World Journal of Surgery

Published Online: 7 February 2007

World J Surg (2007) 31: 450–464
DOI: 10.1007/s00268-006-0616-1

GREY TURNER LECTURE—DURBAN, SOUTH AFRICA

The Role of Prophylactic Surgery in Cancer Prevention

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Abstract

Background: Since the human genome has been sequenced many mysteries of cell biology have been unravelled, thereby clarifying the pathogenesis of several diseases, particularly cancer. In members of kindreds with certain hereditary diseases, it is now possible early in life to predict with great certainty whether or not a family member has inherited the mutated allele causing the disease. In hereditary malignancies this has been particularly important, because in affected family members there is the possibility of removing the organ destined to develop cancer before malignancy develops or while it is in situ. At first consideration, it would appear that ''prophylactic surgery'' would have a place in many hereditary malignancies; however, the procedure has applicability only if certain criteria are met: (1) the genetic mutation causing the hereditary malignancy must have a very high penetrance and be expressed regardless of environmental factors; (2) there must be a highly reliable test to identify patients who have inherited the mutated gene; (3) the organ must be removed with minimal morbidity and virtually no mortality; (4) there must be a suitable replacement for the function of the removed organ; and (5) there must be a reliable method of determining over time that the patient has been cured by ''prophylactic surgery.''

Conclusions: In this monograph we review several hereditary malignancies and consider those where prophylactic surgery might be useful. As we learn, there are various barriers to performing the procedure in many common hereditary cancer syndromes. The archetype disease syndromes, which meet each of the five criteria mentioned above and where prophylactic surgery is most useful, are the type 2 multiple endocrine neoplasia (MEN) syndromes: MEN2A, MEN2B, and the related familial medullary thyroid carcinoma. An additional benefit of the Human Genome Project, has been the development of pharmacologic and biologic compounds that block the metabolic pathway(s) activated by specific genetic mutations. Many of these compounds have shown efficacy in patients with locally advanced or metastatic cancers, and there is the likelihood that they will prove beneficial in preventing the outgrowth of malignant cells in patients destined to develop a hereditary cancer.

Despite highly aggressive therapeutic interventions, malignant neoplasms remain a major cause of death in the United States. Over the last decade, there has been an increased emphasis on cancer prevention strategies that target patients at highest risk for developing a malignancy. Until recently, the management of patients with a known genetic predisposition for hereditary cancer has included surveillance for early clinical diagnosis and treatment, and in some cases, chemoprevention. With the advent of direct DNA analysis to detect

Presented at the Grey Turner Lecture, International Surgical Week, Durban, South Africa, 2005

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germline mutations characteristic of a specific hereditary cancer, the use of prophylactic surgery has assumed major importance. Prophylactic surgery can be defined as the pre-emptive operative removal of an organ prior to malignant transformation or while the cancer is in situ.[1]

Prophylactic surgery should only be considered if the benefits of removing a noncancerous organ from an asymptomatic individual outweigh the risks of the operation. Several conditions need to be met. First, there should be either near-complete penetrance of the mutation causing a specific malignancy, or a near-certain lifetime risk of developing a specific hereditary cancer. Second, there must be a reliable means of identifying patients destined to develop the malignancy. This typically involves genetic screening, defined as the analysis of a person or a group of people to determine genetic susceptibility to a particular disease. Third, there must be a sensitive method for determining whether the patient becomes disease-free, and remains so after surgery. Fourth, the operative morbidity must be acceptably low. Finally, the function of the removed organ must be restored as completely as possible. Additional impetus for surgical prophylaxis may include the lack of effective surveillance or chemoprevention, the inability to cure the malignancy once clinically evident, and the psychological relief of patient anxiety.

Prophylactic surgery may be indicated in several of the hereditary cancer syndromes, where the molecular pathogenesis is known and DNA-based testing is available.[2] Examples include nevoid basal cell carcinoma; neurofibromatosis types 1 and 2; retinoblastoma; Wilms' tumor; hereditary diffuse gastric cancer; hereditary carcinoma of the breast, ovary, or colon; and multiple endocrine neoplasia (MEN) types 1 and 2. This article focuses on the role of prophylactic surgery in patients with hereditary breast-ovarian cancer, hereditary colorectal cancer, and the type 2 MEN syndromes. Prophylactic thyroidectomy in patients with MEN2A, MEN2B, and familial medullary thyroid carcinoma (FMTC) represents the prototype for testing the hypothesis that genetically based prophylactic surgical intervention can prevent or cure a solid organ malignancy (Table 1).

HEREDITARY BREAST AND OVARIAN CANCERS

Familial clustering of breast and ovarian cancers has long been recognized, with 10%–20% of all patients identifying an afflicted first-degree relative.[3] Approximately 90% of hereditary breast cancers arise from mutations in the *BRCA 1* and *2* genes, which are responsible for the hereditary breast–ovarian syndrome. Among white women in the United States, a *BRCA* mutation is present in 5%–10% of those with breast cancer and in 10%–15% of those with ovarian cancer.[4]

The *BRCA 1* (chromosome 17) and *BRCA 2* (chromosome 13) genes were characterized in 1994[5,6] and 1995.[7,8] Both genes encode for tumor suppressor proteins involved in DNA repair. The *BRCA* 1 gene product additionally functions in cell-cycle checkpoint control, protein degradation, and chromatin remodeling.[9] Genetic testing for *BRCA* mutations has been incorporated into clinical practice because these mutations are highly penetrant. The lifetime risks for breast and ovarian cancer in the general population are 3.8% and 1.5%, respectively.[10] In contrast, *BRCA 1* mutation carriers face an 85% lifetime risk for breast cancer and a 54%–63% risk for ovarian cancer; the corresponding rates are 86% and 23%–27% for *BRCA 2* mutation carriers.[11,12] Additionally, *BRCA 1*-associated breast cancers are more likely to affect young women, to occur bilaterally, and to lack estrogen-receptor (negative in 75%) or tyrosine kinase receptor ERBB2 (negative in 95%) expression.[9] Compared to sporadic tumors, hereditary breast cancers are more often high-grade, have atypical medullary histology, and exhibit increased (*BRCA 1*) or decreased (*BRCA 2*) mitotic count.[13]

Genetic testing for *BRCA* mutations, however, is complex because there is a wide spectrum of known *BRCA* mutations. Most pathogenic mutations are deleterious and result in protein truncation with a nonfunctioning product. The nondeleterious missense mutations, however, cannot be clinically interpreted because they may represent neutral polymorphic variants rather than pathogenic mutations. At present, commercial genetic testing protocols sequence the exons and flanking regulatory regions of *BRCA1* and *2* and test for five specific large genomic rearrangements in *BRCA1*. The mutation detection rate using this technique is 88% at best (Myraid Genetics Inc. Salt Lake City, UT).[14] Among those who have a negative test, approximately 12% are found to actually carry a large genomic deletion or duplication in a *BRCA* gene when further tested by multiplex ligation-dependent probe amplification (MLPA).[4] These intricacies of genetic testing underscore the need for proper genetic counseling.

A means to detect disease must exist in order to determine the efficacy of prophylactic interventions. The best available surveillance methods for breast cancer include clinical breast examination by the woman and

Table 1.
Considerations for prophylactic surgery in candidate hereditary cancer syndromes

Criterion	Incidence of organ malignancy (%)[a]	Reliability of diagnostic test (%)[b]	Operative morbidity	Restoration of organ function	Method of assessing disease status postoperatively
Ideal candidate syndrome	(100)	(100)	No	Yes	Yes
Hereditary breast/ovarian cancer	*BRCA1:* Breast (85) Ovary (54–63) *BRCA2:* Breast (86) Ovary (23–27)	(88)	No	No	No
Hereditary colorectal cancer	FAP (100) HNPCC (70–82)	FAP (80–90) HNPCC (54–80)	No	No	Yes/No
MEN 1 (pancreatic islet carcinoma)	(50–60)	(70–90)	Yes	No	Yes/No
MEN 2 (medullary thyroid cancer)	(Nearly 100)	(88–95)	No	Yes	Yes

[a] Defined as the proportion of patients with mutant genotype who actually develop hereditary cancer.
[b] Defined as mutation detection rate, reported for various testing methods. Data adapted from GeneReviews (www.geneclinics.org) as well as other references as cited in text.
FAP: familial adenomatous polyposis syndrome; HNPCC: hereditary nonpolyposis colorectal cancer syndrome; MEN: multiple endocrine neoplasia syndrome.

her physician, annual mammograms, and magnetic resonance (MRI) imaging. Recently, MRI has been shown to be not only sensitive for detecting early-stage breast cancer but also cost-effective when used in *BRCA 1* carriers between the ages of 35 and 54 years and *BRCA 2* carriers with mammographically dense breasts.[15] Detection of ovarian carcinoma is difficult and involves pelvic ultrasound and measurement of the tumor marker CA-125. However CA-125 is not specific and may be elevated in several benign and inflammatory conditions. Nonetheless, the efficacy of prophylactic mastectomy (PM) and prophylactic oophorectomy (PO) have been evaluated relative to surveillance.

A prospective study followed 139 women with pathogenic *BRCA1* or *BRCA2* mutations for a mean of 2.9 years, and reported a significantly reduced incidence of breast cancer (0 out of 76) in those treated by PM compared to those managed by surveillance (8 of 63; $p = 0.003$).[16] In another study of 26 *BRCA* mutation carriers, no cancer occurred after PM with a median follow-up of 13.4 years, translating to a risk-reduction of 89.5% –100%.[17] In a multi-center study, 105 women undergoing PM were matched with 378 controls by mutation type, age, and treatment center. After a mean follow-up of 6.4 years, 2 (1.9%) patients undergoing PM, compared to 184 (48.7%) controls, developed breast cancer, suggesting that PM was associated with a 90% risk reduction in women with intact ovaries and a 95% risk reduction in women who had previous or concurrent oophorectomy.[18]

Similar studies have demonstrated the efficacy of PO in reducing the risks for breast and ovarian cancers. In a prospective nonrandomized study of 170 women with *BRCA1* or *BRCA2* mutations, 98 elected to have PO and 72 chose surveillance. After a mean follow-up of 2 years, 3 patients in the PO group developed breast cancer and 1 developed primary peritoneal cancer. Among the women who chose surveillance, breast, ovarian, and peritoneal cancers were diagnosed in 8, 4, and 1 patients, respectively. Considering patients having risk-reducing PO, the hazard ratios for developing breast cancer was 0.32 (95% CI: 0.08–1.20) and for developing *BRCA*-related gynecologic cancer was 0.15 (95% CI: 0.01–1.31).[19] These findings were later supported by a multicenter case-matched study with significantly longer follow-up (at least 8 years): PO reduced the combined risk of ovarian and peritoneal cancers by 96% and the risk of breast cancer by 53%.[20] Recently, an international study prospectively followed 1828 women with *BRCA1* or *BRCA2* mutations. After adjusting for covariates including age, mutated gene, country of origin, prior history of breast cancer, oral contraceptive use, parity, and breastfeeding, PO was found to reduce the risk for ovarian, fallopian tube, and peritoneal cancers by 80% (Hazard

ratio, 0.20; 95% CI: 0.07–0.58).[21] Taken together, these studies demonstrated that PM and PO are highly effective in cancer risk reduction. However, their impact is imperfect. Failures have been reported after PM, particularly when subcutaneous mastectomy is performed because 10%–20% of the breast tissue is left behind during preservation of the nipple–areolar complex. After PO, patients remain at measurable risk for peritoneal cancer. The reported cumulative risk has ranged from 0.5% to 10.7%,[22] and it was 4.3% at 20 years after oophorectomy in a prospective international study.[21]

Reported complication rates associated with PM and PO have varied because of the many operative procedures used in practice. Prophylactic mastectomy operations have included total, subcutaneous, or skin-sparing mastectomy with or without reconstruction.[23] Either laparoscopic or open oophorectomy with or without hysterectomy have been performed for PO.[22] Although the morbidity associated with PO is minimal (1.5%[24]), it may be substantial after PM, where complication rates of 22%–64%[24–27] and reoperation rates as high as 49%[27] have been reported. Higher complication rates occur following tissue or implant reconstruction. Common immediate complications include skin necrosis, bleeding, and infection, while delayed complications include capsular contracture, pain, and loss of sensitivity. Furthermore, the optimal timing for surgical prophylaxis is largely undefined. Available genotype–phenotype correlation studies suggest that women with mutations located 5′ to nucleotide 2401 or 3′ to nucleotide 4191 of the *BRCA1* gene carry lower risks for ovarian cancer.[28,29] However, there has been no established stratification of disease aggressiveness based on genotype to guide the optimal timing of prophylactic intervention. Only model-based studies have demonstrated that life expectancy gains from PM or PO diminish when these operative procedures are performed at an increasing age above 30 years,[30] and they have emphasized the need to perform PM and PO in asymptomatic women if the maximal gain in life expectancy is to be realized (up to 5.3 years for PM, 2.6 years for PO, and 6.0 years for both).[31,32] In practice, there is consensus that PO may be delayed until completion of child-bearing, a strategy that may be supported by the low incidence (2.3% and 3.1%) of occult ovarian cancer reported at the time of PO.

Significant reservations regarding PM or PO also arise from concerns about body image, femininity, surgical menopause, and related deterioration in quality of life (QOL). In a survey of 595 patients who had chosen to undergo PM, 9%–25% reported adverse effects on emotional stability, stress, self-esteem, sexual relations, or femininity, and 36% felt dissatisfied with body appearance, although most (74%) reported substantial relief of emotional concern regarding cancer risk.[33] After PO, restoration of ovarian function with hormone replacement therapy (HRT) is problematic. Its impact on breast cancer risk is unknown, although a decision analysis projected detrimental effects (loss of 0.79–1.09 years in life expectancy) only when HRT was continued beyond 50 years of age after PO.[34] In contrast, withholding HRT leaves the patient at risk for osteoporosis, adverse lipid profiles, coronary artery disease, and menopausal symptoms.[3] Thus, although physiological and psycho-emotional losses resulting from PM and PO are not easily restored, they are accepted by the majority of patients in exchange for the psychological relief that the incidence of developing breast or ovarian cancer is markedly reduced. In retrospect, nearly all patients report satisfaction with their decision to undergo prophylactic surgery.[27]

Practice pattern studies have shown that up to 54% of the known *BRCA* mutation carriers opt for PM or PO.[35] Although these rates appear incongruent with the demonstrated efficacy of PM and PO in reducing cancer risks, they highlight the many concerns regarding these procedures. Given the imperfect mutation detection rate, the measurable residual cancer risk after PM or PO, the associated operative morbidity, and potential psychophysiological sequelae, the decision to undergo these ablative procedures remains highly personal.

HEREDITARY COLORECTAL CANCER

At least 20% of all patients with colorectal cancer harbor a familial risk, in that two or more first- or second-degree relatives either have or have had the disease. Clinical disorders characterized by adenomatous polyps are exemplified by the classic familial adenomatous polyposis (FAP) syndrome, the variant attenuated FAP (AFAP) syndrome, and the newly characterized autosomal recessive disorder multiple adenomatous polyposis syndrome (or MYH-associated polyposis, MAP, syndrome).[36] The nonpolyposis familial colon cancer syndromes, on the other hand, are exemplified by the Lynch syndrome (also known as the hereditary nonpolyposis colorectal cancer syndrome, HNPCC), the hallmark of which is defective DNA mismatch repair (MMR) genes,[36] and "Familial Colorectal Cancer Type X," which does not have MMR gene defects.[37] The genetic basis of other rarer polyposis syndromes has been recently elucidated.

Juvenile polyposis syndrome is characterized by mutations in the *SMAD*4 or *BMPRIA* tumor suppressor gene and carries a 38% risk for colorectal malignancies and a 21% risk for upper gastrointestinal tract malignancies.[38] The Cowden syndrome, the hallmark of which is characteristic skin and mucosal lesions, has been linked to mutations in the serine/threonine and tyrosine phosphatase PTEN, and the Peutz-Jegher syndrome, where patients exhibit lentigines (mucocutaneous pigmentation), hamartomatous polyps, and malignancies of the gastrointestinal tract, is characterized by a mutant serine/threonine kinase encoded by the *LKB1* gene.[39,40] Among these various syndromes, genetic testing is most widely available for the classic FAP and HNPCC syndromes. Consequently, standards of clinical management and prophylactic intervention are most highly developed for these diseases.

In 1991, the genetic basis of classic FAP was identified, and the *APC* tumor suppressor gene was characterized.[41,42] Located on chromosome 5q21, the *APC* gene encodes for a multi-domain protein, which regulates cell adhesion, cell-cycle progression, and microtubule and mitotic spindle stabilization.[43] Similar to the case for *BRCA*, detecting germline mutations in *APC* is clinically valuable because FAP is highly penetrant. The lifetime risk for colorectal cancer in the general population ranges from 4% to 6%, with a mean age of onset at 63 years. Patients with classic FAP, however, face a near-certain lifetime risk for colorectal cancer, and the mean age of malignant transformation is 39 years. Premalignant adenomas develop in over 95% of patients by age 35, and cancer is found in over 90% of patients by age 50.[36,43] Additionally, several genotype–phenotype correlations have been noted in patients with FAP. Specific codon mutations have been associated with heightened risks for congenital hypertrophy of the retinal epithelium (mutations spanning the region between codons 543 and 1309), extracolonic malignancies such as desmoid tumors (mutations spanning the region from codons 1310 to 2011) and duodenal and periampullary adenomas (mutations spanning the regions from codons 976 to 1067). Furthermore, patients with mutations at codon 1309 have early development of colorectal carcinoma (Table 2).[40,44]

Table 2.
Genotype–phenotype correlations in familial adenomatous polyposis (FAP)

Phenotype	Mutations in different areas of the *APC* gene
Severe FAP	Codons 1249–1330
Attenuated FAP	Codons 1–163; Codons 1860–1987
Desmoid tumors	Codons 1445–1578
Duodenal/periampullary tumors	Codons 976–1067
CHRPE	Codons 463–1387

CHRPE: congenital hypertrophy of the retinal pigment epithelium

SOURCE: Data from Merg A, Lynch HT, Lynch JF, *et al*. Hereditary colorectal cancer–part II. Curr Probl Surg 2005;42:267–333.

In the late 1980s, kindreds with HNPCC were found to harbor germline mutations in DNA mismatch repair (MMR) genes:[39,45] *MLH1* (50%), *MSH2* (39%), *MSH6* (7%), and *PMS1*, *PMS2*, and *MLH3* (~5%).[46] Defective MMR genes lead to DNA replication errors. Microsatellites are short and repetitive DNA sequences that are particularly prone to these errors, which cause expansion or contraction of the microsatellite length. This phenomenon, termed microsatellite instability (MSI), occurs in 90% of the tumors of patients with HNPCC. The clinical significance of genetic mutations in MMR lies in the 70%–82% lifetime risk for colorectal cancer faced by patients with HNPCC. Their risk for synchronous colorectal disease may be as high as 30%, while that for metachronous disease ranges from 20% to 45%. Like those with FAP, patients are at risk for extracolonic cancers; in particular, female patients face a 42%–60% lifetime risk for endometrial cancer and a 10%–12 % risk for ovarian cancer.

Genetic testing for the classic FAP and HNPCC syndromes is complex. Patients affected by classic FAP exhibit a striking phenotype and are readily diagnosed by well-defined clinical criteria: the presence of more than 100 colorectal adenomatous polyps, or the presence of fewer polyps in association with a first-degree relative known to have FAP.[47] *APC* mutations are detected in 80%–90% of patients meeting these criteria.[36] Over 300 mutations in *APC* have been identified, and approximately 25%–30% of newly diagnosed patients have de novo mutations.[48] The widely used truncated protein test (PTT) is simple but detects only 80% of the mutations in tumors with this molecular derangement. Although direct DNA sequencing is the best test for detecting *APC* mutations, it is expensive and time-consuming. Furthermore, approximately 12% of cases with large or total deletions in the *APC* gene may not be detected.[49] Thus, the current genetic testing methods for FAP warrant further refinement. In contradistinction to classic FAP, the diagnostic criteria for the HNPCC syndrome have been ambiguous and evolving. The Amsterdam I criteria require that three relatives spanning at least two consecutive generations and affecting

at least one relative before age 50 (one being a first-degree relative of the other two) have colorectal cancers. Amsterdam II criteria were expanded to include extracolonic malignancies associated with the syndrome (endometrial, small bowel, ureter/renal–pelvis, ovarian, stomach, etc.).[50] Using these pedigree-based criteria, the detection rate of germline mutations in MMR is only 54%–78%.[36,37,51] With the recently established Bethesda Guidelines (subsequently revised), the sensitivity of genetic testing increased to 82%.[52] However, patients with MMR mutations who do not fit either the Amsterdam or Bethesda criteria have been identified in large-scale tumor genetic screening studies.[53]

Furthermore, because directly sequencing multiple MMR genes is not feasible in clinical practice, a two-stage mixed strategy has been used. Patients are selected for germline mutation testing only after they demonstrate a high pretest probability for MMR mutations, defined by either a MSI-high phenotype in their tumor (i.e., MSI in more than 30% of the markers on the testing panel, by genotyping or immunohistochemistry), or a combination of both pedigree-based and tumor-based criteria.[53–56] Following a recent prospective population-based study, a two-stage model was proposed for predicting MMR mutation status among patients diagnosed with colorectal cancer prior to age 55. Significant clinical predictors included young age, male sex, proximal tumor location, synchronous or metachronous disease, family history of colorectal cancer (youngest affected member < 50 years), and family history of endometrial cancer. When the clinical model was combined with immunohistochemical staining of tumor tissue for MMR proteins, the positive predictive value for germline MMR mutation approached 80% and the sensitivity was 62%.[57] However, the necessity of having tumor tissue for analysis and the heterogeneity of testing techniques have added to the intricacy of predictive genetic testing in this disease. Lastly, some detected missense mutations may not be interpretable clinically because their pathogenic significance is unknown.

Despite the complexities associated with genetic testing, little debate exists regarding the need for prophylactic colectomy (PC) in patients with classic FAP. In the presence of numerous polyps, endoscopic surveillance is impractical, whereas the risk for malignancy is nearly certain. Among symptomatic FAP patients with cancer at the time of total colectomy, the 10-year survival is 41%. But survival rates for asymptomatic patients identified by family screening and undergoing PC were significantly higher (87%–94%).[58,59] For patients with HNPCC, the role of PC remains unclear. When patients present with a premalignant or malignant lesion, PC with ileorectal anastomosis (IRA) may be preferred over segmental colectomy because of the high risk of metachronous disease.[60] In mutation carriers without mucosal pathology, however, the support for PC with IRA has mostly been theoretical and based on expert opinion,[61–63] although a decision analysis study has shown a greater gain in life expectancy after prophylactic IRA than with surveillance.[64]

Defining the risk reduction for colorectal cancer achieved by PC in patients with FAP or HNPCC has been difficult, because both the optimal timing of intervention and the optimal surgical procedure remain controversial. Although several genotype–phenotype correlations have been identified in patients with FAP, clinical variability of the disease has precluded the development of a definitive guide to the timing of prophylactic surgery. On the one hand, for patients with classic FAP, those with mutations between codons 1250 and 1464, especially codon 1309, have been thought to have high a polyp count (median > 4000 in one study), experience disease symptoms in their teenage years, develop malignant transformation by age 30, and face a higher risk of dying from malignancies.[65] On the other hand, patients with mutations at the 5′ end of codon 168 and the 3′ end of codon 1580 have milder disease and a mean onset of malignant degeneration as late as 52 years.[44,66–68] But disease manifestation remains too variable to serve as a reliable guide to the timing of operation. Additionally, the correlation between polyp count and cancer risk is imperfect, as 3.3% of the patients with a low polyp count developed cancer before age 30.[69] Because the risk of cancer increases 2.4 times for each 10-year age interval,[68,69] current guidelines recommend colectomy by age 19 years in patients with mild disease, but as soon after diagnosis as convenient for patients with severe or symptomatic disease.[50,60] For patients with HNPCC, the life expectancy gain afforded by PC over surveillance diminishes to only days if PC is delayed, and it becomes negligent if a malignancy is present at the time of surgery.[64] But no guideline regarding optimal timing of intervention is available.

The three main surgical procedures employed in PC are total proctocolectomy with end ileostomy, total abdominal colectomy with IRA, or total abdominal colectomy with ileal pouch anal anastomosis (IPAA). Although total proctocolectomy removes all at-risk mucosa, it is rarely performed prophylactically because of the need for a permanent stoma and associated pelvic organ dysfunctions. The debate between the two sphincter-sparing alternatives has centered on (1) the risk of malignant transformation in the residual rectum, (2) the complexity

and morbidity of the procedures, and (3) the functional sequelae and QOL outcomes.

Because IRA leaves more residual rectal mucosa than IPAA, the risk of malignant transformation is likely higher after IRA. For patients with classic FAP, the risk of rectal cancer after IRA increases with time, and ranges between 10.4 and 14.5 at 15 years;[58,70,71] and a decision analysis study showed a 1.8-year reduction in life expectancy after IRA when compared to IPAA.[72] For those with HNPCC, on the one hand, a 12% residual risk of rectal cancer has been observed at 12 years after IRA.[73] On the other hand, pouch adenomas or carcinomas can develop after IPAA, most likely as a result of incomplete mucosectomy at the time of IPAA.[60,74] Thus, neither IRA nor IPAA eradicates the risk of colorectal cancer, and close postoperative surveillance is required after both procedures.[43,50,75] At present, the prediction and selection of patients at low risk for rectal cancer based on genotype remains imperfect,[76] and whether cyclo-oxygenase-2 (COX-2) inhibitor therapy after IRA may retard or prevent malignant transformation in the residual rectum remains unclear.

Second, both IRA and IPAA are associated with operative morbidities. Ileorectal anastomosis has generally been regarded as a straightforward operation, but it is still associated with significant postoperative (30-day) adverse events: mortality (0.9%), morbidity (26%), and incidence of reoperation (12.6%).[77] The most common complication after IRA is small bowel obstruction. In contrast, IPAA is a complex and typically multi-stage operation. In a recent case-matched study, laparoscopic and hand-assisted techniques significantly facilitated postoperative recovery compared to the open approach, but the morbidity rate was 33%–37% with either operative approach,[78] although patients undergoing IPAA for inflammatory bowel disease included in the study likely faced a greater risk of complications than the young and healthy cohort undergoing PC for FAP.

Third, both procedures may significantly alter bowel, urinary, and sexual function. The average daily stool frequency of 4 to 6 after IPAA, may be comparable to the stool frequency 3 to 4 after IRA (with up to 25% of the patients reporting more than 5 stools per day).[77,79] No significant difference between bladder dysfunction and sexual dysfunction has been reported between IRA and IPAA, despite the more extensive pelvic dissection with IPAA. While IPAA may be associated with higher frequencies of nighttime defecation and incontinence, the reported incidence of urgency may be higher after IRA.[80] Regardless of functional outcomes, retrospective studies have demonstrated no difference in QOL with either procedure.[50,80] Therefore, designation of the optimal operative procedure remains elusive, and the choice between the two is made on a case by case basis.

In addition to PC, concurrent prophylactic hysterectomy with or without PO should be considered in females with HNPCC. Patients with *MSH6* mutations are at elevated risk for endometrial cancer[36] and may be particularly suitable candidates for the combined procedure. A recent study of 315 women with germline mutations diagnostic of HNPCC compared the benefit of prophylactic hysterectomy ($n = 61$) or prophylactic salpingo-oophorectomy ($n = 47$) to observation in mutation matched cohorts. Endometrial and ovarian cancers were prevented in each of the 108 patients treated by either prophylactic hysterectomy or salpingo-oophorectomy; however, in the matched control groups, there was a 33% incidence of endometrial cancer and a 5% incidence of ovarian cancer after follow-up of 7.4–13.3 years.[81] Patients must contend with the sequelae of surgical menopause following these procedures.

Therefore, while the molecular basis for hereditary colorectal cancer syndromes is being elucidated, the identification of patients genetically destined to develop a colorectal cancer remains imprecise. Although prophylactic colectomy may increase life expectancy, sphincter-preserving procedures that avoid a permanent colostomy do not fully eradicate the risk for malignancy.

HEREDITARY MEDULLARY THYROID CARCINOMA

Medullary thyroid carcinoma (MTC) arises from the parafollicular C-cells of the thyroid gland. It serves as the paradigm for how molecular biology has enabled surgical prophylaxis and has guided the management of patients with this disease. Approximately 5%–10% of patients with thyroid carcinoma have MTC and at least 25% of cases are hereditary and occur as one of three autosomal dominant disorders: MEN2A (60%), MEN2B (5%), or FMTC (35%)[82,83] (Table 3). The impetus for surgical prophylaxis is perhaps strongest in patients with these diseases, because MTC occurs in virtually 100% of affected patients and it is the most common cause of death. Furthermore, unlike breast and colon cancers, no chemotherapeutic or radiotherapeutic regimen has proven effective for patients with locally advanced or metastatic MTC.[1] Thus, the best chance of curing patients destined to develop hereditary MTC is to perform a thyroidectomy before malignancy develops or while it is still confined to the thyroid gland.

Table 3.
Clinical presentations of medullary thyroid carcinoma

Type	Thyroid distribution	Familial pattern	Classic associated abnormalities	Biological agressiveness[a]
MEN2A	Bilateral	Yes	Pheochromocytoma, hyperparathyroidism	2+
MEN2B	Bilateral	Yes/No	Pheochromocytoma, characteristics phenotype	4+
FMTC	Bilateral	Yes	None	1+
Sporadic	Unilateral	No	None	3+

FMTC: familial medullary thyroid cancer.
[a] Increasing number indicates increasing aggressiveness.
SOURCE: Adapted from Wells SA Jr, Franz C. Medullary carcinoma of the thyroid gland. World J Surg 2000;24:953, with permission.

The fundamental requirement for surgical prophylaxis—the existence of a means to identify at-risk patients—was met in the early 1990s. The susceptibility gene for hereditary MTC was localized to the peri-centriomeric region of chromosome 10 (locus 10q11.2) and subsequently identified as the *RET* (REarranged during Transfection) protooncogene.[84–86] The RET protein is a transmembrane tyrosine kinase receptor. Ligand binding to the cysteine-rich extracellular domain of RET, along with its co-receptor, induces formation of a RET homo-dimer. This is followed by autophosphorylation of specific tyrosine residues on the intracellular domain. Specific downstream pathways affecting cellular proliferation are then activated.[87] Genetic testing for RET is highly accurate, and germline mutations are detected in more than 95% of the patients with hereditary MTC.[84,85,88] Three main factors have contributed to this uniquely high accuracy.

First, the clinical diagnostic criteria for the three types of hereditary MTC are well-defined. Virtually all patients with MEN2A develop MTC; however, they less commonly develop pheochromocytoma (42%–50%) or hyperparathyroidism (20%–35%).[89] Patients with MEN2B develop MTC and pheochromocytomas with the same frequency as patients with MEN2A; however, while they do not develop hyperparathyroidism, they do manifest a diffuse ganglioneuromatosis of the lips, tongue, eyelids, and gastrointestinal mucosa, and a characteristic marfanoid body habitus.[83] Patients with FMTC develop MTC only,[90] and the diagnosis requires that there be more than 10 carriers in the kindred, multiple carriers or affected members over 50 years of age, and adequate medical history confirming MTC, especially in the elderly patients.[89]

Second, RET mutations are highly penetrant. Medullary thyroid carcinoma is expressed in virtually all patients with MEN2A and MEN2B, and FMTC.

Third, unlike the multitude of mutations identified in the *BRCA*, *APC*, and *MMR* genes, *RET* mutations cluster at characteristic "hot spots"[91] (Figure 1). Over 80% of patients with MEN2A have mutations in codon 634 (exon 11), and another 10%–15% have mutations in either codon 609, 610, 611, 618, or 620 (exon 10). These mutations alter the disulfide bonds between cysteine residues in the extracellular domain and cause constitutive receptor dimerization and RET activation. In more than 95% of patients with MEN2B, the responsible mutation occurs at codon 918 (exon 16). This mutation alters the substrate specificity of RET in the intracellular tyrosine kinase domain, resulting in receptor autophosphorylation and activation. Among patients with FMTC, about 50% have mutations at the cysteine codons similar to those in MEN2A, and the others have non-cysteine mutations in codon 768 (exon 13) and codons 804 and 806 (exon 14) within the intracellular domain.[88] Elucidation of these mutational "hot spots" has greatly facilitated genetic testing. The most widely used test today directly sequences germline DNA for mutations in exon 10 (codons 609, 611, 618, 620), exon 11 (codons 630 and 634), exon 13 (codon 768), exon 14 (codons 804 and 806), and exon 16 (codon 918).[92] Its near-perfect sensitivity and specificity allow for reliable prediction of patients genetically destined to develop MTC.

The clinical applicability of highly accurate genetic information to surgical prophylaxis was immediately apparent in patients with hereditary MTC.[93] Concurrently, it was realized that the efficacy of prophylactic thyroidectomy (PT) could be readily tested because of the availability of a highly sensitive test to detect the presence of MTC cells. Surveillance for primary or metastatic breast, ovarian, and colon cancers relies on radiological or endoscopic identification of macroscopic disease. The hormone calcitonin (CTN) is secreted by the parafollicular

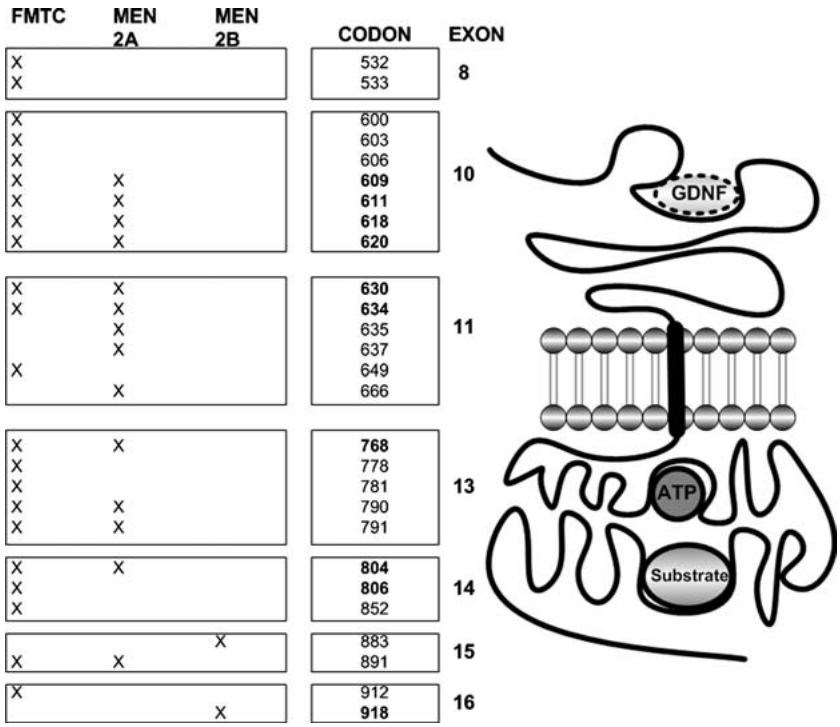

Figure 1. A schematic diagram showing the genotype–phenotype correlations for patients with hereditary MTC associated with type 2 multiple endocrine neoplasia syndromes including MEN2A, MEN2B, and FMTC. The RET receptor is divided into extracellular, transmembrane, and intracellular domains, with tyrosine kinase activity present in the intracellular portion. Known *RET* codon mutations are listed and grouped according to the exons in which they occur. Phenotypically expressed clinical syndromes corresponding to each codon mutation are listed. (GDNF: glial-cell derived neurotrophic factor, a ligand of RET; ATP: adenosine triphosphate. SOURCE: Adapted from You YN, Lakhani V, Wells SA Jr. Medullary thyroid carcinoma. Surg Oncol Clin North Am 2006;15:644)

cells of the thyroid gland and is arguably the best tumor marker for patients with a malignant disease. There is a direct correlation between plasma CTN levels and the MTC cell mass.[94,95] Following thyroidectomy for MTC, the first evidence of persistent or recurrent disease is an elevated plasma CTN level. Furthermore, intravenously administered calcium gluconate and/or pentagastrin are potent CTN secretagogues and markedly increase the clinician's ability to detect the presence of occult MTC cells.[95] Thus, unlike other hereditary cancer syndromes, where the efficacy of surgical prophylaxis is determined by less sensitive radiographic tests, in hereditary MTC the availability of CTN testing provides a much more sensitive measurement of successful PT.

The hypothesis that PT can cure patients with hereditary MTC has been tested in several studies. The first experience was reported in 1994.[93] Thirteen asymptomatic children (mean age 13.2 years) with hereditary MTC were identified by direct DNA analysis to have inherited a mutated *RET* allele. All patients were treated by total thyroidectomy and central neck zone lymphadenectomy. Although half of these patients had normal stimulated plasma CTN levels preoperatively, C-cell hyperplasia or MTC was found in all patients. No patient had metastasis to regional lymph nodes.

Postoperatively, basal and stimulated plasma CTN levels were undetectable in all 13 patients. In 2005, the same medical group expanded their experience to 50 children with germline *RET* mutations characteristic of MEN2A. All children (mean age 10 years; range: 3–19 years) were treated by PT, central zone lymph node dissection, and parathyroid autotransplantation. Histological examination of the resected thyroid gland showed C-cell hyperplasia, microscopic MTC, or macroscopic MTC in 94% of the patients. Lymph nodes metastases were present in three patients. At 5 to 10 years (mean 7 years) after PT, all children were evaluated by physical examination and by measurement of plasma CT levels after calcium and pentagastrin stimulation. On physical examination, no child had evidence of persistent or recurrent MTC, and on biochemical testing, 44 (88%) of the 50 children had undetectable basal and stimulated plasma CTN levels. Of the remaining 6 children, 2 had stimulated plasma CTN levels above the normal range, and 4 had levels that increased above basal but were within the normal range.

Table 4.
Genotype–phenotype correlations in hereditary medullary thyroid cancer (MTC): categorization of disease risk by *RET* proto-oncogene codon mutation and recommendation for prophylactic thyroidectomy

Risk level for MTC	Mutations in the *RET* gene	Recommended age for prophylactic thyroidectomy
1 (high)	Codons 609, 768, 790, 791, 804, 891	No consensus: by 5–10 years; or at first abnormal stimulated calcitonin
2 (higher)	Codons 611, 618, 620, 634	By 5 years
3 (highest)	Codons 882, 883, 918,or known MEN2B	By 6 months, preferably within first month of life

SOURCE: Data from Brandi ML, Gagel RF, Angeli A, *et al*. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001;86:5658–5671; and Kouvaraki MA, Shapiro SE, Perrier ND, *et al*. RET proto-oncogene: a review and update of genotype–phenotype correlations in hereditary medullary thyroid cancer and associated endocrine tumors. Thyroid 2005;15:531–544.

Using a rigorous definition for biochemical cure, this study established that PT can provide durable disease-free periods from MTC in the large majority (88%) of patients with germline *RET* mutations. Whether these patients are cured will require prolonged follow-up. These results were consistent with experiences from several other institutions, which have reported cure rates of 76%–100%. However, compared to the study of 50 patients, these latter studies evaluated fewer patients,[96–98] employed less rigorous criteria for detecting persistent of recurrent MTC, and had less complete or shorter periods of postoperative evaluation.[99–104]

Widespread acceptance of PT has been facilitated by the minimal operative morbidity and functional sequelae associated with the procedure. Although the extent of nodal dissection beyond total thyroidectomy has been debated, operative risks are low regardless of the extent of the procedure. The reported incidence of recurrent laryngeal nerve dysfunction is less than 5%, with minimal incidence of permanent damage.[99,101] Despite a reported 3%–27% risk for transient postoperative hypocalcemia,[99–102] permanent iatrogenic hypoparathyroidism occurs in less than 6% of the patients.[1,99,100] Furthermore, although in situ preservation of parathyroid tissue is often possible, intramuscular autograft of parathyroid glands has been well described and should be performed routinely.[105–107]

In contrast to hereditary breast–ovarian and colon cancer syndromes, risk-stratification based on genotype–phenotype correlations has been possible in hereditary MTC (Table 4). Such knowledge has enabled surgeons and patients to balance the risk for malignant transformation against the risk of surgical morbidity in the very young and arrive at a theoretical optimal time for PT. There is general agreement that patients with MEN2B, or mutations in codons 882, 883, or 918 are at highest risk and should undergo thyroidectomy within the first year of life, and that patients with mutations in codons 611, 618, 620, and 634 are at high risk and should undergo thyroidectomy before 5 years of age. The management of patients with mutations in codons 609, 768, 790, 791, 804, or 891 remains controversial but must involve close surveillance if PT is delayed beyond 5 years of age. To avoid the risk of intervening too late, when the disease has spread beyond the thyroid gland, one practical approach has been to advise thyroidectomy in patients with MEN2B as soon as the diagnosis is made, even in the first months of life, and to recommend thyroidectomy at or before 5 years of age in patients with MEN2A and FMTC, regardless of their codon mutation.

In contrast to the extensive functional and psychological sequelae after PM and PO for patients destined to develop hereditary breast and/or ovarian cancer, and after PC for patients destined to develop hereditary colorectal cancer, there is minimal morbidity following PT, and thyroid function can be fully restored, as oral thyroid hormone replacement is simple, convenient, and associated with little adverse effect.

Taken together, experience with predictive genetic testing and PT for hereditary MTC represents the best proof of the concept that prophylactic removal of an organ destined to develop a malignancy can be curative. However, prophylactic removal of the parathyroid glands or the adrenal glands in patients with MEN2A and MEN2B is not indicated, because the tumors are benign, easily diagnosed, affect less than 50% of patients, and are managed by standard operative procedures.

NONSURGICAL PROPHYLAXIS

Although prophylactic surgery has a variable role in patients with the hereditary neoplastic syndromes described, its invasive nature has stimulated the develop-

ment of new biological or pharmacological "targeted" therapies, designed to inhibit known oncogenic molecular pathways. For women at high risk for breast cancer, tamoxifen has been used as a primary chemoprophylaxis based on its ability to block estrogen receptors. Its efficacy has been demonstrated in the National Surgical Adjuvant Breast and Bowel Project (NSABP)-P1 trial, as well as in the newly released NSABP-P2 trial (The Study of Tamoxifen and Raloxifene, or STAR).[108] For women enrolled in the NSABP-P1 trial who were carriers of *BRCA 1 and 2* mutations, the hazard ratios for breast cancer did not significantly differ after tamoxifen versus placebo (hazard ratio: 1.67, 95% CI: 0.32–10.70 for *BRCA 1* mutation carriers; and hazard ratio: 0.38, 95% CI: 0.06–1.56 for *BRCA 2* carriers).[109] A meta-analysis demonstrated that risk reductions attributable to tamoxifen have ranged only between 13% and 27% for women with *BRCA 1* and *2*, respectively.[110] Therefore, primary chemoprevention with tamoxifen remains unproven among *BRCA* mutation carriers.[109]

For patients with classic FAP, the overexpression of COX-2 in colorectal adenomas and carcinomas had led to the use of COX-2 inhibitors such as aspirin and sulindac as primary chemopreventive agents. Results have been mixed, but a randomized, double-blinded, placebo-controlled clinical trial did not show any significant change in the size and number of the polyps in the treatment and control arms of the study.[111,112] Despite the lack of success with these drugs, they illustrate that understanding the genetic basis of hereditary syndromes may lead to novel treatment strategies and targets.

Although no chemoprevention has been proposed in hereditary MTC, knowledge of the central oncogenic role of the *RET* protooncogene has led to the identification of specific RET tyrosine-kinase inhibitors. In 2002, ZD6474 (Zactima; AstraZeneca, Wilmington, DE), an inhibitor of the RET receptor tyrosine kinase, was discovered to be biologically active in its oral form.[113] At present, the efficacy of ZD6474 in patients with a germline *RET* mutation and metastatic hereditary MTC is being tested in a phase II clinical trial. Early results in 20 patients have demonstrated a partial remission rate of nearly 25%, a stabilization rate of 65%, and a disease progression rate of 15%.[114]

CONCLUSIONS

Prophylactic surgical intervention, based on molecular genetic analysis, illustrates the importance of translational research in the care of patients destined to develop malignant disease. Predictive genetic testing has enabled the identification of patients at risk for malignancy of a specific organ. Prophylactic interventions, targeting a low tumor burden, have the potential to achieve greater cure rates than extensive resections required for clinically evident disease (Figure 2). At present, predictive testing and prophylactic surgery are applicable for patients with select hereditary cancer syndromes; however, continued investigations of these and other hereditary diseases will lead to novel treatment strategies and targets relevant for patients with a broad range of sporadic malignancies.

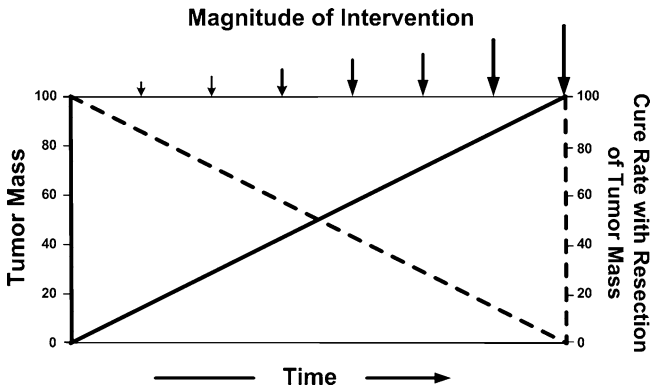

Figure 2. A schematic illustrating that genetically based prophylactic surgical intervention effectively cures solid organ malignancies. Prophylactic surgery targets the at-risk organ prior to malignant transformation or when tumor mass remains minimal, and are therefore often of limited scale. However, early intervention will achieve higher cures rates than extensive resections performed at late stages when the disease burden is high.

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