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Cancer Risk Assessment for the Primary Care Physician

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Summary

Cancer is the second leading cause of death in the United States. Cancer risk assessment can be divided into two major categories: assessment of familial or genetic risk and assessment of environmental factors that may be causally related to cancer. Identification of individuals with a suspected heritable cancer syndrome can lead to additional evaluation and to interventions that can substantially decrease cancer risk. Special attention should also be paid to potentially modifiable cancer risk factors in the course of advising primary care patients regarding a healthy lifestyle. Clinical guidelines targeting both genetic and modifiable cancer risk factors are available, and can facilitate applying these health care principles in the primary care setting.

Keywords

cancer risk; risk assessment; genetics; family history; environmental risk factors; lifestyle

The American Cancer Society estimates that there will be 1.44 million new cases of cancer diagnosed in the United States in 2008. Breast and prostate cancer are the most common malignancies diagnosed among women and men in the US, respectively, accounting for 25% of cancer diagnoses, followed by lung and colon cancer. Cancer is the second leading cause of death in the US population overall, and the leading cause of death among men and women age 60 – 79 (1). Cancer mortality rates have declined over the past two decades, in part due to improvements in screening, which leads to detection of malignancy at an earlier and more treatable stage. A thorough assessment of cancer risk in the primary care setting, with targeted application of appropriate screening strategies, is crucial to maintaining this trend.

Cancer risk assessment can be divided into two major categories: assessment of familial or genetic risk and assessment of environmental factors that may be causally related to cancer. Evaluation of familial risk should include both maternal and paternal lineages, with specific attention to cancers that co-exist in known hereditary cancer syndromes. Evaluation of environmental factors should focus on assessment of known modifiable factors, such as smoking, obesity, diet and physical activity.

Family History Assessment

Family history is a known risk factor for a multitude of chronic diseases, including cardiovascular disease, diabetes and cancer; thus, obtaining a family history of medical illness

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is a recognized and important component of primary care assessment. From the standpoint of cancer risk assessment, a thorough family history should include all of the following components:

- Ethnic background of each grandparent
- Information about both maternal and paternal relatives
- Information on at least first- (parents, siblings, children), and second-degree (aunts, uncles, nieces, nephews, grandparents) relatives
- Type of cancer, age at diagnosis and age at death for each family member with cancer, current age of family members living with cancer
- Environmental exposures (including smoking, radiation, occupational exposures, etc).

Family history information should be briefly updated at each visit. The literature suggests that family history taking in community family practice is sub-optimal. In one study of primary care physicians, family history was discussed during only 51% of new patient visits and 22% of established patient visits (2). Physician factors associated with a greater likelihood of obtaining family history information included fewer years in practice and female gender. Family history was more likely to be discussed at well care visits. Patients 65 years or older were least likely to be asked about family history. A number of substantive barriers to obtaining a thorough family history in the primary care setting have been described, including lack of direct reimbursement (3) and perceived lack of genetic knowledge (4,5).

The US Surgeon General, in conjunction with the Centers for Disease Control and the Department of Health and Human Services, has recently launched a national public health campaign called the US Surgeon General's Family History Initiative. The goal of this effort is to increase awareness among both the general population and health care providers of the importance of knowing and understanding an individual's family history. This initiative has led to the creation of videos aimed at patients that explain the importance of family history in primary medical care, and has also produced a tool for family history taking called "My Family Health Portrait" which is available in both a paper and a web-based format. This tool can be accessed on the internet at http://www.hhs.gov/familyhistory/, and is designed to be completed by patients in conjunction with a primary care medical visit.

Knowledge of family history is important in practice because it can identify individuals with an increased disease susceptibility who may benefit from additional screening and possibly prevention interventions. The American Cancer Society recommends earlier and/or more intensive cancer screening for individuals with a family history of breast, colorectal and prostate cancer (see Table 1). While taking a cancer family history, it is important to pay special attention to cancers that occur as part of specific hereditary cancer syndromes.

Individuals with histories suggesting a hereditary syndrome may be considered for genetic evaluation and counseling by a specialty-trained provider such as a medical geneticist or genetic counselor. These individuals have received specialized training in the unique issues associated with genetic evaluation and testing. They provide education and pre- and post-test counseling, which are extremely important in helping patients understand the complex issues that they face when considering a genetic test for cancer predisposition.

A brief description of specific inherited syndromes associated with some of the more common and preventable cancers, including the involved genes, mode of inheritance, associated cancers, and screening and prevention options is presented below and summarized in Table 2. A more comprehensive listing of known inherited cancer syndromes can be found in the published

clinical catalog of recognizable family cancer syndromes, “Concise Handbook of Familial Cancer Susceptibility Syndromes” (12).

Hereditary Breast and Ovarian Cancer

It is estimated that 5 – 10% of breast cancers occur in women with an inherited susceptibility to cancer (13). The majority of these are women with Hereditary Breast Ovarian Cancer Syndrome (HBOC), which is explained by deleterious mutations in the *BRCA1* and *BRCA/2* genes, although a number of less common genetic disorders, such as Li-Fraumeni Syndrome, Cowden Syndrome and Peutz-Jeghers also include a predisposition to breast cancer (12). These syndromes exhibit autosomal dominant inheritance. Personal and family history features suggestive of HBOC include the following:

- Early onset breast cancer (age <40 or age <50 if Ashkenazi Jewish heritage
- Ovarian cancer occurring in a women with a family history of breast or ovarian cancer
- Breast and ovarian cancer occurring in the same woman
- Bilateral breast cancer
- Male breast cancer
- Ashkenazi Jewish heritage and family history of breast cancer

Women with *BRCA1* mutations have a 50-80% lifetime risk of breast cancer and a 20-40% lifetime risk of ovarian cancer. Women with *BRCA2* mutations have a similar lifetime risk of breast cancer and a 10-20% lifetime risk of ovarian cancer. These women also have a 40-60% lifetime risk of contralateral breast cancer and an increased risk of cancer of the fallopian tube (14). Men in *BRCA2* families have an estimated 15-25% lifetime risk of prostate cancer (15) and an estimated 6% lifetime risk of male breast cancer. In addition, members of *BRCA1/2* families are thought to have an increased risk of pancreatic cancer. The identification of individuals with HBOC has implications for both cancer screening and the application of risk-reducing interventions. Published guidelines recommend that women with known or suspected *BRCA* mutations begin annual mammographic screening at age 25 or ten years prior to the age at diagnosis of the youngest breast cancer case in the family, whichever is sooner (6). In addition, based on data from nonrandomized screening trials and observational studies, the American Cancer Society (ACS) and the National Comprehensive Cancer Network (NCCN) recommend annual screening MRI for women with a strong family history of breast cancer or a known genetic predisposition (6,16). MRI screening should also be considered in certain other high risk populations (see Table 3). Screening for ovarian cancer with yearly CA-125 and transvaginal ultrasound, beginning at age 35, is also generally recommended for *BRCA* mutation carriers, despite there being no proof that this strategy has clinical benefit (17). There are little data on screening recommendations for men with *BRCA* mutations. NCCN guidelines suggest twice yearly clinical breast examination and teaching of breast self-examination. In addition, a baseline mammogram should be considered, and annual mammograms may be reasonable if gynecomastia or glandular density are seen on the baseline exam.

Due to a markedly increased lifetime risk of breast and ovarian cancer, women with HBOC are generally counseled about the option of prophylactic surgery for risk reduction. Bilateral prophylactic mastectomy has been shown in multiple studies to reduce the risk of breast cancer by about 90% (18-20). Prophylactic oophorectomy dramatically reduces the risk of ovarian cancer in this high-risk population, but there remains a residual risk of primary peritoneal cancer (21,22), an intra-abdominal neoplasm that is clinically and histologically indistinguishable from ovarian cancer. Oophorectomy has also been shown to reduce the risk of breast cancer by about 50% (21,22), although the effect varies by age at surgery (23). In

addition, the NCCN recommends that salpingectomy (removal of the fallopian tubes) be performed at the time of surgery, and advocates peritoneal washings and careful pathologic assessment with multiple fine sections of the ovaries and fallopian tubes. Chemopreventive options, such as tamoxifen and raloxifene, which have been shown to decrease the risk of breast cancer by about 50% in women at increased risk of breast cancer based on the Gail Model (see discussion below), have not been well studied in the genetically at-risk population (24-26).

Hereditary Colon Cancer

Approximately 20% of individuals diagnosed with colon cancer have a strong family history (two or more first- or second- degree relatives), and about 3-5% of colon cancers occur in the context of genetically defined high-risk syndromes (27). The two most common of these are Hereditary Non-Polyposis Colorectal Cancer (HNPCC or Lynch Syndrome) and Familial Adenomatous Polyposis (FAP). Both are inherited in an autosomal dominant fashion.

HNPCC-associated cancers result from mutations in one of several genes that participate in DNA mismatch repair, most notably *MLH1* and *MSH2*, which account for approximately 80% of disease, *MSH6*, which is mutated in about 10-15% of cases, and rarely, *PMS2*. The molecular hallmark of colon cancer in individuals with HNPCC is microsatellite instability, which is the result of frequent insertion and deletion mutations in microsatellite repeats caused by defects in DNA mismatch repair (28), and is detectable in tumor tissue. HNPCC-related colon cancer is characterized by an early age at onset (mean age at diagnosis is 45 years compared with 63 years in the general population) and right-sided colonic predominance. Affected individuals have an estimated 80% lifetime risk of colon cancer (29). In addition, there is a substantial risk of both synchronous and metachronous colon cancer, and excess risks in affected family members of endometrial, ovarian, gastric, small intestine, brain and sebaceous skin cancers (30).

As with HBOC, the identification of individuals with HNPCC has important screening implications. NCCN guidelines recommend that these individuals begin annual or biennial screening colonoscopy at age 20-25 years, or 10 years prior to the age at diagnosis of youngest family member (whichever comes first). Total abdominal colectomy should be considered if high grade dysplasia is identified, or if adenomas that are not amenable to endoscopic resection are found. In addition, due to increased risks of ovarian and endometrial cancers and cancers of the urinary collecting system, consideration should be given to urinalysis with urine cytology, and to transvaginal ultrasound and CA-125 screening in women. Prophylactic hysterectomy and salpingo-oophorectomy may also be considered(31).

FAP is caused by mutations in the *APC* gene. This autosomal dominant syndrome is characterized by the presence of hundreds to thousands of adenomatous polyps beginning in the preteen years, which almost invariably undergo malignant degeneration by the age of 40 to 50 years. Since the lifetime penetrance of FAP related colon cancer approaches 100%, prophylactic subtotal colectomy followed by annual rectal endoscopy is recommended for affected individuals, but can be delayed until the polyp burden becomes too high to be safely managed colonoscopically (30).

Familial Prostate Cancer

Familial clustering of prostate cancer has been well described, but to date no specific high penetrance susceptibility genes have been identified, and thus clinical genetic testing is not currently available. A number of candidate genetic loci have been identified in linkage analyses and, more recently, in genome-wide association studies (32). However, the preponderance of data suggests that the genetic basis of prostate cancer is incredibly complex, and this is an area of active research.

Family history is among the strongest risk factors for prostate cancer; risk increases with earlier age at onset among relatives and with the number of affected family members. Estimated relative risks of prostate cancer ranges from about a two-fold increase in risk with one affected relative to a five-fold increase for individuals with two or more affected first-degree relatives (33). An increased risk of prostate cancer is also associated with other known cancer predisposition syndromes, most notably *BRCA2* (34).

Potential screening modalities for prostate cancer include digital rectal examination (DRE) and prostate-specific antigen (PSA) testing, although the utility of these interventions is not well established. The current data are insufficient to determine whether screening for prostate cancer with DRE and PSA lead to a reduction in prostate cancer mortality (10). The American Cancer Society recommends that physicians should offer DRE and PSA screening to all men with a life expectancy of at least 10 years, beginning at age of 50, and to African American men or those with a family history of prostate cancer beginning at age 45. For men with multiple family members with an early age at onset of prostate cancer, it may be reasonable to perform a baseline PSA at age 40. Depending on the result of this initial test, additional testing may not be needed until age 45.

A number of randomized studies, including the highly publicized Prostate Cancer Prevention Trial, have shown that the use of 5-alpha-reductase inhibitors such as finasteride decreases the incidence of prostate cancer in men undergoing prostate cancer screening (35). Although none of these trials looked specifically at men with a family history of prostate cancer, similar reductions in risk were seen in men with and without a family history.

Familial Melanoma

It is estimated that 5-7% of melanoma patients are from genetically at-risk families. Familial melanoma is generally defined by the presence of three or more affected blood relatives in families located in regions of intense sun exposure, or two or more affected family members in areas with less intense sun exposure. Individuals with an inherited predisposition to melanoma are prone to early-onset disease (mean age at diagnosis is 34 years) and tend to develop multiple primary melanomas (36). Mutations in two melanoma susceptibility genes, *CDKN2A* and *CDK4* are thought to be responsible for a large proportion of familial cases; however in greater than 50% of multiple-case families, no mutations in these genes are found, and the clinical utility of genetic testing for *CDKN2A* mutations is widely debated (6). Families with *CDKN2A* mutations have an average melanoma penetrance of 30% by age 50 and 67% by age 80 (37). Carriers of CDKN2A mutations also have a greatly increased risk of pancreatic cancer, with a cumulative lifetime risk approaching 17% (38), and a possible increased risk of breast cancer (39). The Melanoma Genetics Consortium recommends careful surveillance, including yearly or biannual clinical skin examinations, and patient and family education for individuals in whom familial melanoma is suspected (11).

Cancer Risk Assessment Models

Statistical models for cancer risk prediction fall into two broad categories: those that are used to predict the probability of being diagnosed with a particular cancer, and those that predict the likelihood of carrying a gene mutation that predisposes to a particular cancer or set of cancers. A number of commonly used risk assessment models for common cancers are described below.

Breast Cancer

The Gail model provides estimates of a woman's 5-year and lifetime risk of breast cancer based on age, reproductive risk factors, family history and history of previous breast biopsy (40,

41). This model is simple to use and easily accessible on the internet (http://www.cancer.gov/bcrisktool/.) The Gail model has been used to determine eligibility for breast cancer prevention trials in the United States. While this model performs very well on a population level, the accuracy of the model for predicting individual risk has been questioned (42). In addition, the Gail model may underestimate risk in women with a family history of breast cancer, since it only considers first-degree relatives (mothers, sisters, or daughters), and does not include age at diagnosis of relatives. It also does not consider paternal family history or family history of ovarian cancer, which may be of crucial importance in women with HBOC. The Gail Model is most appropriate for use among women over the age of 35 undergoing routine mammographic screening, and in this population can be very helpful in illustrating to a woman how her risk of breast cancer compares to other women of similar age.

The Claus model is useful for assessing breast cancer risk in women with a family history of breast cancer (43,44). This model presents a series of tables with risk estimates based on family history of breast and ovarian cancer, and takes into account second-degree relatives (aunts), and age at diagnosis of family members. This model also considers both maternal and paternal family history. The Claus model is most useful for assessing breast cancer risk among women with a strong family history. In the setting of a strong family history, there are also several models that are currently used to estimate the risk of having a *BRCA1/2* mutation. These include the BRCAPRO, BOADICEA and IBIS models (45). The latter two models incorporate both family history and other risk factors, and produce both mutation probabilities and breast and ovarian cancer risk estimates.

If the family history is strongly suggestive of an inherited susceptibility to breast cancer, referral to a cancer genetics professional should be considered. Referral in this setting will allow for a complete evaluation regarding likelihood of an inherited cancer susceptibility syndrome, pre-test genetic counseling, and genetic testing if appropriate. Cancer genetics professionals can aid in the development of a thorough cancer risk management plan, including screening, chemoprevention, and consideration of other risk-reducing options.

Colon Cancer

A number of models exist for assessing genetic risk of colon cancer. The Amsterdam Criteria (46,47) were established to guide researchers and clinicians in identifying individuals who were likely to have HNPCC. These criteria are based on individual and family history of colon cancer or other HNPCC-related cancers, and take into account the number and relationship of affected family members and the age at diagnosis of affected individuals. The multiplicity of genes implicated in the etiology of HNPCC leads to complexity in confirming the diagnosis, as it is not practical to perform germline mutation testing on all HNPCC-related genes. The Bethesda Guidelines (48) were developed to guide the testing of tumors for microsatellite instability (MSI), and thereby improve identification of individuals with HNPCC. These Guidelines include age at diagnosis, presence of multiple tumors, and number and age at onset of relatives with HNPCC related tumors. Individuals with an appropriate family history and MSI-high tumors comprise a subgroup of subjects upon which germline mutation testing can be targeted. In addition, tumors can be evaluated for expression of the protein products of genes involved in mismatch repair (MMR) by immunohistochemistry. Absence of protein expression related to one of the MMR genes further aids in deciding which gene to test first.

Recently, simpler, more accessible tools have become available to predict the probability of HNPCC in individuals and families. The PREMM1,2 model, takes into account personal and family history of colon cancer, age at diagnosis, and presence of adenomas, endometrial cancer, or other HNPCC-related cancers in the proband and family members (49). This model calculates the probability of carrying a mutation in *MLH1* or *MSH2*, the two genes most

commonly associated with HNPCC, and is available on the internet at http://www.dana-farber.org/pat/cancer/gastrointestinal/crc-calculator/. The MMRpro model is a slightly more complex web-based tool (available at (http://astor.som.jhmi.edu/BayesMendel/mmrpro.html). In addition to the parameters described above, this latter model incorporates information about microsatellite instability testing and genetic testing (if performed), and estimates both the risk of carrying a deleterious mutation and the probability of developing colorectal or endometrial cancer over a specified period of time (50).

Researchers and statisticians at the NCI have also recently developed a colon cancer risk assessment tool (51). Also available online (http://www.cancer.gov/colorectalcancerrisk/), this tool incorporates screening history, family history, and a number of known lifestyle risk factors for colon cancer (such as diet, physical activity and use of non-steroidal anti-inflammatory drugs). It estimates 5-year, 10-year and lifetime risk of colon cancer for non-Hispanic white men and women aged 50 - 85.

Melanoma

It is estimated that more than 62,000 cases of melanoma will be diagnosed in 2008 (1). Melanomas evolve in a step-wise fashion, and survival is strongly influenced by depth of tumor invasion and lymph node status. Melanoma is an ideal example of a disease for which early detection is feasible and effective: it is increasingly common; can be identified non-invasively by visual inspection; and can be definitively diagnosed and cured in its early stages. Investigators at the National Cancer Institute have developed a melanoma risk prediction model that is easily administered by primary care physicians (52). The model incorporates information on patient age and gender, skin tone, tanning history, current geographical location, and skin examination, and produces an estimated 5-year absolute risk of melanoma. This model can be accessed on the internet at http://www.cancer.gov/melanomarisktool/.

Modifiable Cancer Risk Factors

It is believed that cancer may be a fundamentally preventable disease; as many as 90-95% of all cancers are attributed to potentially modifiable behavioral and environmental risk factors (53). Chief among these factors are tobacco, alcohol consumption and obesity. Thus, by assessing and influencing lifestyle factors during primary care visits, the physician may have a considerable effect on cancer incidence and patient outcomes.

Tobacco

Tobacco smoking accounts for one in five deaths each year (54) and one-third of all cancer deaths (53), and is the leading preventable cause of death in the United States. Smoking is associated with at least 14 different types of cancers including cancers of the lung, esophagus, larynx, oral cavity, pancreas, urinary bladder, kidney, stomach, uterine cervix, nasal cavity and nasal sinuses (55). The risk of these cancers increases with the dose and duration of smoking, but also decreases significantly after quitting (55,56). Despite the known harmful effect of tobacco, more than 20% of American adults continue to use it; most of them smoke cigarettes (57). The same is true for adolescents; 25.7% of high school students reported using some kind of tobacco and 20% reported smoking cigarettes (58). A recent CDC report found that while most smokers (70%) are interested in quitting, and about 40% have attempted to quit, less than 5% succeeded (59). Primary care physicians are well positioned to assist patients' attempts to quit smoking. In a recently published meta-analysis, physicians' quitting advice to smokers, even when brief, significantly increased their probability of success (60).

Despite these compelling data, evidence suggests that physicians are not taking full advantage of this unique opportunity. Data from the National Ambulatory Medical Care survey showed that 32% of medical records contained no information regarding tobacco use, 81% of smokers had not received quitting assistance, and less than 2% had received a pharmacological treatment (61). In a recently-published clinical practice guideline that was designed to help physicians intervene most effectively (62), emphasis was placed on the importance of collecting smoking information from every patient, advising all smokers to quit, and providing different cessation strategies based on patients' willingness to stop smoking. Physicians' effort should also be directed toward former smokers in order to support their efforts at remaining tobacco free, and to follow them more closely, as they are still at higher risk of developing cancers compared with those who never smoked. In addition, targeting adolescents is crucial, both for helping young non-smokers avoid initiating tobacco use, as well as supporting those who attempt to stop. Adolescence appears to be a particularly vulnerable developmental stage related to initiating smoking behavior.

Alcohol

Alcohol intake is causally linked to cancers of the esophagus, oral cavity, pharynx and larynx (63), in which 25-68% of the cases are etiologically-related to alcohol (64). Cancer risk at these sites increases with the amount of alcohol consumed, and shows a multiplicative effect with smoking. For example, in the absence of smoking, heavy drinkers (those who consume 60 or more drinks/week) have double the risk of developing oropharyngeal cancers and are eight times more likely to develop esophageal cancers when compared with light or non-drinkers. Heavy smokers (those who smoked ≥25 cigarettes per day for ≥40 years) and heavy drinkers are 80 times more likely to develop oropharyngeal cancers, 12 times more likely to develop laryngeal cancers and 18 times more likely to develop esophageal cancers when compared with light or non-drinkers who don't smoke (65). In addition, alcohol is a well-established risk factor for cancers of the liver (66), colorectum (67) and breast (68).

The epidemiological evidence suggesting a beneficial effect of alcohol consumption for coronary heart diseases (CHD) (69) does complicate formulating a rational alcohol consumption recommendation. However, the weak protective effect for CHD observed only in current drinkers (5-20%), and the attenuation of risk reduction observed in those living outside the Mediterranean region (69) might reflect a confounded association, in which a third factor (such as diet) that is associated with drinking is the cause of the observed protective effect. Additionally, the increased CHD mortality observed in middle-aged men might reflect a survival bias. Given the risk-benefit profile of alcohol, it is important to assess the patients' history of alcohol use, and its intensity. It is also important to assess factors that modulate cancer risk when combined with alcohol such as smoking for upper digestive and respiratory tract cancers, and hepatitis C or B infection for liver cancer.

Obesity

Obesity is a major heath problem and an established cancer risk factor. It accounts for 14-20% of cancer mortality in the U.S. (70). Body mass index (BMI) is the most commonly used measure of healthy weight, in which both weight and height are taken into account. A BMI of 18.5 to 24.9 kg/m^2 is considered "normal"; 25-29.9 kg/m^2 is considered "overweight," and greater than 30 kg/m^2 is considered "obese." According to the most recent National Health and Nutrition Examination Survey (NHANES 2005-2006), more than 30% of American adults are obese (71). Other weight indices include waist circumference and waist-to-hip ratio, which both reflect body fat distribution (72). There is strong evidence that obesity is associated with increased risk of the following cancers: esophagus, colorectum, liver, gall bladder, pancreas, kidney, non-Hodgkin's lymphoma, multiple myeloma, stomach, prostate, breast, cervix and

ovary (70). Furthermore, some studies have suggested a protective role for intentional weight loss on overall cancer risk and on cancers of the breast, colon and endometrium (73). Several health organizations emphasize the role of the primary care physicians in identifying and treating obesity (74,75). However, physicians may lack the training required to effectively provide adequate nutritional education; many have expressed an interest in learning more in the area of weight management (76,77).

The National Heart, Lung and Blood Institute published a clinical guideline to help physicians identify, evaluate and treat obesity (78). According to this guideline, people with BMI of ≥25 kg/m^2 or a high waist circumference (> 88 cm for females and > 102 cm for males), who have at least two obesity-related risk factors, such as diabetes and cardiovascular disease, are candidates for treatment. The guideline recommends an initial goal of 10% loss of baseline weight, at a target rate of 0.45 to 0.90 kg/week, followed by re-evaluation. The guideline also reviews several alternative therapeutic strategies, including dietary modification, increase in physical activity, behavioral therapy, pharmacotherapy and surgery. It is important to remember that obesity is a chronic disease and requires ongoing monitoring with the goal of maintaining healthy weight throughout life.

Diet and Physical Activity

The role of diet and physical activity in modulating cancer risk beyond their effect on weight control is increasingly being recognized. The findings that certain nutrients may protect against specific cancers (79) and that physical activity may regulate sex hormones and alter immune function lend support to the hypothesis that these factors exert independent effects on cancer risk.

A healthy diet may prevent a considerable number of cancer cases. A diet that includes fresh fruits and vegetables is thought to reduce the risk of most epithelial cancers (80). A detailed evidence-based scientific review regarding dietary component and cancer, by cancer site, was recently published by the World Cancer Research Fund/American Institute for Cancer Research (79). In summary, it concluded that there is sufficient evidence of increased risk of liver cancer in people exposed to a diet contaminated with aflatoxin (a naturally occurring toxic metabolite produced by certain fungi (Aspergillus flavis), and found on food products such as corn and peanuts, peanut butter), and lung cancer for those drinking arsenic contaminated water, to warrant active efforts to reduce/avoid these exposures. Conversely, garlic and dietary fiber are suggested to protect against colorectal cancer; lycopene against prostate cancer; and B-carotene and Vitamin C against esophageal cancer.

There is accumulating evidence that physical activity is associated with decreased risks of breast and colon cancer (81). A protective association between physical activity and other hormone-related cancers, such as prostate and endometrial, is also plausible but the evidence for these associations is less robust (81,82). There is also solid evidence that physical activity affects the risk of other chronic diseases such as diabetes and heart disease. The American Cancer Society expert-based recommendations suggest that engaging in moderate to vigorous physical activity for 30-60 minutes on at least 5 days/week will reduce an individual's cancer risk (83). Similar to the data on smoking cessation, a physician recommendation for increased physical activity has been shown to be an effective tool for motivating behavioral change (84,85). However, physicians tend to target people who have chronic diseases, or who are overweight or obese for physical activity advice (86), rather than providing these recommendations more widely.

Summary and Conclusions

Primary care physicians are uniquely situated to identify individuals at increased genetic or environmental risk of cancer. The early identification of a suspected heritable cancer syndrome can lead to additional evaluation and to interventions that can substantially decrease cancer risk. Web-based tools for collecting and summarizing family history information and for predicting individual risks of certain cancers and familial syndromes are easily accessible, and are available for use by the primary care physician. Individuals with a high likelihood of having an inherited syndrome should be seriously considered for referral to a cancer genetics professional for further work-up and treatment, including genetic testing and risk reduction strategies.

Special attention should also be paid to potentially modifiable cancer risk factors in the course of advising primary care patients regarding a healthy lifestyle. The fact that certain modifiable behaviors are associated with increased risk not only of cancers but also of other chronic disease creates an opportunity for early intervention. Clinical guidelines targeting modifiable cancer risk factors are available, and can facilitate applying these health care principles in the primary care setting.

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Table 1

Screening Recommendations for Individuals with a Family History of Selected Cancers

Cancer	Risk Group	Screening Recommendation
Breast Cancer (6,7)	Average Risk	Annual screening mammography starting at age 40; Clinical breast exam (CBE) q3yrs at age 20-39 then annually starting at age 40; Breast self exam (BSE) starting at age 20
	Greater than 20% lifetime risk according to family history based model	All of the above PLUS Annual screening MRI
	Personal or family history of HBOC or other genetic syndrome known to increase breast cancer risk	Mammography beginning at age 25 OR 10 years prior to youngest age at diagnosis in family (whichever is sooner); Annual screening MRI; Annual CBE and BSE
	History of radiation to the chest wall (i.e., for Hodgkin Lymphoma)	As above but beginning screening at age 40 or 8-10 yrs after radiation treatment (whichever is sooner)
Colon Cancer (8)	Average Risk	Begin screening at age 50 years with colonoscopy (preferred), CT (virtual) colonoscopy, flexible sigmoidoscopy, FOBT, or double contrast barium enema; identified polyps should be removed
	Individuals found to have polyps on screening	<2 polyps, <1cm: repeat colonoscopy every 5 years Advanced or multiple adenomas: repeat exam within 3 years >10 adenomas: consider genetic syndrome
	Personal history of endometrial or ovarian cancer at age <60	Begin colonoscopy at age 40; repeat at least every 5 years (sooner if abnormal findings)
	Inflammatory bowel disease	Begin colonoscopy 8-10 years after onset of symptoms; repeat every 1-2 years
	One or more first-degree relative with colon cancer; two or more second-degree relatives with colon cancer	Consider genetics evaluation; begin screening at age 40; screen every 1-5 yrs depending on magnitude of family history
	Known HNPCC	Begin screening at age 20-25 or 10 years prior to youngest diagnosis in family; screen every 1-2 yrs; consider colectomy if not amenable to endoscopic polypectomies; consider prophylactic hysterectomy and/or oophorectomy
	Known FAP	Proctocolectomy or colectomy; annual sigmoidoscopy if retained rectum
Prostate Cancer (9,10)	Average risk	Annual prostate-specific antigen (PSA) testing and digital rectal exam (DRE) should be offered to men with at least a 10-year life expectancy, beginning at age 50
	African-American men or men with one or more first degree relatives diagnosed at age<65	Offer annual screening beginning at age 45
	Men with multiple first degree relatives affected at an early age	Could offer screening beginning at age 40; if first test is normal may not need to screen annually until age 45
Melanoma (11)	Average risk	Currently no evidence to suggest benefit for routine screening
	Family or personal history of melanoma	Head-to-toe skin examination every 6-12 months starting at age 10; Consider clinical photographs or epiluminescence microscopy; Encourage monthly skin self-examination; Excise of any suspicious or changing pigmented lesions; Education regarding sunburn avoidance and characteristics of suspicious lesions

Table 2

Selected Familial Cancer Syndromes, Responsible Genes and Clinical Manifestations (12)

Syndrome	Gene	Clinical Manifestations
Hereditary Breast Ovary Syndrome	*BRCA1, BRCA2*	Early-onset female breast cancer, male breast cancer (female and male); ovarian and fallopian tube cancer; primary peritoneal carcinoma, prostate (*BRCA2*) and pancreatic cancers
Li-Fraumeni	*p53*	Early-onset cancers (50% by age 30) including breast cancer, sarcoma, brain cancers, leukemia, adrenal cortical carcinoma
HNPCC	*MLH1, MSH2, MSH6* *PMS1* *PMS2* MSH3	**Cancers**: Early-onset colorectal cancer; endometrial, ovarian, gastric cancer; biliary, renal pelvis, small bowel, brain cancers **Other**: adenomatous polyps
FAP	*APC*	**Cancers**: Early-onset colorectal cancer; duodenal and pancreatic cancer; brain tumors; **Other**: colon, duodenal and gastric polyps; desmoid tumors
Hereditary Melanoma	*CKDN2A, CDK4*	Melanoma (early-onset and multiple); pancreatic cancer; possible association with astrocytoma and other neural-derived tumors; dysplastic nevi
Cowden Syndrome	*PTEN*	**Cancers**: Breast cancer, thyroid cancer (usually follicular), possibly endometrial cancer **Other**: Facial trichilemmomas, hyperkeratotic lesions of the oral mucosa, face and limbs, hamartomatous polyps
Peutz-Jeghers Syndrome	*STK11*	**Cancers**: Breast cancer, colon cancer, pancreatic cancer, gastric cancer, benign and malignant ovarian tumors (especially granulosa cell tumors), and possibly cervical and testicular cancer **Other**: Pigmented spots on the lips and buccal mucosa, multiple gastrointestinal hamartomatous polyps

Table 3

Recommendations for annual breast MRI screening (16)

Risk Group	Recommendation	Level of Evidence
BRCA mutation carrier	Recommend annual MRI screening as an adjunct to mammography	Based on non-randomized screening trials and observational studies
First-degree relative of *BRCA* mutation carrier		
Lifetime risk of breast cancer ≥20% as defined by family-history based model		
History of radiation to chest wall between age 10 – 30 years	Recommend annual MRI screening as an adjunct to mammography	Based on expert consensus opinion
Li-Fraumeni syndrome and first-degree relatives		
Cowden and Bannayan-Riley-Ruvulcaba syndromes and first-degree relatives		
Lifetime risk of breast cancer 15-20% as defined by family-history based model	Insufficient evidence to recommend for or against annual MRI as adjunct to mammography; decision should be made on individual basis	Insufficient evidence to make recommendation
Pre-maligant breast lesion (lobular carcinoma in situ, atypical lobular hyperplasia, atypical ductal hyperplasia)		
Dense breasts on mammography		
Personal history of invasive breast cancer or ductal carcinoma in situ		
Women at <15% lifetime risk	Recommend against annual MRI screening	Based on expert consensus opinion