An Overview of the Role of Prophylactic Surgery in the Management of Individuals with a Hereditary Cancer Predisposition

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Cancer is the second leading cause of death in the United States [1]. Over the last 20 years, the field of cancer genetics has grown exponentially, and the two-hit mutation model developed by Knudson [2] has served as a framework for studying human carcinogenesis. Several tumor suppressor genes have been identified, and the relevance of germline mutations to cancer development is understood better. One now can identify mutation carriers who are at increased risk for developing cancers and, in some instances, offer prophylactic surgery to reduce that risk. Before deciding on prophylactic surgery, however, individuals who have a genetic predisposition for cancer should consider nonsurgical management options. This article provides an overview for the role of prophylactic surgery for managing individuals who have a genetic predisposition for cancer, particularly those who have a predisposition for breast, colon, thyroid, and gastric cancers. It summarizes the role of prophylactic surgery in individuals who have a genetic predisposition for cancer, and other articles throughout this issue provide a more detailed review of these hereditary cancer syndromes.

The views or opinions expressed in this article are those of the authors and should not be construed as representing the official views of the Departments of the Army, Navy, or Defense.

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It long has been recognized that there is a hereditary component to certain cancers. In 1865, Broca described a case of hereditary breast cancer in relating the incidence of this disease in four generations of his wife’s family [3]. In 1913, Aldrin Warthin [4] described a family, Family G, with a cluster of gastrointestinal (GI) and gynecologic malignancies that is similar to what is now reported in families with hereditary nonpolyposis colorectal cancer (HNPPC). Lynch and colleagues [5] described a series of 34 families with two or more relatives with breast cancer, establishing a hereditary link to some cases of breast cancer. Thus, epidemiologic studies confirmed that cancers cluster in certain families, and improved understanding of the hereditary basis for certain cancers [6]. In the past, high-risk patients were identified on the basis of family pedigree and clinical presentation, and these patients were managed with surveillance and then treated once disease developed. The expanding use of prophylactic surgery for managing individuals with a genetic predisposition for cancer is related directly to the explosion of information regarding the hereditary cancer syndromes. Once the genetic basis for a cancer syndrome is discovered and genetic testing becomes available, the clinical question becomes: If we can identify individuals who are increased risk for developing this disease, what can we do to prevent it? Molecular biology has allowed the identification of an array of mutations responsible for various hereditary cancer syndromes, and, in mutation carriers, prophylactic surgery might be considered as an option to avoid the potential morbidity and mortality associated with a cancer diagnosis.

Once a patient with a genetic predisposition for cancer has been identified, there are generally three management options: surveillance, chemoprevention, and prophylactic surgery. All options carry the potential for benefit and harm, and there are no randomized prospective trials that have assessed the impact of these options in mutation carriers. The suitability of these management options varies, depending on the particular hereditary cancer syndrome. For instance, in women who are at increased risk for developing ovarian cancer, the mortality rate associated with ovarian cancer and the lack of a reliable screening tool might make surveillance a less attractive option. For other cancers, chemoprevention might be an acceptable option, although chemopreventive agents may have adverse effects. Finally, prophylactic surgery should be considered, but only after its potential risks and benefits are discussed in detail.

You and colleagues [7] described five major criteria that should be met before the widespread use of prophylactic surgery is implemented for managing individuals with a genetic predisposition for cancer. Specifically, there should be a high penetrance (likelihood of developing cancer) associated with the mutation, a reliable genetic test to identify mutation carriers, an effective surgical procedure with low morbidity to remove the organ at risk, a suitable replacement for the function of the organ removed, and finally, a means to determine if the patient is disease-free over time.
Penetrance of disease

Ideally, individuals considered for prophylactic surgery should carry mutations with complete penetrance (100% chance of developing cancer). Mutations responsible for many of the hereditary cancer syndromes, however, generally have a high but incomplete penetrance. In the general population, the lifetime risk of breast and ovarian cancer is 12.7% and 1.4% respectively [8]. For BRCA1 and BRCA2 mutation carriers, however, the risk of breast cancer by age 80 is about 90% and 40%, respectively, and the corresponding risk for ovarian cancer is about 24% and 8% [9–11]. High-penetrance mutations also are associated with hereditary colon cancer syndromes. Almost 100% of individuals who carry the mutation for familial adenomatous polyposis (FAP) will develop colon cancer by age 50 [12], while those with hereditary nonpolyposis coli have a 70% to 82% lifetime risk of developing colon cancer [13]. Individuals who have the multiple endocrine neoplasia (MEN) 2 syndrome have almost a 100% risk of developing medullary thyroid cancer [14]. In individuals who carry the mutation for hereditary diffuse gastric cancer (HDGC) syndrome, the lifetime risk of gastric cancer is about 70% [15,16]. The cumulative risk of developing gastric cancer may vary between men and women, however, with a cumulative risk of gastric cancer by age 80 being 67% in men and 83% in women [17]. Although many mutations are associated with a high penetrance, complete penetrance never is observed. As a result, there always will be a certain number of mutation carriers who would not have developed cancer, but will be offered prophylactic surgery. Environmental and nongenetic factors may modify penetrance [18]. For example, in BRCA2 mutation carriers, pregnancy appears to increase breast cancer risk [19]. Age of menarche, spontaneous abortion, breast feeding, and oral contraceptive are additional factors that may modify penetrance in BRCA mutation carriers [18]. Modifying genes (genes which modify penetrance) also may alter cancer risk, and have been associated with hereditary breast and colon cancers [12,20,21]. In the future, these genes may help identify individuals who are at increased cancer risk and may benefit from prophylactic surgery.

Genetic testing

Genetic testing for cancer susceptibility is suitable if the test is associated with a high specificity and sensitivity. A genetic predisposition for hereditary cancer syndromes should be considered after careful assessment of clinical findings and family pedigree. In the early 1990s, linkage studies were undertaken to determine an individual’s likelihood of having a genetic predisposition for hereditary cancer syndromes [22]. These studies paved the way for the discovery of mutations responsible for various hereditary cancer syndromes, thereby providing a more reliable means of identifying asymptomatic carriers. Despite the available technology, genetic testing for hereditary
cancer syndromes remains a complex issue. Unlike other genetic diseases such as sickle cell anemia, hereditary cancer syndromes rarely are associated with a single gene mutation. In most cases, there are several mutations that may lead to a particular cancer, and commercial testing does not identify every mutation. Consider, for example, the case of hereditary breast cancer, often associated with mutations in the BRCA1 and BRCA2 tumor suppressor genes. Currently, genetic testing for BRCA1/2 mutations may identify up to 88% of all individuals who have a genetic predisposition for breast cancer, with false-negative results often attributed to other mutations, such as those in the p53, PTEN, STK11/LKB1, CDH1, and CHEK 2 genes [23,24]. Complete DNA sequencing may detect approximately 80% of all mutations in individuals who have FAP [25,26].

In some instances, there are only a limited number of gene mutations associated with a particular cancer, as evident in the association between the RET proto-oncogene and medullary thyroid cancer, and this simplifies genetic testing [3]. Although most genetic testing for cancer predisposition is highly reliable, it is not infallible, and interpretation of the results of these tests must be considered in light of these facts.

**Approach to patient**

Individuals who might potentially benefit from genetic testing should be selected carefully. A detailed family history should be obtained, and the patient’s clinical history considered also. Before genetic testing, counseling is essential. The issues raised by genetic testing are complex and may have long-lasting implications for patients and their families. The implications of a positive, negative or inconclusive test should be discussed before testing. Studies have shown that patients handle the results of testing better if counseling occurs before testing [27–29]. In addition, the financial cost of testing should not be ignored, and concerns have been raised about the potential impact of genetic testing on overall health care costs [30]. Yet, very few studies have addressed these issues, and the impact of genetic testing and prophylactic surgery on health care costs in the United States is understood poorly. Cost analyses undertaken in countries with centralized (government-sponsored) health systems, however, indicate an overall positive benefit [31]. If one selects individuals who may benefit from genetic testing carefully, then this may improve the overall cost-effectiveness. The cost of genetic testing varies and may range from $200 to $3000 [32], but this does not include the cost of counseling, which is an essential component.

Many insurance companies indicate that they cover the cost of genetic testing, but others may not and are not required by law to do so [33]. If patients have to incur some of the cost of genetic testing, they are less likely to undergo testing. Also, given the cost of genetic testing services, these services are more likely to be used among patients in higher socioeconomic brackets [34]. Even though insurance companies generally cover the cost
of genetic testing, some patients choose to bear the cost themselves. In a survey of genetic counselors, most indicated that they would not bill their insurance companies for fear of insurance discrimination [35]. A retrospective study examined reasons why women refused to undergo BRCA testing and found similar results. Of 78 women who declined testing, 48 cited concerns about discrimination [36]. There is clearly a widespread fear about the misuse of health care information by insurance companies, although this fear might not be justified [37]. Currently, many insurance companies do not seem to have standard protocols for dealing with patients who have hereditary cancer syndromes. Several years ago, Rodriguez-Bigas and colleagues [38] surveyed insurance companies regarding policies for insurance coverage in individuals who had at least a 50% chance of carrying a significant gene mutation. Most companies indicated that they did not use genetic test results in determining cost of insurance coverage, but only 7.7% of companies responded to the survey, making it difficult to draw any valid conclusions.

In addition to costs incurred from genetic testing, there are additional costs that must be considered if a patient is found to carry a mutation. These include the cost of surveillance, prophylactic surgery, or chemoprevention, should the patient choose any of these management options. As prophylactic surgery gains wider acceptance among mutation carriers, its financial burden on the health care system will have to be evaluated. In a survey of insurance coverage for prophylactic thyroidectomy in patients with familial thyroid cancer or a positive RET mutational analysis, most insurance companies indicated no standard policy. Of the private companies surveyed, 9% provided coverage, 12% provided no coverage, and 72% had no policy; government carriers had a similar pattern in coverage policy [39]. Another survey found similar results with respect to insurance coverage for prophylactic mastectomy or oophorectomy in patients who had BRCA mutations or those who had a strong family history of breast cancer [40]. In that survey, 481 medical directors from the American Association of Health Plans, Medicare, and Medicaid were queried, with a total of 150 respondents. Only 44% had a plan for coverage of prophylactic mastectomy in women who had a strong family history of breast cancer, and 38% had plans for coverage for women with BRCA mutations. Only 20% of those responding had a policy for coverage of prophylactic oophorectomy.

Several states have enacted laws that prohibit insurers’ use of genetic information in pricing, issuing, or structuring of health insurance [41]. The enactment of these laws, however, does not seem to have allayed fears on this issue. As the use of genetic testing and prophylactic surgery increases, guidelines regarding insurance coverage and prevention of insurance discrimination will need to be developed. There is no doubt that, despite the availability of genetic testing, many high-risk individuals decide to forgo genetic testing. Although cost and fear of insurance discrimination might factor into their decision, the full reasons for this have not been well elucidated [42].
Timing of prophylactic surgery

There are several issues that should be considered when discussing the timing of prophylactic surgery. For example, alternative splicing of the APC gene may result in attenuated FAP, and these patients present with fewer polyps and at a later date than individuals who have classic FAP, which may influence the timing of prophylactic proctocolectomy. In MEN syndromes, mutations in the RET proto-oncogene generally result in the development of medullary thyroid cancer at a very early age, and thyroidectomy should be considered very early in life. Lastly, the timing of prophylactic surgery should be compatible with the life choices of the patient. Thus, women may choose to defer risk-reducing salpingo-oophorectomy (RRSO) until after childbearing.

Breast cancer

Genetics

Each year approximately 200,000 women in the United States develop breast cancer, with 5% to 10% of these cases occurring in women who have a genetic predisposition [43]. The most common of the hereditary breast cancer syndromes are caused by BRCA1 and BRCA2 mutations. The BRCA1 gene is located on chromosome 17, while BRCA2 is located on chromosome 13. Both are tumor suppressor genes, characterized in 1994 [44,45] and 1995 respectively [46,47].

BRCA-associated breast and ovarian cancer syndrome

The incidence of the BRCA1 and BRCA2 genes in the general population is 1 case in 150 to 800 individuals [48]. This incidence varies depending on geographic region and is higher in certain populations such as Ashkenazi Jews. Most of the studies done on hereditary breast cancer syndromes involve BRCA mutation carriers. Although both the BRCA1 and BRCA2 genes confer an increased risk of breast and ovarian cancer and often are considered together, there are significant differences between them, particularly with respect to phenotypic expression.

Surgical management

BRCA1 and BRCA2 mutation carriers have a high risk of developing breast cancer, but penetrance varies among different populations. In these mutation carriers, risk-reducing surgical options include bilateral prophylactic mastectomy (in women never diagnosed with breast cancer) and contralateral prophylactic mastectomy (in women already diagnosed with breast cancer). Both generally are performed with either immediate or delayed breast reconstruction. Lastly, prophylactic salpingo-oophorectomy should be considered in BRCA mutation carriers.
Risk-reducing salpingo-oophorectomy (RRSO) also appears to reduce breast cancer risk [49–51]. The magnitude of the risk reduction may vary, however, depending on the age at which this procedure is performed [52]. Rebbeck and colleagues studied 122 women who had BRCA1 mutations and found that these women experienced a significant reduction in the risk of breast cancer following RRSO [53]. These authors subsequently broadened their study to include a total of 551 women with BRCA1 and BRCA2 mutations, and found that RRSO reduced the risk of breast cancer by 53%. Furthermore, stage 1 ovarian cancers subsequently were diagnosed in only 2.3% of these women, and 0.8% received a diagnosis of serous peritoneal carcinoma within 3 years after RRSO. Thus, the risk of ovarian cancer was reduced by over 95% following RRSO [54]. In a more recent study, RRSO was associated with a significant risk reduction of BRCA2-associated breast cancers, and while there was a trend toward a reduced risk of breast cancers among BRCA1 mutation carriers, that risk reduction was not statistically significant [55]. Although RRSO in premenopausal BRCA mutation carriers reduces breast cancer risk, its consequences are not insignificant. The induction of menopause following RRSO may increase cardiovascular risk, osteoporosis, vaginal dryness, and sexual dysfunction. Additionally, it may result in cognitive changes. Hormone replacement therapy (HRT) has been used to treat menopausal symptoms associated with RRSO, but there are concerns that HRT may increase the risk of breast cancer and thereby decrease the utility of RRSO. Yet, in a Markov decision analysis model, RRSO in women between the ages of 30 and 40 was associated with a substantial increase in life expectancy, irrespective of HRT use [56].

In asymptomatic BRCA mutation carriers, bilateral prophylactic mastectomy (BPM) should be considered. Various studies have shown that BPM significantly decreases breast cancer risk, but there are no randomized prospective trials that have addressed this issue [57]. Meijers-Heijboer and colleagues [58] conducted a prospective study of 139 women, and no breast cancers were seen in 76 women in the BPM group, while 8 out of 63 women in the surveillance group developed breast cancer. The mean length of follow-up in this study was only 3 years, however, making it difficult to assess the long-term benefit of BPM. Yet, additional studies that have included larger groups of women have found similar results [59]. In a large multicenter study looking at 483 women, BPM reduced the risk of breast cancer by 95% in women who also had an RRSO and by 90% in women who had intact ovaries [59]. Studies have shown that this benefit continues with longer follow-up, and several of these studies are summarized in Table 1 [60].

Women with BRCA1/2 mutations who develop breast cancer are also at increased risk of developing contralateral breast cancer, and estimates of this risk range from 20% to 42% [61–63]. In a retrospective study, Metcalfe and colleagues found that the incidence of contralateral breast cancer in BRCA mutation carriers was as high as 40% over a 10-year period, and
<table>
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<th>Study</th>
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<th>Mean FU, years</th>
<th>Number of patients undergoing BPM</th>
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<td>177</td>
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*Abbreviations: BC, breast cancer; BPM, bilateral prophylactic mastectomy; FU, follow up; NA, not applicable.*
that risk was greater in BRCA1 mutation carriers than those who had BRCA2 mutations [64]. The risk of contralateral breast cancer was reduced if there was a history of oophorectomy or tamoxifen use. The dramatically increased risk of contralateral breast cancer in this population of women makes contralateral prophylactic mastectomy (CPM) an attractive option, and several studies have shown that CPM may reduce risk by about 90% [65]. BRCA1/2 mutation carriers who have a personal history of breast cancer are often particularly eager to discuss means of preventing development of a second primary. There are several factors, however, that may influence a woman’s decision to proceed with CPM. Women who are younger at diagnosis, have opted for RRSO, and choose mastectomy (rather than breast-conserving therapy) as the surgical treatment for their initial breast cancer are more likely to opt for CPM [66]. Interestingly, Metcalfe and colleagues found that European and Israeli women were less likely to undergo CPM than North American women. This may reflect cultural differences or possibly differences in clinical practices between these countries.

There are several types of prophylactic mastectomy procedures available. Subcutaneous mastectomy is a nipple-sparing procedure that leaves some breast tissue behind. Skin-sparing mastectomy involves removal of almost all the breast tissue and nipple areola complex, but leaves most of the skin overlying the breast intact. Given that these procedures are prophylactic, axillary dissection generally is not indicated. The use of sentinel lymph node biopsy in these procedures might be considered, however, because some women occasionally are found to have occult cancers following prophylactic mastectomy. There have been reports that subcutaneous mastectomy is associated with an increased breast cancer risk, and skin-sparing mastectomy generally is considered the prophylactic procedure of choice [67]. Skin-sparing mastectomy facilitates breast reconstruction, which reduces the disfigurement associated with prophylactic mastectomy. In the past 20 years, the reconstructive options for patients undergoing mastectomy have increased. In addition to artificial breast implants, there are numerous tissue reconstruction options, including the traditional transverse rectus abdominis (TRAM) flap and the latissimus dorsi (LD) flap. Although the cosmetic results are improved, there might be a slightly increased risk of complications associated with reconstructive surgery, including an increased risk of infections and tissue necrosis.

Clearly, risk-reducing surgery is an important option to consider for managing patients who have hereditary breast cancer syndromes. Although there are no randomized controlled trials that have assessed its impact in mutation carriers, the studies outlined seem to indicate that prophylactic surgery is beneficial. Other management options (surveillance and chemoprevention), however, also should be discussed with the patient. Although prophylactic surgery reduces the risk of breast cancer, it does not eliminate it entirely. Women who undergo prophylactic surgery should continue to undergo surveillance.
Colon cancer

Genetics

It was not until the early 1990s that advances in molecular science made genetic testing for colon cancer syndromes possible. In 1993, the HNPCC locus was mapped to chromosome 2P\cite{68}. In 1987, Bodmer and colleagues\cite{69} localized the adenomatous polyposis coli (APC) gene to chromosome 5. This gene eventually was cloned in 1991 \cite{70,71}. The details of the various mutations in the APC gene have been described, and these variations might be responsible for the variable phenotypic expression of FAP\cite{72}. It is estimated that 20% of patients who have colorectal cancer have a genetic predisposition for this disease. Hereditary colon cancer can be divided into two main groups: those presenting with numerous polyps and those denoted by a lack of polyps.

Surgical management

Familial adenomatous polyposis

Familial adenomatous polyposis is the most common adenomatous syndrome. Classic FAP is associated with the development of multiple polyps (hundreds) at a very young age\cite{73}. This syndrome also is associated with extracolonic manifestations, including upper GI polyps and cancers, congenital hypertrophy of the retinal pigment epithelium, desmoid tumors, thyroid tumors, hepatoblastomas in children, and other extracolonic malignancies\cite{12,74}. Attenuated FAP is notable for a later age at presentation and fewer polyps. More recently, a non-APC gene-associated syndrome, MYH–familial polyposis syndrome, has been described\cite{75,76}. As the lifetime risk of colon cancer in FAP approaches 100%, prophylactic surgery is recommended in these patients\cite{7,77,78}. The prophylactic surgical options for FAP patients are subtotal colectomy with ileorectal anastomosis (IRA), proctocolectomy with ileal pouch anal anastomosis (IPAA), and finally proctocolectomy with permanent ileostomy. The timing of surgery remains ill-defined and may be influenced by the number of polyps\cite{79}. Presentation remains too variable to give a definitive timing on surgery, but overall survival likely is improved if surgery is performed prophylactically\cite{80,81}. In a review by Bertario and colleagues\cite{80}, patients without cancer at the time of surgery had a survival probability of 68% at 30 years compared with 41% at 10 years in those with cancer.

IPAA has become the preferred prophylactic surgical option in patients who have FAP. Although IRA eliminates the risk of cancer in the colon, there is still a risk of developing cancer in the rectum. Reports of this risk range from 4% to 8% at 10 years and 26% to 32% at 25 years\cite{82,83}. Although IPAA lowers the risk of cancer in the rectum, it does not eliminate it entirely, because cancer still may occur at the transition zone\cite{84}. In addition, there have been reports of polyps developing in the pouch\cite{85}. No
matter which prophylactic procedure is performed, lifelong surveillance is necessary and remains the only way to rule out disease over time.

The choice of procedure should be determined by the preferences of the patient and the quality of life (QOL) expected after surgery. Initial reports on the complications associated with IPAA include pelvic sepsis, high stool frequency, and fecal incontinence [86]. These complications have decreased with improvements in surgical technique, but there remains an increased perioperative morbidity associated with IPAA when compared with subtotal colectomy with IRA. A total proctocolectomy with permanent ileostomy is rarely necessary, and only in situations where a cancer is already present that involves the sphincter, poor baseline sphincter function, or when the frequency of daily stools might hamper a patient’s lifestyle. In a review of 1895 patients evaluating surgical results and QOL after IPAA, pouch failure requiring pouch excision occurred in 4.1% of patients [87]. Incontinence, night seepage, and sexual dysfunction also were associated with this procedure.

**Hereditary nonpolyposis colorectal cancer**

HNPCC (Lynch syndrome) is an autosomal dominant disorder characterized by a predisposition to early onset colorectal cancer (primarily right-sided) and cancers of the endometrium, ovary, small intestine, hepatobiliary system, kidney, ureter, brain, skin, and pancreas [88,89]. The risk of rectal cancer, although low, is not negligible and has been estimated at 11% [90]. The penetrance of the HNPCC mutation is not as high as that of the FAP mutation, and HNPCC is associated with about an 80% lifetime risk of colorectal cancer [13,91]. Thus, surveillance with colonoscopy might be a more suitable management option in asymptomatic patients [92,93]. Prophylactic subtotal colectomy (with the rectum retained) and prophylactic proctocolectomy (removal of the entire colon to include the rectum) should also be considered as options for managing asymptomatic HNPCC patients, however, particularly those who are anxious or concerned about the safety of repeated colonoscopies. Given the choice between these two prophylactic surgical procedures, many patients may prefer subtotal colectomy with long-term surveillance of the rectum [74].

In HNPCC patients who go on to develop colon cancer (or an adenoma that cannot be resected endoscopically), the optimal extent of surgical resection has not been elucidated fully [94,95]. These patients are at increased risk for secondary colon cancers, so subtotal colectomy should be considered. Alternatively, some of these patients may choose a more limited segmental resection of the colon with frequent follow-up colonoscopies. Unfortunately, no studies have compared outcomes directly between these two surgical options. Nonetheless, it has been suggested that there might be a benefit to subtotal colectomy when compared with segmental resection. A Markov model evaluating the effect of subtotal colectomy versus segmental colectomy on life expectancy seemed to suggest that there was a benefit associated with subtotal colectomy, but this benefit decreased with age [96].
As mentioned previously, HNPCC patients are also at increased risk for the development of extracolonic malignancies, and much attention has focused on their increased risk for endometrial and ovarian cancers [80,95,97,98]. Thus, prophylactic hysterectomy and salpingo-oophorectomy often are recommended, as well as surveillance for other malignancies [92].

**Multiple endocrine neoplasia type 2**

Medullary thyroid cancer (MTC), although a less common form of thyroid cancer, has three main hereditary forms associated with MEN type 2: MEN 2A, MEN 2B, and familial medullary thyroid cancer (FMTC). MEN 2A is characterized by MTC, pheochromocytoma, and parathyroid hyperplasia. Hirschsprung’s disease [99,100] and cutaneous lichen amyloidosis [101] also have been associated with MEN 2A infrequently. MEN 2B syndrome, while also characterized by MTC and pheochromocytoma, has neural gangliomas as an associated feature. All are characterized by an autosomal dominant inheritance pattern and, although highly penetrant, have variable expressivity. The development of pheochromocytoma and hyperparathyroidism in MEN 2A varies, with 42% to 50% of patients developing pheochromocytoma and 20% to 35% developing hyperparathyroidism [102]. Although hyperparathyroidism is not seen in MEN 2B, the incidence of pheochromocytoma is similar to that of MEN 2A. Almost 100% of all patients who have MEN 2A and 2B syndromes, however, will develop MTC in their lifetime.

**Genetics**

Multiple endocrine neoplasias type 2 are caused by germline mutations of the RET proto-oncogene. Initially, individuals with this syndrome were diagnosed by clinical history and family pedigree followed by linkage studies [22,103]. Linkage studies, although accurate, were tedious and required testing of at least two affected family members. The discovery that mutations in the RET proto-oncogene were associated with the MEN 2 syndrome, led to a reliable means of identifying carriers for this disease [104,105]. This genetic test has proved to be a highly sensitive means of identifying carriers for this disease [14,106]. The discovery that mutations in the RET proto-oncogene appear to cluster in certain specific regions of chromosome 10 helps explain the high sensitivity of this test [107]. Also, analysis of these mutations has revealed that genotype–phenotype correlations exist [108,109]. One of the most significant of these is the germline mutation in codon 918 of the RET proto-oncogene seen in MEN 2B. In these patients, MTC appears to present at a very early age, sometimes infancy, and appears more virulent.

**Surgical management**

Most patients who have MEN 2 will develop MTC during their lifetime, and prophylactic thyroidectomy should be considered at an early age. In
patients who have MEN 2, MTC is usually multifocal and bilateral, and it can occur at an early age. Screening for MTC is accomplished by measuring baseline and stimulated calcitonin levels [110]. This is not an infallible method of identifying patients who have MTC, however. In a landmark study by Wells and colleagues [106], DNA analysis was used to identify individuals at risk for MEN 2A. Of those at risk, 13 children, (six with normal and seven with elevated calcitonin levels) underwent total thyroidectomy with central neck dissection and total parathyroidectomy with autotransplantation. All thyroid specimens in this study demonstrated C cell hyperplasia. All seven of the patients with elevated calcitonin levels had microscopic MTC, and two had macroscopic MTC. Of the six patients who had normal calcitonin levels, two had microscopic MTC, and one had macroscopic disease. Overall, 10 of the 13 patients had MTC, and lymph node dissection failed to identify nodal metastasis in all patients. An updated study by the same group, broadened to include 49 children with mutations in the RET proto-oncogene, produced similar results [111].

A larger study by Lips and colleagues [14] reported similar findings. In this study, DNA analysis was used to identify 61 of 80 carriers of the MEN 2A gene. Of these, 14 carriers who were children had normal calcitonin levels, and eight underwent total thyroidectomy. Small foci of MTC were seen in all eight specimens. Additional studies have shown consistently that despite normal calcitonin levels, prophylactic removal of the thyroid invariably shows either microscopic foci of MTC or C cell hyperplasia [112,113]. Given the high incidence of disease found in cases where surgery is performed in asymptomatic individuals, it might be said that surgical intervention is actually therapeutic and not prophylactic. Long-term follow-up studies have shown that asymptomatic carriers have a better chance of cure if surgery is performed at a very early age, preferably before 8 years of age [114]. The lack of chemopreventive options, combined with the poor chances of cure if disease is found, presents a strong argument for the use of prophylactic thyroidectomy in patients who test positive for the RET proto-oncogene. Experience appears to show that the sooner surgery is done the better. The low morbidity associated with total thyroidectomy (as well as the availability of Synthroid as replacement therapy) makes prophylactic surgery an even more attractive management option in these patients.

Hereditary diffuse gastric cancer

Genetics

Mutations in the CDH-1 (E-cadherin) gene are responsible for HDGC syndrome, initially described in Maori families [115–117]. HDGC is characterized by an autosomal dominant inheritance pattern with incomplete penetrance. Mutation carriers may develop gastric cancer at an early age, and
women who carry this mutation also have a high incidence of invasive lobular breast cancer [17,118].

**Prophylactic surgery**

Prophylactic total gastrectomy with a Roux-en-Y esophagojejunostomy reconstruction often is recommended for individuals who carry the CDH-1 mutation [16]. Lewis and colleagues studied six asymptomatic carriers of the CDH-1 mutation who underwent prophylactic gastrectomy [119]. These individuals ranged from 22 to 40 years of age, and all were found to have occult foci of gastric cancer following detailed histologic assessment of the gastrectomy specimens. Similarly, Chun and colleagues [120] described five individuals from the same family with the CDH1 gene mutation who underwent prophylactic total gastrectomy with Roux-en-Y esophagojejunostomy, and occult gastric carcinoma again was found in all specimens. Chun and colleagues reported that all individuals in their study had undergone gastric endoscopy (with biopsies) before surgery, with no evidence of gastric cancer. Other series have reported similar results and these are summarized in Table 2. Thus, the situation with HDGC syndrome is similar to that of MEN 2 syndrome, in that asymptomatic individuals often are found to harbor occult cancer at the time of prophylactic surgery. There is considerable morbidity associated with total gastrectomy (eg, malnutrition and dumping syndrome), however, and patients should be made aware of this. Surveillance methods continue to evolve, and in a recent study, chromoendoscopy was found to facilitate the detection of early gastric carcinoma foci that were not visible with white light gastroscopy [123]. Although several authors recommend prophylactic gastrectomy at a young age in individuals who carry the mutation for HDGC, this should be done after other management options are discussed with the patient [15,78].

**Summary**

The ability to identify asymptomatic carriers of hereditary cancer syndromes through genetic testing has ushered in a new era in medicine. For all syndromes, management options fall into three categories: surveillance, chemoprevention, or prophylactic surgery. Deciding which option to follow

<table>
<thead>
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<th>Study</th>
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<th>Number with incidental gastric cancer</th>
<th>Age range of patients (years)</th>
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<td>Lewis, et al [119]</td>
<td>6</td>
<td>6</td>
<td>22–40</td>
</tr>
<tr>
<td>Chun, et al [120]</td>
<td>5</td>
<td>5</td>
<td>37–47</td>
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<tr>
<td>Huntsman, et al [121]</td>
<td>5</td>
<td>5</td>
<td>22–40</td>
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<tr>
<td>Charlton, et al [122]</td>
<td>6</td>
<td>6</td>
<td>15–43</td>
</tr>
</tbody>
</table>
requires extensive counseling and discussions with the patient. Prophylactic surgery might be considered in three instances:

- In those who undergo genetic testing and are found to carry a mutation
- In individuals who test negative for a mutation but have a strong family history (testing does not cover all mutations)
- In those who have a significant family history but do not undergo testing

Ideally, the latter should be a small group, and testing, if available, should be considered before risk-reducing surgery. The commonly accepted prophylactic surgical procedures for hereditary breast, colon, thyroid, and gastric cancers are outlined in Table 3. Prophylactic surgery is used increasingly for managing familial cancer syndromes and may reduce cancer risk significantly. Although there are no randomized prospective trials that have evaluated the efficacy of prophylactic surgery, current evidence indicates a benefit.

Table 3
Options for prophylactic surgical management of hereditary cancer syndromes

<table>
<thead>
<tr>
<th>Hereditary cancer syndrome</th>
<th>Primary option</th>
<th>Secondary option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast and ovarian cancer syndrome (BRCA mutation carriers)</td>
<td>Bilateral mastectomy</td>
<td>Prophylactic contralateral mastectomy in individuals already diagnosed with breast cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Salpingo-oophorectomy</td>
</tr>
<tr>
<td>FAP</td>
<td>Total proctocolectomy with ileal pouch anal anastomosis</td>
<td>Total proctocolectomy with permanent ileostomy</td>
</tr>
<tr>
<td>HNPCC</td>
<td>Subtotal colectomy with ileorectal anastomosis</td>
<td></td>
</tr>
<tr>
<td>MEN type 2</td>
<td>Total thyroidectomy with or without central neck dissection</td>
<td></td>
</tr>
<tr>
<td>HDGC</td>
<td>Total gastrectomy with Roux-en-Y esophagojejunostomy</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: FAP, familial adenomatous polyposis; HDGC, hereditary diffuse gastric cancer; HNPCC, hereditary nonpolyposis colon cancer; MEN, multiple endocrine neoplasias.*

References


