

8. Scheuer L, Kauff N, Robson, M, et al. Outcome of preventive surgery and screening for breast and ovarian cancer in *BRCA* mutation carriers. *J Clin Oncol* 20(5):1260-1268, 2002.
9. Meijers-Heijboer EJ, Verhoog LC, Brekelmans CTM, et al. Presymptomatic DNA testing and prophylactic surgery in families with a *BRCA1* or *BRCA2* mutation. *Lancet* 355:2015-2020, 2000.
10. Evans DGR, Lalloo F, Shenton A, et al. Uptake of screening and prevention in women at very high risk of breast cancer. *Lancet* 358:889-890, 2001.

Prophylactic colectomy in colorectal cancer. Patrick M. Lynch. *UT M. D. Anderson Cancer Center, Houston, TX.*

Colorectal cancer has consistently been among the top 3 malignancies in terms of incidence and mortality. Because of the well-characterized colorectal adenoma to carcinoma progression, population screening measures have been directed toward early detection and removal of adenomas, thereby potentially preventing invasive cancer. Despite the promise of screening, endoscopic polypectomy, and even chemopreventive strategies, there are several high-risk groups for whom none of these measures has been or is likely soon to be effective. Given sufficiently high risk of cancer and the limitations in early detection/prevention strategies otherwise, prophylactic colectomy has come to be considered the treatment of choice for Familial Adenomatous Polyposis (FAP), chronic ulcerative colitis (CUC), and, to a much lesser extent, Hereditary Nonpolyposis Colorectal Cancer (HNPCC). In FAP, prophylactic colectomy is offered at or within several years of diagnosis of multiple adenomas. Ideally, a patient's APC gene mutation carrier status will have been determined between about age 8 and 15, with surveillance by means of flexible sigmoidoscopy or colonoscopy for earliest signs of polyps. Surgical timing is determined by adenoma burden and social considerations. Extent of resection is controversial. Abdominal colectomy and ileorectal anastomosis (IRA) is favored for those with minimal rectal polyp burden. Such subjects then require follow-up sigmoidoscopy for recurrent rectal adenomas, and medical adjuncts such as NSAIDs may be beneficial. Proctocolectomy and ileal pouch-anal anastomosis (IPAA) is carried out when rectal adenoma burden is great and/or when adherence to follow-up surveillance for recurrent rectal neoplasia is anticipated to be poor. In subjects with attenuated FAP (AFAP), colectomy may be delayed and there may be role for chemopreventive agents such as sulindac or celecoxib. Ulcerative colitis management carries certain similarities and differences, relative to FAP. Diagnosis occurs in reaction to symptoms. When inflammatory bowel disease has been present for 7-8 years or more, subjects are considered at risk of dysplasia and cancer, which occur as consequences of the longstanding colitis. Prophylactic colectomy may be performed on the basis of refractory symptoms or, for our purposes here, when evidence of dysplasia occurs. Demonstration of dysplasia may be a challenge, due to the patchy nature of dysplastic foci, the large and essentially featureless surface to be sampled, and difficulty in microscopically distinguishing true dysplasia from regenerative changes in the background of inflammation. When prophylactic colectomy is performed, subjects more routinely undergo proctocolectomy with IPAA, due to the universal involvement of the rectum with the underlying colitis. Considerable controversy surrounds the issue of prophylactic colectomy in HNPCC. Onset of disease may be late. Indeed, with cancer penetrance of "only" about 80% in Mismatch Repair Gene (MMR) gene mutation carriers, many observers favor a conservative strategy involving early (by age 20-25) and frequent (1-2 years) colonoscopy. Purely prophylactic colectomy is rare and limited to subjects with extreme cancerphobia or inability/unwillingness to undergo surveillance. More "mainstream" is the controversy surrounding extent of resection following diagnosis of colorectal cancer or endoscopically unmanageable adenoma. While experts have long recommended colectomy with IRA at initial diagnosis, many obstacles exist. The diagnosis of HNPCC is often not entertained. When a patient with a positive family history of colorectal cancer develops early onset or right-sided colon cancer, with or without characteristic histology (poor differentiation, extracellular mucin, tumor-infiltrating lymphocytes), an opportunity for clinical diagnosis of HNPCC should not be missed. Given such an index of suspicion, preoperative microsatellite instability (MSI) assays and immunohistochemistry (IHC) for loss of MMR gene-associated protein can easily be carried out on endoscopic biopsies of tumors. Informative MSI or IHC in the right clinical setting essentially confirms a diagnosis of HNPCC, even without germ-line mutation testing. Some feel that even with a definite diagnosis of HNPCC, a conservative surgical approach is warranted, due to the absence of hard data on risk of subsequent cancer. Protocols have been proposed in which subjects are randomized to colectomy versus segmental resection followed by aggressive colonoscopy surveillance. The key features of these diseases, their surveillance and management, will be discussed with an emphasis on the role of prophylactic colectomy.

Risk-reducing surgery in the management of women at increased genetic risk of ovarian, fallopian tube, and endometrial cancer. Mark H. Greene. *Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD.*

The mapping and cloning of a series of human cancer susceptibility genes (e.g., *BRCA1*, *BRCA2*, *PTEN*, *MLH1*, *MSH2* and *MSH6*) have resulted in the ability to identify specific women at increased genetic risk of ovarian, fallopian tube and endometrial cancer. This can be accomplished through genetic risk assessment, counseling and selective testing for germline mutations in these genes among women who are members of cancer-prone families. As a result, patients and their health care providers are faced with a new set of challenging questions regarding how to utilize this information. The goal, of course, is to permit effective health care decision-making, with the intent of improving the quality of life and survival for women who carry mutations in these cancer susceptibility genes. This presentation will review the evidence regarding the risks and benefits of the following surgical management strategies: Ovarian cancer: tubal ligation; risk-reducing oophorectomy; Fallopian tube cancer: risk-reducing salpingectomy; and Endometrial cancer: risk-reducing hysterectomy. In addition, a new, nationwide study (GOG 0199), which has just opened, will be described. It is designed to clarify the some of the important clinical questions related to the surgical management of hereditary ovarian cancer. A series of observations over the past several years has provided a substantial body of evidence to suggest that the fallopian tube is one of the target organs for *BRCA1/2*-related carcinogenesis. For example, data from the Breast Cancer Linkage Consortium document 7 cases of fallopian tube carcinoma (FTC) in their cohort of families: relative risk = 50 (95% CI: 22-111) [D] Thompson et al: *Am J Hum Genet* 2001; 69:387]. Thus, it is clear that the risk-reducing surgical procedure applied to women who carry germline mutations in *BRCA1/2* must include the complete excision of the fallopian tubes in addition to the ovaries. It has been repeatedly observed, but less widely appreciated, that tubal ligation (with retention of the ovaries) is associated with ~50% reduction in the risk of *sporadic* ovarian cancer. More recently, a retrospective analysis of data from 464 *BRCA1/2* mutation carriers suggested a 60% reduction in the risk of ovarian cancer following tubal ligation in women with *BRCA1* mutations, but no protective effect among women with *BRCA2* mutations. [SA Narod et al: *Lancet* 2001; 357:1467-1470] Similar studies have suggested that risk-reducing salpingo-oophorectomy (RRSO) is associated with a dramatic reduction in the subsequent risk of ovarian cancer. Evaluation of the risks and benefits of this procedure is complicated by the entity known as primary peritoneal carcinomatosis, which has been reported among women undergoing RRSO and which for all the world looks and behaves like ovarian cancer. This entity is hypothesized as being derived from the cells of the peritoneum, which share with the ovarian surface epithelium a Mullerian embryologic origin. The first prospective analysis of the protective effect of RRSO among women at increased genetic risk of ovarian cancer has recently been published. It documents a 75% reduction in the risk of ovarian + fallopian tube + primary peritoneal cancer among mutation carriers who underwent RRSO compared with women followed with surveillance. [ND Kauf et al: *N Engl J Med* 2002; 346:1609-1615] Endometrial cancer is the most frequent extra-colonic malignancy which occurs in families with hereditary non-polyposis colorectal cancer. The cumulative lifetime risk of endometrial cancer among women who carry germline mutations in the mismatch repair genes is approximately 43%. [M Aarnio et al: *Int J Cancer* 1995; 64:430-433] It has recently been suggested that the risk of endometrial cancer is particularly high among families in which germline mutations in *MSH6* are the basis for the HNPCC susceptibility. [J Wijnen et al: *Nature Genetics* 1999; 23:142-144] Although risk-reducing hysterectomy is often considered for women from HNPCC families, particularly at the time they are undergoing surgery for newly-diagnosed colorectal cancer, this is an issue which has not been studied, and for which evidence of benefit is lacking. The available data do suggest that endometrial cancer is a relatively uncommon cause of death within HNPCC families. Endometrial cancer has recently been added to the list of syndrome-defining malignancies in Cowden syndrome, a hamartomatous disorder with documented excess risk of both breast and thyroid carcinoma. [C Eng. *J Med Genet* 2000; 37:828-830] The absolute risk of endometrial cancer in this disorder, which has as its genetic basis germline mutations in the *PTEN* gene, has not been defined. There is no information in the literature regarding risk-reducing hysterectomy in this syndrome. Finally, it is worth noting that a nationwide, prospective study of the natural history of the post-risk-reducing salpingo-oophorectomy state has recently been opened to patient accrual through a tri-partite collaboration between NCI's Clinical Genetics Branch, the Gynecologic Oncology Group and the Cancer Genetics Network. Designated GOG 0199, this non-randomized study is enrolling women with a $\geq 20\%$ probability of being a *BRCA* mutation carrier. Women who elect to retain their ovaries are followed with a novel ovarian cancer screening algorithm ("ROCA," Risk of Ovarian Cancer) developed by Dr. Steven Skates, in which longitudinal changes in CA-125 are used to estimate the likelihood that a participant has ovarian cancer. [S Skates et al: *J Am Stat Assoc* 2001; 96:429-439] Women who elect RRSO will undergo careful collection, examination and analysis of their surgical specimen, and prospective assessment of the development of

ovarian, peritoneal and breast carcinoma. Both groups of women will provide detailed quality of life information at baseline and every 6 months during follow-up, which is planned for 5 years. The accrual goal is 1000 subjects in the surgical "arm" of the study; and 2400 subjects in the screening "arm."

Prophylactic surgery and the multiple endocrine neoplasia syndromes.
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The Multiple Endocrine Neoplasia (MEN) Syndromes are inherited as autosomal dominant traits and characterized by the manifestation of multicentric tumors in several endocrine organs. MEN 1 is characterized by the development of hyperparathyroidism, pituitary tumors and pancreatic tumors. Less commonly, adenomas of the thyroid and adrenal cortex occur. The *menin* gene on chromosome 11 is mutated in patients with MEN 1, however, for a combination of reasons, there is no rationale for operative intervention prior to clinical evidence of neoplasia in one or more of the effected endocrine glands. The MEN 2a and MEN 2b are characterized by the presence of the calcitonin (CT) secreting medullary thyroid carcinoma (MTC) and pheochromocytomas. Virtually all patients with the MEN type 2 syndromes develop MTC, the most common cause of death in patients with these syndromes. Patients with MEN 2a also develop hyperparathyroidism, whereas patients with MEN 2b have a generalized neural hypertrophy and a characteristic physical appearance. Patients with Familial MTC (FMTC) only develop MTC and the disease is more indolent compared to patients with MEN 2a or MEN 2b.

The *ret* gene on chromosome 10 is mutated in patients with the type 2 MEN syndromes. Since the *ret* mutations can be detected by direct DNA analysis it is possible theoretically to identify patients who have inherited a mutation and perform a prophylactic thyroidectomy before they develop MTC. Since 1993 we have performed total thyroidectomies on 60 patients with MEN 2a. All patients were diagnosed by direct DNA analysis and all have been followed for five years since thyroidectomy. The patients had a mean age of 16.1 years and a median age of 13 years. Either C-Cell hyperplasia or MTC was evident in the resected thyroid glands of all but 2 patients. Metastases to regional lymph nodes were found in 7 of the 60 patients and the postoperative plasma CT levels were elevated in 2 of the seven. The postoperative CT level was elevated in none of the patients with negative regional lymph node metastases. None of the patients whose postoperative CT level was elevated has developed clinical evidence of metastatic disease. Prophylactic thyroidectomy is indicated in patients with either MEN 2a, MEN 2b or FMTC, who have *ret* mutations detected by direct DNA analysis.

**FORUM 4: ENHANCING RECRUITMENT, RETENTION,
AND ADHERENCE IN PREVENTION TRIALS: TRICKS OF
THE TRADE**

Recruitment of minorities and the medically underserved to cancer prevention trials. The selenium and vitamin E cancer prevention trial, SELECT, as a prototype. Elise Donaville Cook. *University of Texas M. D. Anderson Cancer Center, Houston, TX.*

Attempts to ensure proportionate representation of minority and medically underserved participants in SELECT has been evident from study design to site selection and continues throughout conduct of this trial. Even though African American men have the highest risk of developing and dying from prostate cancer, representation of this population of men in chemoprevention trials is typically less than 4 percent. At 10 percent, SELECT is recruiting African American men at two and one-half times the rate for any other chemoprevention trial. Design elements in place to assure increased African American participation are as follows: SELECT eligibility criteria includes a lower age requirement for African American participants. Institutions with access to large populations of minority and medically underserved eligible men were included as SELECT sites. A Minority and Medically Underserved Committee was formed to design, develop, and execute the minority recruitment plan. A fulltime, national minority recruitment coordinator was hired to head this effort that included some new initiatives. Partnerships were developed with the National Black Leadership Initiative on Cancer II, NBLIC II, The Study of Tamoxifen and Raloxifene, STAR, and an African American fraternity to extend the promotion of SELECT to the African American community. Several minority recruitment enhancement grants have been awarded to boost minority recruitment programs at the site level. A minority recruitment workshop was held to bring together members from current top minority recruiting sites to identify and share recruitment strategies. Thus far, this multi-pronged approach has allowed SELECT to exceed the recruitment of minority participants seen in prior chemoprevention trials. The newer initiatives were designed to meet the 20 percent African American accrual projection for