



CHAPTER 14. Emerging Trends

ACCESS TO CLINICAL TRIALS

Issues pertaining to access to clinical trials have been integrated into site-specific chapters across the *Plan*.

CANCER SURVIVORSHIP

Issues pertaining to cancer survivorship have been integrated into site-specific chapters across the *Plan*.

COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM)

Issues pertaining to complementary and alternative medicine are now addressed in Chapter 3 Palliation.

ESOPHAGEAL CANCER

Esophageal cancer is a rare cancer in New Jersey and the U.S., although it is common in some areas of the world, including Iran and certain regions in China. Recently, incidence rates of the two main types of esophageal cancer in the U.S. and other western countries have changed dramatically. The incidence of squamous cell carcinoma (SCC) of the esophagus has declined or remained stable in the U.S., while the incidence of esophageal adenocarcinoma increased rapidly, especially among white men.¹ In the U.S., SCC was previously the most common type, accounting for 90% of all esophageal cancer cases, but now accounts for approximately 39% of cases.^{2,3} Racial differences in histologic type exist in the U.S. and in New Jersey. The incidence of esophageal adenocarcinoma is highest among white men, while the incidence of esophageal SCC is highest among black men, even though SCC rates in this group have declined during the past 20 years.^{1,4}

The different temporal trends in the incidence of esophageal adenocarcinoma and SCC suggest distinct etiologies. Cigarette smoking is a risk factor for both cell types, although the association with SCC appears to be stronger.^{1,5} Excessive alcohol consumption increases the risk for esophageal SCC, although it does not appear to increase the risk for esophageal adenocarcinoma.^{1,5,6} Low intake of fruits and vegetables is also a risk factor for both types of esophageal cancer, although the association with SCC is more pronounced.^{1,7}

Obesity or higher body mass index has consistently been found to increase risk for esophageal adenocarcinoma in epidemiologic studies,^{1,6,8,9} but not for esophageal SCC.^{1,8} The prevalence of obesity increased steadily in the U.S. over the past 30 years,¹⁰ and this may explain in part the increasing incidence of esophageal adenocarcinoma. One possible mechanism is that obesity may increase pressure in the abdomen, which promotes the reflux of gastric acid into the esophagus and the development of gastroesophageal reflux disease (GERD).¹ The accompanying irritation and damage to esophageal cells in persons with GERD can cause Barrett esophagus, which is a pre-malignant condition that can progress to dysplasia and esophageal adenocarcinoma.¹ Persons with GERD have increased risk for



esophageal cancer, even if they have not been diagnosed with Barrett esophagus.² Obesity increases the risk for GERD¹¹ and may also influence risk for esophageal adenocarcinoma through additional mechanisms.⁸ Chow et al. reported an increased risk for esophageal adenocarcinoma among both persons with and without a self-reported history of GERD.⁸ An increased risk for esophageal adenocarcinoma associated with obesity was observed in a case-control study conducted in the United Kingdom, after adjusting for a history of GERD.⁶ GERD appears to be very common—the American College of Gastroenterology estimates that 60 million persons in the U.S. (20% of the population) experience symptoms of GERD at least once a month.¹² As the prevalence of obesity continues to increase in the U.S. and many other countries, esophageal adenocarcinoma rates may increase further.

Another possible factor in the increasing incidence of esophageal adenocarcinoma is *H. pylori* infection, which has been linked to reduced risk for this type of esophageal cancer.^{13–15} Due to improvements in sanitation and increasing use of antibiotics, the prevalence of *H. pylori* infection has declined.¹⁶ Possible mechanisms for a protective effect of *H. pylori* infection against the development of GERD and esophageal adenocarcinoma are discussed below in the section on *H. pylori* under Infection and Cancer. In a population-based case-control study conducted in Sweden, a protective effect associated with *H. pylori* infection was observed for esophageal adenocarcinoma, while infection with the Cag-A positive strains of *H. pylori* was found to increase risk for esophageal SCC.¹⁴

Survival for esophageal cancer patients is poor and appears to be similar for the two main types.¹ For New Jersey residents diagnosed with esophageal cancer during 1994–1997, the five-year relative survival rate was only 13%.¹⁷ Effective prevention, early detection, and improved treatments are important to reduce mortality.

Since esophageal SCC and adenocarcinoma have different risk factors, prevention of esophageal cancer varies by cell type.¹ Smoking prevention and cessation programs and programs that promote consumption of fruits and vegetables could help to reduce both types of esophageal cancer, especially SCC, in addition to other types of cancer and chronic diseases. Alcohol abuse prevention and treatment programs could help to further reduce esophageal SCC, as well as provide other health benefits. Effective programs to encourage exercise and healthier diets could aid in the prevention of obesity or weight reduction among obese persons, and thus in the prevention of esophageal adenocarcinoma, GERD, and other diseases.

Currently, there are no early detection tests to screen for esophageal cancer in the general population in the U.S. Since esophageal cancer is a rare cancer, it may be more effective to screen patients who are at increased risk. More research is needed to address the question of whether screening patients with Barrett esophagus is effective in reducing esophageal adenocarcinoma mortality.¹ One issue is that many people with Barrett esophagus are unaware of their condition.

Further considerations should include: (1) encouraging participation of New Jersey institutions in studies of the effectiveness of screening Barrett esophagus patients to reduce esophageal adenocarcinoma mortality; (2) supporting any clinical trials designed to assess whether aspirin or non-steroidal anti-inflammatory drugs can prevent esophageal cancer incidence; and (3) supporting any clinical trials to evaluate the effectiveness of treatments for esophageal cancer patients. In addition, more research is needed to identify why esophageal adenocarcinoma is increasing and any modifiable risk factors.



INFECTION AND CANCER

In this section we review the relationship between infection and cancer, including Epstein-Barr Virus (EBV), Human Immunodeficiency Virus (HIV), *helicobacter pylori*, human papillomavirus (HPV), and hepatitis.

Epstein-Barr Virus

Epstein-Barr virus (EBV) is a human herpes virus. It is the etiologic cause of infectious mononucleosis and is associated with several malignancies. EBV has been strongly associated with nasopharyngeal carcinoma (NPC) and Burkitt's lymphoma.¹⁸ In 1997 the International Agency for Research on Cancer (IARC) concluded there was sufficient evidence for the carcinogenicity of EBV in the causation of Burkitt's lymphoma, NPC, Hodgkin's disease, and immunosuppression-related lymphoma.¹⁹ Varying degrees of evidence link EBV to Hodgkin's disease, gastric carcinoma, lung carcinomas, and neoplasms of smooth muscle origin.²⁰ It has long been suspected that EBV acts in concert with other co-factors in the development of cancer, but those putative co-factors remain unidentified.¹⁸ Age at EBV infection and the host immune response appear to be important in terms of risk for developing EBV-associated cancers.²¹ Alternatively, it has been suggested that EBV is reactivated during the course of development of some of these tumors, and thus that EBV may merely be a marker rather than having any etiologic relationship.

Non-keratinizing NPC, especially the undifferentiated type, is closely associated with EBV. While this cancer is common in South East Asia, Alaska (among Eskimos), and North Africa, occurrence is rare in Western countries, with an annual incidence of less than 0.5 cases per 100,000.²⁰ In geographic regions of high squamous-cell NPC incidence, the proportion linked with EBV is high. In contrast, in low NPC incidence regions, a low proportion is linked with EBV. Another infectious agent, human papillomavirus (HPV), has also been implicated in the pathogenesis of squamous cell NPCs.²⁰ Proposed risk factors for development of NPCs include exposure to salted fish at an early age and certain tumor-producing compounds, such as nitrosamines, that are found in some food products.²² Further, smoking has been established as a major risk factor for development of squamous cell NPCs (though not of non-keratinizing NPCs) and may account for up to two-thirds of squamous cell NPCs.²⁰

Burkitt's lymphoma (BL), a high-grade lymphoma of B cells, is commonly found in equatorial Africa and New Guinea. However, it occurs sporadically in other areas of the world.²³ Over 95% of BL cases in Africa are associated with EBV, but only 20% to 30% of cases in the U.S. demonstrate an association.²³ Baumforth and others hypothesize that the low percentage of EBV-associated cases in the U.S. is related to a loss of EBV at some point in tumor development.²²

Approximately 10% of gastric carcinoma cases worldwide (more than 50,000 cases per year) have EBV integrated into the cancer cells. Germany (18%) and the U.S. (16%) have the highest proportions of gastric carcinomas positive for EBV.²⁴ A study involving a Japanese population reports that the incidence of EBV-positive gastric carcinoma is three times higher in men than in women and is higher for younger men.²⁴

The development of Hodgkin's disease, a relatively uncommon cancer in the U.S., has long been thought to be associated with EBV. Compared to persons without a history of infectious mononucleosis, persons with a history of infectious mononucleosis have a two- to five-fold increased risk of developing



Hodgkin's disease.²⁵ In addition, EBV has been detected in up to 50% of Hodgkin's disease cases in Western nations and in up to 100% of pediatric cases.²⁶

EBV may be involved in the pathogenesis of various other cancers as well. EBV is found in cases of non-Hodgkin's lymphoma (NHL) of the peripheral T-cell type. A consistent association has been described between EBV and nasal angiocentric T/NK-cell lymphoma.²⁶ Lymphoepithelial carcinoma of the salivary gland, a relatively uncommon tumor, is most prevalent in Eskimos and Southern Chinese populations and is associated with EBV. While past cases of Caucasian patients have not demonstrated association with EBV, newer cases have been reportedly associated with EBV.²³ EBV may be involved in the development of oral squamous cell carcinomas, especially given that a proportion of patients with the disease do not smoke or consume alcohol.²³ EBV has been associated with lymphoepithelioma-like carcinoma of the lung in Asian populations but not in Western patients.²⁷ The first report of an EBV-associated smooth muscle tumor of the kidney occurred in 1998.²⁸ EBV-associated smooth muscle neoplasms arising at other locations have been reported previously in patients with AIDS and in recipients of organ transplants.²⁸

Currently there are no therapies or vaccines available for EBV. Since several anti-herpes agents are presently available, it is likely that EBV-specific agents will be developed at some point.²³

In the future, if national clinical trials of treatments for EBV-positive gastric carcinoma commence, we should encourage participation in these trials by New Jersey institutions and persons at risk and consider enhancement of support. Additionally, if national clinical trials of a vaccine for EBV commence, we should encourage participation and consider enhancement of support. In addition, research into the use of immunotherapy to treat early-stage EBV-positive Hodgkin's disease and NPC should be encouraged.²¹ As smoking appears to further increase the risk from EBV for the development of squamous cell nasopharyngeal carcinoma, smoking cessation efforts should be strongly reinforced.

Cancers Associated with the Human Immunodeficiency Virus (HIV) Epidemic

The acquired immunodeficiency syndrome (AIDS) pandemic has been associated with cancer essentially from the outset.²⁹⁻³² The human immunodeficiency virus (HIV) is the etiologic cause of AIDS.³³ HIV has been implicated in the increased incidence of several cancers. In addition, with the advent of more effective anti-retroviral therapies and improved supportive care, many persons are living longer with their HIV infection. Due to lengthening lifespans and the attainment of older ages, at which cancers tend to begin occurring, AIDS patients are now developing malignancies that are not necessarily related to their HIV status. The underlying immunosuppression due to HIV, however, often greatly complicates standard therapeutic cancer approaches. For example, susceptibility to infections is greatly increased, often necessitating reductions in the standard therapeutic doses. Bleeding complications are also more common.

Persons at risk for HIV may also place themselves at increased risk from other environmental exposures. For example, many HIV patients are also injection drug users (IDUs) and often use multiple illicit substances, for which they receive counseling and therapy. Some HIV patients also enter alcohol treatment programs. However, although most IDUs also smoke, this has not generally been perceived to pose a major health threat, so counseling on smoking and smoking cessation components within substance abuse treatment programs are rare. Yet data suggest that smoking tobacco is the drug that in fact increases these individuals' mortality and cancer risk, which raises the issue that smoking cessation programs warrant new emphasis among IDUs.³⁴ Furthermore, both sexual and parenteral exposures put



persons who are at risk for HIV also at increased risk for infection with other agents associated with specific cancers.

The first tumor recognized in association with AIDS was Kaposi's sarcoma (KS). After the discovery of HIV, epidemiologic data suggested that in addition to HIV, a second infectious agent ("agent K")³² might be involved.³⁵ Although a herpes-like virus was linked with Kaposi's as long ago as 1972,^{36,37} it was not until the AIDS epidemic that a specific agent, now called both human herpes virus type 8 (HHV-8) and a Kaposi's-associated herpes virus (KS-HV) was discovered.^{38,39} Almost all HIV-associated KS in the U.S. (note: this is not true in some African countries and other areas) has occurred among men who have sex with men (MSM). In some areas of Africa where KS was common before the AIDS epidemic, KS incidence has increased 20-fold.⁴⁰ However, the evolving epidemiology of HHV-8 has demonstrated evidence of this virus in other risk groups, leaving the puzzle partially unresolved.

Non-Hodgkin's lymphoma, including primary brain lymphomas, also emerged early on as linked with the AIDS epidemic. The Epstein-Barr virus may be involved in the pathogenesis. Although many HIV-infected young adults have been diagnosed with Hodgkin's disease, the high incidence of Hodgkin's lymphoma in young adults has led to uncertainty and controversy as to whether or not it is linked to the HIV epidemic.

In 1993, the Centers for Disease Control and Prevention (CDC) definition of AIDS, for the purposes of U.S. surveillance, newly includes the occurrence of invasive cervical cancer (ICC) in an HIV-infected woman as a sufficient condition.⁴¹ The change was supported by data strongly linking cervical dysplasia with HIV infection,⁴² and by the finding by one group in New York City of an association with ICC.⁴³ Thus, since that time, any woman infected with HIV who has ICC is automatically defined as having AIDS.⁴⁴ This led to an increase in the number of women defined as having AIDS, especially in New Jersey.⁴⁵ However, later data have raised some questions about the nature of the association.^{46,47} Anal carcinoma and squamous dysplasia both appear to have increased among MSM. Both anal carcinoma and cervical carcinoma are strongly associated with certain types of human papillomavirus. It has been difficult to fully untangle the complex relationships, in part because some of the factors placing persons at risk for HPV are also risk factors for HIV acquisition. The role of screening for anal cancer and dysplasia in MSM and others at high risk warrants further clarification.^{48,49}

The New Jersey Department of Health and Senior Services recently reviewed the New Jersey experience concerning the occurrence of cancers among persons with AIDS.⁴⁷ This report serves as a comprehensive overview of the AIDS-related issues in New Jersey and provides relevant statistics. Data from the University of Medicine and Dentistry of New Jersey University Hospital cancer registry^{50,51} indicate increased lung cancers among HIV-infected patients compared to other cancers. Other studies, both from the U.S. and abroad, have also raised the issue of lung cancer and AIDS.^{47,52-55}

A prospective cohort study in New Jersey of men and women at high risk for HIV was begun in 1984.⁵⁶ The increased risk of lung cancer,⁵⁷ when examined in terms of New Jersey yearly incidence data by age, gender, and race for lung cancer,⁵⁸ remains: 8.4-fold increased in those HIV+ compared to expected, 2.7-fold increased in those HIV negative. The 3.1-fold higher rate among those HIV+ within the cohort was not attributable to increased smoking of tobacco or other products. These are the first cohort data to suggest an increase in lung cancer among HIV-infected persons, thereby raising the possibility that lung cancer may emerge as a problem as HIV-infected persons age and also survive longer with the therapeutic advances in HIV care.



Human T-cell lymphotropic virus type I (HTLV-I) is causally associated with an aggressive leukemia and lymphoma syndrome,^{59–62} as well as with neurologic disease. Both HTLV-I and human T-cell lymphotropic virus type II (HTLV-II) are associated with immunologic abnormalities.^{63–66} It remains uncertain whether HTLV-II is linked to an increased risk for cancer.⁶⁷ HTLV-I is uncommon in New Jersey except in people born in the Far East and the Caribbean. HTLV-II is common in New Jersey injection drug users.^{68,69} Current screening of blood donors has nearly eliminated the former risk of transfusion-related acquisition.

Hepatitis B and C viruses are discussed in a separate section on Hepatitis and Liver Cancer. Human papillomavirus is discussed in further detail in the sections on cervical cancer in Chapter 7 Gynecologic Cancers.

Steps that can be taken in the future to address issues in HIV and cancer include: (1) programs focusing on the primary prevention of HIV infection, such as education programs for young people and drug treatment and needle-exchange programs for IDUs; (2) monitoring cancer incidence trends in New Jersey among persons at increased risk for HIV and among those with HIV-infection; (3) encouraging development of clinical trials that seek to improve survival in HIV-infected persons diagnosed with a malignancy; (4) encouraging recruitment of persons for these trials, in light of the fact that many eligible persons are from groups historically less likely to participate in trials; (5) continuing epidemiologic studies examining the risks for cancer among HIV-at-risk groups, including support for efforts exploring whether there are predictive markers or co-factors; (6) continuing emphasis on providing integrated healthcare services to persons at HIV risk, including the routine provision of gynecologic screening services on site at primary healthcare settings, drug treatment programs, and AIDS clinics⁴²; and (7) develop programs targeted to IDUs to reduce excessive use of tobacco products. Highly Active Anti-Retroviral Therapy (HAART) treatment reduces the risk of KS among HIV+ patients and may also reduce the risk for primary central nervous system lymphoma.⁴⁰

Helicobacter Pylori

Helicobacter pylori, a type of bacteria that colonizes human stomachs, has been associated with increased risk for development of peptic ulcer disease and gastric cancers, in particular non-cardia gastric adenocarcinoma and gastric non-Hodgkin's lymphomas of the B-cell type.¹⁶ In 1994, the International Agency for Research on Cancer classified *H. pylori* as a group I carcinogen (e.g., as a definitive human carcinogen) for its role in gastric cancer development.⁷⁰ Patients with chronic atrophic gastritis tend to have a particularly high risk of developing gastric carcinomas.⁷⁰ There is also evidence of a strong association between *H. pylori* and gastric mucosal-associated lymphoid tissue (MALT) lymphoma. Since eliminating *H. pylori* often leads to MALT lymphoma regression, U.S. and European consensus conferences on *H. pylori* have recommended anti-bacterial treatment in cases of low-grade MALT lymphoma.⁷⁰ In contrast, there is no evidence that, once other gastric cancers have developed, treatment of *H. pylori* infection per se changes the natural history of those cancers. Individuals with *H. pylori* colonization, especially by cytotoxin-associated gene-A-positive (CagA+) strains, may also have an increased risk for developing pancreatic cancer.⁷¹

Meta-analyses have reported that *H. pylori* infection increases risk two-fold for gastric cancer development.⁷² More specifically, *H. pylori* infection is associated with a nearly six-fold increased risk of developing non-cardia gastric cancer.⁷³ However, *H. pylori* infection does not increase the risk for development of cardia gastric cancer. Current topographic codes permit description of the primary localization of the cancer within the stomach, when this can be determined. These data suggest that



coding for the specific topography of gastric cancer in data routinely submitted to the New Jersey State Cancer Registry would be useful, given that *H. pylori* infection is associated with the non-cardia gastric cancers, to assess trends with respect to *H. pylori*-related cancers. While this coding scheme already exists, specific research efforts would be needed to assess the extent to which it is being properly abstracted, coded, and submitted and to assess whether efforts to improve the data quality and/or completeness should be undertaken. It is likely that standard reports from clinicians may not currently enable registrars to attain this degree of specificity with regard to the place of origin within the stomach.

The most highly studied types of *H. pylori* have been Cag+ strains, which account for 40% to 60% of strains in the Western world (i.e., Western Europe, the U.S., and Latin America), and “most” of the strains in East Asia. Cag+ colonization is significantly associated with ulceration, gastritis, and gastric adenocarcinoma in the Western world.¹⁶

The cohabitation of humans and *H. pylori* for millions of years implies that some type of symbiotic relationship may exist.¹⁶ In recent years, the prevalence of *H. pylori* has been declining. Factors contributing to the decline likely include: (1) lower birth rates (risk factors for colonization include early childhood crowding), (2) increased antibiotic utilization,¹⁶ and (3) improvements in household sanitation and hygiene.⁷⁰ The fall in *H. pylori* colonization has been mirrored by a decrease in the incidence of gastric cancers.

In addition, there is evidence from some recent studies that *H. pylori* infection increases the risk for pancreatic cancer.^{74,75}

However, there have been increasing rates of various esophageal diseases (i.e., gastro-esophageal reflux or GERD, Barrett’s esophagus, and adenocarcinomas of the lower esophagus), as well as gastric cardia adenocarcinomas.¹⁶ Blaser has speculated that there may be potentially protective effects of *H. pylori*, especially of Cag+ strains, and that perhaps the declining prevalence of *H. pylori* and increased rates of GERD and reflux esophagitis are related to *H. pylori* elimination. *H. pylori*-associated gastritis tempers gastric acid secretion; so eradication of the bacteria may lead to localized increased acid production and subsequent reflux esophagitis.⁷⁶ Infection with Cag+ strains is significantly associated with a reduced risk for adenocarcinomas of the esophagus and gastric cardia.¹³ These results suggest that eradication of *H. pylori* may also produce some harmful effects.

Smoking has been associated with a three-fold increase in the risk of gastric cancer. There is evidence of a much higher risk for non-cardia gastric cancer among smokers with *H. pylori* infection. As compared to uninfected non-smokers, smokers infected with CagA-negative *H. pylori* strains have a 9-fold increased risk of developing non-cardia gastric cancer, while smokers infected with CagA+ *H. pylori* strains have a 17-fold increased risk for non-cardia gastric cancer.⁷⁷

A well-documented risk factor for developing gastric cancer is a family history of this cancer, in the range of 1.5- to 3-fold.⁷⁸ In addition, as compared with uninfected individuals with no family history, individuals with positive family history and infection with the CagA+ *H. pylori* may have a 16-fold risk of noncardia gastric carcinoma.⁷⁸

The theory of intrafamilial clustering of *H. pylori* infection is supported by evidence of *H. pylori* colonization in the parents and siblings of infected children.⁷⁹ A strong association exists between the *H. pylori*-infection status of parents and preschool-aged children, suggesting that transmission may occur from parent to child. Specifically, as compared to children with uninfected mothers, preschool-aged



children of mothers infected by *H. pylori* have an almost 8-fold risk of being infected. As compared to children with uninfected fathers, children of infected fathers have nearly a 4-fold risk.⁸⁰ Further, infected individuals of higher birth order or from larger families may be at increased risk for developing gastric cancer.⁸¹

While the prevalence of *H. pylori* in children may be less than 10%, more than one-half of children in poor socioeconomic conditions may be infected.⁸² Estimates suggest that about 1% of infected children will develop gastric cancer. Thus, the risk for developing gastric cancer in children is limited. The multifactorial basis of gastric cancer development (e.g., *H. pylori* infection, smoking, family history, vitamin C deficiency, etc.) further complicates the issue of screening and treatment. Generalized population screening has not been shown to be beneficial or cost-effective. Imrie et al. suggest that, once an effective vaccine for *H. pylori* is developed, vaccination might be considered for reducing gastric cancer.⁸²

Use of vitamin C has also been suggested as a preventative measure, because it may help to prevent gastric cancer by inhibiting the formation of *N*-nitroso compounds in gastric juice, destroying reactive oxygen metabolites in the stomach and possibly inhibiting *H. pylori* infection.⁸³ Since data are currently insufficient to support this approach, controlled trials will be needed to assess the positive and negative effects of vitamin C.

H. pylori eradication may be a treatment option, especially among individuals at high risk for developing noncardia gastric cancer. Currently, regimens such as triple antimicrobial therapy—a therapy that may include bismuth, metronidazole, and tetracycline,⁸⁴ as well as other equally effective combinations, such as esomeprazole, clarithromycin, and amoxicillin⁸⁵—have been used to effectively treat over 80% of *H. pylori* infections in patients with peptic ulcer disease. However, neither routine screening for *H. pylori* nor empiric treatment in the absence of active disease are currently recommended. Fendrick et al. estimate that *H. pylori* screening may remain cost-effective at rates of cancer risk reduction of less than 30%.⁸⁶ However, controlled studies are needed to prospectively confirm, and determine the amount of, noncardia gastric cancer risk reduction associated with *H. pylori* eradication and further to determine whether any reduction in risks differs among age groups. In addition, the benefits of *H. pylori* elimination should be weighed against a loss of its possible protective effects against esophageal disease. Until benefit is clearly established, the issue of cost-benefit remains moot. An indirect strategy for reducing the risk of developing gastric cancer may involve an intervention that prevents the progression from chronic atrophic gastritis to gastric cancer.⁸⁶

Future strategies should include: (1) emphasizing smoking cessation programs; (2) considering support for clinical trials that screen for *H. pylori* among persons at high risk (e.g., smokers and persons with a family history); and (3) if national clinical trials of the efficacy of vitamin C commence, encouraging participation of New Jersey institutions in these trials among persons at risk. Further, (4) funding should be considered for a research study led by cancer epidemiologists in conjunction with local cancer registrars and the New Jersey State Cancer Registry. This study could examine the extent to which gastric cancer subtype information (e.g., cardia versus non-cardia gastric cancer) is being collected, its adequacy, and the feasibility for improvement, as well as to assess its utility for prospective surveillance. This study should be undertaken in the near term, before further advances in therapy or development of a vaccine for *H. pylori*, so that adequate baseline data may be assessed.



Human Papillomavirus (HPV)

Issues pertaining to HPV are now being addressed in Chapter 7 Gynecologic Cancers.

Hepatitis and Liver Cancer

Primary liver cancers are any malignant tumors that arise in the liver itself, as opposed to having metastasized to the liver. The most common types are hepatocellular carcinoma (HCC) and cholangiocarcinoma, which arise from the liver cells and the bile ducts, respectively.⁸⁷ Cases are usually rapidly fatal.

Infection with either hepatitis B virus (HBV) or hepatitis C virus (HCV) are important risk factors for development of HCC.⁸⁸⁻⁹⁰ Infection with HBV early in life appears to be a much stronger risk factor for HCC than acquisition of HBV in adulthood.⁸⁷ Studies in China found that 40% of babies born to mothers who carried HBV also became infected with HBV, leading to public health efforts to interrupt the chain.⁹¹ Chronic infection with HBV has been associated with HCC even in the absence of detectable serum HbsAg.⁹² Use of a hepatitis B virus vaccine, which provides durable immunity in very young children, will likely prevent most cases of HCC.⁹³ Vaccination against HBV is currently recommended for all children in the United States.^{94,95}

Worldwide, exposure to aflatoxins is also a major risk for HCC.⁹⁶ This risk may be modulated by both genetic factors (which may be increased in some ethnic groups) and environmental factors (such as infection with HBV).⁹⁶⁻⁹⁸

HCC incidence in the United States has recently been rising,⁹⁹ with HCV the suspected cause.¹⁰⁰ Recently reported findings from a prospective cohort study in New Jersey of HCV-infected men and women found an increased risk of 9.7-fold compared to expected (based on New Jersey HCC yearly incidence data, by age, gender, and race).⁵⁸ These New Jersey data are believed to be the first prospective data from the United States supporting an increasing risk for HCC and an apparent link with HCV.⁵⁸

HCV is believed to have spread extensively among injection drug users in the United States during the 1970s and early 1980s, with particularly high rates in New Jersey that reach 99% in one statewide cohort.¹⁰¹ In addition to the HCC risk, HBV and HCV are also associated with substantial morbidity and mortality, with liver failure accounting for 10% of the deaths among IDUs (for both HIV negative and positive persons).^{101,102} HBV and HCV are also related to progressive liver disease in persons with blood-product-related acquisition (e.g., hemophiliacs and persons receiving blood products prior to implementation of effective screening).^{103,104} In the United States, about 2.7 million persons are chronically infected with HCV.¹⁰⁵ Among U.S. patients undergoing liver transplantation, HCV is currently the leading cause of liver failure. People who use illegal drugs or engage in high-risk sexual behavior account for most of those currently infected with HCV in the United States.¹⁰⁵ However, tattooing and body piercing are risk factors for HBV and HCV,¹⁰⁶ as well as other parenterally transmissible pathogens, such as HIV. HIV infection appears to worsen this natural history of chronic parenterally acquired hepatitis C, leading to an unusually rapid progression to cirrhosis.^{107,108}

Studies from Japan have led to estimates that the average time from initial infection with HCV until the development of HCC likely exceeds 20 to 30 years. Thus, the above data from New Jersey are likely the



first harbingers of a forthcoming rapid and significant rise in the number of new HCC cases in our state, as well as globally, over the next one to two decades.

In 1988, the New Jersey Commission on Cancer Research urged primary care physicians to consider the emerging role of prevention strategies in hepatocellular carcinoma.¹⁰⁹ These data reinforce the importance of prevention measures, including the primary prevention approach of vaccination.

Future steps in liver cancer should include: (1) continuing support for vaccination of New Jersey children against HBV in accordance with CDC guidelines; (2) increasing efforts to identify and vaccinate adults at risk for HBV and HCV; (3) support for research in developing a vaccine against HCV; (4) continuing epidemiologic studies examining HCC risk and efforts to explore whether there are predictive markers or co-factors amongst HCV-infected persons; (5) monitoring HCC incidence trends in New Jersey; (6) encouraging clinical trials that seek to improve survival in persons diagnosed with HCC and to develop safe and effective antiviral drugs to treat persons chronically infected with HBV or HCV; (7) considering establishing regulations to reduce HBV, HCV, and retroviral transmission that can occur in establishments engaged in tattooing, body piercing, or similar practices^{110,111}; and (8) drug treatment and needle-exchange programs for IDUs to prevent HCV and HBV transmission in this group.

THYROID CANCER

The thyroid gland is located in the base of the throat and is responsible for the regulation of hormones that play a role in regulating heart rate, blood pressure, body temperature, and weight. Though cancer of the thyroid is rare, surveillance data show a marked increase in incidence rates over the last decade. In 2004, there were 268 cases of thyroid cancer diagnosed in New Jersey. Between 1993 and 2004, New Jersey's thyroid cancer incidence rates approximately doubled for men and tripled for women, leaping to 6.3 and 18.8 per 100,000, respectively. The increase is more pronounced in women than men and in whites than blacks. Both New Jersey and the U.S. have experienced similar increases in thyroid cancer incidence rates.^{3,4}

While little is known about the risk factors for thyroid cancer, the disease is more common in women than men and occurs most frequently in individuals between the ages of 20 and 60. Inherited conditions, such as familial medullary thyroid carcinoma (FMTC) and other hereditary medical conditions, may increase an individual's risk of developing thyroid cancer. Exposure to radiation during childhood is a proven risk factor for one type of thyroid cancer; and a diet low in iodine may also increase the risk. However, most of those who develop thyroid cancer have no known risk factors for the disease. There is no accepted screening test to diagnose the disease before symptoms occur, although the American Cancer Society recommends that all adults over the age of 20 should have their thyroid examined as part of a routine health examination.¹¹²

Research is ongoing into the potential causes for the recent increase in thyroid cancer incidence.



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