Anna H. Wu · Daniel O. Stram *Editors*

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Preface

There are profound differences between countries, ethnic groups, and races in risks of virtually all common cancers; variations in cancer rates by population may reflect the influence of genetic, environmental, or behavioral risk factors and such variations have long motivated speculation about the causes of cancer. Our knowledge about whether the causes of the observed differences in cancer risk are modifiable is greatly enhanced by consideration of migration studies. When rates of a particular disease change rapidly among migrants, then this is supporting evidence that risk of that disease may be at least partly environmentally or behaviorally driven, rather than solely due to differences in the genetic background and therefore not amenable to intervention. This is especially true when risks in migrants approach those seen in the host country.

The most rapidly developing countries in the world today are in Asia, and Asians constitute the fastest growing immigrant populations in the USA. Asian Americans represent a heterogeneous population that includes Asian Indians, Chinese, Filipino, Japanese, Kampuchean (Cambodian), Korean, Vietnamese, and other Southeast Asians. Cancer is the leading cause of death for Asian American men and women. Studies of cancer in Asian Americans can reveal important clues to disease etiology since increases or decreases in cancer rates in Asian Americans can help to identify environmental and lifestyle causes of cancer. This book describes the current state of knowledge about the epidemiology of cancer risks in Asian Americans with specific references to changes in behavior and exposures due to the process of acculturation in the USA. The usual approaches to analytic investigation of epidemiology of complex diseases in US populations, i.e., case–control and cohort studies, have only sometimes or recently included Asian Americans to any large degree. Part of the rationale for this book is to be as thorough as possible in bringing to light what has been learned from these traditional approaches despite the often lack of data on Asian Americans. In addition, an overall theme of the book is the judicious use of ecologic comparisons as a source of information about the Asian American cancer experience, the risk factors underlying that experience, and the relevancy of the Asian American cancer experience to the rest of the Americas and the world, particularly as a source of information about the effects of continued globalization and acculturation on cancer risks.

The first section includes four chapters. Chapter "Resources and Methods for Studying Cancer among Asian Americans" summarizes the resources in the US and established study methods to conduct such studies in Asian Americans. Chapters "Cancer Incidence and Mortality Patterns among Chinese Americans" and "Cancer Incidence and Mortality among Filipinos in the United States and the Philippines: Patterns and Trends" provide a review of the specific cancer patterns in the two largest Asian American groups in the USA. Chapter "Cancer Screening among Asian Americans" examines the utilization of cancer screening tests among selected Asian American ethnic groups and describes the research on factors that are associated with screening. The second section includes eight chapters. Upon migration to the USA, there are increases in the incidence of cancers that are typically associated with westernization and decreases in the incidence of cancers that are linked to an infectious origin and other lifestyle factors that are prevalent in Asia. Chapters "Lung Cancer Among Asian Americans," "Colorectal Cancer among Asian Americans," "Prostate Cancer Among Asian Americans," "Breast Cancer among Asian Americans," and "Endometrial Cancer among Asian Americans" cover the cancer sites (lung, colorectum, prostate, breast, and endometrium) that are traditionally associated with Western lifestyles. Reasons that are favored to explain the increases in these cancers in Asian Americans are explored, including increased prevalence of the higher risk profiles in Asian Americans, timing of exposure to particular risk factors, and the magnitude of risk associations in Asian Americans. Chapters "Liver Cancer Among Asian Americans," "Gastric Cancer Among Asian Americans," and "Cervical Cancer Among Asian Americans" cover cancer sites that are historically very common in Asia; while the incidence rates of these cancers decline in Asian Americans, their rates remain relatively high. In these chapters, reasons that may explain the decline in the incidence of these cancers upon migration are discussed, paying attention to the prevalence of changing risk factors, the importance of timing of exposures, and other cofactors important in the etiology of these cancers. Whenever possible, genetic determinants and gene–environment relationships associated with specific cancers were included in the discussion. As will be evident, most of the information on Asian Americans is based largely on studies conducted in Japanese Americans. While Chinese and Filipino Americans were included in some analytic epidemiologic studies, few studies focused on their risk factors specifically. Even less has been done in the other Asian American groups. As the population of the other Asian ethnicities increases in the USA, there is a need to include other Asian ethnic groups in etiologic studies despite the challenges of small sample sizes, language, and other barriers.

In summary, this book aims to provide important and up-to-date information on cancer trends and risk factor patterns among the large and growing Asian American population in the USA. The chapters place an emphasis on the most common cancers diagnosed in Asian Americans, examining risk factor patterns, but also pointing to the gaps in knowledge as we often had to rely on results from studies conducted in Asia.

Los Angeles, CA

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Resources and Methods for Studying Cancer Among Asian Americans

Ann S. Hamilton, Anna H. Wu, and Daniel O. Stram

Abstract Asian Americans are a diverse group and have a long history of migration to the United States (USA). Large differences in cancer rates between countries of origin and the USA, as well as diversity in lifestyle and environmental exposures, provide an opportunity to identify and study risk factors for specific cancers that can provide insights into cancer etiology and methods of prevention. The migration experience has created a type of natural experiment in which populations with a common genetic background have been exposed to different risk factors in a new environment and provides the opportunity to determine if risk factor changes can be linked to changes in their cancer rates. Multiple data sources are available to study cancer in Asian Americans, including US Census data to provide denominators for rates, cancer registries to assess cancer incidence, as well as observational studies in which personal risk factor information is obtained. Study designs which have been used include the ecologic, cross-sectional, case series, case-control, and cohort studies. Limitations and caveats in using these resources and study designs are described.

Keywords Asian Americans • Cancer • Risk factors • Cancer registry • Study designs • Migration

Introduction

Asian Americans are extraordinarily diverse with respect to country of origin, time since immigration, socioeconomic status, languages and dialects spoken, religion, diet, and other characteristics, many of which may affect health. There has been a long history of migration from Asia to the United States (USA) in substantial numbers and from countries with differing cancer incidence rates, both higher and lower than found in the USA. If cancer rates differ between Asians in their country of origin, migrants, and their counterparts born in the USA, these differences provide important clues to determine environmental and lifestyle risk factors for cancer,

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since these comparison groups generally have a similar genetic background. On the other hand, if cancer rates do not differ between migrants and nonmigrants, this may be due to similar environmental factors in both locations or alternatively due to host/genetic factors.

Asian Americans are defined by the US Census Bureau as individuals with origins in "any of the original people of the Far East, Southeast Asia, or the Indian Subcontinent." Modern Asian immigration to the USA began in the 1880s, when first Chinese and later Japanese, Filipino, and Korean workers were recruited to work on plantations and farms in Hawaii and California (See Chaps. 2 and 3 for details on migration history of Chinese and Filipinos). Various Exclusion Acts limited other forms of immigration by Asians until 1965, when discrimination based on country of origin was prohibited. Asian immigration to the USA has increased steadily since then.

Here, we describe the composition and numbers of Asian Americans in the USA today, sources of data used to assess cancer rates among the various Asian subgroups both in the USA and in their countries of origin, and discuss methodological issues, study designs, and potential biases that should be assessed when studying the role of migration on changing cancer risk factors.

Asian-American Population Characteristics (2000–2010)

Coding for specific Asian ethnic groups was added to the US Census over time beginning in 1870 for Chinese which included all east Asians, 1890 for Japanese; 1920 for Hindu (South Asia Indian), Korean, and Filipino; and 1980 for Vietnamese and Pacific Islander groups. In the past three censuses (1990, 2000, 2010), the racial categories were the same except that the option for listing multiple races was not provided until 2000. In 2010, the US Census obtained a person's race according to the form shown in Fig. 1 [1]. In addition to the specific Asian groups listed as check boxes in the questionnaire (Asian Indian, Chinese, Filipino, Japanese, Korean, and Vietnamese), there was a box for "Other Asian" allowing the person to write in other groups. From this text field, additional Asian groups were identified, including Bangladeshi, Bhutanese, Kampuchean (Cambodian), Hmong, Indonesian, Iwo Jima, Laotian, Malaysian, Mongolian, Nepalese, Okinawan, Pakistani, Singaporean, Sri Lankan, Thai, and other Asian, not specified. In 2010, over 17 million people listed at least one Asian race, and of them, 15.3% or 2.6 million listed more than one race [1]. The total Asian population, including those listing more than one race, comprised 5.6% of the US population. The US population grew by 9.7% between 2000 and 2010; however, the Asian population grew faster during this decade than any other racial group, rising by 43% for those who reported an Asian race alone and by 46% when including those reporting an Asian race in combination with another race.

Among the detailed Asian ethnic subgroups in 2010, the Chinese population was the largest (Table 1); Filipinos were the next most prevalent, followed by Asian Indians, Vietnamese, Koreans, and Japanese. The Asian ethnic subgroups with the

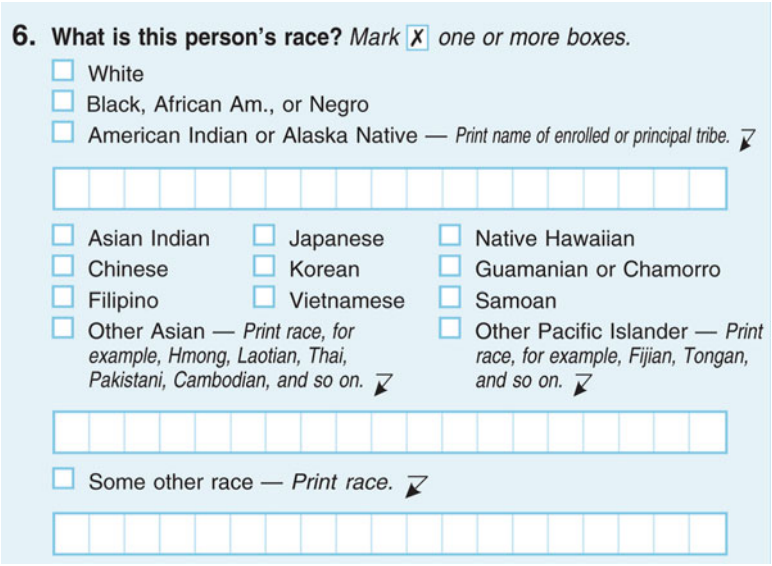

Fig. 1 Reproduction of the question on race from the 2010 Census [1]

Table 1 Total 2010 US population by detailed Asian subgroup [1]

	Asian alone	Asian in combination
Chinese	3,535,382	474,732
Filipino	2,649,973	766,867
Asian Indian	2,918,807	264,256
Vietnamese	1,632,717	104,716
Korean	1,463,474	243,348
Japanese	841,824	462,462

highest proportion of people naming an Asian race in combination with another race were Japanese (35.4 %) and Filipinos (22.4 %). Among the 2.6 million Asian in combination with another race population, 1.6 million named the White race as a second racial group [1].

The increasing Asian-American population over the last decade is reflected in the timing of when foreign-born Asians have come to the USA. Over 30 % of foreign-born males and females have arrived in the USA between 2000 and 2009, and another 5–6 % have arrived since 2010. Over 56 % of the Asians in the USA were foreign born in 2010, including those who were Asian alone or in combination with another race, about 30 % of Asian Americans were in the 35–54 age group, with relatively low percentages in the over 65 age group.

In 2010, the highest proportion of the total Asian population (i.e., Asian alone + Asian in combination with another race) lived in the West (46.2 %), followed by the South (22.1 %), the Northwest (19.8 %), and the Midwest (11.9 %) which was very

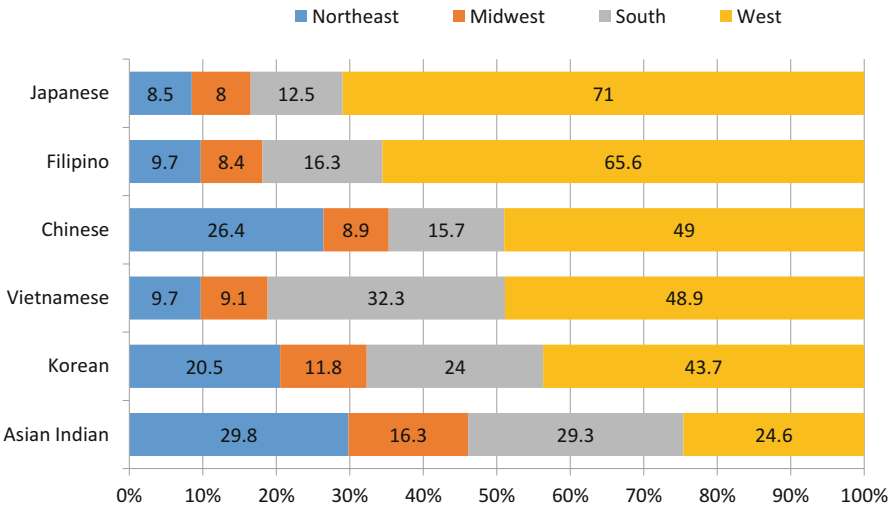

Fig. 2 Percent distribution of geographic location* of detailed Asian subgroups: 2010 US Census [1]. *The Northeast census region includes Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont. The Midwest census region includes Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin. The South census region includes Alabama, Arkansas, Delaware, the District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia. The West census region includes Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming

similar to the distribution in 2000. The states with the greatest numbers of Asians in 2010 were California (5.6 million), New York (1.6 million), Texas (1.1 million), New Jersey (0.8 million), Hawaii (0.8 million), Illinois (0.7 million), Washington (0.6 million), Florida (0.6 million), Virginia (0.5 million), and Pennsylvania (0.4 million) [1]. Although the top five cities with the greatest numbers of Asians included New York, NY; Los Angeles, CA; San Jose, CA; San Francisco, CA; and San Diego, CA, the areas experiencing the highest percentage growth in the number of Asians between 2000 and 2010 were located in the South and Midwest.

There were, however, substantial differences in the geographic distribution of the specific Asian ethnic subgroups in 2010. As shown in Fig. 2, 71.0 % of Japanese and 65.6 % of Filipinos lived in the West, followed by close to half of Chinese and Vietnamese, 43.7 % of Koreans, and about a quarter of Asian Indians. Close to a third of Vietnamese and Asian Indians lived in the South, the highest percentages of any of the Asian ethnic subgroups living in that region. Chinese and Asian Indians were the most likely of any of the groups to live in the Northeast (26.4 % and 29.8 %, respectively). Asian Indians, who were distributed the most evenly across the country, also had the highest percentage of any group living in the Midwest (16.3 %). California had the highest proportion of each of these subgroups living in any state, ranging from 43 % of the Filipinos to 19 % of the Asian Indians.

These results provide insights into where studies of migrant populations may be conducted to include the largest numbers of Asians by specific Asian ethnic subgroup and where the most recently arrived migrant populations are located. In addition, the differences in the proportions of mixed race populations among the Asian ethnic subgroups indicate that there may be different genetic factors to consider when studying the Japanese and Filipino populations, for example, which had the highest proportions of multiple race individuals (35.4 % and 22.4 %, respectively), compared to the Vietnamese who had the lowest (6.4 %).

Comparison of Worldwide Cancer Rates

Information on cancer incidence rates in other countries is necessary to compare differences in cancer incidence rates between countries of origin and the USA. The history of comparison of worldwide cancer rates began with Segi [2] and colleagues who produced a series of reports comparing cancer mortality in 24 countries in the 1950s, showing that the distinctive geographical and racial/ethnic variation in cancer occurrence may provide clues to the etiology of cancer. Recognizing the importance of accurate and timely cancer registration, the International Agency for Research on Cancer (IARC) and the International Association of Cancer Registries (IACR) were established. Since 1966, detailed information of cancer recorded by regional or national registries around the world was published in the series "Cancer Incidence in Five Continents" (CI5), which was updated typically every 5 years [3–5]. The CI5 series provides the major sources of information to compute the country-specific cancer incidence rates which are provided in the online, freely accessible database, GLOBOCAN. As cancer rates may vary considerably within a country, GLOBOCAN national rates (incidence, mortality, and prevalence) are estimated using data from the individual contributing registries, taking into account regional and urban/rural patterns. GLOBOCAN 2012 is the fifth and most recent version that presents cancer incidence and mortality in 184 countries [6].

Given that age itself is one of the strongest risk factors for developing cancer and unadjusted or crude incidence rates are highly dependent on the underlying age distribution of the population, age-standardized incidence rates (ASR) are used for comparison of cancer incidence rates between populations. Age standardization in GLOBOCAN and CI5 are typically calculated using world standard population proposed by Segi [2], but age truncation into 5- or 10-year age groups may be used in different studies.

Cancer Incidence and Mortality in Asian Americans

The development of national population-based cancer registries, which included large populations of Asian Americans within the USA, has provided the basis for studies of cancer incidence and mortality. Efforts on the national level to collect

incidence and mortality data in a systematic way began with the National Cancer Act of 1971 that mandated the collection and analysis of data useful in the prevention, diagnosis, and treatment of cancer. This mandate led to the formation of SEER (Surveillance Epidemiology and End Results), the program that established population-based cancer registries funded by the National Cancer Institute. Regions in the SEER program were selected to represent the diverse racial ethnic composition of the US population. The inclusion of Hawaii and San Francisco at the outset of the program in 1975 and the subsequent addition of Los Angeles County and four counties in the San Jose/Monterey area in 1992 allowed coverage of Asian-American and Pacific Islander (AAPI) population. In 1988, cancer became a reportable condition in California, leading to the establishment of the California Cancer Registry (CCR), and in 1992, the entire state was included in SEER program. Reporting by SEER registries uses a standardized protocol and is centrally monitored, and participation requires meeting quality control standards including promptness, histologic confirmation, and completeness [7].

Data from the CCR have been used to study cancer patterns of the five most populous Asian subgroups in California (Chinese, Japanese, Filipino, Korean, Vietnamese) [8, 9]. Because of small numbers, cancer patterns for Southeast Asian (Vietnamese, Laotian, Hmong, Kampuchean (Cambodian), Thai, Burmese) and the Indian Continent (Asian Indian, Pakistani, Bangladeshi, Nepalese, Sikkimese, Sri Lankan) are often studied as a group [10]. The Los Angeles County Cancer Surveillance Program (CSP), the SEER population-based cancer registry for Los Angeles County, has the longest history of estimating cancer incidence rates for specific Asian ethnic groups. Since 1976, the CSP has reported on cancer incidence rates for four Asian groups (Chinese, Japanese, Filipino, and Koreans), and this was expanded in 1991 to include four additional AAPI groups (Vietnamese, South Asian, Thai/Hmong/Kampuchean (Cambodian)/Laotian, and Hawaiian/Samoan). Thus, since the early studies of Smith and King [11–16] and others who investigated cancer mortality patterns of Chinese and Japanese residing in California, Hawaii, and New York, there are now data resources to study cancer incidence and mortality patterns in multiple Asian-specific populations on a county (Los Angeles), statewide (California), and nationwide (SEER) level.

Methodologic Considerations in Studies of Asian Americans and Cancer

Taken at face value, changes in cancer incidence and mortality rates observed in an Asian ethnic migrant subgroup compared to rates in their home country imply that disease incidence is affected by risk factors which have changed with moving to the new environment, since the migrant population would be expected to have a similar genetic background to those remaining in the home country. However, there are multiple potential sources of bias that should be considered when conducting studies designed to assess the effects of migration and associated changes in lifestyle on cancer risk. These biases may be specific to the type of study design and are

summarized below. Previous reviews have also provided an excellent description of major biases in migrant studies and are still relevant today [17, 18].

All traditional epidemiological observational study designs can be used to study the effect of migration status on cancer risk among Asian Americans, including ecologic, cross-sectional, case series, case-control, and cohort studies and variations such as the nested case-control study [19]. Studies which do not obtain direct individual information or which do not allow for distinguishing the timing between risk factor exposure and disease onset may be considered "descriptive studies" which are helpful for identifying disease patterns and for hypothesis generating or for providing suggestions for possible cause and effect relationships that would require further study to confirm. Analytic designs obtain individual information on exposures of interest and outcome measures, as well as potential confounders. Inference about cause and effect is strengthened if exposure history is available and precedes the outcome being studied. In general, the ecological study and case series are considered to be descriptive studies, while case-control and cohort studies are analytic designs. The cross-sectional design obtains individual information; however, the exposure and outcome are assessed at the same point in time. While this may prevent the assessment of cause and effect for many exposures and outcomes, the temporal sequence between these events can be determined in some circumstances (e.g., exposures occurring in childhood compared to outcomes in adulthood). We present below some examples of the use of the various study designs to investigate the effect of migration on cancer risk among Asian Americans and limitations/potential biases associated with the designs.

Ecological Study Design

This study design is often used in migrant-related studies in which individual data on exposures are not collected and comparisons are based on established datasets including cancer registries, census information, and geographic-based measures of exposures. A comparison of cancer rates between countries and subgroups is used to develop hypotheses about risk factors for cancer based on prevalence of different risk factor profiles between the areas of comparison. No individual level information is obtained.

There are important methodological concerns in the comparison of incidence rates that involve the quality of the numerator and denominator data, as well as the matching of definitions of Asian subgroups between the sources of data.

(a) The ascertainment of the cancer cases (numerator) is related to the quality of cancer registration.

Completeness of case ascertainment may be affected by definitions used to identify cases, diagnostic coding schemes used, rates of histologic confirmation of cases, and criteria used by pathologists [18]. These practices may differ between the country of origin and those in the host country. Differences in the proportion of histologically

confirmed cases and death certificate-only cases are two important indicators used to assess the quality of cancer registries. A summary of cancer registry quality indicators and procedures has been described [20, 21]. In addition, the incidence of certain cancers (e.g., prostate, colorectum, breast, thyroid, etc.) may be quite dependent on screening practices [4].

(b) The quality of denominator data may differ between the country of origin and the host country.

The assessment of accuracy of denominator data is important to assure that the comparison of rates between the country of origin and the USA is based on true differences in cancer incidence. If, for example, the denominator data for the country of origin was underestimated and the numerator reflecting cancer incidence was complete, the cancer incidence rate in that country would be overestimated. Conversely, should the denominator be overestimated, the rate based on it would be underestimated (again assuming the numerator data were complete). In addition to providing cancer incidence rates for 184 countries, GLOBOCAN 2012 has also provided an assessment of the quality of rates by country and the sources of data used for each one [6].

In the USA, denominator data for Asian ethnic subgroups are produced every 10 years when the Census is conducted. For the 2010 Census, data by the detailed Asian subgroups as well as mixed race subgroups is provided in the 2010 Census Summary File 1 [1]. Population estimates need to be projected during intercensal years for each of the specific Asian ethnic subgroups.

The different registries in the USA (e.g., SEER, CCR, and Los Angeles CSP) have developed their own intercensal population estimates for their respective regions. Also there are differences in the availability of rates for the detailed Asian subgroups. The SEER program provides US population files that can be used to calculate rates using the SEER* Stat program by county, state, and age group for the year 1969–2013, but this is only provided as a summarized total for Asians and not by specific Asian ethnic subgroup (http://seer.cancer.gov/popdata/download.html). In SEER, AAPI rates are often presented for AAPI combined and not by specific (or disaggregated) Asian-American ethnic groups. Small numbers of individual AAPI populations in earlier years of SEER and unstable rates are reasons to present rates for AAPI as a group. The CCR has also developed its own population estimates for denominators to calculate Asian race-specific rates using population estimates for California obtained from the 1990 and 2000 census [9]. The CSP has similarly developed its own population estimates for denominators to calculate Asian race-specific rates using population estimates for LA County obtained from the 1970, 1980, 1990, and 2000 US population censuses.

With the rapidly growing AAPI population in the USA, there are now concerted efforts to examine cancer patterns of the eight most populous Asian ethnic populations (Asian Indian/Pakistani, Chinese, Filipino, Japanese, Kampuchean (Cambodian), Korean, Laotian, Vietnamese) [22, 23]. Miller and colleagues [22] included cancer diagnoses among AAPI populations from 1998–2002 identified in 14 SEER registries covering 68 % of the total US AAPI population and presented incidence and

mortality rates by detailed AAPI groups. Gomez and colleagues [23] expanded this analysis by including data for three study periods (1990–1994, 1998–2002, 2004–2008) which allowed assessment of incidence trends over time. In both studies, methodologies were developed to produce a consistent set of denominators using the 1990 and/or 2000 Census population distributions by age, sex, and detailed Asian-American ethnicity of a given geographic area [22, 23].

(c) Matching numerator and denominator definitions of race.

The specific Asian ethnic definitions must be matched between the numerator and denominator data. The coding of race in cancer registries is based on hospital admission forms which may be based on self-report or observation by the admissions staff or from death certificates. Patients are not specifically asked about multiple races. From the CCR, the proportion of Asians in California with multiple races was substantially lower (7.1 %) than those based on the Census data (15.3 %). Thus, the potential bias would be for cancer incidence rates specific to the Asian in combination population to be underestimated. There is also a greater possibility of misclassification of race in the cancer registry records. Swallen and colleagues [24] reported that approximately 20 % of Vietnamese patients with cancer actually were not Vietnamese but were Chinese or other Asians. Similar misclassification may affect other Asian subgroups, but the extent has not been investigated in all Asian subgroups.

(d) Examples of comparisons of cancer rates between subgroups.

In one example, a study compared cancer rates between Asian Americans in the USA with their countries of origin. Matsuno and colleagues conducted a study to examine age-related differences in breast cancer rates between the USA and Japan [25]. Rates were higher among Japanese in Hawaii (72.4/100,000) compared to Japanese in Osaka (21.8/100,000), but the most striking difference was seen in women over age 50 years, where rates continued to increase with age among Japanese in Hawaii, but leveled off after this age among women in Osaka. This pattern of higher rates among postmenopausal women suggests that the increasing rates of postmenopausal, estrogen receptor-positive breast cancer in Western countries are likely due to Western lifestyle, obesity, and use of menopausal hormones. Another possible reason for the higher rates seen in Hawaii may be related to increased screening for breast cancer in Western countries [26].

Another example illustrates comparisons among Asian Americans based on birthplace. Using the CCR, multiple studies have been done to assess rate differences between US born and non-US born for different cancers including lymphoid malignancies [27], papillary thyroid [28], liver [29], non-small cell lung [30], breast [31], and colorectal cancer [32]. Limitations of these studies include the assumptions made to categorize patients according to nativity and potential misclassification, attribution of ecological characteristics to individuals, and possible mismatches between how immigrant status is categorized between numerator and denominator data, as well as by detailed age-specific Asian ethnic subgroups.

It should be noted that cancer rates estimated for specific Asian ethnic groups in the USA represent a composite of rates of first-generation migrants and US-born descendants. Although information on birthplace is available in registry data, this information is incomplete. In addition, obtaining denominators for US born and foreign born of a specific Asian ethnic subgroup is a challenge. Thus, cancer rates reported for a specific Asian-American ethnic population are sensitive to the proportion of US born vs. foreign born. Even among the foreign born, the pattern of migration (e.g., age at migration, reasons for migration) may differ between different Asian ethnic subgroups.

Differences in rates between US-born Asians and non-US-born Asian Americans may be informative about the importance of timing of exposure. If rates for the non-US born remain relatively unchanged (compared to their country of origin) while rates for the US born approach rates for the host country (i.e., the US), then the factors of etiologic importance may be operating early in life. In contrast, if rates have already changed in the non-US born (becoming more similar to the US rate), this may suggest that factors operating in adult life are important. These same methodologies can also be used to compare and contrast changes in cancer rates by birthplace across different Asian ethnic groups.

(e) Summary of issues to consider for ecologic comparison of incidence rates.

Formation of appropriate comparisons between population groups requires a research infrastructure to provide reliable incidence and mortality data and to turn these data into reliable summary statistics by which populations can be compared. At a minimum, reliable ecologic comparisons require that (1) methods of reporting incident and fatal cancers are based on uniform standards, (2) information about racial/ethnic group membership must be available from death records or incidence reports, (3) the size of the populations contributing deaths or incident cases to the specific counts of interest must be clearly defined, and (4) the age structure of the populations also be known.

In addition to issues related to accurate and comparable calculations of incidence rates, there are important selection factors that may affect assumptions about the effect of migration on cancer risk factors. Migrants leaving their home country are usually a selected group who are migrating for various reasons including job opportunities, education, socioeconomic, religious, political, or other reasons. Thus, they may not have the same health status or risk of cancer as nonmigrants in their home country. Such differences would affect comparisons of migrants with rates in the country of origin but could also affect comparisons within the host country if the migrants differ from the US born in terms of access to screening and medical care.

Finally, as indicated earlier, 15.3 % of Asian Americans listed more than one race in the 2010 US Census, and the highest proportions listing another race were among Japanese (35.4 %) and Filipinos (22.4 %). The most commonly mentioned second race was white. This population mixing occurring between migrant populations and the US population will have important consequences for the validity of the assumption that the migrant and nonmigrant groups are genetically similar. While this still may be true for recent migrants, those that have been in the US for longer periods of

time may have less genetic homogeneity with the population in their country of origin. Thus, differences between their cancer rates and those from their country of origin may not be due solely to environmental factors.

Cross-Sectional Study

The cross-sectional study design usually involves a survey which obtains personal information, but in which information on the outcome as well as possible risk factors is obtained at one point in time. For some exposures, it is not possible to determine the sequence of events between the occurrence of the exposure and outcome; thus, identifying a causal relationship between a risk factor and the disease is not possible. However, for some exposures, such as those occurring in childhood, in comparison to an outcome that occurred in adulthood, the temporal sequence can be inferred. This type of study has been routinely used to determine risk factor profiles including smoking [33], alcohol use [34], body mass index [35], as well as factors that are associated with the use of screening programs. As an example, to better understand the lower cancer screening rates among Asian Americans compared to non-Hispanic whites, data from the 2001 California Health Interview Survey was used to determine if this disparity was related to nativity, years in the USA, English language ability, and access to care [36, 37]. Although there are several large cross-sectional surveys in the USA that can provide data on screening and other behaviors related to cancer risk (e.g., diet, physical activity, alcohol consumption, etc.), information on AAPI was added only in recent years [38]. These surveys include the National Health Interview Survey (NHIS), the Behavior Risk Factor Surveillance System (BRFSS), and the National Health and Nutrition Examination Survey (NHANES). Websites for these studies provide additional information about the variables included and how to access data (http://www.cdc.gov/nchs/nhanes.htm; http://www.cdc.gov/brfss/about/about_brfss.htm; http://www.cdc.gov/nchs/nhis.htm). The importance of the recent inclusion of AAPI in these national surveys cannot be overemphasized since these data allow comparison of a range of self-perceived health status, prevalence of selected chronic conditions, and distribution of a number of important biomarkers (in NHANES), as well as the use of health services among AAPI and minority groups in the USA [39, 40].

Case-Only Study

A case-only study consists of review of characteristics of a series of cases, with no comparison to non-diseased persons, and is not linked to population denominators to calculate incidence rates. However, due to the heterogeneous nature of cancer cases, i.e., cancers of a particular anatomic site may have different histological subtypes, the study of cancer cases alone may provide insights into disease risk factors.

Certain subtypes may be more related to diet and environmental exposures than other subtypes. The comparison of the distribution of cancer subtypes between migrants and US-born Asians may provide insights into factors associated with migration that may predict the subtype of cancer that occurs. In a study of cancers of the uterus, US-born Asian women were more likely to be diagnosed with type I cancers, which are mainly low-grade endometrioid adenocarcinomas, and are thought to be associated with unopposed estrogen stimulation, whereas type II cancers are linked to genetic predisposition [41]. These findings suggest that adoption of the Western lifestyle among US-born Asians may be an explanation.

In another study, a comparison of breast cancer subtypes (estrogen/progesterone/epidermal growth factor receptor 2 (ER/PR/HER2)) pointed to differences in subtype distribution by specific Asian ethnic populations, including higher odds of HER2-positive breast cancer subtypes among Korean and other Asian subgroups compared to non-Hispanic White women [42]. Migrant studies may help determine if these differences are due to genetic and/or environmental factors.

Case-Control Study Design

Analytic epidemiologic studies such as case-control studies are necessary to follow-up clues that are suggested by descriptive studies. The case-control study involves a comparison of cases (i.e., those who have the disease of interest) with controls (i.e., those individuals selected to be comparable to the cases but who do not have the disease in question). The goal is to retrospectively assess the differences in exposures of putative risk factors of interest between each of the two groups of individuals, in order to determine if a relationship exists between a risk factor and the disease. This study design has several advantages and disadvantages [43]. In comparison to most cohort studies, it can be conducted relatively quickly, involves fewer subjects, and is less expensive. It can be appropriate to study rare outcomes with longer latency such as cancer, and multiple risk factors or exposures can be studied in association to the outcome of interest. However, drawbacks include finding the appropriate control group, difficulty in validating exposure histories that are based on self-report, and inability to measure all potential confounding variables. Rates of disease in the exposed and unexposed groups cannot be determined. Perhaps of most concern is the possibility of recall bias, where cases may tend to report exposures in more detail than do controls, or they may selectively recall exposures that they think may be related to their disease. When both cases and controls are equally likely to under or overestimate their exposure history, the effect is for the resulting odds ratio to be biased toward the null, and thus the study would be less likely to detect an effect due to the exposure, especially when it is small.

To date, most of the case-control studies of cancer among Asian Americans have been conducted in California or Hawaii where there are existing population-based registries to allow the identification of suitable cases. Identifying suitable control subjects of the same Asian ethnic population remains a challenge in these studies.

The number of cases of a specific Asian ethnic group may be limited in a single geographic area in the USA, and thus recruitment from multiple geographic areas may be necessary.

Despite these challenges, most of the analytic studies on cancer in Asian Americans have been case-control studies, including Japanese, Chinese, or Filipinos but few other Asian ethnic groups. For example, in a series of case-control studies of breast, colorectal, endometrial, gastric, and lung cancers in Hawaii, risk factor prevalence and risk associations between Japanese Americans were compared to other race-ethnic groups in Hawaii [44–48]. To better understand the role of diet and physical activity in the etiology of colorectal cancer, a case-control study was conducted among Chinese in North America and Chinese in China. Sedentary lifestyle, high body mass index, and a high-fat Western diet were major risk factors of colorectal cancer in Chinese Americans, and there were noted differences in risk factor prevalence between Chinese in North America and those in China [49]. A study of prostate cancer among Chinese and Japanese Americans, a low-risk group, allowed the comparison of risk factor prevalence and risk association in Asian Americans with Whites and African Americans who are at intermediate and high risk of prostate cancer, respectively [50]. In a study of breast cancer among Chinese, Japanese, and Filipino women in Hawaii, San Francisco, and Los Angeles County that examined risk factor associations in relation to birth place and history of migration [51], age of menarche, nulliparity, and delay in childbirth, and low soy intake were significant breast cancer risk factors, and the higher prevalence of the at-risk lifestyle factors among Asians in the US compared to their counterparts in Asia is likely contributions to the rising incidence of breast cancer in Asian-American women [52, 53]. A study of breast cancer among Chinese, Japanese, and Filipinos in Los Angeles County allowed the comparison of risk factors separately in the three Asian ethnic groups [54, 55]. Lifetime regular alcohol intake was significantly higher in US-born women, most of whom were Japanese Americans, than in non-US-born Asian-American women, and breast cancer risk was found to increase with increasing alcohol intake among US-born Asian-American women. Since this is a modifiable risk factor, these findings may help prevent the development of breast cancer in this population.

Cohort Study

The cohort study is the ideal type of analytic study in which a population (selected prior to disease onset) is surveyed to determine exposure status and then is followed over time to identify members who develop the disease of interest. Multiple outcomes can be assessed, and incidence rates for disease in exposed and unexposed groups can be determined. In some cohorts, specific exposed and unexposed populations are selected for follow-up, while, in others, all members of specific population may be surveyed for multiple exposures and then followed over time. The prospective cohort involves following a large number of individuals over many years to monitor exposures and development of a sufficient number of outcomes for

study. It can be very expensive and withdrawals and loss to follow-up may occur. If loss to follow-up is due to factors associated with outcomes, it can result in selection bias. For example, if immigrant populations returned home when ill, their outcome status may not be recorded, while nonmigrant (or longer-term migrant) populations may no longer leave the USA if they became ill and thus would have more adverse outcomes recorded as a result.

Very few cohort studies of cancer in Asian Americans have been conducted. To our knowledge, the study of Japanese men in Hawaii was the first such study. As part of the Honolulu Heart Study, 8006 men of Japanese ancestry were enrolled in a cohort study [56]. From 1971 to 1975, 6860 of the men were examined again, and blood samples were obtained for measurement of serum cholesterol and other biomarkers. Associations of various lifestyle factors and biomarkers and risk of stomach, lung, colorectal, prostate, and other cancers have been published from this seminal work [57]. A more recent cohort, the Multiethnic Cohort (MEC) study, has been designed to assess ethnic differences in risk factors that may be related to cancer and other disease endpoints [58]. Japanese Americans are one of five race-ethnic groups (African American, Latino, Hawaiians, non-Hispanic whites) included in the MEC. This cohort has allowed the investigation of lifestyle factors, genetic susceptibility, and risk of multiple cancers in Japanese Americans compared to other racial/ethnic groups. Results from this cohort are highlighted in many of the subsequent chapters.

Summary

Asian Americans represent an informative group to study lifestyle and environmental factors related to cancer risk because of their large-scale migration from countries of higher or lower cancer rates (depending on the cancer site) to the USA over time. By 2010, there were over 17 million Asian Americans, and their numbers grew by 46 % between 2000 and 2010 compared to a 9.7 % increase in the US population as a whole. This chapter has provided an overview of issues to consider when using different study designs to assess the role that migration may play in affecting cancer risk. For example, when comparing incidence rates between migrants and their country of origin (or between subgroups within the USA), the quality of numerator and denominator data and the matching of definitions of Asian ethnicity between data sources are highly important. Birthplace is a critical variable in the assessment of the role that timing of exposures may play in cancer risk. Ecological study designs are limited in that they do not obtain individual exposure history, but they are relatively quick and inexpensive studies to conduct and provide important clues regarding cancers that are most affected by change in lifestyle and environment. Analytic studies including case-control and cohort designs are needed to further investigate clues suggested by ecologic and descriptive studies. Many insights have been gained regarding cancer etiology from case-control and cohort studies of Asian populations. While limitations exist in studies involving migrants, such as

concerns that Asian Americans may not be genetically identical to their counterparts in the countries of origin due to the increasing numbers of Asians reporting more than one race in the US Census, the use of migrants in observational studies has provided many insights into cancer risk, and these findings are summarized in the following chapters for specific subgroups.

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Cancer Incidence and Mortality Patterns Among Chinese Americans

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Abstract Chinese is the largest Asian ethnic group in the USA with four million individuals accounting for 23.1 % of the total Asian Americans and 1.3 % of the total US population. Given its large population size and the long history of migration to many countries throughout the world, Chinese immigrants are a valuable resource for epidemiologic investigations of cancer and other diseases to identify environmental and lifestyle risk factors and to understand the interactions between genetics and environment in disease etiology. Using data from population-based cancer registries, this chapter examines the sex-specific cancer incidence and mortality rates of common cancers among Chinese Americans and their relative risks as compared to whites or non-Hispanic (NH) whites. Comparisons of incidence trends and age-specific patterns by cancer type between Chinese Americans and Chinese in China are also provided. For most of the cancers examined, Chinese Americans have lower incidence and mortality rates than the NH whites, but they have substantially higher risk for nasopharyngeal, liver, and stomach cancers and slightly higher risk of gallbladder cancer. Except for lung and colorectal cancer, Chinese Americans display intermediate-risk level between the US whites and Chinese in China. The cancer experience of Chinese Americans highlights the significance of environmental and lifestyle factors in cancer development.

Keywords Chinese American • Cancer • Immigrant • Incidence • Mortality • Trend • Rate ratio

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History of Chinese Migration to the USA

Chinese immigration to the USA dates back to the 1820s, according to the official US government records [1]. The first wave of a significant number of Chinese immigrants to the USA arrived in California during the 1850s to join the Gold Rush [2]. More came when the Central Pacific Railroad recruited large number of laborers throughout the 1860s until the railroad's completion in 1869. The number of Chinese seeking permanent legal resident status rose from 32 in the 1840s to 133,139 in the 1870s [1]. The early Chinese immigrants were mostly young uneducated men from the Guangdong province in southern China [3]. Demographic data on Chinese in the USA have been collected since the 1860 US population census.

The Chinese Exclusion Act of 1882, as a result of increasing anti-Chinese racial tension coupled with economic depression that started in 1873, effectively ended the immigration of Chinese laborers. The number of Chinese in the USA gradually decreased as many of the immigrants returned home or left for more hospitable places. However, the repeal of the Chinese Exclusion Act of 1943 granted naturalization rights to foreign-born Chinese and established an immigration quota for China. The Immigration and Nationality Act of 1965 abolished racial discrimination in immigration law, beginning a period of renewed Chinese immigration to the USA. The economic reform and Open Door Policy adopted by the Chinese government in the late 1970s resulted in record numbers of young well-educated Chinese students coming to the USA seeking higher education. As the Chinese economy grew, increasing numbers of Chinese emigrate to the USA through business, investment, family reunification, and a variety of venues, besides education. In addition to mainland China, Chinese immigrants may also originate from Taiwan, Hong Kong, Macau, and other regions of the world.

According to the 2010 census, there were 3.5 million Chinese of single race and 0.5 million of multirace living in the USA [4]. Chinese is the largest detailed Asian American group, accounting for 23.1 % of the total Asian Americans and 1.3 % of the total US population. After Spanish, Chinese was the most widely spoken non-English language in the country, with 2.9 million people speaking it at home in 2011 [5]. The number of Chinese speakers in the USA has more than quadrupled since 1980. Among the nation's Chinese speakers, only 44 % reported speaking English "very well." The Chinese-speaking population was found heavily concentrated in the New York, Los Angeles, and San Francisco metro areas [5]. The number of Chinese speakers includes those speaking any of the many Chinese dialects, such as Mandarin and Cantonese.

In comparison to other Asian Americans and the white population, Chinese Americans generally have lower unemployment rate (4.4 % unemployment rate, as compared to 5.2 % for all Asians and 6.5 % for whites), higher median earnings (median weekly earnings in 2013 of $1093, as compared to $987 for Asian Americans and Pacific Islanders (AAPIs) and $865 for whites), higher levels of education (56.8 % of age 25 and older are college graduate, as compared to 53.4 % of all Asians and 31.9 % of whites), but also higher poverty rate (15.2 % during 2000–2012, as compared to 13.0 % for AAPIs and 13.6 % for whites) [6].

History of Studying Cancer Among Chinese Americans

With its large population size and the long history of migration to many countries throughout the world, Chinese immigrants have been recognized as a valuable resource for epidemiologic investigations of cancer and other diseases to identify environmental and behavioral risk factors and to understand the interactions between genetics and environment in disease etiology.

The first systematic national study of cancer occurrence among Chinese Americans was published by Smith and colleagues in 1956 using the cancer mortality data of 1949–1952 [7]. It documented the different cancer risk profiles of Chinese in the USA as compared to the US whites, confirming findings from the few analyses of clinical and autopsy materials reported prior to that time [8]. Studies of cancer patterns among Chinese Americans in the 1950s and 1960s relied on cancer mortality data that were collected consistently through vital statistics with birthplace information of the deceased [7–9]. Those early mortality-based studies were limited by the relatively small number of Chinese deaths in the older age groups and showed the typical male dominance and origin of the early Chinese migrants from southern China [10].

In contrast to cancer mortality data that capture deaths caused by a specific cancer, cancer incidence data record new cases of cancer diagnosis in a given year. Incidence data provide information that is not captured in mortality data. The National Cancer Institute (NCI) conducted three National Cancer Surveys at three points in time, 1937–1939, 1947–1948, and 1969–1971, providing estimates of cancer incidence rates and establishing the field of modern cancer epidemiology [11]. However, cancer incidence data were not systematically collected in the USA until 1973 by the Surveillance, Epidemiology, and End Results (SEER) program that was established by the NCI, as a result of the National Cancer Act of 1971 [12]. Information specific to cancer incidence among Chinese Americans was not systematically available in a meaningful volume until the 1970s through the population-based SEER registries.

The SEER program and its registries have consistently contributed data to the international cancer statistical reports, such as Cancer Incidence in Five Continents (CI5) series that provide internationally comparable cancer incidence information among countries and populations of the world [13]. Although the SEER registries collect detailed racial/ethnic information on cancer patients, the lack of official annual population estimates with corresponding racial/ethnic classification limited the examination of cancer risk specifically among Chinese and other disaggregated Asian American ethnic groups in the SEER program as a whole. However, SEER registries in San Francisco and Los Angeles have had long tradition in monitoring cancer incidence among the large Chinese American communities in their catchment areas.

The SEER registry in Los Angeles, the Los Angeles Cancer Surveillance Program (LACSP), is a population-based cancer registry established in 1972 at the University of Southern California and joined the SEER in 1992. The LACSP is located in the most populous and racially/ethnically diverse county in the country, the Los Angeles County, California. According to the 2010 population census,

nearly 0.4 million Chinese lived in the catchment area of LACSP consisting of 12 % of the national total of Chinese Americans. LACSP is the only US registry that has continuously contributed to CI5 cancer incidence data of Chinese and other Asian Americans in Los Angeles, making the comparison of cancer incidence trends between Asians living in the USA and elsewhere possible.

As a result of the growing Asian American population, the increasing interest in and awareness of the heterogeneous cancer burdens among Asian subgroups; SEER has made significant strides in developing necessary population estimates and reporting cancer incidence and mortality statistics among the fast-growing AAPI populations [14–16].

Data Sources and Methods

For this chapter, we utilized a variety of data sources to present a contemporary overview of cancer risk patterns among Chinese Americans. These data sources include recently published information based on SEER registry data, special data files from SEER program, international cancer data in the CI5 series published by the International Association of Cancer Registries (IACR), and up-to-date Chinese-specific cancer information from the LACSP.

Previously Published SEER Data

Using SEER data of 14 registries from 1998 to 2002, Miller et al. (2008) reported the age-adjusted (2000 US standard population) overall and cancer site-specific incidence and mortality rates among specific AAPI populations in the USA in comparison with those of NH whites [14]. We extracted the Chinese-specific case counts and age-adjusted rates by sex and cancer site, along with those of NH whites, and compiled for incidence (Table 1) and mortality (Table 2). The cancer sites in each table are sorted and ranked by the rates from high to low. We also calculated the rate

Table 1 Site-specific cancer incidence counts and age-adjusted (2000 US standard) rates and rate ratios by sex among Chinese Americans and NH Whites, SEER registries, 1998–2002

	Chinese American		NH White		Incidence
	Cases	Rate	Cases	Rate	Rate ratio
Men					
All sites	9,175	348.8	649,731	587.0	0.6
Prostate	2,209	84.8	189,678	170.0	0.5
Colorectal	1,400	54.0	71,656	65.6	0.8
Lung	1,340	53.0	98,625	89.2	0.6
Liver	666	24.0	7,445	6.7	3.6

Table 1 (continued)

	Chinese American		NH White		Incidence
	Cases	Rate	Cases	Rate	Rate ratio
Stomach	461	18.3	10,797	9.9	1.8
Bladder	389	15.7	46,682	43.0	0.4
Non-Hodgkin's Lymphoma	401	14.8	27,294	24.6	0.6
Pancreas	243	9.8	14,220	13.0	0.8
Nasopharynx	277	8.9	717	0.6	14.8
Leukemia	231	8.7	18,718	17.3	0.5
Kidney	192	7.2	19,671	17.5	0.4
Oral	166	6.2	18,462	16.2	0.4
Esophagus	124	4.5	9,079	8.1	0.6
Brain and nervous system	123	4.3	9,893	8.9	0.5
Thyroid	96	3.2	4,996	4.3	0.7
Larynx	78	3.0	8,101	7.1	0.4
Myeloma	74	2.7	7,264	6.6	0.4
Testis	57	1.7	7,816	7.0	0.2
Hodgkin's Lymphoma	40	1.3	3,833	3.5	0.4
Melanoma	35	1.2	32,981	29.3	0.0
Gallbladder	24	0.9	768	0.7	1.3
Women					
All sites	8,817	270.4	617,158	448.5	0.6
Breast	2,652	77.6	195,231	145.2	0.5
Colorectal	1,257	40.2	70,298	47.6	0.8
Lung	923	29.7	83,387	59.0	0.5
Corpus uteri	406	12	35,224	26.0	0.5
Stomach	344	11.1	6,430	4.3	2.6
Thyroid	358	10.0	14,103	11.8	0.8
Ovary	335	10.0	20,736	15.3	0.7
Non-Hodgkin's Lymphoma	316	10.0	24,177	17.2	0.6
Liver	258	8.2	3,689	2.6	3.2
Pancreas	209	6.8	14,520	9.8	0.7
Leukemia	188	5.9	13,800	10.0	0.6
Cervix uteri	193	5.6	9,930	8.1	0.7
Bladder	133	4.4	15,480	10.6	0.4
Kidney	126	4.0	11,787	8.5	0.5
Oral	119	3.6	8,996	6.5	0.6
Nasopharynx	125	3.5	315	0.2	17.5
Brain and nervous system	90	2.7	7,911	6.2	0.4
Myeloma	76	2.5	5,986	4.1	0.6
Gallbladder	41	1.3	1,754	1.2	1.1
Esophagus	32	1.0	3,067	2.1	0.5
Melanoma	32	1.0	24,455	19.3	0.1
Hodgkin's Lymphoma	22	0.7	3,348	2.9	0.2

Source of data: Miller AB et al., Cancer Causes Control 2008; 19:227–256. Appendix 1.

Table 2 Site-specific cancer mortality counts and age-adjusted (2000 US standard) rates and rate ratios by sex among Chinese Americans and NH Whites, SEER registries, 1998–2002

	Chinese American		NH White		Mortality
	Deaths	Rate	Deaths	Rate	Rate ratio
Men					
All sites	5,807	167.8	349,031	241.3	0.7
Lung	1,603	47.0	106,623	72.2	0.7
Liver	761	20.3	9,091	6.1	3.3
Colorectal	657	19.5	35,261	24.6	0.8
Stomach	404	11.7	8,395	5.8	2.0
Prostate	292	10.4	37,137	27.7	0.4
Pancreas	291	8.5	18,399	12.6	0.7
Leukemia	216	6.1	15,119	10.6	0.6
Non-Hodgkin's Lymphoma	205	6.0	15,368	10.6	0.6
Nasopharynx	192	4.5	383	0.3	15.0
Esophagus	134	3.8	11,536	7.7	0.5
Bladder	109	3.6	11,682	8.4	0.4
Kidney	102	2.9	9,135	6.2	0.5
Brain and nervous system	94	2.5	9,477	6.3	0.4
Oral	65	1.8	5,605	3.7	0.5
Myeloma	58	1.7	6,454	4.5	0.4
Larynx	33	0.9	3,316	2.2	0.4
Gallbladder	24	0.7	683	0.5	1.4
Melanoma	21	0.6	6,998	4.7	0.1
Women					
All sites	4,537	107.7	341,117	171.7	0.6
Lung	984	23.8	87,084	44.5	0.5
Colorectal	524	12.8	36,430	17.3	0.7
Breast	564	12.3	53,534	27.8	0.4
Liver	308	7.4	5,546	2.7	2.7
Stomach	305	7.3	5,930	2.8	2.6
Pancreas	273	6.7	19,471	9.5	0.7
Ovary	229	5.2	18,962	9.8	0.5
Non-Hodgkin's Lymphoma	172	4.1	14,024	6.8	0.6
Leukemia	132	3.1	12,132	6.0	0.5
Cervix uteri	93	2.2	4,206	2.4	0.9
Corpus uteri	89	2.1	8,368	4.2	0.5
Brain and nervous system	81	1.8	7,602	4.2	0.4
Kidney	63	1.6	5,611	2.8	0.6
Nasopharynx	65	1.4	245	0.1	14.0
Myeloma	49	1.2	5,948	2.9	0.4
Esophagus	45	1.1	3,766	1.8	0.6
Bladder	38	1.0	5,228	2.4	0.4
Oral	34	0.8	3,142	1.6	0.5
Gallbladder	28	0.7	1,675	0.8	0.9
Thyroid	20	0.5	917	0.5	1.0

Source of data: Miller AB et al., Cancer Causes Control 2008; 19:227–256. Appendix 2.

ratio in each table of the Chinese rate in relation to that of the NH whites by cancer site. In Fig. 1, we combined the rate ratios from Tables 1 and 2 by sex to illustrate the differences or similarities in relative cancer risk between Chinese and NH whites by cancer site using both incidence and mortality data.

Updated SEER Data

Using SEER data of 13 registries from 1990 to 2008, Gomez et al. (2013) published the trends in age-adjusted (2000 US standard population) cancer incidence rates for disaggregated Asian American subgroups, including Chinese and NH whites [15]. While they provided more recent data than Miller et al., it only included the top five cancer sites in each Asian-American subgroup. Taking advantage of the availability of the same database that produced the Gomez et al. report [17], for this chapter, we calculated the age-adjusted (2000 US standard population) cancer incidence rates for Chinese Americans during the period of 2004–2008 for the same cancer sites included in the Miller et al. 2008 article by sex, along with those of NH whites for comparison purposes. The results are shown in Table 3. The rate ratios showing the relative risk of Chinese Americans in relation to NH whites are also provided in Table 3. Because the Miller et al. 2008 study and Gomez et al. 2013 study included different time periods and slightly different SEER registries, the incidence rates generated by the two databases are not directly comparable. Nonetheless, in Fig. 2, we compared the incidence-based rate ratios from these two papers to examine any changes in cancer risk patterns over time from 1998–2002 to 2004–2008.

To provide more recent cancer trends, we used recently released data from SEER to update the cancer incidence rates published in the CI5 series for white population in SEER nine registries, and data from LACSP for Chinese Americans in Los Angeles County. We used the same 1960 world standard population, as used in CI5, and extended the age-adjusted incidence rates to 2012 by sex, year, and cancer site, in order to be compared with the trends data from China as published in CI5.

International Cancer Data

To provide a comparison of cancer risk between Chinese Americans and Chinese in China, we utilized the data published in the CI5. The CI5 series of monographs are results of long-standing collaboration between the International Agency for Research on Cancer (IARC) and the IACR. The CI5 is published every 5 years and is a valuable resource for cancer incidence around the world. The CI5 databases provide access to detailed information on the incidence of cancer as recorded and reported by cancer registries (regional or national) worldwide. The most recent CI5 Volume X covers the time period of 2003–2007, containing average age-specific and age-adjusted (1960 world standard population) site-specific cancer incidence rates by sex for each reporting registry/population [18]. CI5 also offers online

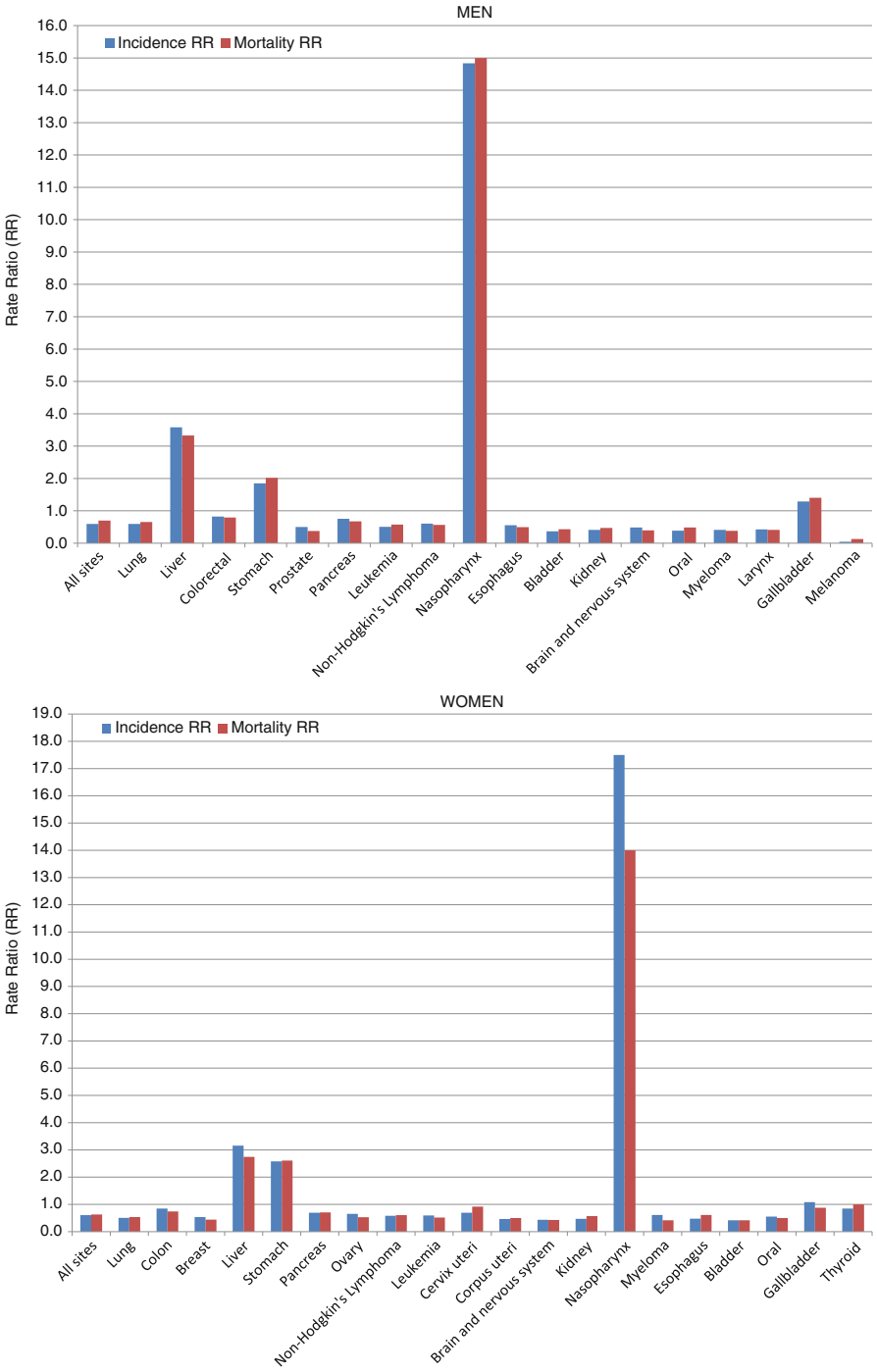

Fig. 1 Comparison of incidence-based rate ratios and mortality-based rate ratios between Chinese Americans and NH whites by cancer site and sex, 1998–2002 (as shown in Tables 1 and 2)

Table 3 Site-specific cancer incidence counts and age-adjusted (2000 US standard) rates and rate ratios by sex among Chinese Americans and NH Whites, SEER registries, 2004–2008

	Chinese American		NH White		Incidence
	Cases	Rate	Cases	Rate	Rate ratio
Men					
All sites	10,705	320.9	572,704	560.2	0.6
Prostate	2,488	74.9	162,504	154.7	0.5
Lung and bronchus	1,678	52.0	74,729	74.0	0.7
Colon and rectum	1,410	42.1	54,752	54.0	0.8
Liver	845	24.1	8,301	7.7	3.1
Stomach	524	16.3	8,832	8.7	1.9
Urinary bladder	506	16.0	43,592	43.8	0.4
Non-Hodgkin Lymphoma	505	14.9	26,059	25.8	0.6
Oral cavity and pharynx	497	13.6	18,112	17.0	0.8
Pancreas	301	9.3	14,086	13.8	0.7
Kidney and renal pelvis	290	8.5	20,888	20.1	0.4
Leukemia	267	7.9	17,055	17.3	0.5
Nasopharynx	282	7.4	590	0.6	12.3
Esophagus	144	4.5	8,722	8.4	0.5
Brain and other nervous system	132	3.7	8,990	9.0	0.4
Thyroid	138	3.6	6,676	6.5	0.6
Myeloma	99	3.1	7,035	6.9	0.4
Larynx	58	1.8	6,050	5.8	0.3
Testis	71	1.7	6,834	7.5	0.2
Melanoma of the skin	43	1.2	37,884	37.1	0.0
Gallbladder	36	1.2	696	0.7	1.7
Hodgkin Lymphoma	34	1.0	3,446	3.6	0.3
Women					
All Sites	11,103	263.4	538,349	440.0	0.6
Breast	3,477	78.8	162,591	135.3	0.6
Colon and rectum	1,447	35.7	53,352	40.6	0.9
Lung and bronchus	1,207	29.9	72,103	56.6	0.5
Corpus uteri	621	14.3	32,452	26.3	0.5
Thyroid	549	12.2	18,712	18.2	0.7
Non-Hodgkin Lymphoma	387	9.4	21,939	17.5	0.5
Stomach	366	9.1	5,058	3.8	2.4
Ovary	352	8.0	17,035	13.9	0.6
Liver	311	7.8	2,898	2.3	3.4
Pancreas	289	7.3	14,013	10.5	0.7
Oral cavity and pharynx	245	5.7	8,119	6.6	0.9
Leukemia	214	5.3	12,586	10.3	0.5
Kidney and renal pelvis	200	4.9	12,288	10.0	0.5
Cervix uteri	209	4.6	6,968	6.8	0.7
Urinary bladder	169	4.3	13,895	10.5	0.4

(continued)

Table 3 (continued)

	Chinese American		NH White		Incidence
	Cases	Rate	Cases	Rate	Rate ratio
Nasopharynx	127	2.8	289	0.2	14.0
Brain and other nervous system	104	2.5	7,006	6.3	0.4
Myeloma	77	1.9	5,249	4.0	0.5
Gallbladder	49	1.2	1,515	1.1	1.1
Esophagus	48	1.2	2,576	2.0	0.6
Melanoma of the skin	43	1.0	27,020	24.3	0.0
Hodgkin Lymphoma	34	0.8	2,996	3.1	0.3

Source of data: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence—SEER 11, plus Greater CA and NJ, Nov 2010 Sub (1990–2008) detailed API plus White Non-Hispanic—projected from populations, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released June 2011 (updated 10/28/2011), based on the November 2010 submission

analysis tools, CI5plus, for time trends up to 2007 and age-specific curves by time period for selected cancer registries/populations [19]. The LACSP is the only US registry that has consistently reported Chinese American cancer information to CI5 and thus included in the CI5plus. Among the three Chinese cancer registries included in CI5plus, we chose as a comparison the data from China's Shanghai registry for its long history of participation in CI5, large population size, representativeness of urban China, and high-quality data.

We downloaded from CI5plus the China-Shanghai registry annual age-adjusted (1960 world standard population) incidence rates by sex and cancer site for 1988–2007, in order to be compared with current data for whites from SEER (nine registries) and Chinese Americans from LACSP (Figs. 3 and 4). Figures 3 and 4 contain the comparisons of age-specific incidence rates by sex and cancer site for 2003–2007 between Chinese in Los Angeles and Chinese in Shanghai with reference to US whites, as downloaded from the CI5plus online analysis tool.

Cancer Incidence and Mortality Patterns Among Chinese Americans

Overview

Chinese Americans, as compared to NH whites, have lower risk in both cancer incidence (Tables 1 and 3) and mortality (Table 2) for all cancers combined and for many specific cancer sites, regardless of sex. However, their risk for cancers of the nasopharynx, liver, and stomach is noticeably much higher than the NH whites. The relative risk patterns by cancer site between Chinese Americans and NH whites are quite similar in either incidence or mortality data (Fig. 1).

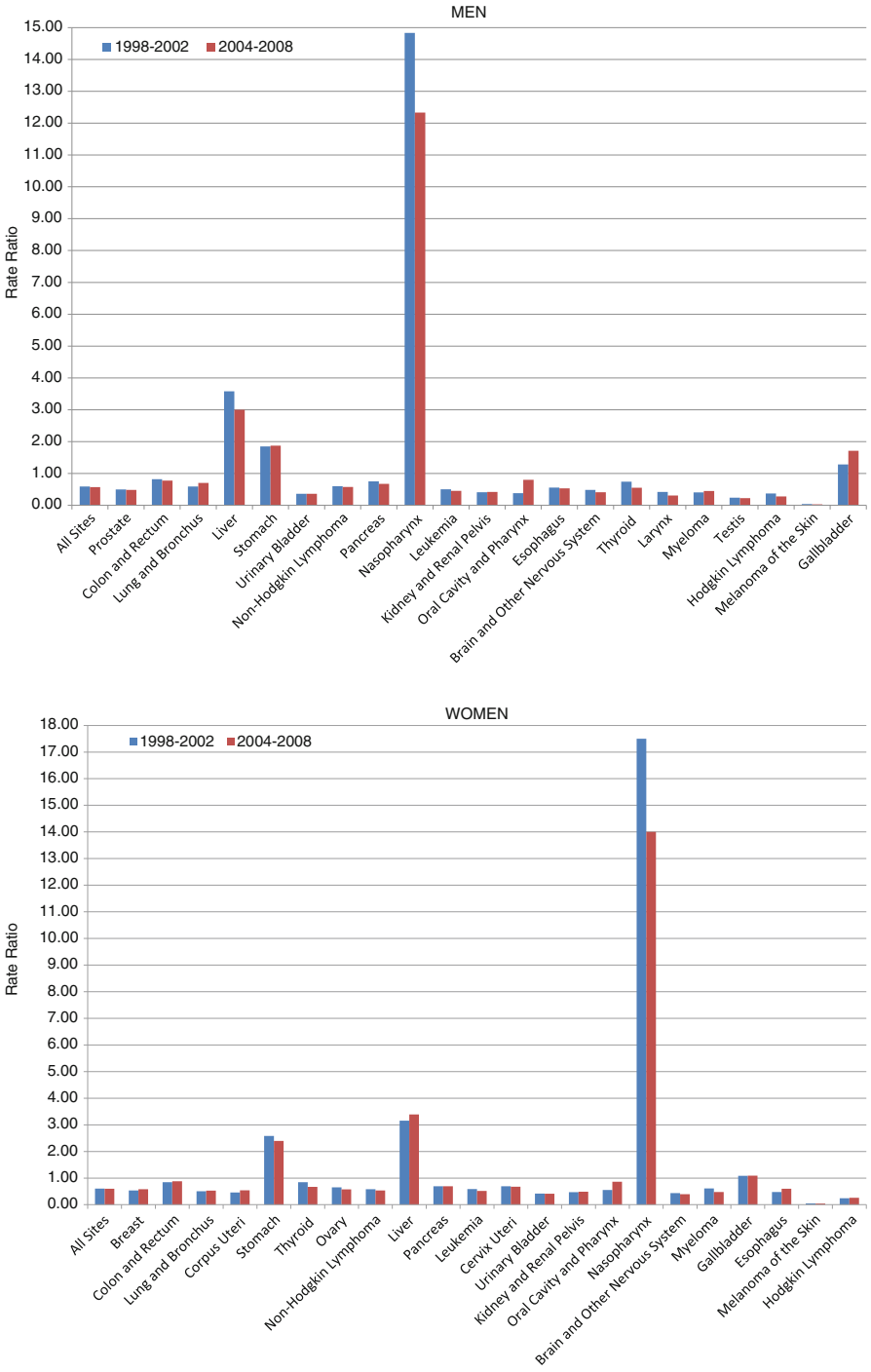

Fig. 2 Comparison of incidence-based rate ratios between Chinese Americans and NH whites by cancer site and sex over time, 1998–2002 vs. 2004–2008 (as shown in Tables 1 and 3)

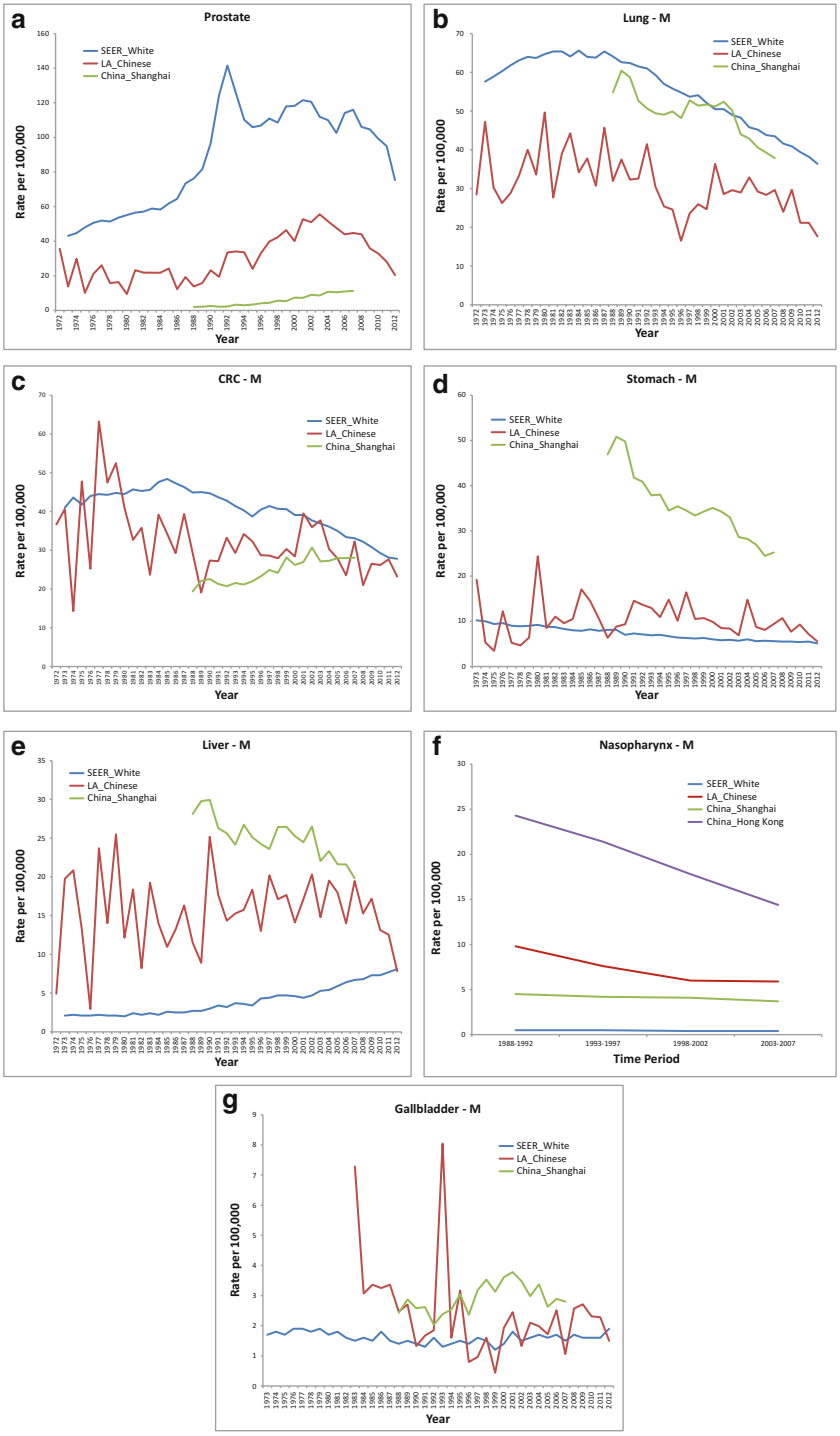

Fig. 3 Time trends of age-adjusted (world population) incidence rates by cancer site among US whites, Chinese in Los Angeles, and Chinese in China-Shanghai, men

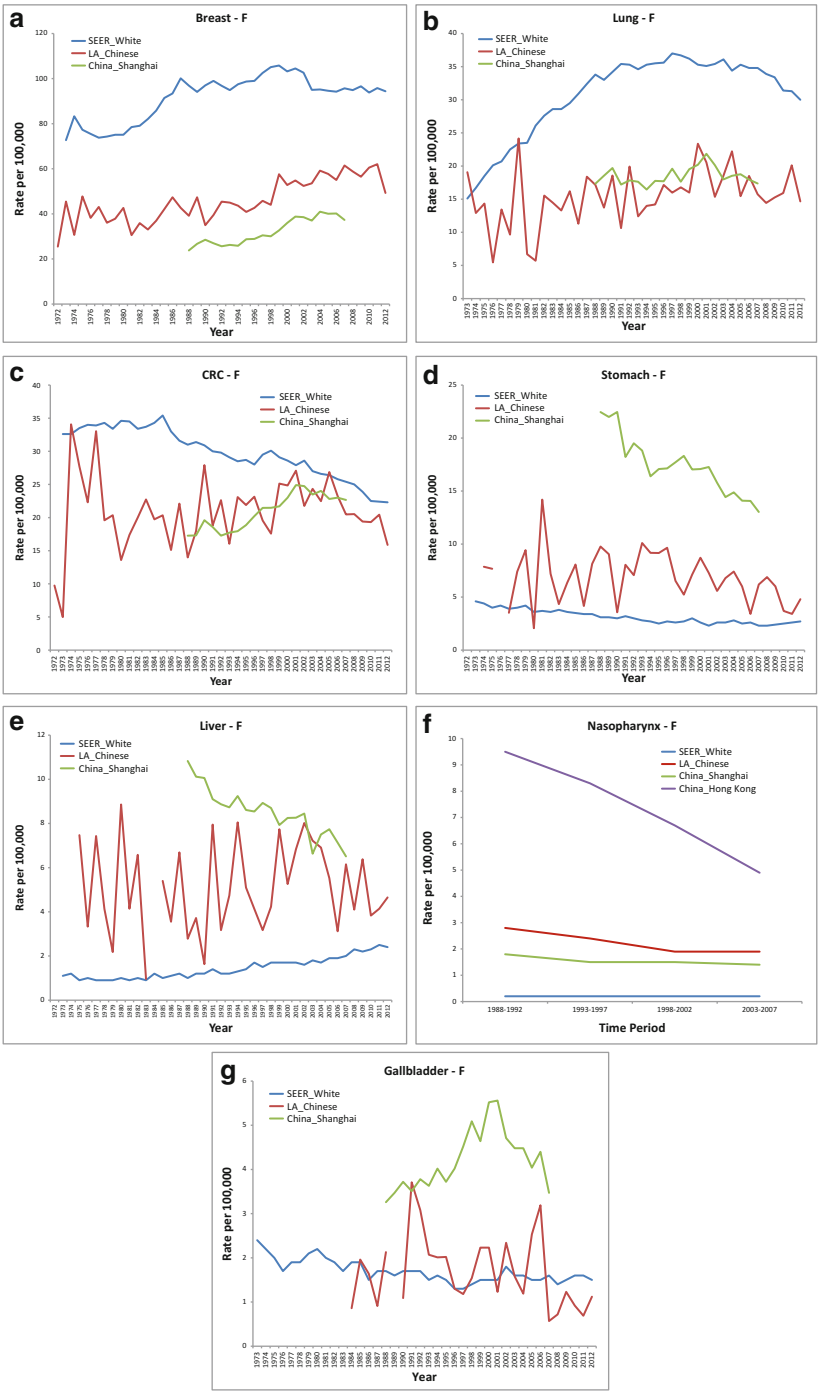

Fig. 4 Time trends of age-adjusted (world population) incidence rates by cancer site among US whites, Chinese in Los Angeles, and Chinese in China-Shanghai, women

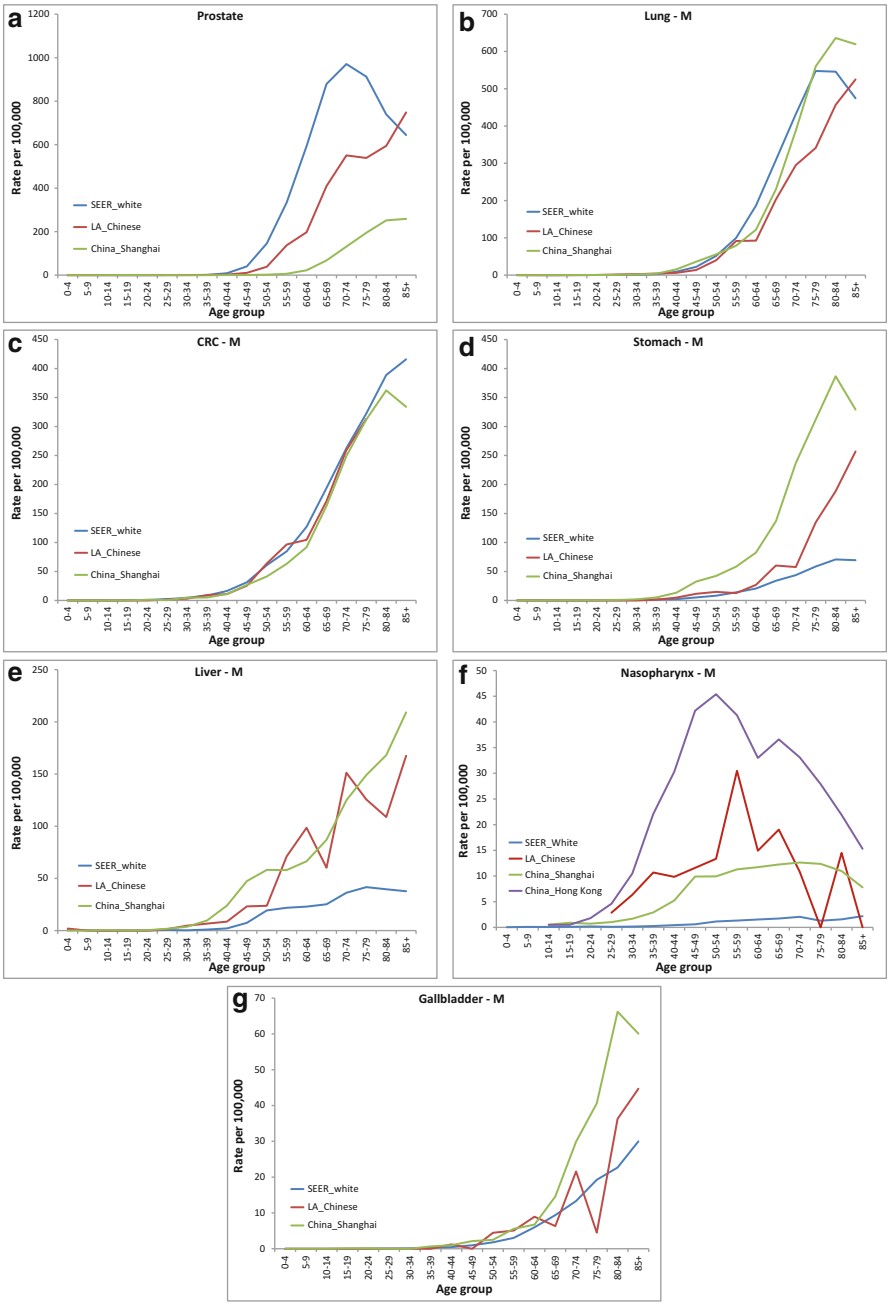

Fig. 5 Age-specific incidence rates by cancer site among US whites, Chinese in Los Angeles, and Chinese in China-Shanghai, men, 2003–2007

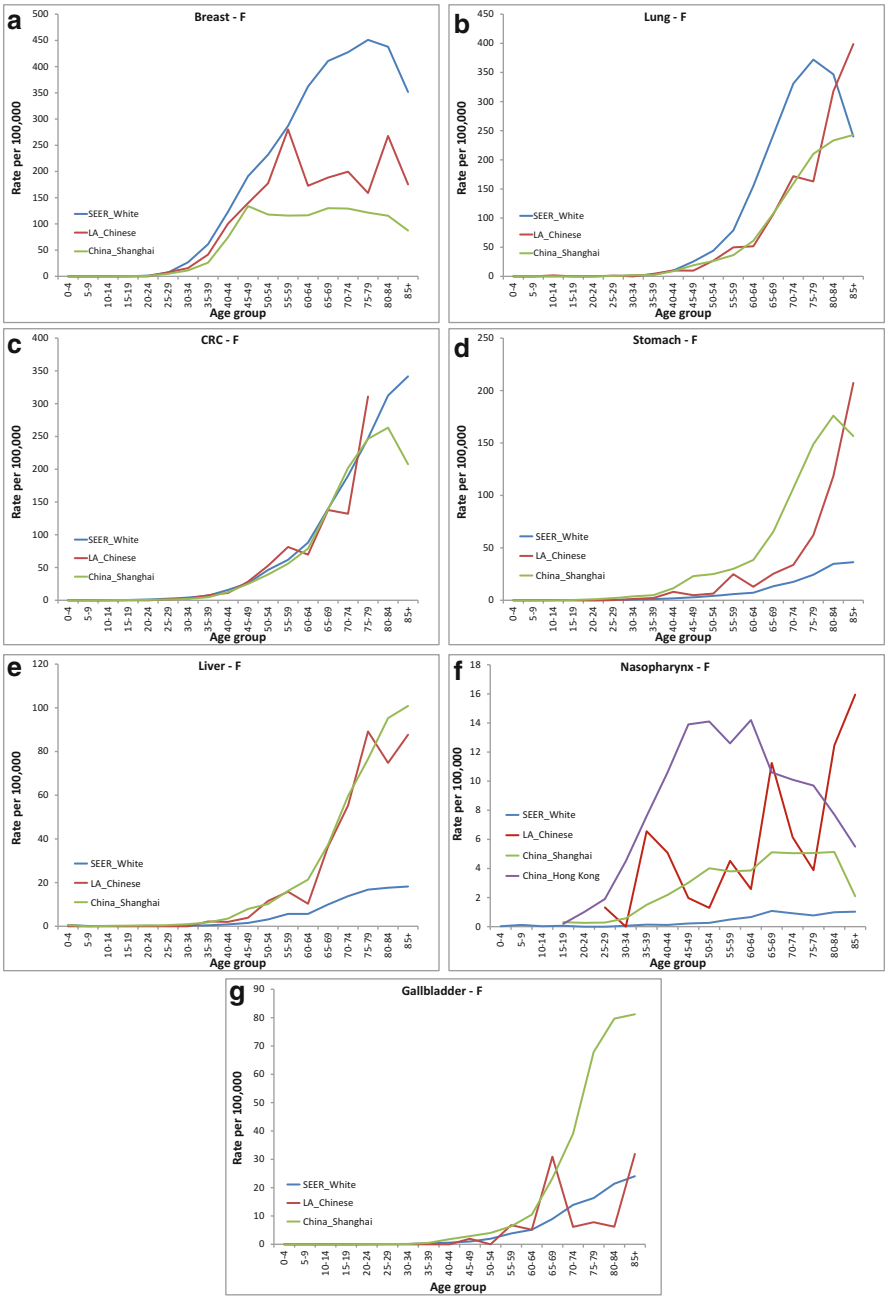

Fig. 6 Age-specific incidence rates by cancer site among US whites, Chinese in Los Angeles, and Chinese in China-Shanghai, women, 2003–2007

Incidence

According to the data published by Miller et al. (2008) for 1998–2002 (Table 1) using SEER registry data [14], the age-adjusted (2000 US standard population) incidence rate (AAIR) among Chinese Americans for all sites combined was 348.8/100,000 in men and 270.4/100,000 in women, about 40 % lower than the AAIR of NH white men or women. The top three most common cancer sites among Chinese-American men were cancers of the prostate, colon and rectum, and lung and bronchus, which was similar to NH white men but with 20–50 % lower AAIRs. The most common cancer among Chinese-American women was breast, followed by colon and rectum and lung. As in men, Chinese-American women also share the same top three most common cancer sites with their NH white counterparts, but with lower risk (50 % lower for breast, 20 % lower for colorectal, and 50 % lower for lung).

In contrast, Chinese Americans had higher AAIRs than NH whites for nasopharyngeal cancer (NPC) (14.8 times in men and 17.5 times in women), liver cancer (3.6 times in men and 3.2 times in women), stomach cancer (1.8 times in men and 2.6 times in women), and gallbladder cancer (1.3 times in men and 1.1 times in women) (Table 1).

More recent SEER data for Chinese Americans during 2004–2008 showed slight decrease in AAIR overall and some changes in site-specific AAIRs (either increasing or decreasing) (Table 3). But due to the differences in cancer and population data between the two different studies, the AAIR estimates are not directly comparable. However, the rate ratios between Chinese Americans and NH whites by sex and cancer site for 2004–2008 reveal very similar patterns as for 1998–2002 (Fig. 2).

Mortality

Cancer of the lung and bronchus is the deadliest for both Chinese Americans and NH whites in both men and women (Table 2), but the age-adjusted (2000 US standard population) mortality rate (AAMR) among Chinese-American men (47.0/100,000) is about 30 % lower than the rate among NH white men (72.2/100,000), while the AAMR for Chinese-American women (23.8/100,000) is about 50 % lower than that of the NH white women (44.5/100,000). Similar to NH whites, colorectal, prostate, and breast are among the top five most common causes of cancer deaths in Chinese-Americans. Unlike NH whites, liver and stomach cancer rank among the top five cancers with higher cancer mortality among Chinese-Americans regardless of sex.

Similar to cancer incidence, as compared to NH whites, Chinese Americans have higher mortality due to nasopharyngeal cancer (15.0 times in men and 14.0 in women), liver cancer (3.3 times in men and 2.7 times in women), stomach cancer (2.0 times in men and 2.6 times in women), and gallbladder cancer (1.4 times in men and 0.9 times in women). For the remaining cancer sites, as well as for all cancer sites combined, Chinese Americans have markedly lower AAMR than NH whites.

The sex-site-specific rate ratios in Chinese Americans relative to NH whites based on incidence closely resemble those based on mortality (Fig. 1).

Incidence Trends and Age Patterns

In the following, we examine the age-adjusted (1960 world standard population) incidence trends and age-specific incidence patterns for the top three most common cancers in Chinese Americans, as well as cancers that show higher risk among Chinese Americans than US whites.

Breast Cancer

Breast cancer is the most commonly diagnosed cancer among Chinese-American women (Table 3). Incidence rate among Chinese in LA has been rising since the 1980s (Fig. 4a); current rates are 60 % of that of the US white women. Rates in Chinese-American women are intermediate across age groups as compared to women in Shanghai and US white women. The differences in rates are particularly pronounced in postmenopausal years. Unlike US whites, breast cancer incidence among Chinese Americans plateaued after menopause, similar to the pattern in Shanghai (Fig. 6a).

Increasing breast cancer risk among Chinese-American women has been reported previously [14, 15, 20, 21]. Acculturation and adoption of Western lifestyles among immigrant Chinese and in many developing countries including China are likely to explain the rising incidence [22–25]. Specifically, the fall in number of births, low physical activity level, and obesity were results of urbanization and westernization that are directly linked with the increase in breast cancer risk in China in recent decades [25–27]. The much higher incidence rates for postmenopausal than premenopausal breast cancer among Chinese in LA as compared to Chinese in Shanghai point to the stronger impact of environmental changes associated with immigration and acculturation on postmenopausal disease and support the suggestion that postmenopausal breast cancer risk is modifiable [28–30].

Prostate Cancer

Prostate cancer is the most common cancer diagnosed in Chinese-American men (Table 3). The incidence trend for Chinese men in LA rose throughout the 1990s and peaked around 2003 before the subsequent downward trend started around 2012 returning to the incidence level observed in the 1980s (Fig. 3a). These changes are clearly associated with the FDA approval of the PSA testing in 1986 and subsequent widespread PSA screening for prostate cancer [32]. However, there was about a 10-year delay in the rise and peaking of the incidence rate among Chinese men in LA

as compared to the rates of white men which rose sharply since 1986 and peaked around 2002. Chinese men in Shanghai experienced a steady increasing trend in prostate cancer incidence starting in late 1990. The rise in prostate cancer risk occurred at slightly different ages; rates markedly increased around ages 45–49 among Chinese men in LA, compared to ages 40–45 for white men and ages 55–59 for Chinese men in Shanghai (Fig. 5a). While prostate cancer incidence was highest and peaked at ages 70–74 and then declined in US white men, rates among Chinese men in LA continue to increase with increasing age and surpassed the risk in white men at ages 85+.

The higher prostate cancer risk among Chinese men in LA as compared to Chinese men in Shanghai may be explained, in part, by more widespread PSA screening in the USA [31–33]. Although Western diet (i.e., high calcium, processed meat, milk, and dairy products) has been linked with increased prostate cancer risk [34], while consumption of green tea and soy foods has been associated with decreased prostate cancer risk [35, 36], the evidence for a role of dietary factors in explaining east-west differences in incidence is weak. The consistently lower incidence rate in Chinese American men as compared to white men likely underlines the genetic and etiologic differences between the two populations [37–41].

Lung Cancer

Lung cancer is the second most common cancer among Chinese-American men and third most common cancer among Chinese-American women (Table 3). Lung cancer incidence is lower among Chinese men in LA compared to US white men and Chinese men in Shanghai; all share a similar declining trend in incidence rate (Fig. 3b). Lung cancer risk was lower in Chinese men in LA than US white men across all ages, particularly after age 60 (Fig. 5b). Chinese women in LA and those in Shanghai have comparable rates, which are about half of that of US white women. Rates in all three groups are beginning to decrease (Fig. 4b). The age-specific lung cancer incidence rates are also similar between Chinese women in LA and their counterparts in Shanghai, which are lower than those of US white women, until around 80 years of age (Fig. 6b).

Prevalence of current smokers is low among Chinese Americans with 16.1 % in men and 4.9 % in women, compared to 40.0 % and 26.6 % in US white men and women [42]. Acculturation appeared to have opposite effects on smoking behaviors in immigrant Asian men and women. Smoking rate tends to decrease with acculturation among men but increase with acculturation among women [43], which may partly explain the lower lung cancer risk among Chinese men in LA than Chinese men in Shanghai and the comparable risk level among women between the two locations. Lung cancer incidence in Chinese women appeared to be unusually high given that most were never smokers [44–47]. Besides active smoking, other risk factors, including secondhand smoking, environmental pollution, cooking methods, diet, previous lung diseases, and reproductive and genetic factors, have been implicated [48–57]. The complex risk patterns and disparate trends of lung cancer among subpopulation groups warrant continued surveillance and research among diverse populations [58, 59].

Colorectal Cancer (CRC)

Cancer of the colon and rectum ranks third in Chinese-American men and second among Chinese-American women (Table 3). Compared to NH whites, the risk of developing CRC is about 20 % lower in Chinese-American men and 10 % lower in Chinese-American women (Table 3). With the steady decline in CRC risk among US whites since the 1980s, the risk difference between Chinese Americans and their white counterparts is narrowing in recent years (Figs. 3c and 4c). Chinese in LA and Shanghai and US whites displayed very similar age-specific risk patterns (Figs. 5c and 6c).

Risk of CRC is strongly associated with familial and lifestyle factors [60–64]. Economic development and adoption of Western lifestyle have resulted in the rising incidence of CRC and other cancers in China [65, 66]. Screening has been credited as having considerable impact on the steady reduction in CRC incidence and mortality in the USA since the late 1980s [67]. Differences in access to CRC screening have contributed to the risk disparities among different population groups stratified by racial and socioeconomic characteristics [68–70]. Chinese-Americans are known to underutilize CRC screening [71–73]. Research has shown that education programs specifically designed to address cultural characteristics can significantly improve CRC screening among Chinese-Americans [74].

Stomach Cancer

Stomach cancer is one of the cancers that Chinese-Americans are at higher risk than NH whites; this is particularly striking after age 70 (Figs. 5d and 6d). Chinese-American men and women are 1.9–2.4 times more likely than NH whites to be diagnosed with stomach cancer (Table 3). Stomach cancer incidence rates for Chinese men in LA are about two-thirds lower than rates of Shanghai Chinese men in recent years (Fig. 3d); these differences are observed across all age groups. Risk patterns in women are similar to those in men. Rates in US whites as well as Chinese in LA are declining steadily (Fig. 4d).

The effect of migration on stomach cancer risk reduction among Japanese Americans has been well documented [75–77]. The much lower stomach cancer risk among Chinese in LA than in Shanghai can largely be explained by the lower prevalence of stomach cancer risk factors in the USA, such as *Helicobacter pylori* (*H. pylori*) infection, tobacco consumption, and certain dietary patterns, as well as better food preservation [78–85].

Liver Cancer

Compared to NH whites, liver cancer incidence is 3.1 times higher in Chinese-American men and 3.4 times higher in Chinese-American women (Table 3). In both sexes, the age-adjusted liver cancer risk for Chinese in LA is intermediate between those of Chinese in Shanghai and US whites. In contrast to the clear steady declining

incidence among Shanghai Chinese, risk trends appear to be on the rise among US whites and stabilizing among Chinese in LA (Figs. 3e and 4e). Chinese in LA and in Shanghai display almost identical age-specific liver cancer incidence rates that are much higher than those of US whites across all ages, especially in older age groups (Figs. 5e and 6e).

Chronic infection with hepatitis B virus (HBV) causes more than half of liver cancer cases worldwide [86, 87]. While HBV is rare (1 %) in NH whites, 11.5–21.4 % of Chinese Americans carry the virus [88–90]. HBV carriers have much higher risk of developing liver cancer than noncarriers. HBV vaccination has proven to be very effective in reducing liver cancer risk and contributed to the sustained decline in liver cancer incidence around the world, especially in high-risk regions including China [91]. However, studies have shown that knowledge of the relationship between HBV and liver cancer and participation in HBV screening are both low among Chinese-Americans. Over 50 % of Chinese Americans never had HBV test, and about one-third had been vaccinated [92–94]. There are other risk factors of liver cancer including alcohol-related liver diseases, smoking, obesity, diabetes, and infection with hepatitis C virus (HCV) [95–97]. Unlike HBV, currently, there is no vaccination available for HCV. The increase in liver cancer incidence rates among US whites is likely related to the increasing HCV infection in the population [88, 98].

Nasopharyngeal Cancer (NPC)

NPC is a rare cancer worldwide. It ranks as 12th and 16th as the most common cancer among Chinese-American men and women, respectively. However, the incidence rates of NPC among Chinese Americans are 12.3 times higher than NH white men and 14.0 times higher than NH white women (Table 3). Chinese men and women in LA have higher incidence of NPC than both US whites and Chinese in Shanghai, but their risk is lower than that of Chinese in Hong Kong. These risk differentials likely reflect the striking high-risk patterns of NPC in China, particularly in southern coastal China. Incidence of NPC in LA Chinese declined throughout the 1990s and appeared to have now stabilized (Figs. 3f and 4f). The age-specific NPC incidence pattern in Chinese men in LA differs from that of US white men and Chinese men in Shanghai, but resembles that of Chinese men in Hong Kong; incidence peaks between ages 50 and 60. Interestingly, NPC risk appears to continue to increase with age among Chinese women in LA (Figs. 5f and 6f).

Nasopharyngeal cancer is a prevalent disease in southern China, particularly among the Cantonese living in Hong Kong and Guangdong province. Southern Chinese who migrated to low-risk regions still retain a much higher incidence rate compared to local populations [99–102]. But the risk seems to decrease with longer duration of residence and with succeeding generations [103–105]. Such decline in risk may also be attributable to a mixture of Chinese immigrants originating from high- as well as low-risk areas in China [100]. The incidence rates of NPC in China and other high-risk regions have been declining in the past decades, which seem to

be associated with rapid economic development in the regions [106–109]. Well-established risk factors for NPC include Epstein-Barr virus (EBV), consumption of salt-preserved fish (particularly during weaning) and vegetables, family history of NPC, tobacco and alcohol consumption, and certain genotypes [99–102]. Despite the strong indication that both environmental factors and genetic traits contribute to the development of this cancer, understanding of its complex etiology is incomplete. Current strategies to reduce the risk of NPC include reducing the consumption of salt-preserved fish and other preserved foods, smoking cessation, reduction of alcohol use, and increase intake of fresh fruits and vegetables.

Gallbladder Cancer

Although generally considered a rare disease, gallbladder cancer has widely varied risk patterns around the world. The incidence rates are low in the USA and most Western and Mediterranean European countries, but high in Asia and Latin America [13]. It is one of the four cancers that Chinese-Americans are at higher risk in incidence than NH whites, more so in men (30 % higher) than in women (10 % higher) (Table 1 and Fig. 1). Regardless of sex, Chinese in LA have much lower incidence rates than Chinese in Shanghai, similar to the NH whites (Figs. 3g and 4g). While incidence in China showed a notable decline in the beginning of the 2000s, it remained relatively stable in the USA. Higher gallbladder cancer risk among Chinese in Shanghai than US whites is consistent across age in both men and women. Between ages 50 and 65, gallbladder cancer risk among Chinese men in LA is comparable to that of Chinese men in Shanghai, higher than that of US white men. The risk reduction for Chinese in LA, as compared to Chinese in Shanghai, seems to occur after age 70 in both sexes (Figs. 5g and 6g).

The risk factors of gallbladder cancer include gallstone, chronic gallbladder inflammation, gallbladder polyps, tobacco use, obesity, and diabetes [110–113]. A family history of gallstone and other gallbladder diseases increases the risk of developing gallbladder cancer [114, 115]. Environmental exposures to heavy metals and radon [116, 117] and a diet high in fried and oily foods have also been implicated in gallbladder cancer incidence [118–120]. The progression of gallbladder cancer is frequently rapid and silent, resulting in late diagnosis and dismal prognosis. Studying the risk variation in different populations, especially immigrants from high-risk regions, will aid identification of genetic and environmental risk factors, early detection, and development of primary prevention strategies to conquer this fatal disease.

Summary

Chinese-Americans demonstrate distinctive cancer risk patterns that are different from the white or NH white population. Although for most of the cancers examined Chinese-Americans have lower incidence and mortality rates than the NH whites,

their risk for nasopharyngeal cancer, liver cancer, and stomach cancer is substantially higher, in addition to their slightly higher risk of gallbladder cancer. Except lung and colorectal cancer, Chinese Americans display intermediate-risk level between the US whites and Chinese in China, highlighting the significance of environmental and lifestyle factors in cancer development. Among Chinese-American men, liver cancer incidence seems to be stabilizing. Among women, risk is climbing for breast cancer, lung cancer, and even possibly liver cancer. Continued effort to monitor the cancer trends and develop effective cancer control programs in this special population is both necessary and important. The unique age-specific risk patterns by cancer type among Chinese Americans may offer clues for generating etiologic hypothesis. Focused research on specific racial/ethnic populations with migration history is likely to offer new understanding and opportunities in the fight against cancer.

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Cancer Incidence and Mortality Among Filipinos in the USA and the Philippines: Patterns and Trends

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Abstract Background Filipino Americans are the second largest Asian-American ethnic group, comprising 3.4 million persons in 2010. This population has grown rapidly, nearly doubling in size from 2000 to 2010. With their varied migration patterns over time, sociodemographic diversity in the USA, and growing presence,

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this group is a significant Asian-American population in which to evaluate cancer incidence and mortality patterns.

Methods Two decades (1990–2010) of incidence data from the NCI Surveillance, Epidemiology, and End Results (SEER) registry and population estimate data from the 1990, 2000, and 2010 US Census are used to calculate incidence rates and trends. Incidence rates from available registries in the Philippines, obtained from the Cancer Incidence in Five Continents database, are presented. US cancer mortality rates from 36 states (from 2003 to 2011) are also presented. All rates and 95 % confidence intervals (CI) are calculated as cases or deaths per 100,000 persons. Annual rates are presented as trends, determined using joinpoint regression models to identify distinct changes in trends.

Results Overall, cancer rates are higher for males than females in both the USA and the Philippines. Among US Filipino males, the five most common cancer sites are (1) prostate, (2) lung and bronchus, (3) colon and rectum, (4) non-Hodgkin lymphomas (NHL), and (5) liver, while these sites among males in the Philippines are (1) lung and bronchus, (2) prostate, (3) colon and rectum, (4) liver, and (5) stomach. Among US Filipina females, the three most common sites are (1) breast, (2) colon and rectum, and (3) lung and bronchus, with thyroid and corpus uterus changing as the fourth and fifth most common sites across the time period; in contrast, these sites among females in the Philippines are (1) breast, (2) cervix uteri, (3) colon and rectum, (4) lung and bronchus, and (5) ovary in 1993–1997 and (1) breast, (2) colon and rectum, (3) lung and bronchus, (4) cervix uteri, and (5) corpus uteri in 2003–2007. With regard to cancer mortality, lung, colorectal, prostate, liver, and pancreatic cancers were the five sites contributing most to cancer-related deaths among Filipino males in the USA and Philippines, while lung, breast, colorectal, pancreatic, and ovarian cancers were the five most common sites of cancer-related deaths for females in both populations. Incidence of breast, lung, thyroid, kidney, and bladder cancers is increasing among US Filipinas, and incidence of kidney cancer is increasing among US Filipino males.

Conclusions The incidence and mortality patterns and trends presented for Filipinos in this chapter provide data to support targeted areas for cancer prevention, such as obesity for reducing the risks of uterine, colorectal, and breast cancers, and smoking prevention and cessation for lung, kidney, oral cavity and pharyngeal, bladder, and pancreatic cancers. For those sites that demonstrate changing trends or dramatic differences between Filipinos in the USA and in the Philippines, further targeted studies can leverage these incidence patterns to elucidate environmental and modifiable risk factors.

Keywords Cancer • Philippines • Filipino • Incidence • Mortality • Race • Asian Pacific Islander • SEER • Cancer Incidence in Five Continents

Introduction

Filipino Americans are the second largest Asian-American ethnic group, comprising 3.4 million persons in 2010, and exceeded in numbers only by Chinese Americans at 4.0 million [1]. In recent years, the Filipino American population has grown rapidly, nearly doubling between 2000 and 2010 and now representing nearly 20 % of the total Asian-American population. Among Filipinos in the USA, 43 % live in California (where they are the largest Asian-American ethnic group), 10 % live in Hawaii, and 4 % live each in Illinois, Texas, and Washington State. In the 2010 Census, Filipinos had the second highest proportion (25 %), after Japanese, self-reporting as multiple race: 19 % identified with another non-Asian race, 4 % with multiple Asian groups and another non-Asian race, and 3 % with multiple Asian race groups.

The sociodemographic characteristics of the contemporary Filipino American population reflect their historical migration patterns to the USA. During the American colonial period (approximately between 1899 and 1946), when Filipinos were US nationals, the first Filipino migrants arrived in the mainland USA primarily as laborers. The 1934 Philippine Independence Act then restricted immigration to 50 Filipinos per year. However, with the 1964 Immigration Act, which abolished national-origins quotas and allowed 170,000 immigrants per year from Asia [2], came a second large wave of Asian immigration. Filipino immigrants in this wave were more likely to be women, to come from cities than the countryside, and arrived in the USA to settle permanently. Between 1966 and 1970, 65 % of nearly 40,000 Filipinos admitted to the USA under the occupational category were professional or technical workers, emigrating to escape the regime of Ferdinand Marcos and to seek better employment opportunities. Among these immigrant professionals, the majority were physicians and nurses; however, for physicians, the costs to obtain a US medical license were prohibitive, and many Filipino doctors were underemployed in the USA as nurses, nurses' aides, or laboratory assistants, for which licensure was less involved [2].

According to data from the 2010 Census and 2007–2009 American Community Survey, 53 % of Filipino Americans in this time period were foreign-born. Although 57 % spoke a language other than English at home, 82 % also reported speaking English very well, reflecting the widespread use of English in the Philippines [3]. Because Filipino Americans comprised a large number of skilled laborers after 1964, they are relatively well-educated, with a bachelor's or graduate/professional degree obtained by 46 % (compared with 29 % of the non-Hispanic White population and 49 % of the Asian combined population). However, at $25,799, Filipinos' per capita household income was lower than that of non-Hispanic Whites and all Asians combined ($29,418 and $28,342, respectively). 5 % of Filipino American households lived in poverty (relative to 8 % of non-Hispanic Whites and 8 % of Asians combined), and 11 % lacked health insurance (relative to 13 % of non-Hispanic Whites and 14 % of Asians combined).

With their varied migration patterns over time, contemporary diversity in the USA, and growing presence, Filipino Americans represent a significant Asian-American population in which to evaluate cancer incidence and mortality patterns. The vast heterogeneity among Asian-American ethnic groups translates into substantial variability in cancer incidence and mortality patterns [4–6]. Therefore, examining cancer patterns for distinct ethnic populations is necessary for identifying disparities and effectively targeting future research, health policies, and intervention efforts [7]. To provide a broad overview of cancer occurrence among US Filipinos, this chapter presents incidence and mortality rates and trends over approximately 20 years, for the ten most common cancer sites in each gender/outcome group. These statistics are based on data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, the National Center for Health Statistics (NCHS), and the US Census. For comparison, we present incidence rates from the International Agency for Research on Cancer (IARC) for two regions in the Philippines.

Methods

US Cancer Incidence Data

Cancer incidence data for all invasive cancers newly diagnosed during the 21-year period 1990–2010 were obtained from 13 US SEER cancer registries (Table 1) [8]. Catchment areas for these population-based registries cover nearly two-thirds of the Filipino American population [9]. SEER data on race and Hispanic ethnicity are generally based on patients' medical records; for this analysis, Filipinos were included regardless of Hispanic ethnicity. Based on an algorithm developed by the North American Association for Central Cancer Registries, information on birthplace and surname was used to assign race/ethnicity when a specific race designation was lacking [10].

US Mortality Data

Mortality rates are based on the underlying causes of death in Filipino decedents from 36 US states over the period 2003–2011, as reported in detail in [11]. Death counts were obtained from the NCHS; the 36 states were chosen based on adoption of the 2003 death certificate standard, which captures detailed coded Asian race categories [12]. Death certificates are completed by medical examiners and may be subject to misclassification of race/ethnicity [13, 14].

US Population Data

Detailed population data for Filipino Americans are available from the 1990, 2000, and 2010 US censuses. Intercensal estimates were developed from linear interpolation between censuses [15]. Due to Hawaii's mixed Asian-American population, the SEER Hawaii registry developed state population estimates derived from sample

Table 1 Annual counts and distribution of Filipino populations by Surveillance, Epidemiology, End Results (SEER) registry and Census year

Census Year		N	%
	1990	1,040,610	–
	2000	1,420,523	–
	2010	1,793,997	–
1990			
	California	768,495	73.85%
	Connecticut	5,319	0.51%
	Atlanta (Metropolitan)	2,184	0.21%
	Hawaii	152,957	14.70%
	Iowa	1,574	0.15%
	Detroit (Metropolitan)	9,689	0.93%
	New Jersey	54,591	5.25%
	New Mexico	2,154	0.21%
	Utah	1,958	0.19%
	Seattle (Puget Sound)	41,689	4.01%
2000			
	California	1,017,248	71.61%
	Connecticut	8,938	0.63%
	Atlanta (Metropolitan)	5,681	0.40%
	Hawaii	200,386	14.11%
	Iowa	2,959	0.21%
	Detroit (Metropolitan)	13,743	0.97%
	New Jersey	91,022	6.41%
	New Mexico	3,895	0.27%
	Utah	4,310	0.30%
	Seattle (Puget Sound)	72,341	5.09%
2010			
	California	1,341,360	74.77%
	Connecticut	14,291	0.80%
	Atlanta (Metropolitan)	8,963	0.50%
	Hawaii	169,694	9.46%
	Iowa	4,851	0.27%
	Detroit (Metropolitan)	17,444	0.97%
	New Jersey	119,314	6.65%
	New Mexico	6,784	0.38%
	Utah	8,241	0.46%
	Seattle (Puget Sound)	103,055	5.74%

survey data collected by the Hawaii Department of Health [16]. Population data for mortality rates were calculated from the 2000 and 2010 Censuses, with interpolated population estimates for years between surveys, and the interpolated value for 2007 as the interval average [17].

Population counts of Filipinos by SEER region for the three censal years (1990, 2000, and 2010) are shown in Table 1.

Cancer Incidence and Population Data in the Philippines

Cancer incidence data for the Philippines were available from the Cancer Incidence in Five Continents (CI5) database, a collaboration between the International Agency for Research on Cancer (IARC) and the International Association of Cancer Registries (IACR) [18, 19]. This database provides detailed information on cancer incidence recorded by registries worldwide for 5-year time periods; indices of data quality are available by cancer site and registry (http://ci5.iarc.fr/CI5I-X/Pages/Quality_sel.aspx). For the Philippines, data are included in CI5 from two registries: (1) Manila, including the highly urbanized city of Manila, and several local cities and municipalities (population approximately 29 million) and (2) Rizal province, representing 14 municipalities (population approximately 32 million) (Table 2) [18, 19]. As these registries collected data for different time periods, we limited our analyses to the two time periods (1993–1997, 2003–2007) when both registries contributed data. The data, which were available as 5-year aggregated case counts and population totals by registry, sex, cancer site, and age at diagnosis (5-year age group), were converted into a SEER*Stat database for computing incidence rates for comparison to US Filipino rates [20]. Percent change was calculated between the two time periods.

The Manila and Rizal registries provided case counts for 16 or 17 age groups, depending on the time period. Given that there are 18 age groups for cancer case numerator data, we combined cases in age groups for which no population data were available (80–84, 85+, unknown age) [21]. Using the combined oldest age groups, we produced incidence rates for the two Philippine registries age-standardized to the US 2000 Standard Million population.

Table 2 Annual counts and distributions of Filipinos in the Philippines (Manila and Rizal), based on the Cancer Incidence in Five Continents (CI5) database

5-Year Period in CI5		N	%
	1993–1997	51,646,820	–
	2003–2007	61,915,826	–
1993–1997			
	Manila	25,379,745	49.14%
	Rizal	26,267,075	50.86%
2003–2007			
	Manila	29,280,897	47.29%
	Rizal	32,643,929	52.72%

Statistical Analysis

All rates and 95 % confidence intervals (CI) were calculated as cases or deaths per 100,000 persons. Incidence rates were calculated using SEER*Stat software (http://seer.cancer.gov/seerstat/). Mortality rates were computed in R. Rates were suppressed for case counts <10 [22]. Annual rates are shown graphically as trends, determined using joinpoint regression models to identify distinct slopes in the trends. Annual percentage change (APC) statistics (95 % confidence intervals (CI)) are used to characterize the trends' magnitude and direction [23]. A maximum of five joinpoints were allowed based on single year data. Rate estimates and trend lines from the trends based on joinpoint analyses are plotted on a semilogarithmic scale [24, 25].

Results and Discussion of Incidence and Mortality Patterns

Overview of the Most Common Cancer Sites and Trends

Overall cancer rates were higher for males than females in both the USA and the Philippines. Among US Filipino males, the five most common cancer sites were (1) prostate, (2) lung and bronchus, (3) colon and rectum, (4) non-Hodgkin lymphomas (NHL), and (5) liver (Table 3). The relative rank order of these five sites remained unchanged over the 21-year period. Among US Filipino females, the three most common sites were (1) breast, (2) colon and rectum, and (3) lung and bronchus, with thyroid and corpus uterus changing as the fourth and fifth most common sites across the time period (Table 4).

In contrast, the most common cancer sites among Filipino males in the Philippines differ somewhat, with the five most common sites for the two periods (1993–1997 and 2003–2007) being (1) lung and bronchus, (2) prostate, (3) colon and rectum, (4) liver, and (5) stomach (Table 5). Among females in the Philippines, the five most

Table 3 Age-adjusted incidence rates and 95 % confidence intervals (CI) of the top ten cancer sites, by time period, Filipino males, United States

1990–1995			
Rank	Site	Count	Rate (95 % CI)
	All Sites	8,823	399.2 (390.8, 407.7)
1	Prostate	2,757	133.1 (128.1, 138.2)
2	Lung and Bronchus	1,521	68.8 (65.3, 72.3)
3	Colon and Rectum	1,024	46.7 (43.9, 49.7)
4	Non-Hodgkin Lymphoma	427	18.5 (16.8, 20.4)
5	Liver	299	13 (11.6, 14.6)
6	Leukemia	297	11.8 (10.5, 13.3)
7	Urinary Bladder	234	10.9 (9.5, 12.4)
8	Pancreas	225	10.7 (9.4, 12.2)
9	Stomach	236	10.7 (9.4, 12.2)
10	Oral Cavity and Pharynx	251	10.6 (9.3, 12.0)

(continued)

Table 3 (continued)

1996–2000			
Rank	Site	Count	Rate (95 % CI)
	All Sites	8,883	392 (383.4, 400.1)
1	Prostate	2,628	121.2 (116.6, 126.0)
2	Lung and Bronchus	1,623	72.3 (68.8, 75.9)
3	Colon and Rectum	1,096	48.1 (45.2, 51.0)
4	Non-Hodgkin Lymphoma	450	19.3 (17.5, 21.2)
5	Liver	340	14.2 (12.7, 15.9)
6	Urinary Bladder	264	12.3 (10.9, 13.9)
7	Stomach	243	10.9 (9.6, 12.4)
8	Oral Cavity and Pharynx	271	10.8 (9.5, 12.2)
9	Leukemia	261	10.6 (9.3, 12.0)
10	Kidney and Renal Pelvis	231	9.7 (8.4, 11.0)

2001–2005			
Rank	Site	Count	Rate (95 % CI)
	All Sites	10,219	369.6 (362.3, 377.0)
1	Prostate	3,182	117.7 (113.5, 122.0)
2	Lung and Bronchus	1,795	66.9 (63.8, 70.1)
3	Colon and Rectum	1,312	47 (44.5, 49.7)
4	Non-Hodgkin Lymphoma	513	18.4 (16.8, 20.2)
5	Liver	419	14.6 (13.2, 16.2)
6	Urinary Bladder	299	11.4 (10.1, 12.8)
7	Leukemia	278	9.6 (8.5, 10.8)
8	Oral Cavity and Pharynx	279	9.4 (8.3, 10.6)
9	Kidney and Renal Pelvis	283	9.2 (8.2, 10.4)
10	Pancreas	228	8.7 (7.6, 9.9)

2006–2010			
Rank	Site	Count	Rate (95 % CI)
	All Sites	11,576	352.2 (345.6, 358.9)
1	Prostate	3,350	101.9 (98.3, 105.5)
2	Lung and Bronchus	1,879	60.3 (57.5, 63.1)
3	Colon and Rectum	1,488	44.6 (42.3, 47)
4	Non-Hodgkin Lymphoma	587	18.2 (16.7, 19.8)
5	Liver	532	15.7 (14.3, 17.1)
6	Kidney and Renal Pelvis	487	13.7 (12.5, 15.0)
7	Urinary Bladder	330	10.7 (9.6, 12.0)
8	Pancreas	318	10 (8.9, 11.1)
9	Oral Cavity and Pharynx	337	9.5 (8.5, 10.6)
10	Leukemia	308	9.5 (8.4, 10.6)

Table 4 Age-adjusted incidence rates and 95% confidence intervals (CI) of the top ten cancer sites, by time period, Filipina females, United States

1990–1995			
Rank	Site	Count	Rate (95% CI)
	All Sites	7978	273.8 (267.4, 280.3)
1	Breast	2702	85.7 (82.4, 89.2)
2	Colon and Rectum	728	28.1 (25.9, 30.4)
3	Lung and Bronchus	608	23.1 (21.2, 25.2)
4	Thyroid	532	15.6 (14.2, 17.0)
5	Corpus and Uterus, NOS	456	14.3 (13.0, 15.8)
6	Non-Hodgkin Lymphoma	329	12.6 (11.1, 14.1)
7	Cervix Uteri	401	12.4 (11.1, 13.7)
8	Ovary	346	11 (9.8, 12.3)
9	Leukemia	220	7.8 (6.7, 9.0)
10	Pancreas	166	7.1 (5.9, 8.3)

1996–2000			
Rank	Site	Count	Rate (95% CI)
	All Sites	9091	280.5 (274.6, 286.5)
1	Breast	3371	97.2 (94.0, 100.6)
2	Colon and Rectum	842	27.8 (25.9, 29.9)
3	Lung and Bronchus	703	24.1 (22.3, 26.0)
4	Corpus and Uterus, NOS	590	17.1 (15.7, 18.6)
5	Thyroid	595	16.7 (15.4, 18.2)
6	Non-Hodgkin Lymphoma	359	12.1 (10.8, 13.4)
7	Ovary	352	10.5 (9.4, 11.7)
8	Cervix Uteri	360	10.3 (9.2, 11.4)
9	Pancreas	183	6.6 (5.6, 7.7)
10	Leukemia	186	6 (5.2, 7.0)

2001–2005			
Rank	Site	Count	Rate (95% CI)
	All Sites	11,725	286.1 (280.9, 291.5)
1	Breast	4,142	96.1 (93.2, 99.1)
2	Colon and Rectum	1,147	29.5 (27.8, 31.3)
3	Lung and Bronchus	1,000	26.1 (24.5, 27.9)
4	Corpus and Uterus, NOS	866	19.8 (18.5, 21.2)
5	Thyroid	805	18.5 (17.2, 19.8)
6	Non-Hodgkin Lymphoma	467	12.1 (11, 13.3)
7	Ovary	433	10.4 (9.4, 11.4)
8	Cervix Uteri	358	8.4 (7.6, 9.3)
9	Pancreas	278	7.5 (6.6, 8.4)
10	Leukemia	237	6.1 (5.3, 7.0)

(continued)

Table 4 (continued)

2006–2010			
Rank	Site	Count	Rate (95 % CI)
	All Sites	14,852	298.9 (294.0, 303.8)
1	Breast	5,190	100.2 (97.4, 103.0)
2	Colon and Rectum	1,407	29.2 (27.6, 30.7)
3	Lung and Bronchus	1,358	28.6 (27.1, 30.2)
4	Thyroid	1,195	23.8 (22.4, 25.2)
5	Corpus and Uterus, NOS	1,174	22.2 (20.9, 23.5)
6	Non-Hodgkin Lymphoma	598	12.6 (11.5, 13.6)
7	Ovary	506	10 (9.2, 10.9)
8	Pancreas	397	8.7 (7.8, 9.6)
9	Cervix Uteri	355	7 (6.3, 7.8)
10	Leukemia	312	6.7 (6.0, 7.5)

Table 5 Age-adjusted incidence rates and 95 % confidence intervals (CI) of the top ten cancer sites, by 5-year time period (1993–1997 and 2003–2007), males, Philippines (Manila and Rizal)

1993–1997			
Rank	Site	Count	Rate (95 % CI)
	All Sites	23,476	314.6 (309.3–319.9)
1	Lung and Bronchus	5,429	77.9 (75.4–80.5)
2	Prostate	1,601	40.0 (37.8–42.3)
3	Colon and Rectum	2,356	33.6 (31.9–35.4)
4	Liver	2,629	32.0 (30.4–33.6)
5	Stomach	994	15.7 (14.5–17.0)
6	Non-Hodgkin Lymphoma	859	9.0 (8.2–9.9)
7	Larynx	626	8.9 (8.1–9.8)
8	Nasopharynx	936	8.6 (7.8–9.3)
9	Bladder	483	8.0 (7.2–9.0)
10	Leukemia	1,281	7.6 (7.0–8.3)

2003–2007			
Rank	Site	Count	Rate (95 % CI)
	All Sites	32,398	335.6 (330.8–340.3)
1	Lung and Bronchus	6,347	71.3 (69.2–73.5)
2	Prostate	3,708	63.4 (61.1–65.8)
3	Colon and Rectum	4,175	43.9 (42.2–45.7)
4	Liver	3,269	30.6 (29.3–32.0)
5	Stomach	1,052	12.5 (11.5–13.4)
6	Non-Hodgkin Lymphoma	1,125	9.4 (8.6–10.1)
7	Leukemia	1,763	8.8 (8.2–9.5)
8	Bladder	622	8.0 (7.2–8.8)
9	Larynx	726	7.7 (7.0–8.4)
10	Nasopharynx	1,072	7.2 (6.6–7.8)
10	Skin	648	7.2 (6.5–7.9)

Table 6 Age-adjusted incidence rates and 95% confidence intervals (CI) of the top ten cancer sites, by time period (1993–1997 and 2003–2007), females, Philippines (Manila and Rizal)

1993–1997			
Rank	Site	Count	Rate (95% CI)
	All Sites	29,632	268.2 (264.6–271.9)
1	Breast	7,975	66.8 (65.1–68.5)
2	Cervix uteri	3,400	26.6 (25.5–27.6)
3	Colon and Rectum	2,187	25.8 (24.5–27.0)
4	Lung and Bronchus	1,807	21.4 (20.3–22.6)
5	Ovary	2,079	15.6 (14.8–16.4)
6	Corpus and Uterus, NOS	1,331	12.2 (11.5–13.0)
7	Thyroid	1,646	11.7 (11.0–12.4)
8	Liver	928	10.8 (10.0–11.7)
9	Stomach	726	8.6 (7.9–9.4)
10	Leukemia	1,123	6.2 (5.7–6.8)

2003–2007			
Rank	Site	Count	Rate (95% CI)
	All Sites	44,776	295.1 (291.9–298.3)
1	Breast	13,051	80.4 (78.8–81.9)
2	Colon and Rectum	3,846	32.3 (31.1–33.5)
3	Lung and Bronchus	2,684	22.8 (21.9–23.8)
4	Cervix uteri	3,999	22.4 (21.6–23.2)
5	Corpus and Uterus, NOS	2,655	16.2 (15.5–16.9)
6	Ovary	2,776	16.0 (15.3–16.7)
7	Thyroid	3,056	15.2 (14.6–15.9)
8	Liver	1,369	11.8 (11.1–12.5)
9	Leukemia	1,644	8.0 (7.5–8.5)
10	Stomach	839	7.2 (6.6–7.8)

common sites were (1) breast, (2) cervix uteri, (3) colon and rectum, (4) lung and bronchus, and (5) ovary in 1993–1997 and (1) breast, (2) colon and rectum, (3) lung and bronchus, (4) cervix uteri, and (5) corpus uteri in 2003–2007 (Table 6).

From 1990 through 2010, US Filipino males experienced a decrease (APC = −1.2%, 95% CI: −1.5, −0.9) and US Filipinas experienced an increase (APC = 0.6, 95% CI: 0.4, 0.7) in cancer incidence overall (Tables 7 and 8). Among males, the decrease reflected a decline in the most common cancers (e.g., lung and prostate (Table 7, Fig. 1)). However, the incidence of less common cancers, including kidney and liver, increased notably over the 21-year period (Fig. 2), with kidney cancer ranking as the sixth most common cancer among US Filipino males in 2006–2010 (Table 3). In contrast, leukemia dropped from being the sixth most common cancer in the early 1990s to being the tenth most common cancer in the most recent 5-year period for US Filipino males (Table 3). Among US Filipinas, the most common cancers, including breast, lung, thyroid, and corpus and uteri, increased in incidence over the 21-year

Table 7 Annual Percent Change (APC) and 95 % confidence intervals (CI) in cancer incidence rates from 1990 to 2010, Filipino males, USA

Site	Time Period	APC (95 % CI)
All Sites	1990–1993	6.4 (1.5, 11.5)
	1993–2010	−1.2 (−1.5, −0.9)
Prostate	1990–1993	13.6 (0.6, 28.3)
	1993–2010	−2.3 (−3, −1.6)
Lung and Bronchus	1990–1996	3.0 (−0.6, 6.6)
	1996–2010	−1.9 (−2.7, −1.0)
Colon and Rectum	1990–2010	−0.4 (−1.0, 0.2)
Non-Hodgkin Lymphoma	1990–2010	−0.2 (−0.9, 0.6)
Liver	1990–2010	1.1 (0.2, 2.0)
Kidney and Renal Pelvis	1990–2010	3.4 (2.3, 4.5)
Leukemia	1990–2010	−1.4 (−2.3, −0.5)
Oral Cavity and Pharynx	1990–2010	−1.0 (−2.1, 0.2)
Urinary Bladder	1990–2010	−0.1 (−1.1, 0.9)
Pancreas	1990–2010	−0.3 (−1.6, 1.0)

APCs are computed using the SEER Joinpoint program, which identifies changes in trends

Table 8 Annual Percent Change (APC) and 95 % confidence intervals (CI) in cancer incidence rates from 1990 to 2010, Filipina females, USA

Site	Time Period	APC (95 % CI)
All Sites	1990–2010	0.6 (0.4, 0.7)
Breast	1990–2010	0.8 (0.4, 1.1)
Colon and Rectum	1990–2010	0.3 (−0.5, 1.1)
Lung and Bronchus	1990–2010	1.5 (0.9, 2.1)
Thyroid	1990–2004	1.4 (0.4, 2.4)
	2004–2010	6.4 (3.8, 9.1)
Corpus and Uterus, NOS	1990–2010	2.8 (2.2, 3.4)
Non-Hodgkin Lymphoma	1990–2010	0.2 (−0.8, 1.2)
Ovary	1990–2010	−0.6 (−1.7, 0.5)
Cervix Uteri	1990–2010	−3.8 (−5.0, −2.6)
Pancreas	1990–2010	1.5 (0.4, 2.7)
Leukemia	1990–2010	−0.4 (−2.1, 1.2)
Kidney and Renal Pelvis	1990–2010	2.5 (1.0, 4.1)
Urinary Bladder	1990–2010	1.9 (0.1, 3.7)

APCs are computed using the SEER Joinpoint program, which identifies changes in trends.

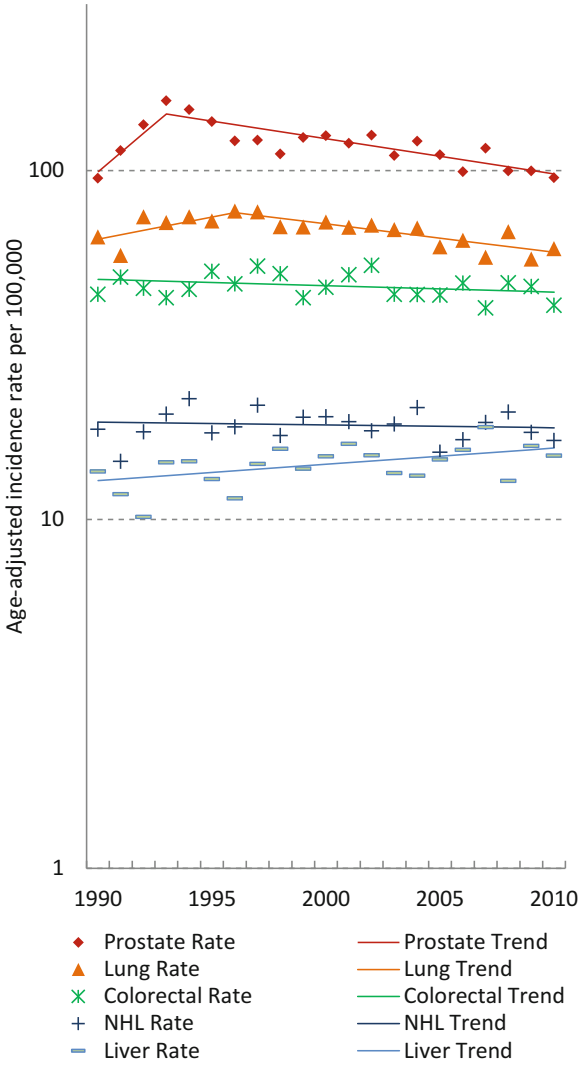

Fig. 1 Trends in incidence of the five most common cancers in US Filipinos, 1990–2010, males

period (Table 8, Fig. 3). For thyroid cancer, the increase was dramatic, averaging 6.4 % (95 % CI: 3.8–9.1) per year from 2004 through 2010. Less common cancers (pancreas, kidney, and bladder) also showed slight increases in incidence over time (Fig. 4). The only notable rate decrease among Filipinas was for cervical cancer, declining 3.8 % per year (95 % CI:−5.0,−2.6). For NHL and colorectal and ovarian cancer, incidence rates were relatively stable (Figs. 3 and 4).

In the Philippines, overall cancer incidence increased between 1993–1997 and 2003–2007. Among males, the greatest increases occurred for prostate cancer and colorectal cancer, while lung and stomach cancer rates declined. Among females,

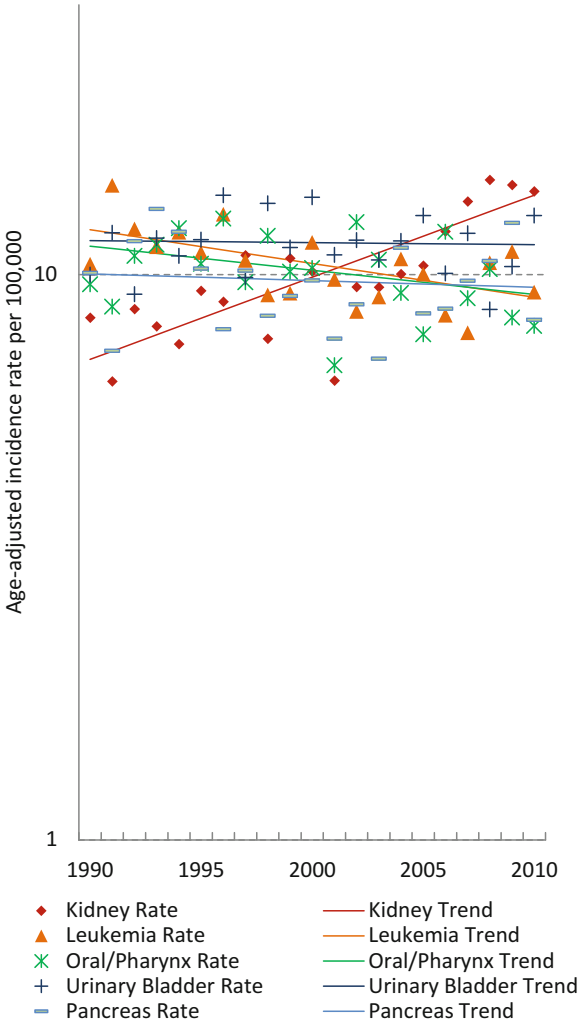

Fig. 2 Trends in incidence of the next five most common cancers in US Filipinos, 1990–2010, males

rates of cancers of the breast, colorectum, and thyroid, and of leukemia increased, while rates of cervical and stomach cancers declined. Incidence rates of NHL and liver cancer were stable in both males and females during this time (Fig. 5).

With regard to cancer mortality among Filipinos in the USA, lung, colorectal, prostate, liver, and pancreatic cancers were the five sites contributing most to cancer-related deaths among males (Table 9), while lung, breast, colorectal, pancreatic, and ovarian cancers were the five most common sites of cancer-related deaths for females (Table 10).

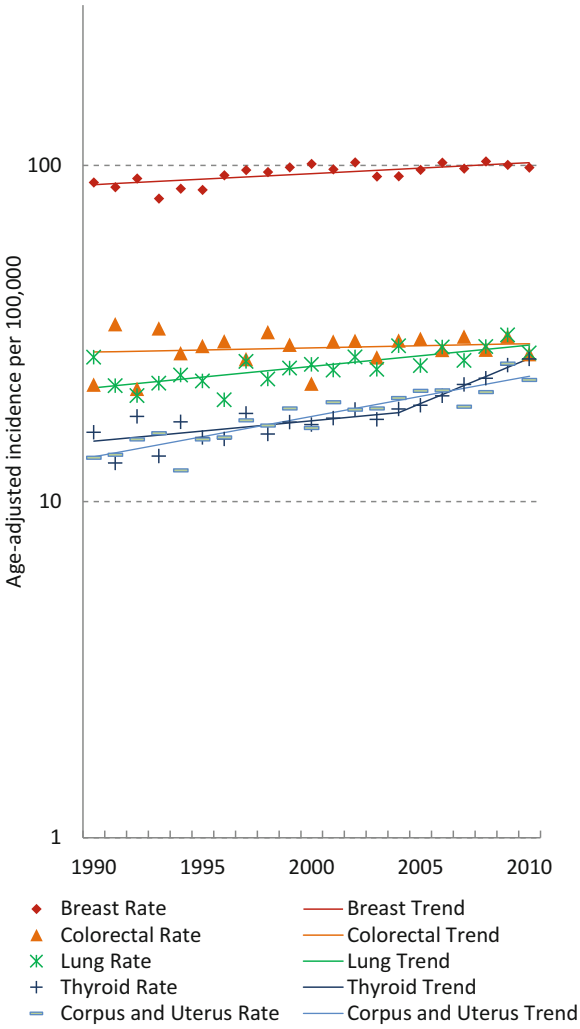

Fig. 3 Trends in incidence of the five most common cancers in US Filipinos, 1990–2010, females

Site-Specific Patterns and Trends

Prostate Cancer

Prostate cancer ranked as the most common cancer site among US Filipino males over the entire 21-year period, despite steady rate declines after 1993 (APC = −2.3 %, 95 % CI: −3.0, −1.6), representing the largest incidence decrease of any cancer site (Fig. 1). In contrast, among males in the Philippines, the rate of prostate cancer increased by 50 % from 1993–1997 (40.0 per 100,000) to 2003–2007 (63.4 per 100,000), while remaining considerably lower than in the

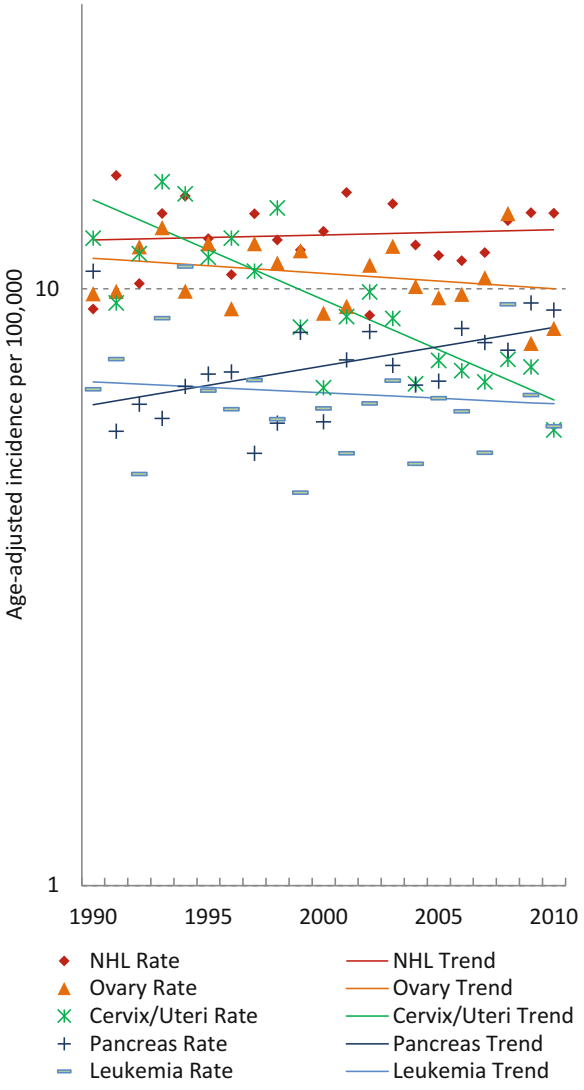

Fig. 4 Trends in incidence of the next five most common cancers in US Filipinos, 1990–2010, females

USA (101.9 per 100,000). Increased PSA screening has been attributed as the cause of much of the incidence differential between the two countries. While very little is known about nongenetic risk factors for prostate cancer, the dramatic differences in incidence between Filipinos in the USA and in the Philippines suggest that environmental factors may be relevant. Given the high burden of this disease and the migrant experience of Filipinos, research in this population may help to elucidate the etiologic role of lifestyle factors such as increased consumption of animal protein and dietary fat and decreased consumption of phytochemicals common in traditional Asian diets [26] (Fig. 6).

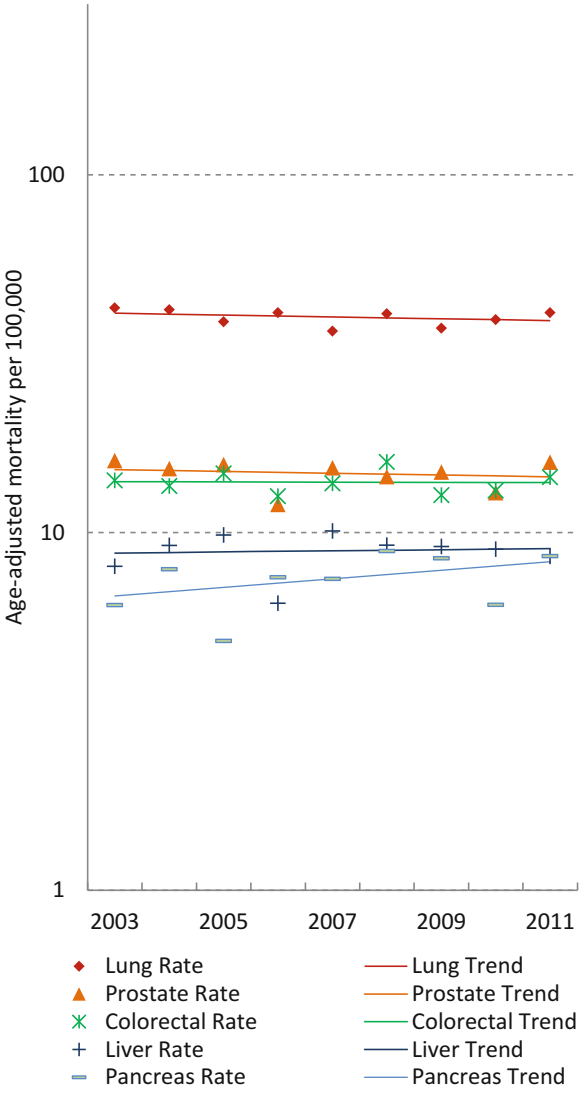

Fig. 5 Trends in mortality of the five most common cancer deaths in US Filipinos, 2003–2011, males

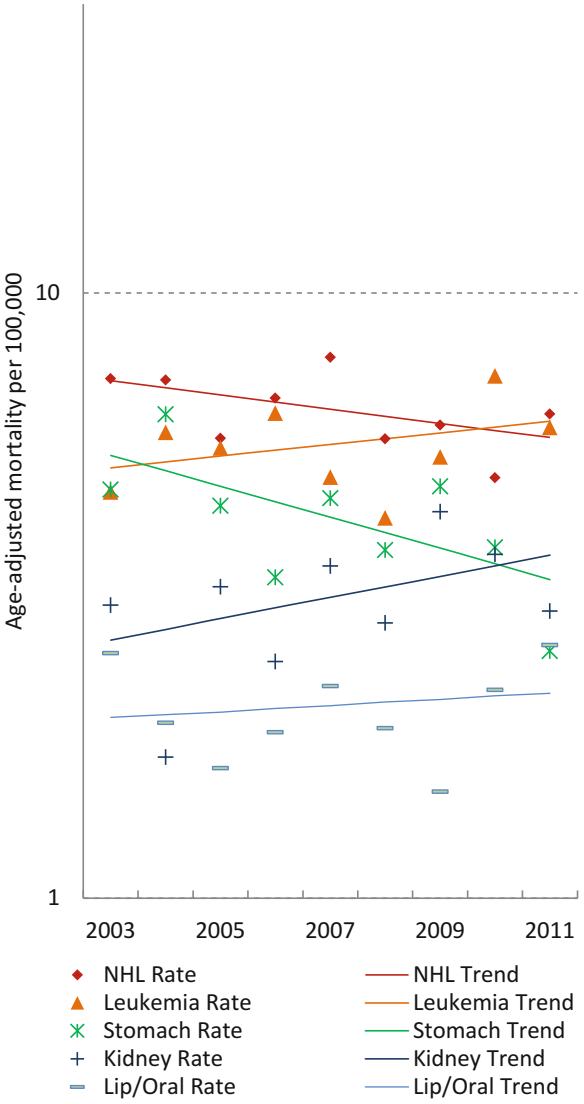

Fig. 6 Trends in mortality of the next five most common cancer deaths in US Filipinos, 2003–2011, males

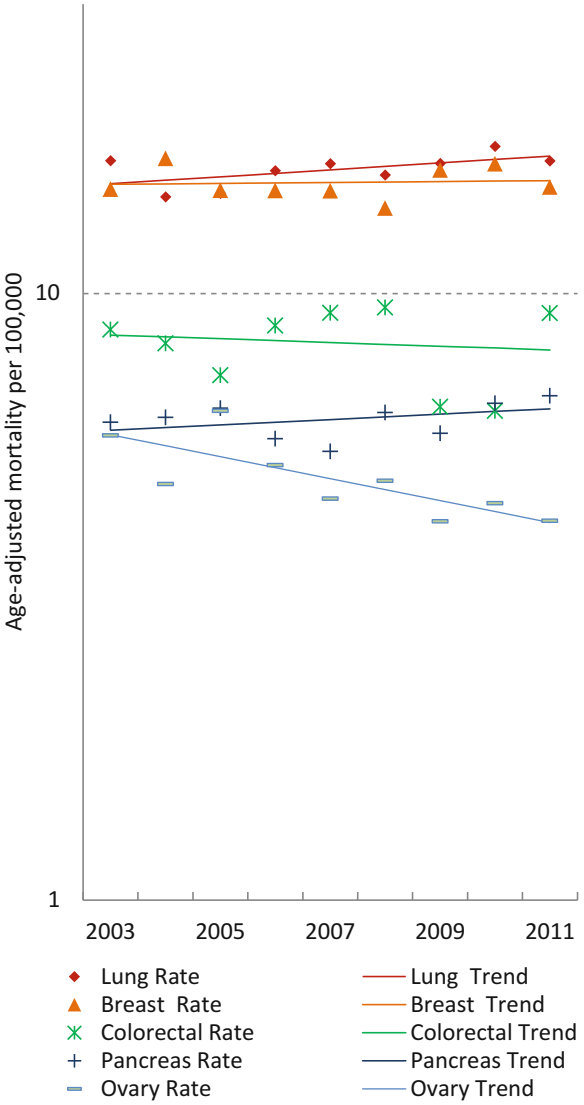

Fig. 7 Trends in mortality of the five most common cancer deaths in US Filipinos, 2003–2011, females

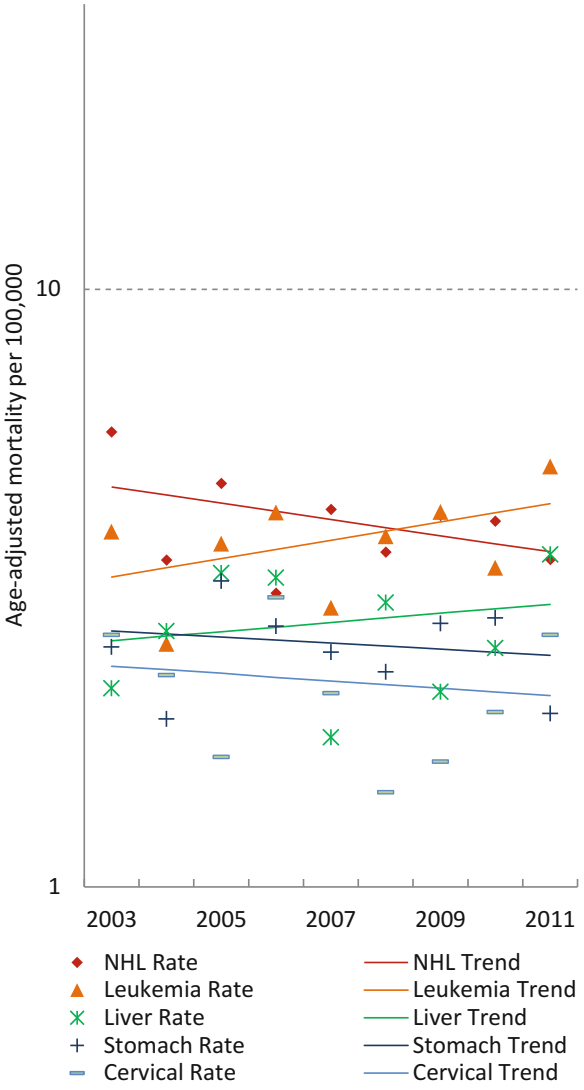

Fig. 8 Trends in mortality of the next five most common cancer deaths in U.S. Filipinos, 2003–2011, females

Breast Cancer

Among Filipina females in the USA and in the Philippines, breast cancer is the most commonly diagnosed cancer, with rates steadily increasing from 1990 to 2010 (APC = 0.8 %, 95 % CI: 0.4, 1.1), or by almost 15 % from the 1990–1995 rate to the 2006–2010 rate (Fig. 3). In the Philippines, the rate increased by 20 % from 1993–1997 to 2003–2007 (Tables 4 and 6). The increasing trends in breast cancer incidence contrast with the well-documented declines among US non-Hispanic White women [27–29] but are consistent with reports showing considerable differences in

Table 9 Age-adjusted mortality rates and 95% confidence intervals (CI)for total cancers and top 10 cancer sites in Filipinos, 2003-2011, males, United States

2003–2011			
Rank	Site	Count	Rate (95%CI)
	All Sites	9526	131.6 (128.8, 134.3)
1	Lung and Bronchus	2926	39.9 (38.4, 41.4)
2	Prostate	849	14.6 (13.5, 15.6)
3	Colon and Rectum	1027	13.8 (12.9, 14.7)
4	Liver	721	8.8 (8.2, 9.5)
5	Pancreas	545	7.4 (6.8, 8.1)
6	Non-Hodgkins Lymphoma	444	6.4 (5.8, 7)
7	Leukemia	409	5.6 (5.1, 6.2)
8	Stomach	296	4.2 (3.7, 4.7)
9	Kidney	254	3.1 (2.7, 3.6)
10	Lip/Oral cavity	166	2.1 (1.7, 2.4)

Table 10 Age-adjusted mortality rates and 95% confidence intervals (CI) for total cancers and top 10 cancer sites in Filipinos, 2003-2011, females, United States

2003–2011			
Rank	Site	Count	Rate (95% CI)
	All Sites	10360	87 (85.2, 88.7)
1	Lung and Bronchus	1871	16.1 (15.3, 16.8)
2	Breast	2023	15.2 (14.5, 15.9)
3	Colon and rectum	935	8.2 (7.7, 8.8)
4	Pancreas	692	6.2 (5.7, 6.7)
5	Ovary	621	4.9 (4.5, 5.3)
6	Non-Hodgkin Lymphoma	446	4 (3.6, 4.4)
7	Leukemia	434	3.8 (3.5, 4.2)
8	Liver	303	2.7 (2.4, 3.1)
9	Stomach	292	2.5 (2.2, 2.8)
10	Cervix uteri	287	2.1 (1.9, 2.4)

California rates between US-born and foreign-born Filipinas and dramatic increases in incidence over time among US-born Filipinas [30, 31]. The secular trends seen here for Filipinas in the USA and the Philippines are consistent with the increases seen among women living in other Asian countries [32, 33]. Because mortality rates have not declined (Fig. 7), it is likely that these incidence patterns reflect changes in lifestyle risk factors, including menstrual and reproductive factors, diet, obesity, and physical activity, and, to a lesser extent, increases in mammographic screening. As US Filipinas are diagnosed with proportionally more tumors that are positive for Her2Neu relative to non-Hispanic Whites [34], it would be worthwhile to examine trends in incidence rates by breast cancer subtypes (Fig. 8).

Colorectal Cancer

Among US Filipinos, colorectal cancer incidence was stable in males and females from 1990 through 2010 (Figs. 1 and 3). However, a recent study of cancer incidence for the period 1988–2007 in California reported an increase in colorectal cancer incidence in Filipinas (APC = 1.6 %, 95 % CI: 0.5, 2.6) and stable rates among Filipinos [35]. In recent years (2006–2010), colorectal cancer was the third most commonly diagnosed cancer among US Filipinos (44.6 per 100,000) and second among US Filipinas (29.2 per 100,000) and the second and third most common cause of cancer death among US Filipinos and Filipinas, respectively. In the Philippines, colorectal cancer incidence rates increased considerably since the 1990s for both men and women, such that in 2003–2007, they were comparable to the US rates. In the USA, rates of colon and rectal cancer separately were stable over this time period for both Filipino males and females (data not shown). Some hereditary traits are important risk factors for this disease, including familial polyposis (formation of numerous polyps in the colon), familial nonpolyposis colorectal cancer (HNPCC), history of inflammatory bowel disease, and first-degree family history of colorectal cancer [36]. Additional risk factors include excessive alcohol use, obesity, and smoking [37]. Data from the California Health Interview Survey (CHIS) show increases from 2007 to 2014 in the percentage of adults who are overweight for both Filipino males and females (BMI > 25: 56.2 %–69.5 % among males, 31.5 %–38.7 % among females), although data for Asian-specific BMI cut points are not available. Future research efforts should focus on the prevention (both through lifestyle modifications and screening) and early detection of colorectal cancer in this population, in addition to evaluating the role of specific cultural dietary effects on colorectal cancer incidence in this population.

Lung Cancer

Among US Filipinos, lung cancer was the second most common cancer among males and third among females, but it was the leading cause of cancer death among both genders. In the Philippines, lung cancer is the most common cancer among males (71.3 per 100,000), with rates higher than for US Filipino males (60.3 per 100,000). Among Filipinas, rates are slightly lower in the Philippines (22.8 per 100,000) than in the USA (28.6 per 100,000). The trends of lung cancer in the USA also differ by gender, with a significantly declining trend among males (APC = −1.9 %, 95 % CI: −2.7,−1.0) during 1996–2010 and an increasing trend among females (APC = 1.5 %, 95 % CI: 0.9, 2.1) during 1990–2010 (Tables 7 and 8). Incidence trends varied, however, by tumor histology, reflecting the relative role of tobacco use in lung cancer occurrence in this population [38]. Among US Filipino males, rates of adenocarcinoma were unchanged over time, while rates of other subtypes (including small cell, squamous cell, and unspecified histology) declined significantly over time [38]. In contrast, rates of adenocarcinoma among females increased significantly over time. While all histologic subtypes are strongly associated with

tobacco use, adenocarcinoma is less strongly associated with tobacco use, which is consistent with findings from a recent population-based case series that 70 % of Asian-American women diagnosed with lung cancer were lifetime never-smokers (in contrast to 14 % of Asian-American men) [39]. Although tobacco use appears to decrease with acculturation among Asian-American males (not specific to Filipinos), it increases with acculturation among Asian-American females [40]. This pattern with acculturation among women is suggested in the CHIS data, with higher prevalence of current smokers by English language fluency (very well vs. poor/well) among Filipinas (11 % vs. 1 %) [41]. Therefore, smoking prevention, particularly among US Filipinas, is imperative. However, given their low smoking prevalence, and the few known lung cancer risk factors among US never-smoker populations (some risk factors such as tuberculosis and other previous lung diseases, exposure to second-hand smoke, and other indoor and outdoor air pollution have been identified in Asia), additional research into etiologic risk factors may elucidate knowledge and progress against lung cancer among never-smokers.

Cervical Cancer

From 2006 through 2010, cervical cancer was the ninth most common cancer diagnosed in US Filipinas and the fourth most common cancer diagnosed among females in the Philippines. The incidence rate in the Philippines was threefold higher than the USA (22.4 vs. 7.5 per 100,000) during the time period 2003–2007. While cervical cancer was significantly more common in the Philippines, the rate declined by 16 % from 1993–1997 to 2003–2007. A significant decline also occurred from 1990 through 2010 among US Filipinas (APC = –3.8, 95 % CI: –5.0, –2.6) (Table 8, Fig. 4). Cervical cancer was the tenth most common cause of cancer-related death in US Filipinas, but a leading cause of cancer-related death among women in the Philippines [42, 43]. Stage at diagnosis differed considerably between the USA and the Philippines; the majority of cases in the USA are diagnosed at the localized or regional stage, while in the Philippines, the majority are diagnosed at a late stage (stage III) [42]. The most important risk factor is infection with types 16 and 18 of the human papillomavirus (HPV), which are associated with sexual behavior variables. HPV infection is reported to cause approximately 70 % of cervical cancers worldwide [44, 45]. In the Philippines, these high-risk HPV types are commonly found in women with cervical cancer [42]. While HPV prevalence among US Filipinas has not been reported, among women of all races in the USA, the most common high-risk HPV type is 53 (5.8 %), followed by 16 (4.2 %); type 18 is less common (1.8 %) [46]. The variation in prevalence of high-risk HPV types may explain the incidence rate disparity between the two populations. Other risk factors include a history of cigarette smoking and high parity [47, 48]. Differences in rates of screening (Pap smears), treatment options, and survival between the US Filipina population and women in the Philippines have been reported, with 5-year survival significantly lower in the Philippines (68.8 % vs. 42.9 %) [49]. Future research should focus on prevention measures, including the effects of screening guidelines and vaccination against HPV.

Thyroid Cancer

Among US Filipinos, thyroid cancer was the 4th most common cancer among females and the 12th most common among males from 2006 through 2010 (Table 4). Among US Filipinas, rates increased rapidly since 2004 by an annual average of 6.4 % (95 % CI: 3.8, 9.1) (Table 8, Fig. 3). The incidence rates for women (15.2 per 100,000) and for men (5.0 per 100,000) in the Philippines were lower than rates in the USA for Filipino women and men (23.8 and 7.3 per 100,000, respectively) but mirror the increasing trends in the USA in more recent years (14 % increase from the period 1993–1997 to 2003–2007 among women in the Philippines). While screening for thyroid cancer has become extensive in Asian countries such as Korea and Japan and hypothesized to account for some of the large incidence (but not mortality) rate increases over the past decade [50], we are not aware of similar expansion in thyroid cancer screening in the Philippines. Although changes in diagnostic imaging and over-screening may account for some of the increase in the USA, it has been a subject of debate whether better diagnostics and increased screening behavior alone account for the increase [51–53]. Known risk factors for thyroid cancer include exposure to ionizing radiation, a family history of thyroid cancer, and high body mass index; hormonal and reproductive factors, such as age at menarche and reproductive history, have also been implicated [51, 54–57]. Dietary factors such as consumption of fish and shellfish have been suggested to decrease risk, while low iodine increases risk of follicular thyroid cancer [58–60]. However, how diet influences thyroid function and thyroid hormone levels remains incompletely understood.

Corpus and Uteri Cancer

Cancer of the corpus and uteri (among which the vast majority is uterine (endometrial) cancer) is the most commonly diagnosed gynecologic cancer in women [61]. Incidence rates of uterine cancer in US Filipinas had risen 2.8 % per year (95 % CI: 2.2, 3.4) from 1990 to 2010, from 14.3 to 22.2 cases per 100,000, making uterine cancer the fifth most commonly diagnosed cancer. In the Philippines, rates were lower, but uterine cancer incidence also increased over time. Uterine cancer is believed to be caused by exposure to unopposed estrogen, through early age of menarche, nulliparity, late age at first birth, estrogen-only hormone therapy, or high-dose estrogen in oral contraceptive pills are also implicated. Obesity is one of the strongest and most important modifiable risk factors for this cancer, and US Filipinas have the highest body mass index of all Asian-American ethnicities [62, 63], with prevalence of obesity rising sharply in the past 20 years. Recent immigrants have been disproportionately affected due to adoption of high-fat western diet and reduced physical activity. In 2008, the 15-year increase in obesity prevalence was 164 % in long-term Filipino immigrants and 256 % in recent Filipino immigrants, representing the most dramatic increases of any Asian group [64]. Efforts should be taken to prevent weight gain and obesity prevalence among Filipinas in the U.S. and Philippines.

Liver Cancer

Liver cancer was the fifth most commonly diagnosed cancer among US Filipino males (15.7 per 100,000) and the fourth leading cause of cancer death in this group from 1990 through 2010. This cancer is comparatively less common among Filipinas, as the 14th most common cancer and eighth leading cause of cancer deaths. Incidence rates among US Filipino males increased by an average of 1.1 % per year (95 % CI: 0.2, 2.0) since 1990. In the Philippines, the incidence rate during the time period 2003–2007 was almost twice the US rate (30.6 vs. 15.7 cases per 100,000) among males, ranking as the fourth most common cancer. Liver cancer among women in the Philippines was also more common than among Filipinas in the USA (11.8 per vs. 4.6 cases per 100,000; 2003–2007). The most significant risk factor for liver cancer worldwide is infection with hepatitis B virus (HBV); coinfection with hepatitis C virus (HCV) increases risk further [65]. A recent study of hepatitis B surface antigen seroprevalence in the Philippines determined that 16.7 % of randomly sampled adults were seropositive, corresponding to an estimated 7.3 million infected people, which likely explains some proportion of the higher rates in the Philippines as compared to the USA [66]. Additional risk factors, particularly among Filipinos in the USA, include excessive alcohol intake over a long period of time, cirrhosis of the liver (often a result of excessive alcohol intake), and obesity. Immunization against HBV, especially in newborns, reduces the incidence of liver cancer [65, 67]. Successful efforts to provide HBV immunizations and education regarding HBV transmission will impact future liver cancer incidence worldwide.

Kidney and Renal Pelvis Cancer

Kidney and renal pelvis cancer is currently the sixth most commonly diagnosed cancer among US Filipino males and the ninth leading cause of death. In males, the incidence rate in the most recent 5-year period (2006–2010) was 13.7 per 100,000, having increased steadily by an average of 3.4 % per year since 1990 (95 % CI: 2.3, 4.5) (Table 7, Fig. 2). In females, the incidence rate was less than half that for males (4.5 per 100,000) but also rose steadily since 1990 (2.5 % per year; 95 % CI: 1.0, 4.1). From 2003 through 2007, incidence rates for US Filipinos were twice those for males and females in the Philippines (6.2 and 2.8 cases per 100,000, respectively). In addition to increasing age, other established risk factors for kidney and renal pelvis cancer are cigarette smoking, obesity, and hypertension [68]. According to 2011/2012 data from the CHIS, 18.1 % of Filipino men in California are current smokers, while 27.9 % are former smokers [41], with little change since 2007 [69]. For women, smoking prevalence was low but appears to be increasing, up from 4.6 to 7.8 % from 2007 to 2011/2012. CHIS data show increases from 2007 to 2011/2012 in the percentage of adults who are overweight for both Filipino males and females (BMI > 25: 57.7–69.5 % among males, 32.4–42.4 % among females). While it is not clear why kidney cancer incidence rates are higher in Filipinos in the USA than in the Philippines, differences in smoking rates and increase in body weight due to acculturation, in addition to increased screening rates and changes in diagnostic procedures, may be relevant.

Non-Hodgkin Lymphomas (NHL)

NHL was the fourth most common cancer among US Filipino men and the sixth most common cancer among US Filipino women from 2003 through 2007. In the USA, it ranked as the sixth most common cause of cancer death among Filipino men and women. Incidence rates were higher for Filipino males and females in the USA (18.2 and 12.7 per 100,000, respectively) than in the Philippines (9.4 and 7.1 per 100,000, respectively) during 2003–2007. A prior assessment in California found nearly identical incidence rates for foreign-born and US-born Filipinos [70]. NHL incidence trends have been stable since the 1990s. Risk factors for NHL are not well understood, but rates were higher among men than among women, both in the USA and in the Philippines, and it is slightly more common among men older than 65 years of age. Immune system deficiency, such as that occurs with infection with HIV, is associated with an increased risk. Rates of NHL are substantially lower among Filipinos (and all Asian ethnic groups in the USA and Asia) than non-Hispanic Whites [71]. As NHL represents an assortment of subtypes heterogeneous with respect to histologic, clinical, prognostic, and (likely) etiologic characteristics, incidence of distinct NHL subtypes should be assessed among Filipinos. Evidence from a prior analysis of NHL subtype incidence in all Asians combined showed increasing risks of indolent lymphoma subtypes (follicular lymphoma, chronic lymphocytic leukemia/small cell lymphoma) among Asians with US birthplace and neighborhood acculturation indicators, pointing to an important influence of environmental factors that change with immigration and acculturation to a Westernized lifestyle [70].

Ovarian Cancer

In recent years, ovarian cancer was the seventh most common cancer type among US Filipinas and the sixth most common cancer type among women in the Philippines; in the USA, it was the fifth leading cause of cancer death. The incidence rate was lower in the USA (10.0 cases per 100,000) than in the Philippines (16.0 cases per 100,000) from 2003 through 2007, but incidence rates have remained stable in both populations. Risk factors for ovarian cancer include increasing age (55 years and older), nulliparity, and the use of hormone replacement therapy. A family history of ovarian cancer is also a strong risk factor; it is estimated that heredity constitutes 5–10 % of all ovarian cancers [72–77]. Factors that reduce risk include the use of oral contraceptives, surgical tubal ligation, and hysterectomy [76]. Study of the prevalence of these risk factors, specifically the use of oral contraceptives and postmenopausal hormone replacement therapy, as well as certain genetic mutations (e.g., BRCA) among the US Filipina and Philippines populations, should be conducted to better understand the higher incidence of ovarian cancer in the Philippines vs. US Filipinas.

Leukemia

From 1990 to 2010, the incidence of leukemia in US Filipino males declined. In the early 1990s, this cancer ranked as the sixth most commonly diagnosed cancer among Filipino males and in the most recent time period (2006–2010) as the tenth most common cancer, with an incidence rate of 9.5 cases per 100,000. Among US Filipinas, the rate has remained stable or declined slightly; for 2006–2010, it was 6.7 cases per 100,000. Leukemia is ranked as the seventh leading cause of cancer death in both Filipinos and Filipinas in the USA. From 2003 through 2007, the incidence rates for males in the Philippines and in the USA were similar (8.8 vs. 9.2 cases per 100,000, respectively), but among females, the incidence rate in the Philippines was 80 % higher than the US rate (8.0 vs. 6.3 cases per 100,000, respectively). For the period 1973–1986, incidence rates similarly had been reported as higher in the Philippines than in the USA among females, but not males [78]. Smoking and exposure to radiation and certain chemicals, particularly benzene, are risk factors for leukemia [79, 80]. However, risk factors differ by leukemia subtype, so future studies should compare incidence rates of leukemia by subtype in the Philippines and the USA to better understand the geographical differences in incidence among females.

Oral Cavity and Pharyngeal Cancers

Cancers of the oral cavity and pharynx were the ninth most common type of cancer among US Filipino males but, at 15th, was considerably less common among females. From 2006 to 2010, the incidence rate for US Filipino males was twice that for females (9.5 vs. 4.2 per 100,000), and this group of cancers is ranked the tenth leading cause of cancer death among US Filipino males (2.5 per 100,000). From 1990 through 2010, the incidence rate in the USA declined significantly among females (APC = –2.8 %; 95 % CI: –4.0, –1.5) and was stable among males. Only nasopharyngeal cancer incidence rates are reported in the Philippines data, which were slightly lower than the US rates for oral and pharyngeal cancers among males and females (7.2 and 2.9 per 100,000, respectively) [18, 19]. Risk factors for these cancers include diet, cigarette smoking, and chewing tobacco, as well as heavy alcohol use and infection with Epstein-Barr virus and HPV [81, 82]. As described above, smoking prevalence among US Filipino males has remained relatively stable in recent years but increased among females, which may have an effect on future trends of oral and pharyngeal cancer in this group [41].

Bladder Cancer

Bladder cancer was the 7th most common cancer diagnosed in US Filipino males and the 17th most common cancer in US Filipinas from 2006 through 2010. The incidence rate among US Filipino males in the most recent 5-year period was more than three times that among females (10.7 vs. 2.9 per 100,000). For males, annual

rates have been stable, while for females, rates increased by an average 1.9 % per year from 1990 through 2010 (95 % CI: 0.1, 3.7). Bladder cancer incidence rates were slightly lower in the Philippines than in the USA for males (8.0 per 100,000) and similar for females (2.8 per 100,000) during 2003–2007. Cigarette smoking, occupational exposures, various medical conditions, and related treatment are major risk factors for this cancer [83, 84]. The increasing incidence rates among US Filipinas may be related to smoking patterns, given evidence of increases in smoking rates among Filipinas [41, 69]. In the USA, approximately 80 % of bladder cancer diagnoses are considered noninvasive or "superficial," meaning many of these cancers may be cured [83]; indeed, mortality is low and the 5-year survival for this cancer in the general population is estimated to be 77 % [85]. Further study into differences in smoking patterns between the USA and Philippines and its impact on bladder cancer (and other smoking-related cancers) warrant study.

Pancreatic Cancer

Pancreatic cancer was the eighth most common cancer in US Filipino males and females from 2006 through 2010, and the fifth and fourth leading cause of cancer death, respectively. Although US Filipino males had a higher incidence rate than Filipinas (10.0 and 8.7 per 100,000), incidence has increased among females since 1990 (1.5 % per year; 95 % CI: 0.4, 2.7) and was stable in males. Incidence of this cancer in the Philippines (7.1 and 6.7 per 100,000) from 2003 to 2007 was slightly lower than in the USA for both males and females (10.0 and 8.7 per 100,000) from 2006 to 2010. Risk factors for pancreatic cancer are not well understood, but they include cigarette smoking, obesity, chronic pancreatitis, diabetes, family history of pancreatitis or pancreatic cancer, and mutations in the BRCA2 gene [86, 87]. This cancer has a poor prognosis in all racial/ethnic groups, with approximately only 7 % of all diagnoses surviving 5 years. Current smoking patterns may affect future incidence of pancreatic cancer, particularly increasing prevalence with acculturation among US Filipino females. It has recently been shown that pancreatic cancer risk dropped quickly after smoking cessation, suggesting that smoking may be a late-stage carcinogen [88].

Summary

The incidence and mortality patterns and trends presented for Filipinos in this chapter provide data to support targeted areas for cancer prevention, such as obesity for reducing the risks of uterine, colorectal, and breast cancers, and smoking prevention and cessation for lung, kidney, oral cavity and pharyngeal, bladder and pancreatic cancers. The continuing increases in rates of breast, lung, thyroid, kidney, and bladder cancers among Filipinas and of kidney cancer among Filipino males are of particular concern and warrant further attention. For those sites that demonstrate

changing trends or dramatic differences between Filipinos in the USA and in the Philippines, further targeted studies can leverage these incidence patterns to elucidate environmental and modifiable risk factors.

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Cancer Screening Among Asian Americans

Annette E. Maxwell, Victoria M. Taylor, and Roshan Bastani

Abstract Cancer screening tests such as mammograms, Pap smears, and colonoscopies can help detect cancer at an early stage, before symptoms appear. Some screening tests such as colonoscopy and Pap smears can also detect precancerous abnormal tissue, which if removed can prevent the occurrence of cancer. Generally, the earlier cancer is detected, the easier it is to treat. Survival and mortality outcomes are also much better for cancer detected at an early versus late stage. However, in addition to benefits, some screening tests carry risks, and finding the cancer early does not always improve the person's health or help the person live longer [1].

This chapter will examine the utilization of cancer screening tests among selected Asian American ethnic groups and describe the research on factors that are associated with screening. We will give examples of interventions to promote cancer screening that have been tested in Asian American populations and summarize both the scientific knowledge and research gaps regarding cancer screening. The chapter will close with recommendations and next steps for research and practice on cancer screening among Asian Americans.

Keywords Chinese Americans • Japanese Americans • Filipino Americans • Southeast Asians • Vietnamese Americans • Korean Americans • Hmong • Breast cancer screening • Cervical cancer screening • Colorectal cancer screening • Hepatitis B virus testing • Correlates of screening • Interventions to promote cancer screening

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Introduction

Cancer screening tests such as mammograms, Pap smears, and colonoscopies can help detect cancer at an early stage, before symptoms appear. Some screenings tests such as colonoscopy and Pap smears can also detect precancerous abnormal tissue, which if removed can prevent the occurrence of cancer. Generally, the earlier cancer is detected, the easier it is to treat. Survival and mortality outcomes are also much better for cancer detected at an early versus late stage. However, some screening tests carry risks, and finding the cancer early does not always improve the person's health or help the person live longer.

Many organizations, including the American Cancer Society, issue cancer screening guidelines, but the guidelines issued by the US Preventive Services Task Force are the most commonly referenced and utilized. The US Preventive Services Task Force, which is an independent, volunteer panel of national experts in prevention and evidence-based medicine, develops recommendations for or against screening tests based on a review of high-quality scientific evidence and by weighing the potential benefits and harms of each screening test. The Task Force also periodically updates its recommendations based on new scientific evidence [2]. Table 1 shows the current recommendations relevant for cancer screening. Only tests that receive a Grade A or B are recommended.

Few studies have examined utilization of cancer screening tests among Asian American populations, and most have focused on utilization of *mammograms* for early detection of breast cancer, *Pap smears* for early detection of cervical cancer, and *fecal occult blood tests and colonoscopies* for the prevention and early detection of colorectal cancer. Compared to other racial/ethnic groups in the USA, Asian Americans have a relatively high risk of infection with hepatitis B virus (HBV), which accounts for 80 % of liver cancer cases in this group. HBV testing can lead to earlier detection and hence potentially reduce the onset of serious sequelae of chronic liver disease. In addition, testing and, if indicated, vaccination can reduce HBV transmission (*see* Chap. 10). Thus, *hepatitis B testing* is recommended for Asian American populations, and studies have been conducted on this topic in a number of Asian American ethnic groups.

There is scant research among Asian Americans on *human papillomavirus* (*HPV) testing*, on the utilization of *lung cancer screening* and on *BRCA risk assessment* for high-risk Asian American groups. Asian Americans experience high incidence and mortality rates of stomach cancer (see Chap. 11). *Stomach cancer screening* using photofluorography or upper endoscopy is recommended in some Asian countries (e.g., Japan and South Korea). However, we will not discuss screening for stomach cancer in this chapter since there is no screening recommendation in the USA. *Prostate cancer screening* using prostate-specific antigen is no longer recommended by the US Preventive Services Task Force and will also not be discussed.

As described in the previous and subsequent chapters, specific Asian ethnic groups in the USA exhibit varying risk profiles of cancer incidence and mortality due to differences in migration history, lifestyle, and environmental exposures. In addition, there are vast differences among Asian ethnic groups with respect to

Table 1 US Preventive Services Task Force recommendations relevant for cancer screening

Topic	Description (date of most recent recommendation)	Grade
Breast cancer screening	The USPSTF recommends biennial screening mammography for women aged 50–74 years (November 2009)	B
Cervical cancer screening	The USPSTF recommends screening for cervical cancer in women aged 21–65 years with cytology (Pap smear) every 3 years or, for women aged 30–65 years who want to lengthen the screening interval, screening with a combination of cytology and human papillomavirus (HPV) testing every 5 years (March 2012)	A
Colorectal cancer screening	The USPSTF recommends screening for colorectal cancer using fecal occult blood testing (annually), sigmoidoscopy (every 5 years), or colonoscopy (every 10 years) in adults beginning at age 50 years and continuing until age 75 years. The risks and benefits of these screening methods vary (October 2008)	A
Lung cancer screening	The USPSTF recommends annual screening for lung cancer with low-dose computed tomography in adults aged 55–80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery (December 2013)	B
Hepatitis B screening: nonpregnant adolescents and adults	The USPSTF recommends screening for hepatitis B virus infection in persons at high risk for infection (May 2014)	B
Hepatitis B screening: pregnant women	The USPSTF strongly recommends screening for hepatitis B virus infection in pregnant women at their first prenatal visit (June 2009)	A
BRCA risk assessment and genetic counseling/ testing	The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with one of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (*BRCA1* or *BRCA2*). Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing (December 2013)	B
Prostate cancer screening	The USPSTF recommends against prostate-specific antigen (PSA)-based screening for prostate cancer (May 2012)	D

Notes. A: The USPSTF recommends the service. There is high certainty that the net benefit is substantial
B: The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial
D: The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits

socioeconomic status, acculturation, access to care, and other factors that are known to impact cancer screening rates. Therefore, it is important to examine cancer screening in specific Asian ethnic groups, rather than in all Asian ethnic groups combined, to obtain a fine-grained picture of screening uptake as well as factors that may facilitate or impede screening.

Data Sources to Estimate Cancer Screening Rates

There is no national resource that allows for estimation of cancer screening rates among Asians in the USA. Therefore, screening estimates must be compiled from a patchwork of sources of varying breadth and quality. Most information on cancer screening for the general US population is obtained from survey research, and this is the case for information on Asians as well. Among Asian Americans, surveys have generally been conducted by telephone or in face-to-face settings. Some surveys have included randomly selected samples of participants (population-based sample), while others have utilized convenience samples, often recruited with the help of community organizations that serve members of the target population. In both type of surveys, screening is assessed through self-reports, which may suffer from recall bias and social desirability response bias.

Very few *population-based surveys* that assess cancer screening have included sufficient Asian American participants, thereby limiting ability to analyze data and report screening rates for specific Asian American groups [3]. Some surveys such as the California Health Interview Survey have included adequate samples of a few of the largest Asian ethnic groups to be able to obtain subgroup level estimates of screening rates. The California Health Interview Survey is a telephone survey that has been conducted every 2 years since 2001 in English, Spanish, Chinese (Mandarin and Cantonese dialects), Vietnamese, and Korean. The survey oversamples Asian ethnic groups so that each group's total sample of adults reaches a target of 500 [4]. Because California is home to about 5.5 million Asian Americans, almost one third of all Asian Americans in the USA [5], and because the California Health Interview Survey is conducted in four Asian languages which allows non-English speakers to participate, its data are frequently used to estimate cancer screening among Asian Americans nationally (e.g., [6–8]). However, even population-based surveys including the California Health Interview Survey have several limitations: Recent immigrants who may have limited English fluency and who do not speak one of the survey languages cannot participate. Surveys usually include only a few questions each on a large number of topics and do not provide much detail on cancer screening and on factors that are associated with screening such as awareness of a screening test or barriers to screening. Since these surveys are designed to assess health issues in the general population, they may only ask questions on health topics that are relevant for the majority of respondents; health issues that are important for Asian Americans but not for all racial/ethnic groups, such as hepatitis B testing and vaccination, may not be assessed in these surveys. Population-based surveys typically do not provide data on smaller Asian American groups such as the Hmong, Thai, Native Hawaiians, and Pacific Islander populations.

Community surveys are often conducted in specific Asian American ethnic groups in various Asian languages, typically with help from Asian American community organizations. While some community surveys recruit participants in a systematic fashion, such as through community directories or by selecting common names from telephone directories [9, 10], others use snowball sampling or recruit individuals at specific locations such as faith-based organizations, Asian grocery

stores, and nail salons [11, 12]. Surveys are often conducted face-to-face, taking advantage of existing relationships with community members and allowing interviewers to establish some rapport with respondents. These convenience samples often include individuals with low levels of income and education and recent immigrants who may be less likely to respond if they received a "cold call" from a university or survey firm asking them to participate in a survey. Many of these surveys are conducted in a single Asian American ethnic group, but comparison of screening rates across Asian ethnic groups and across surveys is usually possible because most surveys assess cancer screening using standard questions such as "have you ever had (specific screening test)?" and, if yes, "when did you receive the last (specific screening test) for routine screening?" Comparison of knowledge and beliefs related to specific screening tests across Asian ethnic groups can be more challenging because there is less homogeneity in how questions are phrased and because translations into many different Asian languages can introduce small differences in meaning. Few community-based surveys include more than one Asian American ethnic group [13–15].

Both population-based samples and convenience samples have strengths and limitations. Therefore, we use both as data sources for reporting screening rates and factors that are associated with screening among Asian Americans. More recently, *electronic health records* have been utilized to assess cancer screening and to conduct comparisons among members of various racial/ethnic groups [16]. Electronic health records are usually considered the gold standard for assessing receipt of medical care and don't suffer the limitations of self-report. However, even if obtained from a large health-care organization serving an ethnically diverse patient population, electronic health records only include patients with access to care, and some reports are further limited to "active" patients who have used at least one primary care-related visit during a specific time period, for example, the past 2 years [16]. While these data sources are informative, many patients without health insurance, who often have the lowest cancer screening rates [17], are not included in electronic health records.

Cancer Screening Rates Among Asian Americans

Mammography Screening

Although some organizations such as the American Cancer Society recommend mammography screening for women 40 years and older, the US Preventive Services Task Force currently recommends biennial mammography screening only for women between 50 and 74 years of age. Many reports on mammography screening include women 40 years and older, especially if they are based on studies that were conducted before the US Preventive Services Task Force changed their guidelines from women 40 years and over to women 50–74 years of age. Estimates for screening rates vary among different surveys, but most surveys indicate that Asian American women underutilize mammography screening relative to White and

Table 2 Breast and cervical cancer screening rates among Asian American ethnic groups, California Health Interview Survey 2011–2012 (mammogram in past 2 years) and 2007 (Pap test in past 3 years), % (95 % confidence interval)

Asian American ethnic group	Had a mammogram in the past 2 years (women 40+)	Had a Pap test in the past 3 years (women 18+)
Filipina	78.2 (70.2–86.2)	75.4 (68.7–82.2)
Vietnamese	75.6 (67.8–83.4)	76.2 (66.1–86.3)
Chinese	72.8 (66.9–78.7)	64.9 (58.8–71.0)
Korean	51.8 (42.6–60.9)	71.0 (63.4–78.5)
South Asian	68.8 (57.0–80.6)	73.4 (63.3–83.5)
Japanese	84.1 (77.3–90.9)	75.2 (66.3–84.1)

Source: http://healthpolicy.ucla.edu/publications/Documents/PDF/2014/mammogramsfactsheet_apr2014.pdf and AskCHIS

African American women. For example, in the 2010 National Health Interview Survey, 64 % of Asian American women 50–74 years of age reported receipt of a mammogram in the past 2 years, compared to 73 % of non-Hispanic White and African American women [3].

Based on the data from the 2011–2012 California Health Interview Survey (http://healthpolicy.ucla.edu/publications/Documents/PDF/2014/mammogramsfactsheet_apr2014.pdf, accessed 11/12/14), 72 % of Asian American women 40 years and older reported receipt of a recent mammogram in the past 2 years, compared to 83 % of African American, 81 % of White, and 77 % of Latina women. Screening rates among women 40 years and older from different Asian American ethnic groups ranged from 52 % (95 % confidence interval 43–61 %) among Korean American women to 84 % (95 % confidence interval 77–91 %) among Japanese American women (see Table 2), a difference of 32 % points. Screening rates are slightly higher among women 50 years and older, but the screening pattern remains unchanged.

One of the Healthy People 2020 national goals for improving the health of Americans is to increase the proportion of women who receive a mammogram according to the guidelines to 81 % (https://www.healthypeople.gov/2020/topics-objectives/topic/cancer/objectives, accessed 11/20/14). Japanese American women residing in California have already achieved this goal and Filipina-, Vietnamese-, and Chinese Americans residing in California can potentially achieve this goal. However, given the current screening rate, it is unlikely that South Asian- and Korean American women will achieve this goal by 2020.

Cervical Cancer Screening

Asian American women also underutilize cervical cancer screening, but disparities among Asian American ethnic groups are less pronounced than for mammography screening. Based on the 2007 California Health Interview Survey, which assessed receipt of a Pap test but not HPV screening, adherence to screening guidelines

ranges from 65 % among Chinese American women to 76 % among Vietnamese women, a difference of 11 % points (see Table 2). Screening rates in all Asian American groups are substantially lower than rates among non-Hispanic Whites (87 %), African Americans (88 %), and Latinas (85 %). The Healthy People 2020 goal is to increase the proportion of women who receive cervical cancer screening according to the guidelines to 93 %. Given the current screening rate, it is unlikely that any Asian American ethnic group will achieve this goal by 2020.

Colorectal Cancer Screening

The American Cancer Society recommends receipt of a guaiac-based fecal occult blood test (FOBT) or fecal immunochemical test (FIT) ever year, *or* flexible sigmoidoscopy every 5 years, *or* colonoscopy every 10 years, *or* double-contrast barium enema every 5 years, *or* CT colonography (virtual colonoscopy) every 5 years for men and women 50 years and over at average risk for developing colorectal cancer. The US Preventive Services Task Force recommends colorectal cancer screening tests only for individuals between age 50 and 75. Between 2001 and 2009, the California Health Interview survey assessed receipt of a stool blood test and sigmoidoscopy or colonoscopy in five cross-sectional surveys. Figure 1 shows the proportion of respondents 50 years of age and older who are adherent to colorectal cancer screening guidelines based on receipt of a fecal occult blood test within the past 12 months or a colonoscopy or sigmoidoscopy within the past 5 years, since not all survey years distinguished between these two procedures. Estimates include colorectal cancer screening for any reason to maintain consistency across survey years and are standardized to the age and gender distribution of the 2001 California population. Analyses were conducted using survey replicate weights for Asian ethnic groups with sufficient sample size [18].

As shown in Fig. 1, there is an upward trend in colorectal cancer screening utilization among all racial/ethnic groups. The proportion of Asian Americans that are up to date with colorectal cancer screening is estimated to be above 60 % in 2009, which is slightly lower than the estimate for Whites and African Americans. The lower panel in Fig. 1 suggests that disparities in colorectal cancer screening widened from 2001 to 2005 and narrowed between 2005 and 2009. In 2009, the last survey year in which colorectal cancer screening was assessed in the California Health Interview Survey, higher screening rates were observed among Japanese-, Chinese-, and Vietnamese Americans and lower screening rates among Korean- and Filipino Americans. There were no statistically significant differences in screening rates between males and females in any of these Asian ethnic groups (AskCHIS).

The Healthy People 2020 goal is to increase the proportion of adults 50–75 years who receive a colorectal cancer screening according to the guidelines to 70.5 %. While Japanese-, Chinese-, and Vietnamese Americans residing in California are close to achieving this goal, it is uncertain that Korean- and Filipino Americans will achieve the 2020 goal, given the current screening rates and temporal trends. It should also be noted that screening rates in California are relatively high compared

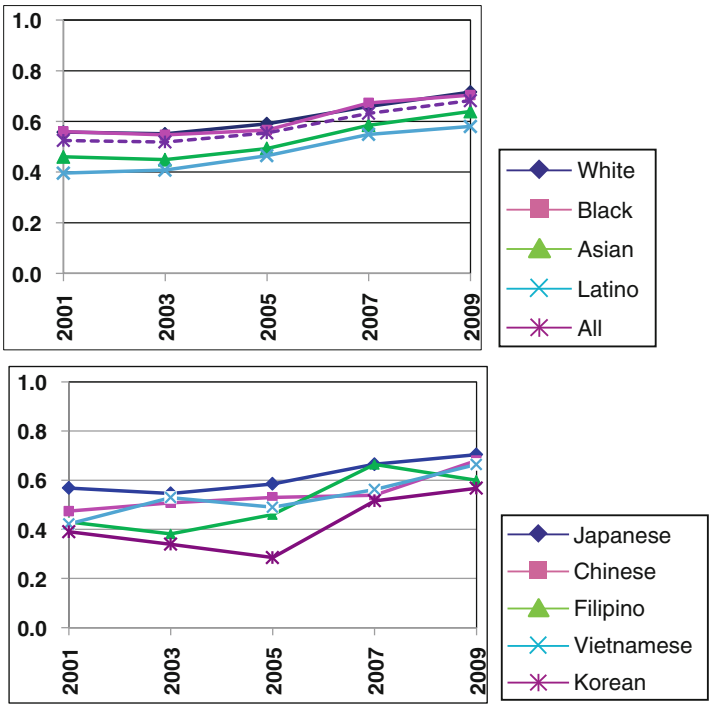

Fig. 1 Estimated age- and gender-standardized proportion of California residents aged 50 years and older who are adherent to colorectal cancer screening guidelines, California Health Interview Survey 2001–2009 (2001–2005 data were previously published in [18])

to other states. Based on data from the Behavioral Risk Factor Surveillance System, California ranks number 14 out of 51 states with regard to colorectal cancer screening prevalence [19]. According to the data from the 2010 National Health Interview Survey, only 46% of Asians residing in the USA are up to date with colorectal cancer screening [19].

Hepatitis B Testing

Because Asian Americans are at increased risk for hepatitis B infection and resulting liver disease and liver cancer (see Chap. 10), the US Preventive Services Task Force and the American Association for the Study of Liver Diseases recommend screening for hepatitis B and subsequent vaccination, if appropriate [20, 21]. Screening is important because approximately 65% of those who are infected with hepatitis B do not know that they are infected [22]. Screening is an effective method of limiting the spread of hepatitis B by identifying uninfected individuals who will need vaccination to prevent future infection and by identifying infected individuals who will need monitoring or treatment and counseling to reduce verti-

cal (from mother to child) and horizontal transmission to close contacts (e.g., household members). The standard test for hepatitis B infection involves the detection of the hepatitis B surface antigen, HBsAg [23].

Despite their elevated disease risk, hepatitis B testing rates among Asians in the USA are suboptimal with estimates ranging from 11 to 65 % based on self-reports in different Asian ethnic groups [9, 12, 24–31]. As shown in Table 3, only few studies have assessed hepatitis B testing rates in Asian American samples. The huge

Table 3 Hepatitis B screening rates among Asian American ethnic groups

Citation	Asian American population, study area	% ever screened for HBV	Study sample, age, source of study sample, survey method, and year(s) of study
Taylor et al. (2006) [28]	**Chinese immigrants** in Seattle	48	*N* = 395, ages 20–64 years; identified through Chinese last names from a telephone directory; in-person interviews; survey cooperation rate 58 %; **2005**
Tanaka et al. (2014) [24]	**Chinese immigrants** in Washington, DC area	65	*N* = 252, age > 50 years; recruited from Chinese-speaking physicians' offices; patients had at least one doctor's visit in the past 2 years; telephone survey; response rate 49 **%; 2008–2011**
Bastani et al. (2007) [29]	**Korean** in Los Angeles, CA	56	*N* = 141 adults; recruited at 5 Korean churches and one Korean-serving primary care clinic; in-person interviews, self-administered questionnaires or self-administered in a group setting; **2003**
Bastani et al. (2015)[31]	**Korean** in Los Angeles, CA	35	*N* = 866 adults; recruited at 52 Korean churches**;** face-to-face survey; **2007–2010**
Strong et al. (2012) [25]	**Chinese, Korean, and Vietnamese** in Maryland	54, 46, and 39	303 Chinese, 294 Korean, and 280 Vietnamese adults; recruited at community organizations, faith-based organizations, language schools, grocery stores, and nail salons; self-administered survey; **2009–2010**
Ma et al. (2010) [12]	**Chinese, Korean, Vietnamese, and Cambodian** in Greater Philadelphia area, New Jersey, and New York City	38, 32, 20 and 11	718 Chinese, 289 Korean, 305 Vietnamese, and 291 Cambodian adults; recruited at Asian American community organizations; in-person interviews; **2005–2006**
Grytdal et al. (2009)[30]	**Cambodian** in Massachusetts; **Vietnamese** in California	49; 63	353 Cambodian adults, 1696 Vietnamese adults; CDC Racial and Ethnic Approaches to Community Health Risk Factor Survey; telephone survey; interview completion rate 25–31 %; **2010**
Nguyen et al. (2010) [26]	**Vietnamese** in Northern California and Washington, DC	62	*N* = 1704 adults; identified through Vietnamese surnames; telephone survey; response rate 27.4 %; **2007–2008**
Taylor et al. (2011) [27]	**Cambodian** in Seattle	50	*N* = 667, ages 18–64; identified through Cambodian last names from a telephone directory; in-person interviews; completion rate 70 %; **2010**
Chen et al. (2013) [9]	**Hmong** In Greater Sacramento CA area	18	*N* = 490 adults; identified through Hmong surnames; telephone survey; **2007–2008**

variations in screening rates, even among different studies conducted in the same Asian ethnic group, are probably due to sample differences in demographic characteristics, as well as the variety of sampling and recruitment strategies and interviewing methods that were used.

Correlates of Screening Among Asian Americans

Individual health behaviors related to cancer screening are influenced by a complex myriad of individual, health system, community, and societal level factors. In the following section, we use a conceptual framework, the Health Behavior Framework, to systematically address the multiple determinants of cancer screening and to summarize some of the major findings among Asian Americans. The **Health Behavior Framework** (Fig. 2) is a multidimensional model derived from varying theoretical orientations [32]. It assumes that individual variables and provider and health-care system factors influence behavioral intentions which in turn influence health behavior. Intentions do not automatically translate into behavior. Rather, this connection depends on the absence of barriers and/or presence of supports which may function at the level of the individual (e.g., cultural beliefs), the health system (e.g., practice patterns), or society (e.g., impoverished neighborhood). Some model variables are mutable and are therefore potential targets for interventions (e.g., individual and provider and health-care system factors), while others are immutable, such as demographic factors. Despite some differences, the major drivers of behavior tend to be similar across populations. The Health Behavior Framework

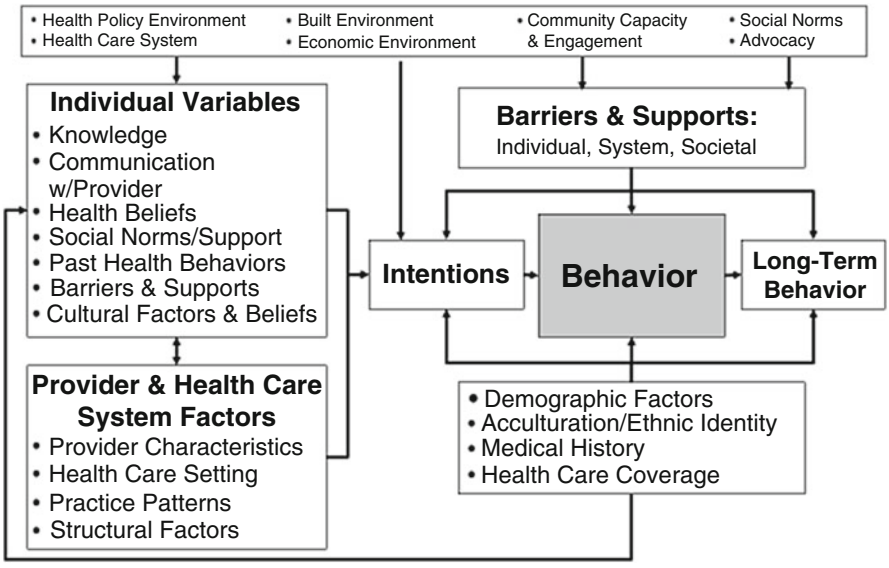

Fig. 2 The Health Behavior Framework

also recognizes the influence of broad socio-ecological factors on cancer screening such as health-care policy and social norms. These factors are theoretically mutable, for example, through health-care reform and long-term community engagement activities or campaigns.

Frequently, factors that have the potential to influence cancer screening and screening behaviors are identified at the same point in time through a survey [7, 11, 25]. This cross-sectional research design allows us to identify *correlates* of screening. Other studies examine the effects of factors identified at baseline on subsequent screening behaviors [33]. Such a longitudinal study design provides stronger evidence than cross-sectional data regarding *predictors* of cancer screening.

Demographic Factors, Acculturation, and Health-Care Coverage

Being married, higher level of income, being proficient in English, and having health insurance have been consistently associated with cancer screening among Asian American ethnic groups, including colorectal cancer screening [11, 34, 35], breast and cervical cancer screening [7, 11, 36], and hepatitis B testing [12, 37]. Several studies have examined the associations between acculturation and cancer screening using various measures of acculturation, such as length of residency in the USA, percent of lifetime in the USA, language proficiency, and language use. Generally, immigrants who have assimilated to the behaviors and beliefs of the host society are better able to obtain health care and have higher screening rates [11], but this is not always the case. A study among Vietnamese Americans found *lower* hepatitis B screening rates among those who had lived in the USA for more than 10 years and spoke Vietnamese less fluently compared to more recent immigrants. The authors suggest that efforts to promote testing in the USA have focused on more recent immigrants and that recent immigrants may be receiving medical care in immigrant and/or refugee clinics, where the providers may be more aware of the need for hepatitis B testing in Asian populations [26]. A study that examined the relative impact of access to care versus acculturation on breast and cervical cancer screening among Asian American women concluded that access explained more variation than acculturation alone for most Asian American ethnic groups that were studied [38]. Since demographic factors and acculturation are not mutable factors, they help to identify population groups with the lowest cancer screening rates that can then be targeted for screening promotion programs rather than inform the content of intervention programs to promote screening.

Individual Variables

Individual variables that influence cancer screening have been widely studied in many different Asian American ethnic groups. The most important variables that have emerged are not being aware of the screening test and the need for screening and

lack of physician recommendation to receive screening [25, 26, 29, 33, 34, 39–41]. For cancer screening tests that require periodic retesting (breast, cervical, colorectal cancer screening), having had a test in the past is an important predictor of future testing [42]. Health beliefs are generally associated with cancer screening in the expected direction: screening is associated with high perceived susceptibility, high perceived severity of the disease, and low barriers to cancer screening [29, 37, 43].

Provider and Health-Care System Factors

The influence of provider and health-care system factors on cancer screening has not been comprehensively assessed among Asian Americans, although most cancer screening tests require a physician exam or referral, suggesting that these factors are extremely important. Strategies that fall into this category and have been shown to increase cancer screening include physician education, physician reminder systems, physician assessment and feedback regarding the proportion of patients that are up-to-date with cancer screening guidelines, and reminder mailings for patients [44–47]. Patient navigation is another strategy that has been shown to increase cancer screening in several Asian American ethnic groups [9, 47–49]. One study in an outpatient health-care organization serving a large number of Asian Americans in Northern California found that screening completion for breast and cervical cancer was positively associated with patient-provider gender concordance, i.e., female physicians had significantly higher breast and cervical cancer screening rates among their Asian American patients [16]. This finding corresponds well with the fact that many Asian American women prefer a female provider for these exams [50, 51].

Barriers to Cancer Screening

Many of the variables discussed above can be conceptualized as barriers, including lack of health insurance, lack of knowledge/awareness of specific screening tests and guidelines, lack of a physician recommendation to get tested, and health beliefs that do not support routine checkups in the absence of symptoms. These are common barriers for many ethnic groups, including Asian Americans. Other barriers that are frequently cited by Asian Americans are lack of time to obtain a screening test, not knowing where to obtain the test, lack of transportation, fear of finding a health problem, and embarrassment or shame [12, 29, 34]. A few studies have reported culturally specific attitudes and beliefs that may function as barriers to cancer screening in specific Asian American ethnic groups, such as the belief that illness is a matter of karma or fate [52, 53]. However, these barriers are less frequently assessed and are not endorsed by all Asian American ethnic groups and not for all cancer screening tests [29].

Overall, correlates of cancer screening among Asian American ethnic groups are similar to those of other US populations. In addition to barriers to screening that are

faced by most ethnic groups, Asian Americans also experience culturally specific barriers to screening which need to be addressed in screening promotion efforts.

Intervention Research to Promote Cancer Screening Among Asian Americans

To address the low utilization of cancer-related screening tests among Asians Americans, many intervention studies have been implemented to test the most effective ways to increase screening participation. The majority of these studies have been conducted in metropolitan areas with relatively large Asian populations such as Los Angeles, San Francisco, Seattle, New York, and Washington, DC.

Study designs that involve concurrent comparison groups and prospective measurement of outcomes, and document actual receipt of screening tests, provide the strongest evidence for the effectiveness of cancer control interventions [54, 55]. This section focuses on studies that used experimental designs (i.e., randomized individuals or groups of people to experimental and control status) or quasi-experimental designs (i.e., compared an experimental group with a nonequivalent control group, no random assignment) and included screening test completion, assessed by self-report or provider report, as an outcome. Control groups for these studies either received no intervention, usual care, a minimal screening-related intervention (e.g., pamphlet), or a non-screening-related intervention (e.g., a physical activity program).

Cancer control interventions can be classified as provider directed (e.g., physician reminders) or client directed (e.g., health education). Client-directed interventions include one-on-one education (tailored or non-tailored), group education, small media (audiovisual and print), navigation (to reduce structural barriers to screening), and mass media [56]. Most previous cancer control initiatives for Asian Americans involved multiple intervention components [55].

Interventions to increase the use of cancer-related screening tests by Asian groups have been delivered in health-care settings, in community settings, and to entire communities. The interventions that were delivered in community settings can be broadly categorized as lay health worker (LHW) outreach or community-based group education. LHW outreach interventions have included one-on-one or group education combined with small media and/or peer navigation. Community-based group education interventions have been delivered by Asian health educators and usually included other components.

The following sections provide information about interventions that were delivered in health-care settings, LHW outreach and community-based group education interventions, one-on-one education and small media interventions, and community-level interventions. These studies focused on individuals who were nonadherent to breast, cervical, and colorectal cancer screening guidelines as well as individuals who had never been screened for HBV. As discussed previously, guidelines for cancer screening have changed over time. Eligibility criteria for cancer control intervention studies were based on the guidelines when they were conducted. Table 4 gives examples of individual and cluster-randomized controlled trials that evaluated cancer control inter-

Table 4 Examples of individual and cluster randomized trials that resulted in increased cancer screening rates

Intervention type(s) Publication	Participant characteristics Study location(s)	Experimental group intervention component(s) Control group intervention	Primary evaluation method(s) Sample size(s)	Key finding(s)
Breast cancer screening				
LHW outreach Nguyen et al. [61]	**Vietnamese** ≥40 years Santa Clara County, California	Group education Peer navigation Media-based education Mammography media-based education	Baseline survey Follow-up survey after an interval of 5 months 1,100 randomized 1,089 with follow-up data	Mammography in the previous 2 years increased significantly in the experimental group (65–82 %, $p<0.001$) but not in the control group (74–76 %, $p>0.05$)
Group education Lee et al. [67]	**Korean** immigrant ≥40 years No mammogram in past year Cook County, Illinois	Group education Couples discussion activity Nutrition group education	Follow-up survey 15 months after intervention 428 randomized 395 with follow-up data	56 % of the experimental group and 42 % of the control group reported mammography ($p=0.004$)
Group education Lee-Lin et al. [68]	**Chinese** immigrant ≥40 years No mammogram in past year Portland, Oregon	Group education Telephone counseling Navigation English language mammography brochure	Follow-up survey 12 months after intervention 300 randomized 280 with follow-up data	71 % of the experimental group and 43 % of the control group reported mammography ($p<0.001$)
Cervical cancer screening				
LHW outreach **Small media** Taylor et al. [64]	**Chinese** 20–69 years No Pap test in past 2 years or not intending to get Pap test in next 2 years Seattle, Washington Vancouver, British Columbia	*Experimental 1:* One-on-one education Chinese language video and print materials Peer navigation *Experimental 2*: Chinese language video and print materials None	Follow-up survey 6 months after randomization 482 randomized 402 with follow-up data	39 % of experimental group 1, 25 % of experimental group 2, and 15 % of the control group reported Pap testing (experimental group 1 versus control, $p<0.001$; experimental group 2 versus control, $p=0.03$; experimental group 1 versus experimental group 2, $p=0.02$)

LHW outreach Mock et al. [60]	**Vietnamese** ≥18 years Santa Clara County, California	Group education Peer navigation Media-based education Pap testing media-based education	Baseline survey Follow-up survey after an interval of 4 months 1,005 randomized 952 with follow-up data	Pap testing ever increased significantly in the experimental group (66–82 %, $p<0.001$) and the control group (70–76 %, $p<0.001$) but the experimental group increase was significantly greater than the control group increase ($p<0.001$)
LHW outreach Taylor et al. [62]	**Vietnamese** 20–79 years No Pap test in past 3 years (aged 20–69) Never had Pap test (aged 70–79) Seattle, Washington	One-on-one education Vietnamese language video and pamphlet Physical activity print materials	Follow-up survey 6 months after randomization 234 randomized 174 with follow-up data	33 % of the experimental group and 18 % of the control group reported Pap testing ($p=0.02$)
Colorectal cancer screening				
Health care system Tu et al. [57]	**Chinese** 50–78 years No FOBT in past year or colonoscopy in past 10 years Seattle, Washington	One-on-one education Chinese language video and print materials FOBT kit and instruction sheet Usual care	Medical records review 6 months after randomization 210 randomized	70 % of the experimental group and 28 % of the control group completed FOBT ($p<0.001$)
Group education Maxwell et al. [70]	**Filipino** 50–70 years No FOBT in past year, sigmoidoscopy in past 5 years or colonoscopy in past 10 years Los Angeles, California	*Experimental 1*: Group education Filipino language information packet and pamphlet FOBT kit Reminder letter *Experimental 2*: Same as experimental group 1 but no FOBT kit Physical activity group education	Follow-up survey 6 months after intervention 548 randomized 432 with follow-up data	30 % of experimental group 1, 25 % of experimental group 2, and 9 % of the control group completed colorectal cancer screening in an intent-to-treat analysis (experimental group 1 versus control, $p<0.001$; experimental 2 versus control, $p<0.001$; experimental group 1 versus experimental group 2, $p>0.05$)

(continued)

Table 4 (continued)

Intervention type(s) Publication	Participant characteristics Study location(s)	Experimental group intervention component(s) Control group intervention	Primary evaluation method(s) Sample size(s)	Key finding(s)
One-on-one education **Small media** Walsh et al. [80]	**Vietnamese** 50–79 years Santa Clara County, California	*Experimental 1*: Telephone counseling Vietnamese language brochure FOBT kit *Experimental 2*: Same as experimental group 1 but no telephone counseling Usual care	Baseline survey Follow-up survey after an interval of 12 months 793 with baseline data 640 with follow-up data	FOBT in the previous 12 months increased in experimental group 1 (53–79 %), experimental group 2 (56–65 %) and the control group (46–58 %) but the experimental group 1 increase was significantly greater than the control group increase ($p=0.006$) and the experimental group 2 increase ($p<0.001$)
Hepatitis B screening				
LHW outreach Chen et al. [9]	**Hmong** 18–64 years No previous HBV test Greater Sacramento, California	One-on-one education Peer navigation Nutrition LHW outreach	Follow-up survey 6 months after randomization 260 randomized 217 with follow-up data	24 % of the experimental group and 10 % of the control group reported HBV testing ($p=0.006$)
Health care system Hsu et al. [45]	**Chinese or Vietnamese** 18–64 years No record of HBV test Sacramento, California	Provider prompt Usual care	Medical records review 3 months after clinic visit 175 randomized	34 % of the experimental group and 0 % of the control group completed HBV testing ($p<0.001$)
LHW outreach Taylor et al. [63]	**Kampuchean (Cambodian)** 18–64 years No previous HBV test Greater Seattle, Washington	One-on-one education Khmer language video and pamphlet Physical activity LHW outreach	Follow-up survey 6 months after randomization 250 randomized 199 with follow-up data	22 % of the experimental group and 3 % of the control group reported HBV testing ($p<0.001$)
Group education Bastani et al. [31]	**Korean** 18–64 years No previous HBV test Los Angeles, California	Group education Korean language print materials Physical activity and nutrition group education	Follow-up survey 6 months after intervention 1123 randomized 961 with follow-up data	19 % of the experimental group and 6 % of the control group reported HBV testing ($p<0.001$)

ventions for Asian Americans. The tabulated examples are trials that demonstrated an intervention effect in primary analyses that included the whole study group. Quasi-experimental studies, negative trials, and trials that only demonstrated an intervention effect in secondary subgroup analyses are not included in the table.

Evaluations of Interventions Delivered in Health-Care Settings

Tu and colleagues have conducted two studies of colorectal cancer screening interventions for patients of a community clinic system serving Asian patients. Both interventions were delivered during routine clinic visits. In the first study, Chinese patients who were eligible for screening were randomized to a health educator intervention group or usual care control group. The intervention had a highly significant effect on fecal occult blood testing (FOBT) completion rates [57]. In the second study, trained medical assistants routinely provided Vietnamese language videos and pamphlets at an experimental clinic but not at a control clinic. Adherence to screening guidelines did not increase significantly in either clinic during the intervention period. However, subgroup analyses showed a significant intervention effect for guideline adherence among patients who were nonadherent at baseline [58].

Provider prompts about HBV testing were evaluated in a cluster-randomized trial, with primary care physician as the randomization unit. The study group included Chinese and Vietnamese patients of a primary care clinic network who had no record of HBV testing. Experimental group physicians received electronic health record prompts before scheduled appointments. Patients of experimental group physicians were significantly more likely to complete HBV testing than patients of control group physicians [45].

Lay Health Worker Outreach Trials

The Vietnamese Community Health Promotion Project in San Francisco has conducted one quasi-experimental study and two trials of LHW group education. The quasi-experimental study focused on both breast and cervical cancer screening. LHWs conducted over 200 small-group educational sessions and distributed small media in an experimental area (Tenderloin District of San Francisco). Mammography and Pap testing rates increased significantly in the Tenderloin District but not in the control area (Sacramento) [59]. One of the trials addressed breast cancer screening and the other trial addressed cervical cancer screening. Both trials compared LHW group education and peer navigation combined with media-based education to media-based education alone. The combined intervention was more effective in increasing mammography, as well as Pap testing levels [60, 61].

Multiple trials have evaluated LHW outreach interventions for Asian groups that included one-on-one education combined with small media and/or peer navigation. These trials focused on promoting Pap testing among women who underutilized Pap

testing or HBV testing among men and women who had never been tested for HBV. All but one of these studies were conducted in the Pacific Northwest. The LHW interventions were effective in promoting Pap testing in Chinese and Vietnamese communities, as well as HBV testing in Kampuchean (Cambodian) and Hmong communities [9, 62–64]. However, they were not effective in promoting Pap testing among Kampuchean (Cambodian) women or HBV testing among Chinese men and women [65, 66].

Community-Based Group Education Studies

Two trials have documented that group education, delivered in community settings, can positively impact mammography completion rates among immigrant women who have not been recently screened. One of these studies evaluated group education for Korean immigrant women and their husbands combined with a couple discussion exercise that was subsequently completed at home [67]. The other study evaluated group education combined with telephone counseling and navigation for Chinese immigrant women [68].

Los Angeles researchers conducted cluster-randomized trials of breast and cervical cancer screening group education, as well as colorectal cancer screening group education (with or without the provision of FOBT kits) for Filipinos. Both trials involved group education by Filipino health professionals [69, 70]. In the breast and cervical cancer screening trial, equivalent increases in mammography and Pap testing rates were observed in experimental and control arms. However, mammography increased significantly more in the experimental arm than in the control arm among recent immigrants [69]. In the colorectal cancer screening trial, experimental arm participants were significantly more likely to be adherent to screening guidelines than control group participants at follow-up (regardless of whether or not they received FOBT kits) [70]. In another trial in the Korean community, this Los Angeles group found that small-group education and small media significantly increased HBV testing [31] .

Researchers from the Center for Asian Health in Philadelphia have evaluated group education combined with navigation, including arranging appointments with clinical partners, language translation, assisting with paperwork, and transportation. Their studies have focused on cervical cancer screening among Chinese women, recruited from four Asian community organizations (two experimental and two control), and colorectal cancer screening among older Koreans, recruited from six churches (three experimental and three control). At baseline, study participants were nonadherent to screening guidelines. While these studies had relatively small sample sizes, they both demonstrated a strong intervention effect ($p < 0.001$) [48, 49].

One evaluation of group education included multiple Asian groups (Chinese, Koreans, and Vietnamese). This study focused on HBV testing. Experimental group participants were recruited through 15 community organizations in Baltimore, and control group participants were recruited through 12 community organizations in Washington, DC. Group education was provided by Asian health educators and included use of Asian language videos and photonovels. Control group participants

received an English language brochure about HBV. The intervention had a significant effect on HBV testing rates among participants who were untested at baseline [15].

Trials of One-on-One Education and Small Media

Wu and colleagues examined the effect of telephone counseling about mammography for Chinese women who were nonadherent to screening guidelines. Control group participants received an English language mammography brochure. While mammography uptake after 4 months was equivalent in the experimental and control groups, there was a significant intervention effect among women with insurance coverage for breast cancer screening [71]. A comparative effectiveness trial tested two alternative mammography videos for Chinese women who had not received a mammogram in the previous year. Participants were randomized to receive a culturally targeted video, generic video, or fact sheet. All the small media were provided in Chinese. Primary analyses that included all randomized women found neither of the videos was effective. However, secondary analyses found the culturally targeted video was effective among a subgroup of women with low acculturation [72]. Another three-arm trial addressed approaches to promoting FOBT among Vietnamese patients of a primary care clinic network. Both experimental groups received a culturally and linguistically tailored brochure and FOBT kit by mail, and one of the experimental groups also received telephone counseling (provided by Vietnamese community health advisors). The trial findings indicated that telephone counseling was effective in increasing FOBT completion rates, but the culturally tailored brochure was not [73].

Quasi-experimental Studies of Community-Level Interventions

Four quasi-experimental studies evaluated breast and/or cervical cancer screening community interventions for Korean and Vietnamese women in California. The interventions included use of Asian language mass media combined with other components such as distribution of Asian language educational materials, workshops at Korean churches, and continuing medical education for Vietnamese physicians. Only one of these studies had positive findings [74–78].

Nguyen and colleagues assessed the impact of a community intervention to increase colorectal cancer screening levels among Vietnamese. Intervention components included a Vietnamese language media campaign, distribution of Vietnamese language educational materials, and continuing medical education for Vietnamese physicians. The proportions of participants who had never received a colonoscopy or sigmoidoscopy increased significantly in the experimental community (44 % at preintervention to 65 % postintervention) and a control community (37 % at preintervention to 47 % postintervention), but the increase was significantly greater in the experimental community. There was no intervention effect for FOBT [79].

Discussion

While intervention studies with positive findings are more likely to be published than intervention studies with negative findings, there is reasonably good evidence that LHW outreach and community-based group education (combined with other intervention components) can increase the use of cancer-related screening tests among Asian Americans [80]. However, trials of LHW outreach and community-based group education have not all demonstrated intervention effects. Since many Asian immigrant communities are relatively small and self-contained with strong social and extended family networks, it is possible that educational messages were disseminated to control groups in some of the negative trials [65, 66].

Researchers have reported relatively modest or no intervention effects from most quasi-experimental studies of community-level interventions to increase mammography and Pap testing levels among Asian women [55, 80]. Some of these interventions may have had insufficient reach, and their components may have lacked adequate intensity [75, 77]. Other factors that may have contributed to negative study results include the diffusion of intervention components from experimental to control communities, as well as the implementation of unanticipated and competing cancer screening programs in control communities [75, 77, 78].

The majority of cancer control intervention studies with Asian participants have used self-reports of screening test completion to measure outcomes [55]. There is some evidence that the reliability and validity of survey responses among Asians is relatively low, possibly because of a cultural tendency toward acquiescence [55, 81, 82]. While a few studies have attempted to verify self-reports with provider reports, Asian naming systems can result in the misfiling of test results, and health-care facilities that lack computerized technology can have difficulty locating medical records [62, 63, 83]. Recent initiatives to increase the use of electronic health records should facilitate the use of provider reports for outcome ascertainment in future studies [84].

Recommendations and Next Steps

In order to monitor cancer screening rates and to identify groups that underutilize cancer screening tests, it is important to continue to collect detailed information on ethnicity and acculturation among Asian Americans when assessing cancer screening. As many Asian Americans have limited English proficiency, it will be critical to provide linguistically appropriate access to health care to facilitate screening test use. In addition to promoting cancer screening in clinical settings, community venues can reach Asian Americans that may not have a regular health-care provider. Most cancer control interventions for Asian Americans have focused on Chinese, Koreans, and Vietnamese, and there is little information about evidence-based interventions for other large Asian groups (e.g., Indians) or for smaller groups such as the Hmong [5, 80]. Additionally, very few interventions have been tailored for use

in more than one Asian group [55, 80]. More research is needed on how to balance the need for culturally appropriate interventions in settings that serve multiple ethnic groups, which is the case in most clinics. Finally, most interventions have sought to change individual factors (e.g., beliefs about screening tests) rather than factors related to health-care providers and systems [80]. Future cancer control research initiatives should develop and evaluate interventions for previously understudied Asian groups. They should also focus on the health-care system and other interventions that could be tailored to multiple Asian groups.

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Lung Cancer Among Asian Americans

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Abstract Among Asian-American men and women, lung cancer is the second most commonly occurring cancer and primary cause of cancer-related mortality. Collectively, Asian-American men and women have a lower incidence rate of lung cancer than their non-Hispanic white counterparts. However, there is considerable heterogeneity in incidence rates across Asian-American subgroups, some of whom experience increasing rates of lung cancer and/or rates similar to non-Hispanic Whites. Active cigarette smoking is the primary risk factor for lung cancer; cigarette smoking may be influenced by education, acculturation, and access to health care. Among never smokers, Asian-American women experience a higher risk of lung cancer in comparison to Asian-American men and non-Hispanic white women; and additional risk factors such as indoor- and outdoor air pollution, passive smoking, and lifestyle factors should be considered. In order to aid in disease prevention and improve survival through early stage diagnosis, further work towards understanding risk factors in never smokers as well as identifying at-risk individuals in this growing US population are needed.

Keywords Lung cancer • Asian Americans • Epidemiology • Smoking • Never smokers

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Introduction

Lung cancer is the second most commonly occurring cancer and the primary cause of cancer death in men and women in the United States (US). In 2015, approximately 221,200 Americans were diagnosed with lung cancer [1]. Asian Americans, defined as those who are ethnically East, South East, or South Asian, represented 5.6 % of the US population in 2010 with approximately two-thirds born outside of the US and a quarter who immigrated within the past decade [2]. It is estimated that by 2050, the Asian-American population will double and increase to 10.1 % of the US population [3]. Therefore, understanding the epidemiology of lung cancer in Asian Americans is a public health priority.

Trends

Incidence

Considered broadly, lung cancer incidence rates (IRs) among Asian American/Pacific Islanders (AAPI) are lower than that of their non-Hispanic White and non-Hispanic Black counterparts. Surveillance, Epidemiology, and End Results (SEER) data from 20 US geographical areas reported that in 2012, the lung cancer IRs among AAPI men and women were 46.7 and 27.9 per 100,000, respectively [4]. In comparison, IRs among non-Hispanic White men and women were 69.7 and 54.1 per 100,000, respectively.

However, specific Asian-American subgroups experience a higher burden of lung cancer. Table 1 presents the IRs of lung cancer across eight major Asian-American

Table 1 Incidence rates[a] of lung cancer (2004–2008)[b] for the eight largest Asian-American subgroups and non-Hispanic Whites, stratified by sex

	Lung cancer incidence rate IR (95 % CI)	
Asian-American subgroup	Men	Women
Asian Indians and Pakistanis	30.1 (26.0–34.6)	12.4 (10.3–14.9)
Chinese	52.0 (49.5–54.6)	29.9 (28.2–31.7)
Filipinos	68.4 (65.3–71.7)	30.1 (28.4–31.9)
Japanese	52.4 (49.1–55.7)	27.9 (26.1–29.9)
Kampucheans	51.7 (38.0–68.3)	26.7 (19.0–36.3)
Koreans	57.5 (52.1–63.1)	28.0 (25.2–31.1)
Laotians	70.6 (54.0–90.2)	27.1 (18.4–38.3)
Vietnamese	73.4 (67.4–79.7)	31.8 (28.5–35.4)
Non-Hispanic Whites	74.0 (73.5–74.6)	56.6 (56.2–57.1)

[a]IRs are presented as per 100,000 and adjusted to the US standard population
[b]Data abstracted from Gomez et al., JNCI, 2013 [5]

subgroups and non-Hispanic Whites from 2004 to 2008 [5]. In men, IRs for Filipinos, Vietnamese, and Laotians were comparable to non-Hispanic Whites (Table 1) (68.4, 73.4, and 70.6, respectively, compared to 74.0 per 100,000), while Asian Indians and Pakistanis had the lowest rate (30.1 per 100,000) [5]. In women, lung cancer IRs among subgroups of Asian Americans were about half that of non-Hispanic White women. Asian Indian and Pakistanis had the lowest IR (12.4 per 100,000) while Vietnamese had the highest IR (31.8 per 100,000) [5]. For the other Asian-American subgroups of women, IRs ranged from 26.7 in Kampucheans (Cambodians) to 30.1 in Filipinos (Table 1) [5]. While among all subgroups of Asian-American men the IRs for lung cancer from 1990 to 2008 were stable or decreasing, a 2.1 % annual increase was seen for both Filipina and Korean women, although this was only statistically significant in Filipina women [4, 5]. The increasing trends in Asian-American women may be due to their higher smoking rates among those more acculturated (see section "Smoking").

Lung cancer incidence varies by socioeconomic status (SES) among Asian Americans, but with a stronger correlation among men than women. In a study based on the California Cancer Registry (CCR), in which a neighborhood composite index of SES was used, AAPI men residing in the lowest neighborhood SES quintile had a higher risk of lung cancer than those residing in highest neighborhood SES quintile (relative index of inequality (RII) = 1.46, 95 % CI: 1.33–1.60) [6]. In AAPI women, this increased risk was less pronounced (RII = 1.16, 95 % CI: 1.02–1.33) between the lowest and highest SES neighborhoods [6]. These differences between AAPI men and women may be due to differences in smoking patterns and other risk factors associated with SES.

While collectively the lung cancer IRs are lower for Asian-American men and women compared to non-Hispanic White men and women, IRs by smoking status, the primary risk factor for lung cancer, and factors that influence smoking, -such as nativity, birth place, and acculturation, vary substantially. For example, among never smokers, lung cancer incidence has been found to be more common among women than men and this disparity may be greater in Asian Americans [7]. A pooled study of never smokers from 13 large cohort studies found that White men and women had IRs of 11.2 (95 % CI: 9.8–12.6) and 12.4 (95 % CI: 11.3–13.5) per 100,000, respectively, whereas IRs among Asian men and women were 12.9 (95 % CI: 6.7–19.1) and 15.0 (95 % CI: 10.4–19.7), respectively [8]. Furthermore, in a study utilizing CCR data (1998–2003), foreign-born Asian men and women had a 35 % higher rate of non-small cell lung cancers (NSCLCs) than US-born Asian men and women [9]. In Asian men, a higher rate of NSCLCs was consistent with the higher smoking prevalence in foreign-born Asian men (46 %) compared to US-born Asian men (35 %), but a higher rate of NSCLCs was not consistent with the lower smoking prevalence in foreign-born Asian women (11 %) than in US-born Asian women (22 %) [9]. These findings suggest that, particularly for Asian-American women, risk factors beyond smoking should be evaluated (see section "Risk Factors").

Stage of Disease, Survival, and Mortality

In the US, results from SEER showed that 5-year relative survival for lung cancer in all racial/ethnic groups was 17.4 %, and lower in men (15.6 %) than women (21.1 %) [4]. The 5-year relative survival was similar between AAPI women (21.9 %) and white women (21.2 %), but AAPI men had a slightly lower 5-year relative survival (15 %) than white men (16.1 %) [10].

Stage of disease is the most important prognostic indicator for lung cancer survival. Among White men and women, the 5-year relative survival (year of diagnosis 2005–2012) was 49.7 % and 60.3 %, respectively, for localized disease and 3.3 % and 4.8 %, respectively, for distant disease [10]. Compared to White men and women, AAPI men and women had better 5-year relative survival for both localized (52.9 % and 68.6 %, respectively) and distant (5.6 % and 6.4 %, respectively) disease [10]. However, all eight subgroups of AAPI men and women were more likely to be diagnosed with distant stage disease (men ranged from 45 to 60 %, women ranged from 48 to 59 %) than non-Hispanic white men (42 %) and women (40 %) [11].

The mortality and survival rates of lung cancer differ across Asian-American subgroups. Using data from 13 SEER registries (1991–2007) in a competing risk analysis, compared to non-Hispanic Whites, five of the seven Asian subgroups (Japanese and Koreans were the exceptions), had lower lung cancer-specific mortality (hazard ratios (HR) range = 0.71–0.88) [12]. When comparing within Asian subgroups, another study of NSCLC cases, using CCR data, found that most Asian American subgroups (with the exception of Indians/Pakistanis) presented with a poorer overall and disease-specific survival than Chinese [13].

Differences in survival can be also attributed to SES, access to healthcare, cancer treatment, as well as other environmental or biologic factors [13]. For instance, the lower survival observed among other AAPI and Vietnamese men may be related to more recent immigration to the US, lower SES, and less access to healthcare [2]. However, the SES differences do not explain the reported lower survival among Japanese Americans than other Asian groups [13]. Similar to Whites, 87–90 % of Asian Americans with stage 1 or 2 lung cancer received definitive treatment (surgical resection) for lung cancer, but three of the seven Asian-American groups (Chinese, Filipinos, and others) with stage 3 lung cancer were less likely to receive definitive treatment (54–55 %) compared to Whites (62 %) [12]. In a meta-analysis of randomized control trials (RCTs) to assess response to cytotoxic chemotherapy in NSCLC patients, Asians had a higher median overall survival (10.1 months vs. 8 months) and higher overall response rate (32.2 % vs. 25.9 %) than Whites [14]. The higher proportion of epidermal growth factor receptor (EGFR)-positive adenocarcinoma (see sections "Histopathology" and "Somatic Mutation") among Asian populations may play a role in improved survival among this population and additional studies are needed to investigate the contribution of genetic markers to clinical response rates and overall lung cancer survival.

Histopathology

The four major histologic cell-types of lung cancer are squamous cell carcinoma (SCC), large cell carcinoma (LCC), adenocarcinoma (AC), and small cell lung cancer (SCLC) [15]. SCC, LCC, and AC are classified under the group of NSCLC. The majority of SCCs and SCLCs occur in the central compartment of the lung, while the majority of ACs occurs in the periphery. Prior to the mid-1980s, SCC and AC were the most common histologic cell-type in US men and women, respectively [16]. However, since the 1990s, AC has become the predominant cell type in both US men and women [17–19]. This shift in histology has been attributed to the changing composition of the tobacco blend and the cigarette design over time, such as the introduction of cigarettes with filtered tips. This resulted in alterations in smoking behavior, such as greater smoking intensity (deeper inhalation) for the same delivery of nicotine, and more lung carcinogen exposures in the lung periphery [17, 20]. In the past 10 years, among non-Hispanic White men, IRs for the four main histologic-specific cell-types have been steadily declining. However, among non-Hispanic White women, during the same period, IRs declined for SCLC and LCC whereas the IRs for SCC and AC continued to increase and only have recently appeared to stabilize. This increase in non-Hispanic White women may be due in part to a cohort effect with their later adoption of smoking (started in 1920s and 1930s), roughly 20–30 years later than men [21].

Based on SEER data since the 1990s, lung cancer IRs showed a similar shift in histologic cell-type from SCC to AC in most Asian-American men [11]. In Asian-American women, AC remained the more common histologic cell-type. In a SEER report of registry data from 1990 through 2010, annual percent increases in AC were found in several Asian-American groups, including Chinese men (1.3 %, 95 % CI: 0–2.5), Filipino women (2.6 %, 95 % CI: 1.7–3.5), and Korean women (3.0 %, 95 % CI: 1.6–4.4) [11]. For most AAPI men and women, the other major histologic cell-types (SCC, SCLC, and LCC) were stable or decreased during this time period, similar to non-Hispanic White men and women. A noted exception was an annual percent increase in SCC (2.4 %; 95 % CI: 0.7–4.2) in Japanese women [11]. Better understanding of the risk factors influencing the rise in AC in some Asian-American subgroups is needed.

Somatic Mutations

While there is limited data on somatic mutations associated with lung cancer in Asian Americans, studies conducted in Asia suggest differences in the types and frequency of somatic mutations between Asians and Whites.

For example, K-Ras mutations have been found to occur in 15–25 % of AC among Whites in Western countries [22, 23], but it was generally found to be less common in Asian populations (range 3–10 %) [24–26]. In a study in Japan, KRAS

mutations occurred in 6 % of females and 3 % of males; and in 5 % of never smokers and 4 % of ever smokers [24]. Similar low prevalence estimates were reported in studies of NSCLC in Taiwan and Hong Kong [25, 26].

P53 tumor suppressor mutations are common in lung cancer, especially smoking-related lung cancer, and has been found in approximately 33 % of AC and approximately 70 % of SCLC [27]. For lung cancer, common *p53* mutation hotspots occur in codons 157, 248, and 273 [28] and most frequently present as a GC to TA transversion. There is a correlation between GC to TA transversions and tobacco exposure, both in the quantity and duration of smoking [28, 29]. Among studies conducted in Asia, *p53* mutation frequencies varied widely from 1 to 70 %, but many of these studies were small and did not examine differences by sex, smoking status, or histologic cell-types [30–34]. In one of the larger studies in Asia (69 SCC and 67 AC), *p53* mutations were found in 70 % of smokers and 65 % of nonsmokers and 69 % of SCC cases and 67 % of AC cases [32].

EGFR gene mutations are commonly found in AC, but are virtually absent in other histologic cell-types [23]. They occur most frequently in AC of never smokers (51–68 %), women (42–62 %) and persons of East or Southeast Asian descent (>49 %) compared to persons from Western countries (≤26 %) [35–39]. Mutations in the human epidermal growth factor receptor II (*HER2)* gene, also a member of the EGFR family, are also more commonly found in AC, women, nonsmokers, and those of Asian descent [40]. *EGFR* mutations in AC are of particular importance as this mutation is particularly responsive to tyrosine kinase inhibitors (TKI) such as gefitinib and erlotinib for lung cancer treatment [38]. A meta-analyses of 14 RCTs found that in NSCLC patients, TKI therapy was particularly effective among never smokers but was less so for former/current smokers [41]. This study, however, did not evaluate the efficacy of TKI therapy in never smokers by EGFR mutation status.

Other common lung cancer mutations that differ in frequency across race/ethnicity include the liver kinase B1 (*LKB1*) and anaplastic lymphoma kinase (ALK) mutations. In a study of 144 lung tumors of primarily Whites, *LKB1* mutations were more common in AC (34 %) than in SCC (19 %) [42]. *LKB1* mutations have been reported to be less common in Asians (113 NSCLCs) than Whites (143 NSCLCs) for both AC (8 % and 19 %, respectively) and SCC (0 % and 13 %, respectively) [43]. Lastly, the fusion of echinoderm microtubule-associated protein-like 4 (EML4)-ALK genes has been found in 3–5 % of NSCLC, primarily AC. Patients with this fusion are more likely to be nonsmokers and younger than those without this fusion gene [44–47]. It has been suggested to be more frequently occurring in Asians (3–6.7 %) than Whites (~1 %) [44–47].

Reasons for differences in the frequency of tumor mutations between Asians and Whites remain unclear. Studies are needed to clarify the distribution of common lung cancer mutations by sex, and smoking status across Asian-American subgroups. This may provide additional insight into the relationships between somatic mutations, lung cancer histologic cell-types, etiology, and progression.

Risk Factors

Active Smoking

The primary risk factor for lung cancer is tobacco use, primarily from cigarette smoking [48]. Cigarette smoke is comprised of at least 4000 chemicals, of which over 70 are established carcinogens [48]. In the US, approximately 90 % of lung cancer deaths in men and 75–80 % of lung cancer deaths in women are caused by smoking [49, 50].

Cigarette smoking is associated with all lung cancer histologic cell-types but the association is weaker for AC. Results from a large pooled analysis (13,169 cases and 16,010 controls) from Europe and Canada [51] and a study from Japan [52] suggest differences in risk associated with current smoking by histology, sex, and by race/ethnicity (Table 2). These studies also showed that in all populations, greater quantity smoked (e.g., pack-years, duration of smoking, or cigarettes per day) were associated with an increasing trend in lung cancer risk for all groups by histology, sex, and race/ethnicity [51, 52].

Epidemiologic data suggests that, at least for some Asian-American subgroups, per smoking dose, the relative risk for lung cancer may be lower. In the Multiethnic Cohort study (MEC), the largest racially/ethnically diverse prospective US study with a focus on etiologies of cancer, it was found that Japanese Americans had a 75 % reduction in lung cancer risk (95 % CI: 0.18–0.36) for the stratum of ≤ 10 cigarettes per day (CPD) in comparison to African Americans, and for the heaviest smokers (≥ 31 CPD), Japanese-Americans had a 25 % reduction in risk (95 % CI: 0.57–1.00) in comparison to African Americans [53]. This is consistent with an earlier report from Le Marchand et al., who found that, compared to White men and women, respectively, for the same quantity smoked, Japanese American men and women had a lower risk of lung cancer (OR = 0.68, 95 % CI: 0.50–0.93 and OR = 0.36, 95 % CI: 0.11–1.2, respectively) [54]. For Japanese Americans, the difference in risk of disease may be partly explained by their slower metabolism of nicotine, thereby resulting in lower nicotine uptake and less exposure to tobacco carcinogens (see genetic risk factors) [55].

Table 2 Summary of the association between active smoking (current vs. never) and lung cancer risk in Whites[a] and Japanese[b] by sex and histologic cell-types

Lung cancer histologic cell-types	White men (pooled) OR (95 % CI)	White women (pooled) OR (95 % CI)	Japanese men OR (95 % CI)	Japanese women OR (95 % CI)
SCLC	45.7 (29.9–70.0)	21.7 (15.5–30.1)	13.1 (4.8–36.2)	85.7 (25.7–286)
SCC	45.6 (34.3–60.6)	13.6 (10.5–17.7)	10.4 (5.8–18.6)	15.0 (6.4–35.1)
AC	10.8 (8.7–13.3)	4.2 (3.5–5.0)	2.3 (1.7–3.2)	1.3 (0.9–1.3)

[a]Data abstracted from Pesch et al., IJC, 2012 [51]
[b]Data abstracted from Seki et al., Cancer Science, 2013 [52]

However, it is not known whether these differences in risk at a given level of smoking in Japanese Americans are applicable to other Asian-American subgroups. This was explored by Le Marchand et al. in a case–control study that also included Filipino and Chinese men and women. Although this study had limited statistical power to detect significant differences, results suggested that Japanese Americans may have lower risk of lung cancer at a given level of smoking than other Asian-American subgroups [54].

It is likely that overall lung cancer risk is lower in Asian Americans as a result of their lower prevalence of current smoking (9 %) compared to non-Hispanic Whites (19.4 %) [56]. On average within Asian-American subgroups, in both men and women, Chinese, Asian Indians, and Japanese had lower prevalence of being current and ever smokers compared to Koreans, Vietnamese, Cambodians, and Laotians [57]. In all Asian-American subgroups, the prevalence of ever smoking was higher in men than women. Although the lower prevalence of ever smoking in Asian Americans is somewhat consistent with their lower risk of disease, the variation within subgroups and particularly the risk in women cannot be entirely explained by the differences in smoking prevalence.

The prevalence of smoking in AAPI is influenced by nativity, education, English proficiency, duration of residence in the US, and ethnic enclave [58]. In particular, level of acculturation is strongly associated with smoking initiation, prevalence, and cessation but differs between Asian-American men and women. Asian-American men, with longer residence in the US (i.e., more acculturated) were found to be 53 % less likely to smoke than those with shorter residence [59]. The prevalence of smoking was also lower among English proficient Asian-American men (18 %) than non-English proficient Asian-American men (33 %) [60]. In contrast, smoking prevalence was five times higher in more acculturated than less acculturated Asian-American women [59] and smoking prevalence was higher among Asian-American women, who were English proficient than those who were less proficient in English [61]. In addition, early smoking initiation influences smoking addiction, resulting in difficulty in cessation, hence a greater likelihood of remaining a current smoker. While the risk of early smoking initiation among Asian-American adolescents is a third of that of Whites, there is marked variation across subgroups [62] and it has been found that tobacco companies currently market specifically to AAPI [63]. Therefore, an increase in smoking prevalence among Asian-American youth may be expected.

The benefits of smoking cessation are well known [64]. In a report from the Million Women Study in the UK, compared to never smokers, former smokers who permanently stopped smoking had higher risk of lung cancer-related mortality. However, those who stopped at 25–34 years of age were at lower risk of lung cancer mortality (rate ratio = 1.84, 95 % CI: 1.45–2.34) than those who quit at 35–44 years of age (rate ratio = 3.34, 95 % CI: 2.76–4.03) [65]. Similar patterns of results were found in an earlier study of men and women in Japan [66]. While the absolute risk of lung cancer in former smokers will not decrease to that of never smokers, the rate in which their absolute risk increases is lower than that of current smokers. Thus, among current smokers, smoking cessation remains the best preventable measure for lung cancer, reinforcing the importance of smoking cessation as a public health priority. Detailed data on the benefits of smoking cessation by Asian-American subgroups are lacking at this time.

Passive Smoking

Secondhand smoke is the complex mixture formed from the escaping smoke of a burning tobacco product and smoke exhaled by the smoker. Exposure to secondhand smoke is also referred to as involuntary smoking or passive smoking. Passive smoking is an established risk factor for lung cancer in never smokers. In a large international study that pooled data from 18 case–control studies including 2504 never smoking lung cancer cases (men and women), passive smoking was associated with a 31 % increased risk of overall lung cancer (95 % CI: 1.17–1.45) [67]. This study found that in never smoking Asians, passive smoking was associated with a 20 % increase in lung cancer risk (95 % CI: 0.98–1.45). This lower risk estimate in Asians may be due to a greater proportion of AC in never smoking Asians compared to never smoking Whites, with a lower passive smoking risk association seen in AC than the other histologic cell-types. The proportion of lung cancers in never smokers attributable to passive smoking has been estimated to range from 20 to 25 % [68] to 37 % [69]. Passive smoking may be more relevant to lung cancer risk in Asian American women than men, as there is a greater proportion of never smoking lung cancer cases among women than men, but its contribution to the burden of lung cancer in these never smoking women is unclear [70–74].

Indoor and Outdoor Air Pollution

Indoor Air Pollution

Indoor air pollution may originate from outdoor or indoor air pollution exposures such as radon from soil and/or water and combustion, passive smoking, and burning coal, wood or cooking fumes.

Radon is a decay product from radium. Residential radon has been found to be associated with lung cancer in smokers due to the interaction between smoking and radon [48, 75]. In studies from Western countries, residential radon has been associated with an increase in lung cancer risk in never smokers [76]. A meta-analysis of 13 European case–control studies in never smokers found that >100 Bq/m^3 cumulative radon exposure during 5–30 years before lung cancer diagnosis or death was associated with an increase in lung cancer risk (100–199 Bq/m^3: OR = 1.23, 95 % CI: 1.02–1.48) [77]. There have been a few studies of residential radon exposure and lung cancer risk in Asia. In a large pooled study of residential radon and lung cancer in China that included both men and women never and ever smokers, exposure to >100 Bq/m^3 radon was associated with a 33 % increase in risk (95 % CI: 1.01–1.36) [78]. Results by smoking status were not presented for this study in China. Little has been done in the study of residential radon and lung cancer risk among never smokers in Asia. Also, it has been suggested that there may be a potential synergism between radon exposure and passive smoking in relation to lung cancer risk in never smokers, which has not been thoroughly explored in either Western or Asian countries [76].

In Asia, indoor air pollution from solid fuel combustion (from coal and wood) as well as cooking oil vapors have been found to be risk factors for lung cancer, particularly among never smoking women [79, 80]. Smoky coal and wood have been classified as a human carcinogen (group 1) and probable human carcinogen (group 2a), respectively, by the International Agency for Research on Cancer (IARC) [81]. In China and other regions in Asia, smoky coal and wood in unventilated homes are the primary heating source for both heating and cooking. One pooled study and two meta-analyses consistently found that indoor air pollution from solid fuel was associated with an approximately two-fold increase in lung cancer risk in Asian men and women, and ever and never smokers [82–84]. As coal use is more common in Asia, in a meta-analysis of three studies, household coal use in never smoking Asian women was associated with an almost three-fold increase in lung cancer risk (1.40–6.12), a risk estimate was not available for never smoking Asian men [84]. Only one meta-analysis presented the associations by histologic cell-type and found that in primarily Asian men and women, ever and never smokers, coal use was associated with a significant two- to three-fold increase in risk for both AC and SCC lung cancers [83].

In China, it is also common practice to cook with rapeseed and soybean oil at extremely hot temperatures, resulting in oil vapors that are genotoxic and a source of indoor air pollution [85]. Nonsmoking Chinese women who reported exposure to cooking oil fumes ("high" exposure measured by greater cooking frequency) compared to those with "no to little" exposure have shown significantly elevated lung cancer risk, ranging from ORs = 1.4–3.8 [86–88]. Furthermore, Taiwanese nonsmoking housewives who did not use fume extractors in the kitchens when they stir-fried, fried, or deep fried had significantly higher lung cancer risk (OR ranges of 3.2–12.2) [89]. In the US, there have been no studies of fumes from extremely hot cooking oil and lung cancer risk, although studies assessing indoor air quality in the US have reported harmful levels of both ultrafine particle and other air pollutant emissions associated with this method of cooking [90, 91].

Household coal combustion and cooking oils at high temperatures may be important risk factors for Asian Americans as many are foreign-born with potential exposure to indoor air pollution prior to migration to the US. Additionally, this exposure may continue even after immigration, among the Asian Americans who continue to cook with oils at high temperatures in the US.

Outdoor Air Pollution

In 2013, IARC classified outdoor air pollution and particulate matter (PM) as carcinogenic to humans (Group 1) and a cause of lung cancer [92]. In a meta-analysis of 14 studies, the risk for lung cancer per 10 μg/m^3 increase of $PM_{2.5}$ and PM_{10} was 1.09 (95% CI: 1.04–1.14) and 1.08 (95% CI: 1.00–1.17), respectively [93]. The $PM_{2.5}$ and lung cancer association was more pronounced for former smokers (HR = 1.44, 95% CI: 1.04–2.01), intermediate for never smokers (HR = 1.18, 95% CI: 1.00–1.39), and weaker for current smokers (HR = 1.06, 95% CI: 0.97–1.15) [93]. In a Japanese cohort study, lung cancer risk increased significantly in relation to $PM_{2.5}$ among women who never smoked (RR = 1.16; 95% CI: 1.02–1.33) [94].

Air pollution and risk of lung cancer has not been studied in Asian Americans but may be particularly important as Asians Americans are more likely to live in areas with high levels of ambient air pollution exposures [95–105], including high traffic volume [95] and $PM_{2.5}$ [96, 97], and in US counties that exceed the U.S. Environmental Protection Agency (EPA) health standards for $PM_{2.5}$ [106].

Occupational Exposures

Occupational exposures to radon, asbestos, metals, polycyclic aromatic compounds, vinyl chloride, volatile organic compounds, dust, and particulates have been associated with an increased risk of lung cancer [107]. Many of these compounds have been classified by the IARC as known carcinogens [108]. These compounds may induce lung cancer through a carcinogenic mechanism and/or an inflammatory mechanism, that may involve the development of chronic obstructive pulmonary disease (COPD), a known risk factor for lung cancer [109]. The occupational risks for lung cancer in Asians remain unclear, particularly among never smokers as there are few published studies in this population that were adequately powered [110, 111]. Also, we are not aware of studies that have investigated the role of specific occupational exposures and risk of lung cancer in Asian Americans.

Previous Lung Diseases

Numerous studies have investigated the role of previous lung diseases and risk of lung cancer [71, 112–118]. Brenner et al. conducted a comprehensive meta-analysis of studies in Asian and Western populations. Subgroup analysis of studies in Asia found an increased risk of lung cancer in men and women associated with a history of chronic bronchitis (RR = 2.01; 95 % CI: 1.43–2.81), pneumonia (RR = 1.84; 95 % CI: 1.37–2.46), and tuberculosis (TB) (RR = 1.96; 95 % CI: 1.54–2.50) [113]. However, smoking status was only considered in the individual studies and thus residual confounding from smoking quantity cannot be ruled out. In a subgroup analysis restricted to never smokers in Asian and Western populations (results were not presented for Asians only), the association was not significant for chronic bronchitis (RR = 1.18; 95 % CI: 0.88–1.58) and emphysema (RR = 1.22; 95 % CI: 0.97–2.81), but remained significant for pneumonia (RR = 1.36; 95 % CI: 1.10–1.69), and TB (RR = 1.90; 95 % CI: 1.45–2.50) [113]. This study also found that TB was associated with increased lung cancer risk among Asian never smoking women (RR = 2.23; 95 % CI: 1.38–3.61) [113]. Meta-analyses for the other lung diseases (aside from TB) and lung cancer risk in Asian never smoking men or women were not presented. In 2008, the incidence rate of TB was 23 times higher among Asian Americans (25.6 per 100,000) than non-Hispanic Whites (1.1) [119]; accordingly, TB infections may be a relevant risk factor among never smoking Asian Americans. Although asthma was not investigated in the above meta-analysis [113], a

meta-analysis of US studies, consisting of primarily Whites, found that never smokers with a history of asthma had an elevated risk of lung cancer risk (RR = 1.8; 95 % CI: 1.3–2.3) [120]. These findings suggest that in never smokers, a prior history of lung diseases may play a role in lung carcinogenesis. However, there is no prospective study that systematically examines previous lung diseases in relation to lung cancer risk in never smoking Asian Americans.

Infectious Disease

Infection with *Chlamydia pneumonia* (*C. pneumoniae*) and human papillomavirus virus (HPV) have been implicated in the development of lung cancer. In a nested case–control study from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a higher prevalence of antibody markers for *C. pneumoniae* (Chlamydia IgA titers) was associated with an increased risk of lung cancer (OR = 1.6; 95 % CI: 1.0–2.3) [121]. Subsequently, a meta-analysis of four prospective and eight case–control studies (four in Asia), reported an association of seropositive Chlamydia IgA titers with lung cancer risk (OR = 1.48, 95 % CI: 1.32–1.67) [122]. This association was detected in both prospective (OR = 1.16, 95 % CI: 1.00–1.36) and retrospective (OR = 2.17, 95 % CI: 1.79–2.63) studies. However, not all studies accounted for smoking status [123] and the largest of the four Asian studies, in nonsmoking women, found no association [124]. This study used IgG and IgA assays, which has been shown to have modest reliability [125]. In fact, in a nested case–control study in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial, the *C. pneumoniae* IgG or IgA antibodies assay were not associated with lung cancer risk, but the Chlamydia heat shock protein-60 (CHSP-60) IgG antibodies, possibly a more reliable assay, was associated with lung cancer (OR = 1.30, 95 % CI: 1.02–1.67) and this association remained even for seropositivity detected at 2–5 years prior to lung cancer diagnosis [126]. Such studies in Asian Americans have not been conducted.

HPV, particularly HPV 16/18, is a well-established risk factor for cervical, penile, anal, and squamous cell skin cancers [127]. HPV can activate carcinogenesis via the E6/E7 proteins of HPV by inactivating p53 and RB [128]. HPV infection in lung cancer may be of particular importance in Asian Americans. In an extensive review of 53 studies, HPV positivity was higher in lung cancer cases from Asia (36 %) than from Europe (17 %) or from the US (15 %) [129]. A higher HPV prevalence in Asians was found in another comprehensive analysis that considered histologic cell-type, showing significantly higher HPV positivity in Asian than in European populations for SCC (33.2 vs. 9.5 %, respectively) but not for AC (9.8 vs. 6.8 %, respectively) [130]. In a subset of studies with information on smoking status, HPV positivity was significantly higher in never smokers from East Asia (33.9 %) than those in Europe (14.8 %) [130]. The prospective investigations of these infections in relation to lung cancer risk are needed to better understand the prevalence of infectious exposure and risk in ever and never smoking Asian Americans.

Reproductive History and Hormone Exposure

The association of reproductive history with risk of lung cancer is unclear. Estrogen receptors (ER-alpha and ER-beta) are expressed in normal and tumor lung tissues but it is unclear whether the expression of these receptors differs by sex and/or smoking status. In a study of resected NSCLC tumors from Taiwan, significantly higher ER-beta expression was found in tumors from never smokers (53.5 %) than in smokers (36.6 %), and also higher in never smoking women (58.3 %) than never smoking men (40.9 %) [131]. In cohort studies of never smoking Chinese women in Shanghai and Singapore, there were suggestive lower risks of lung cancer associated with later age of menopause and higher parity [132], but higher risk associated with later age at menarche [133]. However, these findings were not seen in never smoking Japanese women [134]. The use of hormone replacement therapy (HRT) in Asia has been reported to be low [135] and not associated with lung cancer risk in these Asian studies [132–134]. However, in the Women Health Initiative study and a pooled international study, HRT use was more prevalent and was associated with a lower risk of lung cancer [136, 137].

Body Size

The role of body mass index (BMI, kg/m^2) and risk of lung cancer is best considered in never smokers because of the confounding effects of active smoking and preexisting lung disease [138–140]. In a meta-analysis of five prospective studies among never smoking men and women, primarily of European descent, BMI was not associated with lung cancer risk [141]. However, BMI is an interesting risk factor to explore among Asian Americans given that adverse BMI-related outcomes, such as cardio-metabolic diseases, manifest in this population at lower BMI measures than in Whites [142, 143]. To date, studies of never smokers from Korea [144], China [145], and a meta-analysis of cancer mortality in the Asia-Pacific Cohort Studies Collaboration [146] have not found consistent results.

Diet

Fruit and Vegetables

A review by the IARC concluded that diets high in fruits and vegetables are inversely associated with lung cancer risk, particularly in current smokers [147]. In a large meta-analysis of prospective studies, a 100 g/day increase in fruit and vegetable intake was associated with a 4 % decrease in lung cancer risk (95 % CI: 0.94–0.98) [148]. For smoking status-specific findings, the highest intake of fruits and vegetables compared to the lowest intake was inversely associated with lung cancer risk in

current smokers (RR: 0.90; 95 % CI: 0.81–1.00), but not in never (RR: 0.94; 95 % CI: 0.70–1.27) or former smokers (RR: 0.95; 95 % CI: 0.83–1.10) [148]. The associations did not appear specific to a histologic cell-type, but data stratified by histologic cell-types were available in only a few studies. When restricting studies to those conducted in Asia, the inverse association for vegetables (five studies, RR = 0.98, 95 % CI: 0.93–1.04) or fruits (six studies, RR = 0.94, 95 % CI: 0.83–1.06) was not detected, although inverse associations for cruciferous (two studies, RR = 0.94, 95 % CI: 0.88–1.00) or leafy green vegetables (three studies, RR = 0.90, 95 % CI: 0.82–0.99) were found [148].

Cruciferous vegetables are rich in isothiocyanates. Isothiocyanates have been found in animal studies to reduce the formation of the carcinogenic metabolites from polycyclic aromatic hydrocarbons (PAHs), found in tobacco smoke, through the inhibition and induction of xenobiotic metabolizing pathways, cytochrome P450s (phase I enzymes) and glutathione S-transferase (phase II enzymes), respectively [149, 150]. A meta-analysis of ten studies in women found an inverse association between cruciferous vegetables and risk of lung cancer after adjusting for active smoking (RR = 0.75; 95 % CI: 0.63–0.89) [151]. This association was statistically significant in never smokers (RR = 0.70; 95 % CI: 0.58–0.85) but not in current smokers (RR = 0.77; 95 % CI: 0.41–1.46), and also stronger in studies conducted in Asia (RR = 0.66; 95 % CI: 0.55–0.81) [151]. Results from another meta-analysis of studies in men and women confirmed a significant inverse association between cruciferous vegetables and lung cancer risk in never smokers (OR = 0.78; 95 % CI: 0.64–0.95), which was more pronounced among those with the glutathione S-transferase theta 1 (*GSTT1*) null genotype (OR = 0.41; 95 % CI, 0.26–0.65; *P* for interaction was 0.01) [152]. The frequencies for *GSTT1* null genotype are higher in Asians (37–63 %) than those of European descent (10–28 %) [153].

Supplements

Specific antioxidant micronutrients, such as beta-carotene, vitamins C and E, selenium, that are commonly found in fruits and vegetables have been extensively studied for their role in lung cancer. Early epidemiologic studies and animal studies suggested that beta-carotene may have anticarcinogenic effects and was inversely associated with lung cancer risk [154]. However, RCTs to evaluate the effect of beta-carotene supplementation on lung cancer incidence in primarily White smokers found either no effect [155, 156] or an increased incidence of lung cancer at high doses of beta-carotene (≥20 mg/day) [157–159], including a meta-analysis of eight RCTs in men and women combined [160] and among current smokers [160, 161]. Prospective epidemiologic studies of lung cancer risk have reported neither benefit nor harm associated with beta-carotene supplementation or dietary consumption of beta-carotene [154, 162, 163]. Results from trials on selenium supplementation also showed no benefit [164, 165]. Similarly, a large prospective study in the US that investigated supplement use and lung cancer risk

found no association between vitamins C and E use and risk of disease [166]. In contrast, a large prospective study of nonsmoking women in Shanghai found dietary intake of foods containing vitamin E was associated with a reduced risk (≥14 mg/day of vitamin E vs. less: HR = 0.78; 95 % CI: 0.60–0.99), yet vitamin E supplement use was associated with an increase in risk (HR = 1.33; 95 % CI: 1.01–1.73), with a stronger association for AC (HR = 1.79; 95 % CI: 1.23–2.60) [167]. Chemoprevention trials of lung cancer found that beta-carotene, alpha-tocopherol, or selenium have not demonstrated reproducible associations [168]. In 2013, the U.S. Prevention Services Task Force (USPSTF) concluded that beta-carotene supplementation increases risk of lung cancer among high risk individuals, such as heavy smokers and/or asbestos workers and that neither vitamins C nor E were associated with risk of lung cancer [169]. Given the large number of null results mostly from studies in Whites, there is little motivation for additional studies of dietary supplementation and lung cancer risk among less-studied groups such as Asian Americans.

Alcohol

Studies on alcohol and lung cancer risk have yielded inconsistent results by type of alcohol and in men and women [170, 171]. In a meta-analysis of never smokers ($n = 1913$ lung cancer cases), lung cancer risk was not associated with alcohol intake (per 10 g/day, RR = 1.01; 95 % CI: 0.92–1.10) [172], suggesting that confounding or effect modification by smoking likely occurred in prior studies reporting positive associations between alcohol and lung cancer risk [170, 171]. In a meta-analysis restricted to Chinese men and women, including smokers and nonsmokers, alcohol was not associated with risk of lung cancer (four case–control and two cohort studies, OR = 1.39; 95 % CI: 0.93–2.07) [173].

Soy

Soy foods are rich in phytoestrogens, namely isoflavones, and have been found to have anticarcinogenic effects, particularly in hormone-related cancers by binding competitively to estrogen receptors [174]; they also have antioxidative and anti-inflammatory properties [175]. Three meta-analyses of overlapping studies found a significant inverse association (17–41 %) between the highest quantile of soy intake and risk of lung cancer [176–178]. In stratified analyses, the inverse association was seen in nonsmokers (high vs. low intake RR = 0.59; 95 % CI: 0.49–0.71); in women (RR = 0.79; 95 % CI: 0.67–0.94); and in Asians (RR = 0.83; 95 % CI: 0.70–0.99) [177]. The risk for per gram of soy protein intake per day was 0.98 (95 % CI: 0.96–1.00) [178]. It is of note that the inverse association was present when restricted to a meta-analysis of the four cohort studies (RR = 0.85; 95 % CI: 0.74–0.97) [177, 178].

Tea

Tea may have anticarcinogenic effects due to its antioxidant components including catechins, flavonols, lignans, and phenolic acids. In a meta-analysis of 26 case–control studies and 12 cohort studies (59,041 lung cancer cases and 396,664 controls) from China, Japan, and Western countries, any tea consumption (green or black or the two combined), compared to nondrinkers, was inversely associated with risk of lung cancer (RR = 0.78, 95 % CI: 0.70–0.87) [179]. Stratified analyses showed that this association was found for both green and black tea consumption. Also, the association for any tea consumption was significant only in women (RR = 0.76; 95 % CI: 0.62–0.93) and not in men (RR = 0.88, 95 % CI: 0.72–1.07) [179]. This association did not differ by smoking status (in smokers RR = 0.79, 95 % CI: 0.59–1.07 and in nonsmokers RR = 0.88, 95 % CI: 0.72–1.07). However, the inverse association for green and black tea consumption and lung cancer risk was primarily seen in case–control studies (OR = 0.72, 95 % CI: 0.63–0.83), but not in prospective studies (RR = 0.91, 95 % CI: 0.77–1.08). Tea consumption is greater in some Asian-American subgroups and may be a protective factor against lung cancer.

Other Dietary Factors

Other dietary risk factors that have been considered include red meats, processed meats, saturated fat and cholesterol, which have been associated with increase in lung cancer risk in some studies [180, 181]. However, the findings from prospective studies have been conflicting, and therefore the lung cancer associations for these factors are inconclusive [182–185]. These dietary factors have not been systematically studied in Asian-American populations.

Genetic Susceptibility

Globally, approximately 15 % of men and 53 % of women diagnosed with lung cancer are never smokers [186]. An estimate of 15–20 % of smokers will develop lung cancer over their lifetime [187]. Individuals with a first-degree relative with lung cancer have been found to have a 1.51-fold increased risk of lung cancer, accounting for smoking and other potential confounders (95 % CI: 1.39–1.63) [188]. Furthermore, among never smokers, family history of lung cancer has been associated with an increased risk of disease (OR = 1.25; 95 % CI: 1.03–1.52). These findings suggest that genetic susceptibility and gene–environment interactions play a role in lung cancer risk. Single nucleotide polymorphisms (SNPs) associated with lung cancer risk in Asians will be reviewed in three categories: those identified through genome-wide association studies (GWAS), xenobiotic metabolic genes, and DNA repair genes.

GWAS of Lung Cancer

The majority of GWAS of lung cancer have been conducted in populations of European descent. The identified genomic regions include variants at 15q25, *TERT-CLPTM1L* at 5p15.33 and at 6p21.33 [189–191]. The susceptibility region on 15q25 encodes for the cholinergic nicotine receptor genes in *CHRNA5-CHRNA3-CHRNA4* [192–194]. These genes are likely involved in nicotine addiction, and influence smoking initiation and the amount smoked; thereby, increasing an individual's risk of lung cancer. However, three large studies have reported conflicting findings, where it is unclear whether the association between SNPs in *CHRNA5-CHRNA3-CHRNA4* and lung cancer risk are independent or dependent on active smoking [192, 193, 195]. Smaller studies in Japan, China, and Korea did not replicate, at a genome-wide significance level ($p<5x10^{-8}$), the risk associations for SNPs in *CHRNA5-CHRNA3-CHRNA4* that were previously identified by GWAS of lung cancer in European populations; the frequency of these risk variants were considerably lower in Asians than in Europeans [196–198]. However, other variants in the same region were strongly associated with lung cancer risk in GWAS of lung cancer in Asian populations, especially among ever smokers and those with SCC [198], indicating the importance of this region for lung cancer in Asians and population-specific risk variants.

GWAS in Asians have not confirmed associations found in populations of European descent in 6p21.33, which contains the *BAT3-MSH5* genes. However again, there are indications that population-specific variants may play a role, in particular a low-frequency missense (protein changing) allele in the *BAT3* coding region (also in the same cluster of genes) was associated with lung cancer in a Chinese population [199].

The 5p15.33 region near the telomerase reverse transcriptase (*TERT*) and cleft lip and palate transmembrane 1-like protein (*CLPTM1L*) genes has been identified as a lung cancer susceptibility locus. *TERT* encodes for the catalytic subunit of telomerase, which maintains telomeres, the chromosomal ends. *CLPTM1L* has been found to resist apoptosis caused by genotoxic agents. Two SNPs in *TERT* have been reported to be associated with lung cancer in both European and Asian populations, for both smokers and nonsmokers [198, 200]. Also, a study showed that a genetic risk score of seven *TERT* SNPs, identified to be associated with longer telomeric length, was associated with risk of lung cancer in never smoking women in Asia (OR = 1.51, 95 % CI: 1.34–1.69) [201].

GWAS in populations of Asian descent (Chinese, Japanese, and Korean) have identified several other additional risk variants including: rs12296850 (in 12q23.1, genes: SLC17A8-NR1H4), which was associated with SCC [202], rs7216064 (17q24.3) and rs3817963 (6p21.3) [200], which were associated with AC, and rs2131877 (3q29), which was associated with NSCLC [203]. These four lung cancer risk variants did not appear to be specific by smoking status.

Xenobiotic Metabolic Genes

Candidate gene studies of a number of variants (e.g., deletions) not necessarily well captured in GWAS studies have identified associations between xenobiotic genes (e.g., *GSTT1*, *GSTM1*, *GSTP1*) and lung cancer risk. Some of these associations have been found to be population-specific such as the *GSTM1* null genotype, which appears as a risk factor for the major histology types in Asians but not in Europeans [204]. The *GSTT1* null genotype was found to be predictive of risk in Asian ever smokers but not in never smokers [205].

The cytochrome P450 (CYP) enzymes play a role in the metabolism of nicotine and in many other compounds commonly found in cigarettes. Associations with variants in these genes have been found in Asians and Europeans [206, 207]. Cytochrome P450 2A6 (*CYP2A6*) catalyzed C-oxidation accounts for >75% of nicotine metabolism [208]. Variations in the rate of nicotine metabolism have been found to influence smoking behavior [55]. Studies have found that internal smoking dose, measured by nicotine equivalents per cigarette, is lower in Asian Americans than in non-Hispanic Whites. This has been attributed to Asians having a larger proportion of *CYP2A6* alleles that correlate with poor or no CYP2A6 enzymatic activity [209–211]; this may contribute to their lower risk of lung cancer [53, 55, 212, 213].

DNA Repair Genes

The carcinogens from cigarette smoke results in DNA damage. Therefore, it is possible that variants in the DNA repair pathway may be associated with lung cancer risk, especially in smokers or in cell-types with greater associations with smoking. A meta-analysis of genetic variants for lung cancer susceptibility in East Asians ($n = 6287$ cases) found variants in DNA repair genes, *APE1*, *ERCC2*, and *XRCC1*, were associated with the risk of lung cancer [207]. There is some indication that the effects of these variants may be stronger in the cell types more strongly associated with smoking.

GWAS in Never Smokers

It has been suggested that lung cancer in never smokers may be a different disease. In GWAS of lung cancer among never smoking Asian women (5510 cases and 4544 controls from 14 studies from mainland China, South Korea, Japan, Singapore, Taiwan, and Hong Kong), susceptibility loci have been identified at 10q25.2 (rs7086803, OR = 1.28, 95% CI: 1.21–1.35, $P = 3.54 \times 10^{-18}$), 6q22.2 (rs9387478, OR = 0.85, 95% CI: 0.81–0.90, $P = 4.14 \times 10^{-10}$), and 6p21.32 (rs2395185, OR = 1.17, 95% CI: 1.11–1.23, $P = 9.51 \times 10^{-9}$) [214]. In a study of Korean never smoking men and women (434 cases and 1000 controls), 18p11.22 rs11080466 (OR = 0.68, 95% CI: 0.58–0.79, $P = 1.1 \times 10^{-6}$) was inversely associated with risk of NSCLC [215].

Another GWAS of never smoking Japanese and Korean men and women (2098 AC cases and 11,048 controls) found that rs10937405 in the tumor protein 63 (*TP63*) gene at 3q28 was associated with lung cancer risk (OR = 0.76; $P = 7.26 \times 10^{-12}$) [216]. This association was replicated in a study restricted to never smoking women from 10 studies conducted in Taiwan, mainland China, South Korea, and Singapore (3467 cases and 3787 controls; OR = 0.82, per allelic increase, 95 % CI: 0.76–0.86). This study found that the association was present for both AC ($n = 2529$ cases, OR = 0.80, 95 % CI: 0.74–0.87) and SCC ($n = 302$ cases, OR = 0.82, 95 % CI: 0.67–0.99) [217].

Also, a recent meta-analysis of four imputed GWAS of lung cancer in never smoking Asian women (6877 cases and 6277 controls) found three novel loci to be associated with lung cancer risk: rs7741164 at 6p21.1 (OR = 1.17; $P = 5.8 \times 10^{-13}$), rs72658409 at 9p21.3 (OR = 0.77; $P = 1.41 \times 10^{-10}$), and rs11610143 at 12q13.13 (OR = 0.89; $P = 4.96 \times 10^{-9}$) [218]. Findings by histologic site were not presented; however, >80 % of the cases in this study were AC.

The majority of GWAS of lung cancer in Asians have been conducted in East Asian populations; additional work in South and Southeast Asians are needed to determine whether these variants found in populations of East Asian or European descent are generalizable to other Asian populations. Also, tests for gene and environmental interactions are needed to determine whether lifestyle factors may modify these genetic effects. Lastly, many of the associated variants do not directly alter protein coding and further mechanistic studies are needed to understand how these variants influence gene activity and risk.

Lung Cancer Screening

In 2013, the U.S. National Lung Screening Trial (NLST) of ever heavy smokers reported low-dose thoracic Computed Tomography (CT) scans reduced the mortality from lung cancer by 20 % [219]. Subsequently, the USPSTF recommended that "adults aged 55–80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years [NLST criteria] should be screened by low-dose CT annually" [220]. It was estimated that at a 75 % screening rate by low dose CT could prevent more than 8000 premature lung cancer deaths at an annual cost of $240,000 per prevented death [221]. Low-dose CT screening was also found to prevent an even greater proportion of lung cancer deaths when screening was conducted in populations at highest risk of lung cancer death, those who were identified using a lung cancer death risk model, as opposed to only the USPSTF recommendation [222]. On the other hand, this screening may be overly sensitive, as at least 20 % of NLST participants who underwent low-dose CT screening required further follow-up that may have included invasive procedures such as surgical lung biopsies [223].

While this screening recommendation can improve lung cancer survival by detecting lung cancer at an earlier stage, many Asian Americans may not meet the

screening criteria of heavy smoking (a 30 pack-year smoking history and currently smoke or have quit within the past 15 years). On average this population has a smoking history of less than 30 pack-years, and the majority of Asian-American women diagnosed with lung cancer are never smokers. However, in the only published study of lung cancer screening using the USPSTF recommendation in Asian Americans, it was found that the percentage of Asian Americans eligible for screening was similar to the general US population [224]. In conclusion, while low-dose CT screening for lung cancer under the NLST criteria has been shown to have many benefits, additional work should be conducted to better identify at risk individuals for lung cancer screening. This will help to reduce the proportion of unnecessary invasive follow-up procedures as well as address populations that are at risk of non-tobacco-related lung cancer.

Conclusions

Lung cancer is the second most common cancer in Asian-American men and women. While incidence is lower for Asian Americans compared to non-Hispanic Whites, in some Asian-American populations the incidence is increasing and smoking rates are rising. The Asian-American population is particularly heterogeneous, and comprises many different ethnicities and a range in the levels of SES and acculturation, all of which influences smoking status as well as the exposure to other known lung cancer risk factors. Further research understanding how these risk factors impact the Asian-American community is essential as this population rapidly grows in the US and lung cancer is a highly preventable and survivable with the respective smoking cessation strategies and early stage diagnostic technologies.

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Colorectal Cancer Among Asian Americans

Song-Yi Park and Loïc Le Marchand

Abstract The Asian ethnic subgroups that migrated to the USA are experiencing an increase in colorectal cancer (CRC) rates. This is in contrast to the decline in invasive CRC incidence reported for non-Hispanic whites in the USA, which has been widely attributed to an increase in screening rates. Studies have shown that at least some of the Asian ethnic subgroups are less likely to undergo screening. A number of lifestyle-related factors have been associated with CRC. Indeed, the evidence for a causal link between certain types of dietary factors (e.g., dietary fiber, folate, calcium, vitamin D, red meat, processed meats), alcohol, medications, obesity and physical inactivity and CRC is stronger than for any other common types of cancer. However, it has been suggested that differences in the distribution of known/suspected lifestyle risk factors account for only a portion of the excess risk in Asian Americans for CRC and that other factors, possibly including genetic susceptibility (in particular, gene–environment interactions), are important contributors to the observed disparities in incidence. Based on the available evidence, it is unlikely that risk factors for CRC in Asians differ markedly from those in non-Hispanic whites and other ethnic/racial groups. Further research is warranted to better understand the relationship between genetic and environmental factors that increase the CRC risk of Asians when they migrate to the USA. Most importantly, utilization of screening services should be further promoted to reduce the incidence of this disease in Asian Americans.

Keywords Asian Americans • Colorectal cancer • Diet • Epidemiology • Genetics • Physical activity • Screening • Smoking

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Introduction

Colorectal cancer (CRC) is a common cancer among Asians who migrated to the USA, particularly for those populations that migrated several generations ago. For example, Japanese Americans who migrated to Hawaii and California between 1886 and 1924 have had one of the highest incidence rates in the world for this cancer starting in the early 1980s [1]. Similarly, Asian migrant subgroups that more recently migrated to the USA are now also experiencing an increase in CRC rates. Importantly, a similar pattern of raising rates has taken place for this cancer in recent decades in Asian countries (e.g., Japan, Korea) where lifestyle and diet have become more westernized (Fig. 1). In this chapter, we briefly review CRC rates in USA Asians and focus on what is known of the risk factors that may explain this alarming pattern. Cancer epidemiological research in Asian-American populations often involves several types of comparisons: (1) among different Asian ethnic subgroups and with non-Hispanic whites or other racial/ethnic groups; (2) with the population of their home country; or (3) by duration of residence in the USA or between migrants themselves and subsequent generations. We report on these types of comparisons, when available.

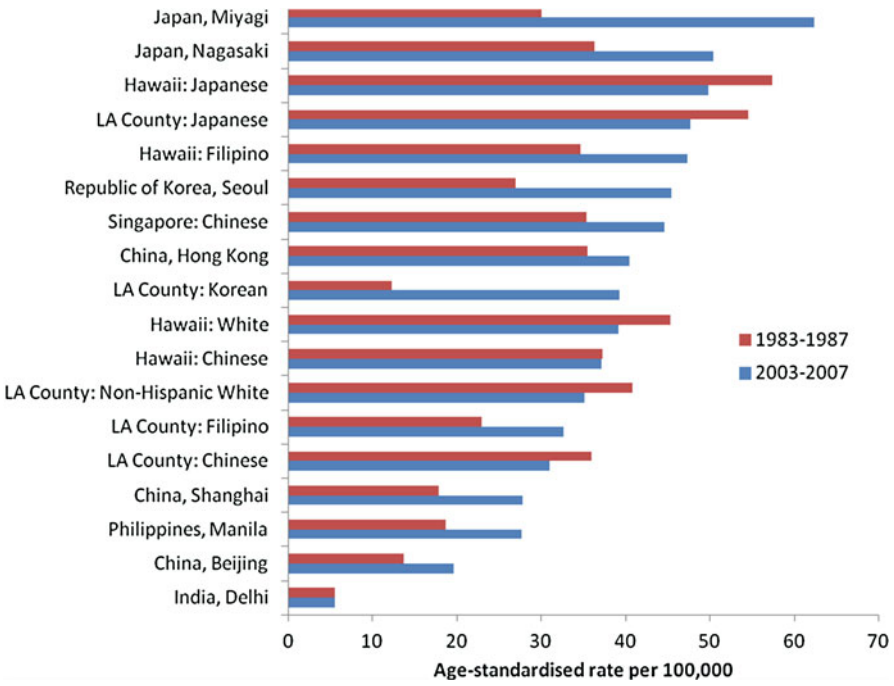

Fig. 1 Male colorectal cancer incidence in selected countries for the periods 1983–1987 and 2003–2007 [2, 3]

Rates and Characteristics of CRC in US Asians

In a recent analysis of the Surveillance, Epidemiology, and End Results (SEER) data for 2004–2008 that included eight Asian subgroups (Asian Indians/Pakistanis, Chinese, Filipinos, Japanese, Kampucheans (Cambodians), Koreans, Laotians, and Vietnamese), Japanese (66.6 per 100,000 for men and 43.0 per 100,000 for women) and Koreans (58.2 for men and 40.9 for women) had the highest CRC incidence rates, higher than or comparable to non-Hispanic whites (54.0 for men and 40.6 for women), as illustrated in Fig. 2 [4]. When comparing incidence trends across three time-periods, 1990–1994, 1998–2002, and 2004–2008, trends varied across the eight Asian subgroups [4]. Sharp increases in incidence were observed for Korean, Kampuchean (Cambodians), Laotian, and Vietnamese men and women and among South Asian and Filipina women. This is in contrast to the decreasing trend in incidence observed for non-Hispanic white men and women in the USA. Similar trends were reported in an analysis of the 1988–2007 California Cancer Registry data [5]. Although decreasing trends in CRC incidence were observed in California among all major racial/ethnic groups, including Asians/Pacific Islanders as a whole, CRC incidence was actually increasing among some Asian subgroups, namely, Korean males and females, as well as South Asian and Filipino females.

Consistent with the incidence patterns, Japanese Americans have been reported to experience the highest mortality rate from CRC, compared to the other Asian subgroups (Chinese, Filipinos, Vietnamese, and Koreans) and non-Hispanic whites in the USA [6] and in California [7, 8]. Based on the 1988–2007 SEER data, 5-year CRC-specific mortality was lower in Asian-American patients (hazard ratio, HR = 0.90; 95 % confidence interval, CI: 0.87–0.94), compared to non-Hispanic

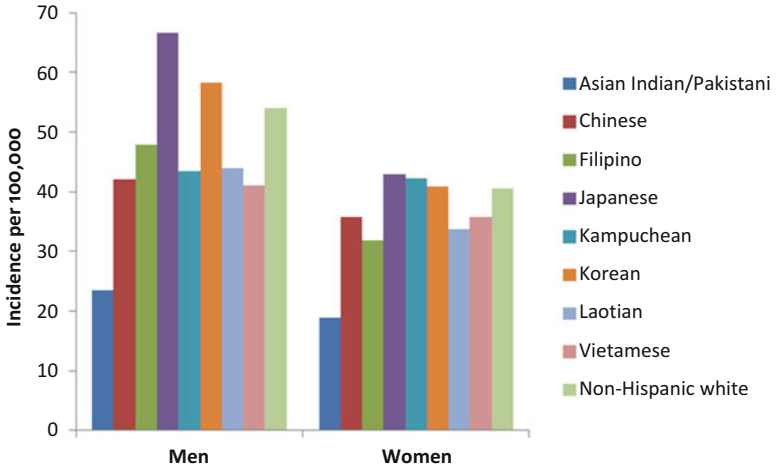

Fig. 2 Age-adjusted incidence rates of colorectal cancer among Asian-American populations, 2004–2008 [4]

white patients after adjustment for demographic factors, stage at diagnosis and other factors [9]. In analyses stratified by Asian-American ethnic groups, CRC-specific mortality was lower in each of the Asian ethnic subgroups of patients (Chinese, Filipino, Japanese, Korean, other Asian, South Asian, and Vietnamese), compared to non-Hispanic white patients but this difference was statistically significant only in Japanese (HR = 0.84; 95 % CI: 0.77–0.92) and South Asian-American patients (HR = 0.72; 95 % CI: 0.56–0.92) (1991–2007 SEER) [10].

In a study comparing Japanese CRC patients living in Hawaii and in Japan (1996–2002), there were significant differences in age distribution, with Japanese American patients ($n = 410$) being older, and more often female, with normal preoperative carcinoembryonic antigen levels, and with a tumor located in the cecum or transverse colon, compared to patients in Japan ($n = 621$). However, tumor characteristics (stage, tumor size, and grade) of Japanese American patients were similar to those for the general American population in SEER [11]. In Massachusetts during 1997–2001, Asian/Pacific Islanders had over two times the incidence rate of the left colon cancer (28.1 per 100,000) compared with right colon cancer (13.6 per 100,000), whereas non-Hispanic whites had a 1.3 times higher incidence rate for the left colon (32.7 per 100,000) than the right colon (24.6 per 100,000) [12]. The North American Association of Central Cancer Registries (NAACCR) data for 1995–1999 showed that among Asians/Pacific Islanders, the rate of distal colon cancer (17.7 per 100,000) was higher than the rate of proximal colon cancer (15.2 per 100,000) in male, with little variation in rates across subsites in female (12.3 per 100,000 and 13.1 per 100,000, respectively) [13]. In contrast, among white males and females, proximal colon cancer rates were over 25 % higher than the rate of distal colon cancer. Chinese patients in China were more likely to have distal CRC and developed the disease at a significantly earlier stage than non-Hispanic white patients in the USA [14].

Migrant Studies

Like other migrant populations, Asians immigrants to the USA experienced changes in lifestyle and often have substantially different cancer rates from those in their home country. These differences often become more marked after two or three generations. Therefore, studies in migrants provide unique research opportunities to understand cancer etiology by comparing cancer risk in populations with a similar genetic background living in different physical and social environments, or in populations of different genetic background living in the same environment [1, 15, 16] (see Hamilton et al., chapter “Resources and Methods for Studying Cancer among Asian Americans”).

Like for other cancers, the general trend has been for the CRC rates of migrants to move to an intermediate level between the risks of their home and host countries. However, several groups have exhibited a rapid and complete transition to the risk of the host country [15]. Among migrant groups displaying this complete transition, Japanese Americans have been studied the most extensively [1]. In a study of

Japanese migrants to Hawaii during the period from 1973 to 1977, the incidence of colon cancer in Japan was 25 % that of whites in Hawaii, whereas the incidence rates for first generation migrants and their descendants were the same as, or slightly higher than, that of non-Hispanic whites [17]. A study of Chinese migrants to the USA for 1968–1972 showed that the colon cancer mortality rate among first generation also exceeded that of non-Hispanic whites [18, 19]. These early studies showed that the increase in CRC risk occurred rapidly in the first generation migrants; however, these studies included limited numbers of second generation migrants. A later study of CRC incidence rates (per 100,000) during 1973–1986 among Asian Americans in Hawaii, San Francisco/Oakland SMSA, and western Washington state showed that US-born Japanese (142.5 for men and 90.1 for women) had a higher incidence rate of CRC compared to Japan-born Japanese (69.3 for men and 63.5 for women) or US-born non-Hispanic whites (89.9 for men and 64.3 for women) [20]. This is in contrast to US-born Chinese (66.9 for men and 40.9 for women) who had a lower rate compared to China-born Chinese (87.8 for men and 44.7 for women) [20].

Colorectal Cancer Screening

Wide spread screening is critical to reducing the public health burden posed by CRC since it results in a decrease in incidence (by the removal of precursor lesions) and in improved survival (through the diagnosis of tumors at an earlier stage). The nationally reported decline in invasive CRC incidence in non-Hispanic whites in the USA has been widely attributed to an increase in screening rates; however, some Asian-American groups are less likely to undergo screening [4] (see chapter "Cancer Screening among Asian Americans").

The percentage of adults (≥40 years) who receive CRC screening was 64.8 % overall and 52.5 % in Asian Americans in 2010 in the National Health Interview Survey [21]. In an analysis of the 2010 Behavioral Risk Factor Surveillance System (BRFSS) data that included adults aged 50–75 years, the rate of self-reported CRC screening [by fecal occult blood test (FOBT), sigmoidoscopy, or colonoscopy] was 59.6 % overall [22]. The rate was highest in non-Hispanic whites (62.0 %), followed by African Americans (59.0 %), Native Hawaiian/Pacific Islanders (54.6 %), Hispanic-English (52.5 %), American Indians/Alaska Natives (49.5 %), Asians (47.2 %), and Hispanic-Spanish (30.6 %). Similarly in the California Health Interview Survey data for 2001, 2003, and 2005, the CRC screening rate (46.8 %) for Asian Americans (Chinese, Japanese, Koreans, Filipinos, South Asians, and Vietnamese) and Pacific Islanders (AAPIs) considered as an aggregated group (≥ 50 years) was lower than that of non-Hispanic whites (57.7 %) [23]. When the AAPI group was disaggregated, further disparity was noted: Koreans showed the lowest CRC screening rate (32.7 %), whereas Japanese had the highest (59.8 %). Over the 5-year period, CRC screening rates increased slightly for most AAPI subgroups, except for Koreans who showed a decreasing trend from 2001 to 2005 (Fig. 3).

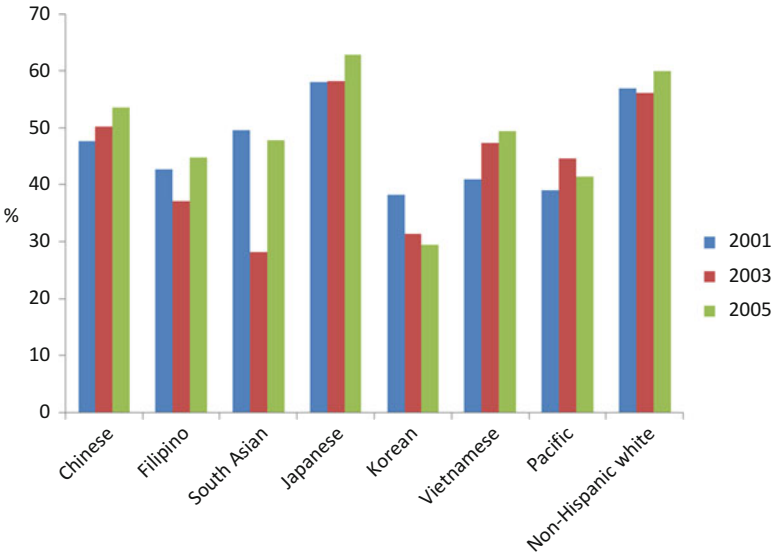

Fig. 3 Colorectal cancer screening rates in California in 2001, 2003, and 2005 [23]

In an analysis of electronic health records in Northern California among adults aged 50–75 years [24], Asian Indians had the lowest rate (45.6 %) of CRC screening among Asian subgroups (Japanese: 63.8 %; Chinese: 66.7 %; Filipinos: 59.0 %; Koreans: 66.2 %; Vietnamese: 65.8 %; Native Hawaiians/Pacific Islanders: 53.8 %), well below that of non-Hispanic whites (63.7 %).

The length of time spent in the USA has been shown to be a significant predictor of CRC screening in different Asian-American subgroups. In the 2001 California Health Interview Survey, Asian-American immigrants who have lived in the USA for less than 15 years were less likely to undergo CRC screening (odds ratio, OR = 0.48; 95 % CI: 0.32–0.71) compared to those born in the USA [25]. In addition to the length of residency in the USA, various factors were shown to affect CRC screening in Asian Americans, including socioeconomic status, English fluency, cancer knowledge, social support, access to health care services, and comorbidity [26–35].

Intervention trials in Asian Americans found that culturally tailored approaches are effective in improving screening rates [36–42]. For instance, among Vietnamese Americans, a controlled trial of a public education and provider intervention was conducted including a Vietnamese-language CRC screening media campaign from 2004 to 2006 in one community vs. no intervention in a control community [39]. The post- to pre-intervention OR for having ever had a CRC screening was 44 % greater (95 % CI: 1.03–1.99) in the intervention community than in the control community. In an educational intervention conducted in Michigan to promote CRC awareness using Asian-language media throughout local Asian Indian, Chinese, Filipino, Hmong, Japanese, Korean, and Vietnamese American communities, 78 %

of those receiving the educational intervention reported to have been screened in the last 12 months, compared with the 37 % who said to have ever been screened prior to the study [42].

Lifestyle-Related Risk Factors

A number of lifestyle-related factors have been associated with CRC risk. Indeed, the evidence for a causal link between certain types of diet, obesity, diabetes, alcohol, medications and physical inactivity and CRC is stronger than for any other common types of cancer.

Obesity

Obesity increases risk of developing CRC in both men and women. The 2007 World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) Second Expert Report based on the most comprehensive systematic literature reviews concluded that there was convincing evidence that body fatness and abdominal fatness, and adult attained height as a marker for genetic, environmental, hormonal, and nutrition factors affecting growth, are causes of CRC [43]. A meta-analysis also suggested that central obesity, as measured by waist-to-hip ratio, may be particularly important in increasing risk of CRC compared to overall obesity measured by body mass index (BMI, kg/m^2) [44]. It has been noted that Asians have a higher percentage of body fat and, especially, visceral adiposity for the same BMI compared with European-origin populations [45–49].

In a cohort of Japanese-American men in Hawaii initiated in 1965, a BMI of $\geq$25.8 kg/m^2 was associated with an increased risk of colon cancer (relative risk, RR = 1.38; 95 % CI: 1.01–1.90), compared to a BMI < 21.7 kg/m^2 [50]. Several cohort studies conducted in Asia have also reported an increased risk of CRC with obesity. In cohort studies in Shanghai, China, both a measure of general adiposity (BMI) and measures of central adiposity (elevated waist-to-hip ratio (WHR) and waist circumference (WC)) were significantly associated with an increased risk of colon cancer in men but not in women [51]. HRs for colon cancer in men in the highest compared with the lowest quintiles were 2.15 (95 % CI: 1.35–3.43; *P* for trend < 0.001) for BMI, 1.97 (95 % CI: 1.19–3.24; *P* for trend < 0.001) for WHR, and 2.00 (95 % CI: 1.21–3.29; *P* for trend < 0.001) for WC. A cohort study in South Korea reported that obese men (BMI $\geq$ 30 kg/m^2) were at increased risk for colon cancer (RR = 1.42; 95 % CI: 1.02–1.98), but not obese women (RR = 1.01; 95 % CI: 0.72–1.42); the average ages of men and women in this cohort was 45.0 and 49.4 years old [52]. In another Korean cohort of postmenopausal women (mean age 55.9), BMI was related to an increased colon cancer risk (HR for a one unit BMI increase = 1.05; 95 % CI: 1.02–1.08) [53]. A pooled analysis of eight

prospective cohort studies in Japan found that the risk of CRC increased with increasing BMI; the adjusted HRs for a one unit BMI increase were 1.03 (95 % CI: 1.02–1.04) for males and 1.02 (95 % CI: 1.00–1.03) for females [54]. In a Chinese cohort in Singapore, a significant increase in CRC risk was observed in subjects with BMI ≥ 27.5 kg/m^2, compared to those with BMI 21.5–24.4 kg/m^2 (HR = 1.25; 95 % CI: 1.01–1.55). The BMI-cancer association was similar in men and women. However, this association was more pronounced in never smokers (HR = 1.35; 95 % CI: 1.04–1.76) than in ever smokers (HR = 1.08; 95 % CI: 0.74–1.58) [55]. Although data are limited for Asian Americans, the evidence suggests that obesity is a modifiable risk factor for CRC in Asians, especially in men and irrespective of where they live.

Diabetes

Type 2 diabetes has been associated with an increased risk of cancer at several sites including colorectum [56]. A recent meta-analysis of observational studies found that diabetes was related to a 27 % increased risk of CRC (summary RR = 1.27; 95 % CI: 1.21–1.34) [57]. The observed associations between diabetes and cancer could be either causal (e.g., caused by hyperglycemia or hyperinsulinemia) or because of confounding from common risk factors such as adiposity [57]. However, studies showed that diabetes is a risk factor of CRC independently of obesity. In the Multiethnic Cohort Study (MEC) that was established to study lifestyle and genetic factors and cancer in African American, Native Hawaiian, Japanese American, Latino, and non-Hispanic white older adults living in Hawaii and Los Angeles in 1993–1996 [58], participants with a history of diabetes had a significantly greater risk of CRC than those without such a history with adjustment for BMI in the entire cohort (RR = 1.19; 95 % CI: 1.09–1.29) and in Japanese Americans (RR = 1.27; 95 % CI: 1.09–1.47) [59]. A later study in the MEC showed that despite their lower BMI, Asian Americans had a higher diabetes risk than whites [60]. Similarly, in a cohort study in Korea, elevated fasting serum glucose levels and a diagnosis of diabetes were independent risk factors for CRC [61].

Smoking

The association between cigarette smoking and CRC was recently reevaluated by an expert panel assembled by the International Agency for Research on Cancer (IARC), with the conclusion that smoking is a risk factor for both colon and rectal cancer [62]. Although IARC and the American College of Gastroenterology CRC screening guidelines highlight cigarette smoking as a risk factor, cigarette smoking is still an arguably underappreciated risk factor for the disease in the USA [63].

In a meta-analysis of 25 prospective cohort studies, the risk of CRC was higher in current (RR = 1.20; 95 % CI: 1.10–1.30) and former smokers (RR = 1.18; 95 % CI: 1.12–1.25), compared to never smokers [64]. In a subset analysis limited to five studies in Asian countries, the RRs were similar: 1.21 (95 % CI: 1.07–1.36) for current smokers and 1.17 (95 % CI: 1.02–1.35) for former smokers. Other meta-analyses in populations of European ancestry have all shown an increased CRC risk associated with smoking, with possibly a greater risk for rectal cancer [63, 65]. Smoking has also been related to a poor survival among CRC patients. In a meta-analyses of 62,278 CRC patients from 16 studies, HR for all-cause mortality was 1.26 (95 % CI: 1.15–1.37) for current smokers and 1.11 (95 % CI: 0.93–1.33) for former smokers, compared with never smokers [66]. In the Seattle Colon Cancer Family Registry, current smokers had a significantly elevated risk of CRC-specific (HR = 1.30; 95 % CI: 1.09–1.74) and all-cause (HR = 1.51; 95 % CI: 1.24–1.83) mortality compared to never smokers [67].

In the cohort study of Japanese American men in Hawaii, current smokers had a higher risk of colon (RR = 1.42; 95 % CI: 1.09–1.85) and rectal (RR = 1.95; 95 % CI: 1.25–3.04) cancer, compared to never smokers [50]. In a population-based case–control study conducted among Caucasians, Japanese, Native Hawaiians, Filipinos, and Chinese in Hawaii, ever smokers were at an increased risk of CRC compared with never smokers (OR = 1.23; 95 % CI: 0.99–1.52 for men and OR = 1.27; 95 % CI: 1.01–1.59 for women). ORs for the highest quartile of pack-years vs. never smokers was 1.48 (95 % CI: 1.12–1.96) in men and 1.38 (95 % CI: 0.91–1.95) in women [68]. In ethnic-specific analyses, the positive association was observed in all of the three largest ethnic groups (Japanese, Caucasians, and Native Hawaiians). The evidence indicates that smoking is a risk factor for CRC in Asia and among Asian Americans.

Diet and Alcohol

In the 2011 WCRF/AICR report [43], the evidence that food containing dietary fiber decreases CRC risk and that red and processed meat, and alcohol (in men), increase risk, was considered to be convincing. The report also concluded that consumption of garlic, milk, and calcium probably protects against this cancer. Only a limited number of studies have been performed in Asian Americans and have examined the diet–CRC relationship.

In the MEC that measured dietary intake by a quantitative food frequency questionnaire, dietary fiber consumption was associated with a lower risk of CRC in men (RR = 0.62; 95 % CI: 0.48–0.79 for the highest vs. lowest quintile) but not in women (RR = 0.88; 95 % CI: 0.67–1.14) after multivariate adjustment that included age, ethnicity, and other lifestyle and dietary factors. This inverse association was observed in Japanese-American men but not in Japanese-American women [69]. The association with dietary fiber was recently reevaluated in the MEC with a larger number of cases ($n = 4388$) and an inverse association was observed in women who

never used menopausal hormone therapy (MHT) [70]. The magnitude of this association was similar to that found in men, and was suggested to be present in each ethnic group. There was also evidence that dietary fiber did not exert an additional protective effect against CRC among woman who ever used MHT over that afforded by MHT alone. In a large, multicenter, case–control study of Chinese residing in North America, consumption of non-fiber carbohydrate, i.e., the digestible non-fiber portion of carbohydrates that stimulates insulin release, was associated with an increased risk of CRC in North-American Chinese men (OR = 1.7; 95 % CI: 1.1–2.7 for the highest vs. lowest tertile) and women (OR = 2.7; 95 % CI: 1.5–4.8) [71]. In contrast, in the MEC, carbohydrate intake was inversely associated with CRC risk in women (RR = 0.71; 95 % CI: 0.53–0.95 for the highest vs. lowest quintile) but not in men (RR = 1.09; 95 % CI: 0.84–1.40) [72]. A meta-analysis of 12 cohort studies (including the MEC) found no significant association between CRC risk and carbohydrate intake (summary RR = 0.93; 95 % CI: 0.84–1.04 for high vs. low intake) [73].

Intake of fruits and vegetables, rich sources of dietary fiber and bioactive phytochemicals, among the MEC participants was reported to be related to a decreased CRC risk in all men combined and in Japanese American men specifically, but not in all women combined or in Japanese American women [74]. A cohort study of Chinese men in Shanghai found an inverse association with fruit intake but not with vegetable consumption [75]. However, a cohort study of Singapore Chinese men and women reported no significant association of CRC risk with dietary isothiocyanates from cruciferous vegetables [76] or a dietary pattern characterized by a high vegetable, fruit, and soy food intake [77].

In the MEC, no association with CRC risk was detected for total meat, red meat, or processed meat intake or for total or specific heterocyclic amine intake either overall or in Japanese Americans [78]. Neither total nor specific types of fats were associated with CRC risk. However, individuals consuming a dietary pattern rich in meat and fat were at increased risk of CRC (RR = 1.20; 95 % CI: 1.08–1.35 for the highest vs. lowest quartile; P for trend <0.001) but the association was attenuated in multivariable models adjusting for other risk factors (P for trend = 0.10) [78]. A cohort of Chinese women in Shanghai, China, reported a decreased risk of CRC with intake of polyunsaturated fatty acids [79] and an increase risk with cholesterol intake [80]. In the case–control study of Chinese residing in North America and China, saturated fat intake was significantly associated with CRC risk; ORs per 100 kcal from saturated fat were 1.8–2.9 ($P<0.001$) in North America and 1.1–1.6 in China depending on sex and anatomic site [81]. The association between saturated fat and CRC was stronger among the sedentary than among the physically active participants. Risk among sedentary Chinese Americans increased more than fourfold from the lowest to the highest category of saturated fat intake.

In a meta-analysis of 6 cohort studies and 13 case–control studies conducted in Japan, the summary RR (95 % CIs) for the highest vs. lowest categories of red meat consumption was 1.16 (1.001–1.34) and 1.21 (1.03–1.43) for colorectal and colon cancer, respectively, and that for processed meat consumption was 1.17 (1.02–1.35) and 1.23 (1.03–1.47) for colorectal and colon cancer, respectively. Poultry consumption was associated with a lower risk of rectal cancer, with a summary RR (95 % CI) of 0.80 (0.67–0.96) [82]. The corresponding pooled OR for fish was 1.03

(0.89–1.18) and 0.84 (0.75–0.94) for cohort and case–control studies, respectively [83]. A meta-analysis of three Asian cohort studies (from Japan and Singapore) found that dietary fat was not associated with CRC risk [84].

In the prospective cohort of Japanese-American men in Hawaii initiated in the 1960s, saturated fat intake was associated with a lower risk of colon cancer (RR = 0.44; 95 % CI: 0.23–0.83 for the highest vs. lowest quintile) [85]. Serum triglycerides and glucose levels were not associated with CRC [86]. Serum cholesterol levels were associated with a decrease in risk for colon cancer (*P* for trend = 0.01) but not for rectal cancer [87]. These findings were not consistent with those from a meta-analysis of prospective studies mostly performed in Europe and North America showing that serum triglycerides (summary RR = 1.18; 95 % CI: 1.04–1.34 for high vs. low concentrations) and cholesterol levels (summary RR = 1.11; 95 % CI: 1.01–1.21) were related to an increased risk of CRC [88].

Calcium intake was found to be inversely associated with CRC risk in the MEC and this association was strongest among Japanese Americans (RR = 0.69; 95 % CI: 0.52–0.91 for the highest vs. lowest quartile; *P* for trend = 0.008) [89]. However, calcium intake was not related to the risk of colon cancer in the Japanese men cohort in Hawaii, regardless of whether it came from dairy or nondairy sources [90]. While vitamin D intake was not related to risk overall or in any ethnic/racial group in the MEC [89], pre-diagnostic plasma 25-hydroxyvitamin D levels in a case–control study nested within the MEC were associated with a lower risk of CRC overall (OR = 0.60; 95 % CI: 0.33–1.07; *P* for trend = 0.01) and, in an ethnic-specific analysis, the inverse trend was only significant in Japanese Americans (*P* for trend = 0.03) [91]. In a case–control study of plasma levels of B vitamins nested in the MEC, folate levels were inversely associated with CRC risk among nondrinkers (OR for > median vs. ≤ median = 0.55; 95 % CI: 0.31–0.95). PLP (pyridoxal-5′-phosphate, the active form of vitamin B6) levels were related to a lower risk overall (OR = 0.49 for the highest vs. lowest quartile; 95 % CI: 0.29–0.83; *P* for trend = 0.009) [92]. Ethnic-specific analysis did not show any heterogeneity in the association of CRC with plasma PLP. However, in Chinese cohorts in Shanghai, plasma folate levels were not associated with CRC risk in both men [93] and women [94].

Calories from alcohol (≥ 14 %) was associated with a higher risk of colon (RR = 1.88; 95 % CI: 1.38–2.56) and rectal (RR = 2.51; 95 % CI: 1.59–3.97) cancer, compared to nondrinkers in the Japanese American men cohort in Hawaii [50]. Alcohol intake in the MEC was also related to an increased risk of CRC in Japanese American men (HR = 1.54; 95 % CI: 1.19–2.01 for ≥ 40 g/day of alcohol vs. nondrinkers) but not in women (unpublished data). Although a meta-analysis of ten case–control studies in Chinese populations found no significant association between alcohol consumption and CRC risk (pooled OR = 1.58; 95 % CI: 0.90–2.76) [95], another meta-analysis of 19 studies in Asia reported an increased risk of CRC with a pooled RR of 1.21 (95 % CI: 1.03–1.43) for all drinkers and 1.81 (95 % CI: 1.33–2.46) for heavy drinkers compared to non-/occasional drinkers [96].

The Shanghai cohorts reported a decreased risk of CRC with intake of green tea both in men [97] and women [98], whereas the Singapore Chinese cohort found an increased risk with green tea consumption [99]. Coffee consumption was related to a decreased risk of CRC in the Singapore Chinese cohort [100].

The evidence to date suggests that red meat and alcohol increase risk and that dietary fiber and calcium decrease risk of CRC in Asian Americans. The evidence for the association of CRC with other dietary factors (e.g., soy or green tea) is still inconclusive for this population.

Physical Activity

The evidence that physical activity protects against colon cancer was considered as convincing by the WCRF expert panel [43]. In a dose–response meta-analyses, total physical activity (expressed as METs-hour/day) was associated with a significant decreased risk for colorectal (RR = 0.97 for an increase of five METs-hour/day; 95 % CI: 0.94–0.99), as well as for colon cancer (RR = 0.92; 95 % CI: 0.86–0.99) but not rectal cancer.

In the cohort of Japanese American men in Hawaii, physical activity was found to be associated with a lower risk of colon cancer; RRs were 0.56 (95 % CI: 0.39–0.80) and 0.71 (95 % CI: 0.51–0.99) for the middle and upper tertiles of a physical activity index, respectively, compared to the lower tertile [101]. In the population-based case–control study of Chinese in North America and China, on both continents and in both sexes, CRC risks increased with increasing time spent sitting [81]. ORs for CRC among Chinese American men were 2.4 ($P < 0.05$) for 5–9 h sitting and 3.9 ($P < 0.001$) for ten or more hours sitting, compared with less than 5 h sitting.

Two cohort studies in Japan reported an inverse association between physical activity and CRC. In the Japan Public Health Center-based Prospective Study (JPHC study), men in the highest quartiles of MET hours per day had a 31 % lower risk (95 % CI: 0.49–0.97), compared to those in the lowest quartile [102]. In the Miyagi Cohort Study, time spent walking was inversely associated with CRC risk in men. Men who walked 1 h or more per day had a 43 % lower risk (95 % CI: 0.38–0.83), compared to those who walked 0.5 h or less (P for trend = 0.003) [103].

Overall Effect of Lifestyle on CRC Risk

A study in the MEC investigated whether the higher age-adjusted CRC risk of Japanese Americans (RR = 1.40; 95 % CI: 1.21–1.61 in men and RR = 1.38; 95 % CI: 1.17–1.62 in women), compared to non-Hispanic whites, may be explained by the effects of lifestyle risk factors. After accounting for obesity, cigarette smoking, physical activity, alcohol consumption, and dietary intakes of red meat, dietary fiber, calcium, folate, and vitamin D, CRC risk still remained significantly elevated in Japanese Americans (RR = 1.27; 95 % CI: 1.09–1.48 in men; RR = 1.49; 95 % CI: 1.24–1.78 in women), relative to non-Hispanic whites [104]. These findings suggest that differences in the distribution of known/suspected lifestyle risk factors

account for only a modest proportion of the excess risk in Japanese Americans for CRC and that other factors, possibly including genetic susceptibility, are important contributors to the observed disparities in incidence.

Medications

Although conclusive evidence is still lacking, epidemiologic studies and randomized trials [105] suggest that long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) exerts chemopreventive properties against CRC [106, 107]. In a meta-analysis of 12 cohort studies (Europe and USA), an inverse association between aspirin use and CRC was observed both overall (RR = 0.74; 95 % CI: 0.64–0.83 for aspirin dose; RR = 0.80; 95 % CI: 0.75–0.85 for frequency of aspirin use; RR = 0.75; 95 % CI: 0.68–0.81 for years of aspirin use) and in subgroups stratified by sex and cancer site [108]. A meta-analysis of 19 case–control studies also reported that regular use of aspirin or NSAID was associated with a reduced risk of CRC [109]. No study of NSAIDs and CRC risk has been published for Asian-American populations. In a cohort of CRC patients in Singapore, the risk of CRC relapse or death from CRC was approximately 60 % lower compared to patients who were not post-operative aspirin users (HR = 0.38; 95 % CI: 0.17–0.84) [110]. In the MEC, NSAID user had a lower risk of CRC (HR = 0.82; 95 % CI: 0.70–0.95) among Japanese American men but not among Japanese American women (HR = 0.93; 95 % CI: 0.78–1.11) (unpublished data).

Epidemiological evidence suggests that estrogen is probably involved in the physiology of the large bowel and the etiology of CRC [111]. While initially protective against CRC, once the tumor has developed, estrogens are thought to increase proliferation. Consequently, oral contraceptives and MHT may be effective against CRC development. However, further data on the risk-benefit profile of short-term MHT use are needed and will determine whether there is any role for estrogens in the chemoprevention of CRC [112]. In the MEC, MHT users at baseline had a 25 % lower risk of CRC compared to never users among Japanese American women (Park et al., under review), while oral contraceptive use was not associated with CRC risk (HR = 0.98; 95 % CI: 0.78–1.23) (unpublished data).

Genetic Susceptibility

Genetics may explain a sizable portion of CRC incidence through the direct effects of susceptibility genes, as well as their possible interactions with environmental and lifestyle factors [113, 114]. It is currently believed that even sporadic CRC cases, i.e., those occurring outside familial syndromes (e.g., Familial Adenomatous Polyposis, Lynch Syndrome), are influenced by low-penetrance genes or gene combinations. These susceptibility loci have very modest effect sizes, with ORs for developing CRC in risk allele carriers usually from 1.1 to 1.3 [115].

In early years, genetic studies for CRC were limited to examining genetic polymorphisms in candidate genes. Genes involved in mutagenesis (carcinogen metabolism, DNA repair and synthesis and maintenance of genome integrity) were naturally prime candidates, alongside a few genes involved in cell signaling and transcriptional control [114]. With rapid technological advances in genotyping, a global interrogation of the genome became possible through genome-wide association studies (GWAS). These studies identified a greater number of variants related to CRC risk [116, 117].

Family History

A history of CRC among one's first-degree relatives is known to confer an increased risk of the disease. A meta-analysis of 47 studies, including eight studies conducted in Asian countries, reported a risk estimate of 2.24 (95 % CI: 2.06–2.43) for one affected first-degree relative, rising to 3.97 (95 % CI: 2.60–6.06) for two or more [118].

In a population-based multiethnic case–control study in Hawaii, which was included in the above meta-analysis, first-degree relatives of cases were found to have a 2.5-fold increased risk of CRC compared with relatives of controls (95 % CI: 1.8–3.4). This increase in risk was stronger in Japanese American (OR = 3.0; 95 % CI: 2.1–4.6) than in Caucasians (OR = 1.8; 95 % CI: 1.2–2.9) (P for interaction = 0.07) [119].

Candidate Gene Studies

A meta-analysis of the literature for 267 genetic variants in 150 candidate genes found that 62 variants in 50 genes showed a nominally significant association with CRC risk ($P < 0.05$) [120]. In this analysis, epidemiological evidence for a significant association with CRC risk was considered to be "strong" for eight variants in five genes (*APC*, *CHEK2*, *DNMT3B*, *MLH1*, and *MUTYH*), "moderate" for two variants in two genes (*GSTM1* and *TERT*), and "weak" for 52 variants in 45 genes. Although this meta-analysis reported that genetic variants in *MTHFR*, involved in one-carbon metabolism, showed no relation to CRC risk [120], another meta-analysis of 21 Asian studies found a significant association of the *MTHFR* 677T allele with a decreased risk of CRC (OR = 0.91; 95 % CI: 0.85–0.98) [121]. In a study of the *MTHFR* C677T polymorphism [122] in the MEC, OR for the TT vs. CC genotype was 0.77 (95 % CI: 0.58–1.03) overall. This inverse association was statistically significant in Japanese Americans (OR = 0.59; 95 % CI: 0.36–0.95), suggested for whites (OR = 0.62; 95 % CI: 0.34–1.15) and not observed in Latinos (OR = 0.96; 95 % CI: 0.56–1.15). This association was also similar in both sexes, stronger at high levels of folate intake, and limited to light and nondrinkers (P for interaction with ethanol = 0.02).

A number of interactions between genetic variants and diet have been suggested to play a role in CRC etiology [123]. Interactions have been reported in prospective studies for meat with *NAT1*, *NAT2*, *ABCB1*, and *NFKB1*, cruciferous vegetables with *GSTM1*, *GSTT1*, and *CCND1*, calcium with *VDR*, vitamins C and E and carotene with *MGTM*, dietary fiber with *IL10*, and alcohol with *PPARG*, *ADH*, and *ALDH* [123, 124]. However, these findings need replication in independent, well-characterized cohort studies before conclusions regarding these interactions and the underlying biological mechanisms can be reached [123, 125].

In a Korean population, subjects with low-methyl diets (as defined by a combined low intake of folate and high intake of alcohol) had higher risk of CRC (OR = 2.32; 95 % CI: 1.18–4.56) than did those with high-methyl diets among *MTHFR* CC/CT carriers, whereas the amount of dietary methyl did not affect the CRC risk among carriers with the TT homozygous variant (*P* for interaction = 0.65) [126].

A Chinese case–control study found that the *NQO1* 609 CT and TT genotypes were associated with an increased risk of CRC (CT: OR = 2.02, 95 % CI: 1.55–2.57; TT: OR = 2.51, 95 % CI: 1.82–3.47), compared with the CC genotype. Moreover, NQO1 609C > T appeared to have a multiplicative joint effect with both tobacco smoking and alcoholic drinking (*P* for multiplicative interactions were 0.0001 and 0.013, respectively) on CRC risk [127].

In a Singapore Chinese population, individuals with both the *GSTM1* and *GSTT1* null genotypes were reported to have a 57 % reduction in CRC risk among high vs. low consumers of isothiocyanates-rich cruciferous vegetables (OR = 0.43; 95 % CI: 0.20–0.96), in particular for colon cancer (OR = 0.31; 95 % CI: 0.12–0.84) [76]. However, no statistical interactions were detected between cruciferous vegetable intake and *GST* gene variants on the odds of CRC in a case–control study in Shanghai, China [128].

GWAS

Studies in twins have suggested that heredity is responsible for approximately one-third of the susceptibility to CRC [129]. This is in contrast to the known familial forms that account for less than 6 % of all CRC cases [130]. This has led to the suspicion that there may be other genes that, when mutated, predispose to CRC with or without polyposis [115]. To date, more than 50 chromosome regions harboring common variants conferring altered CRC risk have been identified using the GWAS approach [116, 117, 131]. Although these CRC susceptibility SNPs have been shown to only explain a small proportion of the genetic risk, it is not clear how much of the heritability remains to be explained by other, yet unidentified, rarer SNPs that would have a greater penetrance [132].

While most GWAS have been conducted in European-ancestry populations [133], multiple GWAS have identified novel loci associated with CRC risk in Asian populations.

A trans-ethnic GWAS of CRC conducted in two populations (Japanese and African Americans) identified a new susceptibility locus in *VTI1A* and replicated this association in cases and controls of European ancestry [134]. This variant was associated with risk in all three populations.

In a GWAS of 7456 CRC cases and 11,671 controls conducted as part of the Asian Colorectal Cancer Consortium [135], three new loci at 5q31.1 (near *PITX1*), 12p13.32 (near *CCND2*), and 20p12.3 (near *HAO1*) were associated with CRC risk. Also, a new CRC risk variant was identified in the *SMAD7* gene among East Asians [136]. Further, a large-scale GWAS in East Asians (14,963 CRC cases and 31,945 controls) identified 6 new loci associated with CRC risk at 10q22.3, 10q25.2, 11q12.2, 12p13.31, 17p13.3, and 19q13.2 [137].

A GWAS in a Japanese population identified a novel locus (rs7758229 in *SLC22A3*) in the 6q26-q27 region associated with distal colon cancer and replicated this association in a Korean population [138].

A number of studies have also tested whether CRC risk variants identified in CRC GWAS conducted in European-ancestry populations are generalizable to Asians. In the five ethnic/racial groups of the MEC, among 11 risk variants for CRC identified by GWAS in populations of European ancestry, an increased risk of CRC/adenoma was confirmed for the 8q24, 11q23, and 15q13 loci in whites, and for the 8q24 and 20p12 loci in African Americans [139]. Statistically significant cumulative effects of risk alleles on CRC/adenoma risk were found in every population (OR per allele = 1.07–1.09, $P \leq 0.039$), except in Japanese Americans (OR = 1.01, $P = 0.52$).

GWAS-identified variants for diseases related to CRC (e.g., diabetes, obesity) were also tested for association with CRC in various populations, including Asians. In a case–control study within the MEC, the risk variants (24 SNPs in 15 loci) identified in GWAS of BMI and waist size were also examined in relation to CRC risk [140]. Risk alleles for two obesity SNPs were associated with CRC risk: *KCTD15* rs29941 (OR for C allele = 0.90; 95 % CI: 0.83–0.98) and *MC4R* rs17782313 (OR for C allele = 1.12; 95 % CI: 1.02–1.22) without heterogeneity observed across race/ethnic groups. Nineteen Type 2 diabetes GWAS SNPs were tested in the MEC for association with CRC [141]. Four SNPs were associated with CRC: rs7578597 (*THADA*), rs864745 (*JAZF1*), rs5219 (*KCNJ11*), and rs7961581 (*TSPAN8*, *LGR5*). For rs7578597 (*THADA*), a significant inverse association with the diabetes risk (T) allele was observed overall (OR = 0.84; 95 % CI: 0.75–0.95), with the strongest effect seen among Japanese Americans (OR = 0.52; 95 % CI: 0.36–0.75).

A genetic variant on chromosome 10p14, first identified to be associated with CRC risk in a GWAS in Europeans, was tested in a Chinese population [142]. OR per A allele was 0.71 (95 % CI: 0.54–0.94). A meta-analysis by the same authors further confirmed the significant association, reporting an OR per A allele of 0.91 (95 % CI: 0.89–0.93) in European-descent populations and 0.86 (95 % CI: 0.78–0.96) in Chinese. A common SNP, rs3802842 at 11q23 identified in CRC GWAS, was also tested in a Chinese population and found to be significantly associated with CRC risk [143]. A meta-analysis of 25 studies, including four conducted in Asian populations, also provided convincing evidence that the same SNP, rs3802842 at 11q23, significantly contributed to CRC risk [143]. Whether 7 SNPs associated with gastric cancer were also associated with CRC

was tested in a Chinese population [144]. Two of the five SNPs located at 10q23 (rs3765524 and rs2274223) were found to have significant protective effects against CRC, with equal OR per allele (OR = 0.31). Two other gastric cancer risk SNPs located on 1q22 (rs4072037 and rs4460629) similarly showed a weak association with CRC.

The GWAS SNP, rs961253 in 20p12.3, associated with increased risk of CRC in Europeans was also found to be related to CRC (OR per A allele = 1.60; 95 % CI: 1.26–2.02) in a Chinese population. This association was confirmed with an OR of 1.34 (95 % CI: 1.20–1.50) for the Asian studies included in a meta-analysis of the published literature [145]. The association of rs7758229 in 6q26-q27 with distal colon cancer, identified in a GWAS in Japan, was not found to be associated with CRC risk in a Chinese population [146]. This inability to replicate the Japanese GWAS findings among Chinese might be partly due to inadequate power (>75 %).

Eleven GWAS risk loci identified in European-ancestry populations were investigated in a Singapore Chinese population [147]. Only SNPs at 1q41, 8q23.3, 11q23.1, 16q22.1, and 18q21.1 showed evidence of associations with CRC risk, with ORs ranging from 1.13 to 1.40. Half of the loci did not show any evidence for association with CRC in Singapore Chinese, which could be due to different linkage disequilibrium patterns and allelic frequencies or genetic heterogeneity. Two CRC risk SNPs in the 8q24 region were assessed in Japan [148]. An increased risk of CRC was observed with rs6983267 but not with rs10090154.

Overall, these studies indicate that fine-mapping studies of the CRC GWAS risk loci are needed to identify the variants responsible for a potential association with CRC in Asians. For instance, a fine-mapping study of the 21 known risk loci in African Americans in the MEC identified two markers at two known loci that may better predict CRC risk in that population than the previous index SNPs [149].

Conclusion

Among Asian Americans, increased susceptibility to CRC in some groups (Japanese, Koreans) and upward incidence trends for other groups have been documented. The available data suggest that it is unlikely that risk factors for CRC in Asians differ markedly from those in other ethnic/racial groups. However, it remains unclear why some Asian groups in the USA have a clearly elevated risk for CRC, compared to whites. It is conceivable that they may experience increased exposure to some risk factors (e.g., central obesity, hyperinsulinemia), or a greater risk associated with a given exposure (e.g., smoking, alcohol, red meat). These effects may reflect specific genetic susceptibilities. Further research is warranted to better understand the interplay of genetic and environmental factors that increase CRC risk in Asians when they migrate to the USA. Utilization of screening services should be further promoted to reduce the incidence of this disease in Asian Americans.

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Prostate Cancer Among Asian Americans

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Abstract Prostate cancer, the most commonly diagnosed cancers in men, is a clinically heterogeneous disease. Some tumors remain indolent with little impact on morbidity and survival, while others are aggressive and rapidly progress to advanced and lethal disease. Studies of prostate cancer incidence have shown considerably higher incidence rates among Asian-American men living in the United States (US) relative to Asian men living in Asian countries. Although differences in screening practices by prostate-specific antigen (PSA) testing likely account for some of the differences in incidence, the adoption of Western lifestyles with migration to the US may play a role and involve the interplay between genetic and environmental factors. Epidemiological studies have examined migration-related risk factors among Asian Americans, capitalizing on the unique heterogeneity of specific Asian populations by generational status and acculturation. Age, race/ethnicity, family history, and genetic susceptibility are established risk factors for prostate cancer. Additional risk factors that have been implicated include hormonal and infection/inflammatory factors, body mass index, diabetes, physical activity, smoking, and dietary intake of animal and polyunsaturated fat, soy products, and green tea. In this chapter, we summarize our current understanding of the epidemiology of prostate cancer in Asian-American populations.

Keywords Asian American • Prostate cancer • Risk factors • Epidemiology • Body mass index • Smoking • Isoflavones

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Introduction

Prostate cancer develops in the prostate, a gland in male reproductive system that functions to produce seminal fluid to nourish and transport semen. It is one of the most common cancers in men, typically diagnosed in men ages 50 and older, who are often asymptomatic and identified by screening, with the majority of deaths due to prostate cancer occurring in men ages 75 and older. While many of the symptoms of prostate cancer are similar to benign prostate hyperplasia (BPH), the enlargement of the prostate, prostate cancer and BPH are distinct conditions. The presence of BPH may increase the detection of indolent prostate cancer through transurethral resection of the prostate (TURP) or prostate-specific antigen (PSA) testing; however, BPH is not a risk factor for disease. Prostate cancer is generally an indolent disease, yet some cases are aggressive and fast growing that rapidly progress to lethal prostate cancer. Autopsy studies have revealed an increase in prostate cancer prevalence with each decade of age, with an estimated prevalence of 59 % by age >79 years [1]. This indicates a high proportion of indolent tumors. It is clear that strategies are needed to distinguish between indolent and aggressive forms of the disease.

Incidence

In 2009–2013, the incidence rate of prostate cancer in Asian Americans/Pacific Islanders was 68.9 per 100,000 [2]. In comparison, incidence rates of prostate cancer among non-Hispanic Whites and African Americans were 1.8- and 3.0-fold higher, respectively [2]. In spite of the lower incidence rates of disease in Asian Americans, prostate cancer is the leading incident cancer site in Asian-American men. Notably, variation in the incidence rate of prostate cancer has been seen across specific Asian American populations, with four-fold variation in rates seen across groups [3]. For Asian Indian and Pakistani, Chinese, Filipino, and Japanese men in the US, prostate cancer was the most commonly diagnosed cancer from 1990 through 2008 [3]. From 1990 through 1993, Filipino men experienced a 19 % annual percent increase in prostate cancer rates and Japanese men demonstrated a similar sharp increase in incidence [3]. Asian Indian and Pakistani men in the US experienced a 2.2 % annual percent increase in prostate cancer incidence rates in the 1990s, followed by a sharp 3-year decline, and another significant increase from 2006 to 2008 [3]. Korean men also experienced an increase in incidence rates of prostate cancer at 2.9 % per year from 1990 through 2006, which subsequently decreased thereafter [3]. Prostate cancer rates were relatively stable in Chinese men during this period, while rates in Vietnamese and Laotians rose steadily. The trends in Filipino and Japanese largely followed the pattern seen in the US population; a rapid rise in the early 1990s that peaked in 1992 and a subsequent decline and stabilization after 1996 attributable to the introduction and adoption of PSA screening

in the population [4]. The patterns in South Asians were similar with a delayed peak the early 2000s. Yet, the stable rates in Chinese and increasing rates in Koreans, Vietnamese, and Laotians may be related to differences in the adoption of PSA screening and changing health behaviors associated with US acculturation.

Mortality

The mortality rates of prostate cancer in Asian Americans/Pacific Islanders at 9.1 deaths per 100,000 in 2009–2013 were the lowest in comparison to the other major racial/ethnic groups in the US—Hispanics (17.1), non-Hispanic Whites (19.2), American Indians (15.0), and African Americans (44.2) [2]. Recent data from 2002 to 2011 displayed a stable mortality rate of prostate cancer among Asian Americans/Pacific Islanders [5]. The racial/ethnic differences in cancer survival have been primarily attributed to underlying biological factors [6] and the receipt of quality cancer care [7]. In a national study comparing cancer-specific survival between Whites and Asian Americans, no differences in the prevalence of definitive treatment were seen for stage 1 prostate cancer, but significant differences were seen with stage 2 disease (range, 75.3 % among Filipinos to 81.9 % among South Asians) and stage 3 disease (range, 91.4 % among Filipinos and 99.2 % among South Asians) [8]. In a competing risk analysis among these men, accounting for known factors to affect survival outcomes, Japanese (relative risk (RR) = 0.54; 95 % CI = 0.38–0.78) and Filipinos (RR = 0.63; 95 % CI = 0.48–0.84) displayed significantly lower risk of prostate-cancer-specific mortality in comparison to Whites, while other groups such as Chinese, Korean, and Vietnamese had nonsignificant lower risks of mortality [8].

Prostate Cancer Heterogeneity

Prostate cancer has an extremely heterogeneous clinical behavior. Some tumors will remain indolent with little impact on morbidity and survival, while others are aggressive and progress rapidly in a potentially lethal manner. The adoption of PSA screening has led to a vast increase in the number of presumably indolent tumors that remain difficult to distinguish from aggressive disease. Asian-American men were reported to present with a greater proportion of advanced-stage [9–12] and high-grade disease [10, 12] than White men, which has significant implications for treatment and prognosis. In a large, multiethnic, population-based study that categorized prostate cancer patients into low-, intermediate-, and high-risk profiles based on clinical stage, Gleason score, and PSA levels at diagnosis, six Asian-American groups—US-born Chinese, foreign-born Chinese, US-born Japanese, foreign-born Japanese, foreign-born Filipino, and foreign-born Vietnamese—were found to have a more unfavorable clinical risk profile compared to non-Hispanic White men [13]. The odds ratios for high versus intermediate risk of disease ranged from 1.23 for

US-born Japanese men to 1.45 for Filipino men, and these associations appeared to be driven by higher grade and higher PSA values [13]. In a study of Asian-American prostate cancer patients, who were treated in an equal access health-care system, Asian Americans presented with a lower clinical stage but worse biopsy grade than other groups [11]. In addition, Asian Americans treated with radical prostatectomy or radiation therapy were more likely to have less prostate cancer progression and improved survival than other groups [11]. The observation that Asian-American men have a better prognosis in spite of their presentation with poorer prognostic features suggests that race/ethnicity may have an independent effect on prostate cancer progression.

Prostate Cancer Screening

Screening for prostate cancer by PSA testing was introduced in the US in the early 1990s and became widespread by the mid- to late-1990s [14], resulting in large increases in prostate cancer incidence rates across all racial/ethnic groups [2, 3]. Due to concerns for over-detection and -treatment of indolent disease and the results of clinical trials, documenting no or little reduction in mortality associated with PSA screening [15], the US Preventive Services Task Force (USPSTF) reversed the 2008 PSA screening guidelines. In 2008 the USPSTF recommended against screening for men aged 75 and older [14] and in 2012 recommended against PSA screening for all men regardless of age [16].

Data on PSA screening (never received a test, received a test 1 year or less, received a test more than 1 year ago) by Asian-American ethnicity are available from the 2009 California Health Interview Survey (CHIS), a population-based survey of California populations [17]. Strengths of CHIS data include over-sampled racial/ethnic minority groups and availability of the telephone survey in English, Spanish, Chinese (Mandarin and Cantonese), Korean, and Vietnamese. The proportion of Asian-American men in California aged 40–79 who have never received a PSA screening test ranged from 52.5 % among Japanese to 86.8 % among Vietnamese (Fig. 1), in comparison to 47.6 % among non-Hispanic Whites, 71.2 % among Latinos, and 63.6 % among African Americans. The proportion who received a test within the past year ranged from 8.5 % among Vietnamese to 27.8 % among Japanese and 27.5 % among South Asians. The generally higher rates of nonadherence to cancer screening guidelines among most Asian-American ethnic groups compared to non-Hispanic Whites has been attributed to cultural factors and stigmas related to disease prevention [18–22], but may also be due to provider factors [23, 24]. Prior research of factors associated with decreased prostate cancer screening (by PSA and other modalities) among Asian-American men suggests lack of awareness, not having regular health-care access, no recommendations from providers, being unmarried, being of lower SES, financial issues, time constraints, fear of a cancer diagnosis, and embarrassment [25–29].

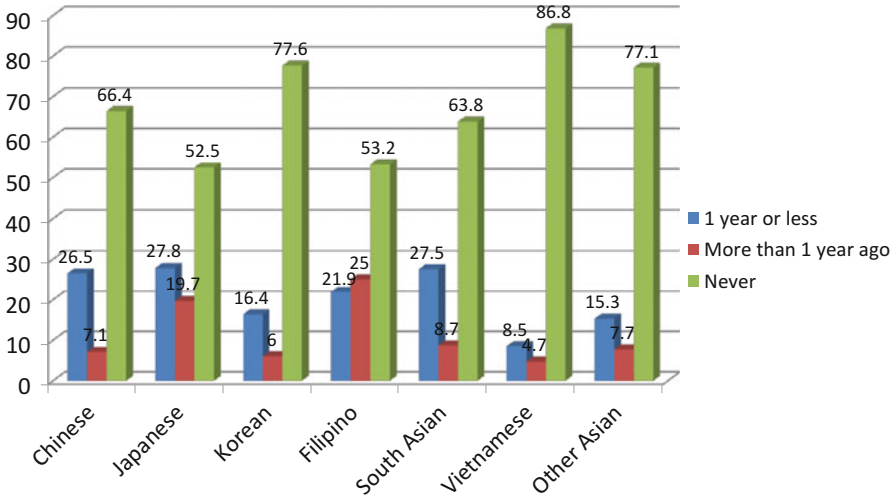

Fig. 1 Prostate-specific antigen screening for prostate cancer among men aged 40–79, California Health Interview Survey, 2009

Migrant Studies

Epidemiologic studies of risk of disease among persons or populations who migrate from one country to another lower- or higher-risk country can inform the relative contributions of environmental versus genetic risk factors and aid in the identification of putative risk factors [30–32]. International descriptive studies of prostate cancer incidence have shown considerably higher incidence rates among Asian-American men in the US relative to Asian men living in Asian countries [33]. In data from the International Association for Cancer Registries (IACR), prostate cancer incidence during the period 1998–2002 was about three times higher among Asian Americans than Asians living in Asia (Fig. 2) [34].

However, international differences in PSA screening has been cited as being a major driver of the incidence differences between Asians in the US and Asia [33], thus limiting interpretation of the incidence differentials, and the degree to which changes in prostate cancer incidence is due to changes in lifestyle and other exposures upon migration from Asia to the US. Moreover, to the extent that prostate cancer primarily impacts older men (e.g., 56.7 % of cases in the US are diagnosed among men aged 65 and older [2]) and incidence increases with increasing age, differences in life expectancy and competing causes of death across countries may also confound the interpretation of international descriptive statistics. Ito et al. compared the mortality/incidence rate ratio by Asian country and found considerably higher ratios among Asians in Asia than their counterparts in the US; for example, the mortality rate to incidence rate ratio was 0.42, 0.52, and 0.22 in China, the Philippines, and Japan, respectively, compared to 0.11, 0.14, and 0.15 among

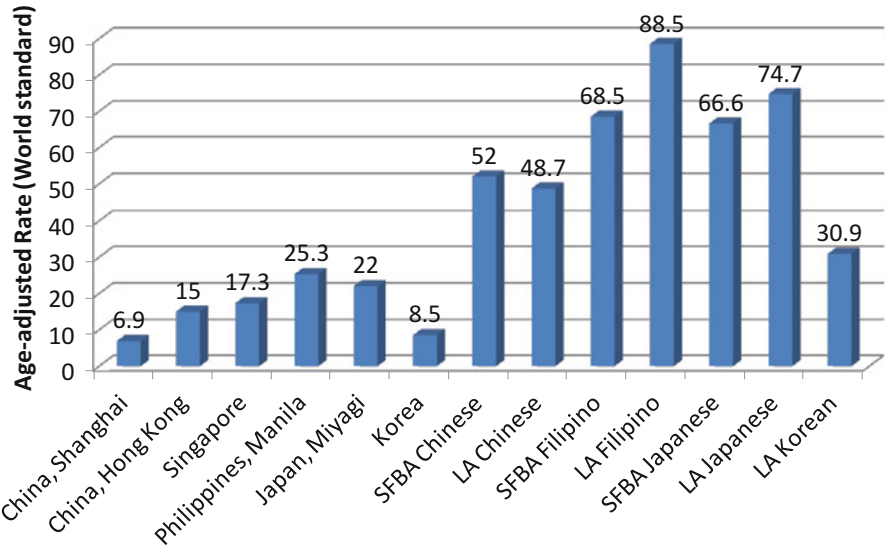

Fig. 2 Age-standardized incidence rates (1998–2002) by country and US Asian American ethnic group (data from Cancer Incidence in Five Continents, Vol. IX). Abbreviations: SFBA, San Francisco Bay Area, California; LA, Los Angeles County, California

California Chinese, Filipinos, and Japanese, respectively [33]. The lower ratios in the US Asian populations indicate a higher proportion of screen-detected cancers associated with lower mortality [33]. Indeed, the proportions of patients with metastatic disease are considerably higher in Asia, ranging from 26 % in a hospital-based cancer registry in Japan in 1998–2002 to 76.6 % in China in 2005–2007, compared to 3.1 % among Asian Americans in a hospital registry in Washington, DC, in 1989–2007 [33].

Risk Factors

Age, race/ethnicity, family history, and genetic susceptibility represent well-established risk factors for prostate cancer. Studies have investigated putative risk factors, including hormonal and infection/inflammatory factors, body mass index (BMI), diabetes, physical activity, smoking, and dietary intake. However, no definitive risk factor has emerged, particularly for incident prostate cancer. The lack of consistent associations with prostate cancer incidence likely reflects the heterogeneity in prostate cancer, specifically indolent screened cancers that likely have a different etiology than advanced cancers. Furthermore, the correlation between lifestyle factors with screening behavior may also confound these associations. In contrast, mortality and survival studies avoid screening-related biases

and may highlight risk factors associated with aggressive and lethal disease phenotypes. The underlying etiology of prostate carcinogenesis likely involves the interaction of genetics and lifestyle factors, with differential effects by stage and disease characteristics.

Studies have examined migration-related risk factors among Asian-American populations, capitalizing on the unique heterogeneity in risk factor prevalence and disease risk with length of residency in the US. In particular, many studies have focused on the role of dietary factors that may differ by nativity and acculturation. Prominent cohorts have examined risk factors for prostate cancer in Asian Americans: (1) a cohort study among men of Japanese ancestry in Hawaii that were interviewed and examined as part of the Honolulu Heart Program from 1965 to 1968 [35] and (2) the Multiethnic Cohort (MEC), a population-based prospective study of African Americans, Native Hawaiians, Japanese Americans, Latinos, and Whites in Hawaii and Los Angeles that enrolled participants from 1993 to 1996 [36]. Another important study, a multicenter population-based case–control study in the US (Hawaii, Los Angeles, San Francisco) and Canada (Vancouver) used registry data to identify cases diagnosed between 1989 and 1991 of Black, White, Chinese American, or Japanese American race/ethnicities (with at least three grandparents all of same ethnicity) [37].

Age

Advancing age is an established risk factor for prostate cancer. Although prostate cancer incidence is extremely rare before the age of 40, the incidence rate increases exponentially up to the age 80 with advancing age [38, 39]. This rapid age-dependent rise in incidence is greater than any other cancer in Western countries; yet, this pattern is less evident in China and Japan [39, 40].

Race/Ethnicity

Race/ethnicity is an established risk factor for both prostate cancer incidence and mortality [2]. Asian Americans have lower incidence and mortality rates compared to other US racial/ethnic groups—African Americans, Hispanics, and Whites [33]. The key etiologic factors influencing racial/ethnic differences in prostate cancer epidemiology are complex. Genetic susceptibility may play an important role [41–43]; yet, the influence of other factors, such as racial/ethnic-specific differences in lifestyle, obesity, and diet, remains largely unknown. Further studies are needed to elucidate the underlying factors driving the lower risk among Asian Americans and thereby clarify the role of protective factors and potential interactions with genetic and environmental factors.

Family History

Family history is among the strongest epidemiologic risk factors for prostate cancer. Having one, two, or three affected first-degree relative(s) with prostate cancer has been found to increase the risk of prostate by 2.2-, 4.9-, and 10.9-fold, respectively [44]. While the prevalence of a father, brother, or son with prostate cancer has been reported to be lower in Asian Americans (4 %) in comparison to Whites (7 %) and Blacks (5 %), Asian Americans displayed a similar two- to threefold increased risk of prostate cancer associated with such a family history as other groups [45]. It has been estimated by a large study of twins that 42 % of the risk of prostate cancer is explained by inherited factors [46].

Genetic Susceptibility

Genome-wide association studies (GWAS) have successfully identified over 100 risk loci for prostate cancer to date. However, the majority of these studies have been conducted among men of European ancestry, with two studies conducted among Chinese [47] and Japanese [48] men in Asia and only one US study conducted among Japanese-American men in the MEC [49]. In a prostate cancer GWAS of 1033 Japanese-American prostate cancer cases and 1042 Japanese-American controls, no novel risk loci were discovered, and the majority (79 %) of established risk variants for prostate cancer at that time ($n = 56$) were positively associated with prostate cancer [49]. The cumulative effect of these variants were associated with a per allele odds ratio (OR) = 1.10; $P = 2.7 \times 10^{-25}$ [49]. In a study that examined 69 established prostate cancer risk variants, 64 variants were observed (frequency ≥ 0.01) in Japanese subjects (cases/controls = 2563/4391) with 84 % (54/64) positively associated with risk and 41 % (26/64) nominally statistically significant ($P < 0.05$) [43]. In addition, fine-mapping findings suggest that the 10q26 locus may be a Japanese-specific risk region as risk variants in this region are common across populations, yet strong associations with prostate cancer risk were only seen in Japanese and not in other racial/ethnic groups [43]. A separate study that included 288 Asian-American prostate cancer cases and 2938 controls examined 99 prostate cancer risk variants and found that 68 % (67/99) were in the same direction as previously reported [41]. Comparing the highest to lowest deciles of a risk score of these variants resulted in an OR = 3.38 (95 % CI, 1.91–5.97) for Asian Americans [41]. These findings indicate that the established risk variants for prostate cancer significantly contribute to risk in Asian Americans.

Androgens and Insulin-Like Growth Factors

The physiological development of the prostate is primarily regulated by testosterone and its most active metabolite, dihydrotestosterone (DHT), and androgens have long been hypothesized to play an etiologic role in prostate cancer [50, 51]. However,

epidemiologic data on the relationship between endogenous androgens and prostate cancer have been inconclusive [52]. In a pooled analysis of 18 prospective studies consisting of 3886 men with incident prostate cancer and 6438 control subjects, no associations were found between risk of prostate cancer and pre-diagnostic serum androgens (total and free testosterone, DHT, and others) and estrogens (total and free estradiol), with no evidence of heterogeneity by length of time between blood collection and cancer diagnosis [52]. There was, however, a modest, inverse association between sex hormone-binding globulin (SHBG) and prostate cancer risk [52]. The lack of support of an androgen-prostate cancer risk link may reflect that these findings were based on androgen levels determined late in adult life. It may be that androgen levels in early adulthood may represent a more etiologically relevant period for the pathogenesis of prostate cancer. Population differences in testosterone levels of young men have been significantly associated with regional population disparities in the incidence of prostate cancer in older men [53]. There is limited evidence supporting racial/ethnic differences in testosterone or metabolites of testosterone in older men that correspond with respective population incidence rates [54, 55]. Similar levels of testosterone and 3α-androstanediol glucuronide have been found among middle-late-aged Singapore Chinese and Japanese American populations, whereas higher levels of testosterone or its metabolites have been found in middle-late-aged US Whites than Singapore Chinese [54], Japanese American [54, 55], Chinese American [55], and African American [55] men. Other growth factors, such as insulin-like growth factors (IGF) and their related binding proteins (IGFBP), may have an independent role in carcinogenesis as well as interact with the androgen signaling pathways [56].

The few studies conducted in Asian-American men observed null associations between androgens, SHBG, IGFs, and prostate cancer risk [57, 58]. In a case–control study (467 cases and 934 controls) nested in the MEC, pre-diagnostic serum levels of testosterone, DHT, SHBG, 3α-androstanediol glucuronide, IGF-I, IGF-II, IGFBP-1, and IGFBP-3 were not associated with risk of prostate cancer in all groups and in Japanese Americans [58]. In a prospective study (control arm of the multicenter case–control study in the US and Canada), null associations were observed for pre-diagnostic levels of IGF-I and IGFBP-3 with risk of developing prostate cancer in Asian Americans, yet the study was limited by the small number ($n = 33$) of prostate cancer cases [57].

Infection/Inflammation

Inflammation has an etiological role in the pathogenesis of cancers [59], and prostatitis and sexually transmitted infections (STIs) may represent important risk factors for prostate cancer by inducing inflammation processes and chronic inflammation within the prostate [60]. Prostatitis is a common condition in men with an estimated prevalence ranging from 5 to 9% [61] and includes acute and chronic bacterial infection of the prostate [62]. A meta-analysis of 20 case–control studies, primarily

in Western countries, supports positive associations between prostatitis and prostate cancer with a stronger association in Chinese (meta-analysis OR=4.67; 95 % CI = 3.08–7.07 based on two studies in China) than US (meta-analysis OR=1.50; 95 % CI = 1.25–1.80) populations [63]. Additional meta-analyses, again relying primarily on case–control studies and studies conducted in Western countries, support modest associations of gonorrhea [64, 65] and any STI [65] with prostate cancer risk. The relationship between prostatitis, STIs, and prostate cancer risk was examined in the California Men's Health Study, representing an important study given the prospective study design of a large racial/ethnically diverse cohort of African American, Asian American, Latino, and White men from Northern and Southern California Kaiser Permanente [66]. After a median follow-up of 2 years (maximum 4 years), men reporting a history compared to those with no history of prostatitis had a significant 1.3-fold increased risk (95 % CI = 1.10–1.54; 1658 cases) in the entire cohort and a nonsignificant positive association (RR = 1.95; 95 % CI = 0.89–4.24, 89 cases) in Asian Americans. Asian Americans experienced a significant positive association with history of syphilis (RR = 3.72; 95 % CI = 1.35–10.26) and chlamydia (RR = 5.55; 95 % CI = 1.70–18.09). Larger effects were observed among foreign-born versus US-born Asian Americans. For instance, among foreign-born Asian Americans, there was a significant 2.7-fold increased risk (95 % CI, 1.02–6.95; 38 cases) of prostate cancer associated with a history of prostatitis. Further cohort studies are needed to clarify the role of chronic inflammation and infectious agents in relation to prostate cancer susceptibility, especially among foreign-born Asian Americans.

Body Size and Obesity

Studies of the association between obesity and prostate incidence have been inconsistent [67, 68]. Studies of body size and obesity have examined BMI (kg/m^2) at various ages (pre-, early, middle, or late adulthood) [37, 69, 70], weight and weight change since early adulthood [71], waist circumference or waist-to-hip ratio as a measure of abdominal adiposity [37, 69], and various upper arm or skinfold thickness measurements [69, 70, 72]. A dose–response meta-analysis of 13 prospective studies (only one study from Japan) observed dual effects of obesity on risk of prostate cancer: a significant 6 % (RR=0.94; 95 % CI, 0.91–0.97) decreased risk for localized cancers but 9 % (RR=1.09; 95 % CI, 1.02–1.16) increased risk for advanced cancers per 5 kg/m^2 increase in BMI [68]. However, the prospective study in Japan showed nonsignificant increased risk with higher BMI at middle adulthood for both localized and advanced cancers [73]. A population-based case–control study in Shanghai, China, found a positive association with waist-to-hip ratio for both localized and advanced prostate cancers (quartile 4 versus 1, OR = 4.20; 95 % CI = 1.88–9.36 and OR = 2.09; 95 % CI = 1.18–3.70, respectively) yet no associations with adult BMI or BMI at various ages [69]. Detection bias may influence the ability to detect early-stage prostate cancers in obese men due to lower PSA values as

observed in healthy US [74, 75] and Chinese men [76]. According to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) 2014 report, there is strong evidence that being overweight or obese increases the risk of advanced (i.e., high-stage or grade) prostate cancers [67]. Obesity is also associated with 20 % (95 % CI 0.99–1.46) higher risk of prostate cancer-specific mortality per 5 kg/m^2 increase BMI [77]. Obesity-related biological, clinical, and lifestyle factors have been hypothesized as potential underlying mechanisms for the aggressive and lethal prostate cancer phenotype in obese men [78].

In Asian-American men, one case–control study [37] and three prospective cohorts [70–72, 79] examined obesity and prostate cancer risk with mixed results. In a multicenter population-based case–control study in the US and Canada, no consistent or convincing associations between BMI (at reference year or prior decades of life) and prostate cancer were observed in Chinese Americans (283 cases, 272 controls) or Japanese Americans (326 case, 329 controls) [37]. In contrast, a cohort study of Japanese-American men in Hawaii observed positive associations between obesity and prostate cancer risk with 20 years of follow-up ($n = 174$ cases identified 1965 through 1986) [72] and confirmed in a subsequent study ($n = 306$ cases identified 1965 through 1992) [79]. High BMI at baseline was associated with increased prostate cancer risk (BMI ≥ 26 versus <22 kg/m^2, RR = 1.21; 95 % CI = 0.87–1.68, p trend < 0.01) [79]. In a large, multiracial cohort of male subscribers to the Kaiser Permanente Medical Care Program, there was no evidence of an association between BMI at comprehensive medical examination (ages ranged from 18 to 84 years with 50 % of the men in their 30s or 40s) and prostate cancer risk among Asian Americans ($n = 53$ cases) or the other racial/ethnic groups ($n = 2026$ cases) after an average follow-up of 19.5 years [70]. The associations did not vary consistently by BMI at various ages or stage of prostate cancer at diagnosis [70]. In the MEC, an inverse association of borderline significance was observed between BMI at baseline and prostate cancer risk ($n = 1382$ cases in Japanese American men) after an average follow-up of 9.6 years (obese versus normal BMI, RR = 0.78; 95 % CI = 0.57–1.08; p trend 0.07) [71], but after an average 13.9 years of follow-up, no significant associations with baseline BMI were observed overall and across racial/ethnic groups [80]. It is uncertain whether length of follow-up affects the magnitude of association; however, the results from prospective studies appear mixed regardless of length of follow-up time [81]. Age (especially at early ages), duration of obesity, or significant weight gain may be etiologically relevant for prostate cancer development [82], and further studies are needed to clarify the association between obesity and prostate cancer in Asian Americans.

Diabetes

Diabetes is associated with increased risk for several cancers [83], yet evidence, primarily in White populations, suggests a significant decreased risk for prostate cancer [84]. A recent meta-analysis of 29 cohort and 16 case–control studies

revealed an opposite pattern in Western versus Asian countries, with an inverse association between diabetes and prostate cancer risk in Western populations (meta-analysis RR = 0.81; 95 % CI = 0.76–0.85 for 37 studies in Western populations) and a positive association in Asian populations (meta-analysis RR = 1.64; 95 % CI = 1.0–2.28 for eight studies in Asian counties) [84]. The underlying mechanisms for the potential heterogeneity in the relationship between diabetes and prostate cancer risk in Western versus Asian populations are unknown.

In the MEC after a mean follow-up of 13.9 years, history of diabetes was significantly negatively associated with prostate cancer risk in multivariable models adjusted for BMI and smoking in all racial/ethnic groups combined (RR yes versus no diabetes = 0.78; 95 % CI = 0.72–0.85) and in Japanese Americans (RR yes versus no diabetes = 0.85; 95 CI = 0.72–0.85) [80] that confirmed earlier results from the MEC [85]. History of diabetes was related to a decrease risk of both localized and advanced tumors, and the inverse association persisted after adjustment for PSA screening history [80]. Proposed underlying mechanism of the lower prostate cancer risk associated with diabetes may involve low testosterone levels driven by insulin-related pathways. Although potential heterogeneity may exist early in the disease processes, hyperinsulinemia may drive a positive relationship; in contrast, with the progression of diabetes, hypoinsulinemia may result in an inverse relationship with prostate cancer [86].

Physical Activity

The WCRF/AICR 2014 report concluded that there was no convincing evidence to support the relationship between physical activity and prostate cancer risk [67]. Physical activity was not associated with prostate cancer risk in a cohort study of Japanese men in Hawaii [35] or in the MEC [80]. In the population-based case–control study, physical activity was not related to prostate cancer risk either in Asian American, White, or African American men [37].

Smoking

Cigarette smoke is a preventable risk factor for several cancers and contains known human carcinogens [87], yet the role of smoking in prostate cancer etiology appears inconsistent and may be relevant for prostate cancer mortality and more aggressive cancers. A recent systematic review and meta-analysis of prospective cohort studies showed a possible association between smoking and increased risk of prostate cancer in studies with case identification up to 1995 or earlier, representing the pre-PSA screening era (meta-analysis RR ever versus never smoking = 1.06, 95 % CI = 1.00–1.25, p heterogeneity = 0.23), although studies completed afterwards or

in the post-PSA screening era showed a null or inverse association (meta-analysis RR ever versus never smoking = 0.90, 95 % CI = 0.86–0.93, p heterogeneity < 0.001) [88]. Inverse [89, 90] or equivocal [91] associations were observed for studies in Japan, Korea, and Singapore. A recent large study in Europe (4623 cases) found current smoking was significantly negatively associated with risk of localized and low-grade prostate cancer, but nonsignificantly positively associated with advanced and high-grade prostate cancers [92]. The inverse smoking-prostate cancer association may reflect differences in screening behavior and health-care service availability among smokers versus nonsmokers [93]. More consistent associations have been documented between smoking and prostate cancer deaths in a meta-analysis of 21 studies conducted primarily in Western populations, with a modest increased (meta-analysis RR = 1.18; 95 % CI = 1.11–1.24) risk of mortality for ever versus never smokers and evidence of a dose–response with number of cigarettes smoked per day [88].

In a cohort study of Japanese-American men in Hawaii, although initially smoking was associated with a nonsignificant reduced risk of prostate cancer with 20 years of follow-up (n = 174 cases identified 1965 through 1986) [35], a subsequent study (249 cases identified 1971 through 1995) found a nonsignificant positive association between smoking and prostate cancer risk (OR current smokers versus nonsmokers = 1.3, 95 % CI = 0.8–2.0) [94]. In a recent study in the MEC, with an average follow-up of 13.9 years (through 2010), smoking (≥20 cigarettes per day) was inversely associated with prostate cancer risk in all racial/ethnic groups combined (RR current versus never smoker = 0.72; 95 % CI = 0.63–0.83; 7115 cases) and in Japanese Americans (RR current versus never smoker = 0.72; 95 % CI = 0.55–0.93; 2056 cases) that persisted after adjustment for PSA screening history [80]. These inverse associations were only observed for localized and not for advanced tumors [80]. Smoking is likely a weak risk factor for incident prostate cancer and subject to biases associated with PSA screening that make it difficult to unravel the complex relationships and heterogeneity by stage and disease characteristics.

Dietary Factors

Some dietary components have been implicated to increase prostate cancer risk (e.g., processed and red meats, milk and dairy products), whereas others are hypothesized to be protective (e.g., lycopene, selenium, legumes, alpha-tocopherol). However, according to the WCRF/AICR 2014 report that represents the most rigorous, systematic, global analysis of scientific research currently available on prostate cancer, there was no strong evidence to support the role of diet in prostate cancer risk including lycopene, vitamin D, and beta-carotene (either through food or supplements) [67]. Only a limited number of studies have examined the diet–prostate cancer relationship in Asian American populations as discussed further.

Fat

A traditional Asian diet is more plant-based and likely contains less fat, particularly animal fat, compared to the Western diet. Thus, dietary fat intake has been speculated to contribute to the lower risk of prostate cancer in Asian men compared to White men given its potential carcinogenic role [95]. The limited data of dietary fat intake and prostate cancer risk in Asian Americans have been inconclusive. In an ecological study of diet and cancer conducted in Hawaii during the 1970s, the ethnic-sex-specific fat intake of a representative sample of 4657 adults aged ≥45 years and corresponding population-based cancer incidence rates were compared across the five major ethnic groups [96, 97]. In general, fat intake was highest in Whites, followed by Hawaiians, lower in Japanese and Chinese, and lowest in Filipinos. Although total fat intakes in the five ethnic groups were not correlated with the corresponding incidence rates of prostate cancer [97], animal ($r=0.90$) and saturated ($r=0.87$) fat intakes were significantly positively correlated with prostate cancer incidence rates [96, 97]. In a subsequent population-based case–control study in the US and Canada, dietary fat, especially saturated fat, were associated with a higher risk of prostate cancer in Chinese Americans (quintile 5 versus 1, OR = 1.5; 95 % CI = 0.37–5.8; p trend < 0.01) and Japanese Americans (OR = 4.1; 95 % CI = 1.4–11.8; p trend < 0.01), while there was no association in African Americans and Whites [37]. In a cohort in Japan, intakes of some specific saturated fatty acids were related to an increased risk of prostate cancer; quartile 4 versus 1, RR = 1.62; 95 % CI = 1.15–2.29; p trend < 0.01 for myristic acid and RR = 1.53; 95 % CI = 1.07–2.20; p trend = 0.04 for palmitic acid [98]. However, a cohort study of Japanese-American men in Hawaii found no relationship between fat intake including saturated and unsaturated fat and prostate cancer risk [35]. In the MEC, no association was found with various types of dietary fat in Japanese men [99] or other racial/ethnic groups. However, circulating palmitic acid was associated with a higher risk of prostate cancer in Japanese men (tertile 3 versus 1, OR = 3.21; 95 % CI = 1.21–8.53; p trend < 0.01) in a case–control study nested within the MEC [100]. The increased risk of prostate cancer with higher levels of palmitic acid in blood was also found in other prospective studies of men with European ancestry (Norway [101], European Prospective Investigation into Cancer and Nutrition (EPIC) study [102], Australia [103]).

Processed and Red Meat

Red meat intake has been examined in relation to cancer as it is a major source of cancer-promoting components including saturated fat, zinc, and heme iron. Also, heterocyclic amines, potent carcinogens, are formed when red meat is cooked and processed at high temperature. In a cohort study of Japanese American men in Hawaii, meat and processed meat intake were not related to prostate cancer risk [35]. In the MEC, no associations were found between various meat, including red meat, intakes and prostate cancer risk in Japanese men or in other ethnic groups

[99]. In a nested case–control study conducted within the MEC, well-done red meat consumption and *N*-acetyltransferase (*NAT*)*1* or *NAT2* genotypes, as modifiers of the carcinogenic effect of heterocyclic amines, were not related to prostate cancer risk [104].

Fruits/Vegetables

Fruits and vegetables contain various bioactive components with anticancer properties. In a case–control study of Chinese and Japanese men in the US and Canada, intake of carrots was related to a lower risk of prostate cancer in both Japanese (tertile 3 versus 1, OR = 0.58; 95 % CI = 0.38–0.87; *p* trend = 0.01) and Chinese men (OR = 0.49; 95 % CI = 0.30–0.81; *p* trend = 0.01) [105]. A decreased risk of prostate cancer was observed with a higher intake of yellow-orange vegetables in Japanese men (OR = 0.61; 95 % CI = 0.40–0.93; *p* trend = 0.02) and with a higher intake of cruciferous vegetables in Chinese men (OR = 0.68; 95 % CI = 0.37–1.24; *p* trend = 0.03) [105]. In contrast, in a cohort study of Japanese-American men in Hawaii, fruit intake was not associated with prostate cancer risk [35]. In the MEC, no associations were observed with intake of fruits and vegetables in Japanese Americans or in other racial/ethnic groups [106].

Soy

High intake of soy products or isoflavones has been hypothesized to contribute to the significantly lower incidence rate of prostate cancer among Asian compared to European/North American men [107]. The anticancer properties of isoflavones have been explored in animal and in vitro studies and support a potential beneficial role in the prevention of prostate cancer [108]. Meta-analyses of 15 studies suggested that soy food consumption is associated with a reduction in prostate cancer incidence and mortality, with a combined adjusted RR/OR of 0.74 (95 % CI = 0.63–0.89) [109, 110]. Yet, the findings of individual studies were mixed, and the protection against prostate cancer may be dependent on the type and quantity of soy products consumed [110].

One case–control study and two cohort studies have examined soy intake in relation to prostate cancer risk in Asian Americans. In a case–control study in the US and Canada, soy food intake was not associated with prostate cancer risk in Japanese and Chinese men [105]. In a cohort study in Hawaii of Japanese-American men, there was an initial suggestive association between higher tofu consumption and decreased risk of prostate cancer with 20 years of follow-up ($n = 174$ cases identified 1965 through 1986; 139,727 person-years) [35], but a subsequent study found tofu intake was not associated with prostate cancer risk ($n = 304$ cases identified 1972 through 1995; 113,159 person-years) [111]. Furthermore, more recently in 25,052 Japanese-American men in the MEC, no association was found with intake of soy product, based on food frequency questionnaire, and prostate cancer risk

($n = 1062$ cases) after an average follow-up of 8 years [112]. Similarly, in a case–control study nested in the MEC, no association was seen between isoflavone intake, based on urinary biomarkers, and prostate cancer risk in Japanese men ($n = 70$ cases, $n = 122$ controls matched on age, race/ethnicity, date/time specimen collection) [113].

Green Tea

It has been hypothesized that the lower incidence of prostate cancer in Asian men may be due to the consumption of green tea [114]. Green tea contains high concentrations of polyphenols with potential anticancer properties [115]. Although green tea appears to be effective in prostate cancer prevention in a recent review, most studies have been conducted in Asian countries [114]. Contrary to the hypothesis, green tea consumption (ever versus never) was associated with a nonsignificant increased risk of prostate cancer (HR = 1.47; 95 % CI = 0.99, 2.19; $n = 174$ cases) in a cohort study of Japanese-American men in Hawaii followed for 20 years [35].

Micronutrients

An ecological study found no correlation between the ethnic-sex-specific intakes of vitamins A and C and corresponding prostate cancer incidence rates in the five major ethnic groups in Hawaii [96]. In the MEC, no association was observed with intakes of vitamins A, C, and E, carotenoids [106], vitamin D, and calcium [116] from foods and supplements in Japanese Americans. In addition to dietary intakes estimated by questionnaires, blood levels of micronutrients were examined in relation to prostate cancer risk. In a cohort of Japanese-American men in Hawaii, serum selenium was associated with a lower risk of prostate cancer [94], while no association was found for serum levels of vitamin D metabolites [117] and micronutrients including carotenoids, retinoids, and tocopherols [118]. In a nested case–control study within the MEC, serum zinc was positively associated with prostate cancer risk in Japanese Americans [119], while serum selenium, tocopherols, and carotenoids [120] and plasma 25-hydroxyvitamin D [121] were not associated with prostate cancer risk in Japanese-American men.

Others

According to the WCRF/AICR 2014 report, there is limited–suggestive evidence of an increased risk of prostate cancer associated with the intake of dairy products and no conclusion have been reached for alcohol drinks [67]. A dose–response meta-analysis of 32 studies showed a statistically significant 7 % increase per 400 grams of dairy products per day (meta-analysis RR = 1.07; 95 % CI = 1.02–1.12) [122]. Alcohol and milk consumptions were examined in a cohort study of

Japanese-American men in Hawaii and were not related to prostate cancer risk [35, 123]. In the MEC, milk and dairy product intakes were not associated with prostate cancer risk among Japanese-American men [116]. Serum uric acid, a potent antioxidant, was associated with a higher risk of prostate cancer in a cohort of Japanese-American men in Hawaii (quartile 4 versus 1, RR = 1.5; 95 % CI = 1.1–2.1; *p* trend = 0.04) [124].

Conclusion

Asian Americans are more likely to have advanced-stage, high-grade disease and overall a less favorable risk profile at diagnosis of prostate cancer than White men, with variation by Asian populations and nativity. This suggests that Asian-American men may be more susceptible to aggressive phenotypes, despite their low mortality rate of prostate cancer. Furthermore, variation in the incidence rates of prostate cancer has been seen across specific Asian-American populations. Yet, data on prostate cancer risk factors across Asian-American populations is limited as studies have focused primarily on Japanese and Chinese Americans. Additional studies are needed in other Asian-American populations as each Asian population has its own distinct culture, lifestyles, health behaviors, and prostate cancer risk profiles. Overall, studies in Asian-American men have found no consistent or convincing associations with BMI, dietary factors, including soy and green tea, or hormonal factors. Inverse associations of diabetes and smoking with prostate cancer have been observed that are consistent with associations observed in other US racial/ethnic groups. Infections of the prostate have emerged as important risk factors with potential higher risk among foreign-born Asian Americans. Inherited factors, including established risk variants for prostate cancer, are important risk factors for Asian Americans, similar to other US racial/ethnic groups. Further research is needed to better understand the interplay of genetic and environmental factors that influence prostate cancer risk, particularly in specific Asian populations by nativity and disease characteristics.

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Breast Cancer Among Asian Americans

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Abstract Breast cancer is the most commonly diagnosed cancer in women. Studies of breast cancer incidence have shown consistently two to threefold higher incidence rates among Asian-American women living in the United States (USA) relative to Asian women living in Asia. For example, breast cancer incidence in Japanese Americans is now approaching rates in Non-Hispanic (NH) Whites after two or three generations living in the USA. Epidemiologic data from studies conducted in Asian Americans, NH Whites, and in Asia reviewed in this chapter show that differences between incidence rates in NH Whites and US-born Asians are explained, in part, by menstrual and reproductive factors, body size, and use of hormonal replacement therapy. Changing prevalence of risk factors likely have had a major role in explaining the rise in breast cancer incidence with migration while the magnitude of risk associations for most of the risk factors are comparable to those of NH Whites. We review etiological risk factors that may explain the continued differences in rates between Asian Americans, Asians, and NH White women.

Keywords Asian Americans • Menstrual and reproductive factors • Exogenous and endogenous hormones • Body size • Alcohol • Diet • Mammographic density • Genetics

Incidence Rates and Secular Trends

Breast cancer is the most common cancer in Asian Americans as it is in other racial/ethnic groups in the USA. In 2007–2011, breast cancer incidence among Asian Americans/Pacific Islanders (AAPI) was 86.0 per 100,000 women, about 33 % lower than the incidence in NH Whites (127.6) [1]. However, the incidence of breast

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Table 1 Breast cancer incidence in different Asian ethnic groups in the United States and in Asia compared to rates in Non-Hispanic Whites

	In the United States[a]			In Asia[b]	
	1990–1994	1998–2002	2004–2008	1990	2013
Asian Indian/Pakistani	56.1	76.2	88.3	40.8[c]	62.4[c]
Chinese	66.1	75.5	78.8	33.2[d]	55.0[d]
Filipino	85.8	99.2	103.7	42.4	87.5
Japanese	98.8	120.1	104.9	29.7	45.4
Kampuchean (Cambodian)	19.6	35.3	43.4	24.3	54.9
Korean	34.9	53.9	69.5	23.2	33.3
Laotian	22.5	34.4	41.3	22.4	48.2
Vietnamese	52.3	54.0	63.0	26.7	21.4
Non-Hispanic Whites	140.5	148.9	135.3		

[a]Data from Gomez et al. [2]
[b]Data from Global Burden of Disease Cancer Prevention (2015) [216]
[c]Based on average of rates in India (22.4 in 1990 and 31.4 in 2013) and Pakistan (59.1 in 1990 and 93.4 in 2013)
[d]Based on average of rates in China (21.6 in 1990 and 32.8 in 2013), Singapore (50.1 in 1990 and 61.3 in 2013) and Taiwan (27.5 in 1990 and 71.0 in 2013)

cancer varied more than twofold across different Asian ethnic groups. Data from 13 Surveillance, Epidemiology, and End Results (SEER) registries for 2004–2008 showed that breast cancer incidence was highest in Japanese (104.9) and Filipinas (103.7), intermediate among Asian Indians/Pakistani (88.3) and Chinese (78.8), lower in Koreans (69.5) and Vietnamese (63.0), and lowest in Laotians (41.3) and Kampucheans (Cambodians) (43.4) [2] (Table 1).

Steady increases in incidence were observed in nearly all Asian ethnic groups between 1990 through 2008 (Table 1). The annual percent increases ranged from 1.2 % in both Chinese and Vietnamese to 4.7 % in Koreans and there was no indication of a leveling in breast cancer incidence across these groups [2]. Japanese Americans displayed an incidence pattern that was most similar to that of NH Whites with rates increased steadily between the early 1990s and 2000s and appeared to be on a downward trend since the early 2000s [2].

Age at Diagnosis

Asian Americans present at a younger mean age at diagnosis of breast cancer than NH Whites [3, 4]. Data from the California Cancer Registry (CCR) (2000–2011) showed that the mean age at diagnosis was 56.4 years in Asian Americans and 62.4 years in NH Whites. Among Asian-American ethnic groups, mean age at diagnosis was youngest in Koreans (54.2), intermediate in Chinese (56.3) and Filipina (56.9), and oldest in Japanese (61.9) [3]. Age of breast cancer diagnosis also tended to be younger in Asia than in the West [5–7]. However, a recent study that included

invasive breast cancer data (1988–2009) from five cancer registries in Asia, and made longitudinal extrapolations adjusting for calendar-period changes and conditioned upon birth cohort suggested that the age distributions of breast cancer are becoming more similar between Asian and Western women than previously recognized [8].

Stage and Tumor Characteristics

Asian Americans had slightly later stage at diagnosis than NH Whites but this varied by Asian ethnic groups [3, 4, 9]. Results from SEER (2000–2006) showed that the respective prevalences of stage III and IV cancers were less common among Chinese (7.8 and 2.9 %) and Japanese (6.2 and 2.7 %) but these later stages were more common among Filipina (10 and 4.4 %) and Asian Indian/ Pakistani women (11.2 and 5.2 %) than NH Whites (8.9 and 4.2 %) [9]. Similar patterns in Asian-American subgroups were found in other SEER-based studies [4, 10]. Differences in the distribution of tumor stage by Asian ethnicity may be attributable to differences in the prevalence of breast cancer screening and access to medical care, but may also reflect differences in tumor biology and tumor aggressiveness.

Breast cancer is a heterogeneous cancer consisting of a number of subtypes that are now recognized to have distinct risk factors, molecular characteristics, response to treatment, and prognosis [11]. Hormone receptor (HR) (estrogen receptor (ER) and progesterone receptor (PR)) and human epidermal growth factor receptor 2 (HER2) are classified in SEER database as positive, negative, borderline, not tested, not recorded, or unknown [12, 13]. In a review of over 220,000 invasive breast cancers among women ages 40–79 years, Asian Americans as a group had a lower proportion of breast cancers classified as ER + PR+ (66.2 %) than NH Whites (68.4 %), and were more likely to have ER-PR- tumors (21.1 % in Asian Americans and 18.6 % in NH Whites; OR 1.2, 95 % CI 1.2–1.3). Except for Japanese Americans who had a lower proportion of ER-PR- tumors (14.4 %), a higher proportion of breast cancers in Korean (26.1 %), Vietnamese (25.6 %), Asian Indian/Pakistani (25.6 %), Filipina (22.8 %), and Chinese (20.4 %) were ER-PR- compared to NH Whites [9]. In a CCR-based study of breast cancers (2000–2006) that also considered HER2 status, the diagnosis of HER2+ breast cancer was more common in Asian Americans (28 %) than NH Whites (19 %), particularly among Koreans (36 %) and Filipina (31 %). The proportion of triple negative tumors was similar between Asian Americans (12 %) and NH Whites (12 %) [12]. A subsequent study using CCR data from 2000 to 2011 classified breast cancer into eight subtypes based on ER, PR, and HER2 status. This larger study confirmed that HER2+ tumors were more common in Asian Americans (25 %) than in NH Whites (18 %), showing an excess of both ER + PR+ HER2+ (11.6 % vs. 8.8 %) and ER-PR-HER2+ (9.4 % vs. 5.6 %) tumors; this was most apparent among Korean and Filipina-Americans [3].

There is also tremendous interest to classify breast cancer into intrinsic subtypes using ER, PR, HER2, and ki-67 status (or tumor grade) or by gene expression profiling. However, to date, these studies tended to include few Asian Americans and the results were presented for Asian Americans as a group [14] or the sample size was too sparse to conduct meaningful analysis by Asian ethnicity [15]. In one study that classified breast cancer subtypes into four intrinsic subtypes, compared to NH Whites ($n=14,268$), Asian Americans ($n=533$) showed similar distributions of luminal A-like (48.0 % vs. 47.4 %) and triple negatives (15.3 % vs. 15.9 %), but were less likely to have luminal B-like (25.8 % vs. 29.8 %) and more likely to have HER2-type tumors (10.9 % vs. 7.9 %) [14]. In a study of gene expression profiling (e.g., PAM50) to classify breast cancer subtypes ($n=1319$ women, 72.6 % NH Whites, 9.2 % Asian Americans), the proportion of luminal A tumors were the same in Asian Americans (55.2 %) and NH Whites (55.2 %) but basal-like tumors was less common in Asian Americans (5.0 %) than in NH Whites (8.2 %) [16, 17]. Further studies by specific Asian-American subgroups will be needed to characterize the distribution of breast cancer intrinsic subtypes and to investigate risk factors by breast cancer subtypes.

Survival

In a study of invasive breast cancer diagnosed between 1988 and 2008 from 17 registries in SEER, the 5-year overall survival rate was better in Asian Americans (85.5 %) than NH Whites (79.8 %). Asian Americans also had better breast cancer-specific survival rate than NH Whites after adjusting for ER, PR, tumor grade, disease stage, radiation therapy, year of diagnosis, and age at diagnosis (HR = 0.92, 95 % CI 0.89–0.95) [4]. The more favorable breast cancer-specific survival rates was clearest among Japanese (HR = 0.63), Korean (HR = 0.92) and Chinese (HR = 0.98) but this was not found in Filipina (HR = 1.06), Asian Indians/Pakistani (HR = 1.14), and Vietnamese Americans (HR = 1.14) [4, 9]. Receipt of definitive treatment by stage [18] and guideline concordant treatment for specific breast cancer subtypes [10] was high in Asian-American patients and was comparable to that reported in NH Whites. Reasons for the more favorable outcome in Japanese Americans are not known. The California Breast Cancer Survivorship Consortium (CBCSC) harmonized and pooled lifestyle information on 12,210 patients, including 1505 Asian Americans, to explore reasons for these outcome differences. Results from the CBCSC showed that breast cancer-specific mortality was significantly better in Asian Americans than NH Whites (HR = 0.60, 95 % CI 0.37–0.97) after adjustment for tumor and lifestyle characteristics (e.g., smoking, alcohol) [19]. Although high waist–hip ratio [20] and a history of comorbidities including previous cancer, diabetes, and myocardial infarction [21] were associated with increased breast cancer-specific mortality in Asian Americans, high body mass index (BMI), physical inactivity, and neighborhood characteristics were not associated with outcome and did not explain the lower breast cancer-specific mortality in Asian

Americans [20, 22–24]. A limitation of this analysis was that the sample size of Asian Americans was modest and did not allow analysis separately by specific Asian ethnic subgroups. Thus, further investigation is needed to better understand the more favorable outcome in some Asian-American breast cancer patients.

Breast Cancer Risk Factors

Despite the numerous epidemiologic studies of breast cancer, only a handful of studies have included enough Asian Americans to be able to report statistically meaningful findings for this population. The Multiethnic Cohort (MEC) conducted in Hawaii and Los Angeles County is an ongoing prospective cohort study of over 200,000 men and women, ages 45–79 years, that has included 45,000 Japanese American women, who were recruited between 1993 and 1996 [25, 26]. In addition, three case–control studies have reported on findings on breast cancer in Asian Americans: (1) a case–control of 183 Japanese breast cancer cases and corresponding controls, ages 45–74, from Hawaii (1975–1980) [27, 28]; (2) a case–control study of 597 Chinese, Japanese, and Filipina breast cancer cases and 966 controls (aged 20–55 years) from Hawaii, the San Francisco Bay Area, and Los Angeles County (1983–1987) (referred to hereafter as CA-HW study); and (3) a case–control study of 2303 breast cancer cases (929 Chinese, 547 Japanese, 827 Filipino) and 2035 controls (923 Chinese, 518 Japanese, 594 Filipino), ages 30–79 years old, from Los Angeles County (1995–2006) (referred to hereafter as LAC study) [29]. Thus, our coverage of breast cancer risk factors in Asian Americans will be based on results of Japanese Americans from the MEC, and those of Chinese, Japanese, and Filipina women from the CA-HW and LAC case–control studies that were conducted 10–15 years apart. Results of Japanese Americans in the MEC represent mainly data on postmenopausal women and allowed comparison to those of NH Whites in the MEC. The CA-HW focused on primarily premenopausal or perimenopausal women, and had higher proportion of US-born Asians (46 % of cases and 42 % of controls), mainly from Hawaii and the San Francisco Bay Area. In contrast, the LAC study included both pre- and postmenopausal women, was based on a single geographic area, and consisted of mostly migrants (79 % of cases and 73 % of controls were non-US born) but this differed for the three Asian ethnic groups (95 % of Filipina, 86 % of Chinese, and 26 % of Japanese control women were foreign born) [30].

Menstrual and Reproductive Factors

Age at Menarche

Early age at menarche is a well-established risk factor that is attributed to extended exposure to estrogens and possibly progesterone [31]. In some studies, the earlier onset of menstrual cycles was related to more intensive exposure to estrogen and a

persistent effect of age at menarche on estrogen concentration [32]. The most comprehensive international evaluation showed that breast cancer risk increased by a factor of 1.05 (95 % CI = 1.044–1.057) for every year of younger age at menarche; results were similar in pre- and postmenopausal women [33]. In the CA-HW study, there was a trend of lower risk associated with later age at menarche, the risk reduction for each year that menarche was delayed was 0.94 (95 % CI 0.86–1.03) [34]. In the LAC study, there was also a significant trend of lower risk with later age at menarche, but this was only observed in premenopausal Asian-American women (*P* trend = 0.03) and not in postmenopausal women (*P* trend = 0.67) [35]. The mean age of menarche of LAC Asian-American control women (12.9) was similar to that of Whites and African Americans in the Women's Contraceptive and Reproductive Experiences (CARE) case–control study (12.5) [36] but considerably younger than that reported for the Japan Public Health Center (JPHC) (14.4) or Miyagi (14.4) cohorts [33]. Although results were not statistically significant in some studies, the strength of the overall evidence implies that the steady decline in age at menarche among Asian Americans [34] and in Asia [37, 38] will continue to have an important impact on their breast cancer risk [39].

Parity, Age at First Birth, Breastfeeding

With westernization and urbanization, there have been striking changes in reproductive patterns in Asia and in Asian Americans, including increases in age at first birth and nulliparity and decreases in number of births and breastfeeding. Most of the established reproductive variables related to breast cancer risk are observed in Asians and Asian Americans. In some cases, changes in the reproductive patterns in the countries of origin (e.g., China's one child policy) [40] have been as dramatic as those in migrant groups to the USA. Thus, reproductive variables may underlie both secular increases in risk and some risk difference between Asians in the USA and in Asia.

Studies conducted in Asian Americans show a strong increased risk associated with nulliparity [34], similar to the findings in western populations [26, 36]. In both CA-HW and LAC studies, parous Chinese, Japanese, and Filipina American women displayed a significant trend of decreasing risk with increasing number of births [34, 35]. The respective ORs for 0, 1, 2, 3, 4+ births were 1.0, 0.94, 0.72, 0.58, 0.33 (*P* trend < 0.001); the risk pattern was similar in pre- and postmenopausal Asian Americans [35]. A significant increase in risk per 5 year delay in first birth was observed in the CA-HW study (OR = 1.22, 95 % CI 1.05–1.42) [34] and also the LAC study although the effect in the latter study was weaker [51]. Nulliparity and later age at first birth were statistically significant risk factors for Japanese Americans, as well as NH Whites in the MEC [26]. The prevalence of nulliparity among Asian Americans in LAC (16.8 %) [30] and Japanese Americans in the MEC (12.9 %) was similar to that of NH Whites in the MEC (15.5 %) [41] but considerably higher than that in Japan (5–6 %) [42, 43] and Shanghai China (3–4 %) [44]. A striking change was in the age at first birth; few Asian Americans

had a first birth before age 21 (5.4 % of LAC Asian Americans, 10.9 % of Japanese Americans in the MEC and 30.8 % of NH Whites in the MEC) and many had delayed their first birth to after age 30 (26 % of LAC Asian Americans, 10.2 % of Japanese Americans in the MEC and 7.2 % of NH Whites in the MEC) [30, 41]. Delay in first birth to age 30 or later was also common in Shanghai, China (23 %) [44], but less frequent in Japanese cohorts (5–8 %) that were conducted during the same time periods [42, 45].

An international pooled analysis of 47 studies showed a significant 4.3 % (95 % CI 2.9–5.8 %) reduction in breast cancer risk for every 12 months of breastfeeding [46]. In studies conducted in the early 1970s and 1980s, long duration of breastfeeding (i.e., >3 years) had a profound protective effect on breast cancer risk in urban China [47–49]. However, the breastfeeding-breast cancer association was weak in Asian-American women [34], and recent studies in Japan [42, 45, 50] and Shanghai, China [44]. While approximately 80 % of Asian women have breastfed in recent studies conducted in Asia [42, 44, 45], the duration of breastfeeding was short. For example, the highest category of breastfeeding (18 months or more) was reported by 23 % of Chinese control women in Shanghai in the 1990s [44] whereas 41 % reported 3 or more years of breastfeeding in Shanghai in the mid-1980s [48]. Also, the prevalence of breastfeeding was lower (48 %) among Asian Americans in LAC and only 18 % had breastfed for 1 year or longer [51]. The interrelated changes in number of births, age at first birth, and breastfeeding [52] have likely played a very important role in contributing to changes in breast cancer incidence in both Asian women in the USA and in Asia.

Menopause

The timing of natural menopause is an important risk factor for breast cancer. Women who experience later natural menopause have higher rates of breast cancer than do women with earlier natural menopause. In an international pooled analysis, breast cancer risk increased by a factor of 1.029 (95 % CI 1.025–1.032) for every year older at menopause [33]. Late age at natural menopause was associated with an increased risk of breast cancer in LAC Asian Americans but the effect was weaker (RR per 5 year delay in natural menopause was 1.02, 95 % CI 0.99–1.04, $P = 0.17$) [51]. Although age at menopause did not differ between NH Whites, Japanese, and Chinese Americans in the Study of Women's Health Across the Nation (SWAN) study [53], age at natural menopause was later in Japanese than NH Whites in the MEC, after accounting for age at menarche, parity, body mass index, and smoking [54]. Among women who had a natural menopause in the MEC, 42.7 % of Japanese Americans vs. 33.7 % of NH Whites experienced menopause at or after age 55 [54]; this proportion of Japanese with a late menopause was considerably higher than women (5–8 %) in the Miyagi and JACC cohorts [43, 45]. Better understanding of the lifestyle determinants of age at natural menopause in Asian Americans and Asians is needed.

Use of Exogenous Hormones

Oral Contraceptives

In an international pooled analysis of mostly studies in western women, risk of breast cancer increased in relation to any oral contraceptives (OC) use (OR = 1.10, 95 % CI 1.02–1.19) and recent use within 5 years (OR = 1.20, 95 % CI 1.1–1.20) [46]. In the CA-HW study, OC use increased with time since migration and was reported by 49.6 % of Asian women born in the USA compared to 15.0 % of Asia-born women who had lived in the USA for less than 8 years. OC use was inversely associated with risk; relative to Asian-American women who were nonusers, those who used OCs for 1–12, 13–60, 60+ months showed ORs of 1.20, 0.81, and 0.71, respectively (P trend = 0.03). The pattern of risk reduction was found in all three Asian ethnic groups [55] and also in the recent LAC study [51]. OC use was not approved in Japan until 1999 and usage is still low. There is little evidence of an increased risk between OC use and breast cancer risk in recent studies conducted in Japan [45, 56], Shanghai, China [57], or elsewhere in Asia (see review [55]). However, duration of OC use was typically short among users in Asia and the factors associated with use may differ between Asian and NH White women. Pharmacokinetic differences in metabolism of OCs between Asians and Whites have been suggested [58, 59]. Nevertheless, while OC use has increased among Asian Americans, there is little suggestion that OC use is positively associated with breast cancer risk in Asian Americans or in Asia and thus OC use cannot explain the elevated risk observed in Asian women who migrated to the USA.

Hormone Replacement Therapy

Results from the Women's Health Initiative (WHI) trial with <2 % of Asian-American women support findings from previous observational studies that current or recent use of estrogen–progestin therapy (EPT) use is associated with an increase in breast cancer risk [60]. Use of hormone therapy (HT) has been uncommon in Asia and Asian Americans until recently, but has become more prevalent especially among Japanese Americans. In the MEC, reported use of estrogen alone therapy (ET) and EPT were similar between Japanese Americans and NH Whites at baseline. Among Japanese Americans, 25.2 % were current EPT users, 18.5 % were current ET users, 9.6 % were past EPT users, and 13.0 % were past ET users; the corresponding percentages in NH Whites were 25.3, 20.1, 14.4, and 16.4 %. For Japanese Americans, the hazard ratios per 5 years of current EPT and current ET use were 1.33 (95 % CI 1.24–1.43) and 1.18 (95 % CI 1.08–1.30), respectively; similar to the risk estimates observed in NH Whites [61]. Results from LAC showed that HT use was highest in US-born Asians (69 %), intermediate (55 %) in migrants who have lived in the USA for 21+ years, and lowest (31 %) in recent migrants who have lived in the USA for less than 21 years. In LAC Chinese, Japanese, and Filipina American women, the risk of breast cancer per 5 years of current EPT use was 1.26

(95 % CI 1.04–1.52) but there was no increased risk associated with current ET use 0.99 (95 % CI 0.83–1.19) [35]. Studies on HT use and breast cancer risk in Asia generally show no statistically significant associations but these studies had low statistical power as use of HT was uncommon (<5 %) and duration of use was rarely considered in the analyses [42, 44, 45]. Thus the increase in HT, particularly EPT use among Asian Americans can explain, in part, the elevated risk observed in postmenopausal women.

Anthropometric Measures

There is extensive evidence that body size measures from birth, young adult life, to late adult life have profound effects on risk of breast cancer although these associations are more consistent and better understood in relation to risk in postmenopausal than premenopausal women. Adult height may serve as an indicator of childhood or adolescent nutrition and energy balance in that shorter women may have been energy restricted during childhood and adolescence. The predominant hypothesis is that after menopause, adipose tissues becomes the primary site of estrogen production through the aromatization of androgens, and that the higher concentrations of circulating estrogens are associated with increases in breast cancer risk [62].

Adult Body Size Measures and Risk in Premenopausal Women

Most studies conducted in western populations found that height was weakly positively associated with breast cancer risk in premenopausal women [63]. Height was significantly associated with breast cancer risk in premenopausal Asian Americans in the CA-HW study (RR 1.9, 95 % CI 1.1–3.6 for ≥167.6 vs. ≤149.9 cm; *P* trend = 0.03) but this was not observed in the LAC study (*P* trend = 0.63). In a meta-analysis of six studies that included Asians and Asian Americans, the RR per 10 cm increase in height was 1.02 (95 % CI 1.00–1.03); the corresponding RR in Whites was 1.03 (95 % CI 1.02–1.05) [64].

Results on BMI before diagnosis and risk of breast cancer in premenopausal Asian-American women have not been consistent. In the CA-HW study, higher risk was seen with higher BMI (90th vs. 10th percentile = 1.60, 95 % CI 0.87–2.94) [65] but in the LAC study, risk was lower with higher BMI (RR for Q4 vs. Q1 = 0.67, 95 % CI 0.48–0.98, *P* trend = 0.07) [35]. In a meta-analysis of studies in Asians (nine in Asia and one among Asian Americans; eight case–control, two cohort), the RR was 1.05 (95 % 1.01–1.09) per 5 kg/m^2 increase in BMI [64]; this is in contrast to a RR of 0.93 (95 % CI = 0.91–0.95) in premenopausal white women from 16 studies (nine case–control, seven cohort) [64]. Thus while high BMI is inversely associated with breast cancer risk in premenopausal Whites, the evidence in Asians suggests a positive association [64]. Interestingly, despite the Asian-white difference in the BMI-risk association in premenopausal women, high waist/hip ratio (WHR)

appeared to be a risk factor for premenopausal breast cancer in both Whites and Asian women. In a meta-analysis of six studies in Whites and four studies in Asians that had information on both WHR and BMI, in Asians, the respective RR per 0.1 increase in WHR was 1.05 (95 % CI = 1.01–1.08) and per 5 kg/m^2 in BMI was 1.19 (95 % CI = 1.15–1.24); the corresponding RRs in Whites were 1.05 (95 % CI = 1.01–1.09) and 0.90 (95 % CI 0.86–0.94) [64]. Better understanding is needed of the differing roles of general adiposity, measured by BMI, and the comparable roles of central obesity, measured by WHR, in the etiology of premenopausal breast cancer in Asia as well as among Asians and Whites in the USA.

Adult Body Size Measures and Risk in Postmenopausal Women

Height, current BMI, weight changes, and WHR are all significantly positively associated with breast cancer risk in postmenopausal Asian Americans as in western populations [66, 67]. In the MEC, the RRs associated with height (per 10 cm), current BMI (per 5 kg/m^2), and weight gain (per 5 kg since age 21) were 1.21 (95 % CI 1.07–1.36), 1.25 (95 % CI 1.1–1.36), and 1.16 (95 % CI 1.12–1.21), respectively, among Japanese Americans; the corresponding RRs among NH Whites were 1.09 (95 % CI 0.98–1.21), 1.06 (95 % CI 1.00–1.14), and 1.06 (95 % CI 1.03–1.09) [41]. High BMI at age 21 was inversely associated with breast cancer risk in postmenopausal Japanese and NH Whites; the respective ORs per 5 kg/m^2 increase was 0.85 (95 % CI 0.74–0.98) and 0.82 (95 % CI 0.72–0.95). Results from the LAC study showed that high BMI and weight gain increased the risk of postmenopausal breast cancer in Chinese, Japanese, and Filipina in a manner similar to the results observed in the MEC. In addition, high WHR was a significant risk factor for postmenopausal breast cancer among Asian Americans; RR was 1.48 (95 % CI 1.02–2.15) for highest vs. lowest category of WHR [35] which is similar to the meta-analysis findings of 1.33 (95 % CI 1.19–1.48) [66]. In a pooled analysis of eight cohort studies in Japan, the risk among postmenopausal women was 1.06 ($P < 0.001$) per 1 kg/m^2 increase in BMI [68]. Although BMI at age 20 years was unrelated to breast cancer risk in postmenopausal women in Japan [69] and Shanghai, China [70], weight gain between age 20 years and current weight appeared to be significantly associated with risk in Japan [69–71].

Birth Weight

In utero exposure to elevated concentrations of estrogens has been hypothesized to adversely affect risk of breast cancer [72]. Findings from meta-analyses of studies conducted mainly in western populations show a significant positive association between breast cancer risk and body size, measured by birth weight, birth length, or head circumference [73, 74] although the confounding effect of adult height may exist [75]. Results from the few studies on birth weight and breast cancer risk in Asian Americans and Asians are mixed. Nonsignificantly reduced risk of breast

cancer in association with higher birth weight was found in a small study conducted among Asians and Whites in Hawaii [76] and in Shanghai, China [77]. However, among Chinese, Japanese, and Filipina women in the LAC study, women in the highest birth weight category (≥4000 g) compared to those in the lowest (<2500 g) category had a doubling of risk after adjustment for age at menarche, adult BMI, and other potential confounding factors. Risk increased (RR = 1.08, 95 % CI 0.99–1.19) per 500 g increase in birth weight [30]. With the current trends of increasing birth weight in Asians and Asian Americans [78, 79], further investigation of the influence of birth weight is warranted since birth weight has been found to influence age at menarche [80, 81] and mammographic density [82, 83].

Physical Activity

Numerous studies have investigated the role of physical activity in relation to breast cancer risk based on the hypothesis that regular activity may beneficially influence the profile of endogenous hormones and growth factors, and lessen inflammation [84, 85]. A meta-analysis of 31 prospective studies (including three studies from Asia) found lower breast cancer risk (RR = 0.87, 95 % CI 0.83–0.91) in association with highest vs. lowest category of physical activity in multivariable models with adjustment for BMI; 0.77 (95 % CI 0.65–0.81) in premenopausal and 0.87 (95 % CI 0.83–1.05) in postmenopausal women [86]. The combined effect associated with high vs. low activity was similar (RR 0.82, 95 % CI 0.87–1.08) for the three cohort studies from Asia which investigated risk in relation to leisure-time physical activity including walking [87, 88] and occupational physical activity [89]. In the LAC study, Asian-American women showed a trend of decreasing risk with increasing years of physical activity (0–4, 5–9, 10–19, 20+ years); the respective ORs were 0.94, 0.77, and 0.57 (P trend <0.01) [35].

Diabetes

Diabetes has been implicated as a breast cancer risk factor; the postulated mechanisms are activation of insulin and insulin-like growth factor pathways and regulation of endogenous sex hormones [90]. In a meta-analysis of observational studies (15 case–control, three cross-sectional, 22 prospective) conducted in mostly western populations, prediagnostic diabetes was associated with breast cancer risk (RR = 1.27, 95 % CI 1.16–1.39) [91]. In LAC, Asian Americans who had a history of diabetes had a higher risk of breast cancer (RR = 1.71, 95 % CI 1.15–2.54) after adjustment for BMI, WHR, and other covariates, this was statistically significant in postmenopausal but not in premenopausal women [92]. Although diabetes was unrelated to breast cancer risk in a pooled analysis of six cohort studies from Japan (RR = 1.03, 95 % CI 0.69–1.56) [93], diabetes was a significant risk factor for breast

cancer in a prospective cohort from Korea [94]. Given the secular increase in diabetes in Asia and in Asian Americans, even a small increase in breast cancer risk among diabetics will have substantial public health implications.

Dietary Factors

The role of diet in the causation of breast cancer continues to be controversial. According to the 2014 updated report from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), alcohol intake is the only dietary factor that shows consistent positive associations with risk of breast cancer. The role of specific nutrients and foods (dietary fat, specific fats, red meat, fruits, and vegetables) remains unclear with reports of significant results in some prospective studies but contradictory results in others (see below). There are suggestions that specific dietary patterns and intake of soy may be associated with breast cancer risk. The traditional Asian diet is rich in plant foods and low in animal protein and fat with soy as a staple. These dietary patterns may underlie risk differences and have been investigated in numerous studies in the past two decades.

Alcohol

Alcohol consumption is a well-established risk factor for breast cancer; the association is thought to be largely hormonally driven. A meta-analysis of 98 studies reported a 10 % increase in breast cancer risk per 10 g of alcohol (~one 12 oz bottle or can of beer, one 4 oz glass of wine, or a 1.5 oz drink or shot of liquor) per day [95]. Although alcohol intake was unrelated to breast cancer risk in Asian Americans in the CA-HW study [96], results from the larger LAC study that allowed analysis by Asian ethnicity showed that alcohol intake was associated with breast cancer risk among Japanese Americans (per 5 g/day RR = 1.17, 95 % CI 0.99–1.39, $P = 0.073$) but not among Chinese and Filipina Americans. Regular alcohol intake was less common among Chinese (14 %) and Filipina (14 %) compared to Japanese Americans (27 %) in the LAC study [29]. Intake of alcohol was lower among Japanese American (17.0 % consumed <10 g/day and 3.7 % consumed ≥10 g/day) than NH Whites in the MEC (34.3 % consumed <10 g/day and 24.3 % consumed ≥10 g/day). However, the RR per 10 g/day was 1.08 (95 % CI 1.01–1.15) in Japanese Americans, similar to the risk estimate for NH Whites (RR = 1.04, 95 % CI 1.02–1.07) [97]. Alcohol intake also emerged as a breast cancer risk factor in Japan. In the JACC cohort, the RR for current drinkers was 1.27 (95 % CI 0.87–1.84) compared to nondrinkers and risk was significantly increased for women who consumed ≥15 g/day of alcohol (RR = 2.93, 95 % CI 1.55–5.54) [98]. In the JPHC, consumption of 10 g ethanol/day was associated with a 6 % (95 % CI 1–13 %) (P trend = 0.047) increase in the risk of breast cancer [99]. These results in Asian Americans and in Japan are important given that alcohol intake is one of the few modifiable risk factors for breast cancer.

Dietary Fat

Dietary fat has been the major focus in the search for dietary causes of breast cancer for decades, and despite compelling results from ecologic and animal studies, findings from analytic epidemiologic studies have been inconsistent. In the large MEC study, breast cancer risk in postmenopausal women was unrelated to intake of total fat and by type of fat. These null results were found in Japanese Americans as well as the other racial/ethnic groups in the MEC and remain unchanged when body mass index and age at menarche were removed as adjustment factors to avoid adjusting for intermediate variables in the pathway from dietary fat and breast cancer risk [100].

The generally null findings in the MEC are consistent with pooled analyses of cohort studies that have found no association between dietary fat and breast cancer risk [101], although a positive association with total fat was suggested in a meta-analysis of 31 case–control and 14 cohort studies [102]. In addition, findings from the WHI dietary trial showed that after 10 years of intervention, those in the low-fat arm with a goal of consuming 20 % of energy from fat showed a small reduction in risk (HR 0.91, 95 % CI 0.83–1.01) [103] although the risk reduction was no longer evident with additional years of follow-up [104]. Recent results from the NIH-AARP [105], the EPIC [106], and VITAL [107] cohorts suggest that risk of breast cancer, and particularly certain subtypes of breast cancer in postmenopausal women, may be positively associated with intake of total fat, saturated fat, and specific fatty acids. A meta-analysis of 21 cohort studies found that high intake of marine *n*-3 polyunsaturated fatty acids (PUFA) was inversely associated with breast cancer risk (RR = 0.86, 95 % CI 0.78–0.94); this effect was stronger (RR = 0.69, 95 % CI 0.56–0.86) [108] in the subset of studies conducted in Asia [109–111]. Meta-analysis of another six prospective nested case–control studies and five cohort studies found a significantly 6–10 % lower breast cancer risk in association with high dietary or serum ratio of *n*-3/*n*-6 PUFA [112]. Results from the JPHC cohort suggests that the effects of total fish (the major dietary source of *n*-3 PUFAs in this population), *n*-3 PUFA and *n*-6 PUFA on breast cancer risk may vary by ER/PR status. A significant positive association was reported between intake of *n*-6 PUFA and risk of ER + PR+ breast cancer [113].

Meat, Red Meat, and Processed Meat Intake

Results from prospective cohort studies have found no consistent associations between breast cancer risk and meat intake [114, 115]. However, an updated meta-analysis of 14 prospective studies (one from China, 13 from western populations) reported elevated summary RRs for the highest vs. the lowest categories for red meat (RR = 1.10, 95 % CI 1.02–1.19) and processed meat (RR = 1.08; 95 % CI 1.01–1.15) [116]. Results from the LAC study showed elevated risk of breast cancer in Asian Americans with increasing intake of meat (RR per 23 g/1000 kcal=1.12, 95 % CI 1.02–1.22) [117]. Breast cancer risk was also positively associated with intake of

total meat and red meat in case–control studies conducted in Shanghai, China [118, 119]; there was a significant trend of increasing risk with increasing intake of all meats (Q5 vs. Q1 RR = 2.18, 95 % CI 1.82–2.61), and red meat (Q5 vs. Q1 RR = 1.45, 95 % CI 1.22–1.72) [119]. The association with red meat intake may be due to a combination of nutritionally related factors, such as content of fat, protein, iron [120, 121] and/or meat preparation methods including the presence of carcinogenic compounds such as the heterocyclic amines and polycyclic aromatic hydrocarbons by-products that are produced in the process of high-temperature cooking of red meats [122].

Plant Foods—Fruit and Vegetable Intake

Fruits and vegetables are rich sources of carotenoids, flavonoids, and glucosinolates, and have been hypothesized to reduce the risk of breast cancer. Results from the Pooling Project of Prospective Studies of Diet and Cancer that included 20 cohort studies (including the JPHC cohort) found no overall association between breast cancer risk and intake of fruits (*P* trend = 0.36), vegetables (*P* trend = 0.77), or fruits and vegetables combined (*P* trend = 0.30) [123]. In subgroup analysis by hormone receptor status, the pooled RR comparing the highest vs. lowest quintile of total vegetable intake was 0.83 (95 % CI 0.74–0.90) for ER- but not for ER+ breast cancer [123]. In the LAC study, risk of breast cancer in Asian Americans decreased in association with intake of vegetables (RR per 89 g/1000 kcal = 0.90 (95 % CI 0.82–0.99), fruits and nuts (RR per 109 g/1000 kcal = 0.95, 95 % CI 0.86–1.04), and legumes (RR per 30 g/1000 kcal = 0.87, 95 % CI: 0.79–0.95) after adjustment for relevant covariates [117]. Although breast cancer risk was unrelated to intake of both fruits and vegetables, or specific types of vegetables in the JPHC cohort [124], intake of vegetables (RR per 200 g/day = 0.77, 95 % CI: 0.47–1.24), but not fruits (RR per 200 g/day = 1.04, 95 % CI 0.88–1.25) was inversely associated with risk in the Singapore Chinese Health Study [125]. Intake of total vegetables (particularly allium vegetables and fresh legumes) but not fruits was significantly inversely related to breast cancer risk in Shanghai, China [119]. A meta-analysis of eight studies, including three studies from China found that high intake of cruciferous vegetables was significantly associated with reduced risk (RR = 0.85, 95 % CI 0.77–0.94) [126]. In a pooled analysis of eight prospective studies (including the MEC) that used prediagnostic blood samples, statistically significant inverse associations with breast cancer were observed for total and specific carotenoids; associations appeared to be stronger for ER- breast cancers [127].

Soy Products

Soybeans are a rich source of isoflavones, which are hypothesized to be natural estrogen receptor modulators that possess both estrogen-like and anti-estrogenic like properties. In the CA-HW study, high intake of tofu was significantly inversely

associated with breast cancer risk in Asian Americans [128]. In the LAC study that included a more complete assessment of soy intake among Chinese, Japanese, and Filipinas, there was a significant trend of decreasing risk with increasing intake of isoflavones. Specifically, Asian Americans who were high consumers during adolescence and adult life, derived the strongest benefit [129]. In a 2008 meta-analysis of mostly case–control studies, a dose–response relationship was observed with a statistically significant trend of decreasing risk with increasing soy food intake. Compared to the lowest level of soy food intake (≤5 mg isoflavones per day), risk was intermediate (OR = 0.88, 95 % CI 0.78–0.98) among those with modest (~10 mg isoflavones per day) intake, and lowest (OR = 0.71, 95 % CI 0.60–0.85) among those with high intake (≥20 mg isoflavones per day). This inverse association was observed in pre- and postmenopausal women [130]. However, there is concern the effect of soy may be due to residual confounding by correlated foods and other factors associated with traditional Asian lifestyle. In the MEC, self-reported soy food intake based on food frequency questionnaire did not show a statistically significant inverse association in all postmenopausal women but the association was borderline statistically significant in Japanese Americans (upper vs. lower quartile RR = 0.86, 95 % CI 0.70,1.05, *P* trend = 0.06) [131]. In addition, in a case–control study nested within the MEC, a significantly lower breast cancer risk was observed in postmenopausal women with higher urinary prediagnostic isoflavone excretion levels, especially among Japanese American women (upper vs. lower quartile RR = 0.53, 95 % CI 0.24, 1.16, *P* trend = 0.005) [132]. A meta-analysis of mainly prospective studies [133] as well as a systematic review of studies from Japan are supportive of a role of soy food in the etiology of breast cancer [134].

Dietary Patterns

Studies of the role of diet and breast cancer have expanded to include investigation of dietary patterns which can accommodate the complex interplay of foods within a diet. These studies aim to reduce a large amount of original data (food items/groups and portion sizes) into indices or factors that might reflect the composite dietary habits. In the LAC study, breast cancer risk in Chinese, Japanese, and Filipina American women decreased significantly with increasing intake of a vegetable-soy pattern (*P* for trend = 0.013) [117]. In the prospective Singapore Chinese Health Study [125] and case–control studies conducted in Japan [135], Korea [136], and southern China [137], breast cancer risk was inversely associated with higher consumption of a dietary pattern comprising fruit, vegetables, soy, and soy-bean products. However, in a case–control study in Shanghai, China, breast cancer risk was not associated with intake of a "vegetable and soy" pattern [138]. Identification of the key factors within the Asian fruit-vegetable-soy dietary pattern that are responsible for observed inverse relationships with breast cancer is needed.

Green and Black Tea

Green tea is rich in tea catechins and have many cancer chemopreventive attributes including anti-oxidation, anti-inflammatory, anti-proliferative, and anti-angiogenic effects [139]. Asian-American women who were regular green tea drinkers had a significantly lower risk of breast cancer in the LAC study [140]. Supportive results also were found in case–control studies in China [141, 142]. The combined OR from these case–control studies was 0.70 (95 % CI 0.61–0.79) for women who drank green tea regularly compared to non-green tea drinkers [143]. However, cohort studies from Japan [144–146], Singapore [147, 148], and Shanghai, China [149], showed no association between breast cancer risk and green tea intake (combined OR = 1.06, 95 % CI 0.93–1.20). In a meta-analysis, black tea intake was not associated with breast cancer risk [150].

Active Smoking, Passive smoking

Experimental studies have shown that compounds found in tobacco smoke, such as polycyclic hydrocarbons, aromatic amines, and N-nitrosamines, may induce mammary tumors [151, 152]. Although smoking has been suggested to have antiestrogenic effects [153], recent results have found higher concentrations of androstenedione, testosterone, and estrogen concentrations in postmenopausal women who were current smokers than nonsmokers [154, 155].

While many epidemiological studies conducted in western populations have found no association or at most a weak positive association with active smoking (see review [156]), recent cohort studies [157–159] including the MEC [160] have reported elevated risk of breast cancer among smokers. A 2013 meta-analysis of prospective studies estimated a combined risk of 1.12 (95 % CI 1.08–1.16) for current smokers and 1.09 (95 % CI = 1.04–1.15) for former smokers. Risk was also elevated among those who started smoking at a young age and smoking before first birth suggesting that a long duration of smoking may have a deleterious effect [159]. With few exceptions [161], active smoking was not significantly associated with breast cancer risk in studies conducted in Japan [162, 163]. Prevalence of active smoking is generally low in Japan and lifetime history of smoking was often not ascertained in studies of breast cancer.

The evidence on passive smoking and risk of breast cancer is also controversial. A meta-analysis of case–control studies in China reported a significant positive association between passive smoking and breast cancer risk (RR = 1.67, 95 % CI 1.27–2.21) [164] but null results (RR = 1.01, 95 % CI 0.96–1.06) were found in a meta-analysis of ten prospective studies; the RR was 0.82 (95 % CI 0.54–1.23) for the four studies conducted in Asia [165]. Breast cancer risk was unrelated to passive smoking in most studies in Japan [161, 163, 166] but results from the Takayama cohort differed [167]. Results from the EPIC study found that breast cancer risk increased significantly by 10–16 % in association with passive and active smoking

[158]. With the large numbers of active smokers in China and elsewhere in Asia, the potential effects of passive smoking on breast cancer risk requires continued monitoring but differences in active smoking and passive smoking are unlikely to explain the increase of breast cancer in Asian Americans.

In summary, results described in the above sections show clear effects of menstrual and reproductive factors, body mass index (postmenopausally), use of hormone therapy, and intake of alcohol and soy, but less clear effects of other specific dietary factors as explanations of the rising incidence of breast cancer among Asian Americans. Besides the above factors, there are three other factors, genetics, endogenous hormones, and mammographic density, that could underlie racial/ethnic differences in risk and substantial new information on Asians and Asian Americans have become available in studies conducted in the past two decades.

Family History

Studies conducted in Western populations have consistently reported a two to threefold increased risk of breast cancer in association with a family history of breast cancer among mothers or sisters [168]. Family history of breast cancer is a significant risk factor in Asian Americans [27, 28, 35] and in the LAC study, in both premenopausal (RR = 2.44, 95 % CI 1.55–3.87) and postmenopausal Asian Americans (RR = 1.64, 95 % CI 1.12–2.41) [35]. The prevalence of family history of breast cancer among LAC Asian Americans was 9–11 %, similar to that of Japanese Americans in the MEC (10 %) [41], but higher than prevalences of 1–5 % reported in Singapore, China, or Japan [42, 45, 169, 170].

Examination of the familial risk as above implies that close relatives have similar risk profiles. These shared risk profiles may be environmental or behavioral but may be also indicative of an important role for genetic variation as underlying risk of this disease. The relative importance of genetic variation, compared to modifiable causes, and how much they explain the risk patterns seen in Asian Americans must be judged in light of the experience of migration. The fact that risk increases dramatically with migration to the USA (especially for ER+ postmenopausal disease) indicates the complexity of the disease, and implies an interplay of genetics, environment, and behavior causes.

Genetic Susceptibility

Familial breast cancer accounts for 5–10 % of all breast cancers and are due to genetic predisposition caused by germline mutations; the most commonly tested genes are *BRCA1/BRCA2*. Among Asian Americans with a strong family history of breast cancer, mutation prevalence was 11.5 % for *BRCA1* and 13.2 % for *BRCA2*, the corresponding estimate in Whites was 25–40 % for *BRCA1* and 6–15 % for *BRCA2* [171, 172]. However, among Asian Americans and in Asia, the prevalence

of *BRCA1/BRCA2* mutations (BRCA1: 0.5–4.1 %; BRCA2: 1.1–4.4 %) was comparable to Western populations (1.8–3.6 %) [173]. In a comprehensive analysis of the frequency and mutation spectrum from 11 Asian countries, the overall prevalence of *BRCA1/BRCA2* in Asians was comparable to that in other ethnic groups [173].

In addition, genome-wide association studies (GWAS) have identified approximately 100 genetic loci associated with breast cancer risk [174–176]. Approximately ten of these loci were initially identified in GWAS conducted in East Asian descendants [177]. In a consortium analysis that included 23,637 breast cancer cases and 25,579 controls of East Asian ancestry and tested 70 SNPs previously associated with breast cancer mostly in studies of European descendants, 31 loci was associated with breast cancer risk at $P<0.05$ in a direction consistent with previous reports [178]; 21 of them remained statistically significant at a Bonferroni-corrected significance level. These common genetic variants explain a lower fraction of excess familial risk of breast cancer in Asian (~10 %) than in European-ancestry populations (~14 %) [178]; this is expected since most known common genetic variants were identified in GWAS conducted in European-ancestry populations, and they tended to show a stronger association in European than Asian-ancestry populations. In addition to these SNPs reported from the collaborative analysis, two GWAS of East Asian women identified four additional susceptibility loci (1q32.1, 5q14.3 and 15q26.1 [177] and 2q34 [179]). When three of these four SNPs were tested in women of European ancestry, all three SNPs showed associations in the same direction ($P<0.05$), but the magnitude of association was weaker than in women of East Asian ancestry [177].

Lee et al. [170] created a genetic risk score based on 51 genetic variants identified in previous GWAS and tested this in a nested case–control study of 411 breast cancer cases and 1212 controls within the Singapore Chinese Health Study. They found that the genetic risk score was an independent predictor of breast cancer risk, and improved the classification of 6.2 % of women for their absolute risk of breast cancer in the next 5 years. These findings indicate that the established risk variants for breast cancer also contribute to risk in Asian women.

Endogenous Hormones

Many of the breast cancer risk factors, particularly, those related to menstrual and reproductive factors and some lifestyle factors (e.g., body weight) can be understood as measures of the cumulative exposure of the breast to estrogen, and perhaps progesterone. A compelling body of epidemiologic and experimental data implicates endogenous estrogens in the etiology of breast cancer [180–182].

Prospective studies have provided convincing evidence. An international pooled analysis of nine prospective studies found that prediagnostic estrogenic (including estrone, estradiol) and androgenic (including testosterone, androstenedione) steroid sex hormones were significantly positively associated with increased breast cancer risk in postmenopausal women, and that sex hormone binding globulin (SHBG)

was significantly inversely associated with risk even after adjustment for BMI and other factors [62, 183]. However, this evidence was based primarily in White women; only 23 cases and 45 controls were from Japan. Results from a nested case–control study conducted in the MEC further strengthened the evidence that high endogenous estrogen levels confer a similar or slightly higher risk of breast cancer in Japanese Americans relative to NH Whites and other race/ethnicities. The risks associated with a doubling of estradiol levels was 2.88 (95 % CI 1.63–5.10) in Japanese Americans and 1.87 (95 % CI 1.17–2.99) in the other racial/ethnic groups combined. A significant twofold increased risk in association with a doubling of estrone, estrone sulfate, free estradiol levels were observed in postmenopausal Japanese Americans [184].

The evidence on circulating sex hormones and breast cancer risk in premenopausal women is less consistent but points to a role of androgens in nested case–control studies that were conducted in EPIC [185] and the NHS [186] studies. We are not aware of such prospective studies conducted among premenopausal Asian Americans or in Asia.

While findings from earlier cross-sectional studies of mostly convenience samples tended to show lower urinary or blood estrogen levels among women in Asia, and Asian Americans compared to Whites in the USA, body weight and other potential confounders were usually not adjusted for (see review [187, 188]). In fact, postmenopausal Japanese American in the MEC study ($n=96$) had similar levels of estrone, estradiol, bioavailable estradiol, and other hormones to that of NH Whites ($n=91$) in age-adjusted analyses, but showed 15 % higher estradiol ($P=0.036$) and 18 % higher bioavailable estradiol ($P=0.024$) levels than NH Whites after adjustment for BMI and age at menarche [155]. There is little evidence in contemporaneous cross-sectional studies that reproductive hormones are lower in Asian Americans than in NH Whites [189] or lower in non-US-born Asian Americans than US-born Asian Americans [190, 191].

Mammographic Density and Screening

Mammographic density reflect the distribution of fat, connective tissue, and epithelium in the breast. Boyd and colleagues hypothesized that the relative amount of epithelium and connective tissues or the mammographic densities represent the cumulative exposure to factors that stimulate growth of breast cells since puberty and would influence the risk of breast cancer development [192, 193]. Numerous studies conducted in North America and Europe have shown that women with densities greater than 75 % of the breast have a 4–6 times higher breast cancer risk than women of the same age with no densities [192, 194].

A few studies have investigated mammographic density and risk of breast cancer in Asian Americans. In a study of Chinese, Japanese, and Filipina Americans in LAC (143 cases, 67 controls), which also included NH Whites (280 cases, 227 controls) for comparison, the OR per 10 % increase in percent density was 1.30 (95 %

CI 1.05–1.61) in Asian Americans, and 1.15 (95 % CI 1.04–1.27) in NH Whites. Per 10 % increase in percent density, breast cancer risk increased 10 % (95 % CI 0.84–1.45) in the younger (<50 year-old) and 59 % (95 % CI 1.09–2.32) in the older (≥50 year-old) Asian Americans. The risk associations in NH Whites were 1.10 (95 % CI 0.96–1.26) and 1.24 (95 % CI 1.05–1.34), respectively [195]. Results were similar in the MEC; the OR per 10 % increase in percent density was 1.15 (95 % CI 1.04–1.27) in Japanese Americans, and 1.33 (95 % CI 1.18–1.51) in NH Whites [196]. Among Chinese in Singapore, after multivariable adjustment, the 76–100 % density category had an OR of 5.54 (95 % CI 2.38–12.9) compared with 0–10 % [197]. Thus there is general consistency that mammographic density is an equally strong breast cancer risk factor for Asian women in the USA as in NH Whites [195–197].

In cross-sectional studies that use a quantitative method to compare mammographic densities in Asian Americans and NH Whites [198–200], women of Asian ethnicities tended to have lower absolute density but higher percent densities than NH Whites because of their relatively small breast size. These differences in percent densities tended to attenuate after adjustment for BMI, parity, and other factors [199–201]. In a study that compared breast densities of Japanese Americans in Hawaii to those in Japan, absolute breast density was higher among Japanese Americans in Hawaii than among women in Japan reflecting the higher breast cancer risk of Japanese in Hawaii [202, 203], although the specific factors responsible for the high densities are not clear. However, percent densities do not differ consistently between US-born and non-US-born Asian Americans [200] or by measures of acculturation [200, 204]. Results from these studies suggest that absolute but not percent mammographic density reflects the lower breast cancer incidence rates of Asian Americans in relation to those of NH Whites [199].

Data from twin and family studies suggest that genetic factors explain 30–60 % of the variation in mammographic density, when adjusted for age, BMI, and other covariates [205–207]. However, only a few genetic loci (*ZNF365, LSP1*, and *RAD51L1*) have been associated with mammographic density, mainly in European Whites [208–210]. In one of the larger studies involving Asian women, a candidate gene approach was used and identified SNPS in *PPARγ* and *TGFB1* to be associated with mammographic density in Singapore Chinese women [211, 212]. A recent study that investigated 36 SNPs, mostly GWAS-identified, found that 6q25.1 region near *ESR1* was associated with mammographic density in Malaysian Chinese women [213]. However, the previously reported PPARγ-density association in Singapore Chinese was not replicated and the *TGFB1* SNP was not evaluated (i.e., did not pass genotyping quality control).

Data on mammography screening by Asian-American ethnicity are reviewed in detail (see Chap. 4). Briefly, data from the 2011 to 2012 California Health Interview Survey of women ages 40 and over showed that 72 % of Asian Americans reported a recent mammogram in the past 2 years compared to 83 % of African Americans, 81 % of Whites, and 77 % of Latinas [214]. In analysis by specific Asian ethnicity, screening rates were lowest in Koreans (52 %), intermediate in Filipina (78 %), Vietnamese (76 %), Chinese (73 %), and other South Asians (69 %), and highest in Japanese Americans (84 %). These differences remained after adjustment for accul-

turation, sociodemographic characteristics, access to health care, and breast cancer risk factors. In addition to Korean ethnicity, low screening rates were found among women with low level of acculturation, lack of health insurance, and low level of education [215]. Thus, continued efforts to promote utilization of screening services need to be emphasized in Asian Americans.

Conclusion

The adoption of a westernized lifestyle with migration to the USA, characterized by early age at menarche, few children, delayed age at first birth, less breastfeeding, and a sedentary lifestyle have contributed to the risk of breast cancer in Asian-American women. Diabetes, increase in body weight, and use of menopausal hormones are additional risk factors for breast cancer in postmenopausal Asian-American women. High alcohol intake, a dietary pattern that is low in vegetables and soy, and high in meat are contributing factors as well. The pattern of dietary differences remains highly suggestive of a contributing role, especially between breast cancer between Asians and the USA. Failure to identify dietary factors in analytic studies could be due to measurement errors, correlation between dietary components, and assessment of dietary patterns during adult life when diet during earlier life (e.g., before puberty) may be more relevant.

Three other factors, genetics, endogenous hormones, and mammographic density, are also significant risk factors for breast cancer in Asian-American women. Thus, the available data suggest that it is unlikely that risk factors for breast cancer in Asian Americans differ markedly from those in other racial/ethnic groups. While we now have excellent data on Japanese Americans from the MEC, information on other Asian ethnic groups is still sparse. Most studies typically present results for Asian Americans combined and not separately for Asian ethnic subgroup. It is quite likely that changes in various lifestyle exposures are not identical across different Asian race/ethnicities such that the relative importance of each individual risk factor will depend on the changing prevalence of these risk factors.

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Endometrial Cancer Among Asian Americans

Veronica Wendy Setiawan

Abstract Endometrial cancer is the most common cancer of the female reproductive organs. While the incidence rates of endometrial cancer in Asian Americans are lower relative to non-Hispanic whites, their rates are increasing steadily. Between 1990 and 2008, all Asian groups in the United States (USA) have experienced a statistically significant annual increase in endometrial cancer incidence. Migrant studies showed that US-born Asians had higher endometrial cancer incidence than among their Asian-born counterparts suggesting that environmental exposures in Asian Americans may explain these observed increases. In this chapter, we discuss the epidemiology of endometrial cancer including tumor characteristics, risk factors (lifestyle and genetics), and survivorship in Asian-American women.

Keywords Asian Americans • Endometrium • Obesity • Diabetes • Exogenous hormones

Introduction

Clinical Description of Endometrial Cancer

Endometrial cancer is a type of cancer that starts in the cells that line the uterus. The most common type of endometrial cancer is endometrioid adenocarcinomas which are cancers of the cells that form glands in the endometrium. Endometrial cancer is rare in women under 45 years of age, and approximately 75 % of cases are found in women aged 55 and older. The majority (up to 80 %) of endometrial tumors are type I which are of endometrioid histology, present at an early stage, and have good

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prognosis. The much less common types (up to 20 %), type II, are of serous or clear cell histology and are associated with poor prognosis. The key symptom of endometrial cancer is abnormal vaginal bleeding which present in 90 % of endometrial cancer patients. Because the majority of endometrial cancers are found at an early stage, the overall prognosis for this cancer is generally good. The established treatments for endometrial cancer include surgery, radiation therapy, hormonal therapy, and chemotherapy which depend largely on the type of cancer and stage of the disease when it is diagnosed.

Descriptive Epidemiology

Endometrial Cancer Trends

In the USA, endometrial cancer is the most common cancer of the female reproductive organs and the fourth most common cancer in women with estimated 60,050 incident cases and 10,470 deaths in 2016 [1]. Relative to non-Hispanic whites, the incidence rates of endometrial cancer in Asian Americans are lower, but their rates are increasing [2], while the rates among non-Hispanic whites are stable [3]. Approximately 7600 cases were diagnosed per year in Asian-American women [4]. Cancer incidence data from 13 Surveillance, Epidemiology, and End Results (SEER) registries show that endometrial cancer is the fourth most frequent incident cancer in Chinese-, Filipina-, and Japanese Americans during 2004–2008. Among Asian ethnic groups, the overall incidence rates are highest in Filipina- (22.0 per 100,000) and Japanese Americans (20.0 per 100,000) which are approaching the rates in non-Hispanic whites (26.3 per 100,000) [2]. While endometrial cancer is the third most frequent cancer diagnosed in Asian Indian/Pakistani women, the rate of 16.4 (per 100,000) is lower compared to Filipina- and Japanese Americans but similar to the rates of Chinese Americans (14.3 per 100,000) [2]. Between 1990 and 2008, all Asian groups have experienced a statistically significant annual increase in endometrial cancer incidence: 1 % in Japanese, 3 % in both Asian Indians and Filipinas, and 7 % in Chinese, while the rates in non-Hispanic whites remain stable [2].

Figure 1 shows the age-adjusted incidence rates of endometrial cancer by racial/ethnic group (non-Hispanic whites and Asian-American ethnic group) from the same 13 SEER registries with additional 2 years of observation (1990–2010); patterns were similar to that described above. While the rates among Asian groups are still lower than those of non-Hispanic whites, the rates in all Asian subgroups (i.e., Japanese, Chinese, Filipinos, Koreans, Vietnamese) have continued to increase steadily. The rates in Filipino (22.9 per 100,000) and Japanese (20.3 per 100,000) women in 2008–2010 are approaching the rates of non-Hispanic white women (27.1 per 100,000). Of particular interest is the substantial increase in rate among Filipinas. Among these Asian subgroups, Korean women have the lowest rate; the incidence rate in 2008–2010 was 7.9 per 100,000. Changes in the prevalence of endometrial cancer risk factors, especially overweight and obesity, may explain these observed increases.

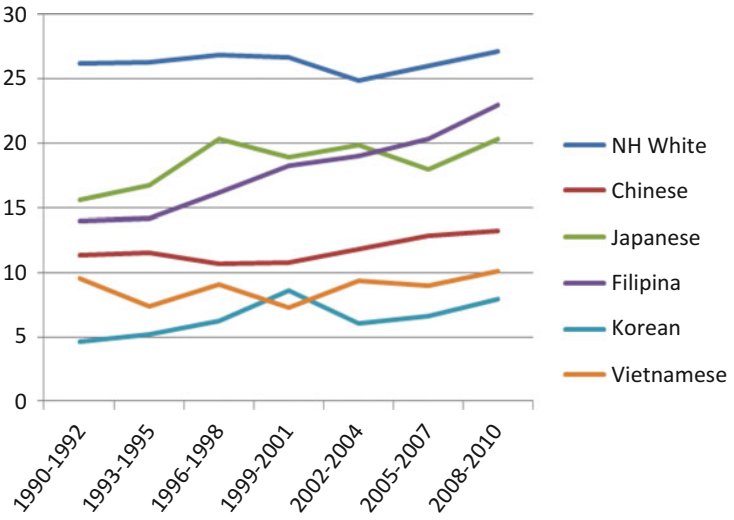

Fig. 1 Age-adjusted incidence rates of endometrial cancer per 100,000 SEER 13 1990–2010

Migrant Studies of Endometrial Cancer

Studies of women emigrating from low-risk countries to the USA and studies of descendants of these women show that the incidence of endometrial cancer is highest in whites, intermediate in Asians born in the USA, and lowest in Asian-American women born in Asia [5]. US-born Chinese and Japanese had higher endometrial cancer incidence than their Asian-born counterparts, but the rates among US-born and Asian-born Filipino women were similar [5]. While incidence rates for endometrial cancer was lower among Koreans in the USA than whites, the rates of Korean Americans were 2.9 times higher than the rates in Korea [6]. Recent data from Korea showed that between 1999 and 2012, the incidence rates of endometrial cancer have been increasing steadily, with an average annual percentage increase of 5.8 % [7].

A study covering data from 2001–2009 among Asians in the USA showed that US-born Asian women were more likely to be diagnosed with type I endometrial cancer (i.e., endometrioid histology, early stage) compared with foreign-born Asians (65 % vs. 56 %; $P < 0.01$) [8]. These migrant studies suggest that possible environmental and/or cultural differences in the exposure to endometrial cancer risk factors may include differences in the prevalence of obesity, menopausal hormone use, and/or dietary patterns as discussed below.

Endometrial Cancer Characteristics in US Asians

While differences in tumor characteristics between African Americans and non-Hispanic whites are widely recognized, with African Americans more likely to be diagnosed with higher stage, grade, and more aggressive type II tumors [9–11], very

little data are available in Asian-American populations [12]. Based on studies using data from the SEER program, compared to whites, Asian-American women tended to present at a younger age at diagnosis (58 years in Asians vs. 65 in whites) [12, 13]. Furthermore, recent data (1988 to 2009) showed a slightly higher prevalence of advanced stage disease (III–IV) (15.6 % vs. 13.3 %; $p=0.04$) and aggressive histology subtypes (serous/clear cell) (10.6 % vs. 9.6 %; $p=0.04$) among Asian women compared to non-Hispanic whites [13]. However, results from a Department of Defense database study [14] and the Multiethnic Cohort (MEC) [9] did not show significant difference in the stage at presentation or histology between Asians/Pacific Islanders and non-Hispanic whites. In the MEC, Japanese Americans and non-Hispanic whites showed the same proportions of localized cancers (82 %) and nonaggressive histology (91 %) and a comparable proportion of high grade tumors (20 % vs. 19 %) [9].

Risk Factors

Epidemiologic studies have identified several risk factors associated with an increased risk of endometrial cancer. Most of these factors are related to an imbalance between estrogen and progesterone exposures, including the use of unopposed estrogen therapy and obesity. The use of combined oral contraceptives (OCs), which is associated with progesterone-dominant states, reduces the risk of endometrial cancer. Other hormonal risk factors include nulliparity, early menarche, and late menopause. Smoking has been associated with reduced risk, while metabolic syndrome including type 2 diabetes has been associated with higher risk of developing endometrial cancer. The majority of these etiologic studies have been conducted in non-Hispanic white populations. There have been a few analytic epidemiologic studies of endometrial cancer in Asian Americans; these include a case–control study conducted among Japanese, Chinese, and Korean women in Hawaii [15] and the prospective Multiethnic Cohort (MEC) that included a large number of Japanese Americans [9]. There are very few large endometrial cancer studies in Asia; they include a population-based case–control study in Shanghai, China [16], and a prospective cohort study in Japan [17].

Obesity

In the USA, the majority of epidemiologic studies have been conducted in non-Hispanic whites. A few migrant studies among Asian Americans suggest potential influences of diet and lifestyle exposures on endometrial cancer etiology. Obesity is one of the strongest risk factors for endometrial cancer. The exact biological mechanism is unknown, but it is thought that the effect of excess fat on endometrial cancer is mediated through endogenous hormones. In postmenopausal women, adipose

tissue is the primary source of estrogen production by aromatization of androstenedione. Obesity has been associated with increased production rates of androgens, increased peripheral conversion of androgens to estrogens, and decreased levels of progesterone and sex hormone-binding globulin. Increased exposures to estrogens unopposed by progesterone in obese women may stimulate mitotic activity of endometrial cells, leading to hyperplasia and subsequent cancer [18].

Data from the National Longitudinal Study of Adolescent Health showed that the acculturation to American diet and lifestyles, including a high-fat diet and decreases in physical activity, was associated with an increase in obesity in first-generation migrants which further increased in successive generations [19]. This is consistent with the observed increase in endometrial cancer incidence in US-born Asian women compared to immigrants. While the prevalence of overweight and obesity (BMI ≥ 25 kg/m^2) in US Asians remained lower than that of non-Hispanic whites, the prevalence was higher in Japanese (28.3 %) and Filipina women (33.5 %) compared to other Asian groups (Chinese 18.6 %, Vietnamese 16.9 %, Korean 17.3 %) [20].

In the MEC, the association between obesity and endometrial cancer risk was much stronger among Japanese Americans than among African Americans, non-Hispanic whites, and Latinas [21]. The relative risk for endometrial cancer comparing obese (BMI ≥ 30 kg/m^2) to normal weight (BMI < 25 kg/m^2) women was 4.6 (95 % CI: 2.61, 8.11) in Japanese Americans and ~3.0 in non-Hispanic whites (95 % CI: 1.71, 4.43), African Americans (95 % CI: 1.51, 6.28), and Latinos (95 % CI: 1.59, 5.94). Furthermore, Japanese Americans, who were generally leaner than women of the other MEC ethnic groups, had an increase in endometrial cancer risk with a much smaller weight gain (~5 %) than the other three ethnic groups where a greater gain (~35 %) was needed to observe similar effects. These findings suggest that a lower percentage of weight gain in Japanese women may result in sufficient hormonal changes to influence their endometrial cancer risk. It is also possible that ethnic variation in adiposity phenotype may contribute to these observations. Previous studies have shown that Asian women had a higher body fat percentage than non-Hispanic whites with a comparable BMI [22]. In the MEC, Japanese American relative to non-Hispanic whites had higher circulating levels of estrogens independent of BMI [23].

Body fat distribution might influence endometrial cancer risk. In a pilot study in the MEC that included 60 non-Hispanic white and Japanese American women who had a comprehensive body fat analysis using both DEXA and MRI, Japanese Americans had significantly greater waist to hip ratio (WHR), trunk fat mass, and visceral/abdominal fat and lower leg fat mass compared to non-Hispanic whites of similar BMI [22]. These data showed that Asian women carried greater abdominal and visceral fat when compared to non-Hispanic whites with similar overall BMI. The largest case–control study of body fat distribution and endometrial cancer in Chinese women from urban Shanghai (832 cases and 846 controls) showed that increasing WHR and waist circumference was significantly associated with endometrial cancer risk after BMI adjustment [24]. The odds ratios (OR) associated with the highest quartile versus lowest quartile of WHR and waist circumference were 2.6 and 3.9, respectively. In fact, the association of BMI with endometrial cancer was weakened

substantially after waist circumference was included in the model; increasing BMI was associated with endometrial cancer risk ($P<0.01$), but after waist circumference was adjusted in the model, the trend became nonsignificant ($P=0.79$).

Estimates of population attributable risk for endometrial cancer associated with excess body weight in Asian studies ranged from 17–19 % for two studies in China [16, 25] to 33 % for a study in Korea [26]. However, the upper BMI cut point for these studies varied, ≥23 kg/m^2 in the Korean study and ≥23 or ≥25 kg/m^2 in the Chinese studies. We are not aware of published data on the population attributable risk for endometrial cancer associated with excess body weight in Asian Americans.

Hormone Use: Menstrual and Reproductive Factors

Estrogen therapy for postmenopausal women is an established risk factor associated with an increased risk for endometrial cancer [27, 28]. Women with breast cancer are at increased risk of endometrial cancer, and the risk was tripled among women who had used tamoxifen for chemoprevention for breast cancer [27], because of tamoxifen's estrogenic effect on the endometrium. Other exogenous hormones, such as combined oral contraceptive use, have been associated with reduced risk of endometrial cancer by approximately 50 % [28, 29]. In the MEC, women who used combined oral contraceptives longer than 5 years had a 40 % reduced risk of endometrial cancer (RR = 0.60; 95 % CI: 0.39, 0.91) compared to women who never used oral contraceptives [9]. Early menarche and late menopause are additional known risk factors for endometrial cancer [27, 28]. In the MEC, an inverse association between increasing age at menarche and risk of endometrial cancer was observed but this was not statistically significant ($P=0.24$) after adjustment for other risk factors. Among postmenopausal women, later age at natural menopause was significantly associated with increased endometrial cancer risk (p trend = 0.002). The RR comparing to age at natural menopause ≤44 years was 1.67 and 1.79 for those with age at menopause of 50–54 and ≥55 years, respectively [9].

Nulliparity is associated with a two- to threefold increased endometrial cancer risk [28], and it is believed to be related to infertility which is due to anovulation and progesterone deficiency. Risk of endometrial cancer decreases with increasing number of children. In the MEC, compared to nulliparous women, those with 3–4 children and ≥5 children had significantly lower risk of developing endometrial cancer (respective RR was 0.72 and 0.68) [9]. In a large pooled analysis of 17 epidemiologic studies, late age at last birth was associated with reduced endometrial cancer risk [30]; the risk reduction was observed among Asian women in the study (OR per 5 years increase in age at last birth = 0.92, 95 % CI: 0.84, 1.02; P trend = 0.09), albeit to a lesser extent compared to the risk reduction in white women (OR = 0.87, 95 % CI: 0.84, 0.89; P trend <0.0001). Most studies have found that there is no significant association between age at first birth and risk of endometrial cancer. No pooled analysis data on risk of endometrial cancer and age at menarche or age at menopause in Asian women are currently available.

Diabetes

Results from recent meta-analysis of 23 studies showed a 1.6–1.9-fold higher risk of endometrial cancer in diabetic versus nondiabetic women [31]. Studies from Taiwan showed that history of diabetes was associated with 40–70 % increased risk of endometrial cancer [32–34]. Diabetes has been associated with endometrial cancer independent of BMI [35]. This is particularly important for Asians because of the high prevalence of type 2 diabetes despite their relatively low body weight. Studies have been inconclusive with respect to the role of diabetic drugs, such as metformin, in lowering risk of endometrial cancer among diabetics. Studies in the USA and UK did not support a protective effect of metformin [36, 37]. A recent study in Taiwan, however, showed that the use of metformin in Chinese women with type 2 diabetes was associated with a reduced risk of endometrial cancer with a significant dose–response relationship [38].

Physical Activity

In a recent meta-analysis of 33 studies on physical activity and endometrial cancer risk [39], high physical activity was associated with reduced risk of endometrial cancer (RR = 0.80; 95 % CI: 0.75, 0.85). The inverse association was observed mainly among overweight and obese women (BMI ≥ 25 kg/m^2) (RR = 0.69; 95 % CI: 0.52, 0.91) and not among women with a BMI < 25 kg/m^2 (RR = 0.97; 95 % CI: 0.84, 1.13). When comparing studies that adjusted for BMI with studies that did not adjust for BMI, there was no difference in the summary risk estimates ($P = 0.39$). The majority of the studies included in this meta-analysis were conducted among Caucasians in Europe and the USA. The combined analysis using data from two case–control studies from China and one from Japan yielded a RR of 0.69 (95 % CI: 0.51, 0.93) comparing high to low physical activity. Plausible mechanisms linking increased physical activity to lowered endometrial cancer risk include decreased levels of sex steroids, insulin resistance, and chronic inflammation [39]. It is possible that physical activity is indirectly associated with endometrial cancer risk by lowering body weight.

Cigarette Smoking

The inverse association between cigarette smoking and endometrial cancer is well established, with a greater reduction in risk among current smokers than former smokers compared to never smokers. Some have speculated that cigarette smoking is related to endometrial cancer risk through relationships with other known risk factors such as by lowering body weight; however, a recent study showed that the

effect of smoking on endometrial cancer risk is not significantly modified by any endometrial cancer risk factor [40]. Suggested mechanism linking smoking with endometrial cancer risk is related to smoking's effect on estradiol production and metabolism [41].

Dietary Factors

The role of diet in endometrial cancer etiology is unclear. Most of the diet studies in the USA have been conducted in non-Asian populations. A few dietary factors have been associated with endometrial cancer including soy, coffee, and alcohol consumption, albeit with some inconsistencies across studies.

Soy intake is part of the traditional Asian diet. Soy foods are an almost exclusive dietary source of a class of phytoestrogens called isoflavones which are structurally similar to endogenous estrogens. It is particularly important for endometrial cancer because isoflavone possesses both estrogenic and antiestrogenic effects. A 2009 meta-analysis of 7 studies concluded that high soy intake was inversely associated with risk of endometrial cancer (RR = 0.70; 95 % CI: 0.57, 0.86) [42]. However, results from two prospective cohort studies published since 2009 are not in agreement. In the MEC that included Japanese Americans, higher soy intake was associated with a reduction of risk by about 30 % [43] In contrast, in a prospective cohort study in Japan, intake of soy food and isoflavones was not associated with risk of endometrial cancer [17]. Furthermore, a study from China suggested that body mass index may be a potential modifier of the soy–endometrial cancer association [44]. Specifically, the association differed by BMI category ($OR_{\text{highest vs. lowest quartile}} = 0.51$; 95 % CI: 0.31 to 0.84 for overweight and $OR_{\text{highest vs. lowest quartile}} = 0.79$; 95 % CI: 0.52 to 1.20 for non-overweight women) although the test for interaction was not statistically significant [44].

Alcohol intake has been associated with increased circulating concentrations of estrogen, and it can further increase estrogen levels among postmenopausal women who are taking estrogen replacement therapy [45, 46]; therefore, it is plausible that women who consume alcoholic beverages are at increased risk of endometrial cancer. In a meta-analysis of alcohol and endometrial cancer risk [47], there was no overall association between alcohol drinking and risk in cohort studies (RR combined = 1.04; 95 % CI: 0.91, 1.18) and case–control studies (OR combined = 0.89; 95 % CI: 0.76, 1.05). However, in analysis by type of alcoholic beverages, an increased risk associated with hard liquor (RR combined = 1.22; 95 % CI: 1.03, 1.45) was suggested.

Coffee is one of the most widely consumed beverages in the world. It contains various phytochemicals having potential antioxidant and antimutagenic properties [48]. Recent data show increasing coffee consumption is associated with reduced endometrial cancer risk [49–51]. Three Japanese studies showed a 20–30 % reduction in risk per additional cup of coffee per day [52–54]. The association of coffee with endometrial cancer risk is independent of BMI and diabetes. Tea consumption, primarily green tea, was not associated with endometrial cancer risk in studies conducted in Japan and China [49].

Family History and Genetic Susceptibility

Women with a first-degree family history of endometrial cancer had approximately a twofold increased risk of endometrial cancer compared to those without a family history [55]. Women with a first-degree relative with colorectal cancer had approximately a 17 % increased risk of endometrial cancer [55]. Twin studies have suggested that familial aggregation of endometrial cancer cases is more likely to be due to a combination of shared environmental factors than shared genetics [56]. Previous studies have also shown an increased risk of endometrial cancer associated with a family history of endometrial cancer in second (i.e., grandparents, aunts, uncles, nieces, nephews, half siblings) and third (i.e., first cousins, great grandparents) degree relatives indicating genetic causes [57–59]. None of these epidemiologic studies, however, were conducted in Asian-American women. The case–control study conducted in China found a positive association between family history of endometrial, breast, or colorectal cancer and endometrial cancer risk (OR = 2.24; 95 % CI: 1.54, 3.28) [16].

Women with hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome, a familial syndrome associated with germline mutation in DNA mismatch repair genes, have a higher lifetime risk of endometrial cancer (50–60 %) [60]. Other studies, however, have reported that a family history of endometrial cancer is associated with an increased risk of endometrial cancer in women from families without Lynch syndrome [59, 61, 62]. One study also has reported that a family history of early-onset colorectal cancer is associated with an increased risk of endometrial cancer [59]. These studies suggest the existence of inherited genetic defects other than mismatch repair gene mutations may predispose women to endometrial cancer. To date, genome-wide association studies (GWAS) have identified only one locus associated with endometrial cancer risk at the 17q21 (*HNF1B*) locus [63]. A follow-up fine mapping study of *HNF1B* identified additional variants associated with endometrial cancer risk which is likely to be mediated via altered gene expression [64]. A meta-analysis of existing GWAS is currently underway to identify additional loci for endometrial cancer; however, data on Asian populations are scarce.

Survivorship

The 5-year survival rates for endometrial cancer across all stages are 70 to 80 %, ranging from 90 % for patients with stage I cancer to 20 % for those with stage IV cancer. Differences in endometrial cancer survival between African-Americans and non-Hispanic whites are well documented, but there are currently limited data on survival in Asian-American populations. In a study conducted among women treated in the US Department of Defense system between 1988 and 1995, Asians/Pacific Islanders were found to have poorer survival compared to non-Hispanic whites [14]. Two SEER-based studies, however, showed that Asians diagnosed with endometrial cancer had a significantly improved overall survival compared to non-Hispanic whites [12, 13], with one study suggesting that this overall survival

advantage experienced by Asians may be attributable to their younger age at the time of diagnosis [12]. The SEER study conducted using 1988–2009 data also suggested that Asian immigrants had better overall and cancer-specific survival compared to US-born Asians [13]. It was suggested that in addition to younger age at diagnosis, Asian immigrants may be more likely to retain lifestyle practices (e.g., lower body weight, diets rich in soy) from their country of origin which may have favorable impact on cancer outcome.

Concluding Remarks

Based on the 2012 Census Bureau figures, Asian women are the fastest growing immigrant populations in the USA. We observed a trend toward an increase in endometrial cancer incidence among Asian women in the USA, particularly among those born in the USA. With increasing obesity, metabolic syndrome, and physical inactivity, the incidence of endometrial cancer is expected to increase further. Studies are warranted to examine the role of diet and other environmental exposures on the risk of the development of endometrial cancer in Asian women.

Financial Disclosure None

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Liver Cancer Among Asian Americans

Channa R. Jayasekera and Mindie H. Nguyen

Abstract Asian Americans represent a highly heterogeneous racial group in the USA, defined by the US Census as persons having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent. Currently accounting for 5.6 % of the US population, over two-thirds of the Asian American population is foreign born, and it has been the fastest-growing racial group with an average growth rate of 45.6 % between 2000 and 2010. The five largest Asian American subpopulations are those of Chinese (28 %), Filipino (19.7 %), Indian (18.3 %), Vietnamese (10 %), and Korean (9.8 %) origin. Just under half of the Asian American population resides in the Western USA, followed by 21 % in the South, 20 % in the Northeast, and 11 % in the Midwest.

Primary liver cancer, which includes hepatocellular carcinoma and cholangiocarcinoma, is among the three cancers with rising incidence and is the fastest-growing cause of cancer-related death in the USA. Asian Americans represent one of the highest-risk groups for both incidence and mortality due to primary liver cancer in the USA. This chapter provides an overview of the epidemiology, clinical outcomes, and avenues for further research on primary liver cancer among Asian Americans.

Keywords Ethnicity • HCC • HBV • HCV • Epidemiology • Treatment

AASLD	American Association for the Study of Liver Diseases
AFP	Alpha-fetoprotein
BCLC	Barcelona Clinic Liver Cancer
CDC	Centers for Disease Control and Prevention
HBIG	Hepatitis B immune globulin
HBV	Hepatitis B virus

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HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
MELD	Model for end-stage liver disease
SEER	Surveillance, Epidemiology, and End Results
TACE	Trans-arterial chemoemobolization
TARE	Trans-arterial radioembolization
UCSF	University of California, San Francisco
USPSTF	United States Preventive Services Task Force

Epidemiology

Primary liver cancer, over 85 % of which is hepatocellular carcinoma (HCC) with the remainder due to cholangiocarcinoma and rarer cancers such as hepatoblastoma, is the seventh leading contributor to cancer burden in the USA [1]. This chapter will focus primarily on HCC among Asian Americans.

Hepatocellular Carcinoma Incidence

HCC is one of the three cancers with rising incidence in the USA, where it is also the fastest-growing cause of cancer-related death over the past two decades [2, 3]. Data collected by the Surveillance, Epidemiology, and End Results Program (SEER) and other national registries show that Asian Americans have the highest age-adjusted incidence of HCC compared to other groups in the USA [2, 4]. The age-adjusted incidence of HCC (per 100,000 persons) during 2006–2010 for Asian American men and women combined stands at 11.7 compared to 9.5 in Hispanics, 7.5 in African Americans, and 4.2 in non-Hispanic whites [2] (Fig. 1). In analyses stratified

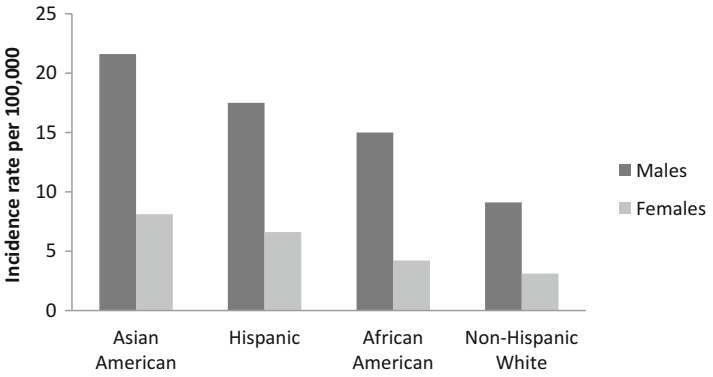

Fig. 1 Age-adjusted incidence of hepatocellular carcinoma (per 100,000) by race and gender [1]

by age groups, Asian Americans have the highest HCC incidence in the 35–49 age group and over 65 age group (4.7 and 54.7 per 100,000 persons, respectively). The incidence of HCC in the 50–64 age group (23.5 per 100,000 people) is slightly lower than that of Hispanics (24.3) and African Americans (26.9) [2]. While HCC incidence rates in the general US population increased during the 2000–2010 period, the rate of rise is decreasing (5.4 % per year during 2000–2007 and 2.3 % per year during 2007–2010). Among Asian American men and women, the annual incidence of HCC appears to have plateaued during the 2000–2010 period [2].

The incidence of liver cancer in Asian Americans is notable for significant within-group disparities. Data (2004–2008) from SEER registries showed that age-adjusted incidence of liver cancer was the leading cancer in Kampuchean (Cambodian) men (52.7 per 100,000) and second leading cancer among Laotian (64.5 per 100,000) and Vietnamese men (58.5 per 100,000), while it is not among the top five leading cancer sites in Asian Indian/Pakistani or Japanese men [5]. This large range in liver cancer incidence among Asian American ethnic groups is corroborated by data from the statewide California Cancer Registry (Table 1). This registry notes a nearly sevenfold difference in liver cancer incidence among the different Asian ethnic subgroups, highest in Vietnamese men (57.0) and lowest among Asian Indian/Pakistani men (7.9). Patterns are also comparable between Asian-American men and women (Table 1). While there is an apparent plateauing in HCC incidence in the general Asian American population in the 2000s, the trends of Asian American subpopulations over the 1990–2008 period demonstrate a mixed picture with declines in some populations and increases in others (Fig. 2) [2, 5].

Figure 1 also demonstrates the markedly higher incidence of liver cancer in men than in women; Asian American men have an age-adjusted incidence of 21.2 per 100,000, compared to 8.0 per 100,000 in Asian American women. This male to female ratio of approximately 2.7:1 in Asian Americans is comparable to that observed in non-Hispanic whites (3.0:1), African Americans (3.6:1), American Indian/Alaska Natives (2.2:1), and Hispanic/Latinos (2.8:1) [1]. Stage at diagnosis, an important predictor of outcome, appears to be comparable between racial groups in the USA [4]. In a study based on the large National Cancer Database, the distribution by pathologic stage among Asian American HCC patients (37.9 % stage I, 29.8 % stage II, 24.9 % stage III, and 7.4 % stage IV) did not differ from that of African American and White patients with HCC [6].

Table 1 Age-adjusted incidence of hepatocellular carcinoma (per 100,000) in California, 2004–2008 (Personal communication, Gomez)

	Males	Females
White non-Hispanic	8.2	7.0
Asian Indian/Pakistani	7.9	4.3
Chinese	23.8	7.9
Filipino	16.5	5.2
Japanese	11.0	9.0
Korean	29.1	10.8
Laotian	41.1	–
Vietnamese	57.0	19.5

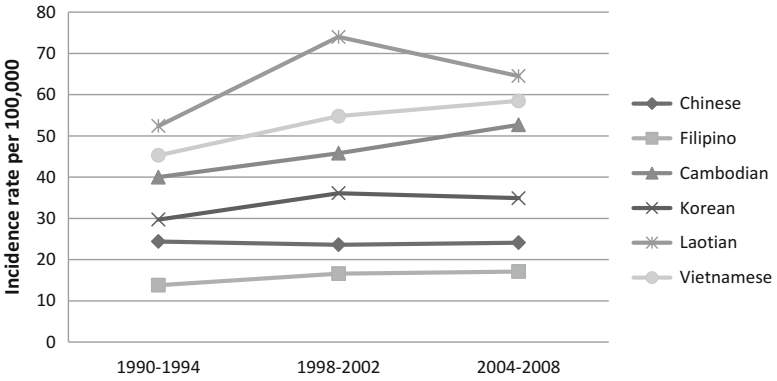

Fig. 2 Trends in age-adjusted incidence (per 100,000) of hepatocellular carcinoma by Asian American subpopulation men [5]

Hepatocellular Carcinoma-Related Mortality

Trends in liver cancer mortality follow those in incidence, attesting to the dismal outcomes seen with this malignancy. Five-year survival among patients with liver cancer remains relatively unchanged over the past decade, at approximately 17 % [7, 8]. Outcomes of HCC are highly dependent on stage of disease at diagnosis. Five-year survival rates are 30 % for patients with localized disease, 11 % for those with regionally advanced disease, and 3 % for those with distant metastatic disease [8]. The cumulative survival can be much higher for patients who receive optimal treatment. For example, based on SEER registry data, patients who met criteria for and underwent partial hepatectomy or liver transplantation had 5-year survival rates of 65 % and 77 %, respectively [9]. Other potentially curative, local tissue destruction therapies such as radiofrequency ablation have demonstrated 5-year survival rates over 50 % [10]. These comparatively high survival rates demonstrate that earlier detection and better access to appropriate care may dramatically improve liver cancer survival.

Asian Americans, owing to their higher incidence of disease, have the highest liver cancer mortality rates compared to other race/ethnic groups in the USA. Mortality rates in men (14.5 per 100,000) and women (6.1 per 100,000) are more than double the mortality rates in non-Hispanic white men (7.3 per 100,000) and women (3.0 per 100,000) (Fig. 3) [8].

Between 2000 and 2010, overall liver cancer mortality increased by 2.1 % per year in the USA; the steepest rise was observed in the 50–64 age group (5.6 % per year). Asian Americans showed an overall decline in liver cancer mortality during this time period (−1.6 % per year). The declining trend in liver cancer mortality in Asian Americans was seen in all age groups, but the magnitude of decline differed

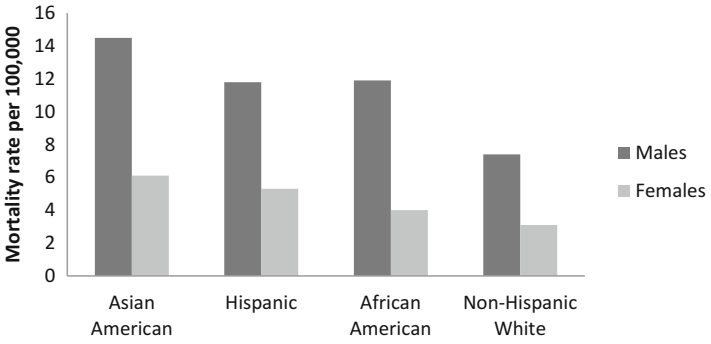

Fig. 3 Hepatocellular carcinoma-related mortality rate (per 100,000) by race and gender [1]

by age; it was steepest in the 35–49 age group (−4.3 % per year), intermediate in the 50–64 age group (−2.4 % per year), and weakest in the 65+ age group (−0.8 % per year) [2]. The increase in HCC mortality for the overall US population may be a reflection of the aging hepatitis C virus birth cohort which is not a major component of the Asian-American population at risk for HCC. Multivariate survival analysis of HCC patients with localized stage cancer, in fact, shows that Asian Americans have higher 5-year survival rates (hazard ratio 0.66) compared to non-Hispanic whites and African Americans [9].

Significant within-group mortality disparities also exist among the specific Asian American subgroups. Results from SEER between 1998 and 2002 showed that liver cancer mortality rates (per 100,000) in men were highest among Vietnamese (33.8), intermediate in Korean (26.3) and Chinese (20.3), and substantially lower in Asian Indian (5.3) and Japanese men [11]. In an analysis of 6028 Californians of Asian ancestry with HCC diagnosed in 1988 to 2007, survival outcome was found to differ among the nine Asian American ethnic groups. The cause-specific mortality risks were higher among Laotian/Hmong (adjusted HR = 1.51, 95 % CI 1.28–1.79) and Kampuchean (Cambodians) (HR = 1.24, 95 CI 1.02–1.48) than the other Asian American ethnic groups (adjusted HRs were less than 1.0) [12]. These disparities are likely reflections of poorer access to care, and thereby higher rates of delayed diagnosis and ineligibility for potentially curative therapies, among Laotian and Kampuchean (Cambodian) patients compared to other Asian American subpopulations.

Risk Factors for Hepatocellular Carcinoma

The risk factors for HCC include cirrhosis of any etiology—including alcoholic cirrhosis, chronic hepatitis B and C, nonalcoholic steatohepatitis, autoimmune liver diseases, and metabolic liver diseases such as alpha-1 antitrypsin deficiency,

hereditary hemochromatosis, and Wilson's disease—as well as chronic hepatitis B without cirrhosis. Cirrhosis is believed to underlie approximately 80 % of cases of HCC in the general population [7, 13].

Hepatitis B and C

A viral etiology—either hepatitis B or C virus—is believed to underlie the approximately 90 % of HCC in Asian Americans, as opposed to approximately 65 % of non-Asian Americans [14]. The relative contributions of chronic hepatitis B and C differ considerably by racial groups with chronic hepatitis B accounting for approximately 50 % of cases in Asian Americans, 16 % in African Americans, and 6 % in non-Hispanic whites and chronic hepatitis C accounting for approximately 50 % in non-Hispanic whites and African Americans and 30 % in Asian Americans [15]. Similarly, data from the United Network for Organ Sharing (UNOS) indicate that among Asian Americans who underwent liver transplantation for HCC, 50 % had underlying chronic hepatitis B, compared with 14 % of African Americans, 7 % of non-Hispanic whites, and 4 % of Hispanic/Latinos [16].

In addition to hepatitis B virus, the importance of hepatitis C virus in the development of HCC in Asian Americans has also been well borne out. In a retrospective analysis of over 500 Asian Americans with HCC in California, Lin et al. demonstrated that chronic hepatitis B was the underlying etiology of 78 % of HCC among Chinese patients, 61 % of Korean patients, and 47 % of Southeast Asian-origin patients (Vietnamese, Filipino, Indonesian, Kampuchean (Cambodians), Malaysian, Burmese, Laotian, Singaporean), but hepatitis C virus was also found to be a significant cause of HCC accounting for 38 % of HCC in Southeast Asians, 28 % in Koreans, and 14 % in HCC among Chinese [17]. In addition, in the aforementioned UNOS analysis, 39 % of Asian Americans undergoing liver transplantation for HCC in the USA also had underlying hepatitis C virus infection [16]. Thus, both hepatitis B and hepatitis C virus are important etiologic entities in certain Asian-American subpopulations.

In individuals with chronic hepatitis C, HCC almost always occurs in the presence of advanced fibrosis or cirrhosis. While hepatitis B virus is an independent risk factor for HCC irrespective of the presence of cirrhosis, the majority of cases of HCC in hepatitis B virus-infected persons also tend to occur in the presence of cirrhosis [18]. For instance, among Asian Americans where the dominant risk factor for HCC is chronic hepatitis B, the prevalence of underlying cirrhosis appears to be in the 50–80 % range, suggesting that cirrhosis and hepatitis B virus have a synergistic influence in the development of HCC [17, 19, 20]. Other risk factors that independently accelerate the development of HCC in hepatitis B-infected patients include elevated serum alanine aminotransferases, advanced age, male gender, concurrent alcohol intake, family history, and, importantly, hepatitis B viral DNA levels. For example, individuals with hepatitis B DNA levels greater than 10^6 copies/mL have a sixfold risk of developing HCC compared with those who have undetectable, medically suppressed hepatitis B DNA levels [21]. Additional consideration

with regard to both hepatitis B and C virus in Asian Americans is the chronicity of infection—wherein Asian Americans are more likely to have acquired these infections early on in life, and the longer duration of infection is believed to elevate the risk of HCC [3, 22]. In addition to HCC, recent evidence suggests that hepatitis B and C virus are also risk factors for intrahepatic cholangiocarcinoma and mixed hepatocellular carcinoma [23].

The high prevalence of these chronic viral hepatitides as the dominant drivers of HCC in Asian Americans highlights the importance of vaccination against hepatitis B, screening for chronic hepatitis B and C, appropriate treatment of chronic hepatitis B and C, and appropriate surveillance for liver cancer in patients with cirrhosis or chronic hepatitis B in this population [24]. These aspects will be discussed further in the prevention subsection of this chapter.

Non-viral Etiologies

While non-viral etiologies account for a smaller share of liver cancer among Asian Americans, several lines of evidence suggest that nonalcoholic fatty liver disease—a condition strongly associated with metabolic syndrome (coexistence of at least three of the following: central obesity, hypertension, impaired fasting glucose or diabetes, hypertriglyceridemia, or low levels of high-density lipoprotein)—may play an increasingly important role in this population. For instance, while Asian Americans have a lower average body mass index compared to other racial groups in the USA, the prevalence of metabolic syndrome has been recently found to be unexpectedly higher than their non-Hispanic white counterparts in a large cohort of over 40,000 patients in California [25, 26]. Nonalcoholic fatty liver disease also has been found to account for a considerable proportion of chronic liver disease in several Asian countries, although robust data regarding the prevalence of nonalcoholic fatty liver disease among Asian populations in the USA are lacking [27, 28]. Finally, whether nonalcoholic fatty liver disease progresses to liver cancer at the same rate in Asian Americans as in other racial groups is also uncertain at this time.

Treatment

Treatment Modalities and Outcomes

Treatment of HCC is broadly categorized in modalities that aim to cure and those that aim to palliate. The most robust criteria, and that which is recommended by the American Association for the Study of Liver Disease for treatment decision-making in HCC, is the Barcelona Clinic Liver Cancer (BCLC) classification (Fig. 4) [29–31]. The BCLC classification considers the extent of disease on computed tomography or magnetic resonance imaging (number of tumors present within and outside

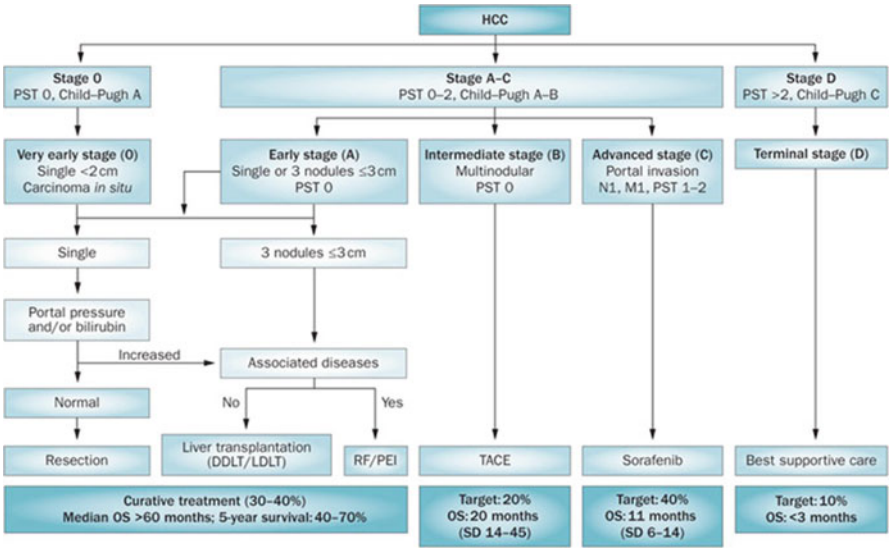

Fig. 4 The Barcelona Clinic Liver Cancer (BCLC) classification (Image copyright of: [29])

the liver, the size of the intrahepatic tumors), the severity of underlying liver disease, and the patient performance status as guides to therapy. Stages 0 (very early) and A (early) portend a relatively good prognosis where therapies with curative intent—liver transplantation, partial hepatectomy, radiofrequency ablation, or percutaneous ethanol injection—have been shown to provide clinical benefit. Liver transplantation, when performed within criteria defined by Mazzaferro et al. (the Milan Criteria) or by Yao et al. (the UCSF Criteria), has demonstrated the best 5-year survival rates, ranging between 70 and 80 % [32, 33]. Partial hepatectomy for resection of solitary lesions less than 2 cm in diameter provides approximately a 60 % 5-year survival although with a substantially higher rate of HCC recurrence [34]. Local tumor destructive therapies such as radiofrequency ablation—also considered potentially curative—have achieved 5-year survival rates over 50 % [11]. However, less than 25 % of patients in the USA are diagnosed at stages 0 and A, and the overall 5-year survival of patients in the USA is consequently close to 17 % [2, 7, 8, 33]. With adjunctive treatment modalities such as trans-arterial chemoembolization (TACE) and trans-arterial radioembolization (TARE), some patients who present beyond stage A may be "down-staged" in order to be within eligibility criteria for curative-intent therapies, and this strategy is successful in approximately 40–50 % of patients [36–38].

Disparities exist in the age at diagnosis, treatment modalities employed, and clinical outcomes between Asian Americans and other major ethnic groups and between the different Asian-American subpopulations. In large retrospective cohorts, Asian Americans excluding Pacific Islanders were shown to present at later

age, but with lower rates of liver decompensation, comparable BCLC stages, and equal likelihood of meeting Milan or UCSF criteria, compared to non-Asian Americans [14, 39]. Despite these apparently favorable presenting characteristics and despite lower rates of tobacco and alcohol use and lower body mass index—factors that may influence better treatment outcomes—Asian Americans meeting Milan or UCSF criteria for liver transplantation were more likely to not receive liver transplantation or to be declined for transplant listing due to comorbidities, nonadherence, and psychosocial issues [39–41]. Based on the large National Cancer Database of the American College of Surgeons and other smaller cohorts, Asian Americans, however, appear to have an equal or higher likelihood of receiving partial hepatectomy or local tumor destructive therapies [6, 10, 39]. Data on within-group treatment disparities in the Asian-American community are limited, but preliminary analyses from California appear to show lower rates of receiving any therapy with curative intent in Vietnamese and Filipino patients who met Milan criteria, compared to patients of Chinese origin [42].

Despite the lower likelihood of receiving curative-intent therapy, 5-year survival rates among Asian Americans with HCC, on the whole, appear to exceed those of their white and African American counterparts. Devaki et al., using SEER registry data, demonstrated that among patients with localized HCC who received any therapy or no therapy, Asian Americans had a cumulative 5-year survival rate of 53 %, compared with 42 % in whites and 29 % in African Americans. Moreover, 5-year survival rates after receipt of these curative therapies did not differ between Chinese, Korean, Vietnamese, and Japanese patients included in this analysis [43].

Public Health Challenges and Prevention

Asian Americans with HCC, as a group, are unique in that approximately 90 % of the burden of disease stems from chronic hepatitis B and C—infections that can be readily screened and treated. Furthermore, at-risk individuals can be readily vaccinated against in the case of hepatitis B as means of preventing the development of HCC. Moreover, in patients with chronic hepatitis B or C and/or cirrhosis, the justification of routine screening for HCC meets the tenets set by the World Health Organization (Wilson and Jungner Criteria) that the burden of disease is significant, early disease is insidious and thereby requires formal testing, the natural history of disease is well understood such that patients can be risk-stratified and treated systematically, there are effective treatments available, and screening is likely cost-effective [44, 45]. In this context, while screening guidelines for both viral hepatitis and HCC have been developed, a key factor in the rates of delayed diagnosis of viral infection and poor adherence to HCC surveillance as well as nonreceipt of timely or appropriate therapy for viral hepatitis and HCC among Asian Americans may be inherently poorer healthcare access and cultural differences in health beliefs. These will be discussed further in this section.

Vaccination Against Infection with Hepatitis B Virus

The hepatitis B virus vaccination series has been available since 1982 and is included in the Centers for Disease Control and Prevention's (CDC) standard vaccination guidelines in the USA. It is also increasingly being implemented as mandatory by vaccination programs globally. The vaccination schedule includes three doses of the monovalent hepatitis B virus vaccine given at birth, at 1–2 months of age, and at 6–18 months of age. In addition, children of mothers with chronic hepatitis B should be administered the hepatitis B immune globulin (HBIG) within 12 h of birth. The combination of the vaccination series and birth dose of HBIG prevents approximately 95 % of hepatitis B virus transmission from infected mothers to their newborns [46]. While it is believed that concerted, community-based, multilingual efforts to engage higher-risk groups such as recent Asian immigrants have contributed substantially to expanding hepatitis B virus vaccination over the past 20 years, millions of at-risk individuals in the USA remain unvaccinated [47, 48].

Screening for Hepatitis B Virus

Chronic hepatitis B portends an annual cumulative risk of approximately 0.5 % of developing HCC in the absence of cirrhosis and between 3 and 10 % in the setting of cirrhosis [15]. Given that most cases of chronic hepatitis B in Asian Americans are contracted at birth or in early childhood, the American Association for the Study of Liver Diseases (AASLD) currently recommends a one-time hepatitis B virus serologic screen in Asian-American males over 40 years and Asian-American females over 50 years [49]. The CDC has adopted a broader definition of those at risk, recommending testing all persons born in regions of high and intermediate hepatitis B endemicity and those who were born in the USA to parents born in those regions [50]. Most recently, in early 2014, the US Preventive Services Task Force (USPSTF) also initiated recommendation for hepatitis B virus screening in foreign-born individuals from regions with hepatitis B virus prevalence of 2 % or higher [51]. While there has been considerable focus on this issue with nationwide efforts such as the Department of Health and Human Services' National Viral Hepatitis Action Plan, it is believed that the majority of hepatitis B-infected Asian Americans remain undiagnosed [47]. For instance, in a study of over 3100 Asian Americans screened for hepatitis B in California, 65 % of those found to have chronic infection were unaware of their status [52].

Screening for Hepatitis C Virus

The annual cumulative risk of HCC in patients with chronic hepatitis C without cirrhosis or advanced fibrosis is considered to be very low but is 3–5 % per year in the setting of cirrhosis [53, 54]. Despite the considerable hepatitis C burden in

some subgroups of Asian Americans, much of which is likely contracted in early childhood via iatrogenic exposure, there are no specific, dedicated screening guidelines for the Asian American population. Instead, the AASLD, CDC, and USPSTF recommend a one-time hepatitis C screen in individuals born between 1945 and 1965 (the "baby boomer" birth cohort) and in patients with specific risk factors such as drug abuse, hemodialysis, etc. [55–57]. The specific risk factors for hepatitis C virus infection in Asian Americans are poorly understood, but it is well documented that immigrants from countries with high or intermediate endemicity—which includes much of Asia—have high rates of chronic hepatitis C and that iatrogenic exposure during routine dental and medical practices is the most likely transmission route. Given that infection with hepatitis C virus is likely underdiagnosed among first-generation Asian immigrants, screening for hepatitis C virus in these individuals—particularly those originating in countries with hepatitis C virus endemicity—may be one strategy to improve case detection in this higher-risk group [58, 59].

Antiviral Therapy for Chronic Hepatitis B and C

A proportion of individuals with chronic hepatitis B would require initiation of long-term (likely lifelong) antiviral therapy depending on serum alanine aminotransferase levels, serum hepatitis B HBV DNA levels, the degree of liver inflammation and fibrosis, and the presence of cirrhosis or HCC. The strongest evidentiary support for hepatitis B viral suppression as a means of preventing HCC comes from a randomized trial of lamivudine versus placebo in patients ($N=651$) with high hepatitis B virus DNA levels and advanced fibrosis or cirrhosis (stage 3–4). This trial was terminated early at 32 months of median follow-up due to the rate of HCC among treated patients being 3.9 % versus 7.4 % in the placebo arm [60]. Entecavir and tenofovir as long-term oral therapies have demonstrated superior efficacy, resistance, safety, and tolerability profiles compared with lamivudine, adefovir, telbivudine, and injectable interferon, and there have been cohort studies suggesting benefits with reduced HCC incidence in treated patients, especially those with cirrhosis [61–64]. However, studies in the USA comprising mostly of Asian Americans have suggested that there is significant under-evaluation and undertreatment of patients who have been diagnosed with infection with hepatitis B virus [65–69].

Hepatitis C treatment has seen dramatic changes in recent years. In comparison to onerous regimens of injectable interferon with oral ribavirin for 6–12 months, chronic hepatitis C can now be treated with remarkably high efficacy (virologic cure often exceeding 90 %), safety, and tolerability with 3–6-month courses of all oral regimens with direct-acting antivirals in most patients [70]. Although pan-genotypic regimens are likely to be approved before 2017, hepatitis C treatment currently remains tailored by genotype—a factor that must be considered in Asian American patients who predominantly carry genotypes 1, 3, and 6, which are endemic in their countries of origin [71].

HCC Surveillance

Among patients with risk factors for HCC, the benefit of HCC surveillance has been demonstrated mostly by observational studies and one randomized trial in Chinese patients with chronic hepatitis B. This randomized trial utilized biannual liver ultrasonography and alpha-fetoprotein (AFP) versus no screening in 18,816 patients aged 35–59 in Shanghai, China, where biannual screening was found to detect far more subclinical HCC (52 vs. 0) and reduce HCC mortality by 37 % [69]. Subsequent analyses have demonstrated insufficient sensitivity and specificity of AFP for diagnosis of HCC, and therefore, the AASLD currently recommends biannual imaging with liver ultrasonography as the sole surveillance modality [72]. However, the sensitivity of liver ultrasonography alone is poor, and most other practice guidelines recommend the combination of both liver ultrasonography and serum AFP biannually for HCC surveillance. This combination approach appears to be more widely preferred in the USA [45, 73]. Rates of surveillance with ultrasonography by community medical practitioners however have been exceptionally low, with a meta-analysis by Singal et al. revealing that only 18.4 % of patients with clear HCC risk factors underwent appropriate screening.

Based on SEER registry data, Asian Americans appear to have the highest—albeit still grossly below target—rate of HCC diagnosed via screening (28.1 %) compared with Hispanic (16.8 %), white (14.9 %), and African American (12.2 %) patients [74]. Adherence to HCC screening in a cohort of 1333 patients with chronic hepatitis B was found to be even poorer in patients without cirrhosis compared to those with cirrhosis, and consequently, in a cohort of approximately 500 hepatitis B virus-related HCC patients, most of whom were Asian Americans, patients without cirrhosis were more likely to present with symptoms and had poorer survival compared to those with cirrhosis [75, 76].

Conclusions

Individuals of Asian origin are the highest-risk ethnic group for HCC in the USA. Chronic hepatitis B and C remain the leading risk factors for HCC in this group, accounting for approximately 90 % of cases. Despite available screening and treatment guidelines, a large proportion of individuals with chronic hepatitis B and C remain undiagnosed and/or untreated. Screening for HCC in Asian Americans with risk factors (e.g., cirrhosis, chronic hepatitis B), while better than other groups, remains poor. Asian Americans appear to present at comparable HCC stages to other population groups but the least likely to receive liver transplantation, the treatment modality with the highest rates of recurrence-free survival. Nevertheless, possibly owing to higher rates of other curative-intent therapies such as partial hepatectomy and radiofrequency ablation and better performance status at presentation, Asian Americans demonstrate a higher than average 5-year overall survival rate.

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Gastric Cancer Among Asian Americans

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Abstract Gastric cancer is the third leading cause of cancer mortality worldwide. It remains the eighth most commonly diagnosed cancer among Asian American men and women in the United States (USA) with considerable heterogeneity in incidence rates across Asian American subgroups, highest in Korean American men. Because of the lack of routine screening for gastric cancer in the USA, patients are usually diagnosed at a late stage because of symptoms. While infection with *Helicobacter pylori* is the primary risk factor for gastric cancer, only a small proportion of those infected go on to develop gastric cancer, which means that better understanding of the interactions between *H. pylori* infection and other lifestyle factors (e.g., cigarette smoking, dietary factors) are needed to better characterize persons who eventually develop gastric cancer. Treatment benefits can vary by ethnicity and region of the world, possibly due to host-related factors. Continued efforts to improve treatment outcome by considering race/ethnicity, country of birth, and other parameters should be a priority.

Keywords Gastric cancer • Asian Americans • *Helicobacter pylori* • Smoking • Diet • Screening • Treatment

Introduction

Gastric cancer is generally categorized by anatomic subsite as either in the cardia of the stomach, including the gastroesophageal junction, or more distally (non-cardia), including the fundus, corpus, and antrum. Although cardia and non-cardia gastric cancers appear to have different etiologies, and the incidence of cardia cancers may

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have increased (or did not decline) in recent years, non-cardia cancers still constitute the majority (estimated at 80–90 %) of gastric cancers worldwide [1]. Gastric cancers include a collection of histologies including adenocarcinoma, lymphoma, and gastrointestinal stromal tumors. Adenocarcinomas, cancers arising from the epithelium of the stomach, comprise about 90–95 % of the cases [2, 3]. This chapter is focused on gastric adenocarcinoma, herein called gastric cancer, and includes both cardia and non-cardia gastric cancers. Although many studies did not distinguish between gastric cardia vs. non-cardia gastric cancers, the differences between gastric cardia versus non-cardia will be mentioned if the data are available.

Incidence and Mortality Trends

Incidence Patterns

The incidence of gastric cancer has declined dramatically over the last half of the twentieth century. However, it remains the fifth most commonly diagnosed cancer worldwide with over 951,000 new cases (6.8 % of the total incidence) and the third most common cause of cancer death with over 723,000 deaths (8.8 % of the total deaths) [4]. The incidence rate of gastric cancer has declined steadily since the 1950s in North America and Europe and more recently in East Asia and Latin America [4]. Gastric cancer rates vary worldwide, highest in East Asia including Korea, Japan, and China (age-adjusted incidence rates are 35.4 per 100,000 men, 13.8 per 100,000 women) and lowest in Western Africa (3.3 per 100,000 men and 2.6 per 100,000 women) and North America (5.5 per 100,000 men and 2.7 per 100,000 women) [4]. Migration studies show a consistent decline in gastric cancer incidence within two generations when individuals migrate from a high-risk country to a low-risk country, particularly among Asian migrants to the USA [5]. Gastric cancer incidence is about two times higher in men than in women across both high-risk and low-risk regions in the world [4].

An estimated 24,590 new gastric cancer cases and 10,720 gastric cancer deaths are expected in the USA in 2015 [6]. Rates of gastric cancer also vary by race/ethnicity and sex in the USA [6]. In 2008–2012, the age-adjusted incidence rates (per 100,000) were lowest for non-Hispanic white men (8.3) and women (3.7). Rates among Asian/Pacific Islander (API) men (14.5) and API women (8.8) are comparable to those in non-Hispanic black men (14.6) and women (8.4) as well as those in Hispanic men (14.2) and women (8.4) [7].

Gastric cancer incidence rates vary considerably among Asian ethnic groups living in the USA [8, 9]. Gastric cancer remains one of the five most commonly occurring malignancies among Chinese, Japanese, Korean, and Vietnamese men and among Japanese and Korean women in the USA [8]. SEER-based registry studies show that in the most recent study period (2004–2008), incidence (per 100,000) was highest among Korean American men (52.5); intermediate among Japanese (24.2), Vietnamese (21.2), and Chinese (16.3) men; and considerably lower in Laotian, Filipino, Kampuchean (Cambodian), and Asian Indian/Pakistani men (<10) [8].

A similar pattern was observed among Asian-American women; rates were highest in Korean-American women (27.4) which were 50–60 % higher than the rates in Japanese, Vietnamese, and Chinese American women [8]. During the past two decades (1990–2008), significant annual percent declines in gastric cancer incidence were observed among Chinese, Vietnamese, and Japanese men, ranging from −1.3 % per year to −3.2 % per year, and comparable declines were found among their female counterparts in the USA [8]. However, the decline in gastric cancer incidence is much less among Korean American men (−0.6 %) and women (0.3 %) during this same time period [8].

Mortality Patterns

Gastric cancer mortality follows a pattern similar to incidence rates. In the USA, mortality rates (per 100,000) are highest in non-Hispanic blacks (9.2 in men and 4.4 in women), followed by API (7.9 in men and 4.7 in women) and Hispanics (7.2 in men and 4.2 in women), and lowest in whites (3.6 in men and 1.8 in women) [7]. Data from the Los Angeles County Cancer Surveillance Program (CSP) for 1988 to 2006 ($n = 13{,}084$) showed that median survival was better in Asian (16.3 months) than whites (8.4 months) with gastric cancer ($P < 0.001$); the hazard ratio (HR) in Asians compared to whites was 0.76 (95 % CI 0.72–0.82) after adjusting for age, gender, tumor location, histology, grade, stage, and treatment [10]. The more favorable survival in Asian Americans was also found in a California Cancer Registry (CCR)-based study that included 47,647 patients diagnosed between 1988 and 2005. Compared to non-Hispanic whites, Asian Americans had lower adjusted HRs for localized (HR = 0.63, 95 % CI 0.55–0.71), regional (HR = 0.81, 95 % CI = 0.76–0.85), and distant/remote (HR = 0.92, 95 % CI 0.87–0.97) stage at diagnosis as well as for all stages combined (HR = 0.81, 95 % CI 0.78–0.83) [11]. A SEER-17 registry-based study of 49,058 gastric cancer patients diagnosed between 1998 and 2008 found that Asian Americans had significantly better overall survival for all stages and better disease-specific survival in stage I and II, but not stage III or IV when compared to whites [12]. Survival may also differ between different Asian American ethnicities. For example, in the Los Angeles County-CSP study of 1817 Asian Americans treated for gastric cancer between 1988–2006, median survival was longest among Koreans (22.4 months) but shortest among Filipinos (10.3 months) [13].

Pathology

Lauren classified gastric adenocarcinomas into intestinal and diffuse type. Intestinal-type tumors composed of moderately to well-differentiated gland-like structures, and diffuse-type tumors composed of solitary cells or small groups of cells

infiltrating normal gastric tissues, without formation of glands [14]. These two types have different morphological features, risk factors, clinical presentations, and outcomes. The differences stem from intrinsic biological differences between these two histologies [15]. The intestinal type resembles the adenocarcinomas arising in the intestinal tracts and is more frequently associated with *Helicobacter pylori* (*H. pylori*) infection, whereas diffuse-type cancers arise when there is a germ line or somatic mutations resulting in loss of expression of E-cadherin, an adhesion molecule that maintains the organization of the epithelial cells [16].

Lauren classification is not routinely used and reported in Western countries; therefore, it is difficult to ascertain differences in the incidence of these two types between Asian Americans and non-Hispanic whites. For example, in the CCR-SEER-based study mentioned above, 21.1 % of gastric cancers were classified as diffuse, 4.6 % as intestinal, but information was missing on 74.1 % [11]. In another SEER-based study that specifically recoded the histologic classification of gastric cancer into the intestinal and diffuse, the comparison was between whites, blacks, and other race groups combined, which included Asian Americans [17].

Risk Factors

There is a wealth of literature on gastric cancer risk factors but only a few of these studies were conducted among Asian Americans, and most of the work was led by Nomura and colleagues at the University of Hawaii. They conducted three cohort studies in Hawaii. The first was a cohort of 7990 Japanese men from the Hawaiian island of Oahu who were enrolled from 1965 to 1968, provided detailed information on diet and other lifestyle factors, and donated blood specimens, and some also participated in a physical examination [18]. The second cohort study enrolled 11,907 randomly selected Japanese residents of Hawaii (6297 women and 5610 men) who completed a short dietary questionnaire at enrollment between 1975–1980 [19]. The third cohort is the large Multiethnic Cohort (MEC), an ongoing population-based prospective study with >215,000 men and women; over 50,000 are Japanese men and women from Hawaii and California (mainly Los Angeles County) and were enrolled between 1993 and 1996 [20]. Several case–control studies that included Asians in the USA have also been conducted [21, 22]. In particular, a population-based case–control study was conducted among 300 gastric cancer cases and 446 control subjects in Hawaii in the 1990s; most of the participants (233 cases and 330 controls) were Japanese, Filipino, Korean, and Chinese Americans [21]. A subset of these participants (212 cases and 336 controls) provided blood specimens, representing one of the few studies in Asian Americans to investigate risk factors separately for those who were positive for *H. pylori*/CagA infection (160 cases, 164 controls) and negative for *H. pylori*/CagA (52 cases, 172 controls) infection [23].

Helicobacter pylori (H. pylori)

Since the discovery of *Helicobacter pylori* (*H. pylori*), a gram-negative microaerophilic spiral bacteria in 1979–1982 by Marshall and Warren [24, 25], the epidemiology of *H. pylori* has been extensively studied [26–30] culminating in its classification by the International Agency on Research in Cancer (IARC) in 1994 as a class I human carcinogen and a major cause of gastric cancer [31]. The evidence on *H. pylori* and gastric was confirmed in 2009 by a second IARC working group which more precisely quantified the association between *H. pylori* and non-cardia gastric cancer [32]. It is now known that *H. pylori* can colonize the gastric mucosa for years, and their presence is strongly associated with chronic, diffuse, and superficial gastritis of the fundus and antrum. *H. pylori* has an etiologic role in gastritis and may progress over several decades to chronic atrophic gastritis, an established precursor of gastric carcinoma [33].

One of the first prospective studies on *H. pylori* infection and risk of gastric cancer was conducted among 5908 Japanese-American men in Hawaii [34]. In this nested case–control study, 94 % of the 109 men with gastric cancer and 76 % of the 109 matched control men tested positive for *H. pylori* antibodies in pre-diagnostic blood samples that had been stored for more than 20 years (adjusted odds ratio (OR) 6.0, 95 % CI 2.1–17.3) [34]. This significant risk association was observed for non-cardia gastric cancer which represented 95 % of gastric cancers in this cohort of men [34]. A subsequent analysis investigated the association of distal gastric cancer with *H. pylori* and particularly the cytotoxin-associated gene A (CagA) type of *H. pylori* infection, which is present in 60 to 70 % of *H. pylori* strains and has been found to elicit a more marked inflammatory response [35]. This analysis of 261 Japanese American men with gastric cancer and an equal number of control men found an adjusted OR of 3.0 (95 % CI 1.8–5.0) for *H. pylori* and 1.9 (95 % CI 1.3–2.8) for colonization by a cagA+ *H. pylori* strain. Persons who were *H. pylori* and CagA positive had an OR of 4.1 (95 % CI 2.2–7.7) for intestinal gastric cancer compared with those who were seronegative for both *H. pylori* and CagA antibodies [36]. This study in Japanese-American men was included in an international pooled analysis of 12 studies which found an overall OR of 3.0 (95 % CI 2.3–3.8) for non-cardia gastric cancers and no association with gastric cardia cancers (OR = 1.0, 95 % CI 0.7–1.4). When the analysis was restricted to cases occurring at least 10 years after diagnosis of *H. pylori*, the OR for non-cardia gastric cancer increased to 5.93 (95 % CI 3.41–10.37) [37]. The attributable fraction for *H. pylori* infection in non-cardia gastric cancers is between 74.7 to 89.0 % [1, 38]. The declining incidence of gastric cancer has been attributed to the reduction of *H. pylori* infection in successive birth cohorts in Asian countries, which is presumably related to changing childhood environment, improved food preservation practices, and other factors [39, 40].

Although infection with *H. pylori* is an established risk factor for non-cardia gastric cancers, only a small proportion of those infected go on to develop gastric cancer, which means that better understanding of the interactions between host factors, environmental factors, and *H. pylori* infection is needed to better characterize persons who eventually develop this cancer.

Tobacco Smoking

There is convincing evidence that tobacco smoking moderately increases the risk of both cardia and non-cardia gastric cancers. Japanese-American men who were current smokers had a significant 2.7 (95 % CI 1.8–4.1) risk of gastric cancer compared with never smokers [18]. In the MEC, Japanese Americans who were current smokers had a higher risk of gastric cancer (RR = 1.75, 95 % CI 1.2–2.5); this magnitude of smoking effect was comparable across different racial/ethnic groups [41]. In the MEC as in other studies, the effect of smoking tended to be stronger in men than in the women. In a pooled analysis of 42 case–control and cohort studies [42], the risk of gastric cancer was 1.62 (95 % CI 1.50–1.75) among male current smokers and 1.20 (95 % CI 1.01–1.43) among female current smokers compared to never smokers. Smoking is associated with increased risk of both cardia (RR = 1.87, 95 % CI 1.31–2.67) and non-cardia (RR = 1.60, 95 % CI 1.41–1.80) gastric cancer [42]. The smoking-gastric cancer association was similar in studies conducted in Asia (RR = 1.57, 95 % CI 1.47–1.68), Europe (RR = 1.72, 95 % CI 1.13–2.61), and the USA (RR = 1.84, 95 % CI 1.25–2.70) [42].

The extent to which infection with *H. pylori* modifies the smoking-gastric cancer association has been studied in only a few studies. In a cross-sectional study of whites and nonwhites using NHANES data, the prevalence of H. *pylori* infection was higher in current smokers (prevalence OR = 1.9 (95 % CI 1.4–2.5) and former smokers (prevalence OR = 1.3 (95 % CI 1.0–1.7) compared with never smokers [43]. In a case–control study conducted in Hawaii which included mostly Asian Americans, the increased risk of gastric cancer among smokers was statistically significant among those who were *H. pylori* and/or CagA+ positive ($p = 0.0004$) but not among those who were *H. pylori* and/or CagA+ negative ($p = 0.21$) [23]. These observations are supportive of the suggestion of increased inflammatory reaction to *H. pylori* infection among smokers [44] and that smokers are more likely to have persistent *H. pylori* infection due to adverse effects of smoking on the immune system [45]. The combined deleterious effects of tobacco smoking and *H. pylori* infection may be particularly important for some Asian-American subgroups such as Korean Americans who are at high risk for both risk factors. In combination with a high *H. pylori* infection rate, the current smoking prevalence among Korean-American men and women is about two to three times higher than other Asian Americans [46], which may explain, in part, the slower decline and persistently higher rates of gastric cancer among Korean men and women in the USA [8].

Alcohol

Alcohol intake appears to be unrelated to risk of cardia gastric cancer but may be positively associated with risk of non-cardia gastric cancer, particularly among heavy alcohol consumers. In the cohort study of Japanese-American men in Hawaii, risk of gastric cancer was not significantly increased among alcohol drinkers

(RR = 1.1) after adjusting for age and smoking history [18]. Risk was unrelated to increasing amount of alcohol intake from all sources or specifically from beer, wine, or hard liquor [18]. In a case–control study of mostly Asians in Hawaii, alcohol use was also not associated with gastric cancer risk [21], irrespective of *H. pylori*/CagA+ status [23].

The null findings in Asian Americans are compatible with the overall evidence from meta-analyses of case–control and cohort studies [47–49]. However, a weak positive association cannot be ruled out for non-cardia gastric cancer and for heavy alcohol drinking. For example, in the meta-analysis conducted by Tramacere et al. [48], the overall RR based on 44 case–control and 15 cohort studies was 1.07 (95 % CI = 1.01–1.13); a positive association was found for non-cardia (RR = 1.07, 95 % CI = 0.91–1.26) but not for cardia (RR = 0.94, 95 % CI = 0.78–1.13) gastric cancers. In the subset of 13 studies on heavy alcohol drinking (four or more drinks per day), the overall RR was 1.20 (95 % CI 1.01–1.44) which was stronger for non-cardia (RR = 1.17, 95 % CI 0.78–1.75) than for cardia (RR = 0.99, 95 % CI 0.67–1.47) gastric cancers. A possible effect of heavy alcohol intake among never smokers was evident in a population-based cohort of older men in Shanghai, China [50]. It will be informative in future meta-analysis to pool the results of studies that allow investigation of the effect of alcohol in the presence and absence of smoking. Nitrosamines present in alcoholic beverages [51], acetaldehyde, a metabolic intermediate of ethanol and an animal carcinogen [52], and alcohol intake may enhance the deleterious effects of tobacco carcinogens. Alcohol may also influence the pathogenesis of gastric cancer development by enhancing the penetration of tobacco carcinogens [51].

Dietary Factors

Many studies have investigated the role of diet and risk of gastric cancer. In general, the associations with specific dietary factors were stronger in case–control studies than in cohort studies. Depending on the specific dietary factor of interest, the associations were generally more evident for non-cardia gastric cancer.

Total Meat and Processed Meat

The intake of red meat is a potential risk factor for gastric cancer, for both cardia and non-cardia gastric cancer, but the positive findings were based primarily on case–control studies. In a meta-analysis conducted by Zhu et al. [53], the risk of gastric cancer was increased in association with high intake of red meat (RR = 1.45, 95 % CI 1.22–1.73), for both cardia (RR = 1.26, 95 % CI 1.05–1.52) and non-cardia (RR = 1.26, 95 % CI 0.92–1.71) gastric cancer. The RR was 1.56 (95 % CI 0.93–2.63) for studies conducted in Asia and 1.52 (95 % CI 1.16–2.00) in European populations. However, there was no significant association with red meat intake in the four cohort studies (RR = 1.02, 95 % CI 0.90–1.17). In contrast, in the same

meta-analysis, the risk of gastric cancer was increased in association with intake of processed meat (RR = 1.45, 95 % CI 1.26–1.65); this was also observed in the cohort studies (RR = 1.18, 95 % CI 1.00–1.38). The processed meat association appeared to be observed for non-cardia gastric cancer (RR = 1.27, 95 % CI 1.07–1.52) but not for cardia cancer (RR = 0.95, 0.76–1.19). The risk association appeared to be similar for studies conducted in Asian and Western populations; the respective RRs were 1.58 (95 % CI 1.06–2.37) and 1.50 (95 % CI 1.18–1.91) [53].

In the case–control study of gastric cancer among Asian and non-Asian residents in Hawaii, gastric cancer in men was increased significantly by twofold among those with high intake of processed meat and bacon, but this was not observed in women [21]. In a subset of participants with information on *H. pylori*/CagA status [23], high intake of processed meat and bacon was associated with significant increase risks among those who were *H. pylori* CagA positive (ORs for low, medium, and high intake of bacon were 1.0, 0.8, 1.7, *P* trend = 0.02). Although results were similar among those who were *H. pylori*/CagA negative, the finding was weaker (respective ORs were 1.0, 0.9, and 1.4, *P* trend = 0.26), which may be related to the modest sample size. The increased risk associated with red and processed meat intake and gastric cancer may involve heme iron, more abundant in red meat than white meat [54], and may contribute to endogenous formation of carcinogenic N-nitroso compounds which have been linked to gastric cancer [55]. N-nitroso compounds are also formed in processed meat containing high amount of salt, nitrate, and nitrite compounds [56].

Fruits and Vegetables

In a meta-analysis of cohort studies of intake of fruit and vegetables and risk of gastric cancer, high intake of fruit was inversely associated with risk of gastric cancer (RR = 0.90, 95 % CI 0.83–0.98), but a weaker association was observed with intake of vegetables (RR = 0.96, 95 % CI 0.88–1.06) [57]. The inverse association with intake of fruit was observed for both cardia (RR = 0.88, 95 % CI 0.76–1.02) and non-cardia gastric cancer (RR = 0.89, 95 % CI 0.77–1.02), whereas the inverse association with intake of vegetables was only observed for non-cardia (RR = 0.94, 95 % CI 0.81–1.09) but not for cardia gastric cancer (RR = 1.06, 95 % CI 0.90–1.25).

In cohort studies conducted of Japanese men in Hawaii [5, 18, 58] and of Japanese men and women in Hawaii [19], high assumption of fruits and/or vegetables (≥80 g/day or ≥7 times per week) was associated with 40 % lower risk of gastric cancer compared to the lowest level of intakes. In the case–control study conducted among mostly Asians in Hawaii, high intake of total vegetables, dark-green vegetables, and yellow vegetables was significantly inversely associated with risk in both men and women [21]. However, in analysis by *H. pylori*/Cag status [23], significant inverse trends in association with intake of total and green vegetables and cruciferous vegetables were found only among *H. pylori*/CagA positive

individuals but not among *H. pylori*/CagA negative persons. Further investigation of the role of cruciferous vegetables may be warranted since it was suggested to be inversely associated with gastric cancer risk in a meta-analysis [59].

Salt

High intake of salt in cooking, processing, and preserving meat has been implicated as a gastric cancer risk factor. Experimental data suggest that high salt intake can cause mucosal damage and inflammation [60, 61]. In a meta-analysis of prospective studies, compared to low salt intake, gastric cancer risk was increased with moderately high (OR = 1.41, 95% CI 1.03–1.93) and very high salt intake (OR = 1.68, 95% CI 1.17–1.41) [62]. Although the evidence on high salt intake and risk was strong in studies conducted in Japan, the association was less consistent in an investigation among Japanese in Hawaii which may be related, in part, to the relatively modest number of gastric cancer cases ($n = 108$) [19]. Further investigation of the role of salt intake among more than 50,000 Japanese Americans in the ongoing MEC will be informative [41].

Clinical Features

In countries such as Japan and Korea where routine screening is offered, many patients are diagnosed with cancer before development of symptoms. In contrast, in the USA, the majority of gastric cancer patients present with symptoms and have advanced disease at the time of presentation. Symptoms at presentation are typically nonspecific and include weight loss, abdominal pain, nausea, vomiting, and difficulty swallowing [63]. With disease progression, many patients develop gastric outlet obstruction, ascites, and other presentation of metastatic disease such as jaundice. Knowledge of the higher incidence of gastric cancer among Asian Americans forces clinicians to be more attentive to the early signs in patients of Asian descent and therefore allows earlier diagnosis and possibly better outcome.

Diagnosis

In the unscreened population, patients are diagnosed based on their symptoms, which prompt providers to use diagnostic tools such as endoscopy or CT scan. Diagnosis is usually made using endoscopy to visualize the tumor and take a tissue sample for histological confirmation. Alternatively patients with metastatic disease may have a CT scan with findings of liver metastases or peritoneal involvement. To confirm the diagnosis and to start treatment, it is required to have histologic

confirmation of gastric cancer. In contrast, the screened patients are asymptomatic at diagnosis and endoscopic examination combined with biopsy results will identify gastric cancer.

With histological diagnosis, patients undergo staging workup which includes imaging techniques such as CT and/or PET scans. The goal of staging workup is to identify subjects who are possible candidates for surgery or in the case of metastatic disease to initiate palliative chemotherapy. Although there is no uniform way to stage gastric cancer, a rational approach is to obtain a CT scan of the abdomen and chest to assess the extent of the disease and whether metastatic disease to liver or peritoneum is present. In the absence of metastatic disease by a CT scan, many providers will require a combined PET/CT scan to confirm the lack of occult evidence for metastatic disease before determining treatment [64]. In patients who are candidates for perioperative chemotherapy, an endoscopic ultrasound will assess the depth of the tumor and establish the clinical stage [65]. Given that CT and even PET/CT have limited capability to identify peritoneal disease, recent data support the use of diagnostic laparoscopy for direct visualization as well as peritoneal washing for assessment of peritoneum prior to the planned laparotomy [66].

East–West Differences

As noted above, Asian Americans with gastric cancer appear to have more favorable outcome than non-Hispanic whites. Overall survival of patients with gastric cancer in Japan and Korea is better than that in Western countries [67, 68]. The reasons for this observed difference are not completely clear. Although better surgery in eastern countries with removal of the tumor and a higher number of lymph nodes has been suggested as a possible explanation for better outcomes, a large randomized Dutch trial failed to show improvement in survival with extended lymph node removal in Western populations [69, 70]. The possibility exists that the biology of gastric cancer in eastern and Western populations may differ, contributing to differences in outcome.

Prognosis of gastric cancer depends on the stage at the time of diagnosis. There are, in fact, differences in the staging classification between Western countries and Japan [71, 72]. Staging in Western countries is outcome driven, while the Japanese staging system provides guidance for treatment. These differences in staging may result in some of the reported outcome differences between Western countries and Japan [73].

In Western countries, the conventional staging system is TNM (tumor, node, metastasis). Using TNM criteria tumors are staged broadly from stage I–IV. Japanese staging classification has three locations for cancer: upper, middle, and lower. Additionally, visual appearance of cancers (superficial, mass, ulcerative, infiltrative ulcerative, diffuse infiltrative, and unclassifiable) is recorded on the pathology report. Lymph nodes are reported by their station (location of the lymph nodes and their proximity to major organs surrounding stomach) and provide a guide to the

required degree of surgical resection based on the location of the tumor. However, we are not aware of any studies that used both TNM and the Japanese stage classification in the same study to directly compare the two methods.

Treatment

Patients with gastric cancer require multidisciplinary care by a group of specialists including gastroenterologist, surgeon, medical oncologist, and radiation oncologist. Extent of the disease dictates the type and number of specialists involved in patient care. For example, for patients with early-stage disease (i.e., no distant metastasis and no involvement of structures surrounding stomach) who are candidates for surgical resection, the team will include a surgeon, medical oncologist, and radiation oncologist while for those with late-stage diagnosis who are candidates for palliative treatment, the team may include a medical oncologist, gastroenterologist, and palliative care specialist. In the following section, the modalities of treatment as well as the role of each of the specialist are discussed. It is important to point out that models of care in the USA differ from the practice in Asian countries including Japan, Korea, and China. In the USA, only medical oncologists administer chemotherapy, while in Asian countries, surgeons frequently administer chemotherapy, making the coordination of care less cumbersome.

Surgical Interventions

For patients with early-stage disease, surgery is the treatment of choice. Currently the only way to achieve cure is to have surgical removal of the tumor and regional lymph nodes. Endoscopic removal of the tumor (endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD)) is an acceptable approach in selected patients with low likelihood of nodal involvement [74, 75]. Although endoscopic removal of the tumor is minimally invasive, the follow-up is extensive and requires regular endoscopy. The data for endoscopic removal of gastric cancer is from Asian countries as this procedure is not commonly performed in the USA and Europe [76]. In the USA, the frequency of this procedure is unknown and patients are not candidates due to a higher stage at diagnosis. For patients with higher-stage gastric cancer, surgery may involve total or partial gastrectomy. Partial gastrectomy is an option for patients with cancers in the distal part of the stomach. Recent data show that laparoscopic surgeries are generally safe, require shorter duration of hospital stay, and provide equivalent outcomes [77, 78].

There are also differences in the timing and extent of surgical approach between Western countries compared to practices in Korea and Japan [79]. In Western countries many patients undergo perioperative chemotherapy (neo-adjuvant

chemotherapy followed by surgery and then adjuvant chemotherapy) on the basis of favorable results from several randomized trials showing the effectiveness of this approach compared to surgery alone. However, the approach in Korea and Japan is primarily up-front surgery.

Adjuvant and Neo-adjuvant Therapies

Results of multiple clinical trials have established that in patients who undergo surgery for gastric cancer, surgery alone is no longer an accepted standard of care. However, there is no consensus on the best approach to manage these patients. Two large trials conducted in Asia have established that adjuvant chemotherapy with fluoropyrimidine alone or in combination with platinum significantly improved overall survival. The Japanese trial established that 1-year treatment with S1 (an oral fluoropyrimidine) improved the 3-year survival rate from 70 % in the surgery alone arm to 80 % in the surgery + S1 arm [80]. The second trial from Korea and China showed that 6 months of treatment with capecitabine + oxaliplatin (fluoropyrimidine + platinum) improved the 3-year survival rate from 59 % in the surgery arm to 74 % in the surgery and chemotherapy arm [81]. Despite these findings, adjuvant chemotherapy alone is not an accepted modality in Western countries because of differences in patient identification and surgical techniques and that S1 is not available in the USA and has limited availability in Europe [82]. In the following section, we describe the landscape of adopted modalities of adjuvant and neo-adjuvant therapies in the Western world.

Chemotherapy alone around the time of surgery and chemotherapy combined with radiation (chemoradiation) after surgery are both efficacious strategies established in different randomized clinical trials, but there is no head-to-head comparison between these two strategies.

As for chemotherapy, it is administered in the perioperative setting with surgical intervention sandwiched between chemotherapies [83, 84]. Results from the MAGIC trial, one of the largest chemotherapy trials, showed that chemotherapy improved the likelihood of survival. In this trial, the probability of 5-year survival was 36 % in recipients of perioperative chemotherapy compared to 23 % in those who received surgery alone (HR for death, 0.75; 95 % CI: 0.60 to 0.93) [83]. In the French trial, another large chemotherapy trial in Western countries, the 5-year survival rate was 38 % in recipients of perioperative chemotherapy compared to 24 % for surgery alone (HR for death: 0.69; 95 % CI 0.50 to 0.9) [84]. The most active agents used in these trials are believed to be 5-FU and cisplatin [84]. However, at best only 50 % of the patients are able to complete the treatment due to toxicities [83, 84]. Interestingly, a small study did not confirm these findings in Korean population; the findings were presented in abstract in the ASCO annual meeting in 1996 and never published in manuscript [85].

Chemotherapy combined with radiation or chemoradiation is a treatment modality initially studied in USA [86]. Although the initial study revealed a 35 %

reduction in the rate of death from gastric cancer in recipients of chemoradiation, the study was criticized for suboptimal surgery and the fact that radiation compensated for inadequate lymph node dissection. Furthermore, a retrospective study using Oregon Cancer registry suggests a lower rate of survival benefit for chemoradiation in gastric cancer patients [87]. Thus the overall benefit of chemoradiation may be less than the reported rates in randomized trials. Regarding the chemotherapy agent that is used with radiation, standard chemotherapy is a 5-FU-based treatment in the adjuvant setting followed by concurrent 5-FU with radiation. The addition of platinum agent to 5-FU may be beneficial in a subset of patients with node-positive disease based on a recent analysis for a study that was conducted in Asia [88].

It is evident that the interaction between race/ethnicity and treatment selection and efficacy in the literature is not well defined. This is because the randomized trials for assessment of efficacy are conducted in different areas of the world with different population characteristics. In international trials analysis of subgroups is not always possible due to limited numbers and therefore inadequate prediction power. We hope that with improvement in the understanding of the racial/ethnic differences in risk factors, predisposition, and outcomes, future efforts for conduct of the international trials would take the racial/ethnic factors into account at the time of trial design and provide the information that can improve our understanding of the treatment-specific differences among different racial/ethnic populations.

Palliative Treatments

For patients who are not candidates for curative therapies, palliative treatments, including chemotherapy, radiation, palliative surgeries, and hospice and end-of-life care are other options. Chemotherapy plays a significant role in prolongation of survival and palliation of symptoms. In a recent meta-analysis, combination chemotherapy is associated with 63% improvement in survival from a median of 4.3 months to 11 months [89]. Although there is no consensus on the best regimen in the first-line setting, platinum-containing regimens are considered standard of care, and oxaliplatin-containing regimens are widely used in the USA [90, 91].

Radiation plays a role in alleviating symptoms of obstruction for gastroesophageal junctional cancers, cessation of bleeding, or alleviating symptoms at metastatic sites such as bone lesions.

Palliative surgeries such as gastrojejunal bypass or placement of tubes for relief of intractable vomiting and feeding are available to selected patients with incurable disease. Finally, all patients should receive supportive care for their symptoms of pain, depression, nausea, and vomiting. Hospice is an appropriate disposition for patients who have poor performance status and are not candidates for aggressive interventions.

Two targeted agents have established role in gastric cancers. Trastuzumab confers a survival benefit in patients with HER2 positive cancers [92]. Additionally, ramucirumab is shown to have survival benefit in the second-line setting as a single agent or in combination with chemotherapy [93, 94]. The data for ramucirumab suggests that there is a preferential benefit for Caucasian patients, while Asian patients achieve a lower degree of benefit from these interventions [95].

Screening and Prevention

Although there is a debate in whether screening reduces mortality from gastric cancer, Korea, Japan, and Venezuela have screening programs for gastric cancer at a population level [96–99]. The modality of screening varies between different countries. In Korea upper endoscopy every 2 years starting at age 40 is the standard of care, and it has proven to be cost-effective from a societal perspective [100].

Many professional societies recommend treatment for incidental finding of *H. pylori*; however, a randomized trial to assess the role of treatment in prevention of gastric cancer found no statistically significant reduction in the risk of gastric cancer in the treated population [101].

Conclusion

Despite decline in the incidence of gastric cancer, it remains one of the major causes of cancer mortality worldwide with significant variation in the geographic, racial, and socioeconomic distribution. Gastric cancer is heterogeneous with multiple genetic and environmental risk factors, variable disease presentation, and outcome; furthermore, practices for diagnosis and management of the disease are diverse across the world. In recent years, we have learned that treatment benefits can vary by race/ethnicity and region of the world, possibly due to host-related factors and differences in disease etiology. The consistent difference in outcome in Asian patients compared to non-Asian patients after controlling for stage at diagnosis emphasizes the importance of considering race/ethnicity and specifically Asian ethnicity in international trials.

Efforts to better understand the disease course and risk factors will provide a framework to better classification of this cancer into homogenous categories and lead the way for uniform approach to the diagnosis and management of the disease with significant impact on outcome. Continued efforts to improve outcomes through consideration of race, ethnicity, and country of birth in their diagnostic algorithm are needed.

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Cervical Cancer Among Asian Americans

Patti E. Gravitt, Ruby H.N. Nguyen, and Grace X. Ma

Abstract Cervical cancer is a leading cause of female cancers worldwide. Infection with one or more of the carcinogenic types of human papillomavirus (HPV) is considered to be a necessary, but insufficient cause of cervical cancer. Other coinfections, cigarette smoking, and hormonal influences of pregnancy and oral contraceptive use appear to synergistically increase the risk of HPV-associated cervical cancer progression. Geographical and ethnic variation in cervical cancer incidence may thus reflect differences in exposure to HPV due to different sexual mores or susceptibility to infection, differences in prevalence of cofactors, or differences in the availability or effectiveness of cervical cancer prevention programs such as Pap smear and HPV screening. Although the incidence of cervical cancer in Asian Americans is lower than the other racial/ethnic groups in the USA, incidence rates are heterogeneous among different Asian ethnic groups, which may be related to the level of endemicity of high-risk HPV types in the Asian countries of origin, with some variation in findings potentially related to selective socioeconomic migration of immigrants. It is unclear how screening influences cervical cancer survival because Asian Americans lag systematically behind the general US population in screening uptake. The lack of knowledge of the benefits of early detection and screening guidelines, cultural factors, and access barriers is associated with the low screening rates. Similar disparities, and their driving forces, result in insufficient HPV immunization,

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similar to the low screening coverage reported in Asian-American communities. Future dissemination of effective culturally appropriate educational intervention programs for the reduction of access barriers shows great promise in reducing previous cervical cancer disparities in Asian-American women.

Keywords Asian American • Cervical cancer • Gynecologic cancer • Human papillomavirus • Disparities

Cervical Cancer Incidence and Mortality

Cervical cancer is the fourth leading cause of cancer incidence and mortality worldwide [1]; the age-adjusted incidence (world standard) is 14.0 per 100,000 with an estimated 528,000 new cases diagnosed in 2012. Incidence rates averaged 12.7 per 100,000 in Asia, which is intermediate of the high rates in Africa (27.6) and the low rates in North America (6.6). Cervical cancer incidence varied substantially within Asia, higher in South-Central (19.3) and Southeast (16.3) Asia and lower in Eastern (7.9) and Western (4.4) Asia. Cervical cancer ranks fourth as a cause of cancer death in women worldwide. The age-adjusted mortality rate is 6.5 per 100,000 in Asia, also intermediate of the high death rates in Africa (17.5) and the low rates in North America (2.6) [1].

In the USA, cervical cancer incidence rates (per 100,000) are considerably lower in Asian American (6.4) and non-Hispanic white women (7.1) than in African American (10.2) and Hispanic (10.5) women [2]. Squamous cell and adenocarcinoma are the two main histologic types of cervical cancer; the former accounts for approximately 70 % of the cervical cancers in Asian Americans compared to 64 % in non-Hispanic whites and 75 % in Hispanic and African American women [3].

As cervical cancer incidence varies in Asia, there are distinct differences in cervical cancer incidence across Asian ethnic subgroups in the USA. Wang and colleagues [3] conducted one of the first comprehensive analysis of cervical cancer incidence by specific Asian groups using 1996–2004 data from the five SEER registries (Hawaii, Los Angeles, Seattle-Puget Sound, San Francisco-Oakland, and San Jose-Monterey) with the highest proportion of Asian Americans or Pacific Islanders. This analysis showed that cervical cancer incidence was highest among Vietnamese (18.9), intermediate in Koreans (11.9) and Filipinos (10.0), and lower in Japanese (6.7), Chinese (5.8), and Asian India/Pakistan (4.5). This heterogeneity in cervical cancer incidence among Asian ethnic groups is also evident in two other updates that used additional SEER registry data [4, 5] and extended the analyses to include smaller Asian ethnic groups, such as Kampuchean (Cambodians) and Laotians. A 2013 study included cancers diagnosed in ten SEER registries during 1990 to 2008 and identified the top five cancer sites during each of three study periods (1990–1994, 1998–2002, and 2004–2008) by specific Asian ethnic groups. Cervical cancer was one of the top five cancer sites for Kampuchean and Laotian women in the USA

during each of the three study periods; the respective rates were 16.7 and 17.1 per 100,000 during the most recent study period (2004–2008) [5]. Although cervical cancer incidence was also high for Koreans during 1990–1994 (18.6 per 100,000), rates for this group had declined in excess of 50 % by 2004–2008 (8.1 per 100,000). Similarly, cervical cancer rates for Vietnamese women were reduced from 38.6 to 13.1 per 100,000 between the study periods 1990–1994 to 2004–2008 (Gomez, personal communication).

Thus, cervical cancer rates have been declining steadily in Asian Americans as in other race/ethnic groups in the USA. From 2000–2009, there was a significant −3.0 % average annual decline in cervical cancer rates among Asian/Pacific Islanders, which was comparable to the changes observed in African American (−3.0 % per year) and Hispanic (−3.9 % per year) women [6]. However, the rates of decline are not uniform across the different Asian ethnic groups. In an analysis that estimated the average annual percent change in cervical cancer incidence between 1990–2004 in six Asian ethnic groups residing in California (Chinese, Filipino, Japanese, Korean, South Asian, Vietnamese), the decline was highest in Vietnamese (−8.7 % per year) and lowest in South Asian women (−1.0 % per year) [7]. In the nationwide SEER study mentioned above, the annual decline was −8.5 % per year in Vietnamese, −7.3 % per year in Laotian, but only −2.3 % per year in Kampuchean women [5].

In Japanese and non-Hispanic white women, cervical cancer incidence peaked at ages 45–64 years, but in the other Asian ethnic groups, the incidence continued to increase with increasing age [3]. A recent study showed that differences in invasive cervical cancer incidence in African Americans versus non-Hispanic whites were likely underestimated because SEER rates do not adjust for hysterectomy status [8]. Thus, more complete data regarding age-specific hysterectomy prevalence among the Asian ethnic subgroups are needed to calculate a hysterectomy-corrected estimate of the cervical cancer rates to allow for more accurate comparison.

Racial/ethnic differences in cervical cancer mortality largely mirrored these differences in incidence patterns. In the study conducted by Jemal and colleagues [6], cervical cancer mortality (per 100,000) was lowest in Asian Pacific Islanders (2.0) and non-Hispanic whites (2.2), intermediate in Hispanics (3.0), and highest in African Americans (4.3). The average annual percent decline in mortality rates was highest in Asian Pacific Islanders (−4.0 %) and lowest in non-Hispanic whites (−1.9 %).

Risk Factors

Natural History of Cervical Cancer: Overview

Substantial progress has been made in our understanding of the etiology of cervical cancer. Nearly 100 % of invasive cervical cancer is caused by infection with one of approximately 14 high-risk or oncogenic types of human papillomavirus, two of which—HPV16 and HPV18—account for well over half of all invasive cervical cancer worldwide (Fig. 1).

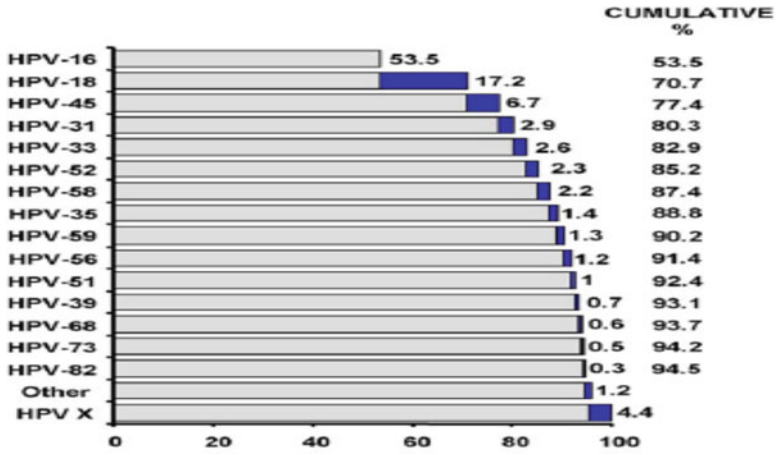

Fig. 1 Oncogenic types of human papillomavirus genotypes and worldwide attributable fraction of CxCa; Clifford et al. Vaccine 24S3 (2006) S3/26-S3/34

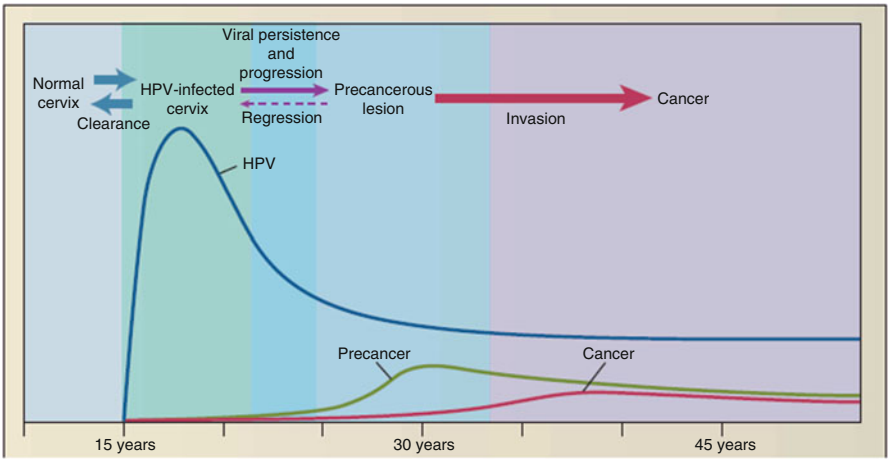

Fig. 2 The natural history of HPV and cervical cancer. Schiffman M, Castle P (2005) N Engl J Med 353(20):2101–2104

Over the past 20 years, several large epidemiologic studies have been conducted in many global regions to define the natural history of HPV infection leading to cervical cancer (Fig. 2). HPV is transmitted predominately through sexual contact, with peak prevalence observed among young women around the age of sexual debut. Natural history studies have observed that most (~90 %) of HPV infections detected at the cervix will become undetectable within 2 years of first detection (reviewed in [9]). Uncertainty remains as to whether the loss of HPV detection within 1–2 years of acquisition reflects viral eradication or clearance or control of virus below limits of detection (i.e., HPV latency) [10]). However, it is clear that

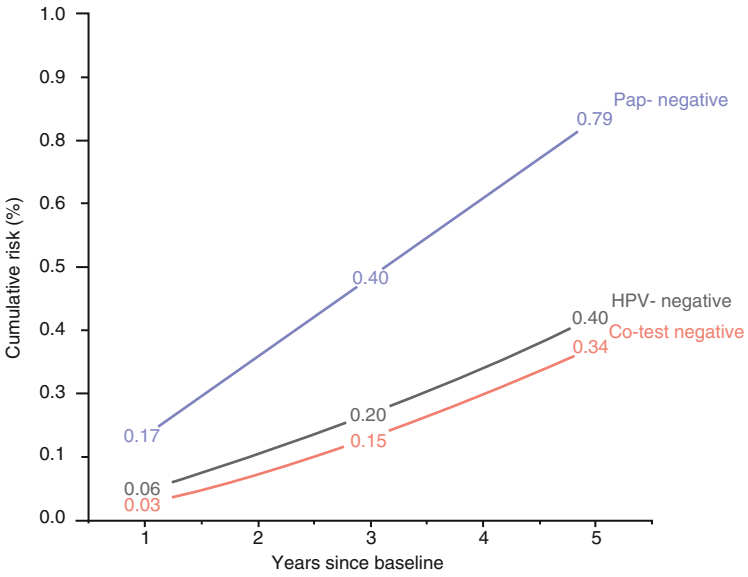

Fig. 3 Cumulative risks of cervical intraepithelial neoplasia grade 2 or more severe among women aged 30–64 years. Blue line indicates cumulative risk of CIN2+ among women with negative Pap cytology (regardless of HPV result), black-line women with a negative HPV test (regardless of Pap result) and red-line women with both HPV and Pap negative test results. Reprinted with permission from Gage JC, Schiffman M, Katki HA, Castle PE, Fetterman B, Wentzensen N, Poitras NE, Lorey T, Cheung LC, Kinney WK (2014) Reassurance against future risk of precancer and cancer conferred by a negative human papillomavirus test. JNCI 106(8):pii:jhu153. doi: 10.1093/jnci/dju153

persistent detection of oncogenic types of HPV is the strongest predictor for progression to high-grade squamous intraepithelial lesions and cancer [9]. Figure 3 represents the 5-year cumulative risk of high-grade squamous intraepithelial lesions and cancer progression following negative Pap cytology, HPV testing, or Pap+HPV co-testing screening results, demonstrating the high negative predictive value over the short term following an HPV negative test result [11]. These observations form the basis for the utility of HPV testing in cervical cancer screening programs [12]. As expected from this natural history model, the burden of HPV correlates significantly with the cervical cancer burden in populations [13].

Cervical Cancer and Human Papillomavirus (HPV) Genotype Distribution in Asia

Infection with HPV is established as a necessary cause of invasive and preinvasive cervical cancer. The generally lower rates of cervical cancer incidence in Asian Americans compared to Hispanic and African American women likely reflect

differences in the prevalence of HPV infection in Asia compared to Africa, the Caribbean, Central America, and South America [1], since the relative risk of cervical cancer associated with HPV infection is similar across world regions [14]. Similarly, the heterogeneity in cervical cancer incidence among specific Asian ethnic groups in the USA may reflect rates of HPV infection and cervical cancer in the countries of origin in Asia. A recent meta-analysis estimated the prevalence and genotype distribution of HPV in women with normal cytology and across a range of cervical disease lesions and invasive cervical cancer by world geographic region [7]. Table 1 summarizes the overall prevalence of HPV in women with normal cytology (reflects the general population prevalence of detectable HPV) and women with invasive cervical cancer. Among women with normal cytology, overall HPV prevalence was lowest in Western/Central Asia (8 %), intermediate in Eastern Asia (12 %) and Europe (9 %), and considerably higher in Africa (22 %) and South/Central America (24 %) [7].

HPV16 accounts for the majority of cervical cancers in all world regions (53–73 %), with a minor exception of Asia where a lower HPV16 prevalence in Eastern Asia (68 %) compared to Western/Central Asia (82 %) has been reported. Some variation in genotype-specific prevalence of non-HPV16 cancers can be observed. Specifically, HPV52 and HPV58 are overrepresented in cervical cancers in Eastern Asia compared to other world regions (Fig. 4). The higher relative contribution of HPV58 in cervical cancers in Eastern Asia is supported by the similar 16-year cumulative risk of cervical cancer among HPV58/non-HPV16 positive women (10.3 %) and HPV16 positive women (13.5 %) in a large cohort study conducted in Taiwan [15]. It is not clear whether prevalence of HPV52 and HPV58 is also observed in higher frequency among Asian Americans.

In addition to these macro-level genotype-specific differences observed in invasive cervical cancer across geographical region, efforts have been directed to study intratypic HPV variants as these genetic variants may affect the clinical outcome of HPV infection. In fact, significant intratypic variation in HPV16 has been well described [16, 17]. The Asian variants of HPV16 have been consistently found to confer a higher relative risk of progression to high-grade squamous intraepithelial lesions and cancer compared with the more commonly detected European variant [18–20]. The higher carcinogenicity of the Asian HPV16 variant is supported by several in vitro studies demonstrating enhanced ability compared with E variant to

Table 1 Human papillomavirus prevalence in women with normal cervical cytology and invasive cervical cancer by geographic region [7]

Region	Normal cytology (%)	Invasive cervical cancer (%)
Eastern Asia	12	91
Western/Central Asia	8	90
Europe	9	90
North America	21	90
Africa	22	90
South/Central America	24	86

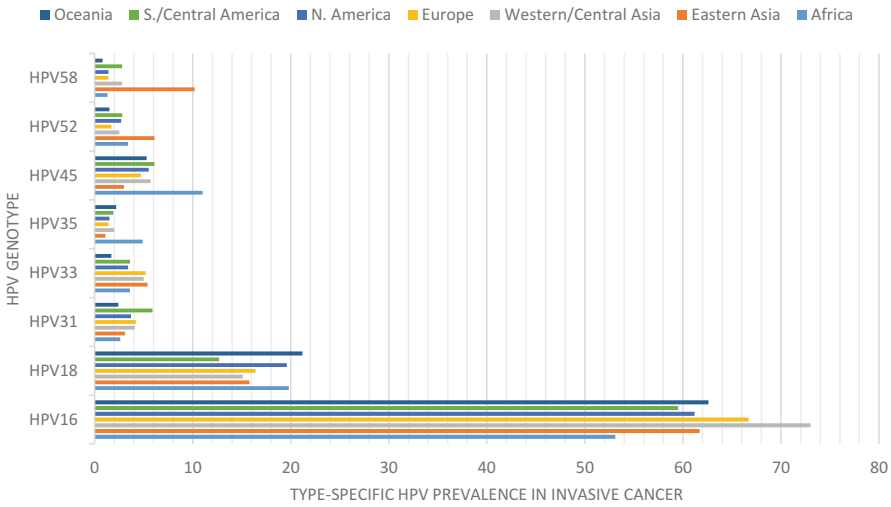

Fig. 4 Type-specific prevalence of HPV16, 18, 31, 33, 35, 45, 52, and 58 in invasive cervical cancer by geographic region. Adapted from [7]

Table 2 Cervical cancer rates and HPV16/18 prevalence among women with normal cytology (representative of population prevalence of HPV 16/18) in Asian ethnic subgroup countries of origin [25]

Country	Country-specific invasive cervical cancer rates (per 100,000)	HPV 16/18 prevalence in women with normal cytology (%)
China	9.4	3.8
India	20.2	5.0
Japan	14.5	1.9
Korea	13.5	6.3
Laos	9.8	3.0
Philippines	13.9	2.9
Vietnam	11.3	2.1

drive life cycle in raft cultures to cancer: more severe dysplasia and higher E6/E7 expression [21–23]. In addition, the Asian HPV16 variant is found at higher frequency in adenocarcinoma compared to squamous cell carcinomas of the cervix, consistent with the higher proportion of adenocarcinomas in cervical cancers diagnosed in Asian American women compared with African American and Hispanic women [24].

Similar to the heterogeneity of cervical cancer incidence among Asian ethnic subgroups in the USA, there is also significant heterogeneity across the Asian countries of origin. Table 2 reports the data in the summary reports for China, India, Japan, Korea, Laos, the Philippines, and Vietnam compiled by the Institut Catala d'Oncologia (ICO) Information Centre on HPV and Cancer [25]. In gen-

eral, cervical cancer rates are positively correlated with the population prevalence of HPV16/18, a phenomenon that has been better demonstrated globally using HPV seroprevalence data [26]. In this respect, differences in cervical cancer rates among the Asian immigrants in the USA may reflect the overall HPV endemicity in the country of origin. The patterns observed in Vietnamese and Chinese-American women may reflect this phenomenon, where the higher rates of invasive cervical cancer in Vietnam and lower rates in China parallel their respective rates in the USA [27–29]. However, other countries show distinct differences in rates in the country of origin compared to immigrant populations in the USA. For example, the reported rates of cervical cancer are quite high in India [25], yet the invasive cervical cancer rates in South Asians living in the USA are among the lowest by Asian specific ethnicity [3], possibly reflecting a socioeconomic difference, namely, higher socioeconomic status among immigrant South Asian populations compared to the majority populations in the country of origin.

The most consistent predictors or HPV infection relate to measures of sexual activity [29]. Little is known about sexual practices related to HPV acquisition and transmission among Asian Americans and in Asians living in the country of origin. This is likely due to cultural taboos that restrict the assessment of sexual activity in many studies and the reluctance of participants to discuss sexual behaviors even when these questions are asked. In addition, other factors including cultural isolation and practices of male partners may contribute significantly to the HPV burden in many regions. For example, an earlier study among cytologically normal women in Hanoi and Ho Chi Minh City in Vietnam observed a nearly fivefold difference in HPV prevalence (10.6 % in Ho Chi Minh versus 2.0 % in Hanoi), despite common sampling and HPV testing protocols [30]. It is speculated that the relative isolation of North Vietnam during its war with America and the resultant socialist isolation may contribute to the lower HPV prevalence in this population at the turn of the twenty-first century. It is likely, however, that regional and cultural differences in the norms of sexual behavior influence the overall HPV prevalence in Asian populations, a phenomenon that may persist for generations even after immigration.

Other Risk Factors

While HPV is the central cause of cervical cancer, only a small proportion of women infected with HPV develop invasive cervical cancer. Cofactors including other sexually transmitted infections, smoking, reproductive factors, and the use of oral contraceptives (OCs) are likely to act in conjunction with HPV infection in the pathogenesis of cervical cancer [31–38]. Although information on cofactors and risk of cervical cancer in Asian-American women is largely absent, studies from Thailand, the Philippines, India, Japan, Taiwan, and elsewhere in Asia have found that the influence of these cofactors on risk of cervical cancer is generally consistent with the results obtained in studies conducted in western populations. Even if risk

associations with these cofactors are similar by geographic or ethnic subgroups, differences in the prevalence of these cofactors may contribute to differences in cervical cancer rates.

Cervical Cancer Prevention Through Screening and HPV Immunization in Asian Americans

There are two types of tests for cervical cancer screening: the Pap test and the HPV test.

The Pap test can find early cell changes that are not yet cancer. Cell changes can be treated and prevented from becoming cervical cancer. The Pap test also can find cervical cancer at a stage that is easy to treat. The HPV test finds certain HPV infections that can lead to cell changes. These cell changes can progress to cervical cancer if not treated. Cell changes can be surgically removed from the cervix and prevented from becoming cervical cancer [12]. Over the past 30 years, there has been a steady decrease in cervical cancer incidence and mortality in the USA [39] due to the development of the Pap test. The US Preventive Service Task Force [40] currently recommends screening women ages 21–65 years with cytology or the Pap test every 3 years or, for women ages 30–65 years who want to lengthen the screening interval, screening with a combination of the Pap test and HPV test every 5 years.

Despite the proven survival benefits associated with screening and early detection of cervical cancer, the screening rate among Asian-American women lags far behind that of the general US population [41–49]. Specifically, Asian-American women have the lowest rates of screening (66 %) compared with Hispanic (74 %), Native Americans (82 %), African American (78 %), and non-Hispanic white women (78 %) [50]. Furthermore, cervical cancer screening rates among Asian-American women fall well below the Healthy People 2020 national objectives, which calls for 93 % of women aged 21–65 to be screened for the Pap test every 3 years [51].

Studies suggest that various factors, including lack of knowledge, psychosocial and cultural beliefs, and access barriers, are associated with nonadherence to cervical cancer screening among Asian-American women [41, 47–49, 52, 53]. Many Asian-American women do not know the recommended guidelines for cervical cancer screening and lack of knowledge about HPV infections [49, 54]. For example, Korean-American women with limited knowledge of cervical cancer had lower rates of screening, whereas women who were familiar with screening guidelines were three times more likely to have had a Pap test [52, 55]. Vietnamese women who believed that a Pap test can detect cervical cancer early were twice as likely to have had a Pap test compared to women who did not hold this belief [49]. Many Asian-American women have reported that they avoided the Pap test due to embarrassment. Indeed, shyness and cultural beliefs about modesty are often negatively associated with cervical cancer screening [54]. Ma and colleagues [49] reported that physician recommendation for screening and having health insurance was positively associated with cervical cancer screening. Furthermore, noncompliance

with guidelines tended to be high even among Asian Americans who were ever screened [48] and that the reasons associated with noncompliance with screening guidelines may differ from those associated with never having been screened.

The few interventions that have been developed for Asian-American women demonstrate that targeting factors including transportation, language barrier, insurance, knowledge, and others can yield significant increases in screening rates. However, it is important to note that the effectiveness of educational interventions is often attenuated if access barriers are not adequately addressed. For example, to reach a larger number of individuals in the community, several programs have utilized media-based approaches. Results suggested that the media campaign had significantly increased intention to undergo cervical cancer screening, but it did not result in meaningful differences in actual screening rates [56]. Interventions employing a combined approach have been found to yield greater impact on cervical cancer screening rates [46, 57–62]. Access barriers, including the cost of screening, lack of insurance, and language difficulties, pose formidable challenges and are the most often cited factors influencing screening behavior [41, 48, 63].

Therefore, interventions that include essential components, such as the use of community-based approaches, culturally and linguistically appropriate educational tools and resources, as well as navigation assistance, are more likely to be successful in increasing cervical cancer screening rates.

The development of HPV vaccines increases the potential of prevention of cervical cancer and mitigates the long-standing disparities in cervical cancer [64]. As described above, some Asian-American subgroups (e.g., Vietnamese and Korean) have persistently higher incidence rates of cervical cancer. The two highly efficacious vaccines (Gardasil® and Cervarix®) against HPV genotypes 16 and 18, which cause 70 % of the HPV infections that cause cancer, afford an important opportunity to reduce cervical cancer disparities. These vaccines are currently recommended for adolescents ages 11–12 years, with catch-up vaccination to age 26 years for females and 21 years for males, in a three-dose regimen over a 6-month period [65–67]. Reducing disparities in cervical cancer depends on adequate vaccine uptake by those at greatest risk.

The National Immunization Survey conducted using telephone interviews in six languages shows that 44 % of US girls 13–17 years old had at least one dose, 29 % had one, and only 11 % completed the entire three-dose course [68]. The CDC estimates that 32 % of girls aged 13–17 had received all three HPV vaccine doses and that dose completion was significantly lower among the uninsured (14 %) [6]. In a community sample of 113 Vietnamese women who had at least one HPV vaccine dose, only 11 (10 %) had all three doses [68]. In a separate study of Chinese-American women, only 19 % had heard of HPV [69]. Further, Chinese-American girls and women with limited English language proficiency had low HPV awareness and HPV vaccine acceptance rates. Due to various cultural factors, language barriers, and healthcare access barriers, it would be more difficult for Chinese Americans to understand the importance of the HPV vaccination.

Preliminary results from Ma and colleagues showed that knowledge, attitudinal, cultural, and access barriers specific to Asian populations prevent the uptake of HPV vaccination. Asian Americans, especially the low income and under-

served, have generally lower levels of knowledge about HPV infection and vaccination, increased parental reluctance to vaccinate children due to the association with sexually transmitted diseases, a lower perception of benefits, and increased barrier to access to preventive services. Therefore, evidence-based and culturally relevant interventions are needed to increase adherence to the recommended regimen for the diverse Asian-American populations. The availability of the new technology for cervical cancer prevention and control provides a unique opportunity to address cervical cancer disparities in Asian Americans.

Overall, community-based cervical cancer screening programs have demonstrated promise in addressing existing cervical cancer disparities by increasing awareness and knowledge and promoting recommended screening behaviors. The lessons learned from this body of research will be instrumental in guiding future community-based programs to reduce cancer health disparities among Asian American women.

Conclusion

Historical differences in cervical cancer prevalence among Asian-American women may be associated with high-risk HPV-type endemicity in the country of origin or disparities in knowledge or access barriers in the USA. Little is known about the natural history of HPV infection and cervical cancer in these understudied women. However, there is strong evidence that culturally appropriate primary prevention with educational interventions, in the presence of reduction in access barriers, can increase both screening for cervical testing and HPV vaccination rates in multiple Asian-American subgroups.

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