

ASCO/SSO Review of Current Role of Risk-Reducing Surgery in Common Hereditary Cancer Syndromes

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Background: A significant portion of cancers are accounted for by a heritable component, which has increasingly been linked to mutations in specific genes. Clinical interventions have been formulated for mutation carriers within affected families. The primary interventions for mutation carriers of highly penetrant syndromes are surgical.

Methods: The American Society of Clinical Oncology and the Society of Surgical Oncology formed a task force charged with presenting an educational symposium on surgical management of hereditary cancer syndromes at annual society meetings, and this resulted in a position paper on this topic. The content of both the symposium and the position paper was developed as a consensus statement.

Results: This article addresses hereditary breast, colorectal, ovarian/endometrial, and multiple endocrine neoplasias. A brief introduction on the genetics and natural history of each disease is provided, followed by detailed descriptions of modern surgical approaches, clinical and genetic indications, timing of prophylactic surgery, and the efficacy of surgery (when known). Although several recent reviews have addressed the role of genetic testing for cancer susceptibility, this article focuses on the issues surrounding surgical technique, timing, and indications for surgical prophylaxis.

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Conclusions: Risk-reducing surgical treatment of hereditary cancer is a complex undertaking. It requires a clear understanding of the natural history of the disease, realistic appreciation of the potential benefits and risks of these procedures in potentially otherwise healthy individuals, and the long-term sequelae of such interventions, as well as the individual patient's and family's perceptions of surgical risk and anticipated benefit.

Key Words: Hereditary cancer—Risk-reducing surgery—Surgical prophylaxis—Multiple endocrine neoplasia—Familial adenomatous polyposis—HNPCC.

Although the etiology of solid cancers is multifactorial, with environmental and genetic factors playing a variable role, a significant portion of the burden of cancer is accounted for by a heritable component. Increasingly, the heritable component of cancer predispositions has been linked to mutations in specific genes, and clinical interventions have been formulated for mutation carriers within affected families.¹ The primary interventions for mutation carriers for highly penetrant syndromes such as multiple endocrine neoplasias (MENs), familial adenomatous polyposis (FAP), hereditary nonpolyposis colon cancer, and hereditary breast and ovarian cancer syndromes are primarily surgical. For that reason, the American Society of Clinical Oncology (ASCO) and the Society of Surgical Oncology (SSO) have undertaken an educational effort within the oncology community. A joint ASCO/SSO Task Force was charged with presenting an educational symposium on the surgical management of hereditary cancer syndromes at the annual ASCO and SSO meetings, resulting in an educational position article on this topic. Both the content of the symposium and the article were developed as a consensus statement by the Task Force, with the intent of summarizing the current standard of care. This article is divided into four sections addressing breast, colorectal, ovarian and endometrial cancers, and MENs. For each, a brief introduction on the genetics and natural history of the disease is provided, followed by a detailed description of modern surgical approaches, including a description of the clinical and genetic indications and timing of prophylactic surgery, and the efficacy of prophylactic surgery when known. Although a number of recent reviews have addressed the role of genetic testing for cancer susceptibility,¹ including the richly illustrated *Cancer Genetics and Cancer Predisposition Testing* curriculum by the ASCO Cancer Genetics Working Group (available through <http://www.asco.org/asci/downloads>), this article focuses on the issues surrounding the why, how, and when of surgical prophylaxis for inherited forms of cancer. This is a complex process, which requires a clear understanding of the natural history of the disease

and variance of penetrance, a realistic appreciation of the potential benefit and risk of a risk-reducing procedure in a potentially otherwise healthy individual, the long-term sequelae of such surgical interventions, as well as the individual patient and family's perception of surgical risk and anticipated benefit.

HEREDITARY BREAST CANCER

In 1865 a French surgeon—Paul Broca—described his wife's pedigree of four generations of breast cancer.¹ This observation was cited a century later when Henry Lynch et al. described 34 families with two or more first-degree relatives with breast cancer, including a description of hereditary breast and ovarian cancer.² In 1990, Hall et al.³ noted a linkage between chromosome 17q and early-onset breast cancer. Narod et al.⁴ demonstrated a linkage to this same site in the hereditary breast and ovarian cancer syndrome. The site was soon cloned.⁵ In 1994, a second breast cancer-susceptibility gene, *BRCA2*, was linked to chromosome 13q.⁶

The intervening years have seen an explosion of information regarding the genetic repressor mechanism by which mutations in *BRCA1* and *BRCA2* genes cause inherited susceptibility to breast cancer. The Li-Fraumeni syndrome, associated with breast cancer and soft tissue sarcomas, was first described⁷ as a kindred in 1969; this is caused by a germline mutation in the p53 gene. In 1997, germline mutations of the *PTEN* gene were shown to be associated with Cowden disease, an inherited breast and thyroid cancer syndrome also known as the multiple hamartoma syndrome.^{8,9} A mutation on chromosome 11q, associated with ataxia telangiectasia, has been shown to convey a three- or four-fold increased risk of a variety of cancers. Female carriers of the mutated *ataxia telangiectasia* gene (*ATM*) are at approximately five times the risk of the general population for developing breast cancer¹⁰.

It was initially assumed that a host of other major genetic mutations would be found to account for all familial breast cancer. This hope has not yet been

TABLE 1. Genetic syndromes and lifetime breast cancer risk

<i>BRCA1</i>	56%–87%
<i>BRCA2</i>	56%–87%
Cowden Syndrome	30%–50%
Li-Fraumeni Syndrome	Increased
Heterozygous <i>AT</i>	Increased

Adapted from Srivastava et al.¹¹
AT, ataxia telangiectasia.

realized. The primary genes associated with risk for breast cancer are *BRCA1* and *BRCA2*. However, it is now possible to define the relative risk of having such a mutation from a detailed family history to guide recommendations for genetic testing (Table 1).^{11–14} When a three- or four-generation family tree suggests sufficient risk, testing for these genetic mutations is available commercially, and is often covered at least partially by insurance. The concern that insurance or employment discrimination might result from a positive test has not materialized. However, it should be noted that the perception of potential discrimination continues to pose a significant problem for the high-risk patient. This may explain, in part, why genetic testing for women whose family history suggests a significant risk is still not widely used.

Indications for Risk-Reducing Surgery

Risk-reducing surgery for breast cancer is indicated for three different populations of women. The first group comprises those women who have undergone genetic testing and have been found to express a mutated gene associated with high penetrance breast cancer. Although the risk is specific to a population rather than the individual, this group has a dramatically increased risk of developing breast cancer—between 56% and 87% in the case of *BRCA1* and *BRCA2* mutation carriers, respectively. The specific population risk varies somewhat, depending on the specific mutation. Not only is lifetime risk greatly increased, but these mutations carry a risk of breast cancer developing much earlier in life than is seen with sporadic breast cancer. The second population group comprises those women who present with a strong family history suggestive of hereditary breast cancer, but who test negative for *BRCA1* or *BRCA2*. These individuals are clearly at increased risk, but it is impossible at present to define the magnitude of this increased risk with any accuracy. The third population group is composed of those women who have a strong family history but have not been tested.

When a hereditary cancer syndrome is suspected in a family, the most important person to test is the relative affected with early breast or ovarian cancer.

Once a mutation is identified in an affected family member, the test is considered informative in that family and suitable for testing at-risk individuals. If a woman has not inherited the mutation, she has only the same risk of developing breast cancer as women in the general population—even a bit less, as the general population risk includes some women who are actually at increased risk. Consideration of prophylactic surgery in the absence of genetic testing should be strongly discouraged. However, patients who have tested negative but are perceived to be obligate gene carriers based on a review of their pedigree may also be considered for prophylactic surgery.

Surgical Considerations

Prophylactic surgery for women at high risk of breast cancer has traditionally been discussed in terms of mastectomy. However, in virtually all animal models of breast cancer development, mastectomy has failed to eliminate the risk completely.^{15–17} Clinical studies of reduction mammoplasty, however, show that this procedure—although leaving a generous amount of breast tissue—is associated with a decreased lifetime risk of breast cancer when compared with the sisters of this cohort; the decrease in risk approached 40%.¹⁸ Large series of subcutaneous mastectomy (nipple-sparing) were associated with few subsequent breast cancers. These series were not limited to women of defined risk, however. Dr. Lynn Hartmann and colleagues¹⁹ reviewed the Mayo Clinic series and attempted to define population risk from family history. Their analysis suggested a greater than 90% prevention of subsequent breast cancer by such mastectomies. Although a randomized trial to address this subject in the purest fashion is not feasible, several studies have recently emerged comparing mutation carriers who elected prophylactic bilateral mastectomy with those who did not.²⁰ Reassuringly, this also demonstrated a risk reduction of at least 90%. A larger series has now been published confirming a risk reduction of at least 90% from prophylactic mastectomy in mutation carriers.²¹

Modern surgical approaches to surgical prophylaxis include total mastectomy without an axillary lymph node dissection, skin-sparing total mastectomy, and subcutaneous mastectomy under a new name: “nipple-sparing mastectomy” (Table 2). A final procedure being discussed is areolar-sparing mastectomy. This procedure is a skin-sparing mastectomy in which the skin of the areola is also spared, and only the nipple and breast are removed. There is

TABLE 2. *Types of prophylactic mastectomy*

Type of Mastectomy	Features
Total	All breast tissue, nipple, areola, skin of breast; most effective
Skin-sparing	All breast tissue, nipple, areola; appears equally effective to total
Subcutaneous (nipple-sparing)	All breast tissue, except nipple, areola; anecdotally less effective
Areola-sparing	Few performed, no follow-up data

NOTE: All breast tissue means all apparent breast tissue; a tiny fraction always persists at the periphery of the mastectomy.

insufficient experience with this procedure to make any definitive statements about it, either in terms of its cosmetic advantages (if any) or its oncologic downside (if any). The case for subcutaneous mastectomy arises from the perceived cosmetic advantage of preserving the nipple and areola. To the degree that breast tissue is left in the nipple and immediately beneath the areola, however, the risk of cancer arising is clear. To the degree that this breast tissue is removed, the cosmetic advantage of nipple and areolar sparing is lost, since what remains is essentially a full-thickness skin graft that may heal with considerable distortion. The ability of plastic surgeons to reconstruct and tattoo normal-appearing nipples and areolae detract from any putative benefit. Pathological series showing cancer cells and in situ cancer in the nipple ducts of breast specimens have led to admonitions against subcutaneous mastectomy from surgical oncologists. Although these warnings seem reasonable, they are supported only by anecdotal, not substantive, trial data. In the Rebbeck study,²¹ both failures were in subcutaneous mastectomy patients. As the entire purpose of bilateral prophylactic mastectomy is put at risk by the breast tissue left behind, a strong case can be made for bilateral total mastectomy. This may be performed with a skin-sparing technique. The preserved skin envelope is then immediately refilled by either a transverse rectus abdominis muscle flap (TRAM) or a latissimus flap. In the latter case, an underlying prosthesis or tissue expander of appropriate size may be used. Whenever a prosthesis is implanted, overlying muscle beneath the skin allows a more natural look and feel.

The case for skin-sparing mastectomy is made on a cosmetic basis. It is supported by the finding of large series performed for cancer that show no suggestion of higher failure rates than in skin-ablating total mastectomy.²² Again, these are not randomized, comparative studies that would allow a definitive statement to be made. The downside of this clear risk-reduction benefit is the total loss of all nipple sensation, a loss that women often state is considerably greater than they had anticipated it would be, thus hindering sexual arousal. Satisfaction with this procedure exists for those who have replaced a high level

TABLE 3. *Management options for high risk women*

Prophylactic bilateral mastectomy
Prophylactic salpingo-oophorectomy
Chemoprevention (tamoxifen)
Surveillance (CBE, BSE, mammography, and MRI)

CBE, clinical breast examination; BSE, breast self-examination; MRI, magnetic resonance imaging.

of chronic anxiety about breast cancer with a desire for favorable cosmetic outcome.

Prophylactic mastectomy should be considered with other prophylactic surgical options (Table 3), including prophylactic salpingo-oophorectomy. Many patients find this a preferable prevention compared with prophylactic mastectomy, because it is a “hidden” procedure. It is approximately 90% effective in reducing the risk of subsequent ovarian cancer. Because ovarian cancer is difficult to detect at its earliest stages, it has an appeal purely in terms of preventing ovarian cancer. The data from Kauf et al.²³ and Rebbeck et al.^{21,24} all suggest that a 90% reduction of ovarian cancer risk is accompanied by a roughly 50% reduction in the risk of breast cancer. Because of the dual benefits and the ease with which it can generally be performed laparoscopically, prophylactic salpingo-oophorectomy is a first topic of conversation with mutation carriers. Clearly, this must be placed within a context of timing, family planning, and risk development.

Nonsurgical Alternatives

All prophylactic surgery must be weighed against the alternatives. The first alternative is surveillance with intervention for cause; the second is chemoprevention. The observation from clinical trials of adjuvant tamoxifen for breast cancer demonstrated reduction in the risk of contralateral breast cancer. After 5 years of tamoxifen, this reduction approached 50%. The National Surgical Adjuvant Breast and Bowel Project P1 trial demonstrated the safety of this approach to chemoprevention in women at even moderately increased risk. As data from the Rebbeck study suggest a 50% reduction in risk of breast cancer following oophorectomy, it has been postulated that

tamoxifen may reduce the risk of inherited breast cancer. Narod et al.²⁵ demonstrated a 30% to 40% reduction in the risk of contralateral breast cancer in mutation carriers who received tamoxifen as adjuvant therapy for their first breast cancer. This is at almost the same rate as that seen in general cancer patients. Taken with all the epidemiological data now published on breast cancer risk after prophylactic oophorectomy, it would appear that breast cancer risk in mutation carriers is significantly reduced by decreasing the influence of estrogen on breast tissue. The ultimate phenotype of the tumor does not appear to reflect the influence of estrogen on promotion initiation based on these growing experiences. This would suggest that both *BRCA1* and *BRCA2* mutation carriers would benefit from taking tamoxifen for risk reduction.

If chemoprevention lacks prospective validation in the mutation-positive population, the effectiveness of surveillance for early detection is also still being defined. This is of great importance, because close surveillance remains the option chosen by most high-risk women. The significant number of interval cancers seen in *BRCA1* and *BRCA2* mutation women under surveillance has encouraged several trials of magnetic resonance imaging (MRI) for breast screening of this high-risk population. At present, the general consensus regarding MRI is that the greater the experience, the more accurate the screening. MRI is far more sensitive than mammography, but even less specific. However, when applied to a population with a much higher incidence of breast cancer, the relative loss of specificity may still be acceptable, especially in view of the greater sensitivity afforded by this modality. Morris et al.²⁶ demonstrated this in a large retrospective study of asymptomatic women with a variety of high-risk factors. Brekelmans et al.²⁷ followed nearly 1200 women with familial risk factors, and added MRI to the other screening studies for women with *BRCA1* or *BRCA2* mutations. MRI appeared to be more cost-effective and was of greater benefit than other imaging modalities. Kuhl et al.²⁸ screened 462 women with mammography, ultrasound, and MRI, in addition to clinical breast examination. MRI was the most sensitive (96%, compared with 43% for mammography and 47% for ultrasonography). In yet another trial by Kriege et al.,²⁹ MRI showed a 71% sensitivity, compared with 36% for mammography, with a specificity of 88% for MRI versus 95% for mammography. The concern regarding MRI is that its lower specificity leads to higher recall rates and more biopsies. In a population of greatly increased risk, this may be tolerable. For

women already anxious about increased risk, however, being recalled for additional films, additional imaging studies, or needle aspirations may surely prove anxiety provoking.

Screening women at increased risk with dense breast tissue represents a major challenge. Breast MRI appears to offer sufficient benefit such that some have advocated an annual MRI with an annual mammogram alternatively at 6-month intervals to provide the most intense screening possible. In addition, we routinely recommend monthly breast self-examination (which is already recommended for women at average risk). Although it has been difficult to measure the relative advantages and disadvantages of this technique in detecting interval breast cancers, we have found that breast self-examination is empowering to many women at increased risk. The report on prophylactic mastectomy by Meijers-Heijboer et al.²⁰ included a woman who had elected surveillance and presented 1 year from the time of first evaluation with a 4 cm node-positive tumor. Clearly, the effectiveness of surveillance in a high-risk population is influenced by the compliance of the patient, the radiologic density of her breast tissue, the nodularity or consistency of the breast tissue to palpation, and the availability of excellent breast imaging.

Decisions regarding prophylactic bilateral mastectomy and bilateral salpingo-oophorectomy and the technique to be used, should be made by considering risk over the next decade rather than lifetime risk. In the future, continued progress may improve our ability to prevent cancer. Evidence of benefit from tamoxifen and prophylactic oophorectomy must be shared with these women. High-risk breast clinics offer the opportunity for structured, careful evaluation over time and consideration of both chemoprevention and risk-reducing surgical interventions by those with experience in technique and communication.

FAMILIAL ADENOMATOUS POLYPOSIS (FAP) AND HEREDITARY NONPOLYPOSIS COLORECTAL CANCER

INTRODUCTION

Inherited colorectal cancer primarily comprises two syndromes which predispose to disease by germline mutation transmitted in an autosomal dominant fashion. FAP, which accounts for less than

1% of the annual colorectal cancer burden, is caused by mutations in the tumor-suppressor adenomatous polyposis coli (*APC*) gene and is characterized by the presence of 100 or more adenomatous polyps in the colorectum, nearly 100% penetrance, and an inevitable risk of colorectal cancer at the average age of 40 years if prophylactic colectomy is not performed.^{30,31} In the less severe form, attenuated FAP, patients can present with fewer than 100 colorectal adenomas, which tend to be proximally located. Recently reported are biallelic germline mutations in the base-excision-repair gene *MYH*, which may account for 7.5% of patients with a classical FAP phenotype who have no demonstrable *APC* mutation.³² *MYH*-associated polyposis shows an autosomal recessive pattern of inheritance and often presents as attenuated polyposis.³³

Hereditary nonpolyposis colorectal cancer (HNPCC), also commonly referred to as the “Lynch syndrome,” accounts for 2% to 3% of all colorectal cancer and is due to a germline mutation in one of the DNA mismatch repair (MMR) genes (*hMLH1*, *hMSH2*, *hMSH6*, and *PMS2*).^{34,35} HNPCC is characterized by early-age-of-onset colorectal cancer, a predominance (70%) of lesions proximal to the splenic flexure, an increased rate of metachronous colorectal tumors, and a unique spectrum of benign and malignant extracolonic tumors.³¹ Lifetime risk of colorectal cancer in HNPCC patients is approximately 80%.^{36,37} Microsatellite instability (MSI), reflecting a deficiency in DNA repair secondary to the mutation in the MMR genes, is a common feature of HNPCC-related tumors.³¹

Differences in penetrance, phenotypic expression, and certainty of disease development mandate distinctly different surgical approaches in FAP and HNPCC, including the type and timing of risk-reducing colon and rectal surgery.

Familial Adenomatous Polyposis (FAP)

Risk-Reducing Colorectal Surgery for FAP

Surveillance (based on genetic testing or annual flexible sigmoidoscopy) of at-risk family members should begin around puberty (10 to 12 years). At-risk individuals belonging to families with an attenuated FAP phenotype should undergo screening with a colonoscope due to the proclivity of colonic adenomas to be located proximally in this variant.³⁸ In families with a demonstrated *APC* mutation, informative genetic testing is possible with the protein truncation test, gene sequencing, or analysis for large deletions and rearrangements. These methods detect

mutations in 90% to 95% of FAP pedigrees.³⁹ It is worth noting that deletion studies are increasingly part of the standard clinical panel performed by reference laboratories. Patients with either a positive genotype or adenomatous polyps on sigmoidoscopy should undergo full colonoscopy to establish the severity of polyposis. Timing of surgery depends to some degree on the extent of polyposis, as the risk of colorectal cancer development is partially dependent on colon and rectal polyp burden.⁴⁰ Patients with mild polyposis and a corresponding lower cancer risk can undergo surgery in their mid teens. Patients with severe polyposis, severe dysplasia, tubulovillous architecture, multiple adenomas larger than 5 mm, and symptoms (bleeding, persistent diarrhea, anemia, failure to thrive, and psychosocial stress) should undergo risk-reducing colorectal surgery as soon as is practical after diagnosis.³⁶ However, in carefully selected, fully asymptomatic cases with small adenomas, yet with a strong family history of aggressive abdominal desmoid disease, consideration can be given to delaying prophylactic colectomy, as the risk of a desmoid-related complications may be greater than the risk of developing a colorectal cancer.

The three current surgical options for patients with FAP are total proctocolectomy with permanent ileostomy (TPC), total colectomy with ileorectal anastomosis (IRA), and proctocolectomy with ileal pouch anal anastomosis (IPAA). The selection of the optimal procedure for an individual patient is based on several factors, including characteristics of the FAP syndrome within the patient and the patient's family, differences in likely postoperative functional outcome, preoperative anal sphincter status, and patient preference.^{41,43}

TPC with permanent ileostomy, although rarely chosen as a primary procedure, is employed in patients with unacceptably poor baseline sphincter function, an invasive cancer involving the sphincters or levator complex, or those in whom an IPAA is not technically feasible (secondary to desmoid disease and foreshortening of the small bowel mesentery leading to the inability to bring the ileal pouch to the anus). However, TPC is occasionally chosen as a primary procedure by patients who perceive that their lifestyle would be compromised by the frequent bowel movements (five to six per day) sometimes associated with the IPAA procedure.

In addition to the issues mentioned herein, the key in deciding between an IPAA and an IRA relates primarily to the risk of rectal cancer development if the rectum is left in situ. The risk of rectal cancer after IRA may be as high as 4% to 8% at 10 years and

26% to 32% after 25 years.^{44,45} This risk may be overestimated, however, as most studies were completed before the widespread availability of IPAA.⁴⁶ Thus, patients and physicians may have chosen an IRA even in the setting of extensive rectal disease, as TPC with permanent ileostomy was the only other available option at that time. The magnitude of risk in an individual patient is, however, related to the overall extent of colorectal polyposis. IRA may be considered for patients with fewer than 1000 colorectal polyps (including attenuated FAP) and fewer than 20 rectal adenomas, as these patients have a relatively low risk of rectal cancer.^{36,40,47-49} Patients with severe rectal (>20 adenomas) or colonic (>1000 adenomas) polyposis, an adenoma >3 cm, or an adenoma with severe dysplasia should ideally undergo proctectomy.^{36,40,47,48}

The risk of secondary rectal excision, due to uncontrollable rectal polyposis or rectal cancer, may be estimated by the specific location of the causative *APC* mutation.^{45,49,50} In one study, patients with a mutation located between codons 1250 and 1464 had a 6.2-fold increased risk of rectal cancer compared with those with mutation before codon 1250 or after codon 1464 (mean number of rectal polyps: 42 v 22, respectively).⁴⁵ Although the concept of using genotype-phenotype relations to help guide the management of a specific patient is appealing, it is important to recognize that variability of phenotypic expression even within members of the same family suggest that the current basis for choosing between an IRA and an IPAA should be primarily on clinical, rather than genetic, grounds.

The risk of polyp and cancer development after primary surgery is not limited to patients undergoing IRA. In patients undergoing IPAA, the pouch-anal anastomosis can be hand sewn after complete anal mucosectomy or stapled to the anus, thereby leaving in situ a 1 to 2 cm segment of mucosa called the anal transition zone. Neoplasia may occur at the site of ileal pouch anastomosis, and the frequency appears to be greater after stapled anastomosis (28% to 31%) than after mucosectomy and hand-sewn anastomosis (10% to 14%).^{51,52} Function may be better, however, after stapled anastomosis.⁵² In the case of neoplasia developing at the anal transition zone after a stapled anastomosis, transanal mucosectomy can often be performed, followed by advancement of the pouch to the dentate line.⁵³ Of additional concern is the development of adenomatous polyps in the ileal pouch, which occurs in 35% to 42% of patients by 7 to 10 years of follow-up.⁵⁴⁻⁵⁶ Consequently, after either procedure, lifetime surveillance of the rectal

remnant (after IRA) or the ileal pouch (after IPAA) is required.³⁶

Another important consideration in choosing between an IPAA and IRA is postoperative bowel function and associated quality of life. Some studies have associated IPAA with a higher frequency of both daytime and nocturnal bowel movements, higher incidence of passive incontinence and incidental soiling, and greater postoperative morbidity.⁵⁷⁻⁵⁹ However, other studies comparing IPAA and IRA have shown equivalent functional results⁶⁰ and quality of life.⁶¹ Therefore, although the choice of procedure has to be carefully individualized, when feasible we favor an IPAA for most FAP patients, because of the risk of rectal cancer associated with an IRA. However, an IRA can be a consideration in specific circumstances, such as when there is mild rectal polyposis (as in attenuated FAP) or a young patient not interested in undergoing the multiple procedures that accompany an IPAA and diverting loop ileostomy. However, although we attempt to perform a diverting loop ileostomy in all IPAA procedures, this is not always feasible due to a number of anatomic factors, including body habitus.

Endoscopic surveillance of the rectal segment at 6-month to 1-year intervals after the index surgery is recommended.³⁹ With increasing numbers of adenomas, frequency of surveillance should be increased. Although small (<5 mm) scattered adenomas can be safely observed or removed with a biopsy forceps, polyps larger than 5 mm should be removed with a snare. However, repeated fulguration and polypectomy over many years can lead to difficulty with subsequent polypectomy, reduced rectal compliance, and difficulty identifying flat cancers within a background of scar tissue. The development of severe dysplasia or villous adenoma not amenable to endoscopic removal is an indication for proctectomy.

Nonsurgical Alternatives

A number of nonsteroidal anti-inflammatory drugs, including sulindac, celecoxib, rofecoxib, and the sulindac metabolite exisulind, have been shown to reduce polyp number and size in patients with FAP.⁶²⁻⁶⁷ However, the long-term use of chemopreventive agents for primary treatment of FAP, in lieu of surgery, is not recommended.^{36,68} In a recent randomized, placebo-controlled, double-blind study of genotyped patients, sulindac did not affect the subsequent development of colorectal polyposis.⁶⁹ Furthermore, rectal cancer has developed in patients in whom rectal polyps were effectively controlled with sulindac.^{67,68,70} Finally, these medications re-

quire continued compliance⁶⁵ and may be associated with significant adverse effects. The use of these medications, however, may reduce polyp load and facilitate endoscopic management of polyps in an ileal pouch or retained rectum in those at high risk for polyps or those who refuse proctectomy. Nevertheless, these patients still require careful surveillance (proctoscopy or pouchoscopy) every 6 months, depending on the findings of the previous endoscopy.

Long-Term Considerations from Extracolonic Manifestations

Despite the reduced risk of colorectal cancer-related death after prophylactic colectomy, FAP patients are still at increased risk of mortality from both rectal cancer and other causes relative to the general population. In one study, 222 FAP patients status post-IRA and under regular surveillance had a risk of death three times higher than an age- and sex-matched population.⁷¹ The three main causes of death after IRA were upper gastrointestinal malignancy, progression of desmoid disease, and perioperative mortality. In another report of 354 patients without cancer at the time of diagnosis, and status post-IRA, 27 had died at the time of follow-up. Causes of mortality included rectal cancer in 26%, extracolonic cancer in 30%, desmoid disease in 18%, and other causes in 26%.⁷²

Desmoids

Desmoids are histologically benign tumors arising from fibroaponeurotic tissue.⁷³ They occur in 12% to 17% of patients with FAP^{36,74} and, unlike those found in the general population, tend to be intra-abdominal (up to 80%) and occur after prior abdominal surgery.⁷³⁻⁷⁵ Patients with *APC* mutations located between codons 1310 and 2011 appear to be at increased risk of desmoid tumors.⁷⁶ These tumors often involve the small bowel mesentery (> 50%),⁷⁴⁻⁷⁷ making complete resection difficult or impossible, and may also involve the ureters.⁷³ Presentation with small bowel obstruction is not uncommon.⁷³⁻⁷⁵ Morbidity after attempted resection, which often involves removal of a variable length of small bowel, is substantial. Furthermore, the rate of recurrence is high after attempted resection with recurrent disease is often more aggressive than the initial desmoid.⁷³⁻⁷⁵

Intraabdominal desmoids may be more common and severe after IRA than after IPAA.^{74,75,78} Desmoids involving the small bowel mesentery may preclude the formation of an IPAA secondary to foreshortening of the small bowel mesentery, espe-

cially in patients undergoing proctectomy after an initial IRA.³⁶

Surgery for abdominal wall desmoids should be reserved for small, well-defined tumors with a clear margin.³⁶ When intra-abdominal desmoid tumors involve the small bowel mesentery, they should be treated according to their initial presentation and rate of growth. Tamoxifen or other antiestrogens may be considered when tumors are slow growing or mildly symptomatic.^{79,80} More aggressive desmoids, in particular large intra-abdominal tumors directly invading the abdominal wall which present a formidable surgical challenge associated with high rates of morbidity and mortality, should be considered for treatment with chemotherapy.⁸¹ The combination of vinblastine and methotrexate has achieved a response in 40% to 50% of patients.^{82,83} For desmoids characterized by more rapid growth, therapies used in treatment of sarcomas, such as doxorubicin and dacarbazine, may be instituted.^{84,85} Radiotherapy may also be effective but can result in substantial morbidity secondary to irradiation of the adjacent small bowel. In the case of desmoid tumors that are refractory to all medical treatment and require surgery with extensive small bowel resection, small bowel transplantation may be feasible in selected cases.⁸⁶ Because of the rarity and highly variable natural history of desmoids, efforts to establish uniformity in the staging of the disease⁸¹ will be essential for developing definitive trials and effective therapies.

Upper Gastrointestinal Neoplasms

Approximately 80% to 90% of individuals with FAP will develop duodenal or periampullary adenomas.⁸⁷⁻⁸⁹ Of these, 36% will develop advanced polyposis, and 3% to 5% will develop invasive cancer.^{30,90-92} Although still relatively rare, the risk of periampullary or duodenal cancer in FAP patients is several hundred-fold greater than that in the general population. Although inconsistent, most reports indicate that mutations in exon 15 of the *APC* gene, particularly those distal to codon 1400, are associated with the highest rate of duodenal adenomas.⁹³

Insofar as the most common site of upper gastrointestinal polyps is the ampullary and periampullary region, patients should begin surveillance with side-viewing esophagogastroduodenoscopy and biopsy of suspicious polyps by age 25 to 30. The purpose of periodic endoscopy is to monitor for the development of high-grade dysplasia, rather than the removal of all visible polyps. Small, tubular adenomas without high-grade dysplasia may be biopsied and observed.

TABLE 4. *The Spigelman classification for staging duodenal polyposis^a*

Characteristic	Grade of duodenal disease (points)		
	1	2	3
Polyps (n)	1–4	5–20	> 20
Polyp size (mm)	1–4	5–10	> 10
Histologic type	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Used by permission.³⁰

^a Stage 0, 0 points; stage I, 1–4 points; stage II, 5–6 points; stage III, 7–8 points; and stage IV, 9–12 points.

However, adenomas showing high-grade dysplasia, villous changes, ulceration, or size larger than 1 cm should be removed. Although endoscopic removal (including endoscopic mucosal resection and snare ampullectomy⁹⁴) or a transduodenal excision are options, endoscopic ablation generally requires multiple sittings,^{90,95} and recurrence is high after either procedure.^{90,95,96} Endoscopic ablation is a reasonable initial approach for most patients without invasive cancer as definitive therapy for patients unfit for duodenal resection. For patients with persistent or recurrent high-grade dysplasia in papillary or duodenal adenomas, and for patients with Spigelman stage IV disease (Table 4),³⁰ pancreas-preserving duodenectomy or pancreaticoduodenectomy is recommended.³⁶ Results for duodenal resection in patients with premalignant lesions are encouraging, with good local control and low morbidity.^{90,97–99} Of note, with the exception of one study suggesting a clinical response with celecoxib,¹⁰⁰ chemoprevention has not been proven effective in the management of duodenal adenomas.

Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

Risk-Reducing Colorectal Surgery for HNPCC

The diagnosis of HNPCC (or “Lynch syndrome”) is much more challenging than FAP, as it requires ascertainment of an accurate and detailed family history, and an awareness of the syndrome by the clinician. However, it is important to recognize that although a family history of colorectal cancer is helpful when present, its absence does not exclude HNPCC. The Amsterdam criteria (I and II) require that there be three relatives (one a first-degree relative of the other two) with an HNPCC-related cancer (colorectal, endometrial, small bowel, ureter, or renal pelvis), involving two or more successive generations, with at least one with colorectal cancer diagnosed at younger than 50 years of age.^{101,102} Finally, FAP should be

excluded. It is important to keep in mind that not all individuals with HNPCC will meet these criteria; thus, the clinician has to have a high index of clinical suspicion for HNPCC to diagnose it. It is equally important to recognize that only approximately 60% of families who meet the Amsterdam criteria have a hereditary abnormality in an MMR gene.³¹ The term “familial colorectal cancer type X” has been suggested in order to distinguish families who fulfill Amsterdam criteria but do not have evidence of a DNA MMR defect, because relatives in these families appear to have a lower incidence of colorectal cancer relative to those belonging to a family in whom an MMR mutation has been detected.¹⁰³

The Bethesda criteria, which are more inclusive, were established¹⁰⁴ and revised¹⁰⁵ in order to identify individuals and families in which HNPCC is suspected and for whom MSI testing is indicated (Table 5). Overall, colorectal cancer occurs in 78% to 80% of MMR mutation–positive patients, at a mean age of 46 years.^{30,37,106,107} Endometrial cancer occurs in 43%, gastric cancer in 19%, urinary tract cancer in 18%, and ovarian cancer in 9% of affected individuals.¹⁰⁸

Patients with colorectal cancer belonging to known HNPCC kindreds, or pedigrees suspicious for HNPCC, should be offered screening of their tumor by MSI analysis, with consideration for subsequent immunohistochemical (IHC) evaluation for loss of MMR expression. Recently, however, it has been shown that screening with IHC for loss of MMR protein expression is as effective as screening with the more complex MSI analysis.¹⁰⁹ Although perhaps not as commonly noted as in *BRCA* testing for familial breast and ovarian cancer, MMR testing for HNPCC can disclose variants of uncertain significance or cases of incomplete or variable penetrance which mandate careful counseling. MSI evaluation will be positive (MSI-high) in more than 80% of patients belonging to families that meet Amsterdam criteria. Patients with MSI-high tumors should undergo testing for germline MMR mutations (*hMSH2*, *hMLH1*, and *MSH6* are currently commercially available). IHC staining for *hMSH2* and *hMLH1* protein expression in colorectal tumors have been shown to be highly sensitive and specific in screening for MMR gene defects.¹¹⁰ Recently, *PMS2* staining has been shown to detect additional cases with *hMLH1* germline mutations.¹¹¹ In addition, an abnormal IHC has been shown to have a 100% predictive value for MSI-H.¹¹² In families in which tumor tissue is not available, initial germline testing may be considered. As in FAP, a mutation in an affected individual must be established for testing in at-risk individuals to be conclusive.³⁹

TABLE 5. *The revised Bethesda guidelines for testing colorectal tumors for microsatellite instability (MSI)*

Tumors from individuals should be tested for MSI in the following situations

1. Colorectal cancer diagnosed in a patient who is younger than 50 y of age
 2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors,^a regardless of age
 3. Colorectal cancer with the MSI-H^b histology^c diagnosed in a patient who is < 60 y of age^d
 4. Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed at younger than 50 y
 5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age
-

Used by permission.¹⁰⁵

^a Hereditary nonpolyposis colorectal cancer (HNPCC)-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma, as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

^b MSI-H (microsatellite instability–high) in tumors refers to changes in two or more of the five National Cancer Institute–recommended panels of MS markers.

^c Presence of tumor-infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern.

^d There was no consensus among the workshop participants on whether to include the age criteria in guideline 3 above; participants voted to keep younger than 60 years of age in the guidelines.

Recommended surveillance for HNPCC includes colonoscopy every 1 to 2 years beginning at 20 to 25 years, and annually after age 40. Given the increasing evidence for an accelerated adenoma-carcinoma sequence in HNPCC, annual colonoscopy should be strongly considered.³¹ For females, consideration of annual endometrial aspiration is also recommended starting at 30 to 35 years. Annual esophagogastroduodenoscopy is recommended for patients belonging to kindreds with a history of gastric cancer. Finally, ultrasonography and urine cytology every 1 to 2 years should be considered to screen for urinary tract malignancy in pedigrees with a predilection for genitourinary tumor.¹¹³ It must be noted, however, that in HNPCC the colon and rectum are the only target organs where surveillance has been proven effective for reducing cancer.

Although development of colorectal cancer in HNPCC is not a certainty, the 80% lifetime risk,³⁰ 45% rate of metachronous colorectal neoplasms,¹⁰⁶ and possible accelerated adenoma to carcinoma sequence³¹ mandate consideration of prophylactic surgical options. Patients with HNPCC as defined by genotype or Amsterdam criteria, with a colon cancer or more than one advanced adenoma, should be offered the options of prophylactic total colectomy with IRA or segmental colectomy with annual lower endoscopy.^{46,114–117} In patients undergoing IRA, the goal should be normal rectal and sphincter function. Although the risk of metachronous colon cancers is higher after partial colectomy versus total colectomy with IRA, intensive colonoscopic surveillance and polypectomy may minimize the risk of future cancers in the remaining colon.^{101,113} Careful surveillance is also necessary after total colectomy and IRA because the risk of cancer in the retained rectum is approximately 12% at 10 to 12

years.^{118,119} Although there is no trial demonstrating an improved survival for HNPCC patients undergoing a total colectomy and IRA rather than a segmental colectomy, mathematical models suggest benefit for total colectomy and IRA, especially for younger individuals with early-stage cancers.¹²⁰

Mismatch mutation positive patients with a healthy colon may also be offered prophylactic colectomy in highly selected situations.¹²¹ One rationale for this approach is the similarity of the lifetime cancer risk between patients with *APC* and *MMR* gene mutations, and the fact that total abdominal colectomy with IRA produces less functional disturbance than the prophylactic procedure recommended for FAP (total proctocolectomy with IPAA).¹²¹ However, an alternate strategy in these individuals is surveillance by colonoscopy at 1- to 3-year intervals, which is cost effective^{117,122} and greatly reduces the rate of colorectal cancer development and overall mortality.^{107,123–125} There is a risk of colorectal cancer development in the interval between colonoscopies,^{123,126} but when the interval is less than 2 years, these are often early-stage, curable tumors.^{107,123} A decision-analysis model suggests that prophylactic subtotal colectomy at age 25 may offer a survival benefit of 1.8 years compared with surveillance colonoscopy. The benefit of prophylactic colectomy decreases when surgery is delayed until later in life, and is negligible when performed at the time of cancer development.¹²⁴ However, when quality of life was considered, surveillance provided the greatest benefit in quality-adjusted life years.¹¹⁹ Based on this evidence, prophylactic surgery is clearly indicated only in those patients for whom colonoscopic surveillance is not technically possible or who refuse to undergo regular surveillance.¹²⁵ Thus, the decision between

prophylactic surgery and surveillance for gene-positive, unaffected patients is based on many factors, including penetrance of disease in a particular family, early age of onset in affected family members, functional and quality of life considerations, and the likelihood of compliance with surveillance.

HNPCC patients with an index rectal cancer should be offered the options of total proctocolectomy with IPAA or anterior proctosigmoidectomy with primary reconstruction.^{36,116} The rationale for total proctocolectomy is the 17% to 45% rate of metachronous colon cancer in the remaining colon after an index rectal cancer in HNPCC patients.^{119,126,127} The decision between the two procedures depends, in part, on the patient's willingness to undergo intensive surveillance of the retained proximal colon, as well as issues of bowel function, which differs after each of these procedures.

Management of Extracolonic Cancers

Management of extracolonic cancers in HNPCC patients is less well defined. Prophylactic total abdominal hysterectomy should be offered to female patients whose childbearing is complete or to women undergoing abdominal surgery for other conditions,⁴⁶ especially when there is endometrial cancer in the family. (There is evidence of higher risks for endometrial cancer in *MSH2* and *MSH6* mutation carriers.) This recommendation is based on the high rate of endometrial cancer in mutation-positive individuals (43%),¹⁰⁸ and the lack of efficacy of screening demonstrated by some studies.¹²⁸ Oophorectomy should also be performed because of the high incidence of ovarian cancer in HNPCC (9%),¹⁰⁸ and the frequent coexistence of endometrial and ovarian cancer.¹²⁹ The optimal timing of prophylactic total abdominal hysterectomy is unclear. However, endometrial cancer has been reported in HNPCC patients younger than age 35. At present, it seems reasonable to begin surveillance at age 25 and delay prophylactic surgery until childbearing is complete.³⁶ These issues are discussed in greater detail in Hereditary Ovarian and Endometrial Cancers.

HEREDITARY OVARIAN AND ENDOMETRIAL CANCERS

Hereditary Ovarian Cancer

Germline mutations in the *BRCA1* and *BRCA2* genes strongly predispose women to early onset breast and ovarian cancers. Fallopian tube cancers

are rarer, but also seem to have an increased incidence in these families, and in many instances it is not possible to determine with certainty whether the cancer arose in the ovary or tube. Although only a minority of young women with early onset breast cancer and a strong family history are carriers,¹³⁰ it appears that most familial ovarian cancer is attributable to *BRCA1* and *BRCA2*, which account for approximately 10% of all invasive epithelial ovarian cancers.^{131–133} The risk of ovarian cancer is also increased in HNPCC families, but this accounts for only approximately 1% of all ovarian cancers.¹³¹ The lifetime risk of ovarian cancer increases from a baseline of 1.5% to approximately 5% to 10% in HNPCC carriers, 10% to 20% in *BRCA2* carriers, and 20% to 40% in *BRCA1* carriers.^{134–136} Highly penetrant germline *BRCA* mutations are rare, however, and in most populations are carried by fewer than 1 in 500 individuals. One notable exception is the Ashkenazi Jewish population, with a carrier frequency of 1 in 40.¹³⁷

Ovarian cancer is relatively uncommon, but has a high mortality rate because the majority of cases present at a late stage and effective early detection methods do not exist. As a result, most women present with extensive abdominal carcinomatosis and therapy is generally aimed at achieving remission rather than cure. The strategy of performing risk-reducing salpingo-oophorectomy (RRSO) in *BRCA* mutation carriers has the potential to significantly decrease ovarian cancer mortality in these individuals. In the past, RRSO was performed in women with a strong family history of ovarian cancer, whereas currently the decision to proceed with RRSO is based primarily on the results of *BRCA* mutational analysis.

Genetic Testing As It Relates to Decisions Regarding Prophylactic Oophorectomy

Although *BRCA1* and *BRCA2* play a role in the repair of double-stranded DNA breaks, the molecular basis for the increased risk of breast, ovarian, and fallopian tube cancers—but not other cancer types—in mutation carriers is unclear. At least twice as many *BRCA1* mutations as *BRCA2* mutations are found in high-risk families with a history of ovarian cancer.¹³⁸ Most deleterious *BRCA* mutations encode truncated protein products, but missense mutations that alter a single amino acid have been found to segregate with breast or ovarian cancer in some families.^{138,139} In a significant fraction of high-risk families, *BRCA* testing reveals sequence variants of uncertain significance or no detectable alterations, and these results represent a

counseling dilemma. Incomplete or variable penetrance of disease is another issue that confounds decision making for women considering prophylactic oophorectomy. There is evidence that certain types of *BRCA* mutations may predispose more strongly to ovarian cancer,^{140,141} but the relationship is not strong enough to affect counseling of patients.

Surgeons performing RRSO in high-risk women should be knowledgeable regarding the risks and benefits of prophylactic surgery and prepared to discuss these issues with patients. Genetic counselors should also play a significant role in ongoing patient management. Because it has been feared that misuse of genetic information could have devastating consequences, including difficulty in securing employment and life, health, or disability insurance, clinicians were initially hesitant to record genetic testing results in the medical record. However, because *BRCA* testing is now widely accepted and insurance companies generally cover the costs, patients should be encouraged to allow test results to be recorded in the medical record, as they form the basis for the decision to perform prophylactic surgery.

Because of ovarian cancer's high mortality rate, RRSO should be strongly recommended to all women who carry germline *BRCA1* or *BRCA2* mutations. Fortunately, the incidence of ovarian cancer in mutation carriers does not begin to rise dramatically until the late 30s.¹⁴² This allows women time to bear children before considering RRSO as they approach the end of their reproductive life span. Although oophorectomy is a major surgical procedure, surveys show that approximately three quarters of high-risk women undergoing genetic testing would strongly consider RRSO.¹⁴³ The ovaries are internal organs, and most women experience only modest feelings of altered body image and self-esteem after oophorectomy. In contrast, because cure rates for breast cancer are high and the cosmetic and emotional consequences of prophylactic mastectomy are more significant, surgical prophylaxis is accepted by only approximately one third of women. Insurance companies have almost always paid for RRSO in proven mutation carriers.¹⁴⁴ High-risk women lacking *BRCA* mutations, or those with sequence alterations of uncertain significance, may encounter greater reimbursement obstacles. For younger women who wish to maintain fertility, periodic screening with CA-125 and transvaginal sonography, although of unproven benefit, is often advised. The National Cancer Institute (Bethesda, MD) Cancer Genetics Network is presently performing a pilot study of these modalities in high-risk women.

TABLE 6. *Advantages and disadvantages of risk-reducing salpingo-oophorectomy*

Advantage
Strikingly decreases ovarian and fallopian tube cancer incidence and mortality
Can be delayed to allow completion of childbearing
Laparoscopic approach possible in most cases
Effect on body image generally acceptable
Estrogen replacement can prevent consequences of surgical menopause
Decreases breast cancer risk
Disadvantage
Cost
Potential operative morbidity and mortality
Surgical menopause in premenopausal patients who elect not to take hormone replacement

Risk-Reducing Salpingo-Oophorectomy (RRSO)

RRSO is widely viewed as the most effective means currently available of decreasing ovarian cancer mortality in *BRCA* mutation carriers. The risks and benefits of surgical prophylaxis for hereditary ovarian cancer are summarized in Table 6. First, there is strong evidence that this approach significantly decreases ovarian cancer mortality, and outcomes modeling suggest incremental savings of 2.6 life-years.¹⁴⁵ In addition, RRSO can be performed laparoscopically in most women, with discharge home the same day or after one night of observation in the hospital. In some patients, the laparoscopic approach may be problematic due to obesity, adhesions from prior surgery, or prior pelvic infections. However, it is almost always reasonable to begin the procedure laparoscopically. If insurmountable obstacles are encountered, the surgery can be completed through a small lower abdominal incision. All women who elect to undergo laparoscopic RRSO should be counseled preoperatively regarding the possibility that conversion to laparotomy may be necessary, and this should be documented in the surgical consent form. Morbidity including bleeding, infection, and damage to the urinary or gastrointestinal tracts can occur, but the incidence of serious complications is very low. Postoperative death is a catastrophic event that is exceedingly uncommon after benign gynecologic surgery in middle-age women and is usually related to sepsis after an intestinal injury or complications of general anesthesia. Although the rationale for RRSO is sound and serious complications are infrequent, discussion of the potential for adverse outcomes is particularly important when a healthy individual is subjected to the risks inherent in abdominal surgery.

Surgical menopause after RRSO is associated with several detrimental sequelae, including vasomotor symptoms, vaginal atrophy, decreased libido, and an

TABLE 7. Efficacy of salpingo-oophorectomy in reducing risk of reproductive cancers in *BRCA1/BRCA2* mutation carriers

Study	Salpingo-oophorectomy		Control	
	No.	%	No.	%
Rebbeck et al. ¹⁴⁷				
No. of patients	259		292	
Ovarian cancer at surgery	6	2.3	—	
Median follow-up (y)	> 8		> 8	
Ovarian/peritoneal cancer	2/259	1	58/292	20
Protection against ovarian/peritoneal cancer	.04	95 CI = .01–.16		
Breast cancer		21		42
Protection against breast cancer	.47	95 CI = .29–.77		
Kauff et al. ²³				
No. of patients	98		72	
Ovarian cancer at surgery	3	3	—	
Median follow-up (mo)	20		20	
Subsequent ovarian/peritoneal cancer	1/98	1	5/72	7
Subsequent breast cancer	3/69	4	8/62	13
Protection against breast/ovarian/peritoneal cancer	.25	95 CI = .08–.74		

CI, confidence interval.

accelerated onset and incidence of osteoporosis and cardiovascular disease. In premenopausal women who do not have a personal history of breast cancer, administration of estrogen replacement until approximately age 50 should be considered to ameliorate the deleterious effects of premature menopause.¹⁴⁶ Systemic estrogen levels are lower in oophorectomized premenopausal women taking hormone replacement than these levels would be if the ovaries had been left in place. Any small potential increase in breast cancer risk should be balanced against quality of life issues. The therapeutic benefit of oophorectomy in women with breast cancer has long been appreciated, and more recent studies support the contention that RRSO significantly reduces breast cancer risk in *BRCA* carriers (Table 7).^{23,147,148} Many *BRCA* carriers are identified after developing early onset breast cancer; balancing the potential risks and benefits of estrogen-replacement therapy is most difficult in this group. Despite fears that estrogen replacement might increase the risk of breast cancer recurrence, the available data does not support this contention.

Because the ovaries are small, discrete organs, they are relatively easy to remove completely. Attention should be paid to transecting the ovarian artery and vein on each side of the pelvis at least 2 cm proximal to the ovary so that ovarian remnants are not left behind. This involves opening the pelvic sidewall peritoneum, visualizing the ureter, and then isolation the infundibular pelvic ligament that contains the ovarian blood supply. If there are adhesions between the adnexa and adjacent structures, careful dissection should be performed to ensure complete removal of the ovaries and fallopian tubes. The more problem-

atic issue in performing RRSO is determining whether the risk of malignant transformation is increased solely in the ovaries or in the entire field of Mullerian-derived epithelia. Peritoneal papillary serous carcinoma, indistinguishable histologically or macroscopically from ovarian cancer, has been described in rare instances after oophorectomy.^{150–152} These reports preceded the identification of *BRCA1* and *BRCA2*, however, and it is unclear what fraction of women were mutation carriers. In a more recent study in which 259 known *BRCA* carriers were observed for a median of 8 years, only 1% developed primary peritoneal cancer.¹⁴¹ The origin of “primary peritoneal” cancer after oophorectomy is unclear, but case reports have been published in which retrospective examination of the ovaries has revealed occult ovarian cancers that were not recognized by the pathologist.¹⁵³

The vast majority of *BRCA*-associated ovarian cancers are of the papillary serous histologic type^{3,23,24,154,155} as are most *BRCA*-associated peritoneal and fallopian tube cancers and some uterine cancers. Although there are conflicting reports regarding whether *BRCA* mutations increase the risk of serous cancers of the uterus,^{157–158} the evidence supporting inclusion of serous fallopian tube cancers in this syndrome is stronger.^{159–161} In a population-based study of fallopian tube cancer, five (28%) of 18 women were *BRCA1* or *BRCA2* mutation carriers.²⁸ In another study of high-risk families seeking genetic testing, the fallopian tube cancer risk was increased more than 100-fold in *BRCA1* carriers compared with controls.¹⁶¹ In the presence of abdominal carcinomatosis, it is often difficult to determine with certainty whether the cancer arose in the fallopian tube

or ovary, and some fallopian tube cancers may be misclassified as ovarian, thus leading to an underestimation of the incidence of fallopian tube cancer.

Studies of *BRCA1* and *BRCA2* carriers who have undergone RRSO have added to our understanding of the spectrum of *BRCA* associated gynecological cancers. Some reports purport to demonstrate an increased frequency of epithelial abnormalities (invaginations, inclusion cysts, stratification, and papillations) in *BRCA* carriers,¹⁶² but other studies have not confirmed the presence of a consistent pattern of premalignant histological features.^{163,164} In some series, careful examination of RRSO specimens has led to the identification of occult cancers in as many as 12% of women.¹⁶⁵⁻¹⁶⁷ Malignant cells have also been found in pelvic peritoneal washings from women undergoing RRSO (three of 35 cases), and in some of these cases a primary cancer in the ovary cannot be identified.¹⁶⁹ In view of these data, it seems reasonable to recommend that cytologic washings of the pelvis be obtained routinely in concert with RRSO. Early-stage fallopian tube cancers have been found in *BRCA1* carriers undergoing RRSO.^{167,169} In one study, two women with occult fallopian tube cancer also had positive pelvic peritoneal cytology results and received adjuvant chemotherapy.¹⁶⁹ These data add support to the theory that primary peritoneal cancers occurring years after salpingo-oophorectomy may actually represent recurrences of ovarian or tubal cancer.

The pathologist must be informed of the indication for prophylactic RRSO and multiple sections of the fallopian tubes and ovaries should be examined to exclude the presence of occult carcinoma. When the tubes and ovaries are resected laparoscopically they should be placed in a plastic bag for delivery through a 10 to 12 mm abdominal trocar site. Retrieval may require morcellation of the specimen in the bag, and this may increase the difficulty of pathologic evaluation. Many patients elect to have the uterus removed as part of the surgical procedure because they have completed their childbearing or have other gynecological indications for hysterectomy. Furthermore, the likelihood of future exposure to tamoxifen in the context of breast cancer prevention or treatment, which increases endometrial cancer risk two- to three-fold, also argues for concomitant hysterectomy. Whether hysterectomy is performed as a laparoscopically assisted vaginal hysterectomy or laparotomy, the ovaries and entire fallopian tubes can be removed intact, in an atraumatic fashion, for pathologic examination.

Although hysterectomy often is performed in concert with RRSO after completion of childbearing, this is optional and increases operative time, blood loss, and complications. A few patients will choose not to have a hysterectomy because of concerns that there may be a deleterious effect on sexual function. When hysterectomy is not performed, however, the fallopian tubes should be removed as completely as possible. A small portion of the tube inevitably will be left in the cornu of the uterus, but thus far there are no case reports of fallopian tube cancer developing in such remnants.

There is now strong evidence that RRSO strikingly decreases ovarian cancer incidence and mortality in *BRCA* carriers (Table 7). A recent prospective study that examined the effect of RRSO revealed a 75% lower rate of breast and ovarian cancer over approximately 2 years of follow-up.²³ A separate study on 551 *BRCA1/BRCA2* carriers from various registries was also reported in 2002.¹⁴⁷ Of 259 women who had undergone RRSO, six women (2%) were found to have stage I ovarian cancer at the time of the procedure and two women (1%) subsequently developed papillary serous peritoneal carcinoma. Among the controls who did not undergo RRSO, 58 women (20%) developed ovarian cancer after a mean follow-up of 8.8 years. With the exclusion of the six women whose cancer was diagnosed at surgery, RRSO reduced the risk of epithelial cancer of the fallopian tube and ovary by 96%.

In summary, surgical prophylaxis with RRSO represents the best known approach for decreasing ovarian and fallopian tube cancer mortality in *BRCA* carriers. Although prevention using oral contraceptives¹⁷⁰ or other modalities and/or early detection may prove useful in the future, RRSO remains the standard of care, and should be discussed with all women who carry *BRCA1* or *BRCA2* mutations.

Endometrial and Ovarian Cancer in HNPCC

Although HNPCC typically manifests as familial clustering of early-onset colon cancer,¹⁷¹ there is also an increased incidence of several other types of cancers—most notably endometrial cancer in women.¹⁷² The risk of ovarian cancer is also significantly increased, but to a lesser degree.

As with colorectal cancer, approximately 3% to 5% of all endometrial cancers are associated with a germline mutation in the MMR genes *MSH2* and *MLH1*. *MSH6* mutations are also associated with an increased incidence of endometrial cancer.¹⁷³ *PMS1* and *PMS2*, but not *MSH3*, have been implicated in a small number of these cancers, as well.

Clinical Evaluation

Among families with germline mutations in MMR genes, MSI is seen in greater than 90% of colon cancers and approximately 75% of endometrial cancers.^{174,175} However, MSI is found in 20% to 25% of endometrial cancers¹⁷⁶ and 15% to 20% of colorectal cancers overall,¹⁷⁷ and most of these cases are caused by silencing of the *MLH1* gene due to promoter methylation. Those endometrial cancers with MSI that lack *MLH1* methylation may be among the best candidates for MMR gene mutational analysis,¹⁷⁸ particularly when the family includes a first-degree relative affected by an HNPCC-related cancer.¹⁷⁹

The risk of a woman with HNPCC developing endometrial cancer ranges from 20% to 60% in various reports,^{108,181–182} and in some studies this exceeds the risk of colon cancer for women. In addition, the risk of ovarian cancer is increased to approximately 5% to 12%. Whereas the mean age of women with sporadic endometrial cancers is in the early 60s, cancers that arise in association with HNPCC are often diagnosed before menopause, with the average age in the 40s.^{180,183,184} The clinical features of HNPCC-associated endometrial cancers are similar to those of most sporadic cases (well differentiated, endometrioid, early stage), and survival is approximately 90%.^{183,185} The mean age of onset of ovarian cancer in HNPCC families is in the early 40s, and the clinical features of these cancers are generally more favorable than in sporadic cases.¹⁸⁷ These cancers are usually identified at an early stage, are usually well or moderately differentiated,¹²⁹ and approximately 20% occur in the setting of synchronous endometrial cancers.

Surgical Prophylaxis

Recommendations for screening and risk-reducing surgery are more clearly established for colorectal cancer than for extracolonic malignancies. Surveillance and risk-reducing surgery should be considered early (between ages 25 to 35), generally 10 years before the earliest onset of cancer in other relatives who had an HNPCC related malignancy (Table 7).¹⁸⁴ Transvaginal ultrasonography has been proposed as a screening test for endometrial cancer (and ovarian cancer) in HNPCC families, but it appears to be relatively ineffective.¹²⁸ CA125 may be justified as a means of screening for HNPCC-associated ovarian cancer. Endometrial biopsy may be the only screening test with sufficient sensitivity, and it has been suggested that this should be employed periodically

in asymptomatic individuals beginning at age 30 to 35. Despite this recommendation, there are no published data demonstrating that this approach is superior to biopsies that are performed when abnormal uterine bleeding occurs.

Most authorities believe that risk-reducing hysterectomy has a role in the management of women with HNPCC. A recent retrospective report confirmed the efficacy of this approach for preventing endometrial cancer in women with documented mutations in the MMR genes. In this series, no endometrial cancers were diagnosed in 61 mutation carriers who had undergone hysterectomy, whereas endometrial cancer occurred in 69 of 210 women who did not undergo hysterectomy.¹⁸⁶ Conversely, because most HNPCC-associated endometrial cancers are cured, it is conceivable that risk-reducing hysterectomy may not appreciably decrease mortality.¹⁸⁷ Some women in HNPCC families elect to undergo risk-reducing colectomy because of the significant mortality rate associated with colon cancer. This provides an opportunity to perform a hysterectomy as well. Hysterectomy in concert with colectomy, either via laparoscopy or laparotomy, should not greatly increase operative time or complications. Both are clean contaminated procedures and warrant the use of prophylactic antibiotics.

Rather than simply summoning a gynecologist or gynecologic oncologist to the operating room to perform a hysterectomy, these women should ideally be seen in consultation before surgery. This provides an opportunity to discuss the advantages and disadvantages of risk-reducing hysterectomy and to consider performing a preoperative endometrial biopsy. This is an important consideration because not all women who harbor endometrial cancers have symptomatic uterine bleeding.¹⁸⁸ If cancer is already present in the uterus, surgical staging—including sampling of the regional lymph nodes—can be performed in addition to hysterectomy. Surgical staging allows identification of occult metastases and facilitates individualization of postoperative therapy. When an endometrial biopsy has not been performed before prophylactic hysterectomy, the uterus should be opened intraoperatively and examined carefully. If a visual suspicion of cancer is confirmed by frozen section, surgical staging can then be performed. In view of the increased risk of ovarian cancer in HNPCC syndrome, concomitant RRSO should be strongly considered. Estrogen-replacement therapy after RRSO is not contraindicated in women with HNPCC, as there is no evidence that this adversely affects the incidence of other cancers. In fact, post-

TABLE 8. Clinical features of sporadic MTC, MEN 2A, MEN 2B, and FMTC

Clinical setting	Features of MTC	Inheritance pattern	Associated abnormalities	Genetic defect
Sporadic MTC	Unifocal	None	None	Somatic <i>RET</i> mutations in >20% of tumors
MEN 2A	Multifocal, bilateral	Autosomal dominant	Pheochromocytomas, hyperparathyroidism	Germ-line missense mutations in extracellular cysteine codons of <i>RET</i>
MEN 2B	Multifocal, bilateral	Autosomal dominant	Pheochromocytomas, mucosal neuromas, megacolon, skeletal abnormalities	Germ-line missense mutation in tyrosine kinase domain of <i>RET</i>
FMTC	Multifocal, bilateral	Autosomal dominant	None	Germ-line missense mutations in extracellular or intracellular cysteine codons of <i>RET</i>

MTC, medullary thyroid carcinoma; MEN, multiple endocrine neoplasia; FMTC, familial non-multiple endocrine neoplasia medullary thyroid carcinoma.

menopausal replacement therapy in the general population has been associated with colon cancer risk.¹⁸⁹

Some women with HNPCC may elect to undergo periodic screening rather than risk-reducing colectomy because of the impact on quality of life. In such cases, it is still reasonable to offer hysterectomy for the reasons discussed herein. When a risk-reducing hysterectomy is performed without concomitant colectomy, the operative approach (vaginal *v* laparotomy *v* laparoscopy) can be determined strictly on the basis of gynecologic considerations, such as whether or not the patient has had prior abdominal surgery and whether the ovaries are also to be removed. Although there is no evidence of an increased risk of cervical cancer in HNPCC families, a complete hysterectomy should generally be performed to prevent the subsequent development of cancer in a retained cervical stump.

Prospective trials to determine the efficacy of surveillance and surgical strategies in HNPCC families are needed and would probably be best accomplished in the cooperative group setting.

MULTIPLE ENDOCRINE NEOPLASIA (MEN) TYPE 2 GENE CARRIERS

Medullary thyroid carcinomas (MTCs) account for approximately 5% to 9% of all thyroid cancers seen in the United States. Twenty-five percent of patients with MTC have one of the hereditary MEN 2 syndromes. MTCs arise from the thyroid C cells, also called parafollicular cells, which comprise 1% of the total thyroid mass and are dispersed throughout the gland. The C cells are so named because of their unique ability to secrete the hormone calcitonin. Calcitonin is a specific tumor marker for MTC. It is extremely useful in screening individuals predisposed

to the hereditary forms of the disease and in the follow-up of patients who have been treated.¹⁹⁰⁻¹⁹²

However, as noted herein, the *RET* oncogene screening method is now considered more useful.

MTC is a slow growing tumor in most cases, but causes significant morbidity and death in patients with uncontrolled local or metastatic spread. The tumor may invade local structures, including the recurrent laryngeal nerve, trachea, esophagus, and neck vessels. Regional nodal involvement is present in most patients with palpable tumors, and distant spread occurs to lungs, liver, bone, and brain. A large tumor burden is associated with diarrhea, flushing, weight loss, and inanition.¹⁹³

The MEN type 2 syndromes include MEN 2A, MEN 2B, and familial non-MEN medullary thyroid carcinoma (FMTC). These are autosomal dominant inherited syndromes caused by germline mutations in the *RET* proto-oncogene. The hallmark of these syndromes is the development of MTC, which is multifocal and bilateral and usually occurs at a young age. There is almost complete penetrance of MTC in patients affected by these syndromes; all persons who inherit the disease allele develop MTC. Other features are variably expressed with incomplete penetrance. These features are summarized in Table 8.

In MEN 2A, patients develop multifocal, bilateral MTC associated with C-cell hyperplasia. Approximately 42% of affected patients develop pheochromocytomas, which may also be multifocal and bilateral; these tumors generally develop on a background of diffuse adrenal medullary hyperplasia. Hyperparathyroidism develops in 10% to 35% of patients and is due to hyperplasia; this may be asymmetric, with one or more glands becoming enlarged.¹⁹⁴ Cutaneous lichen amyloidosis has been described in some patients with MEN 2A¹⁹⁵ and Hirschsprung's disease is infrequently associated with MEN 2A.¹⁹⁶⁻¹⁹⁸

In MEN 2B, 40% to 50% of patients develop pheochromocytomas. All affected individuals develop neural gangliomas, particularly in the mucosa of the digestive tract, conjunctiva, lips, and tongue. MEN 2B patients also have megacolon, skeletal abnormalities, and markedly enlarged peripheral nerves. MEN 2B patients do not develop hyperparathyroidism. MTC develops in all patients at a young age (infancy) and appears to be the most aggressive form of hereditary MTC, although its aggressiveness may be more related to the extremely early age of onset rather than the biological virulence of the tumor. MTC in MEN 2B is rarely cured, possibly because it is rarely identified before metastasis.

FMTC is characterized by the development of MTC in the absence of any other endocrinopathies. MTC in these patients has a later age of onset and a more indolent clinical course than that of MTC in patients with MEN 2A and MEN 2B. Occasional patients with FMTC never manifest clinical evidence of MTC (symptoms or a lump in the neck), although biochemical testing and histologic evaluation of the thyroid always demonstrate MTC.

RET Genotype-Phenotype Correlations

Mutations in the *RET* proto-oncogene are responsible for MEN 2A, MEN 2B, and FMTC. This gene encodes a trans-membrane protein tyrosine kinase. The mutations that cause the MEN 2 syndromes are activating, gain of function mutations affecting constitutive activation of the protein. This is unusual among hereditary cancer syndromes, which are usually caused by loss-of-function mutations in the predisposition gene (for example, familial polyposis, *BRCA1* and *BRCA2*, von Hippel-Lindau, and MEN 1). Over 30 missense mutations have been described in patients affected by the MEN 2 syndromes (Table 9).¹⁹⁹⁻²⁰²

There is a relationship between type of inherited *RET* mutation and presentation of MTC. The most virulent form is seen in patients with MEN 2B. These patients most commonly have a germline mutation in codon 918 of *RET* (nucleotide sequence at this codon is changed from ATG to ACG), although other mutations have been described (codons 883 and 922). MTC in MEN 2B has an extremely early age of onset (infancy), and despite distinctive clinical appearance and gastrointestinal difficulties, the disease is often not detected until the patient has a mass in the neck. Metastatic spread is usually present at the time of initial treatment and calcitonin levels often remain elevated postoperatively.

TABLE 9. RET mutations in hereditary MTC

Missense germline mutations in the <i>RET</i> proto-oncogene	
Exon	Codon
MEN 2A, FMTC	
10	609
	611
	618
	620
11	631 ^a
	634
13	790
	791
15	891
FMTC	
8	533
11	630
13	768
14	804
	844 ^a
15	913
MEN 2B	
16	918
	883

MTC, medullary thyroid carcinoma; MEN, multiple endocrine neoplasia; FMTC, familial non-MEN medullary thyroid carcinoma.

^a Clinical features not yet characterized.

In patients with MEN 2A, MTC has a variable course, similar to that of sporadic MTC. Codon 634 and 618 mutations are the most common *RET* mutations associated with MEN 2A, although mutations at other codons (Table 9) are also observed. Some patients do extremely well for many years, even with distant metastases, whereas others develop inanition, symptomatic skeletal metastases, and disabling diarrhea. Recurrence in the central neck, with invasion of the airway or great vessels, may cause mortality. It is difficult to predict the course of MTC in any given individual.

MTC is usually indolent in patients with FMTC. These patients most commonly have mutations of codons 609, 611, 618, 620, 768, 804, or 891, although mutations of other codons have been identified (Table 9). Many patients with FMTC are cured by thyroidectomy alone, and those with persistent elevation of calcitonin levels do well for many years. Occasional patients survive into the seventh or eighth decades without clinical signs of MTC, though pathologic examination of the thyroid reveals MTC or C-cell hyperplasia. It has been suggested that appropriate management of patients with FMTC (particularly those with codon 13 and 14 *RET* mutations) is observation and yearly calcitonin testing, with thyroidectomy only if stimulated calcitonin levels become elevated.²⁰³

TABLE 10. Preventative thyroidectomy series

Series	No. Patients genetically screened	No. Patients with <i>RET</i> mutation	Patients with <i>RET</i> mutation and normal calcitonin	<i>RET</i> mutation, normal calcitonin, MTC/CCH present in thyroid
Lips et al. ²⁰⁴	129	80	14	8/8
Wells et al. ²⁰⁵	58	21	12	6/6
Decker et al. ²⁰⁶	124	34	0	NA
Frilling et al. ²⁰⁷	56	21	11	1/1
Pacini et al. ²⁰⁸	58	21	2	2/2
Learoyd et al. ²⁰⁹	NS	164	7	7/7
Frank-Raue et al. ²¹⁰	178	84	0	NA
Dralle et al. ²¹¹	NS	75	14	14/14

RET mutation carriers with normal calcitonin levels, but MTC found in the thyroidectomy specimen.²⁰⁴⁻²¹¹
MTC, medullary thyroid carcinoma; NS, not stated; NA, not applicable; CCH, C-cell hyperplasia.

Risk-Reducing Thyroidectomy in *RET* Mutation Carriers

In order to test a patient for the presence of a mutation in the *RET* gene, peripheral blood is drawn and DNA is extracted. Regions of the *RET* proto-oncogene are amplified by polymerase chain reaction, and mutations are detected by one of several techniques. These include direct DNA sequencing, analysis of restriction sites introduced or deleted by a mutation, or gel shift analysis (denaturing gradient gel electrophoresis or single strand conformation polymorphism analysis). At-risk individuals from families affected by MEN 2A, MEN 2B, or FMTC, who are found to have inherited a *RET* gene, mutation, are candidates for thyroidectomy regardless of their plasma calcitonin levels. It has been shown in several series (Table 10) that *RET* mutation carriers often harbor foci of MTC in the thyroid gland even when stimulated calcitonin levels are normal.

In a series from Washington University in St. Louis, MO, reported in 1994, Wells et al.²⁰⁵ described the performance of risk-reducing surgery in asymptomatic *RET* mutation carriers. Families of patients with MEN 2A were screened using genetic and biochemical testing. Thirteen children found to be asymptomatic *RET* mutation carriers were subsequently treated with total thyroidectomy, central lymph node dissection, and parathyroid autotransplantation (six had normal plasma calcitonin levels and seven had elevated levels). After surgery, patients were placed on thyroid, calcium, and vitamin D supplementation. Approximately 8 weeks after operation, oral calcium and vitamin D supplementations were stopped. Two weeks later, the serum calcium concentration in each patient was found to be within normal range. All patients had microscopic foci of MTC or C-cell hyperplasia. In 1996, Wells et

al.²¹² reported an updated series to include 49 patients, with similar results. Lips et al., in a series from the Netherlands reported in 1994, identified 14 young members of families affected by MEN 2A who had normal calcitonin testing but who were found on DNA testing to be MEN 2A gene carriers. Thyroidectomy was performed for 8 of these 14 patients, and foci of MTC were identified in all eight. In a recent update, Skinner et al.²¹³ reported on 50 consecutive patients younger than age 20 with MEN 2A who had preventative thyroidectomy, central neck dissection, and parathyroid autotransplantation. All patients were evaluated clinically and biochemically at least 5 years after total thyroidectomy. Basal and calcitonin levels at 5 year follow-up were: age younger than 8 years at surgery, normal preoperative stimulated calcitonin level, and absence of carcinoma in the resected gland. At Washington University, management of the central nodes and parathyroids in these procedures has evolved. Up until 2003, all patients had central neck node dissection and parathyroidectomy with autotransplantation. Since 2003, patients younger than 8 years of age have had total thyroidectomy only. Parathyroid transplantation of individual glands is done in these young patients only if necessary to ensure the survival of the parathyroid tissue.

The identification of carcinoma in the glands of many young patients with normal stimulated calcitonin testing (Table 10) indicates that surgery is often therapeutic, not prophylactic. There is some urgency, therefore, in applying this genetic test to other at-risk individuals and performing thyroidectomy on those who test positive genetically. The ideal age for performance of thyroidectomy in those patients found to be genetically positive has not been determined unequivocally. It is therefore reasonable to perform surgery in patients with MEN 2A and FMTC at 6

TABLE 11. *Advantages and disadvantages of distinct preventative thyroidectomy options*

Technique of preventative thyroidectomy	Advantages	Disadvantages
Total thyroidectomy	Standard, familiar operation	Possible higher risk of local recurrence because the posterior capsule of the thyroid may not be removed (to protect blood supply to parathyroids); leaves central nodes that may be a site of recurrence; subsequent reoperation for recurrent MTC or hyperparathyroidism more difficult
Total thyroidectomy, central neck dissection, parathyroidectomy with autotransplantation	More complete removal of thyroid tissue is possible; potential for central neck recurrence of MTC is theoretically lower; removes potential for subsequent central neck reoperations for hyperparathyroidism	Requires special expertise in identification and management of parathyroids in children

MTC, medullary thyroid carcinoma.

years of age. Patients with MEN 2B should undergo thyroidectomy during infancy because of the aggressiveness and earlier age of onset of MTC in these patients. Patient follow-up over the next two decades will determine whether there is a significant rate of recurrence after a risk-reducing thyroidectomy. At present, it is advisable to observe patients with plasma calcitonin levels every 1 to 2 years. These individuals must also continue to be observed for development of pheochromocytomas and hyperparathyroidism.

Management of the Parathyroids and Central Nodes

A complicated series of issues related to management of the parathyroid are also involved in management of MTC. The first is the adequacy of thyroidectomy for treatment of MTC. The goal of a risk-reducing thyroidectomy is to eliminate any potential for development of MTC during the child's lifetime. However, C cells are normally distributed throughout the thyroid gland and any residual C cells (such as those remaining in the posterior capsule of the thyroid gland) have the potential to transform at a later date. Performance of a total thyroidectomy (hence, complete removal of all C cells) necessitates removal of the posterior capsule of the thyroid, a maneuver that is likely to increase the risk of hypoparathyroidism. In this respect, MTC poses a difficulty similar to that observed in patients who undergo risk-reducing surgery for hereditary breast cancer. A second issue is whether to perform a central node dissection at the time of prophylactic thyroidectomy. These nodes are a prime location for initial metastasis of MTC, and when primary surgery is not curative (indicated by residual elevation of the serum calcitonin, or subsequent development of metastatic disease), it may be necessary to perform a central

compartment dissection in the future—an additional surgical procedure that is inevitably associated with a higher incidence of recurrent laryngeal nerve damage and hypoparathyroidism than would be the case if dissection had been performed at the time of the primary surgical procedure. Finally, there is some probability that a child will subsequently develop hyperparathyroidism, necessitating a separate surgical procedure for this disorder (hyperparathyroidism is almost never observed in childhood before the primary surgical procedure). In some kindreds, particularly those with codon 634 mutations,²¹⁴ approximately one third will develop hyperparathyroidism at some point later in life.

Two approaches have evolved to address these issues (Table 11). The first is performance of a total thyroidectomy, leaving the parathyroid glands (and presumably some portion of the posterior thyroid capsule and associated vasculature) intact.^{206,211} The logic behind this is supported by the findings of studies using this approach, which indicate that 80% or more of patients thus treated show no evidence for recurrent MTC when followed up for one to two decades¹⁹⁵; in addition, development of hyperparathyroidism is uncommon in children observed for one to two decades.¹⁹² These findings are supported by our personal experience as well. It is important, however, to point out that there have been recurrences in children and teenagers treated by the traditional surgical approach. This is not completely surprising because microscopic MTC has been identified in children with MEN 2A at as young an age as 2 years, and metastasis has been described in children as young as 6 years old. These observations concern some clinicians in the field, and suggest the possibility that risk-reducing surgery utilizing the traditional approach, designed to cure these children, may be less than 100% effective. Thus, a second approach has

been developed that addresses some of these concerns.

Until recently, the practice at one institution (Washington University) has been to perform total thyroidectomy, central node dissection, and total parathyroidectomy, with autotransplantation of all of the parathyroid tissue into the muscle of the nondominant forearm during the primary surgical procedure.^{205,212,215} This approach answers several of the concerns discussed previously. First, routine removal of the parathyroids ensures that an adequate thyroidectomy and central node dissection is done without jeopardizing parathyroid function. Recurrence of MTC involves the central nodes in more than 80% of patients.²¹⁵ Central neck dissection for recurrent MTC is very challenging and places the recurrent laryngeal nerves and parathyroids at risk. Parathyroids are extremely difficult to find and preserve in a reoperative situation. Central node dissection is safe and simple to perform; however, the parathyroids are closely associated with nodes draining the thyroid, and in the process of removing these nodes, the parathyroid blood supply is damaged. Parathyroidectomy and autotransplantation at the time of thyroidectomy ensure preservation of parathyroid function. This approach also provides a strategy for dealing with the potential subsequent development of hyperparathyroidism. Instead of necessitating a repeat neck exploration, any separate operative intervention will be limited to the parathyroid graft in the nondominant forearm. This procedure can be carried out under local anesthesia on an outpatient basis, obviating the risk of neck re-exploration. The most compelling argument for this approach is that the technique permits performance of a “complete” thyroidectomy (including the posterior capsule) and central node dissection during the primary surgical procedure, addressing the issues of immediate hypoparathyroidism and subsequent hyperparathyroidism in a way that will simplify management of the patient over the course of a lifetime. Recent follow-up studies, however, have indicated that the likelihood of nodal metastases in patients younger than 8 years is extremely low. Because of this, Washington University now performs total thyroidectomy, leaving the parathyroids in situ, if possible, in children younger than 8. In older patients, total thyroidectomy, central node dissection, and parathyroid autotransplantation are performed.

There is no consensus regarding the correctness of either of these approaches at present. However, long-term surveillance of patients treated with these two different approaches is likely to provide guidance

over the next decade or so. It is important that the surgeon performing an operative procedure for MTC be familiar with the techniques described here. If not, the patient should be referred to a center where these procedures are routinely done.

Identification of *RET* gene mutations in patients at risk for development of the hereditary forms of MTC has simplified management, and has expanded the scope of indications for surgical intervention. Patients who carry this mutation can be offered operative treatment at a very young age, hopefully before the cancer has developed or spread. Those who are found not to have inherited the mutation are spared further genetic and biochemical screening. This achievement marks a new paradigm in surgery—the indication that operation be performed on the results of a genetic test. As with the decision to perform any surgical procedure, meticulous preparation and detailed discussion with patient and family must precede the final recommendation. It is important that the patient and family are involved in preoperative discussions with genetic counselors as well as with the surgical team.

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