Many patients are referred to our program due to concerns about hereditary cancer risks, often based on a clustering of cancers in their family. However, only ~10% of all cancers are due to a hereditary cause. Clusters of cancers in families are likely due to a combination of different factors including shared lifestyle and environmental factors, in addition to genetic factors. It has been estimated that ~50% of all cancers are preventable through lifestyle modifications and that many of these same choices reduce the risk of other diseases including stroke, heart disease, and diabetes. (1,2) It is not clear if or how these lifestyle modifications will affect risk in individuals with a hereditary predisposition to cancer but several studies suggest that some may also reduce risks in high risk individuals. (3,4)

However, data have shown that awareness of modifiable risk factors for cancer is low both among the general public and cancer survivors, particularly body weight, exercise, and alcohol consumption. (5) In addition, cancer patients are often hesitant to recognize their lifestyle choices as possible causes for their cancer. (5) One study showed that health care providers may be unintentionally contributing to this lack of knowledge of modifiable risk factors. (5) Cancer specialists interviewed for this study often spoke to their patients about smoking but rarely spoke about other risk factors, particularly exercise or body weight. (5) Some studies suggest that a cancer diagnosis may represent a “teachable moment” for both cancer survivors and their family and friends as these individuals have been shown to be more interested in and more likely to make positive lifestyle changes. (6,7) In the example of smoking cessation, many individuals indicate that a physician’s advice is an important motivating factor in making changes and yet only half of smokers report that they were asked about their smoking or urged to quit by their primary physician. (8) Therefore, physicians could play a vital role in educating their patients about the modifiable risk factors for cancer and motivating them to make lifestyle changes that will likely propagate through family and social networks having an impact on many individuals.

Here we propose some patient-friendly information that may be useful in speaking to patients about modifiable lifestyle risk factors for cancer:

**TOBACCO**

Many people are aware of the link between cigarette smoking and lung cancer. But did you know that tobacco use increases the risk of a wide variety of cancers and chronic diseases? Tobacco use increases the risk of leukemia and oral, laryngeal, esophageal, pancreatic, liver, stomach, colon, cervical, kidney, and bladder cancers. (1,2) It is estimated that tobacco use causes ~90% of all lung cancers, ~30% of all cancers, and ~30% of all cancer-related deaths in developed countries. (1,2) Smoking is also associated with a higher risk of heart disease, stroke, lung disease, osteoporosis, and pregnancy complications. (2) The dangers of tobacco use are true not only for cigarette smoke but also for cigar, pipe, chewing tobacco and second-hand smoke. (1,2) Quitting smoking will improve health no matter how long an individual has smoked or how old they are and many of the smoking-associated risks decrease rapidly after quitting. There are many smoking cessation...
By the time you read this newsletter I trust that the mountains of snow will be melted, buds will be pushing up from the soil, and spring will finally be here.

We see many patients who are concerned about their cancer risks due to their family history of the disease. Ironically, many of these patients who are worried about cancer are also smokers, obese, or make lifestyle choices that are of greater concern than their hereditary risks. In this issue we will discuss a counseling guide for advising your average patient what he/she can do to reduce the chance of developing cancer. Don’t be afraid to be proactive and direct – as you will read, patients take such advice from their healthcare providers seriously.

Melanoma is often attributed to too much sun exposure. And while sun exposure certainly contributes to melanoma risk, we now know that several genetic mutations increase the risk of this often-deadly cancer. Multiple primary melanomas in one individual, multiple family members with melanoma, melanoma at young ages and the combination of melanoma and other cancers in one family are all risk factors for hereditary melanoma and warrant a referral for genetic counseling and testing. Read more about hereditary melanoma in this issue.

We’ve also provided a summary of some key journal articles from the last six months. It is exciting to see so many research studies in the field of Cancer Genetics across all of our subspecialties. We look forward to the spring, and discussing all of these issues with you in the coming months.

Sincerely,

Ellen T. Matloff, MS
Director, Cancer Genetic Counseling

EXCESS BODY WEIGHT
You probably know that obesity is associated with an increased risk of stroke and heart disease, but did you know that it is also an important risk factor for cancer risk? Obesity and excess weight are associated with an increased risk of colon, endometrial, postmenopausal breast, kidney, and esophageal cancers. (1,2) Obesity may also play a role in other cancers including prostate, liver, gallbladder, stomach, pancreas, thyroid, multiple myeloma, and non-Hodgkin’s lymphoma. (1,2) It is estimated that obesity may account for ~14% of cancer deaths in men and ~20% in women. (2) Body Mass Index (BMI) is one way to determine if your body weight is higher than recommended. A BMI > 30 is considered obese and a BMI between 25 and 29.9 is considered overweight.

PHYSICAL ACTIVITY
Being physically active is well-known to be a healthy lifestyle choice, decreasing the risks of heart disease, diabetes, high blood pressure, osteoporosis and even depression and anxiety. There is now building evidence that decreased physical activity also increases the risk of a number of cancers and that this effect is independent of body weight. (1,2) The most compelling evidence exists for colon and breast cancer. (1,2,9) However, there is also evidence that suggests a link between physical inactivity and endometrial, lung, and prostate cancers. (1,2,9) It is estimated that physical inactivity may account for ~5% of cancer deaths. (1) Physical activity appears to decrease the risk of colon cancer by ~20-25%, breast cancer by ~25%, endometrial cancer by ~20-30%, lung cancer by ~20-40%, and prostate cancer by ~10-20% when comparing risk between the most active and least active individuals. (9,10) Although data is limited, there is some evidence that physical activity may also be associated with a lower risk of recurrence, an increase in survival, and better quality of life for cancer survivors. (11) It is estimated that 30-60 minutes of daily moderate to vigorous intensity physical activity may be required for risk reduction although there is still uncertainty about the ideal timing, duration, intensity, and frequency of activity. (9) The benefit of physical activity for cancer risk reduction may be more pronounced in certain subsets of individuals and/or cancers. For example, physical activity appears to decrease the risk of colon but not rectal cancer and in terms of breast cancer risk the effect appears to be stronger in postmenopausal women. (10)

DIET
A variety of specific dietary factors, vitamins, and supplements have been stud-
ied with regard to their possible association with either increased or decreased cancer risk. However, most have not been consistently shown to affect risk. (1,2)

SUN AND TANNING BED EXPOSURE
Radiation from sun exposure is the primary cause of melanoma and non-melanoma (basal cell carcinoma and squamous cell carcinoma) skin cancers. (1,2) Total lifetime sun exposure increases the risk of both melanoma and non-melanoma skin cancers and melanoma risk, in particular, may be associated even more significantly with repeated blistering sunburns. (1) In addition, UV exposure from tanning beds significantly increases the risk of melanoma with a 75% increase risk in individuals who started using tanning beds before age 35. (1) Therefore, all individuals should avoid tanning bed use, limit their sun exposure, wear hats, sunglasses, and protective clothing, and use a broad-spectrum, water-resistant sunscreen (which protects against UVA and UVB rays) with a Sun Protection Factor (SPF) of at least 30 on a daily basis, year-round.

ALCOHOL USE
Excess alcohol use has been shown to increase the risk of multiple cancers including oral, esophageal, laryngeal, liver, breast, and colorectal. (1) Some data suggests that even moderate alcohol use may increase cancer risk offsetting the potential benefits in terms of decreased heart disease risk. (1) Therefore, individuals who do not drink should not start and those who do drink should limit their intake to <1 drink/day on average for women and <2 drinks/day on average for men. (2)

LIMITING INFECTION BY CANCER-ASSOCIATED VIRUSES
An estimated ~17% of all cancers are due to infections. (2) Many associations between specific infections and specific cancers have been established including human papillomavirus (HPV) with cervical, other anogenital, and head and neck cancers; hepatitis B and C (HBV and HCV) with liver cancer (hepatocellular carcinoma); and human immunodeficiency virus (HIV) with Kaposi sarcoma and non-Hodgkin lymphoma. (2) Most of these infections are spread through blood or bodily fluids and are thus often spread through sexual contact (including oral sex). (1) Therefore, methods of prevention include always following safer sex practices (i.e. using latex condoms for vaginal, oral, and anal intercourse and limiting the number of sexual partners), needle exchange programs, and regulation of tattooing. (1) In addition, vaccinations for HPV and hepatitis are available and a quadrivalent HPV vaccine is recommended for girls and women aged 9 to 26. (1)

References:
1. HEREDITARY CANCER SYNDROMES WITH MELANOMA AS A MAJOR FEATURE

a. Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM) - Mutations in the CDKN2A and CDK4 genes are responsible for some individuals with FAMMM. By age 80, CDKN2A mutation carriers living in the United States have ~76% risk to develop melanoma. (2) Variation in the risk for melanoma has been observed between populations; however, it is not clear whether the variation results from the type of mutation, modifying alleles, environmental exposures, or other not-yet identified genetic variables. Carriers also have an increased risk of developing pancreatic cancer and astrocytomas. The likelihood of detecting a CDKN2A or CDK4 mutation increases with the number of melanomas in the family and the finding of multiple primary melanomas in one individual.

b. Unknown Syndromes/Genes - In approximately 60% of families with a suspected hereditary predisposition to melanoma, current genetic testing is unable to identify the responsible underlying genetic alteration. (1) Therefore the search for other melanoma genes is active and will likely expand clinical testing options within the next decade, particularly with the implementation of whole genome sequencing.

2. HEREDITARY CANCER SYNDROMES WITH MELANOMA AS A MINOR FEATURE

a. Hereditary Breast and Ovarian Cancer Syndrome - An increased risk of melanoma has been identified in individuals with hereditary breast and ovarian cancer syndrome (HBOC). HBOC is associated with mutations in the BRCA1 and BRCA2 genes. The Breast Cancer Linkage Consortium reported an excess of melanoma among 173 BRCA2 families. (3) The risk of melanoma was significant for mutation carriers younger than 65 years, but not for those 65 years or older. (3) BRCA2 mutations also appear to account for up to 4.8% of ocular melanoma cases. (4) Other groups have found that the frequency of melanoma was similar in BRCA1 and BRCA2 carriers. (5) Although the data on melanoma are still insufficient, discussion of melanoma screening may be part of genetic counseling for men and women found to be BRCA2 mutation carriers.

b. Li-Fraumeni Syndrome - People with classic Li-Fraumeni syndrome (LFS) have up to a 50% chance of developing cancer by age 40 and a 90% chance of developing cancer by age 60. The most commonly seen cancers in LFS are osteosarcoma, soft tissue sarcoma, leukemia, breast cancer, brain cancer, and adrenal cortical carcinomas. Melanoma has been found to occur in excess in LFS families, but the risk of developing melanoma is not known. (6)

c. Retinoblastoma - In general, 30-40% of retinoblastomas, a childhood eye tumor, are hereditary. Children with hereditary retinoblastoma have an increased risk of developing osteosarcomas, soft tissue sarcomas, or melanomas in adolescence or adulthood. The incidence of these second primary tumors is ~50% in individuals who have received external beam radiation therapy. (7)

d. Cowden Syndrome (CS) - A rare genetic condition characterized by cancerous and noncancerous tumors of the breast, thyroid, endometrium, and colon as well as unusual skin findings and macrocephaly. Several case reports have documented melanoma in patients with CS. (8-11) However, it is not known whether having CS increases a person’s risk of developing melanoma and there are no published data to clearly establish the risk for melanoma in patients with CS.

3. GENETIC CONDITIONS ASSOCIATED WITH AN INCREASED RISK FOR MELANOMA.

a. Xeroderma pigmentosum (XP) - Individuals with XP cannot repair DNA damage caused by ultraviolet exposure. Individuals with XP have a greater than 1000-fold increased risk of melanoma, basal cell carcinoma, and squamous cell carcinomas. (12-13) Multiple primary cutaneous neoplasms are common.

b. Werner Syndrome - Classic features include premature aging (including gray hair and hair loss, cataracts, and osteoporosis in the teenage years) and an increased risk of cancer. Individuals with Werner syndrome have approximately a 10% risk to develop melanomas, osteosarcomas, soft-tissue sarcomas, and thyroid cancers. (14)

c. Albinism - A genetic condition marked by little or no melanin in the skin, hair, and/or eyes that results in vision problems, nystagmus, white hair, pink or blue eyes, and pale skin. Long-term sun exposure greatly increases the risk of melanoma; however, melanoma is rare in people with albinism who reside in the US. (15) This may be due to sun avoidance, the availability of sunscreens or the social acceptability of wearing clothes that cover most of the exposed skin.

GENETIC COUNSELING

At this time, we recommend that anyone with features of the above syndromes consider genetic counseling. In addition, individuals who meet the following criteria should also be referred for genetic counseling:

1. An individual with melanoma and 2+ family members with melanoma or pancreatic cancer.
2. An individual with two or more primary melanomas.
3. An individual with melanoma who is of Jewish Ancestry.
4. An individual with melanoma who has a significant personal or family history of breast, ovarian, or pancreatic cancer.
PREVALENCE OF BRCA1 AND BRCA2 GERM LINE MUTATIONS AMONG WOMEN WITH CARCINOMA OF THE FALLOPIAN TUBE

Gynecologic Oncology 2010 118;299-302.

This study performed genetic testing on a large series of women diagnosed with cancer of the fallopian tube from the Ontario Cancer Registry and Cedars Sinai Medical Center in Los Angeles, CA. Out of 108 women with fallopian tube cancer, 33 (30.6%) were found to carry a BRCA1 or BRCA2 mutation. Higher rates of mutations were found among women with a family history of breast or ovarian cancer than those without a family history (58.3% vs. 22.8%). Women of Ashkenazi Jewish ancestry were more likely to carry a mutation than women of Non-Jewish ancestry (55.6% vs. 26.4%) and women diagnosed under age 60 were more likely to carry a mutation than those diagnosed over age 60 (40.3% vs. 17.4%). The highest rate of mutations (71.4%) was found among women who had a personal history of a previous diagnosis of breast cancer. Based on this data, all women with a diagnosis of invasive fallopian tube cancer should be offered genetic counseling and testing.

ASSOCIATION OF RISK-REDUCING SURGERY IN BRCA1 OR BRCA2 MUTATION CARRIERS WITH CANCER RISK AND MORTALITY

JAMA 2010 304(9):967-975.

This international, prospective, cohort study followed 2482 women with BRCA mutations for an average of 3-4 years to determine the cancer risk reduction and mortality reduction associated with prophylactic surgeries stratified by previous breast cancer diagnosis and specific mutation. During the ~3 years of follow-up, none of the 247 women who chose to have bilateral prophylactic mastectomy developed breast cancer compared to ~7% (98/1372) of the women who did not have mastectomy. Prophylactic bilateral salpingo-oophorectomy (PBSO) significantly reduced the risk of developing an ovarian-type cancer in BRCA1 or BRCA2 mutation carriers with or without a prior diagnosis of breast cancer. Among women who underwent PBSO, only 1.1% developed ovarian-type cancers. PBSO also significantly reduced the risk of a first breast cancer in both BRCA1 and BRCA2 mutation carriers (by 37% and 64%, respectively). All-cause, breast-cancer specific, and ovarian-cancer specific mortality (HR of 0.40, 0.44, and 0.21, respectively) were all significantly lower in women who underwent PBSO.

WHAT I WISH I’D KNOWN BEFORE SURGERY: BRCA CARRIERS’ PERSPECTIVES AFTER BILATERAL SALPINGO-OOPHORECTOMY


In this publication, the Yale Cancer Center Genetic Counseling Program reports the results of a retrospective study of 98 BRCA carriers who underwent prophylactic bilateral salpingo-oophorectomy (PBSO) with respect to their post-operative symptoms, their recollection of pre-operative conversations with their health care providers, and their informational needs. The 5 most common postsurgical symptoms were: vaginal dryness (52.1%), changes in interest in sex (50.0%), sleep disturbances (46.7%), changes in sex life (43.9%), and hot flashes (42.9%). The majority of women reported that the potential for hot flashes, night sweats, and vaginal dryness as well as the impact of surgery on their ovarian and breast cancer risks, menopausal status, osteoporosis, childbearing ability, and their surgical options were all discussed by their healthcare providers prior to surgery. However, 60% of the most commonly reported symptoms (changes in libido, changes in sex life, and sleep disturbances) were not discussed pre-operatively and ~60-80% of participants report that the availability of sex counseling and the impact of surgery on body image, sex life, and coronary artery disease were never discussed by their healthcare provider. Most women would have liked to have more information about the availability of sex counseling and the impact of surgery on their sex life and their coronary heart disease risk. They suggested that health care providers talking to women about PBSO provide them with as much information as possible, especially about the menopausal, emotional, and sexual changes. However, the majority of participants would pursue this surgery again (96.9%) and would recommend PBSO to another BRCA carrier (97.9%).
We see many patients who are concerned about their cancer risks due to their family history of the disease. Ironically, many of these patients who are worried about cancer are also smokers, obese, or make lifestyle choices that are of greater concern than their hereditary risks.