ptch-1 catalytically suppresses a transmembrane protein called Smoothened (Smo); ligand binding releases smo from their repressed state where they can interact with downstream elements (Gli 1 and 2 factors) to upregulate Hh target genes.

Proliferation of tumor cells in vitro is increased by the addition of Hh ligand and is inhibited by neutralizing antibody. Moreover, constitutive activation of the Hh pathway by overexpression of Gli 1 leads to a

metastatic phenotype in xenograft tumor models. Mutations in the PTCH gene have been found in Gorlin's syndrome, where inactivation of this presumed tumor suppressor gene leads to basal cell carcinoma and medulloblastoma.[50,51] The Hh pathway may be crucially involved in conversion of normal stem cells to cancer stem cells. One potential problem with inhibition of the Hh pathway as a therapeutic intervention in cancer is the adverse effects of Hh antagonists on normal stem cells of tissues such as bone marrow, gut, liver, and skin.

Transforming growth factor β (TGF-β) is a family of multifunctional regulatory peptides involved in a range of processes including development, wound healing, and carcinogenesis. It has 3 mammalian isoforms, each of which is a 25-kDa homodimeric peptide made from 2 identical peptide chains 112 amino acids in length.

Two forms of TGF-β receptor are recognized, Type I and Type II. These are transmembrane structures with an intracellular component that has intrinsic serine kinase or threonine kinase activity. TGF-β binds to the Type II receptor, which has a constitutively active kinase domain. After binding of the ligand, the phosphorylating activity of the Type II receptor causes a conformational change leading to recruitment of the Type I receptor into a heterodimeric complex. This complex formation leads to activation of the kinase domain of the Type I receptor with signal propagation to downstream elements. Intracellular signal transduction is mediated by the Smad family of proteins; SMAD2 and SMAD3 are specific to TGF-β signaling and are recruited to the Type I receptor where they subsequently form a hetero-oligomeric complex with SMAD4, which is a common mediator. This complex translocates to the nucleus, binds to DNA via a Smad-binding element, and induces transcription of target genes. The latter inhibits phosphorylation of Rb protein and retention of E2F factors with cell cycle arrest or lengthening of G1 (Fig 10). Smad4, also known as "deleted in pancreatic cancer" (DPC4), is mutated in at least 50% to 90% of pancreatic cancers.

TGF-β is a component of the complex language of intercellular communication and potentially acts as a switch that permits a biphasic functional profile. TGF-β is a pre-eminent inhibitory growth factor and in the premalignant and early stages of cancer this tumor suppressor activity is sustained. However, as cells pass along the neoplastic continuum, functional disruption occurs and malignant epithelial cells show a reduced or absent response to the growth inhibitory effects of TGF-β. Despite a dominance of growth inhibition in the early stages of carcinogenesis, during growth of a tumor there is a shift in the balance between tumor suppressor and potential pro-oncogenic activity. In the more advanced

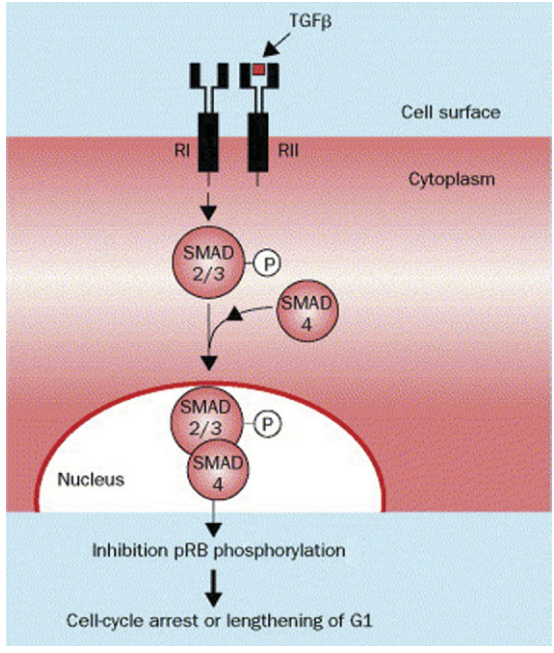

FIG 10. After binding of TGF-β ligand to cognate receptors, signals are conveyed to the nuclear transcription site via intracellular proteins called smads. (Reprinted with permission from Benson JR.[52]) (Color version of figure is available online.)

stages of malignant disease, TGF-β might promote tumor growth indirectly through the combined stimulation of stroma formation, angiogenesis, and immune suppression.[52]

The tumor suppressor activity of TGF-β has generated much interest in the potential role of this growth factor in the process of carcinogenesis and the mediation of response to some therapies. The exact function of TGF-β depends on both tumor stage and cellular context, with relative amounts of ligand and receptor being a crucial determinant of response. TGF-β receptors jointly coordinate a cellular response and mutations in the Type II receptor gene leads to loss of a growth inhibitory response in colon cancer cells lines, which can be restored by transfection of the Type II receptor subunit. The Type II receptor is mutated in HNPCC through a mismatch repair error. Mutations within the TGF-β1 gene have been found in familial breast cancer and represents 1 of several low risk genes (relative risk [RR] $<$1.5), which together with BRCA1 and BRCA2 (and other higher risk genes such as PTEN and p53) contribute to approximately 25% of familial predisposition.[52]

Cytoplasmic Oncosuppressor Genes

The development of colorectal cancers may be attributable to the absence of a normal gene product. One form of colorectal cancer is associated with the hereditary condition familial adenomatous polyposis coli (familial adenomatous polyposis (FAP)), which results in the formation of hundreds of polyps within the colon and rectum. A proportion of these will become dysplastic and thereafter progress to carcinoma.[53] An abnormality on chromosome 5 was originally identified in 1 of these patients and the defective segment localized to 5q21. Furthermore, mutations at this site (the adenomatous polyposis coli (APC) gene) can be found in more than three quarters of cases of sporadic colorectal cancer. By analogy with retinoblastoma, a "two-hit" mechanism may apply; individuals with FAP will inherit a germ line mutation of APC and require 1 further hit for development of cancer (heterozygosity predisposes to polyp formation alone). Sporadic forms of colorectal cancer require 2 somatic hits for tumor formation. Thus, loss of function of tumor suppressor genes seems to be an important mechanism for carcinogenesis. The APC gene and protein product has been characterized and the latter interacts with β-catenin, which is a component of the Wnt/Wingless signaling pathway.[54] Wild-type APC protein associates with β-catenin and targets it for proteosomal degradation. However, when APC is mutated, it is no longer able to negatively regulate β-catenin. Accumulated β-catenin translocates to the nucleus, where it promotes cell cycle progression by interaction with transcriptional factors LEP/TCP (lymphoid enhancer factor/T-cell factor). Mutations in β-catenin have been identified in colorectal cancer and could be linked to abnormalities on chromosomes 17 and 18, which are frequently found in familial (nonpolyposis) and sporadic forms of the disease. Of note, chromosomal 17 mutations might lead directly to p53 dysfunction and impact on the (Rb/p53/p16/p14) signaling network discussed above.[48]

Apoptosis and Cell Death Pathways

Programmed cell death or apoptosis is an essential feature of normal development and is an ongoing process throughout the life of a complex multicellular organism. For example, selective removal of cells during the phase of tissue remodeling in organogenesis is achieved by coordinated activation of cell death programs. This leads to generation of digits and body cavities, for example. Apoptosis is also activated when cells are subjected to an insult, such as DNA damage.[55] There are 2 distinct cellular programs that trigger the intrinsic and extrinsic pathways. The

intrinsic pathway is primarily responsible for apoptosis induced by cellular stress, external injury, and signals emanating from survival pathways. Any of these events will stimulate release of cytochrome C from mitochondria, which subsequently activates a cascade of caspases that result in DNA fragmentation, plasma membrane destruction, and the morphologic features of apoptosis. The Bcl-2 family of proteins determines the net cellular response through the balance of pro- (eg, *bax* or *bad*) and anti- (*Bcl-2*, *bcl-X_L*) apoptotic members. A dominance of proapoptotic Bcl-2 proteins will permeabilize the mitochondrial membrane and permit egress of cytochrome c. By contrast, the extrinsic pathway is activated by ligand binding to cell surface "death" receptors, which include Fas/CD95, tumor necrosis factor receptor, and DF5. The respective cognate ligands are FasL, tumor necrosis factor-alpha and TNF-related apoptosis-inducing ligand. Each of these ligand/receptor complexes can activate the caspase cascade and trigger apoptosis.

Cancer cells possess the ability to evade mechanisms of programmed cell death. Overexpression of the antiapoptotic protein Bcl-2 has been found in 85% of more aggressive lymphomas.[56] The Bcl-2 gene is upregulated by a chromosomal translocation (14:18) and elevated levels of Bcl-2 protein bind to *bad* and other proapoptotic factors (*bax, bid*). Bcl-2 is a potent cell survival factor and prevents cytochrome c release and in turn inhibits cell death. Inactivating mutations of p53 lead to impaired apoptotic pathways. Downstream effectors interact with proapoptotic members of the Bcl-2 family. Functioning p53 protein increases transcription of the *bax* gene, which promotes release of cytochrome c from mitochondria.

Adherent epithelial cells require attachment to substratum and integrin engagement to survive. One of the consequences of a transformed phenotype is the ability to grow under anchorage-independent conditions. Normal cells will undergo apoptosis with the loss of integrin attachment to substratum, a process known as anoikis. Cancer cells can evade anoikis through mutational change and overexpression of integrins, which provide signals mimicking integrin engagement to substrata.

MicroRNA as Oncogenes and Tumor Suppressors

MicroRNAs are small noncoding RNA molecules composed of short sequences of 20 to 22 nucleotides that exert a negative regulatory influence on gene expression in eukaryotic organisms.[57] They generally reduce levels of both transcript and corresponding protein and have been shown to participate in several biological processes including cell proliferation (miR-125b; let-7) where miRNAs may enable stem cells to

overcome the G1/S checkpoint of the cell cycle. These molecules are generated from hairpin-structured precursors by the action of members of the RNase III group of enzymes (Dicer and Drosha). There are 2 proposed mechanisms by which microRNAs might silence genes following binding of microRNAs to complementary sequences located predominantly in the 3′ untranslated regions of genes. First, such binding can result in decreased translation of specific mRNAs and reduced amounts of protein product. Second, binding of microRNA can divert mRNA to the RNA interference silencing complex, wherein mRNA transcripts are broken down and become void. Both of these mechanisms result in decreased expression of the corresponding gene.

Expression profiles of miRNAs differ between normal and malignant cells and cancer-specific miRNA fingerprints have been identified for many types of cancer, including leukemias, lymphomas, breast, liver, gastric, colon and pancreatic. Attention has focused recently on microRNA as a potential tumor suppressor. Abrogation of this negative gene regulation could promote cancer development. Indeed, microRNAs such as mi-R15 and mi-R16 appear to act in this capacity. Thus, downregulation of miR-15/16 results in overexpression of antiapoptotic Bcl-2 and other genes that promotes tumorigenesis. However, overexpression of other types of microRNA such as the polycistron miR-17-92 on chromosome 13q 32-33 can stimulate tumor growth, suggesting that microRNA can have dual roles, depending on which particular genes are negatively regulated. In a mouse model of B-cell lymphoma, overexpression of the miR 17-92 cluster acts coordinately with c-myc upregulation to potentiate formation of B-cell lymphoma. Moreover, miR 155 has been found to be overexpressed in Burkitt lymphoma cells.[58]

It has been proposed that miRNAs act “in cascade” over several cancer-specific protein coding regions, which subsequently modulate transcriptional activity of other protein coding genes as well as noncoding RNAs. These mechanisms could be important in tumor initiation in somatic cells and genetic predisposition in germ line cells.

Epigenetics

Most cancers display epigenetic changes that are reversible and heritable changes in gene expression without DNA sequence alterations. They act as “translators” between the environment and the genome and represent an interface between genotype and phenotype. Cancer cells have an imbalance of DNA methylation; although there is widespread loss of genomic DNA methylation with neoplastic progression, there is aberrant hypermethylation of cytosine residues in CpG islands in the

promoter region of genes.[59] These CpG islands are highly conserved segments of DNA with a guanine cytosine content in excess of 50%. They are found in the promoter regions of almost one half of mammalian genes. These CpG islands are normally protected from methylation, but aberrant methylation is widespread in human cancers and leads to selective gene silencing. Each tumor has its own pathways of methylation and hypermethylation profile. Epigenetic silencing tends to promote genetic instability, with 5-methylcytosine being highly mutagenic and presdisposing to C:G → A:T transitions. For example, in sporadic colon cancers there is evidence of hypermethylation and silencing of the DNA mismatch repair gene MLH1 leading to MSI.[60] Epigenetic silencing represents an important mechanism for inactivation of tumor suppressor genes. The BRCA1 and APC genes can be inactivated by hypermethylation and in the case of the former this can act as a second hit in hereditary forms of breast cancer.[61] In sporadic cancers, there can be hypermethylation of 1 allele and genomic loss of the other allele. Targets for hypermethylation include the estrogen, progesterone, and prolactin receptors as well as the above genes. Hypermethylation of the tumor suppressor gene $p16^{INK4a}$ in lung cancer has been reported. A variety of novel genes that can be epigenetically silenced are likely to be discovered in the future. Furthermore, it may be possible to restore normal gene expression by pharmacologic manipulation of epigenetic changes without the need for genetic engineering.

Epigenetic therapy has focused on developing agents that can alter patterns of DNA methylation or histone modification. 5-Azocytidine is a protoype inhibitor of DNA methylation that inactivates DNA methyltransferases and can induce gene expression and differentiation in vitro. Like other cytotoxic agents, 5-azocytidine is effective in actively dividing S-phase cells, and clinical trials are evaluating these agents in treatment of myeloid leukemias. DNA methyltransferases can also be targeted with antisense molecules. Inhibitors of histone deacetylation can overcome epigenetic silencing and represent an alternative therapeutic strategy. Accumulation of acetylated proteins can switch on silenced genes and this approach may be appropriate if specific enzymes can be targeted (Fig 11). Epigenetic modification as a mechanism for oncogene activation is exemplified by the phenomenon of "loss of gene imprinting." Gene imprinting refers to the process whereby heritable transcriptional activation of the paternal gene allele and repression of maternal allele is ensured by DNA methylation and histone modification. Thus, loss of gene imprinting leads to dual allele activity and hence net overexpression of genes. A well-

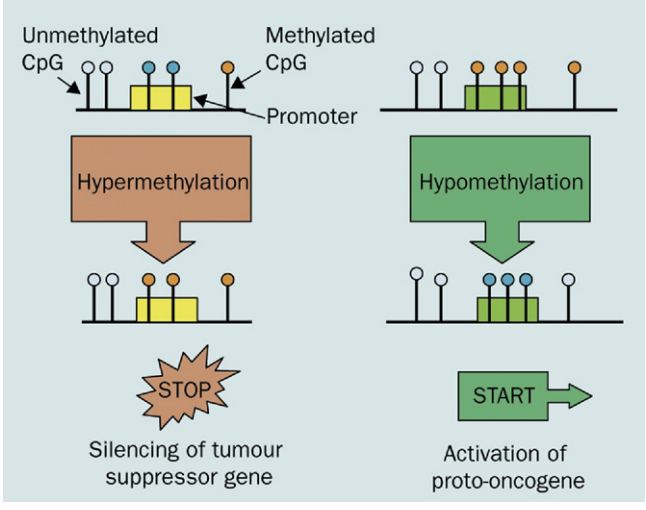

FIG 11. Epigenetic regulation of gene expression by methylation. Methylation of CpG islands in cancer cells leads to silencing of suppressor genes. (Reprinted with permission from Verma M, Srivastava S. Epigenetics in cancer: implications for early detection and prevention. Lancet Oncol 2002;3:755-63.) (Color version of figure is available online.)

documented example is overexpression of the IGF-2 gene in colon cancer, resulting in enhanced downstream signaling and tumor promotion.

Invasion and Metastases

The properties of invasion and metastasis are the sine qua non of the malignant phenotype. These are complex and interrelated processes that are associated with multiple and sequential genetic changes. The transfer of cancer cells from a primary tumor focus to distant sites involves the following steps:

1. Invasion of normal surrounding tissues.
2. Penetration of lymphatic and vascular channels with release of either single tumor cells or small cell clusters into these vessels.
3. Survival within the lymphatic or circulatory systems.
4. Arrest in the capillary beds of distant organs such as the lungs, bone, or liver (or the sinus of a lymph node).
5. Extravasation from the walls of these lymphovascular channels in distant organs and establishment of a viable metastatic focus.

The initial stages of local tissue invasion involve cellular dissociation and migration. These 2 steps are dependent on changes in mechanical pressure

within the tissues, together with release of proteolytic enzymes that reduce the adhesiveness and attachment between cancer cells and normal cells. Epithelial-mesenchymal transition is characterized by loss of cell-to-cell contact with disruption of intercellular tight junctions. The latter maintains the orderly arrangement of cells in monolayers, and loss of cohesion is accompanied by an increase in cell mobility. A group of enzymes called matrix metalloproteinases are key players in the process of tissue invasion and include collagenases, gelatinases, and stromelysins. The genetic basis for invasion remains poorly understood, but so-called "invasion suppressor genes" are being identified. Epithelial-mesenchymal transition is regulated by several growth factor pathways that link up with activation of metalloproteinases (via disruption of a sulfydryl group) and their tissue inhibitors. A checkpoint control for invasion has been proposed involving the ligand-receptor complex termed amphoterin/receptor for advanced receptor glycation end products. This complex assists in generation of the enzyme plasmin that activates metalloproteinases. It is also involved in control of cell motility and modulation of adhesion receptors relating to the e-cadherin system. Mutations in the e-cadherin gene have been described for cancers of the breast, colon, and stomach. Collectively, these mutations are associated with changes in cell morphology, enhanced motility, and activation of the β-catenin/lymphoid enhancement factor pathway.[62]

Hepatocyte growth factor or "scatter factor" is produced by stromal cells and binds to the c-met receptor on cancer cells. Levels of this protein-tyrosine kinase receptor can be elevated by either somatic or germ line mutations in the c-met gene. Amplification of this gene has been found in liver metastases of colorectal carcinomas. Upregulation of the hepatocyte growth factor/c-met signaling pathway activates an invasive program that promotes invasion, migration, and cell survival—and in turn, the metastatic phenotype.[63]

Angiogenesis

Development of a tumor beyond the size of approximately 1 million cells is dependent on an intact microvasculature. Blood vessels not only support further tumor growth by encouraging adequate supplies of oxygen and nutrients to cells deep within a tumor bolus but also provide opportunity for metastasis, especially as newly formed blood vessels tend to be fragile and leaky.

Tumor angiogenesis factors stimulate capillary formation at an early stage of tumor formation, leading to proliferation of endothelial cells that invade the stroma and produce capillary "sprouts." These become tubular

structures that later canalize to form nascent capillary networks. One of the principal signaling pathways in tumor angiogenesis is the vascular endothelial growth factor (VEGF) receptor system. Endothelial cells possess 2 forms of the receptor, VEGFR1 and VEGFR2, which both bind the ligand VEGF-A. However, VEGFR1 is probably the dominant receptor for angiogenesis and ligand binding stimulates endothelial proliferation and formation of a neovasculature.

Normal cells respond to hypoxia by upregulation of a set of hypoxia-inducible genes. VEGF-A represents 1 such gene and levels of VEGF-A are increased by cell hypoxia. This response is mediated by hypoxia-inducible factors (HIF) 1α and 2α, which function as transcription factors and are very sensitive to the ambient oxygen tension. In cancer cells, activity levels of HIF-1α and 2α can remain high despite normoxic conditions. This generates a continuous and potent angiogenic signal, which no longer represents a physiological response to hypoxia. This uncoupling of hypoxia-inducible gene expression from tissue oxygen tension can result from mutations in the von-Hippel-Lindau (VHL) gene. The product of this gene normally targets HIF for proteosomal degradation via the ubiquitin pathway. Loss of this tumor suppressor gene activity leads to accumulation of excess HIF-1α and -2α, which drives tumor angiogenesis. Inactivating mutations of the VHL gene are present in up to 50% of renal cell carcinomas, which characteristically express high levels of VEGF-A. Of course, enhanced angiogenesis in most tumors is not linked to specific mutations of VHL; many other angiogenic factors exist (eg, fibroblast growth factor) and levels of VEGF-A can be increased through other pathways that might involve activated EGFR, erbB2, and mutant ras signaling.[64]

Inhibition of angiogenesis is a potential antitumor strategy and microvessel density is generally inversely correlated with tumor stage and clinical outcome (Fig 12).

Translational Relevance

Increasing understanding of the molecular basis of carcinogenesis, together with complete sequencing of the human genome, has provided the impetus for translational research, models for risk prediction, and novel therapeutic strategies. The latter are underpinned by knowledge of pathobiological processes that facilitate more targeted approaches. The therapeutic goal has shifted from elimination of all cancer cells to reregulation such that tumors can exist symbiotically and without detriment to the host for longer periods; cancers are caricatures of normal tissues with components that are not foreign and genetically disparate, but

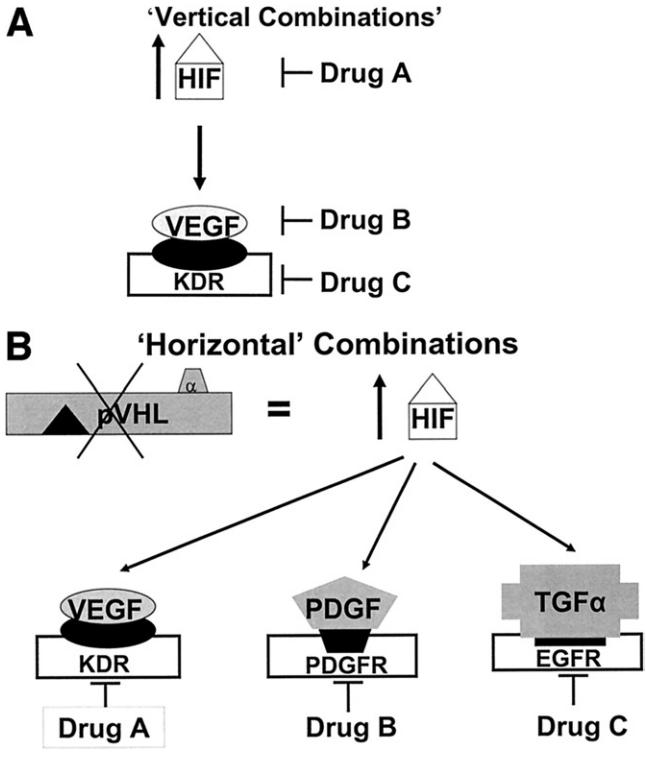

FIG 12. Therapeutic strategies based on disruption of the HIF-VGEF pathway. (A) "Vertical" combination therapies, (B) "horizontal" combinations. (Reprinted with permission from Kaelin WG, et al. The von Hippel–Lindau tumor suppressor gene and kidney cancer. Clin Cancer Res 2004: 106290S-5S.)

rogue cells that possess a finite number of genetic changes.[65] By prolonging disease-free survival, it may be possible to achieve a personal cure until patients succumb from causes unrelated to cancer.[66] This may constitute a more realistic objective than striving for the elusive statistical or clinical cure. Cancer cells have great capacity to adapt and evolve in response to treatments. Targeting of specific growth factor pathways that drive tumor growth has become a clinical reality and this approach is consonant with the paradigm of control rather than cure. Chronic myeloid leukemia is characterized by the fusion gene bcr-abl, which has enhanced tyrosine kinase activity. Selective tyrosine kinase inhibitors have been developed (imatinib) that can cure up to 90% of mice with chronic myeloid leukaemia and are highly effective in clinical trials. Likewise, a humanized monoclonal antibody directed against overexpressed HER2/

neu receptor in breast cancer patients has dramatically improved short-term clinical outcomes. This antibody (Herceptin) downregulates tyrosine kinase activity by internalization of the receptor/antibody complex. Tyrosine kinases provide potent mitogenic signals, and targeting of these pathways demonstrates the success of translational approaches.

The cellular heterogeneity of individual tumors presents a major therapeutic challenge. There is increasing recognition that phenotypic heterogeneity for some cancers may reflect an accumulation of mutations in a large number of less highly penetrant genes rather than being attributable to simple changes in 1 or 2 dominant genes. The sophisticated methods of genetic profiling with DNA microarrays and their integration with proteomics may ultimately allow treatments to be better tailored. If tumors arise from transformation of stem cells (or a closely related progenitor) into malignant stem cells, then the latter must be targeted therapeutically; these cells are either quiescent or cycle relatively slowly and are resistant to conventional chemotherapy. The ability of stem cells to self-renew provides the opportunity for regeneration and clinical recurrence of cancer. Cancer stem cells retain programs for invasion and metastases together with protective mechanisms that favor survival despite exposure to potentially noxious therapies. Future research will focus on identification of biochemical pathways that are unique to cancer stem cells and thereby permit selective targeting of this important subpopulation of tumor cells. Elimination of cancer stem cells will abrogate the capacity for regeneration of tumors and evolution of chemoresistance.

When considering genetic testing for individuals with a possible hereditary predisposition for cancer, the first person tested for a mutation should be a family member most likely to test positive, generally an individual who has developed the cancer of interest at a young age.[67] If a mutation is found, then other members of the family should be tested for the same specific mutation. Informed consent should always be obtained before genetic testing, and the potential risks and benefits discussed in detail.

In the remainder of this monograph, we discuss the management of individuals who have a hereditary predisposition for specific cancers and emphasize the potential role of surgery in reducing cancer risk. For the surgeon, individuals with a genetic predisposition for breast, gastric, thyroid, and colorectal cancers are of particular relevance because, in these patients, the role of surgery in cancer prevention has expanded dramatically in recent years.

Breast Cancer

In the USA, a woman's lifetime risk of breast cancer is approximately 12.7%, and women with a substantially greater risk than this may sometimes consider bilateral prophylactic mastectomy (BPM) to reduce their risk.[68] Thus, women who carry gene mutations that increase breast cancer risk, those with a very strong family history of breast cancer but no identifiable mutation, and women with a very strong family history of breast cancer who refuse genetic testing may sometimes consider BPM. Additionally, women who have had previous breast biopsies showing lobular carcinoma in situ or atypical ductal hyperplasia are at increased risk for developing breast cancer and may occasionally wish to consider BPM, particularly if they have dense breasts.[69] Increased breast density is itself associated with increased breast cancer risk and also makes detection of cancers more difficult with imaging. Finally, women who have been diagnosed with breast cancer in 1 breast are at increased risk for developing cancer in the opposite breast and may wish to consider contralateral prophylactic mastectomy (CPM).[70]

In the USA, approximately 5% to 10% of all breast cancers occur in women who carry gene mutations that increase their risk for the disease.[68] The 2 genes most commonly responsible are the BRCA1 and BRCA2.[71] However, mutations in other genes have been associated with breast cancer as well, including those in the p53, PTEN, STK11/LKB1, CDH 1, ATM, and CHEK 2 genes.[72] The lifetime risk of breast cancer (penetrance) varies considerably among these mutation carriers. The high penetrance mutations (eg, BRCA1, BRCA2, p53, PTEN, STK 11, LKB 1, CDH 1) are generally associated with a breast cancer lifetime risk ranging from 40% to 85%, whereas the low penetrance mutations (eg, ATM, CHEK 2) are associated with a lifetime risk below 40%. It should be noted that these mutations not only increase a patient's risk for breast cancer, but other cancers and diseases as well. For example, BRCA mutation carriers are also at increased risk for ovarian cancer, and that risk is approximately 40% and 20% for the BRCA1 and BRCA2 mutation carriers, respectively.[73]

To reduce breast cancer risk, greater numbers of women have been opting for prophylactic mastectomy (PM) (also referred to as preventive mastectomy or risk-reducing mastectomy).[74] Although patients and clinicians generally assume that PM dramatically reduces breast cancer risk, no randomized prospective trials have been undertaken to test this assumption. Thus, our understanding of the potential effect of PM is largely derived from retrospective and nonrandomized prospective stud-

ies. These studies have important limitations, discussed later in this section of the monograph. Furthermore, patients should be aware that PM does not entirely eliminate breast cancer risk. The possibility of developing breast cancer persists even after PM, although that risk appears to be substantially reduced.

Options for Women at Increased Risk for Breast Cancer

Women who have an increased risk for breast cancer may consider 3 options to reduce that risk: screening (magnetic resonance imaging (MRI), mammography, clinical examination, ultrasound), chemoprevention (with either tamoxifen or raloxifene), and PM.[68] Randomized prospective trials have shown that, in the general population, mammography screening in postmenopausal women reduces breast cancer mortality by approximately 25%, whereas screening with breast self-examination has no benefit.[75] Furthermore, trials are underway in India and Japan to assess the efficacy of screening clinical breast examination (CBE) or ultrasound, respectively, on breast cancer mortality in the general population.[68] At least 6 nonrandomized prospective studies have shown that MRI is more sensitive than mammography in detecting breast cancers in high-risk patients, but no randomized prospective trials have assessed the impact of breast MRI screening on mortality rate.[76]

Randomized prospective studies have shown that tamoxifen reduces breast cancer incidence by approximately 50%, and a trial comparing tamoxifen with raloxifene found that these 2 agents were similarly efficacious.[77,78] Nevertheless, no trials have specifically assessed the efficacy of these agents in mutation carriers. Today, tamoxifen is used as a chemopreventive agent in pre- and postmenopausal women; raloxifene is recommended for use in postmenopausal women only, based on the results of the STAR (Study of Tamoxifen and Raloxifene) trial.[78]

Thus, before embarking on PM, the surgeon should first establish whether a woman has a genetic predisposition for breast cancer. If she does, then the surgeon should inform her of the 3 breast cancer risk-reducing strategies (screening, chemoprevention, and prophylactic surgery). The surgeon should discuss limitations in our understanding of the effectiveness of these strategies, as well as the potential harms and benefits of each strategy.

Surgical Considerations

Three PM procedures have been used: total mastectomy, skin-sparing mastectomy, and subcutaneous (nipple-sparing) mastectomy[68] (Table 2). Total mastectomy refers to removal of the breast, nipple, areola, and

TABLE 2. Options for prophylactic mastectomy

Procedure	Description of procedure	Recommendation
Skin-sparing mastectomy	Removal of breast, nipple, areola	Preferred
Total mastectomy	Removal of breast, nipple, areola, and skin overlying breast	Acceptable
Subcutaneous mastectomy	Removal of breast; preserves nipple and areola	Not recommended

overlying skin. Skin-sparing mastectomy refers to removal of the breast, nipple, and areola, while preserving the overlying skin. Finally, a subcutaneous mastectomy involves removal of the breast alone, leaving the nipple, areola, and overlying skin intact. The reduction in breast cancer risk appears to be similar following either total mastectomy or skin-sparing mastectomy. However, skin-sparing mastectomy is considered the procedure of choice because it facilitates breast reconstruction and thereby results in a better cosmetic outcome. Subcutaneous mastectomy is the least effective means of reducing breast cancer risk and is generally not recommended as a PM procedure.

Breast reconstruction is usually undertaken in conjunction with PM.[79] Either a prosthesis alone or an autogenous tissue (with or without use of a prosthetic) can be used for reconstruction. If a patient opts for prosthesis alone, it is generally placed beneath the pectoralis major muscle at the time of mastectomy. Alternatively, an expander can be placed following mastectomy and inflated gradually over a period of several weeks by injecting solution through a port. This process creates a ptosis, and the injectable port and expander are subsequently removed and replaced with a permanent prosthesis. In some cases, the expander is left in place as the permanent prosthesis. If the patient chooses reconstruction with autogenous tissue, then either a latissimus dorsi (LD) flap or the transverse rectus abdominis muscle (TRAM) flap might be considered. The LD flap does not provide sufficient tissue bulk, and a prosthesis is usually placed beneath the flap to create the breast mound. In contrast, the TRAM flap provides considerable tissue bulk, and a prosthesis is usually not required. Although it might result in an esthetically more appealing outcome, the TRAM procedure is technically more challenging and carries a greater risk of complications. Additionally, microvascular perforator flaps such as the deep inferior epigastic perforator flap and the superficial inferior epigastric artery flap can be used.

Barton and colleagues reviewed the results of 269 women who underwent BPM, followed for a mean of 7.4 years.[80] Nearly 80% underwent breast reconstruction, most with prosthetic implants. Approx-

imately 64% of these patients experienced 1 or more complications following the procedure. The most common complications were pain (35%), infection (17%), and seroma (17%). These potential complications should be discussed with patients before embarking on PM.

With respect to PM, it is important to distinguish between BPM and CPM. Women who have never been diagnosed with breast cancer (but are at increased risk for it) may opt for BPM. The characteristics of these women differ substantially from those who have already been diagnosed with cancer in 1 breast and elect CPM to reduce the risk of developing cancer in the opposite breast. Thus, BPM and CPM are considered separately in this monograph.

BPM and CPM remain controversial. These procedures have the potential for benefit (reduction in breast cancer risk and peace of mind) and harm (invasiveness of the procedure and morbidity). There is now an obvious paradox in the surgical management of breast cancer. Since the advent of breast-conserving therapy, the surgical treatment of this disease has become less radical. Nevertheless, measures taken to prevent the disease are often more radical, with greater numbers of women opting for BPM or CPM. Also, it should be emphasized that we can never be absolutely sure who will develop breast cancer. In women with unilateral breast cancer, we can never be sure who will develop contralateral disease. Thus, many women may undergo BPM or CPM needlessly.

Bilateral Prophylactic Mastectomy

No randomized prospective studies have assessed the efficacy of BPM. However, the results of several retrospective and nonrandomized prospective studies have been published, and we can only discuss a few. Some of these studies assessed the effect of BPM in high-risk women regardless of BRCA status, while others assessed the impact of BPM specifically in BRCA mutation carriers.

There are 2 important studies that have assessed the efficacy of BPM regardless of BRCA status. In a landmark study, Hartmann and colleagues identified 639 women with a family history of breast cancer who had undergone BPM at the Mayo Clinic.[81] On the basis of family history alone, these women were classified as either moderate-risk or high-risk for breast cancer. In the moderate-risk group, the Gail model was used to predict the number of breast cancers expected, while women in the high-risk group were compared with their sisters who had not undergone BPM. According to the Gail model, 37.4 breast cancers were expected in the moderate-risk group, yet only 4 developed following BPM, suggesting that the procedure reduced breast cancer risk by 89.5%. Among

women in the high-risk group, breast cancer was diagnosed in 1.4% following BPM and 38.7% of the sisters who had not undergone BPM, suggesting that the procedure reduced breast cancer risk in these women by more than 90%.

Subsequently, Geiger and colleagues conducted a population-based study to assess the efficacy of BPM in community practices.[82] This was a retrospective case-cohort study that again examined the efficacy of BPM regardless of BRCA status. Women with 1 or more breast cancer risk factors (family history, history of atypical ductal hyperplasia, or breast biopsies with other benign findings) were identified. The authors reported that breast cancer developed in 4% of women who did not undergo BPM, but in only 0.4% of those who did. Thus, this study also suggested that BPM reduced breast cancer risk by approximately 90%.

There are only a few studies that have specifically assessed the efficacy of BPM in BRCA1 and BRCA2 mutation carriers. Meijers-Heijboer and colleagues conducted a nonrandomized prospective study of 139 mutation carriers enrolled in a breast cancer surveillance program at the Rotterdam Family Cancer Clinic.[83] None had been diagnosed with breast cancer at time of initial enrollment, and 76 subsequently underwent BPM while 63 were followed with regular surveillance. After 3 years of follow-up, there were no breast cancer cases in the BPM group, while 8 breast cancers were diagnosed in women followed with regular surveillance ($P = 0.003$).

Hartmann and colleagues obtained blood samples from many of the high-risk women who participated in their previous Mayo Clinic retrospective cohort study and identified 26 with an alteration in BRCA1 or BRCA2.[84] With a median follow-up of 13.4 years, none of these women developed breast cancer following BPM (0 of 26). The authors estimated that 6 to 9 breast cancers should have developed during this period, so BPM appeared to substantially reduce breast cancer risk in mutation carriers.

Subsequently, Rebbeck and colleagues reported results of the Prevention and Observation of Surgical Endpoints (PROSE) study, where 105 BRCA mutation carriers were followed prospectively after BPM and compared with 378 matched controls (BRCA mutation carriers who did not have BPM).[85] After a mean follow-up of 6.4 years, breast cancer was diagnosed in 2 (1.9%) women who underwent BPM vs 184 (48.7%) of those who did not. As the BRCA mutation carriers are also at increased risk for ovarian cancer, the PROSE investigators assessed the impact of prophylactic salpingo-oophorectomy (PSO) on breast cancer risk. It has been reported that, in BRCA mutation carriers, PSO reduces the risk of

ovarian cancer by approximately 90%.[86] Thus, cases and controls were matched according to PSO, and while BPM alone reduced breast cancer risk by 90%, the risk was reduced 95% if the patient underwent both PSO and BPM. PSO alone appears to reduce breast cancer risk by approximately 50%, but it should be noted that PSO reduces this risk only if it is done during the premenopausal years.

Taken together, the studies discussed above suggest that BPM reduces breast cancer risk by approximately 90%. Additionally, premenopausal BRCA mutation carriers may reduce their breast cancer risk by approximately 50% with PSO. Nevertheless, much less is known about what effect, if any, these procedures have on mortality. Again, randomized prospective trials would be required to conclusively determine the effect on mortality, but such trials have not been undertaken. However, 2 of the studies mentioned above reported data on disease-specific (breast cancer) mortality. Hartmann and colleagues examined the mortality effect of BPM among women at high and moderate risk for breast cancer who were not necessarily BRCA mutation carriers.[81] Among the 214 women at high risk, 2 died of breast cancer following BPM, compared with 90 deaths among their sisters who did not undergo BPM. Among the 425 participants in the moderate risk group who underwent BPM, no breast cancer deaths were reported, even though 10.4 deaths were expected according to the Gail model. Thus, women in the high-risk group experienced 81% to 94% reduction in breast cancer mortality while those in the moderate risk group experienced a 100% reduction in breast cancer mortality following BPM. Subsequently, in their prospective cohort study of BRCA mutation carriers, Meijers-Heijboer and colleagues reported no breast cancer deaths among the 76 women who underwent BPM and 1 death among the 63 women who chose surveillance after 3 years of follow-up.[83]

Contralateral Prophylactic Mastectomy

Following diagnosis of unilateral breast cancer, the risk of a cancer diagnosis in the contralateral breast is greatly increased.[87] In more recent years, greater numbers of breast cancer survivors have been diagnosed with contralateral breast cancer. This trend likely reflects the greater number of breast cancer patients who are living longer (due to improvements in breast cancer treatment) and improvements in technology, such as mammography, that enable detection of greater numbers of occult cancers in the contralateral breast. Nevertheless, diagnosis of unilateral breast cancer is itself an independent predictor of increased risk for contralateral breast cancer.[88] For women with Stage I or II breast cancer, the risk of contralateral breast cancer is approximately 1% per year after

initial diagnosis, with a cumulative risk of approximately 17% at 20 years.[89] For women with BRCA mutations, the risk of developing a contralateral breast cancer is much higher, approximately 39% at 15 years.[90] However, it should be noted that the risk of contralateral breast cancer is somewhat reduced among women treated with systemic therapy.

There are several reasons a woman with unilateral breast cancer might choose CPM.[87] Anxiety, the desire for symmetry following unilateral mastectomy (with or without reconstruction), difficulties with surveillance of the opposite breast, and a strong family history of breast cancer are frequently mentioned as reasons. No randomized prospective trials have assessed the impact of CPM on outcomes, so evidence of efficacy is derived from retrospective studies, all of which have important limitations.

Several studies have examined the effect of CPM on subsequent contralateral breast cancer risk. In a retrospective study with a mean follow-up of 6.8 years, Peralta and colleagues observed no contralateral breast cancers among 64 women who underwent CPM, and 36 among 182 women (19.8%) who did not undergo CPM.[91] Subsequently, McDonnell and colleagues reported on the outcomes of 745 women with both a personal history of breast cancer and a family history of breast or ovarian cancer who underwent CPM.[92] After a median follow-up of 10 years, only 8 women (1.1%) were diagnosed with contralateral breast cancer, even though 17.9% were expected according to the Anderson model. Thus, both these studies indicated substantial reductions in risk of contralateral breast cancer following CPM.

More recently, Herrinton and colleagues undertook a retrospective cohort study of approximately 56,400 women from the Cancer Research Network Project who were diagnosed with unilateral breast cancer during the years 1979 and 1999.[93] These authors identified 1072 women (1.9%) who underwent CPM and compared them to a sample of 317 women with similar characteristics who did not undergo CPM. Contralateral breast cancer developed in 0.5% of women with CPM and 2.7% of those without CPM. In the CPM group, 8.1% died of breast cancer, while in the comparison group breast cancer deaths were reported in 11.7%. Thus, CPM appeared to have a profoundly beneficial effect, reducing the risk of contralateral breast cancer by approximately 97%, and the risk of death from breast cancer by 43%.

However, there have been 2 retrospective studies from a group of investigators in Rotterdam that seem to suggest that CPM does not affect breast cancer specific survival in BRCA1 and BRCA2 mutation carriers.[94,95] However, these were relatively small studies with 223 patients

(51 of whom had CPM) and 268 patients (38 of whom had CPM), with a median follow-up period of approximately 5 years.

Biases Associated With Nonrandomized Studies

As indicated previously, there are no randomized prospective trials that have assessed the effects of BPM or CPM. Although the studies discussed above seem to suggest that BPM and CPM reduce breast cancer incidence (and some suggest that they may even reduce breast cancer mortality), these studies have important limitations.[96] In particular, 4 potential biases merit specific consideration: selection, performance, detection, and attrition.[97]

Selection bias refers to systematic differences between the study and control groups with respect to prognosis or treatments.[98] Randomization is the method used to reduce selection bias, but none of the studies mentioned above were randomized trials. Thus, even though the above-mentioned studies suggest that mastectomy reduces breast cancer incidence and mortality, this benefit might not be due to the procedure itself, but partly to other differences between the study and control groups. For instance, one might speculate that women who underwent BPM or CPM had better access to healthcare, and that other unforeseen factors related to improved healthcare access partly accounted for the reduction in breast cancer incidence and mortality.

Performance bias refers to uncertainties in verifying whether the procedure (BPM or CPM) was actually performed.[97] Were medical or surgical records used to confirm that these procedures were done, or did the investigators sometimes rely on self-report? For instance, a patient might report that she had a CPM, when, in fact, she might have undergone a lumpectomy for a benign condition. Alternatively, a patient who underwent a bilateral nipple-sparing mastectomy might not consider this procedure a BPM. Thus, retrospective studies might be associated with ambiguities as to whether a BPM or CPM had been performed in each instance.

The results of the above-mentioned studies may also partly reflect a detection bias.[99] Thus, the breast cancer detection methods likely differed between patients who underwent BPM or CPM and patients who did not. For instance, mammography screening is generally not recommended following bilateral mastectomy, while it is strongly urged for all other women over the age of 40 in the USA. Mammography screening may detect occult cancers with very little malignant potential (such as ductal carcinoma in situ (DCIS) or very indolent invasive cancers). In large randomized trials comparing mammography screening with usual care, a

TABLE 3. Potential benefit of various procedures on breast cancer risk and mortality

	Reduction in breast cancer risk	Reduction in breast cancer mortality
Bilateral prophylactic mastectomy (BPM)	90%	90%
Contralateral prophylactic mastectomy (CPM)	90%	43%
Prophylactic salpingo-oophorectomy (PSO)	50%	
BPM + PSO	95%	

greater incidence of breast cancer was always reported among women who underwent mammography screening.[100] Thus, at least some of the reported reduction in breast cancer incidence following BPM or CPM was likely due to a detection bias, arising from differences in the use of mammography screening between the control and study arms.

Finally, the above-mentioned studies might be associated with an attrition bias.[101] Attrition bias refers to differences in the period of follow-up between patients who underwent BPM or CPM and those who did not. Many women who underwent BPM or CPM might have been discharged from further follow-up, whereas those who retained their breasts may potentially have received closer follow-up. Differences in the extent of follow-up between these 2 groups of patients could potentially have influenced breast cancer detection rates and thereby the results of these studies.

Thus, although the above-mentioned studies indicate that BPM and CPM reduce breast cancer incidence and even breast cancer mortality, these studies have important limitations (Table 3). Prior to embarking on BPM or CPM, patients must be informed of these limitations and of the potential risks and benefits of these procedures. Furthermore, patients should clearly understand that BPM and CPM do not entirely eliminate the risk of initial or contralateral breast cancer, respectively.

Quality of Life

BPM and CPM may have profound effects on quality of life, but little is known about these effects because there have been very few prospective studies addressing these issues.[97,102] Most studies have been retrospective, with important methodological limitations. For instance, in some retrospective studies, women were asked to recall their psychological state before prophylactic surgery, and this was then compared with their psychological state after surgery. Recall bias may have significantly influenced the results of such studies, with many patients unable to accurately recall their psychological state before surgery.[103] Additionally,

it has been reported that many studies used patient satisfaction instruments that had not been validated, and unvalidated instruments may overestimate the level of satisfaction. Nevertheless, most of the published studies (both retrospective and prospective) seem to indicate that PM reduces psychological morbidity (particularly anxiety), but may have adverse effects on sexuality and body image.[102] Clearly, additional studies are needed to further elucidate the effects of PM on these important outcomes.

Surgical Trends

The use of BPM has likely increased dramatically in recent years, but the actual extent of this increase is not fully understood. As the use of genetic testing increases in the years ahead, so undoubtedly will the use of BPM. For patients with Stage I to III invasive breast cancer, the rate of CPM in the USA increased from 1.8% in 1998 to 4.5% in 2003.[104] For patients with newly diagnosed DCIS, the rate of CPM increased from 2.1% in 1998 to 5.2% in 2005.[105] It is not clear what factors are responsible for the increased use of CPM, and to what extent surgeons have influenced these trends. The wider use of genetic testing and breast MRI are perhaps partly responsible.[106,107] Nevertheless, surgeons have a responsibility to tell patients that the potential impact of CPM and BPM on breast cancer incidence and mortality are not fully understood. Additionally, the potential risks of these procedures should be discussed with each patient before surgery. Finally, patients should be informed that these procedures may have considerable effects on quality of life, and that our understanding of these effects is limited. In the years ahead, carefully planned studies will be required to better elucidate the full impact of BPM and CPM on breast cancer outcomes.

Gastric Cancer

Although the incidence of gastric cancer has decreased steadily over the past 5 decades, it is still the second most common cause of cancer death worldwide.[108] There are 2 major histologic types of gastric cancer: (1) intestinal, which is the more common variant and has a strong association with environmental factors, and (2) diffuse gastric cancer (DGC), which is characterized by multifocal signet ring cell infiltrates and is more likely to be attributed to host-factor effects.[109] About 10% of all gastric cancers have family clustering indicating a genetic predisposition.[110]

Hereditary diffuse gastric cancer (HDGC) is an autosomal-dominant cancer syndrome with 70% to 80% penetrance attributed to mutations of the E-cadherin gene, *CDH1*.[111] In 1999, the International Gastric Cancer

Linkage Consortium defined HDGC as "(1) two or more documented cases of DGC in first/second degree relatives, with at least one diagnosed before the age of 50, or (2) three or more cases of documented DGC in first/second degree relatives, independently of age of onset."[112] Approximately 40% of well-defined HDGC families may be found to harbor *CDH1* mutations.[112] Women carrying the mutation also have an approximately 20% to 40% lifetime risk of developing lobular carcinoma of the breast.[113,114]

Because the signet ring cancer cells in HDGC are located in gastric submucosa, surveillance endoscopy has an unacceptably high false negative rate. There is in fact no effective method for detection of cancer in this patient population. Therefore, prophylactic total gastrectomy is recommended for asymptomatic carriers of *CDH1* mutations. Since the discovery of *CDH1* gene mutations in 1998, many totally asymptomatic patients from different kindreds with varying *CDH1* gene mutations and a family history of HDGC have been treated with prophylactic total gastrectomy. Occult signet ring cell carcinoma foci have been found in the stomach in most of those patients.[115-120]

Germline CDH1 Mutation and HDGC

In 1998, Guilford and colleagues identified mutations of the *CDH1* gene in members of Maori families with HDGC.[121] In 1 family, 25 members died of HDGC over 3 decades. Mutation analysis showed a G → T nucleotide substitution in Exon 7 of the *CDH1* subtype of the E-cadherin gene, which leads to a truncated gene product. They noted that diminished E-cadherin expression is associated with aggressive, poorly differentiated carcinomas. To date, more than 100 different germ line *CDH1* mutations have been described in HDGC families in a diverse range of ethnic groups.[122] Of the identified mutations, approximately one half are frameshift or nonsense mutations resulting in nonfunctioning E-cadherin protein.[123] Some mis-sense mutations have been found to have deleterious effect as well, although most of them have no clinical significance.[124]

The *CDH1* gene is located on chromosome 16q22.1. It comprises 16 exons, spanning approximately −100 kb of genomic DNA, which are transcribed into a 4.5-kb mRNA.[125] E-cadherin is encoded by *CDH1*. It is a transmembrane protein with 5 extracellular domains and a cytoplasmic domain that connects to the actin cytoskeleton through a complex with α-, β-, and γ-catenins.[126] *CDH1* acts as a tumor suppressor gene, with a germ line mutation followed by second hit inactivation of *CDH1* leading to tumorigenesis.[127] Fig 13 shows the structure of *CDH1* gene and the 3 distinct mutations found in 3 families treated at our institution.[128]

HDGC families carry *CDH1* heterozygous germ line mutations; their

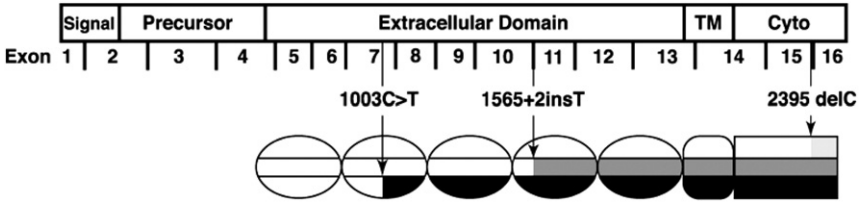

FIG 13. The structure of *CDH1* gene, which is composed of 5 extracellular cadherin repeats, a transmembrane region, and a highly conserved cytoplasmic tail encoded by 16 exons. White represents functional E-cadherin protein. Black, dark gray, and light gray represent nonfunctional protein sequences encoded by *CDH1* mutations in the asymptomatic *CDH1* mutation carriers treated at our institution. 1003C > T is a nonsense mutation resulting in a truncated protein. 1565 + 2insT occurs at a splice-site and disrupts normal protein splicing. 2395delC causes a frame shift in the protein sequence. (Reprinted with permission from Rogers et al.[128])

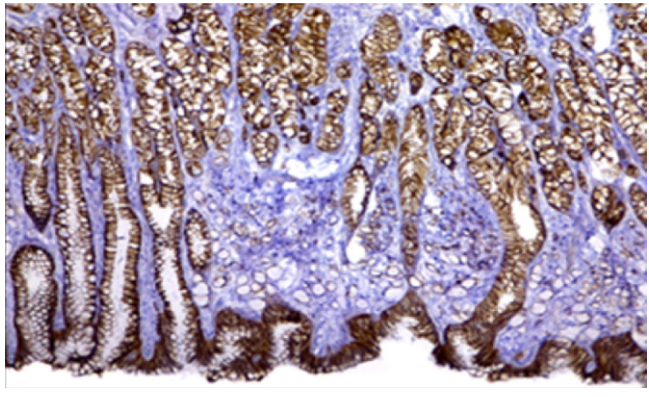

FIG 14. Immunohistochemistry for E-cadherin in signet ring cancer cells from a patient with a *CDH1* mutation and HDGC. Note that the intramucosal signet ring cells stain negative for E-cadherin, showing that the mutation results in a loss of E-cadherin protein that causes the cancer phenotype. (Color version of figure is available online.)

tumors acquire complete *CDH1* inactivation through second-hit mechanisms to inactivate the nonmutated *CDH1* gene on the other allele. Low E-cadherin expression has been found to be present in HDGC tumors compared with the surrounding nonmalignant mucosa (Fig 14), confirming that the nonmutated *CDH1* allele has also been downregulated or lost.[129] Promoter hypermethylation has been found to be the most common cause of the second hit, with somatic mutations a less common cause.[129-131] Interestingly, different neoplastic lesions from the same patient frequently display distinct second hit mechanisms and different second hit mechanisms may even be detected within the same tumor sample.[132]

Genetic Counseling and Testing

The American Society of Clinical Oncology recommends that an individual should not be tested for a cancer predisposition gene unless there is a reasonably high likelihood of detecting a disease-causing mutation, and the result is intended to influence medical management.[133] The current recommendations for genetic screening for *CDH1* mutation include the following: 1) families with 2 cases of DGC and at least 1 case diagnosed before age 50 years; 2) families with 3 cases of DGC diagnosed at any age; 3) isolated individuals diagnosed with DGC before age 35 years; 4) isolated individuals with both DGC and lobular breast cancer; and 5) families with 1 member with DGC and another with either lobular breast cancer or signet ring cell colon cancer.[127,134] In addition, it is appropriate to refer patients with pathologic characteristics strongly suggestive of HDGC for genetic testing. Testing for *CDH1* mutations is also recommended for families with multiple cases of lobular breast cancer with negative testing for BRCA mutations. When to initiate genetic testing for children or young adults in HDGC families is yet to be determined. Most authors recommend starting genetic testing when individuals are in their early 20s. Recently, the New Zealand HDGC Group proposed that all family members should be offered testing at the age of 16 years.[123]

Signet ring cell carcinoma of the colon, a rare subtype of colon cancer, has been found in 2 families with *CDH1* germ line mutations.[114,135] However, the incidence does not appear to be significantly higher than in the general population.[111] Although in some reports, asymptomatic patients underwent colonoscopy to rule out colon cancer at young age, more studies are needed to better define the incidence of colon cancer in HDGC families and the role of early screening colonoscopy.[116]

Genetic counseling is an important part of the management of families with HDGC and should start before genetic testing is performed. The inheritance pattern of the disease, inadequacy of surveillance endoscopy, and risks and benefits of prophylactic gastrectomy must be clearly communicated with family members by a team that includes a geneticist, gastroenterologist, and medical and surgical oncologist.

Surveillance

Endoscopic surveillance for HDGC is ineffective because asymptomatic individuals typically have tiny scattered foci of signet ring cell cancer underlying normal epithelium. In a large series of patients with HDGC, 21/23 (91%) patients were not detected by preoperative esophagogas-

troduodenoscopy.[116] At our institution, only 2 of the 12 individuals had biopsy-proven carcinoma before gastrectomy (Norton JA et al, unpublished data).[128] in 1 case, a single 1-mm focus of intramucosal signet ring cell carcinoma was identified in 1 of 20 biopsy fragments. In another patient, signet ring cell carcinoma was found at lesser curvature and cardia biopsies with infiltration into the lamina propria.

It is reported that the addition of chromoendoscopy with Congo red–methylene blue after white-light gastroscopy improves the sensitivity of detection of early HDGC in New Zealand.[136] In addition, in our previous report, we found that most cancer foci were located within the proximal one third of the stomach.[128] This observed site predilection suggests that surveillance biopsies should be geographically targeted in patients who elect to delay surgical intervention and have no detectable lesion on standard white light and chromoendoscopy. Our finding is also confirmed by the recent report from Barber, in which they show a predominance of foci within the fundus and body with antral sparing.[137] However, reports from the New Zealand groups showed that in some HDGC stomachs the lesion density is highest in the transitional zone between the body and antrum or distal stomatch.[138,139] It is possible that in this regard that HDGC in Maori families behaves differently from HDGC in North America families. The best surveillance results are also from New Zealand with the Congo red–methylene blue method detecting 10 of 33 family members with *CDH1* mutation.[136] However, this finding is not replicable by the North American groups.

No official guidelines exist for the surveillance of E-cadherin germ line mutation carriers who refuses total gastrectomy; however, the second International Gastric Cancer Linkage Consortium International Meeting in 2008 recommended that these individuals be examined by an experienced endoscopist every 6 months with random mucosal biopsies representative of the fundus, body, incisura, and antrum of the stomach. At our institution, most of the surveillance endoscopies were done by a single gastroenterologist. These procedures required much longer block time than the routine endoscopy. High-resolution chromoendoscopy and endoscopic ultrasound were used in these cases. Multiple biopsies were taken with a cardia-to-body ratio of 2:1.

There is clearly a need for the development of improved screening modalities for patients who do not want to undergo prophylactic gastrectomy. Other newly introduced endoscopic modalities include high-resolution endoscopy, magnifying endoscopy, auto-fluorescence endoscopy, and narrow-band imaging. These may be promising techniques and should be evaluated in the setting of HDGC surveillance. Endoscopic

ultrasonography and fluorodeoxyglucose positive emission tomography have not proved useful in these patients.

Screening for lobular carcinoma of the breast is an important part of surveillance for women with *CDH1* mutations. It is recommended that those women with *CDH1* mutation should have annual mammography and MRI, preferably starting at the age of 25. Tamoxifen therapy has been mentioned to reduce the development of breast cancer, but no trials have been reported in *CDH1* patients with HDGC.

Risk-Reducing Prophylactic Gastrectomy

By the time patients with HDGC develop symptoms, they typically have distant metastasis resulting in an unacceptably high mortality rate. Because of the lack of effective screening, prophylactic total gastrectomy is recommended for carriers of *CDH1* germ line mutations. This is similar to surgical prophylaxis for medullary carcinoma of the thyroid, colon cancer in FAP, and Lynch syndrome, and breast cancer in BRCA mutation carriers.

The decision to undergo a prophylactic gastrectomy should not be taken lightly, because the procedure carries an approximately 2% to 4% perioperative mortality and nearly 100% long-term morbidity, including weight loss, lactose intolerance, fat malabsorption and steatorrhea, micronutrient deficiencies, postprandial fullness, and bacterial overgrowth.[140] The risks and benefits of surgery should be discussed in detail. It is important to explain to the patient that disease penetrance of HDGC is only 70% to 80%, and hence a prophylactic gastrectomy would result in 20% to 30% incidence of unnecessary operations.[111] With the assistance of a dietician, they should be counseled on a postgastrectomy diet, expected weight loss, and potential metabolic consequences including vitamin B12, iron, thiamine, and zinc deficiencies.

The age at which prophylactic gastrectomy should be performed has not yet been determined. Some authors propose that it occurs during the second decade of life.[123] Our recommendation is to consider surgery when the individual with a *CDH1* mutation is 5 years younger than the youngest family member who has developed HDGC. This guideline would allow the patients to eat normally and maintain their nutrition for as long as possible, but would still remove the stomach while cancer foci are hopefully small and confined to gastric mucosa.

At our institution, we routinely perform total gastrectomy, omentectomy, D-2 lymph node dissection, and Roux-en-Y esophagojejunostomy for *CDH1* mutation carriers.[115] It is important to actually do a total

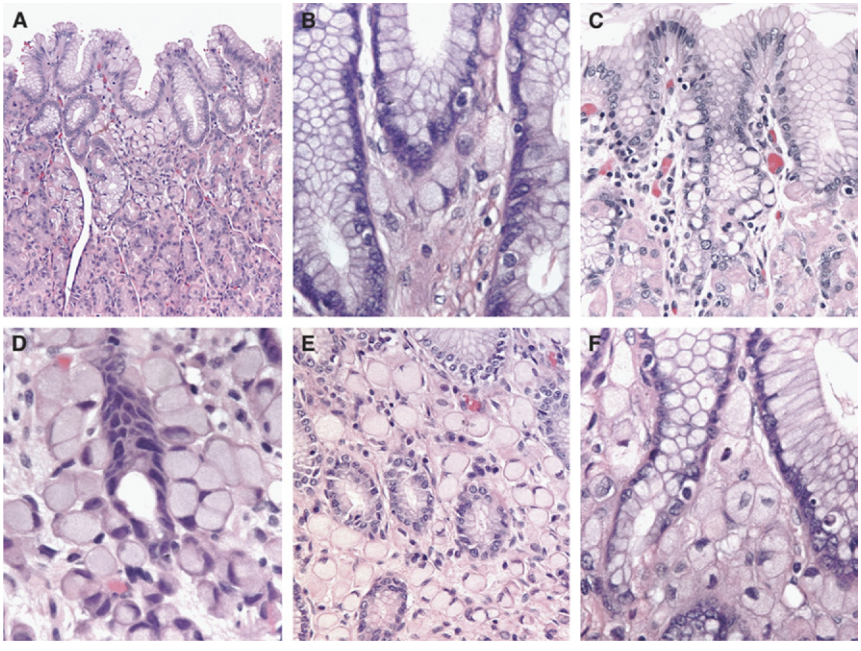

FIG 15. Occult signet ring cell carcinoma in asymptomatic *CDH1* mutation carriers. Foci of invasive signet ring cell carcinoma can be small and subtle and seem to arise in the lower zone of the foveolar epithelium (A, B). Signet ring cell carcinoma in situ (C). Invasive signet ring cells may wrap around and displace gastric glands (D). Neoplastic cells seem to decrease in size with increasing depth of invasion (E). Although most cells show classic signet ring morphology, some may mimic histiocytes with granular to bubbly cytoplasm and centrally placed nuclei (F). (Reprinted with permission from Rogers et al.[128]) (Color version of figure is available online.)

gastrectomy because our pathologic studies have demonstrated that signet ring cell carcinoma is most commonly found in the proximal stomatch near the cardia.[128] The Roux-en-Y esophagojejunostomy does not include a pouch. The end of the esophagus is anastomosed to the side of the jejunum with an end to end anastomosis no. 29 stapler. A gastrografin upper gastrointestinal series to examine the esophagojejunostomy is done on postoperative day 4 to 5. Clear liquid diet is started if there is no leak and rapidly progresses to 6 small feed postgastrectomy diet. The patients generally are discharged home on postoperative day 6 or 7. For all the asymptomatic patients with *CDH1* mutations treated at our institution, there were no major complications or mortality. Most patients have multiple small foci of T1, N0 invasive diffuse gastric adenocarcinoma (pure signet-ring cell type). Fig 15 shows foci of signet ring adenocarcinoma cells, with the characteristic morphology including round discohe-

sive cells with a nucleus compressed to the periphery by abundant intracytoplasmic mucin with the same pale eosinophilic tincture and granularity of that seen in the foveolar mucus neck cells.[128] No patient had lymph node or distant metastases. Each patient has had no new or recurrent cancer on follow-up at 3 years.

We routinely perform D2 lymph node dissection to remove all the lymph nodes around the stomach.[115] Based on our experience, this dissection does not cause significant additional morbidity while providing us an accurate lymph nodes status. A less aggressive approach of D1 lymph node dissection for asymptomatic HDGC patients was also reported.[141] Because of the high rate of metastasis in symptomatic patients and the anatomical ease of dissection, we believe that a more extensive D2 lymph node dissection is justified to better stage patients and direct management.

As some of the postgastrectomy syndromes can be attributed to loss of celiac and hepatic branches of the vagus nerve, Miwa and colleagues reported a new technique of vagus-nerve–sparing gastrectomy with D2 lymph nodes dissection to improve the quality of life for those patients. Patients who underwent vagus-sparing gastrectomy had less weight loss, diarrhea, and gallstone formation compared with those with traditional gastrectomy.[142] Other Japanese groups also reported vagus-nerve–sparing total gastrectomy as well as laparoscopic-assisted gastrectomy.[143,144] However, this approach has not been widely used outside of Japan. More studies, especially randomized controlled trials, are needed to further assess the benefits vs risks of this nerve-sparing approach. Laparoscopic-assisted total gastrectomy has been performed successfully for HDGC patients.[145] Laparoscopy offers patients less pain, faster recovery, and smaller incisions. This may lead to additional patients choosing prophylactic gastrectomy, particularly if postoperative recovery and cosmesis are important considerations.

The diffuse signet ring cell cancer detected in prophylactic gastrectomies almost invariably has been minute, underlying the normal gastric mucosa, with many measuring less than 1 mm in diameter.[115,128] The rate of progression of these small cancer foci to metastatic gastric cancer is still not well understood and is an area of active study. It is possible that some of these microscopic foci are indolent and carry little potential for metastasis.

The management of family members with HDGC without a recognizable *CDH1* mutation is still problematic. It is likely that those individuals may have a mutation of an unknown tumor suppressor gene. We do not

recommend prophylactic gastrectomy in these patients. These patients should be followed up with surveillance endoscopy.

Future Perspectives for HDGC

Because the role of *CDH1* mutations in HDGC was discovered in 1998, tremendous progress has been made in the diagnosis and treatment of this deadly disease. Asymptomatic patients with *CDH1* mutations are now detected with genetic testing alone and offered potentially curative prophylactic gastrectomy. Future work in molecular imaging and improved endoscopy technique are needed to improve the sensitivity of surveillance. Further genetic studies on patients with positive HDGC family history but without *CDH1* mutations, and on patients with missense mutations, will improve the management of these patients. A better plan for prevention, early detection, chemoprevention using estrogen receptor antagonists such as tamoxifen, and prophylactic surgical treatment for lobular cancer of the breast also needs to be established for women with *CDH1* mutations. With regard to prophylactic gastrectomy, the extent of lymphdenectomy, alternative methods of reconstruction incorporating a pouch reservoir, and vagus-nerve–preserving gastrectomy should be evaluated.

Thyroid Cancer

The multiple endocrine neoplasia type 2 syndromes (MEN 2) are rare hereditary cancer and endocrinopathy syndromes caused by germ line activating missense mutations in the *RET* oncogene, a transmembrane receptor tyrosine kinase. Transmission is autosomal dominant. All of these syndromes share the clinical feature of medullary thyroid carcinoma (MTC), a malignancy of thyroid parafollicular C cells. In these patients, MTC occurs with nearly complete penetrance, is multifocal and bilateral, and occurs at an earlier age than sporadic cases. MTC is associated with multicentric C-cell hyperplasia, with an age-related progression to cancer.[146-148] MTC arises from thyroid parafollicular C cells, which produce, store, and secrete calcitonin. Patients with locally advanced MTC present with a palpable mass and may have symptoms of dysphagia, shortness of breath, or hoarseness. Metastases to regional cervical lymph nodes are common in patients with palpable, clinically evident thyroid tumors.[149] Other typical metastatic sites include the upper and anterior mediastinum, lungs, liver, and bone.[149] The clinical features of MEN 2 are variably expressed and the presentation differs between the specific syndromes.

The lifetime penetrance of MTC is near 100% in carriers of *RET* mutations associated with MEN 2 syndromes. Therefore, all patients

diagnosed with MEN 2 should undergo total thyroidectomy. Recommendations for the timing and extent of surgery differ based on the patient's age at diagnosis, clinical presentation, and the risk level of their *RET* mutation.

Clinical Features of MEN 2 Syndromes

MEN 2A. MEN 2A is characterized by MTC, pheochromocytoma, and primary hyperparathyroidism. These patients develop multifocal, bilateral MTC. Pheochromocytoma occurs in 42% to 46% of MEN 2A patients.[150,151] The degree of penetrance for pheochromocytoma in MEN 2A correlates with specific *RET* mutations, with the highest expression in carriers of mutations at codon 634.[152] Parathyroid hyperplasia, in 1 or multiple glands, results in primary hyperparathyroidism in 20% to 35% of MEN 2A patients overall, although this also varies by kindred.[150,153] Cutaneous lichen amyloidosis and Hirschsprung disease (HSCR) also occur, although rarely, in patients with MEN 2A.[154-161]

FMTC. Familial medullary thyroid cancer (FMTC) is characterized by MTC but no other endocrine neoplasms. MTC in these patients tends to be the least aggressive, with a later age of onset and earlier stage at diagnosis. HSCR has been reported in association with FMTC in a few kindreds.[162]

MEN 2B. Patients with MEN 2B also develop MTC and pheochromocytomas but do not develop primary hyperparathyroidism, in contrast to MEN 2A patients. All MEN 2B patients develop MTC, often in infancy or early childhood. Of the hereditary MTCs, those in the setting of MEN 2B present in the youngest patients and are most likely to have an advanced stage at diagnosis.[163] Pheochromocytoma occurs in approximately 50% of MEN 2B cases.[164] MEN 2B patients may have skeletal abnormalities such as scoliosis, club foot deformity, and hip problems.

Mucosal neuromas are another characteristic of MEN 2B. Most commonly they are seen on the lips, tongue, inner eyelids, and conjunctivae, although the gingiva, buccal mucosa, nasal mucosa, and vocal cords may also be involved. Most MEN 2B patients have gangioneuromas of the gastrointestinal tract with a megacolon.

Screening for MEN 2 and the Impact of RET Mutation Testing

Calcitonin is produced by thyroid C cells and is well-established as a tumor marker for MTC. Stimulated calcitonin screening is highly sensitive and specific for MTC. However, the false positive rate is estimated at

5% to 10%, and small foci of early stage MTC have been reported in MEN 2 carriers with negative stimulated calcitonin tests.[165] Germline gain-of-function mutations in the *RET* oncogene are responsible for the development of MEN 2 syndromes.[166-168] Sequencing of the *RET* gene to detect germ line mutations is now the standard screening test for MEN 2 syndromes. *RET* mutation testing can identify young carriers at an earlier stage of disease, often before they develop cancer, and it has lower false positive and false negative rates than calcitonin testing for MEN 2 screening.

Testing for germ line *RET* mutations is indicated in several clinical settings. *RET* mutation testing should be performed routinely for at-risk family members of MEN 2 and FMTC patients. If possible, testing should occur at birth, because carrier status determines the need for clinical screening and preventive surgery. When an index case is identified, all family members at risk should undergo testing, regardless of their age. In families where the transmitted allele is already known, *RET* sequencing can be limited to the site of the known mutation. Those family members who are negative for their kindred's known mutation have the same risk for MEN 2 as the general population, and they need no other screening.

RET mutation testing should also be considered for patients who present with MTC, pheochromocytoma, or Hirschprung diease, who do not have a family history of these disorders. Approximately 5% to 7% of patients presumed to have sporadic MTC are found to have a germ line *RET* mutation.[166-168] Up to 24% of pheochromocytomas are hereditary, with 5% resulting from *RET* mutations.[169] One recent report described 2 new MEN 2A kindreds that were identified by *RET* mutation testing of 2 members who presented with HSCR.[170] Identification of other carriers in these 2 families resulted in thyroidectomies for several relatives, all of whom had C-cell hyperplasia or MTC identified on pathology.

Preventive Surgery for Thyroid Cancer

The best chance for cure or prevention of MTC in MEN 2 patients is thyroidectomy early in life, ideally before MTC has developed. Several studies have demonstrated improved biochemical cure rates and/or decreased recurrence rates from early thyroidectomy, performed after positive screening by calcitonin testing or *RET* mutation testing.[171-174] Those who undergo surgery later in life have a higher risk of metastatic disease. A truly preventive procedure can be achieved most reliably in infancy or early childhood, underlying the importance of screening family members of known carriers at birth. Even in young MEN 2 patients with

normal calcitonin levels, MTC and/or C cell hyperplasia may be detected in thyroidectomy specimens.[165]

RET mutations have been stratified into 3 risk levels for thyroid management, per the consensus guidelines published in 2001.[175] Patients with MEN 2B have the most aggressive form of MTC, with invasive disease reported in patients less than 1 year of age.[175-177] MEN 2B results most commonly from a mutation at codon 918 (>95%), but has also been associated with mutations at codons 883, 922, or dual mutations at codon 804 plus either 806 or 904. These mutations are considered the highest risk level, designated level III. Patients with level III mutations should undergo a total thyroidectomy as early in life as possible.[175] Locating the parathyroid glands can be challenging in infants, so these procedures are best performed by a surgeon experienced in pediatric thyroidectomy.

Patients with MEN 2A have variably aggressive MTC. Mutations in codons 634, 620, 618, and 611 are considered high risk (Level II) according to the consensus guidelines.[175] MTC has been found in thyroidectomies from patients with codon 634 mutations as young as 1 year of age, although this is unusual.[168] Patients with level II mutations should undergo a total thyroidectomy before 6 years of age. Central lymph node dissection should be considered if the preoperative calcitonin level is greeater than 40 pg/mL, or if there is evidence of a thyroid tumor by palpation or ultrasound. However, rates of hypoparathyroidism and recurrent laryngeal nerve injury increase with more extensive resection, and complications of thyroidectomy are higher overall for children under 7 years of age than for other patients.[146,178,179] There is evidence that the risk of lymph node metastasis is very low in MEN 2A patients under the age of 8, with normal calcitonin levels, who undergo thyroidectomy.[180,181] For those patients total thyroidectomy alone, with attempted preservation of the parathyroid glands in situ may be sufficient.[182]

A larger subset of *RET* mutations, associated with MEN 2A and/or FMTC, are considered lowest risk (Level I). These include mutations at codons 768, 790, 791, 804, and 891.[175] Codon 609 was also included as Level I in the consensus guidelines, but since their publication a case report described focal MTC in a 5 year old with a normal stimulated calcitonin level and a mutation at this site.[183] Based on these data, some authors now advocate managing patients with codon 609 mutations as risk Level II. For patients with low risk, level I mutations, total thyroidectomy is recommended, but there are no established guidelines regarding timing; operation before age 5 to 10 is considered appropriate. Some advocate serial pentagastrin-stimulated calcitonin testing, with thyroidectomy at the first positive test.[175] However, pentagastrin is not

available for clinical use in the USA, and basal or calcium-stimulated calcitonin assays may not be as sensitive for early MTC. As with the level II mutations, the need for central lymph node dissection should be guided by calcitonin levels and clinical features of the patient and kindred.

Since publication of the consensus guidelines, several new mutations have been described in association with MEN 2 syndromes, at codons 912, 630, 631, 606, 533, and a 9-bp duplication in Exon 8.[184-189] These are uncommon mutations, and due to lack of clinical experience, their penetrance and aggressiveness are not well characterized. A recent report described a mutation in codon 630 associated with multifocal MTC in a patient 1 year of age and metastatic disease in a 15 year old.[190] Based on this case, some authors now treat it as a high-risk codon, advocating stimulated calcitonin screening from infancy and surgery by 5 or 6 years of age.[190] However, with the exception of codon 630, these are generally thought to be comparable to level I mutations, and principles used for low-risk mutations should guide these patients' management.

Central lymph node dissection and 4-gland parathyroidectomy with autotransplantation should be performed in patients if the basal or stimulated calcitonin level is elevated (greater than 40 pg/mL), or if there is evidence of an intrathyroidal tumor by palpation or ultrasound. Autotransplantation of all or a portion of the gland should be done for any parathyroid if the blood supply is disrupted or if the viability of the gland is uncertain. Primary hyperparathyroidism does not typically develop in MEN 2A patients until adulthood, making it unlikely that they would need this procedure for treatment of parathyroid hyperplasia in childhood. Some surgeons may elect to perform 4-gland parathyroidectomy with autotransplantation to a forearm muscle for selected asymptomatic MEN 2A patients at the time of thyroidectomy, if their mutation or kindred has a high rate of hyperparathyroidism. This may prevent a potentially morbid future neck reoperation if they develop parathyroid hyperplasia later in life. Localization and reoperation at the forearm implantation site is theoretically easier than neck localization and surgery; however, forearm reoperations are not without risk. MEN 2B or FMTC patients will not develop hyperparathyroidism as part of their syndrome, so the sternocleidomastoid muscle may be used for autotransplantation if a parathyroid is are removed.

Postoperative Surveillance and Long-Term Management

The postoperative management of MEN 2 patients with a diagnosis of MTC is similar to that for sporadic MTC patients. Thyroid hormone replacement is required for life. Patients who undergo parathyroidectomy

and autotransplantation will need supplementation with oral calcium and vitamin D for at least 4 to 8 weeks postoperatively. This is gradually withdrawn as the function of the parathyroid autotransplant grafts improves. Serial calcitonin testing is used to monitor for persistent or recurrent MTC. Pentagastrin-stimulated testing is more sensitive than basal testing for a small disease burden, but pentagastrin is not available in many countries, including the USA. In most cases, calcitonin levels stabilize after approximately 72 hours, but they may take up to weeks or months to normalize in some patients.[191,192]

The term "biochemical cure" is used to refer to patients with normal calcitonin levels after surgery for MTC. Complete postoperative normalization of calcitonin has been associated with decreased long-term risk of MTC recurrence, although the evidence is less clear for a survival benefit.[193-195] All patients who have undergone thyroidectomy and central lymph node dissection for MTC should have a basal calcitonin level measured several weeks postoperatively, and annual serial measurements thereafter. A persistent or recurrent elevation in calcitonin indicates residual or recurrent MTC and warrants additional investigation by imaging. However, since most MTC has a fairly indolent course, patients with biochemical evidence of recurrent disease may not have imaging evidence of recurrent or residual tumor. Observation should be considered in these patients. Patients with localized recurrent disease in the neck should undergo reoperation with the goal of removing all remaining disease. These operations may result in long-term survival benefit and prevent complications of recurrence in the neck.[196]

Data are limited regarding the long-term risk of recurrence or metastasis in *RET* mutation carriers with normal preoperative calcitonin, who undergo preventive surgery based on genetic testing alone. Thyroidectomy in these patients may prove to be curative, especially if no MTC is detected in the surgical resection specimen. Annual serial calcitonin measurements are recommended. Outcomes for these patients will be better characterized as more patients undergo treatment based on genetic screening.

The management of MEN 2 syndromes has changed significantly since the syndromes were first characterized in the mid-20th century. The advent of mutation testing in the RET proto-oncogene, and our growing understanding of the relationships between genotype and phenotype, has refined our diagnostic and prognostic capabilities for MEN 2 syndromes. Preventive surgery based on mutation analysis may prove to be a cure for MTC in young MEN 2 patients. More accurate identification of those at risk has reduced the need for screening in many members of MEN 2 kindreds. As

more is learned about the pathogenesis of this disease, treatment can be further tailored to improve outcomes for individual patients.

Colorectal Cancer

Colorectal cancer is the third leading cause of new cancer diagnosis and the second cause of cancer death among both people in the USA.[197] Most colorectal cancer is sporadic, without an obvious familial predisposition, but there is a portion, as many as 10%, that can be attributed to a heritable cause.[198] HNPCC makes up the largest portion of the inherited colon cancers, followed by FAP. In addition to these conditions, nonhereditary diseases, including inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis, are associated with increased risk of developing colorectal cancer. Although these patients who are at high risk clearly warrant increased screening regimens with colonoscopy, prophylactic resection of the at-risk bowel for the prevention of cancer should be considered.

It has long been recognized that genetic factors play a role in the risk for developing cancer. The understanding has been furthered by the discovery of specific genes involved in certain cancer types. As the role of heritability is appreciated and patients/physicians have a better understanding of an individual's cancer risk, the potential role for prophylactic surgery increases. Specifically, 5 criteria have been described when considering the potential benefit of prophylactic resection of the colon or rectum: 1) penetrance of a genetic mutation, 2) reliability of genetic screening, 3) effectiveness of surgery with reasonable morbidity, 4) suitable organ replacement, and 5) follow-up screening to verify a disease-free state.[199]

Prophylactic surgery for hereditary colon cancer has been described as early as 1901 with the first colectomy being reported for a patient with a familial form of polyposis.[200] Since then, the understanding of the role of genetics has evolved as well as the ability to identify specific genetic mutations. With this, the role of prophylactic surgery has become a topic of increasing consideration. Genetic testing is now routinely recommended by the National Comprehensive Cancer Network (NCCN) for patients with who meet established criteria for HNPCC or FAP.[74] Through increased awareness and recommendations such as these, compliance with colonoscopic screening has continued to increase.[201] Moreover, aggressive screening and interventional colonoscopy programs in such high risk individuals have been shown to reduce the risk for the development of colorectal cancer. Through regular biopsies and aggressive polypectomies, premalignant lesions can be identified and removed, reducing the risk of progression to colon cancer by as much as 40% to 80%.[202]

TABLE 4. Characteristics of hereditary nonpolyposis colon cancer

3% to 10% of all colorectal cancers	Average age of cancer diagnosis: 45 years
Genetic mutation:	Proximal colon most common site of disease
MMR genes: hMSH2, hMLH1, hPMS1, hPMS2, and hMSH6	
~80% lifetime risk of colorectal cancer (mutation-dependent)	

Hereditary Nonpolyposis Colon Cancer

HNPCC, also known as Lynch syndrome, accounts for 3% to 10% of all colon cancers (Table 4).[198,203] The lifetime risk of colon cancer in these patients is approximately 80%, with the average age at diagnosis of 45 years. The cancers tend to occur more commonly in the proximal colon.[204] In addition, there are a variety of extracolonic manifestations of HNPCC, including gynecologic malignancies in women.

HNPCC is an autosomal-dominant condition caused by a mutation in the DNA mismatch repair genes, which act as tumor suppressor genes. These mutations lead to ineffective repair of errors in DNA replication, which in turn leads to an uncontrolled growth of adenomas and accelerated evolution into carcinoma. There are at least 5 known mismatch repair genes genes in which mutations account for the majority of HNPCC cancers: hMSH2, hMLH1, hPMS1, hPMS2, and hMSH6. The most common, hMSH2 and hMLH1, comprise approximately 90% of the mutations.[205] Although sporadic large bowel cancer can take decades to develop, the progression of adenoma to carcinoma in HNPCC individuals can occur within several years.[204,205] Pathologically, HNPCC is often found to have histologic features of poorly differentiated adenocarcinoma. In addition, in contrast to sporadic tumors, peritumoral lymphocytic infiltration can be seen. HNPCC is generally considered to have a better prognosis than sporadic colon cancer of similar pathologic stage.[206] Tumors can also be interrogated for the presence of MSI. In virtually all tumors resulting from HNPCC, these repetitive DNA sequences known as microsatellites have a tendency to undergo a high level of genetic alteration or instability. Tumors can be assayed to determine if they exhibit MSI, further supporting a diagnosis of Lynch syndrome.

HNPCC may be associated with various extracolonic manifestations, which can have a bearing on prophylactic surgical recommendations. Gynecologic malignancies are the most common, including both ovarian and endometrial carcinoma.[207] Sites of other extracolonic malignancies include small bowel, pancreas, biliary tract, kidney, ureter, and brain.

The criteria for defining families with HNPCC have gone through a

series of revisions, most recently the Amsterdam II criteria, which set guidelines for surveillance, potential prophylactic resection, and screening for genetic mutations. These criteria include 1) 3 relatives with HNPCC related cancers, 2) 1 being a first-degree relative of the other 2, 3) at least 2 generations affected, and 4) at least 1 cancer diagnosed before the age of 50. FAP must also be excluded. The Revised Bethesda Guidelines further adds to these to include younger age onset colon cancer and the distinctive pathologic findings, as well as testing for and identifying tumors having MSI.[208]

Recommendations for screening in patients with HNPCC have been outlined by the NCCN. In the absence of genetic testing, affected individuals should begin colonoscopy starting between 20 and 25 years of age, or 10 years before the youngest familial diagnosis of colon cancer. Colonoscopy should be performed every 1 to 2 years until the age of 40, then annually. If germ line mutation is known, colonoscopy should be performed annually, given the accelerated carcinogenesis know to accompany HNPCC.[208] The lack of an identifiable genetic mutation in a patient with high suspicion for HNPCC should not preclude them from aggressive surveillance as approximately 45% of patients meeting Amsterdam criteria do not test positive for 1 of the known genetic mutations.[207] Because of the risk of endometrial cancer, women at risk should begin transvaginal ultrsound testing at age 25 to 35. Some also recommend endometrial biopsy in these patients since some studies found ultrasound alone can miss early stage cancers.[208]

Screening alone can have a marked effect on life expectancy, without the need for prophylactic surgery. One study found a 62% decrease in incidence of colorectal cancer with screening alone, and another found that every 3-year colonoscopic evaluation decreased overall mortality by 65% in HNPCC patients.[209,210] Another study evaluated the role of surveillance colonoscopy combined with the addition of prophylactic colectomy in patients with HNPCC. In this report, colectomy offered a marked increase in life expectancy in young patients compared with surveillance alone (13.5 vs 15.6 years gained in those 25 years of age).[211] This benefit decreased as patients became older, with only 0.7 years of life gained with colectomy in patients older than 40 years of age.

Prophylactic Surgery for HNPCC

Prophylactic colon resection can include both resection in at-risk individuals without existing malignancy or the addition of a prophylactic component to a colectomy being performed in the presence of a diagnosed cancer. In patients with HNPCC with existing cancer, the risk

of developing a metachronous tumor within 10 years is approximately 45%. Given the predilection of HNPCC colon cancers to occur proximally, a subtotal colectomy with ileorectal anastomosis (IRA) has become the operation of choice for HNPCC, preserving as much of the gastrointestinal tract as possible. In some cases, even a small portion of the distal sigmoid may be preserved as well. With rectal preservation, bowel function and quality of life are significantly improved.[212] However, care must be taken to maintain surveillance of the residual distal bowel. In 1 report of 71 patients, an 11% incidence of rectal cancer was found at an average of 13 years following rectal-preserving colectomy in those with HNPCC.[213] Patients choosing this prophylactic operation must be willing to undergo routine screening of the remaining large bowel.

Defining a clear role of prophylactic colon resection in patients with HNPCC remains difficult. Given that screening has proven highly effective in reducing colon cancer risk in these patients, along with the varied penetrance and incidence of colonic malignancy in these patients, many have been hesitant to recommend prophylactic resection, particularly in those who have yet to develop an initial cancer. Nevertheless, others cite the high lifetime risk of cancer in these patients as well as the accelerated rate of carcinogenesis. Regardless of the frequency and diligence of colonoscopic screening in these patients, subtle or flat lesions can be missed. Moreover, lifelong annual colonoscopy is not without risk. Finally, there is a negative impact on quality of life resulting from long-term colonoscopy and cancer fear in some patients, some of which can be lessened with prophylactic subtotal colectomy.

The timing for prophylactic surgery in women with HNPCC can sometimes depend on recommendations regarding management of gynecologic cancer risk. Prophylactic hysterectomy, with or without oopherectomy, must be considered when discussing prophylactic colon surgery in these patients. Depending on specific genetic risk and/or family history, some may recommend total abdominal hysterectomy with oophorectomy at the time of colectomy if a woman has completed her child-bearing years.

Familial Adenomatous Polyposis

FAP accounts for approximately 1% of large intestinal malignancies (Table 5). The lifetime risk of colorectal cancer in these patients approaches 100%, with average age of cancer diagnosis of 29. Diagnosis of the polyposis syndrome before the development of invasive malignancy often occurs during the teenage years.[198] In contrast to HNPCC, cancers from FAP are found throughout the large intestine, including in

TABLE 5. Characteristics of Familial Adenomatous Polyposis

1% of all colorectal cancers	Average age of cancer diagnosis: 29 years, later onset for MYH mutation
Genetic mutation: APC gene, MYH gene	Entire colon and rectum are at risk
~100% life time risk of colorectal cancer	

the distal colon and rectum. FAP also has a variety of extracolonic manifestations, including abdominal desmoid tumors seen in those patients with Gardner's syndrome.

FAP is an autosomal-dominant form of hereditary colon cancer with 100% penetrance, classically defined by the development of hundreds of adenomatous colorectal polyps. A variant form, attenuated FAP, is associated with less numerous adenomas. In such cases, the development of invasive cancer can occur somewhat later than with classic FAP. The genetic mutations found in FAP have been localized to the APC gene. These mutations cause truncation of the APC protein, which affects cell adhesion, signal transduction, and transcriptions activation. This defect eventually causes increased transcription of a variety of oncogenes, potentiating the malignant transformation of adenoma to carcinoma.[198]

Another genetic mutation, the MYH gene, has also been found to cause an adenomatous polyposis similar in appearance to FAP, but often discussed as a separate disease. This mutation is autosomal recessive, with later onset of adenomas and cancer than FAP. The MYH mutations cause inhibition of base excision repair pathway, inhibiting repair of DNA damage of APC genes.[214] These are much rarer causes of adenomatous polyposis disease and the risk and progression of colon cancer in these patients are less clear. Despite this, the management of these patients is similar and, if APC testing is negative, MYH testing should be considered.

Screening for patients with known FAP should begin during the teenage years. NCCN guidelines recommend yearly colonoscopy until the age of 24, after which prophylactic surgery is recommended. For those with a FAP, screening can begin later. Screening for duodenal and gastric cancer with endoscopy and random biopsies is also recommended, beginning at 25 to 30 years of age, then every 1 to 3 years.[215]

The role of chemoprevention using nonsteroidal anti-inflammatory agents in patients with FAP has become increasingly advocated by some.[215] However, although potentially reducing the number of adenomas or inducing their regression, no chemoprevention strategy has been shown to remove the risk of cancer. Chemoprevention may be used as an adjunct to endoscopy in an attempt to prolong the duration of screening,

improving endoscopic management and delaying the time to surgical intervention.[216]

Prophylactic Surgery for FAP

Surgical intervention for FAP should always be prophylactic whenever possible, given the extreme risk for developing cancer. Overall survival has been shown to improve significantly when surgery is performed before the diagnosis of cancer is made.[217] In contrast to nonpolyposis syndromes, virtually complete resection with total proctocolectomy (TP) and ileal pouch anal anastomosis (IPAA) or end ileostomy is the operation of choice for classic FAP patients. In these patients, leaving the at-risk rectum is associated with development of invasive malignancies more than 30%.[218]

Despite the reduced risk for the development of rectal cancer following TP-IPAA, some have expressed concern regarding the negative impact on quality of life with this procedure, particularly in older patients. One study evaluating 1895 patients at an average of 4.6 years following TP-IPAA found no difference in bowel frequency but noted a significant increase in nighttime bowel movement and seepage in older patients. Despite these differences, they found no difference in reported quality-of-life scores, with more than 95% recommending TP-IPAA to another person with the same condition.[212]

Prophylactic Surgery in Other Hereditary Syndromes

Familial Colorectal Cancer. The patients meeting Amsterdam criteria but without detectable known genetic mutations can be considered to have familial colon cancer (FCC), sometimes called FCC Type X.[207] These tumors occur an older age than classic HNPCC, have lower occurrence of second colon cancers, and do not manifest the extracolonic cancers seen in HNPCC. In addition, FCC also has a reduced predilection for the proximal colon.[207,219] The role of prophylactic surgery in these patients is based on the individual families history and clinician judgment. Management recommendations either in high-risk individuals or in those with a diagnosis of an initial invasive cancer can be similar to that of HNPCC.

Hamartomous Conditions. Hamartomous colon cancers are least common of the hereditary colon cancer syndromes (Table 6). These include juvenile polyposis (JP), Cowden's syndrome, Bannayan–Riley–Ruvalcaba syndrome (BRRS), Cronkhite-Canada syndrome (CCS), hereditary mixed polyposis syndrome (HMPS), and Peutz-Jeuger syndrome (PJS). Together, these account for approximately 1% of colon cancers. All of

TABLE 6. Hereditary colorectal cancers and lifetime risk of colorectal cancer

Hereditary disease	Lifetime risk of colorectal cancer	Age at diagnosis of colorectal cancer
HNPCC	80% (mutation-dependent)	45 years
FAP	100%	29 years, later for MYH mutation
Familial colorectal cancer	Unknown	>45 years
Inflammatory bowel disease	Up to 40% (UC) Unknown for Crohn's disease	Risk increases with length and severity of disease
Hamartomous colon cancers	50% (disease-dependent)	Disease-dependent

these syndromes are associated with premalignant hamartomous gastrointestinal polyps rather than adenomas. Most are autosomal dominant (JP, BRRS, PJS, and Cowden's) and all have associated identifiable genetic mutations.[220] The progression of these hamartomatous polyps to invasive cancer is less well understood than that of hereditary adenomatous polyps. Management of all these syndromes includes aggressive screening regimens with endoscopic resection of polyps, and partial colectomy when invasive cancers are identified. Prophylactic surgical intervention, typically subtotal colectomy, has been recommended by some for patients with JP as the lifetime risk of colon cancer in these patients can be as high as 50%.[221] For other hamartomatous conditions, prophylactic surgery is typically recommended only for those in whom the polyp burden is too great to allow adequate endoscopic evaluation.[221]

Inflammatory Bowel Disease. Ulcerative colitis and Crohn's disease account for only 1% to 2% of all colorectal cancers.[222] These IBD are thought to be a result of an adaptive immune response in a genetically susceptible individual. Crohn's disease appears to be T-helper-1 cell mediated, potentially affecting the entire gastrointestinal tract. Ulcerative colitis is T-helper-2 cell mediated. This condition is limited to the colon and rectum.[223] IBD is a multi-factorial disease felt to be a complex interaction of genetics, environment, and immune system. The exact genetics of IBD are not well elucidated. The mechanism of carcinogenesis is still unclear, but is thought to be secondary to chronic, prolonged bowel inflammation in combination with the molecular pathways seen in other colorectal cancers such as loss of heterozygosity and MSI.[224]

Although not considered a hereditary condition, patients with IBD, particularly ulcerative colitis, have increased risk for the development of colorectal cancer. This risk in ulcerative colitis is approximately 2% at 10 years, increasing to approximately 18% to 40% at 30 years after diagnosis.[223] The risk of colorectal cancer in Crohn's disease is less well

known, but is generally considered dependent on the severity and location of the disease. Overall the risk of colorectal cancer in IBD may be influenced by a variety of factors, including family history of colon cancer, duration and extent of the colitis, presence of primary sclerosing cholangitis, younger age of onset, severity of histologic inflammation, and evidence of dysplasia.[224]

Prophylactic surgery in ulcerative colitis is generally recommended when persistent inflammation and dysplasia are identified. TP with IPAA is recommended to remove the tissue at risk, particularly the rectum.[225] In most cases, some transition zone is left remaining at the anal canal. As with FAP, this area requires continued endoscopic surveillance to identify any early malignant changes.

The role of prophylactic surgery in Crohn's disease is less well defined. The wide variation in disease burden and severity makes any universal recommendations difficult to validate. Specifically, prophylactic surgery is not typically advised in these patients. Importantly, these patients fare poorly following proctectomy with IPAA. In Crohn's patients who have undergone this procedure, often because of incorrect diagnosis of ulcerative colitis, more than 50% require either a pouch excision or a diversion.[226]

Surgical Considerations in Prophylactic Colon Cancer Surgery

Extent of Resection and Ileoanal Pouch Anastomosis Technique. Although TP with IPAA removes close to all tissue at risk for colorectal cancer, there are mitigating factors that must be considered with this procedure. Specifically, TP-IPAA is a more technically difficult operation. In addition, it is associated with greater risk of morbidity, including pelvic sepsis, higher stool frequency, and sexual dysfunction.[217] Pouch failure requiring excision has been found to be as high as 4.1% in 1 study.[212] Importantly, an apparent complete resection with TP-IPAA typically still leaves a small amount of mucosa at the anal transition zone. Studies have reported cancer development in high-risk individuals in this region in up to 28%.[227,228] There is also a risk of cancer of the ileal pouch itself, making continued endoscopic monitoring a necessary part of postoperative care and long-term follow-up in these patients.[227]

Some have proposed that TP-IPAA may not be necessary in all patients with FAP. In patients with hereditary conditions of somewhat lower risk, including attenuated familial adenomatous polyposis (aFAP), subtotal resection (total or subtotal colectomy) with ileorectal reconstruction can be considered.[229] In 1 study, the risk of recurrence in the rectum varied from 10% to 61% in FAP patients who underwent more limited resection

with IRA, depending on the specific genotype.[230] Although careful surveillance may offer an opportunity to salvage any recurrence, early detection may not be possible, and thus it is best to consider only those with limited polyps within the rectum.

Controversy also exists regarding the technique for performing TP-IPAA. Specifically, some advocate the importance of a complete mucosectomy to excise all the at-risk tissue. However, this technique requires stripping of the distal mucosa, anal dilatation, and a hand-sewn anastomosis within the anal canal and is associated with higher morbidity and diminished postoperative bowel function. More commonly, surgeons perform a stapled IPAA at the level of the levator muscle. This technique is easier to perform and results in improved long-term bowel function.[212,216] However, this method results in approximately 1 cm of residual mucosa that must be monitored to minimize the risk of developing a malignancy in the region of the anastomosis.[231]

In addition to cancer risk, quality of life related to long-term postoperative bowel function is an important factor when counseling patients about the extent of prophylactic resection and reconstruction to be performed. One study that compared the functional outcome after IRA vs IPAA found significantly decreased bowel motion frequency (4.7 vs 6/d), fewer night time bowel movements (1.4 vs 2 per night), improved stool consistency, less use of antidiarrheal medication, and better functional scores in patients with IRA.[216] The risk of reoperation was also higher in IPAA patients. Among those who had IPAA, the risk of incontinence and night time stooling was higher in those undergoing the handsewn technique compared with the stapled technique. Of note, however, in this study, the conversion rate of IRA to IPAA was 23%.

Timing of Prophylactic Colectomy. The optimal occasion in which a prophylactic colon resection is undertaken is the subject of some controversy. When performed fully preventatively, before a malignancy has developed, a more radical resection, including lymphadenectomy, is not required. Particularly in the case of the total proctectomy, the necessity of a total mesorectal excision or perioperative chemoradiation therapy is not required. Postoperative complications are fewer, including urinary and sexual dysfunction. In patients with FAP, the risk of the development of desmoid tumors is thought to be associated with surgical trauma and hormone influences, causing some to advocate delay of prophylactic resection in these patients when appropriate.[225,227]

Any discussion with a patient regarding prophylactic large bowel resection, including timing, necessitates an understanding of the risk of malignancy, quality of life, and perioperative risks. Patients who are at

risk of cancer later in life (eg, aFAP, MYH) are less likely to derive benefits from early aggressive procedures. This was demonstrated in 1 study using a Markov model, which adjusted patient age and extent of colectomy in patients with HNPCC.[232] In this analysis, for example, a 67-year-old patient gains only 1 year of life from subtotal colectomy vs hemicolectomy, whereas a 27-year-old patient gains 5 years of life with the more extensive procedure. Although proctocolectomy may provide the best cancer operation, since patients present at older ages, a subtotal or partial colectomy may be considered since it provides little difference in survival, but may provide a big difference in quality of life.

When a patient presents with an existing malignancy in which a prophylactic component is being considered, the stage of the malignancy must be factored into the recommendation. Patients with more advanced cancer often require additional chemotherapy. In such patients, increasing the extent of bowel resection may result in prohibitively severe diarrhea and dehydration during chemotherapy. IPAA in patients requiring adjuvant pelvic radiation therapy for existing rectal cancer can result in compromised long-term bowel function. Importantly, one must also factor in the RR of long-term survival in patients with more advanced cancer when contemplating the addition of a prophylactic component. Finally, patient age and associated comorbid conditions must be considered when determining the choice of prophylactic bowel resection.[233]

Role of Laparoscopic Resection for Prophylactic Colectomy. Laparoscopic surgery has gained acceptance in recent years for a variety of colorectal procedures. Laparoscopic colectomy has become a routine part of the repertoire of most colorectal surgeons and has been shown to have similar outcomes to open surgery for colon cancer, with similar recurrence rates, infection risk, and postoperative recovery.[234,235] The specific role of laparoscopic resection in hereditary colon cancer is not well defined. However, prophylactic resection may in fact be an ideal indication for the laparoscopic approach as extensive lymphadenectomy is not typically as important. Moreover, laparoscopy offers ease in mobilization of the colonic flexures, which are required with a more extensive colectomy, potentially hastening postoperative recovery.

The role of laparoscopic-assisted surgery in hereditary colon cancer was evaluated in a recent Cochrane review.[236,237] In this analysis, the authors found no difference in mortality or complication rate when comparing techniques, yet laparoscopic procedures were found to take an average of 90 minutes longer. Although there was hope that the less invasive approach would reduce the risk of desmoid formation in FAP patients,

this was not found to be the case.[237] Several other studies have shown safe and similar outcomes with laparoscopic vs open IPAA, similar long-term bowel function and quality of life, with a trend toward faster recovery, decreased pain, and shorter hospital stays.[238-240] As with other complex procedures, studies support that such operations have improved outcomes when performed in specialized high-volume centers.

As the understanding of genetic predisposition to colorectal cancer increases and patients at highest risk are identified, the role of prophylactic surgery will likely increase in use and acceptance. Knowledge of aggressive screening, cancer risk, and possible role of early surgical intervention in diseases associated with high risk for the development of colorectal cancer offers an opportunity to reduce risk when applied in a thoughtful, well-informed approach and as part of an experienced multidisciplinary team.

Conclusions

In this monograph, we have discussed the potential role of surgery in cancer prevention. Most (but not all) candidates for prophylactic surgery will have a hereditary predisposition for cancer, and the wider use of genetic testing has identified greater numbers of these individuals. Thus, individuals with a hereditary predisposition for breast, gastric, thyroid, or colorectal cancers can now be identified and may wish to consider prophylactic surgery. Nevertheless, there are no randomized trials addressing the efficacy of prophylactic surgery in these individuals, so its full impact is not completely understood. All patients should be informed of the potential risks and benefits of prophylactic surgery and alternatives (such as screening and chemoprevention) should be considered as well. In the years ahead, additional studies will be required to better elucidate the role of surgery in cancer prevention. In particular, these studies should address its effects on quality of life.

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