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Cancer characteristics in different generations of Middle Eastern immigrants compared to Non-Hispanic Whites in California

DISSERTATION

Submitted in partial satisfaction of the requirements

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in Epidemiology

by

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2018

DEDICATION

To

My husband, Benjamin Smyth

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ABSTRACT OF THE DISSERTATION

Cancer characteristics in different generations of Middle Eastern immigrants compared to Non-Hispanic Whites in California

By

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Professor Hoda Anton-Culver, Chair

Cancer is the second leading cause of death in the United States (US). Immigrants from the Middle East (ME) constitute one of the growing immigrant populations in the US and particularly in California. However, very few studies have examined the cancer characteristics in different generations of ME immigrants compared to Non-Hispanic Whites (NHW). The overall purpose of this dissertation was to analyze the association between ME immigration status and cancer stage at diagnosis and all-cause and cancer-specific incidence and mortality in different generations of ME immigrants and NHW.

We used data from the California Cancer Registry, a population-based dataset, to identify invasive primary incident cancer cases in three population groups: first generation ME immigrants, second or subsequent generations ME immigrants, and NHW. Proportional Incidence Ratio was used to compare the cancer risk of the 15

selected most common cancers in the 3 population. Logistic regression models were fitted to evaluate the risk of advanced cancer stage in the different generations of ME immigrants and NHW. Cox proportional hazard models were applied to calculate hazard ratios with their 95% confidence intervals for all-cause mortality and cancer-specific mortality among the 3 population groups. Breast cancer in females, prostate cancer in males, and colorectal cancer in both genders were examined in the logistic and Cox proportional models.

The results suggest that differences in cancer risk between first generation ME immigrants and NHW change in second or subsequent generations, approaching the risk level of NHW and indicating the impact of acculturation in this immigrant population. The different generations of ME immigrants had higher odds of advanced cancer stage at diagnosis when compared to NHW. However, first generation ME immigrants had lower all-cause mortality in comparison with NHW.

This study is the first to explore the different cancer characteristics in ME immigrants to California. Our novel study highlights the importance of adapting screening interventions tailored to the ME immigrant population in the US with using an appropriate language and taking into consideration the ME immigrants' specific cultural and religious beliefs.

CHAPTER 1

INTRODUCTION

1.1. Background

1.1.1. Immigration overview

All nations have been experiencing explosive changes for the past 200 years[1]. These multi-level changes are environmental and sociocultural. The environmental changes include air climate and deforestation, and the sociocultural changes cover the increase in immigration rates which has created problems on health, economy, and social-psychological levels[1].

1.1.1.1. Immigration process

People always seek alternatives to improve their life and their health[1]. An immigrant is the individual who voluntarily move from his country and takes a permanent residence in a new society and country[2]. However, this definition is not constant, it differs in different countries, and therefore it is not surprising that immigrant studies include sojourners, ethnic groups, and even refugees are limited.

1.1.1.2. Immigration worldwide

Over the past 17 years, the number of international immigrants has been increasing worldwide to reach 244 million in 2015; a 22 million increase from 2010, as showed in **Appendix A** adapted from the 2016 United Nations (UN) report[3]. In addition,

the number of refugees has increased tremendously and reached the highest number since World War II, with 19.5 million refugees in 2014[4].

The advantages of immigration are not limited to the economic growth on the country of origin given that immigrants send back money to their families. According to the World Bank, there was a 4.4% increase in sending money in 2014 compared to 2013 with a total of 436 billion American dollars[5]. This money goes for education, health, infrastructure, housing, and sanitation to their families back home. However, there is also an advantage of immigration on the host country. Immigrants tend to cover for the shortage in workers and contribute in taxes and social security contributions. Never less, immigrants are vulnerable. They get paid less; they lose their jobs the first, work in worse conditions, and sometimes do not possess health benefits. Immigrants can also suffer from humiliation and abuse. Unfortunately, for some countries, immigration is the only way to escape from hunger, poverty, persecution, and violence. Therefore, the number of international immigrants is increasing.

1.1.1.3. Immigration to the United States

The “land of opportunities”, this is what immigrants called the United States (US). There are opportunities, possibilities, and freedoms that exist in the US, and not in any other nation in the entire world[6]. Immigrants leave their home countries and challenge barriers for a better life and security in the US. Therefore, the US developed different immigration legislations including “the Liberalized Policy Period” in 1965 which allowed immigration from all over the world including the Third World countries. The pattern of immigration has evolved. Earlier immigrants were laborers or “slaves”, whereas

immigrants nowadays are voluntary immigrants or refugees[6]. The number of immigrants has been increasing over the years, with more people applying for their residency in the US, as showed in **table 1.1** adapted from the Homeland Security yearbook[7]. This table shows that the highest number of lawful residents originates from Asian countries followed by North American countries, including Mexico. The UN reported that the largest number of international immigrants resides in the US with a total number of 47 million in 2015 (**Appendix B**)[3]. The number of first generation immigrants is estimated to reach 47.9 million by 2020[8].

Table 1.1: Persons obtaining lawful permanent resident status by region of birth: Fiscal Years 2013 to 2015[7].

Region of birth	**2013**	**2014**	**2015**
Africa	98,304	98,413	101,415
Asia	400,548	430,508	419,297
Europe	86,556	83,266	85,803
North America	315,660	324,354	366,126
Oceania	5,277	5,112	5,404
South America	80,945	73,715	72,309
Unknown	3,263	1,150	677
Total	**990,553**	**1,016,518**	**1,051,031**

1.1.1.4. Immigration from the Middle East

Worldwide, more than half of the international immigrants come from three countries (Syria, Afghanistan, and Somalia), with the highest number immigrating from Syria[3,9]. In addition, immigrants from the Middle East (ME) constitute one of the growing foreign-born immigrant populations in the US and particularly in California[10]. The ME population is a heterogeneous group with different cultures, originating from Southwest Asia and Northeast Africa.

1.1.2. Cancer overview

1.1.2.1. Tumorigenesis

Tumorigenesis or the formation of cancer is a multi-step process requiring clonal expansion. It was elucidated in 2000 by Hanahan and Weinberg[11], who explained the key hallmarks needed for normal cells to transform into malignant derivatives. These capabilities were called “the Hallmarks of Cancer” and are illustrated in **Appendix C**[11]. The authors suggested that most cancers, if not all, acquire these capabilities in their development. These capabilities include 6 different hallmarks: 1) Self-sufficiency in growth signals, 2) insensitivity to anti-growth signals, 3) tissue invasion & metastasis, 4) limitless replicative potential, 5) sustained angiogenesis, and 6) evading apoptosis[11]. As a summary, for cancer to be successful, it needs to overcome six different barriers. Cancer cells need to sustain chronic proliferation through growth factors in large part. They should also manage to get around programs that regulate cell proliferation. Cancer cells need to avoid apoptosis which is critical in cancer development and treatment[12]. Cancer cells need to exhibit unlimited replicative potential, where these

cells remain alive and do not die like most cells. Cancer cells, similarly to normal cells, need nutrients and oxygen essential in their survival, therefore, they need to induce angiogenesis or the formation of blood vessels. Lastly, cancer cells should have the capability of escaping the primary location, invading, and colonizing a new terrain (metastasis)[11,13]. A decade later, and in addition to the 6 hallmarks of cancer explained earlier and illustrated in **Appendix C**[11] **and D**[13], Hanahan and Weinberg developed their theory and added 2 emerging hallmarks, with 2 enabling characteristics (illustrated in **Appendix E**[13]). These 2 new capabilities or hallmarks are: reprogramming of energy metabolism and evading immune destruction[13]. In conclusion, these 2 new capabilities needed for cancer cells to develop are the abilities to 1) "reprogram the cellular energy metabolism in order to support cell growth and proliferation" and 2) "evade from attacks and elimination by immune cells"[13]. These hallmarks have helped understand the complex biology of cancer. Yet, more cancer discoveries are being accomplished every day, with a hope of finding new ways to fight cancer development.

1.1.2.2. Worldwide cancer statistics

Cancer incidence is increasing worldwide and cancer is among the leading causes of death worldwide. The increase in incidence is associated with populations' growth and aging, amelioration in screening behaviors, and the increase in the prevalence of the modifiable cancer risk factors, such as smoking, overweight, and physical inactivity[14,15]. One in seven deaths internationally is due to cancer[16]. Cancer is the second leading cause of death in high-income countries and the third leading cause of death in low- and middle-income countries[16]. Worldwide cancer statistics are derived

from Globocan. Globocan statistics are produced by the International Agency for Research on Cancer (IARC) and present country-specific incidence and mortality rates for 27 types of cancer and for all cancers combined[17]. Data from the latest Globocan has showed that 14.1 million new cancer cases and 8.2 million cancer death occurred in 2012 worldwide[18]. Developed countries had more than 6 million cancer cases and 2.8 million cancer death in 2012. While developing countries had more than 8 million cancer cases and more than 5 million cancer deaths. Cancer incidence was different between countries; prostate cancer was the most common cancer in developed countries, followed by lung and colorectal cancers in males. However, the most common cancer in males in developing countries was lung cancer followed by liver and stomach cancers, predominantly attributable to infection[19]. Breast cancer is the most common cancer in females in developed and developing countries. Yet, colorectal and lung cancers have the second and third place in developed countries, compared to cervix and lung cancers in developing countries. Cervix cancer is also predominantly attributable to infection[20]. There is also a difference in cancer mortality between developed and developing countries in both genders. While lung, colorectal, and prostate constitute the most common 3 cancers to die from in developed countries, the top 3 in developing countries are lung, liver, and stomach cancer in developing countries. Fewer differences exist in females where cervix is the third most common cause of cancer death in developing counties in comparison to developed countries.

1.1.2.3. Cancer statistics in the United States

Cancer is an enormous public health challenge. In 2016, 1,685,210 new cancer cases were estimated to be diagnosed in the US, with 841,390 in men and 843,820 in women. In addition, 595,690 estimated cases of cancer death were estimated in 2016, 314,290 were in men and 281,400 in women[21]. During the last 2 decades and because of cancer research, cancer mortality has dropped in the US with 1.7 million lives saved (23% reduction in cancer death rates from 1991 to 2012)[22,23]. However, the number of cancer deaths is predicted to rise from 595,690 in 2016 to 946,833 in 2030. Cancer is the second most common cause of death after heart disease. By 2013, cancer had overtaken as the leading cause of death in 13 US states. Cancer mortality is higher in men than women and it is the highest in African American men with the lowest cancer mortality for Asian/Pacific Islander women[23,24]. These cancer differences are caused by cancer health disparities, involving but not limited to the following groups: immigrants, racial and ethnic minority groups, individuals who lack or have limited access to health care, refugees or asylum seekers, individuals with low socio-economic status, and elderly people[22].

1.1.2.4. Cancer stages

Cancer stage is important for treatment, prognosis, and survival. The stage is based on the cancer size and the extent in which the cancer is spread in the body[21]. Cancer stage is evaluated through x-rays, lab tests, and other procedures[25]. There are 3 major staging systems: one that is used by clinicians and is known as “TNM staging system”, a second system usually used with patients, and a third system used by

researchers for descriptive and statistical analysis purposes. All cancer staging systems that will follow are adapted from the National Cancer Institute[25]. The TNM staging system is used by hospitals and medical facilities for most cancers (excluding spinal cord tumors, brain, and blood cancers). As a summary of the TNM system, the T refers to the size and extent of the main tumor, the N refers to the number of nearby lymph nodes that have cancer, and the M refers to whether the cancer has metastasized, meaning spread to other parts of the body. While the second staging system usually used to describe cancer for patients. This system includes the following stages: 0, I, II, III, and IV, as showed in **table 1.2**.

Table 1.2: Cancer staging system[25].

Stage	What it means
Stage 0	Abnormal cells are present but have not spread to nearby tissue. Also called carcinoma in situ, or CIS. CIS is not cancer, but it may become cancer.
Stage I, Stage II, and Stage III	Cancer is present. The higher the number, the larger the cancer tumor and the more it has spread into nearby tissues.
Stage IV	The cancer has spread to distant parts of the body.

A third staging system is used by researchers and cancer registries and includes the following groups:

a) In situ: Abnormal cells are present but have not spread to nearby tissues.
b) Localized: Cancer is limited to the place where it started, with no sign that it has spread.
c) Regional: Cancer has spread to nearby lymph nodes, tissues, or organs.
d) Distant: Cancer has spread to distant parts of the body.
e) Unknown: There is not enough information to figure out the stage.

1.1.2.5. Cancer prevention

Cancer is a preventable disease in a big proportion, with more than half of the cancer cases worldwide being attributable to preventable causes[22,26]. The preventable causes of cancer include but not limited to: tobacco use, overweight & obesity, physical inactivity, and failure to comply or use interventions that treat and prevent cancer-related viruses [e.g. Human Papilloma virus (HPV)][18,22,26]. In the US, almost 32% of the estimated 595,690 cancer deaths were attributable to cigarette smoking in 2016. In addition, 20% of the cancers diagnosed in the US were attributable to body fat, physical inactivity, unhealthy diet, and the excess consumption of alcohol[21]. Other cancers are associated with infectious agents such as HPV or Human Immunodeficiency virus (HIV). These cancers can be prevented by vaccination or behavioral changes. Skin cancer or melanoma is also prevented by taking precautions when exposed to sun. Other cancers can be prevented by screening modalities where they can be detected before transformation to cancerous lesions; colorectal cancer and colonoscopy screening is an excellent example. Screening also can lead to early detection and therefore less extensive treatment and better survival.

In summary, cancer early detection and prevention are very important, with the possibility of a big proportion of cancer cases being avoided. Recommendations for early detection are essential for early detection, as showed in **Appendix F**[21]. Unfortunately, most of the cancer research funding is devoted to find ways to understand cancer causes and treat cancer[26]. Not enough resources are focusing on the importance of early detection as an efficacy way to fight cancer.

1.1.3. Breast cancer

1.1.3.1. Anatomy of the breast and breast carcinomas

The breast includes three different parts: lobules, ducts, and connective tissues. The lobules are responsible of producing milk, while the ducts transport the milk to the nipples. The connective tissues are essential for connecting and holding everything together[27]. Breast cancer is the cancer that develops in the breast cells; it is an abnormal growth of these cells. There are different histological types of breast carcinomas with the invasive ductal and lobular carcinomas being the most common types[27].

1.1.3.2. Risk factors

A list of breast cancer risk factors has been established and a few of them are listed below[28–30]:

- Female gender[31].
- Age: breast cancer risk increases with age where most of the cancer cases are diagnosed after the age of 50.
- Family history of breast cancer when women have a first-degree relative with breast cancer or have multiple family members from either side of the family with breast cancer.
- Genetic mutations where women who inherited changes on genes such as BRCA1 and BRCA2 are at higher risk of breast cancer.
- Personal history of breast cancer where women are more likely to develop a second breast cancer.

- Being overweight or obese after menopause.
- Not being physically active.
- Early menopause (before 55) and late to no pregnancy.

1.1.3.3. Epidemiology

In females, breast cancer is the most common cancer worldwide[32–34], with different cancer incidence rates between a country and another. It is also the most common cancer in the US with 252,710 new incident cases estimated in 2017. Breast cancer incident cases have been decreasing due to screening and as a result of discontinuation of hormonal therapy as showed in a report from the Women's Health Initiative[35]. Breast cancer is the leading cause of cancer death worldwide[36] and is the second leading cause of cancer death in the US with an estimated death of 40,610 cases in 2017[31,37]. Breast cancer mortality has also been declining in the recent few years[23] due to screening and adjuvant treatment[38].

1.1.3.4. Screening and treatment

A variety of breast cancer screening imaging has been developed. However, the mammogram or the X-ray of the breast is best studied. A systematic review has showed that mammography reduces breast cancer mortality by 20%[39]. For women at average lifetime risk for breast cancer (lifetime breast cancer risk below 15%), a mammogram is recommended for women ages 50 to 74 years old. However, for women 75 years and older, a mammogram is recommended if women have a life expectancy of more than 10

years[40]. However, breast cancer screening is tailored to the individual woman's risk factors, her values, and her preferences.

Breast cancer treatment depends on the cancer's histology and stage at diagnosis. For non-metastatic with early-stage breast cancer at diagnosis, a surgery (lumpectomy or mastectomy) to the breast and regional nodes, with or without radiation therapy is recommended, followed by adjuvant systematic treatment. However, for locally advanced breast cancer, the best treatment is a multimodality therapy employing systematic and loco-regional therapy[41].

1.1.3.5. Breast cancer prevention

To reduce the modifiable breast cancer risk factors, the Centers for Disease Control and Prevention (CDC) encourages women to take care of their health by[42]:

- Keeping a healthy weight
- Being physically active
- Limiting alcohol consumption
- Sleeping enough time at night
- Avoiding exposure to carcinogens and chemicals that interfere with the normal body function.
- Limiting exposure to radiation
- Breastfeeding children, if possible.
- Being aware of the side effects of hormonal replacement therapy and oral contraceptives.

1.1.4. Prostate cancer

1.1.4.1. Anatomy of the prostate and prostate carcinomas

The prostate, a gland of the male reproductive system, is located in front of the rectum and below the bladder. The prostate gland consists of a base, an apex, an anterior, a posterior, and two lateral surfaces. The main purpose of this gland is to produce fluid for semen, which transports sperm during the male orgasm[43]. It is about the size of the walnut but starts to get larger when the man reaches his late 40s to early 50s. The prostate is close to parts of the digestive, urinary, and reproductive systems. As a result, prostate cancer and its treatment can affect these systems[44]. More than 95% of the prostate cancers are adenocarcinomas. Prostate adenocarcinomas start in the gland cells which make mucus and prostatic fluid, that mix with sperm and other fluids to make semen. Most adenocarcinomas are found in the outer part of the prostate, which is called the peripheral zone[45].

1.1.4.2. Risk factors

While there are many risk factors for prostate cancer, only a few of them are well established[46]:

- Age: rarely any prostate cancer cases occur before the age of 40. However, prostate cancer risk increases tremendously with age **(Appendix G)**[47].
- Race/ethnicity: prostate cancer is more frequent in African-American men and in Caribbean men of African ancestry than in men of other races.
- Family history of prostate cancer: the risk doubles if a man's father had prostate cancer and it triples if his brother had prostate cancer.

Other risk factors include but not limited to the following[45,48,49]:

- Geography: prostate cancer is more common in North America, northwestern Europe, Australia, and the Caribbean islands. It is less common in Asia, Africa, Central America, and South America. This might be due to the differences in prostate screening behaviors.
- Inherited gene changes such as mutations in BRCA2 can increase the prostate cancer risk in certain men.
- Men who eat a high-fat diet, particularly saturated fats. However, the relationship between diet and prostate cancer is not well proven yet.
- Exposure to chemicals such as cadmium, or Agent Orange that was widely used during the Vietnam War.

1.1.4.3. Epidemiology

Worldwide, prostate cancer is the second most common cancer in men with 1.1 million men diagnosed with prostate cancer in 2012, and 70% of those prostate cases occurring in developed countries. Prostate cancer rates were the highest in Australia/New Zealand, Northern America, Western Europe, and Northern Europe. Incidence rates were also relatively high in certain less developed regions such as the Caribbean, Southern Africa, and South America. However, prostate cancer rates remained the lowest in Eastern and South-Central Asia[50]. In the US, prostate cancer is the most common cancer in men with 161,360 new cancer cases estimated in 2017 and estimated 26,730 people will die from prostate cancer **(Appendix H)**[31]. Based on 2012-

2014 data from the US, the age-adjusted rate of prostate cancer was 119.8 per 100,000 men per year, and the number of deaths was 20.1 per 100,000 men per year[51].

1.1.4.4. Screening and treatment

Prostate-specific antigen (PSA) is a glycoprotein produced by the prostate epithelial cells. PSA test was widely adopted in the early 1990s as the standard screening method for prostate cancer in the US, which led to the increase in prostate cancer incident cases **(Appendix I)**[52]. However, PSA has a short half-life and its levels can be elevated by different conditions that affect the prostate. The digital rectal exam (DRE) is another prostate screening test used by clinicians to estimate the size of the prostate and feel for lumps and other abnormalities[53]. As a result of the advancement in prostate screening, prostate cancers are diagnosed at earlier stages and 5-year survival rates have increased tremendously going from 66.0% in 1975 to 99.3% in 2009[52]. Prostate cancer treatment depends on the stage of the disease, the age of the patient, and the other pre-existing morbidities among other things. The treatment includes active surveillance or “watchful waiting” given that prostate cancer grows slowly and some patients may never require treatment, surgery, radiation therapy, hormone therapy, chemotherapy, vaccine treatment, and bone-directed treatment[54].

1.1.4.5. Prostate cancer prevention

The National Cancer Society advises to avoid the lifestyle risk factors for prostate cancer (section 1.1.4.2) and increase the protective factors. The risk factors to avoid are

smoking, being overweight, and not getting enough exercise. While they explained that quitting smoking and increasing exercise are protective factors[55].

1.1.5. Colorectal cancer

1.1.5.1. Anatomy of the colon and rectum and colorectal carcinomas

The colon and rectum are part of the digestive system. The colon is divided into four separate parts: 1) the ascending colon, 2) the transverse colon, 3) the descending colon, and 4) the sigmoid colon. The proximal colon refers to the ascending and transverse sections of the colon, while the transverse colon refers to the descending and sigmoid parts of the colon. The colon is responsible for absorbing water and salt from the remaining food matter. The remaining of the waste goes to the rectum, which is the final 6 inches of the digestive system. The digestive system is showed in **Figure 1.1** adapted from the American Cancer Society[56].

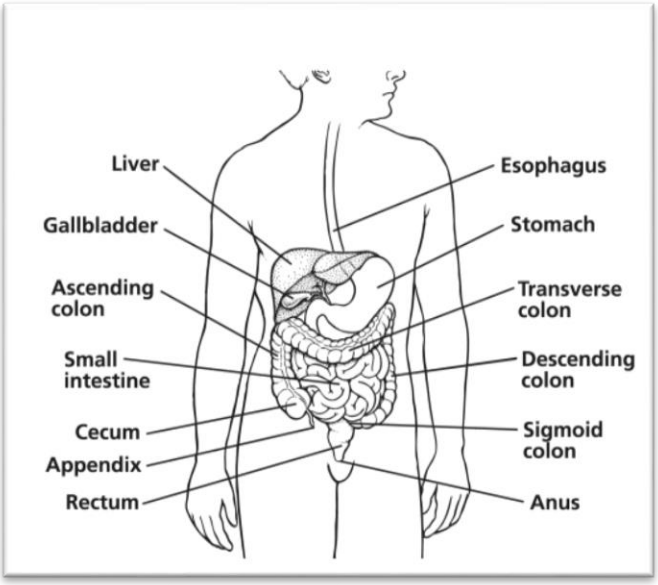

Figure 1.1: The anatomy of the digestive system[56].

Colorectal cancer (CRC) is the cancer that starts in the colon or rectum. Colon cancer and rectal cancer are similar that they are often grouped together and called CRC. The majority of CRCs start by the growth of a polyp in the colon or rectum. In some cases, this polyp transforms into cancer after a few years. However, not every polyp converts into cancer. It all depends on the type of the polyp. There are two types of polyps: 1) Adenomatous polyps or adenocarcinomas which sometimes change to become cancer and 2) hyperplastic polyps and inflammatory polyps which are common but not pre-cancerous in general[56].

1.1.5.2. Risk factors

The risk factors of CRC are divided into three major categories: the factors that affect the screening recommendations, the factors that may influence them, and the risk factors that do not alter the CRC screening recommendations[57].

The factors that affect the screening recommendations are:

- Familial CRC syndromes such as familial adenomatous polyposis and Lynch syndrome.
- Personal or family history of sporadic CRC or adenomatous polyps
- Inflammatory bowel disease such as ulcerative colitis and Crohn disease
- Abdominal radiation. An example will be the adult survivors of childhood malignancies who received these radiations.

However, the factors that may influence the screening recommendations include:

- Race: African Americans have the highest rates of CRC in the US, and CRC occurs at a younger age in African Americans. However, it is not very clear if the association is due to a biological factor or to screening access.
- Gender: CRC is more common in men than women[58] with a higher mortality.
- Acromegaly: a disorder in adults in which the pituitary gland produces too much growth hormone.

Lastly, the factors, that do not alter the CRC screening recommendations, incorporate the following:

- Obesity.
- Diabetes mellitus and insulin resistance.
- Red and processed meat. Long-term consumption of these meats have been associated with a higher risk of CRC, but these results were not consistent in all the studies conducted.
- Consumption of alcohol and tobacco use.

1.1.5.3. Epidemiology

In men, CRC is the third most common cancer worldwide and it is the second most common cancer in women. More than 55% of the CRC cases occur in the developed countries with Australia/New Zealand having the highest estimated age-standardized incidence rates per 100,000 in both genders in 2012[32]. In addition, the highest estimated mortality rates in both sexes was for Central and Eastern Europe and the lowest mortality rate was in Western Africa[32]. In the US, it is estimated that there will

be a total of 135,430 new cases of CRC and a total of 50,260 people who will die from CRC in 2017[58]. CRC is the third most common cancer in the US[59] and represents 8% of all cancer cases. It is most frequent among people aged 65 to 74, with the highest percent of death from CRC being among people aged 75 to 84 years old[58].

1.1.5.4. Screening and treatment

If at average risk (refer to section 1.1.5.2), men and women aged 50 to 75 years are recommended to be screened by high sensitivity fecal occult blood testing (FOBT) yearly, or by sigmoidoscopy every 5 years with high-sensitivity FOBT every 3 years, or by colonoscopy every 10 years[60]. Adults aged 76 to 85 years old are not automatically screened. While adults older than 85 years are not recommended to be screened at all[60]. These methods are used to find polyps and cancer. Other screening methods are mainly used to find cancer. They are: 1) Fecal immunochemical test conducted every year, 2) Guaiac-based fecal occult blood test conducted also every year, and 3) Stool DNA test conducted every 3 years[61]. However, for people who are at higher risk of CRC, screening usually starts before the age of 50 with more frequent screening. **Appendix J** is adapted from the American Cancer Society with cancer screening suggestions for people with increased risk of CRC[61].

As mentioned earlier, colonoscopy can be used as a way to extract polyps. However, to manage a localized tumor, a surgical resection is used. Multi-visceral resection is an appropriate option for locally advanced and potentially resectable primary colon cancers[62].

1.1.5.5. Colorectal cancer prevention

Almost all CRCs start as polyps that are detected and resected by colonoscopy and therefore, CRC can simply be prevented by following the appropriate screening recommendations. However, prevention can and should start earlier. The primary prevention should be focused on the modifiable risk factors to try to eradicate them. Consequently, to prevent CRC, different ways were suggested:

- Changing lifestyle or eating habits.
- Avoiding things known to cause cancer.
- Taking medicines to treat a precancerous condition or to keep cancer from starting.

1.2. Specific aims and hypotheses

Immigrant studies have been useful in determining etiologic associations in disease, particularly cancer[63–66]. They help identify possible cancer causes and the impact of the ethnic, cultural, genetic background, and the environment on the etiology and distribution of cancer[67,68]. More than 1.6 million incident cancer cases were estimated in the US for 2016[21]. Given that first generation immigrants account for more than one in seven US residents[69], it is important to examine cancer and cancer risk factors in foreign-born immigrants. ME immigrants constitute one of the growing foreign-born immigrant populations in the US and particularly in California[10]. According to the US census, NHW refer to any person from European, Middle Eastern, and North African origin[70]. Nevertheless, ME populations are distinct in their diet (e.g. Mediterranean diet), genetic information, cultural preferences, and health behaviors[71]. Reported studies have shown that the overall cancer incidence is lower in ME first generation immigrants compared to other NHW[72–74]. This difference may be explained by the ME population's genetics, their distinct diet (e.g. Mediterranean diet), the lower rates of tobacco use in some of the ME countries[75], and other cultural behaviors such as younger age at first pregnancy[71]. Estimating cancer incidence rates in ME immigrants is a challenge because ME immigrant population denominator data is not available through the US census. Alternative measures including Proportional Incidence Ratio have been used to estimate cancer burden in ME immigrants and other subgroups in the population[76,77]. Acculturation is defined by the immigrants' changes in cultural patterns toward those of the host country[78]. Immigrant studies can evaluate the impact of acculturation by looking at cancer in different generations of immigrants and by duration of residence for first

generation immigrants[79,80]. Studies examining cancer in immigrants and their descendants have suggested that cancer rates across generations approach the native nation rates with succeeding generation[81–83]. However, studies on cancer in ME immigrants are infrequently performed in the US[76,77,84]. In addition, studies looking at cancer in different ME generations are very rare, particularly in California[84].

Immigrants present with more advanced cancer stage at diagnosis[85–87]. Unfortunately, none of the studies looked at cancer stage at diagnosis in ME immigrants. Stage at diagnosis is an important factor for cancer prognosis. With earlier stage at diagnosis associated with better survival, it is important to examine cancer stage at diagnosis in this immigrant population. Immigrant studies have also shown different overall mortality and cancer specific mortality rates between native born versus immigrants[88]. One study looked at cancer mortality in two different generations of ME immigrants in California in comparison with NHW[84]. This study showed that first generation immigrants have higher risk of death from colorectal, breast, and lung cancers in females, and from colorectal and pancreas cancers in males compared to NHW. Furthermore, second or subsequent generations ME immigrants' females have higher risk of death from colorectal and lung cancers while males have higher risk of mortality from colorectal cancer in comparison with NHW. Although, in this study, they distinguished between the different generations of ME immigrants, however ME first generation immigrants were only identified by their place of birth, and no mortality comparison was made between the ME different generations.

The proposed Ph.D. dissertation used data from the California Cancer Registry (CCR) to examine cancer risk, stage at diagnosis, and mortality in different generations

of Middle Eastern immigrants and NHW in California, between 1988 and 2013 [the population groups are identified in chapter 2]. In the following chapters, several aims will be investigated and several hypotheses tested. They are as follows:

Aim 1. Compare cancer risk among first generation Middle Eastern immigrants, second or subsequent generations Middle Eastern immigrants, and Non-Hispanic Whites in California (1988-2013), particularly with respect to the 15 most common invasive primary cancers, with taking into consideration the length of stay in the US for first generation Middle Eastern immigrants prior to their cancer diagnosis.

Hypothesis 1.a: We predict that differences in cancer risk between first generation Middle Eastern immigrants and Non-Hispanic Whites will diminish in second or subsequent generations Middle Eastern immigrants, approaching the risk level of Non-Hispanic Whites.

Hypothesis 1.b: We predict that second or subsequent generations Middle Eastern immigrants will have an increase in risk for cancers related to US environmental factors compared to first generation Middle Eastern immigrants.

Hypothesis 1.c: We predict that with longer duration of residence in the US, first generation ME immigrants will be at higher risk of cancers related to US environmental factors compared with Non-Hispanic Whites.

Aim 2. Analyze the association between Middle Eastern immigration status and cancer stage at diagnosis in different generations of Middle Eastern immigrants and Non-Hispanic Whites in California between 1988 and 2013.

Hypothesis 2.a: We predict that first generation Middle Eastern immigrants will have a higher risk of non-localized (advanced) cancer stage at diagnosis compared to Non-Hispanic Whites for breast cancer in females, prostate cancer in males, and colorectal cancer in both genders, as a result of non-adherence to cancer screening recommendations.

Hypothesis 2.b: We predict that no significant differences will be found in the risk of advanced cancer stage between second or subsequent generations Middle Eastern immigrants and Non-Hispanic Whites.

Aim 3. Analyze the association between Middle Eastern immigration status and all-cause mortality and cancer-specific mortality in different generations of Middle Eastern immigrants and Non-Hispanic Whites in California between 1988 and 2013.

Hypothesis 3.a: We predict that first generation Middle Eastern immigrants will have a higher all-cause and cancer-specific mortality compared to Non-Hispanic Whites as a result of a more advanced cancer stage at diagnosis.

Hypothesis 3.b: We predict that no significant differences will be found in all-cause and cancer-specific mortality between second or subsequent generations Middle Eastern immigrants and Non-Hispanic Whites.

These aims will be tested in the following chapters (chapters 3 through 6). However, cancer stage at diagnosis and mortality will be analyzed together with each chapter representing a different cancer site as follows:

Chapter 4: breast cancer in females

Chapter 5: prostate cancer in males

Chapter 6: colorectal cancer in males and females.

CHAPTER 2

GENERAL METHODS

2.1. Population under study

California is one of the largest and most populated states in the US, with more than 39 million residents as of July 2015[89]. For this study, three different population groups were identified using CCR. The 3 groups included: first generation ME immigrants, second or subsequent generations ME immigrants, and NHW [more details in “Data Sources and Data Management” section].

2.2. Data sources and data management

CCR is California's statewide population-based cancer surveillance system. It monitors incidence and death from cancer among Californians since 1988[90]. CCR captures detailed information on cancer cases, including patient’s demographics (e.g. gender, country of birth, and race), cancer characteristics (e.g. age and stage at diagnosis), treatment, and follow up information. Every cancer diagnosis made in California since 1988 is required by law to be reported to CCR. As a consequence, the CCR completeness rates are high and expand with time[90]. We obtained a de-identified CCR data with no human subjects’ involvement. Therefore, this research did not qualify as human subject research and did not require an Institutional Review Board approval. In CCR, race/ethnicity is divided into five major groups: NHW, Hispanics, Non-Hispanic Blacks, Non-Hispanic Asian/Pacific Islanders, and American Indians. Age at diagnosis is treated as a continuous measurement or categorical divided into eighteen 5-year

interval age groups. The summary stage at time of diagnosis (SEERWHO) is defined as one of the following: in-situ, localized, regional, remote, not abstracted, and unknown or not specified. The tumor grade is categorized as: well differentiated, moderately differentiated, poorly differentiated, undifferentiated/anaplastic, and unknown if differentiated. The country in which the patient was born is classified into different countries with 3 abbreviation letters for each country. Marital status is identified as: single, married, separated, divorced, widowed, unmarried or domestic partner, and unknown. Primary source of payment for the hospital is divided into 21 categories.

2.2.1. Population groups

In 2007, Dr. Nasseri used CCR and developed the Middle Eastern Surname List using five different sources, starting in 1988[91]. This surname list has been validated and is included as a permanent variable (QME) in the CCR dataset. The 3 population groups of interest in this study were: first generation ME immigrants, second or subsequent generations ME immigrants, and NHW. If the patient had a Middle Eastern last name[91] (QME=yes), did not have a Hispanic nor an Asian last name, and was born in one of the Middle Eastern countries (Afghanistan, Algeria, Armenia, Bahrain, Djibouti, Egypt, Iraq, Iran, Jordan, Lebanon, Libya, Morocco, Pakistan, Palestine, Saudi Arabia, Somalia, Sudan, Syria, Turkey, Tunisia, Yemen, and Israel), he/she was considered first generation ME immigrant. If the patient had a Middle Eastern last name[91], did not have a Hispanic nor an Asian last name, was not born in one of the Middle Eastern countries, did not have a missing birth country, he/she was considered second or subsequent

generations ME immigrant. If the patient did not have a ME nor Hispanic nor Asian last name and was identified as White in the CCR database, he/she was considered NHW in our analysis.

2.2.2. Cancer types

Cancer types are identified in CCR using SEERWHO which is SEER's site recode variable based on ICD-O-3 and World Health Organization's (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues (2008)[92]. This coding scheme separates leukemias and lymphomas from site-specific cancers[93]. A list of cancer types was created based on SEERWHO as showed in **Appendix K.**

2.2.3. Duration of residence for first generation ME immigrants

Duration of residence in the US was calculated for first generation ME immigrants by using year at diagnosis and year of issue of Social Security Number (SSN) [duration of residence=year at diagnosis - year of issue of SSN]. Assuming that legal immigrants receive their SSN directly after their arrival to the US[84], the year of issue of SSN can be used to estimate the immigration date. A categorical variable was created with duration of residence less than 20 or 21 years and duration or residence equal to 20 or 21 years or more, depending on the cancer site (chapters 4-6). The cutoff point was selected based on the median duration of residence for first generation ME immigrants for breast cancer in females, prostate cancer in males, and colorectal cancer in both genders.

2.3. Design

2.3.1. Study design

This study is a retrospective cohort study, as illustrated in **figure 2.1**.

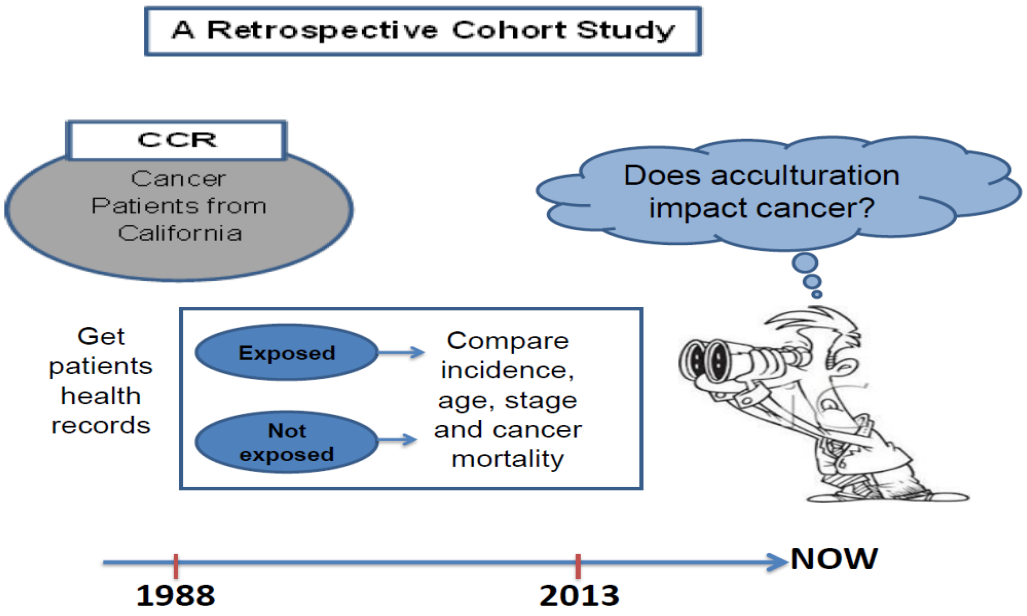

Figure 2.1: Illustration of the CCR study design.

2.3.2. Inclusion and exclusion criteria

Information on inclusion and exclusion criteria can be found in the following chapters for each of the cancer sites.

2.4. Definitions of measurements

2.4.1. Primary exposure:

The main exposure of interest is ME immigration status where I am comparing between the different generations of ME immigrants and NHW. Another exposure of interest was the duration of residence for first generation ME immigrants.

2.4.2. Different outcomes:

The outcomes were as follows:

a. Aim 1: The outcome was cancer risk estimated by the Proportional Incidence Ratios.

b. Aim 2: The outcome of this aim was stage at diagnosis represented as summary stage at time of diagnosis in CCR. The stage at diagnosis was categorized into in-situ, localized, and non-localized, depending on the cancer site. Localized cancer stage was used as the referent stage, with non-localized tumors including regional and distant cancers. Unknown cancer stage at diagnosis was excluded from the analysis.

c. Aim 3: The outcome for this aim was time to event with the event being all-cause death or cancer-specific death. Time is measured from the beginning of follow-up until the event occurs or a reason occurs for the observation to end. An observation is considered to be right-censoring if the observation is terminated before the event occurs. An observation is left-censored when the observation experiences the event before the start of the study. An observation is interval-censored if the only information you know about the survival time is that it is between the values of a and b.

2.4.3. Predictor variables:

The predictor variables in this study included: gender, age at diagnosis, year at diagnosis, tumor grade, SES, health insurance, marital status, chemotherapy, radiation therapy, surgery, and hormonotherapy (when applicable). In addition, Estrogen Receptor (ER) and Progesterone Receptor (PR) were used for breast cancer in females.

a. Gender was included as male or female.

b. Age at diagnosis was included as a continuous measure and a categorical variable depending on the cancer site.

c. Years at diagnosis were divided into 5-year categories with the exception of the last period as follows: 1988 to 1992, 1993 to 1997, 1998 to 2002, 2003 to 2007, and 2008 to 2013.

d. Tumor grade was defined as: well differentiated, moderately differentiated, poorly differentiated, undifferentiated/anaplastic, and unknown if differentiated.

e. SES was kept as 5 categories: lowest SES, lower-middle SES, middle SES, higher-middle SES, and highest SES. This variable was created using “quinyost” that was available till the end of 2005 and “quinyangimputed” that was available from 2006 forward in CCR. Quinyost is the quintile of yostscl which is not a collected data item, but derived from Kathleen Yost’s SES scale of principal component analysis. This principal component analysis was used to create an SES index using 1990 Census[94].

f. A new health insurance variable was created and included the following categories: 1) managed care,HMO,PPO,private, 2) medicaid, 3) medicare, 4) insured, or other type, 5) unknown if insured, and 6) not insured, including self-pay. Another health insurance was created and was categorized into: having insurance, not having insurance, and unknown.

g. Marital status was defined as: single, married, separated/divorced, widowed, and unknown.

h. Chemotherapy treatment was divided into: yes, no, and unknown.

i. Radiation therapy was divided into: yes, no, and unknown.

j. Surgery was divided into: yes, no, and unknown.

k. ER and PR were divided into positive, negative, and unknown.

2.5. Statistical analysis approaches

Descriptive data on demographic characteristics (Race/Ethnicity, Marital Status, Insurance, and SES) and cancer characteristics (Age at diagnosis, stage at diagnosis, tumor grade, year at diagnosis, chemotherapy, surgery, radiation, and ER, PR, and hormonotherapy (when applicable), were stratified by gender and presented for each of the three sample groups and by duration of residence for first generation ME immigrants. Means ± Standard Deviation were used for continuous variables and numbers (percentages) for frequency variables. All tests were two-sided and conducted at the 0.05 level of significance. All data analyses were completed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

[More details of the statistical analysis used can be found in the methods sections in the following chapters].

CHAPTER 3

CANCER RISK IN DIFFERENT GENERATIONS OF MIDDLE EASTERN IMMIGRANTS TO CALIFORNIA, 1988-2013

3.1. Introduction

Immigrant studies are recognized for their value in examining epidemiological associations in cancer etiology[83,95]. These studies, particularly if population-based, identify the impact of the ethnic, cultural, genetic background, and environmental exposures on cancer risk[65]. Three types of immigrant studies have been previously described. The first type compares cancer risk in immigrants with natives from the host country. The second type measures the impact of the environment by studying cancer risk in immigrants compared to people in the countries of origin of the immigrants[96]. The third type evaluates the impact of acculturation, by measuring cancer risk in different generations of immigrants[79,80]. Acculturation is defined as changes in immigrant populations' disease risk over time approaching the risk levels of the host country[78]. This can be attributed to differences in Socioeconomic Status (SES), diet, environmental exposures, or screening habits in immigrant populations. According to the Center for Immigration Studies, the number of first generation immigrants in the

United States (US) is estimated to reach 47.9 million by 2020[8]. Coming from different countries, with different lifestyles, language barriers, and risk factors, first generation immigrants are very heterogeneous and sometimes require special health care[97]. Middle Eastern immigrants (ME) constitute one of the growing immigrant populations in the US[8], and particularly in California[10,98]. They come from a wide geographic area extending from Southwest Asia to Northeast Africa. According to the US census, Non-Hispanic Whites (NHW) refer to all persons from European, Middle Eastern, and North African origin[70]. ME populations are distinct in their diet (e.g. Mediterranean diet), genetic background, cultural preferences, and health behaviors[71]. Cancer risk is not homogeneous worldwide. International studies have shown that cancer incidence in ME populations living in the Middle East is different from cancer incidence in the US[99]. The overall cancer incidence was reported to be lower in ME first generation immigrants compared to other NHW[72–74]. Studies examining cancer in immigrants and their descendants have suggested that cancer rates across generations approach the native host country's rates with succeeding generations[81–83]. However, very few studies focused on cancer in different generations of ME immigrants in the US and particularly in California[77,84]. Accurate data of the ME population in California are not available through the US census. This population is included in population statistics with NHW, which makes calculating cancer incidence rates for ME immigrants a challenge. Previous studies applied surrogate statistical methods to estimate risk including the Proportional Incidence Ratio (PIR) for cancer comparisons. This method was used to compare cancer risk between ME immigrants and other NHW in the US[76], and between the different generations of ME immigrants and NHW[77]. These studies were mainly

conducted in the Metropolitan Detroit Area of Michigan. In this study we are using similar methodology to examine possible changes in cancer risk in ME immigrants first and subsequent generations in California. The main objective of this study is to compare cancer risk among ME first, second or subsequent generations' immigrants, and NHW in California (1988-2013), particularly with respect to the 15 most common invasive primary cancers, taking into consideration the length of stay in the US for ME first generation prior to their cancer diagnosis.

3.2. Methods

3.2.1. Study population

California is one of the largest and most populated states in the US, with more than 39 million residents as of July 2015[89]. California Cancer Registry (CCR) is California's statewide population-based cancer surveillance system. CCR monitors incidence and death from cancer among Californians since 1988[90]. It captures detailed information on cancer cases, including patient's demographics (e.g. gender, country of birth, and race), cancer characteristics (e.g. age and stage at diagnosis), treatment, and follow up information. Every cancer diagnosis made in California since 1988 is required by law to be reported to CCR. As a consequence, the CCR completeness rates are high and expand with time[90]. We obtained a de-identified CCR data (1988-2013). This did not require an Institutional Review Board approval.

In 2007, Nasseri used CCR data and developed the Middle Eastern surname list using: 1) A Middle Eastern surname file extracted from the Social Security Number Identification Database (NUMIDENT), 2) Enhanced California Death Certificate Master

File, 3) Arab Surname List extracted from NUMIDENT, 4) Early California Cancer Registry files, and 5) Expertly collected surnames[91]. This surname list has a sensitivity of more than 90% in men and 86% in women. It has been validated and is included as a permanent variable in the CCR dataset, starting from 1988. Three population groups were selected to be examined in this study using CCR. If a patient had a validated Middle Eastern last name and was born in one of the Middle Eastern countries (Afghanistan, Algeria, Armenia, Bahrain, Djibouti, Egypt, Iraq, Iran, Jordan, Lebanon, Libya, Morocco, Pakistan, Palestine, Saudi Arabia, Somalia, Sudan, Syria, Turkey, Tunisia, Yemen, and Israel), he/she was considered a ME first generation immigrant. If the patient had a validated Middle Eastern last name but was born in the US, he/she was considered a ME second or subsequent generations' immigrant. If the patient did not have a ME last name, was born in the US, and was classified as White in CCR, he/she was considered NHW.

3.2.2. Cancer cases and study participants

We have identified invasive cancer cases using CCR data from 1988 to 2013. If a patient has multiple cancers, only the first cancer was included in the analysis. In this study, we decided to analyze the data with a focus on the 15 most common cancers in each of the three population groups (ME first generation, ME second or subsequent generations, and NHW), for both genders (Figure 1). These 15 cancers, representing the cancers with the highest occurrence, were not the same in each of the three population groups. Therefore, our study covered 19 cancer sites in females and 20 in

males (Tables 2 & 3) with a total number of 435,215 females and 465,639 males for these selected cancers. In females, 7,971 were first generation ME immigrants, 2,642 were second or subsequent generations ME immigrants, and 424,602 were NHW. However, in males, 10,162 were first generation ME immigrants, 2,182 were second or subsequent generations ME, and 453,295 were NHW. Other race/ethnic groups were excluded from our study.

3.2.3. Time from immigration to cancer diagnosis

Time from immigration to cancer diagnosis was calculated by using the year of issue of Social Security Number (SSN), existing in CCR, as estimation for the year of immigration. Assuming that legal immigrants receive their SSN directly after their arrival to the US[84], the year of issue of SSN can be used to estimate the immigration date and therefore the duration of stay in the US. Time since immigration was then categorized into 3 different groups with less than 10 years, 10 to 24 years, and 25 years over.

3.2.4. Statistical analysis

Descriptive data on demographic characteristics (Race/Ethnicity, Marital Status, Insurance, and SES) and cancer characteristics (Age, stage, and year at diagnosis), were stratified by gender and presented for each of the three population groups. Tests for normality were completed for continuous variables. Means ± SD were used for continuous variables and numbers (%) for frequency variables. Age-adjusted PIRs were calculated. The PIR is the observed number of ME immigrants' cancer cases

divided by the number of ME immigrants' cancer cases expected if the ME immigrant population has the same proportion of cancer as that of the NHW population. In more details, the proportions of each of the 19 invasive cancers in females and 20 cancers in males were calculated from all cancers in NHW (all cancers include the cancers that are not part of the 19 or 20 cancers) for each of the 18 different 5-year age groups. Then considering that the ME population has the same proportion of cancer as of that of the NHW population, we estimated the expected number of cases for the 19 invasive cancers in females and 20 cancers in males for each age group in first generation ME immigrants. The PIR was calculated using the total of observed cases divided by the total of expected cases for each cancer for first generation ME, separately in males and females[100]. The comparison of PIR is the NHW group. After calculating the age-adjusted total PIR, 95% Poisson CI was calculated. PIRs > 1 indicate that there are proportionally more cancers of a given site among ME first generation immigrants than among NHW, accounting for differences in the age distribution of the groups. PIRs >1 with 95% CI not containing 1 indicate statistically significant higher proportions. Same analyses were repeated for second or subsequent generations ME immigrants compared to NHW and compared to first generation of ME immigrants, separately in males and females. Additional PIRs were calculated for cancers in first generation ME compared to NHW, stratified by gender and time from immigration to cancer diagnosis. Data analyses were completed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3.3. Results

In females, breast cancer constituted the most common cancer with 38.4% in ME first generation, 33.0% in ME second or subsequent generations ME, and 30.8% in NHW. Prostate cancer was the most common cancer in males in the 3 groups with 28.7% in ME first generation, 27.4% in ME second or subsequent generations, and 27.3% in NHW. In both genders, the second most common cancer in ME first generation was colorectal cancer (CRC); however, it was lung cancer in ME second or subsequent generations and NHW **(Figure 3.1)**.

Table 3.1 shows the demographic and cancer characteristics for participants with the 15 selected most common cancers in each of the 3 population groups and stratified by gender. Overall, 435,215 females and 465,639 males were included. More than 89% of the ME immigrants were identified as NHW. Married and participants with a highest SES accounted for the topmost percentage of cases. Males had higher age at diagnosis compared to females, with NHW having the highest age at diagnosis. Immigrants were diagnosed at later years whereas NHW were diagnosed mostly between 1988 and 1992. More than 40% of the primary invasive cancers were diagnosed at a localized stage in the 3 groups.

Table 3.2 presents the age-adjusted PIRs for first generation and second or subsequent generations ME females compared to NHW females. Of the 19 primary invasive female cancers, nine had significantly higher proportions in first generation but only five in second or subsequent generations' females, four of which were the same in all ME generations. Although the highest PIR was for stomach cancer in all ME

immigrant groups, its PIR was lower in second or subsequent generations' females (PIR=1.46). Same pattern was shown for thyroid cancer where the PIR decreased in second or subsequent generations, however remained significantly higher in comparison with NHW females.

Of the 20 invasive primary cancers, twelve cancers were significantly higher in first generation males and five in second or subsequent generations **(Table 3.3)**. All generations of ME immigrants had a higher risk of thyroid, bladder, and Hodgkin lymphoma cancers with first generation having higher PIRs than second or subsequent generations. First generation immigrants had a higher risk of stomach (PIR=2.13), liver (PIR=1.43), and leukemia (PIR=1.38) cancers while second or subsequent generations were at higher risk of kidney cancer (PIR=1.27) in comparison with NHW males.

Second or subsequent generations had higher risk of malignant melanoma cancer with a PIR of 4.53 (95% CI: 3.52, 5.73) in females and 4.61(95% CI: 3.57, 5.87) in males when compared to first generation of ME immigrants. The PIR for lung cancer was the second highest in females (PIR=2.31) but not in males (PIR=1.20) **(Table 3.4)**.

Table 3.5 presents the age-adjusted PIRs for the 5 most common cancers in first generation ME immigrants compared to NHW, stratified by gender and time from immigration to cancer diagnosis. In females, there was an increase in PIR overtime for CRC. Breast and thyroid cancers maintained significant higher PIRs regardless of the length of time since immigration. In males, the PIR for bladder cancer remained higher regardless of the period since immigration while there was an increase in CRC and Non-Hodgkin Lymphoma cancer risks.

3.4. Discussion

Immigrant studies, using first and subsequent generations, are invaluable in identifying the impact of the ethnic, cultural, genetic predisposition, environmental exposure, and gene*environmental interaction on the etiology and distribution of cancer. The overall aim of this study was to compare cancer risk among ME first, second or subsequent generations' immigrants, and NHW, for the most common invasive primary cancers, taking into consideration the length of time since immigration to the US for ME first generation females and males. Our research question focused on the ME population at large and not on individual Middle Eastern countries.

Our results show that the distribution of invasive cancers is very similar in ME first, second or subsequent generations, and NHW, in both males and females. They confirm previous studies looking at cancer in four countries of the Middle East in comparison with the US[101]. Breast cancer is the most common cancer in females in the 3 population groups, similar to many ME countries including Lebanon[102,103], Iran[104], Tunisia[105], Egypt, and Gaza strip[106]. Prostate cancer is the most common cancer in males in the 3 groups, similar to some ME countries[32], but not all.

Several cancer types have significantly higher PIRs in first generation ME compared to NHW. These cancers include stomach, biliary & gallbladder, thyroid, multiple myeloma, leukemia, CRC, and bladder cancers in females. They also include stomach, bladder, CRC, Non-Hodgkin Lymphoma, brain, and liver cancers in males. These differences were attenuated in second and subsequent ME generations compared to NHW indicating the impact of possible acculturation due to changes

associated with environmental (diet, exposure early in life…), cultural, other non-genetic causes, as well as gene*environment interaction. The reduction in PIR between first and second or subsequent generations ME immigrants is more pronounced for stomach, larynx, liver, bladder, and biliary & gallbladder cancers where second or subsequent ME immigrants are not exposed to environmental agents such as *Helicobacter pylori* and hepatitis B responsible for the increased risk of stomach and hepatobiliary cancers in first generation immigrants.

On the other hand, there is an increase in PIRs in second or subsequent generations ME for kidney cancer in males, and for Hodgkin Lymphoma in females, in comparison with NHW. Hypotheses regarding availability of screening modalities in the US compared to ME countries and more exposure to kidney cancer associated causes in the US compared to the Middle East can be considered while examining acculturation. Several cancer types have significantly higher PIRs in second or subsequent generations ME immigrants in comparison to first generation. These cancers include malignant melanoma, lung, and kidney cancers where second or subsequent generations are more susceptible to social behaviors such as sunbathing[107] and smoking which explain the differences between the different generations.

To further investigate the effect of acculturation, we examined the change in cancer risk in first generation ME immigrants compared to NHW, with the length of stay in the US, starting from immigration to cancer diagnosis. Cancers, such as CRC in both genders and Non-Hodgkin Lymphoma in males, have significantly higher PIRs with more prolonged time since immigration. This unanticipated increase in CRC risk can be explained by: changes in diet particularly the increase in red meat consumption[108],

reduction in physical activity[109], and other gene-environment interaction. Acculturation of ME immigrants and sharing a Westernized lifestyle, particularly replacing their original Mediterranean diet with a Western diet indicates the importance of diet in the etiology of CRC. However, the increase of Non-Hodgkin Lymphoma overtime in first generation immigrants can be explained by differences in SES with more time spent in the US and changes in screening modalities and access to health care between the Middle East and the US. Investigating cancer risk overtime can also be helpful in identifying the effect of genetic predisposition on cancer. Cancers, such as breast and thyroid, have significantly higher PIRs in all generations of ME immigrants compared to NHW. The persistence of this relationship with a longer period of stay in the US for ME first generation female immigrants suggests the role of genetic predisposition on breast[110] and thyroid cancers[111].

Our results add to the limited literature on Middle Eastern immigrants in the US[71,76,77]. To our information, only one other study looked at cancer risk in different generations of ME immigrants[77]. This study was conducted in California and our results are similar with higher risk of cancers such as stomach and liver in ME first generation males, bladder in ME second or subsequent generations' males, stomach and thyroid in ME first generation females, and thyroid in ME second or subsequent generations' females, when compared with NHW.

Literature on ME immigrants in the US is very scarce. Our study adds new insights and contributes to the understanding of acculturation in these ME immigrants to California. To our knowledge, this is the first study to examine cancer risk for the most common cancers in different generations of immigrants from the Middle East to

California, with taking the length of stay from immigration to cancer diagnosis into consideration. We included the 2 approaches needed to investigate the role of acculturation on cancer in immigrants[96] by looking at cancer in first generation of ME immigrants stratified by duration of time since immigration to the US in addition to cancer risk in different generations of ME immigrants. This study is one of few to use the year of issue of SSN as an estimate for year of immigration, and therefore calculate the duration of stay in the US from immigration to cancer diagnosis in ME immigrants. We used CCR which is California's statewide population-based cancer registry, with cancer cases diagnosed between 1988 and 2013. In addition, while calculating the PIRs, we adjusted for age to account for cancer differences due to age at diagnosis in the 3 groups.

This study has some limitations. Maiden name is not accessible for Health Insurance Portability and Accountability Act reasons so we were not able to capture ME females who changed their last name after marriage or children born to ME females but not ME males given that the children usually take the father’s last name in the Middle Eastern culture. In addition, we were not able to identify ME immigrants with missing ME last name or missing place of birth. For this study, we used SSN to estimate the length of stay in the US but not age at immigration. This may influence ME cancer risk and we will use it in future studies. We have small sample sizes for some of the cancers limiting the power of our analysis. Lastly, we don’t have available information on diet, smoking habits, and body composition. Smoking is the highest risk factor for lung and bladder cancers, with smoking rates varying among the Middle Eastern countries, and between males and females[101]. We expect the dietary patterns to be similar between

the Middle Eastern countries. However, immigrants tend to adapt to a more Westernized diet after immigration. Reproductive factors are very important in breast cancer risk and therefore, the availability of these factors may have helped in the interpretation of breast cancer results.

In conclusion, our results suggest differences in cancer risk between ME first generation immigrants and NHW. However, these differences decline in second or subsequent generations, suggesting the impact of acculturation on cancer risk in second or subsequent generations which approaches the risk level of NHW in the US. The differences between the ME different generations and the possible acculturation which takes place particularly in second or subsequent generations have strong potential for creating and testing causal hypotheses for cancer which can be tested and increase our knowledge to plan prevention and control of cancer.

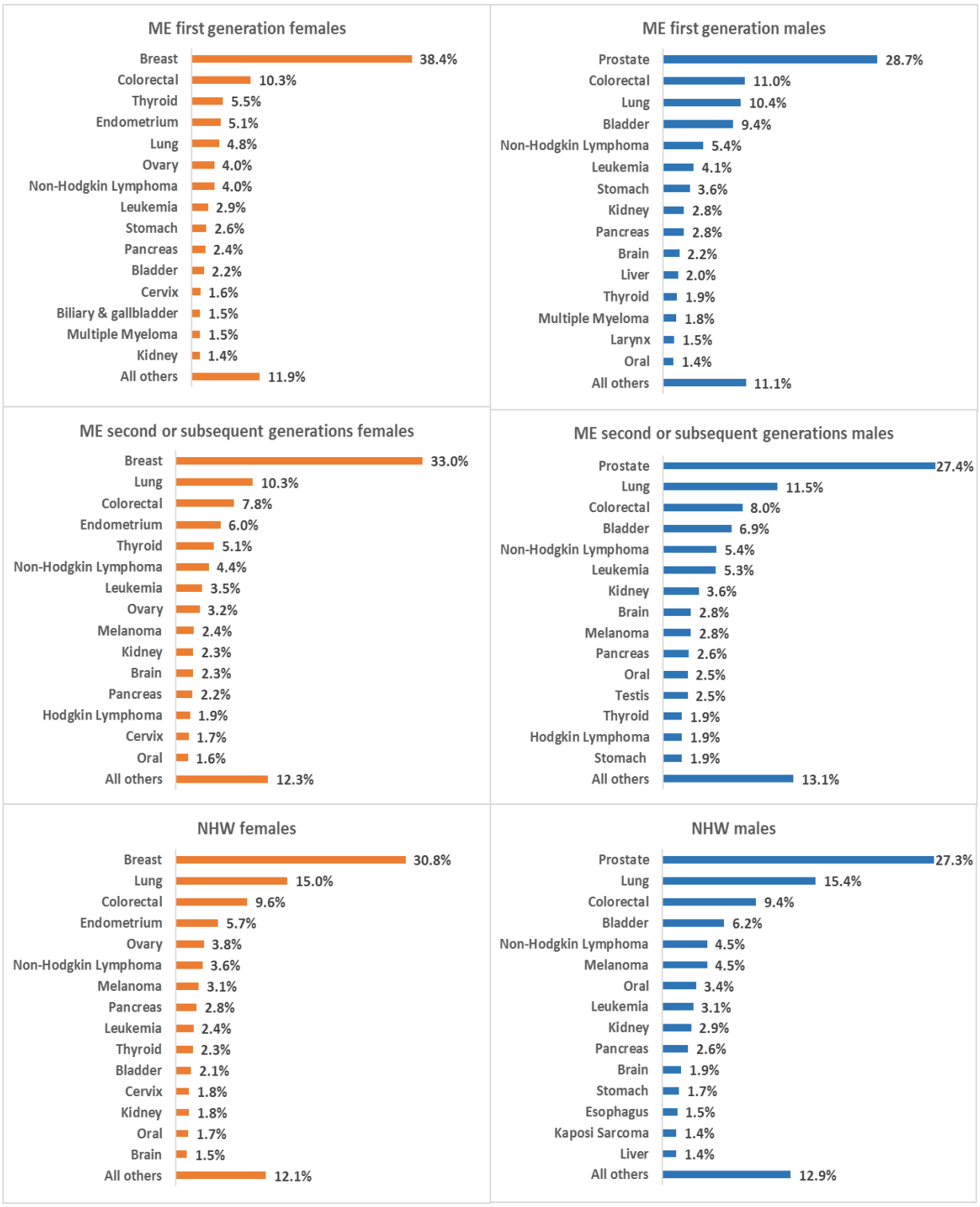

Figure 3.1: Invasive primary cancer case distribution for the 3 population groups in females and males.
Abbreviations: ME: Middle Eastern immigrants; NHW: Non-Hispanic Whites.

Table 3.1: Demographic and cancer characteristics of study participants with the selected most common primary invasive cancers: CCR 1988-2013.

Characteristics	Females (N=435,215)			Males (N=465,639)		
	ME First generation	**ME Second or subsequent generations**	**NHW**	**ME First generation**	**ME Second or subsequent generations**	**NHW**
	N=7,971	**N=2,642**	**N=424,602**	**N=10,162**	**N=2,182**	**N=453,295**
Demographics						
Race/ethnicity. N (%)						
Identified as NHW	7,316 (91.8)	2,364 (89.5)	424,602 (100)	9,422 (92.7)	1,950 (89.4)	453,295 (100)
Identified as other race/ethnicity	655 (8.2)	278 (10.5)	0	740 (7.3)	232 (10.6)	0
Marital status. N (%)						
Single	798 (10.0)	518 (19.6)	50,863 (12.0)	925 (9.1)	475 (21.8)	63,299 (14.0)
Married	4,539 (57.0)	1,313 (49.7)	202,524 (47.7)	7,961 (78.3)	1,345 (61.6)	304,221 (67.1)
Separated/divorced	521 (6.5)	304 (11.5)	53,495 (12.6)	496 (4.9)	176 (8.1)	36,375 (8.0)
Widowed	1,945 (24.4)	461 (17.5)	109,379 (25.7)	498 (4.9)	140 (6.4)	37,525 (8.3)
Unknown	168 (2.1)	46 (1.7)	8,341 (2.0)	282 (2.8)	46 (2.1)	11,875 (2.7)
Insurance. N (%)						

Managed care, HMO, PPO, Private	2,368 (29.7)	1,132 (42.9)	141,585 (33.4)	2,757 (27.1)	812 (37.2)	141,155 (31.1)
Medicaid	1,513 (19.0)	135 (5.1)	14,067 (3.3)	1,435 (14.1)	108 (5.0)	13,076 (2.9)
Medicare	2,268 (28.5)	559 (21.2)	97,983 (23.1)	3,499 (34.4)	563 (25.8)	110,034 (24.3)
Insured, other type	262 (3.3)	138 (5.2)	19,574 (4.6)	280 (2.8)	79 (3.6)	19,030 (4.2)
Not insured/Unknown	1,560 (19.5)	678 (25.6)	151,393 (35.6)	2,191 (21.6)	620 (28.4)	170,000 (37.5)
SES. N (%)						
Lowest SES	554 (6.9)	261 (9.9)	44,977 (10.6)	829 (8.1)	239 (10.9)	47,970 (10.6)
Lower-middle SES	1,187 (14.9)	374 (14.1)	78,619 (18.5)	1,510 (14.9)	326 (14.9)	83,252 (18.4)
Middle SES	1,559 (19.6)	457 (17.3)	94,339 (22.2)	1,835 (18.1)	396 (18.2)	98,482 (21.7)
Higher-middle SES	1,904 (23.9)	636 (24.1)	100,920 (23.8)	2,336 (23.0)	516 (23.7)	106,391 (23.5)
Highest SES	2,767 (34.7)	914 (34.6)	105,747 (24.9)	3,652 (35.9)	705 (32.3)	117,200 (25.8)
Cancer Characteristics						
Age at diagnosis.						
Mean (SD)	61.0 (15.2)	58.1 (18.9)	64.9 (15.5)	65.1 (13.4)	61.0 (19.2)	65.6 (14.2)
Median	62	61	67	66	66	67
Year at Diagnosis.						

N (%)						
1988-1992	903 (11.3)	422 (16.0)	99,351 (23.4)	1,187 (11.7)	401 (18.4)	116,543 (25.7)
1993-1997	1,293 (16.2)	450 (17.0)	90,466 (21.3)	1,824 (18.0)	408 (18.7)	98,407 (21.7)
1998-2002	1,732 (21.7)	509 (19.3)	85,038 (20.0)	2,206 (21.7)	417 (19.1)	85,404 (18.9)
2003-2007	1,766 (22.2)	576 (21.8)	73,550 (17.3)	2,339 (23.0)	449 (20.6)	76,773 (16.9)
2008-2013	2,277 (28.6)	685 (25.9)	76,197 (18.0)	2,606 (25.6)	507 (23.2)	76,168 (16.8)
Stage at Diagnosis. N (%)						
In situ	71 (0.9)	18 (0.7)	2,618 (0.6)	387 (3.8)	50 (2.3)	8,695 (1.9)
Localized	3,468 (43.5)	1,146 (43.4)	178,161 (42.0)	4,546 (44.7)	1,003 (46.0)	194,135 (42.8)
Regional	2,389 (30.0)	719 (27.2)	106,947 (25.2)	2,042 (20.1)	395 (18.1)	88,665 (19.6)
Remote	1,711 (21.4)	647 (24.5)	103,526 (24.4)	2,571 (25.3)	586 (26.8)	118,393 (26.1)
Unknown	332 (4.2)	112 (4.2)	33,350 (7.8)	616 (6.1)	148 (6.8)	43,407 (9.6)

Abbreviations: CCR: California Cancer Registry; ME: Middle Eastern immigrants; NHW: Non-Hispanic Whites; N (%): Sample size (percentage); SES: Socio-Economic Status; SD: Standard Deviation.

Table 3.2: Age-adjusted PIRs (95% CI) for different generations of ME female immigrants compared to NHW females for the most common 19 primary invasive cancers: CCR 1988-2013.

Cancer type	ME first generation				ME second or subsequent generations			
	Total observed	Total expected	PIR	95% CI	Total observed	Total expected	PIR	95% CI
Breast	3,331	2,856.80	1.17[a]	1.13, 1.21	948	877.91	1.08[a]	1.01, 1.15
Colorectal	892	745.01	1.20[a]	1.12, 1.28	225	231.03	0.97	0.85, 1.11
Thyroid	480	253.03	1.90[a]	1.73, 2.07	145	101.55	1.43[a]	1.20, 1.68
Endometrium	442	498.15	0.89	0.81, 0.97	172	151.19	1.14	0.97, 1.32
Lung	416	1,211.10	0.34	0.31, 0.38	296	370.25	0.80	0.71, 0.90
Ovary	347	333.77	1.04	0.93, 1.16	93	108.81	0.85	0.69, 1.05
Non-Hodgkin Lymphoma	346	303.54	1.14[a]	1.02, 1.27	127	101.39	1.25[a]	1.04, 1.49
Leukemia	250	184.31	1.36[a]	1.19, 1.54	101	96.88	1.04	0.85, 1.27
Stomach	227	72.34	3.13[a]	2.74, 3.57	33	22.59	1.46[a]	1.01, 2.05
Pancreas	208	214.98	0.97	0.84, 1.11	62	66.57	0.93	0.71, 1.19
Bladder	190	161.72	1.17[a]	1.01, 1.35	41	50.24	0.82	0.59, 1.11
Cervix Uteri	138	195.21	0.71	0.59, 0.84	49	67.59	0.72	0.54, 0.96

Biliary & Gallbladder	129	56.75	2.27[a]	1.90, 2.70	19	17.46	1.09	0.65, 1.70
Multiple Myeloma	127	83.36	1.52[a]	1.27, 1.81	30	25.55	1.17	0.79, 1.68
Kidney	122	146.84	0.83	0.69, 0.99	66	53.14	1.24	0.96, 1.58
Brain	115	131.88	0.87	0.72, 1.05	65	70.01	0.93	0.72, 1.18
Oral	98	142.91	0.69	0.56, 0.84	46	46.10	1.00	0.73, 1.33
Hodgkin Lymphoma	68	61.17	1.11	0.86, 1.41	55	38.80	1.42[a]	1.07, 1.85
Melanoma	45	313.18	0.14	0.10, 0.19	69	113.29	0.61	0.47, 0.77

Abbreviations: PIRs: Proportional Incidence Ratios; CI: Confidence Interval; ME: Middle Eastern immigrants; NHW: Non-Hispanic Whites; CCR: California Cancer Registry.

[a] Significant higher PIRs

Table 3.3: Age-adjusted PIRs (95% CI) for different generations of ME male immigrants compared to NHW males for the most common 20 primary invasive cancers: CCR 1988-2013.

Cancer type	ME first generation				ME second or subsequent generations			
	Total observed	Total expected	PIR	95% CI	Total observed	Total expected	PIR	95% CI
Prostate	3,149	2,998.80	1.05[a]	1.01, 1.09	650	587.68	1.11[a]	1.02, 1.19
Colorectal	1,208	1,031.30	1.17[a]	1.11, 1.24	190	205.21	0.93	0.80, 1.07
Lung	1,143	1,694.40	0.67	0.64, 0.71	272	333.45	0.82	0.72, 0.92
Bladder	1,034	671.02	1.54[a]	1.45, 1.64	164	133.54	1.23[a]	1.05, 1.43
Non-Hodgkin Lymphoma	589	498.79	1.18[a]	1.09, 1.28	127	116.13	1.09	0.91, 1.30
Leukemia	453	327.30	1.38[a]	1.26, 1.52	126	105.48	1.19	1.00, 1.42
Stomach	399	187.24	2.13[a]	1.93, 2.35	44	37.20	1.18	0.86, 1.59
Pancreas	308	279.60	1.10	0.98, 1.23	61	55.28	1.10	0.84, 1.42
Kidney	310	321.57	0.96	0.86, 1.08	86	67.94	1.27[a]	1.01, 1.56
Brain	238	204.74	1.16[a]	1.02, 1.32	67	69.34	0.97	0.75, 1.23
Testis	91	142.53	0.64	0.51, 0.78	59	55.71	1.06	0.81, 1.37
Melanoma	68	503.97	0.13	0.10, 0.17	66	109.94	0.60	0.46, 0.76
Oral	157	380.75	0.41	0.35, 0.48	59	76.80	0.77	0.58, 0.99

Liver	217	151.63	1.43[a]	1.25, 1.63	31	31.93	0.97	0.66, 1.38
Multiple Myeloma	202	137.70	1.47[a]	1.27, 1.68	36	27.13	1.33	0.93, 1.84
Thyroid	206	94.26	2.19[a]	1.90, 2.51	46	22.95	2.00[a]	1.47, 2.67
Larynx	163	134.50	1.21[a]	1.03, 1.41	18	26.33	0.68	0.41, 1.08
Hodgkin Lymphoma	112	70.99	1.58[a]	1.30, 1.90	45	29.88	1.51[a]	1.10, 2.02
Esophagus	56	163.48	0.34	0.26, 0.44	14	31.94	0.44	0.24, 0.74
Kaposi Sarcoma	59	165.14	0.36	0.27, 0.46	21	43.05	0.49	0.30, 0.75

Abbreviations: PIRs: Proportional Incidence Ratios; CI: Confidence Interval; ME: Middle Eastern immigrants; NHW: Non-Hispanic Whites; CCR: California Cancer Registry.

[a] Significant higher PIRs

Table 3.4: Age-adjusted PIRs (95% CI) for ME second or subsequent generations' immigrants compared to ME first generation immigrants for the selected most common primary invasive cancers, stratified by gender: CCR 1988-2013.

Cancer type	Total observed	Total expected	PIR	95% CI
Females				
Breast	948	1,024.10	0.93	0.87, 0.99
Lung	296	127.97	2.31[a]	2.06, 2.59
Colorectal	225	275.70	0.82	0.71, 0.93
Endometrium	172	134.52	1.28[a]	1.09, 1.48
Thyroid	145	180.08	0.81	0.68, 0.95
Non-Hodgkin Lymphoma	127	117.66	1.08	0.90, 1.28
Leukemia	101	144.68	0.70	0.57, 0.85
Ovary	93	108.73	0.86	0.69, 1.05
Melanoma	69	15.24	4.53[a]	3.52, 5.73
Kidney	66	39.07	1.69[a]	1.31, 2.15
Brain	65	41.07	1.58[a]	1.22, 2.02
Pancreas	62	64.06	0.97	0.74, 1.24
Hodgkin Lymphoma	55	39.69	1.39[a]	1.04, 1.80
Cervix Uteri	49	44.54	1.10	0.81, 1.45
Oral	46	38.62	1.19	0.87, 1.59
Bladder	41	59.05	0.69	0.50, 0.94
Stomach	33	70.68	0.47	0.32, 0.66
Multiple Myeloma	30	38.73	0.77	0.52, 1.11
Biliary & Gallbladder	19	39.70	0.48	0.29, 0.75
Males				
Prostate	650	615.66	1.06	0.98, 1.14
Lung	272	226.70	1.20[a]	1.06, 1.35
Colorectal	190	242.90	0.78	0.67, 0.90
Bladder	164	205.86	0.80	0.68, 0.93
Non-Hodgkin Lymphoma	127	131.51	0.97	0.81, 1.15
Leukemia	126	142.66	0.88	0.74, 1.05
Kidney	86	62.91	1.37[a]	1.09, 1.69
Brain	67	70.08	0.96	0.74, 1.21
Melanoma	66	14.30	4.61[a]	3.57, 5.87
Pancreas	61	61.10	1.00	0.76, 1.28
Testis	59	34.21	1.72[a]	1.31, 2.22
Oral	59	32.03	1.84[a]	1.40, 2.38
Thyroid	46	48.07	0.96	0.70, 1.28
Hodgkin Lymphoma	45	45.95	1.00	0.71, 1.31
Stomach	44	79.25	0.56	0.40, 0.75
Multiple Myeloma	36	40.09	0.90	0.63, 1.24
Liver	31	42.24	0.73	0.50, 1.04

Kaposi Sarcoma	21	12.61	1.67[a]	1.03, 2.55
Larynx	18	31.83	0.57	0.34, 0.89
Esophagus	14	11.06	1.27	0.69, 2.12

Abbreviations: PIRs: Proportional Incidence Ratios; CI: Confidence Interval; ME: Middle Eastern immigrants; CCR: California Cancer Registry.

[a] Significant higher PIRs

Table 3.5: Age-adjusted PIRs (95% CI) for the 5 most common cancers in ME first generation immigrants compared to NHW, stratified by gender and time from immigration to cancer diagnosis: CCR 1988-2013.

Cancer Type	Time from immigration to diagnosis [a]	Total observed	Total expected	PIR	95% CI
Females					
Breast	< 10	766	605.73	1.26[b]	1.18, 1.36
	10-24	1,643	1,307.70	1.26[b]	1.20, 1.32
	>= 25	922	772.63	1.19[b]	1.12, 1.27
Colorectal	< 10	188	175.01	1.07	0.93, 1.24
	10-24	437	437.56	1.00	0.91, 1.10
	>= 25	267	219.21	1.22[b]	1.08, 1.37
Thyroid	< 10	132	61.13	2.16[b]	1.81, 2.56
	10-24	219	119.38	1.83[b]	1.60, 2.09
	>= 25	129	48.58	2.66[b]	2.22, 3.15
Endometrium	< 10	83	131.26	0.63	0.50, 0.78
	10-24	218	238.32	0.91	0.80, 1.04
	>= 25	141	143.14	0.99	0.83, 1.16
Lung	< 10	96	308.56	0.31	0.25, 0.38
	10-24	196	528.32	0.37	0.32, 0.43
	>= 25	124	356.05	0.35	0.29, 0.42
Males					
Prostate	< 10	691	598.32	1.15[b]	1.07, 1.24
	10-24	1,239	1,170.10	1.06	1.00, 1.12
	>= 25	1,219	1,133.70	1.08[b]	1.02, 1.14
Colorectal	< 10	209	218.83	0.96	0.83, 1.09
	10-24	526	456.28	1.15[b]	1.06, 1.26
	>= 25	473	375.97	1.26[b]	1.15, 1.38
Lung	< 10	259	453.83	0.57	0.50, 0.64
	10-24	505	645.48	0.78	0.72, 0.85
	>= 25	379	630.27	0.60	0.54, 0.67
Bladder	< 10	222	144.04	1.54[b]	1.35, 1.76

	10-24	434	313.32	1.39[b]	1.26, 1.52
	>= 25	378	244.37	1.55[b]	1.39, 1.71
Non-Hodgkin Lymphoma	< 10	108	111.73	0.97	0.79, 1.17
	10-24	250	236.56	1.06	0.93, 1.20
	>= 25	231	161.64	1.43[b]	1.25, 1.63

Abbreviations: PIRs: Proportional Incidence Ratios; CI: Confidence Interval; ME: Middle Eastern immigrants; NHW: Non-Hispanic Whites; CCR: California Cancer Registry.

[a] Time from immigration to cancer diagnosis in years

[b] Significant higher PIRs

CHAPTER 4

BREAST CANCER CHARACTERISTICS IN MIDDLE EASTERN WOMEN IMMIGRANTS COMPARED TO NON-HISPANIC WHITE WOMEN IN CALIFORNIA

4.1. Introduction

In the United States (US), breast cancer mortality has been decreasing over the past few decades. Five-year breast cancer specific survival rates have improved from 75.2% in 1975 to 91.3% in 2009[112]. Stage at diagnosis is considered to be the strongest determinant of breast cancer survival[113]. Survival rates vary by stage at diagnosis with 100.0% for in-situ, 98.5% for localized, 84.6% for regional, and 25.0% for distant breast cancers[114].

Studies have shown that immigrants to the US present with more advanced cancer stage at diagnosis and have lower survival rates compared to non-immigrant Non-Hispanic Whites (NHW)[87,115–119]. Access to health care, lower rates of mammography screening, language barriers, genetic factors, and other socio-cultural factors have been suggested to explain these disparities[120,121]. Lower rates of mammography screening among immigrant women have been explained by multiple factors including having a lower education level, being a new immigrant, and not having a public insurance coverage[122]. It has also been suggested that immigrants do not have a clear knowledge of the healthcare system which can be a barrier in breast cancer screening[123].

One of the growing immigrant populations in the US[8], and particularly in California[10,98] is the Middle Eastern (ME) immigrant population. Studies have been conducted to compare breast cancer stage and survival in different immigrant groups in the US[4–10,17,18]. To our knowledge, only two studies investigated stage at diagnosis and survival in the ME immigrant population[126,127]. One of the reasons is that immigrants from the Middle East are not recognized as a separate ethnic group in the US census and are combined with NHW[70]. The study conducted in Michigan has shown that ME immigrants were more likely to be diagnosed at advanced stage, yet had better overall survival than NHW[126]. While the study performed in California has shown similar survival patterns for stage IIA breast cancers only[127].

Immigrant studies can evaluate the impact of acculturation by investigating cancer outcomes by place of birth (different generations of immigrants) and duration of residence in the host country[79,80,128]. Shorter duration of residence in immigrants has been shown to be an important indicator in not receiving guideline-concordant cancer screening[129]. To our knowledge, this is the first study to examine breast cancer stage at diagnosis and survival in different generations of ME immigrants in California and by duration of residence for first generation ME immigrants. First generation ME immigrants are born in the Middle East, while second or subsequent generations ME immigrants are born elsewhere. This study aims to analyze the association between ME immigration status and breast cancer stage at diagnosis and all-cause and breast cancer-specific mortality in different generations of ME immigrants and NHW in California between 1988 and 2013. It also aims to investigate the association between

the duration of residence and breast cancer stage and all-cause and breast cancer-specific mortality in first generation ME immigrants.

4.2. Methods

4.2.1. Data source

California Cancer Registry (CCR) is California's statewide population-based cancer surveillance system. The registry monitors incidence and death from cancer among Californians since 1988[90]. CCR captures information on the patient's demographics, cancer characteristics, treatment, and follow-up information. The demographic information includes marital status, health insurance, and socio-economic status (SES). The cancer characteristics include: age at diagnosis, year at diagnosis, stage at diagnosis, estrogen and progesterone receptors (ER & PR), tumor grade, and cancer histology. Treatment options include surgery and chemotherapy. This study did not require an Institutional Review Board approval.

4.2.2. Study populations

This study cohort consisted of all female patients from CCR who: 1) were diagnosed in California, 2) between January 1st, 1988 and December 31st, 2013, 3) with a primary breast cancer, 4) were younger than 100 years old at diagnosis, 5) had an available social security number (SSN), 6) were part of the 3 population groups of interest (first generation ME immigrants, second or subsequent generations ME immigrants, and NHW), and 7) had a known breast cancer stage at diagnosis.

The 3 population groups of interest in this study were: first generation ME immigrants, second or subsequent generations ME immigrants, and NHW. If the patient had a Middle Eastern last name[91], did not have a Hispanic nor Asian last name, and was born in one of the Middle Eastern countries, she was considered first generation ME immigrant. If the patient had a Middle Eastern last name[91], did not have a Hispanic nor Asian last name, was not born in one of the Middle Eastern countries, and did not have a missing birth country, she was considered second or subsequent generations ME immigrant. Finally, if the patient did not have a ME nor Hispanic nor Asian last name and was identified as White in the CCR dataset, she was considered NHW in our analysis.

4.2.3. Stage at diagnosis and survival

Summary stage at diagnosis existing in the CCR dataset (SUMSTAGE) was used for cancer stage in this study[130]. Breast cancer stage at diagnosis was categorized into: in situ, localized, and non-localized, with non-localized tumors including regional and distant cancers. Regional breast cancers involve cancers that have spread to nearby lymph nodes, tissues, or organs. Distant breast cancers involve cancers that have spread to distant parts of the body. Localized cancer at diagnosis was used as the referent stage in this study.

CCR contains the patient's underlying cause of death, the vital status, and the follow-up time in months. The last date for follow-up observation was December 31st, 2013. Breast cancer specific deaths were classified as codes 1740-1749 of the

International Classification of Diseases (ICD) ninth revision for deaths that occurred between 1988 and 1998 and codes C500-C509 of the ICD tenth revision for deaths that occurred in 1999 and beyond. Cancer survival analysis was completed for invasive primary breast cancer cases only; hence, in-situ breast cancers were excluded from survival analysis.

4.2.4. Other study variables

Age at diagnosis was used as a continuous measurement, in addition to the three age categories created (< 45, 45-54, and $\geq$ 55 years old). Duration of residence in the US was calculated for first generation ME immigrants by using year at diagnosis and year of issue of SSN (duration of residence=year at diagnosis - year of issue of SSN). A categorical variable was created with duration of residence less than 20 years and duration or residence equal to 20 years or more. This cutoff point was selected based on the median duration of residence for first generation ME immigrants. ER and PR were categorized as positive, negative, and unknown. Surgery and chemotherapy treatment were categorized as no, yes, and unknown. Tumor grade was divided into 5 categories: well differentiated, moderately differentiated, poorly differentiated, undifferentiated/anaplastic, and unknown if differentiated. Lastly, cancer histology was categorized into: ductal, lobular, ductal/lobular, mucinous, and others.

4.2.5. Statistical analysis

The descriptive data was stratified and presented for the 3 population groups of interest and by duration of residence for first generation ME immigrants. Means ± standard deviations and medians were presented for continuous variables and numbers (percentages) for categorical variables.

Multinomial logistic regression[131] models were fitted to evaluate the risk of in-situ and non-localized breast cancer stage in comparison with localized cancer (referent stage) among the different generations of ME immigrants and NHW. We started with a model (model 0) containing the main exposure variable (population groups). We then added the following covariates selected a priori: SES to model 1, health insurance to model 2, and marital status to model 3. The time of this study is large (1988 to 2013) and there are differences in breast cancer screening practices and guidelines among these years in the US and the Middle East. Therefore, in the multivariate analyses of risk of advanced stage, age and year at diagnosis were controlled as strata. Additional logistic regression models were applied to evaluate the risk of non-localized (advanced) breast cancer stage in first generation ME immigrants residing in the US for less than 20 years (shorter duration) compared to first generation ME immigrants residing in the US for 20 years or more (longer duration).

Ten-year overall and breast cancer-specific survival percentages with 95% confidence intervals (CIs) were calculated using lifetables. The log-rank test was employed to compare survival curves among the 3 population groups.

Cox proportional hazard models were applied to calculate hazard ratios (HRs) with their 95% CIs for all-cause mortality and breast cancer-specific mortality in the different generations of ME immigrants compared to NHW. They were also applied to evaluate the risk of all-cause and breast cancer-specific death in first generation ME immigrants with shorter duration of residence compared to first generation ME immigrants with longer duration of residence in the US. We began with a model including the exposure variable (population group or duration of residence). We then added stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, and cancer histology to model 1, SES to model 2, health insurance to model 3, and finally marital status to model 4. Age and year at diagnosis were controlled as strata. The proportional hazard assumption was examined by testing the interaction of time with the covariates. There was no violation for this assumption.

All data analyses were completed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

4.3. Results

Female breast cancer cases accounted for 651,270 of the cases in the CCR dataset between 1988 and 2013. Of which, 543,180 female patients had primary breast cancers. We restricted eligibility to women younger than 100 years at diagnosis (N=542,974) and with available SSN (N=541,182). Of those, 3,922 were first generation ME immigrants, 2,448 were second or subsequent generations ME immigrants, and 345,643 were NHW. After excluding breast cancer cases with unknown stage at

diagnosis, our sample included 3,841 first generation ME immigrants, 2,405 second or subsequent generations ME immigrants, and 337,630 NHW women. Survival analysis was performed on invasive breast cancers only. Therefore, the final sample used in the survival analysis was 3,246 breast cancer cases for first generation ME immigrants, 2,056 for second or subsequent generations ME immigrants, and 285,256 for NHW **(figure 4.1)**.

Table 4.1 shows the descriptive characteristics for breast cancer cases for all stages combined (in-situ, localized, and non-localized), stratified by the 3 populations groups. Most of the patients had the highest quintile of SES and had health insurance with first generation ME immigrants having the highest proportion (SES 39.1% and health insurance 82.6%). NHW were older at diagnosis compared to the different generations of ME immigrants. Breast cancer patients in the 3 population groups were diagnosed the most at a localized stage and more than 14.0% were in-situ breast cancers. The largest proportion of the cases had positive ER (57.6% - 64.1%) and positive PR (48.1% - 53.8%), Most of the tumors were ductal (62.9%-65.3%) and were moderately well differentiated followed by poorly differentiated. Most of the patients had surgery and chemotherapy as breast cancer treatments. This table also shows the characteristics of first generation ME immigrants stratified by duration of residence. A higher percentage of first generation ME immigrants residing in the US for 20 years or more (longer duration) had the highest SES (44.4% vs. 34.9%) and had health insurance (91.6% vs. 75.2%) compared to immigrants who have been residents for less than 20 years (shorter duration). Patients with longer duration of residence were older, had less advanced breast cancer stage, were diagnosed more in recent years (2008-

2013), had higher percentage of positive ER and PR, and higher percentage of well differentiated breast tumors compared to first generation ME immigrants residing in the US for shorter duration of residence.

No significant differences were detected in the odds of being diagnosed with in-situ breast cancers (vs. localized stage) among the 3 population groups **(table 4.2)**. **Table 4.3** shows first generation ME immigrants having higher odds of being diagnosed with a non-localized stage (vs. localized stage) when compared with NHW [OR=1.28 with 95% CI (1.20, 1.38)], after adjusting for SES, health insurance, and marital status and controlling for age and year at diagnosis as strata. Second or subsequent generations of ME immigrants also had higher odds of being diagnosed with a non-localized stage (vs. localized stage) when compared with NHW [OR=1.41 with 95% CI (1.29, 1.54)]. No significant differences were shown in the risk of advanced breast cancer stage between first generation ME immigrants and second or subsequent generations ME immigrants.

Table 4.4 shows the association between duration of residence for first generation ME immigrants and breast cancer stage at diagnosis. After controlling for age and year at diagnosis as strata and adjusting for SES, health insurance, and marital status, there were no significant differences in advanced breast cancer stage between ME first generation immigrants with shorter duration of residence compared to first generation ME immigrants with longer duration of residence (OR=1.14 with 95% CI: 0.94, 1.40).

The ten-year overall and breast cancer-specific survival analyses are illustrated in **table 4.5**. Regardless of the breast cancer diagnosis stage, first generation ME immigrants had the highest overall survival, while NHW had the lowest overall survival among the three population groups. First generation ME immigrants also had the highest breast cancer specific survival among the 3 population groups for localized and non-localized breast cancer stages. Survival percentages from breast cancer were higher than overall survival. Non-localized breast cancer cases had lower survival when compared to localized breast cancers. The log-rank test was computed and it showed a significant difference among the 3 population groups, except for breast cancer specific survival in localized cancer stage.

After adjusting for stage at diagnosis, tumor grade, surgery, chemotherapy, ER, PR, cancer histology, SES, health insurance, and marital status, and controlling for age and year at diagnosis as strata, first generation ME immigrants were 14% less likely to die than NHW [HR=0.86 with 95% CI (0.80, 0.92)]. There were no significant differences in all-cause mortality or in breast cancer-specific mortality between second or subsequent generations ME immigrants and NHW, or breast cancer-specific mortality between first generation ME immigrants and NHW [HR=0.97 with 95% CI (0.89, 1.06)] **(table 4.6)**.

Table 4.7 shows the association between duration of residence for first generation ME immigrants and all-cause and breast cancer-specific mortality. There were no significant differences between first generation ME immigrants with shorter duration compared to longer duration in overall mortality [HR=1.02 with 95% CI (0.79, 1.32)] nor breast cancer-specific mortality [HR=1.02 with 95% CI (0.73, 1.44)].

4.4. Discussion

This study found that first generation ME immigrants had higher all-cause survival despite being diagnosed at a non-localized breast cancer stage when compared with NHW. In addition, second or subsequent generations ME immigrants also had higher risk of advanced breast cancer stage at diagnosis when compared with NHW.

Previous studies have shown that immigrants present with more advanced breast cancer stage at diagnosis[87,115,117,132–134]. Our results are similar with first generation ME immigrants having higher odds of non-localized breast cancer stage when compared to NHW. A comparative survey among four ME registries and the US showed more than 45% of the ME registries participants (except Israel-Jewish area) being diagnosed with breast cancer at a regional stage[135]. Multiple factors have been reported to contribute to this advanced stage at diagnosis in immigrants. These factors included: lower mammography screening rates[136,137], lower SES, different cultural beliefs[138], and limited access to health care[139]. Studies have been conducted to look at predictors of mammography screening and breast cancer examination in immigrant groups. These predictors included: having health insurance, having higher income, longer duration of residency in the US, and greater acculturation[140]. Reasons for mammogram non-compliance included not having previous mammograms, fear of mammography, and the lack of time to take the test[141]. A report from Jordan showed that only 7% of the 1,549 population-based randomly selected women, who were 18 years and older, ever had a mammogram[142]. Studies have been conducted to understand factors influencing breast cancer screening and examination in ME women. These factors included perceived

importance of mammography, intent to be screened, and religious/cultural restrictions[143–149]. We hypothesized that a potential reason for first generation ME immigrants to be diagnosed with an advanced breast cancer stage at diagnosis might be the lack of access to health care. However, our results showed that even after adjusting for SES and health insurance, first generation ME immigrants still had higher odds of being diagnosed with non-localized stage compared to NHW. Cultural and immigrated-related barriers might be responsible for these findings, as showed in a study conducted in Washington D.C. area on Jordanian and Palestinian first generation immigrants[150]. ME women tend to get very busy in their houses, prioritize their families, and do not go to the clinician until symptoms appear. Women from the Middle East have their own beliefs in Allah's Will. In some cases, they get strong objections from their partners and their families on getting seen by a clinician (particularly a male clinician). Exposing their female body is forbidden by their Islamic religion. Lastly, they do not have a habit of getting annual check-ups, are not motivated in screening, and have a deep fear from cancer[150].

This study also showed first generation ME immigrants having higher overall survival when compared to NHW. Our results are similar to the limited literature conducted on ME immigrants in the US[126,127]. This higher survival in first generation ME immigrants may be explained by their social support and their adherence to a Mediterranean diet. Studies have shown that women with an increase in their social support system after breast cancer diagnosis had higher survival rates[151]. Furthermore, the absence of emotional support increases their risk of dying from breast cancer[152]. Family is the fundamental social unit in ME families[153–155]. After cancer diagnosis, ME

families play a role as the patient's caregivers. ME families often provide emotional and social support. This can help increase the chance of survival from breast cancer for first generation ME patients. The higher survival in first generation ME immigrants can also be explained by their adaptation of the Mediterranean diet. Studies have shown that adherence to a Mediterranean diet is associated with higher survival[156,157]. The lower mortality pattern in immigrants has also been studied in the Latino community where two different hypotheses have been suggested and tested: salmon bias and healthy migrant effect[158]. Salmon bias, where immigrants tend to return back home to die when they are diagnosed with terminal cancer, has been considered as an explanation for lower mortality in different immigrant groups including ME immigrants to Europe[159]. The US is geographically close to Mexico and so is Europe to the ME countries. We speculate that the lower mortality in ME first generation immigrants is not due to salmon bias given the long travel distance between the US and the countries of the Middle East. However, this lower mortality can be explained by the healthy migrant effect where healthier ME people immigrate to the US.

In this study, we assessed whether acculturation is associated with breast cancer stage at diagnosis and survival by investigating place of birth and looking at different generations of ME immigrants[160]. Second or subsequent generations ME immigrants had higher odds of being diagnosed with non-localized breast cancer stage when compared to NHW. We believe that the same cultural barriers preventing first generation ME immigrants from being screened are possible explanations for the observed advanced cancer stage in second or subsequent generations ME immigrants. However, no significant differences exist in overall mortality between second or

subsequent generations ME immigrants and NHW, suggesting the impact of acculturation on breast cancer survival. Second or subsequent generations ME immigrants tend to adopt a westernized diet which is positively associated with higher mortality[161]. Acculturation was also investigated by looking at the association between duration of residence in first generation ME immigrants and breast cancer stage and overall/breast cancer mortality. No significant differences were detected in the risk of advanced breast stage and the mortality risk by duration of residence. Therefore, acculturation is unlikely to be the main reason for the advanced diagnosis stage in first generation ME immigrants.

This is the first study to investigate breast cancer stage and survival in different generations of ME immigrants in California. We used CCR which is California's statewide cancer registry that captures cancer incidence and characteristics among Californians since 1988. Our study also bares a few limitations. Females who had a ME maiden name but changed their last name after marriage, or children born to ME females but not ME males were not captured in this study. In addition, we were not able to identify ME immigrants with missing ME last name or patients with missing place of birth. Data on HER2 was missing in more than 60% of the cases and therefore, we did not include this variable in the analysis. Our study lacks information on reproductive factors (nulliparity, early menarche, and late menopause) which are known to increase breast cancer risk. It also lacks information on Body Mass Index, smoking, alcohol consumption, and diet. Immigrants tend to adopt a westernized diet after immigration or with further generations. Data on other co-morbid conditions were not available in CCR. These co-morbidities could have clarified some of the survival patterns seen in this

study. We could not measure time since immigration for first generation ME Immigrants. Lastly, there was a significant difference in sample sizes among the 3 population groups, limiting the comparability of our groups.

In summary, first generation ME immigrants were diagnosed at a non-localized breast cancer stage at diagnosis when compared with NHW. However, they had higher survival. Other studies are needed to confirm our results. Furthermore, screening interventions conducted in an appropriate language and tailored to this ME immigrant group with taking into consideration their specific cultural beliefs need to be implemented. Considerations should be made to start breast cancer screening at a younger age in ME immigrants[162,163] and perhaps more frequently.

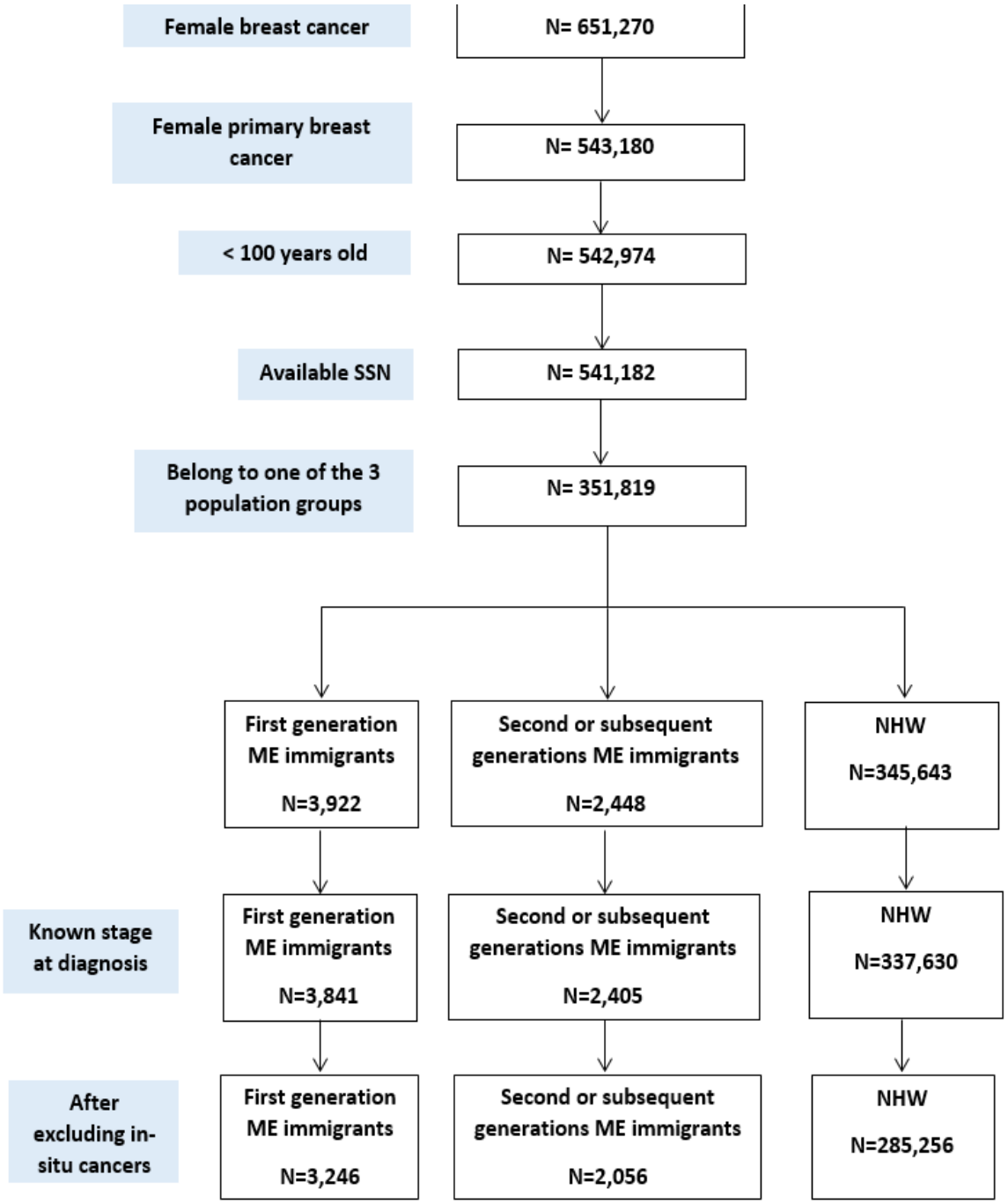

Figure 4.1: Inclusion criteria for study participants with breast cancers: California Cancer Registry, 1988-2013.

Abbreviations: CCR: California Cancer Registry; ME: Middle Eastern; NHW: Non-Hispanic Whites; SSN: Social Security Number.

Table 4.1: Descriptive characteristics of female patients with primary breast cancer stratified by population groups and by duration of residence for first generation ME immigrants: California Cancer Registry, 1988-2013.

Characteristics	First generation ME immigrants			Second or subsequent generations ME immigrants	NHW
	Total	Duration of residence			
		< 20 years	≥ 20 years		
	N=3,841*	N=2,008	N=1,761	N=2,405	N=337,630
Marital status. N (%)					
Single	365 (9.5%)	173 (8.6%)	189 (10.7%)	293 (12.2%)	39,201 (11.6%)
Married	2,487 (64.8%)	1,312 (65.3%)	1,125 (63.9%)	1,509 (62.7%)	191,386 (56.7%)
Separated/Divorced	262 (6.8%)	105 (5.2%)	150 (8.5%)	222 (9.2%)	40,213 (11.9%)
Widowed	651 (17.0%)	376 (18.7%)	266 (15.1%)	328 (13.6%)	59,087 (17.5%)
Unknown	76 (2.0%)	42 (2.1%)	31 (1.8%)	53 (2.2%)	7,743 (2.3%)
SES. N (%)					
Lowest SES	216 (5.6%)	131 (6.5%)	80 (4.5%)	235 (9.8%)	25,916 (7.7%)
Lower-Middle SES	506 (13.2%)	304 (15.1%)	185 (10.5%)	425 (17.7%)	51,593 (15.3%)
Middle SES	710 (18.5%)	401 (20.0%)	291 (16.5%)	438 (18.2%)	70,221 (20.8%)
Higher-Middle SES	906 (23.6%)	472 (23.5%)	423 (24.0%)	551 (22.9%)	85,298 (25.3%)
Highest SES	1,503 (39.1%)	700 (34.9%)	782 (44.4%)	576 (31.4%)	104,602 (31.0%)
Health insurance. N (%)					
Yes	3,172 (82.6%)	1,509 (75.2%)	1,613 (91.6%)	1,937 (80.5%)	246,713 (73.1%)
No	66 (1.7%)	49 (2.4%)	16 (0.9%)	35 (1.5%)	1,828 (0.5%)
Unknown	603 (15.7%)	450 (22.4%)	132 (7.5%)	433 (18.0%)	89,089 (26.4%)
Age at diagnosis. Years					
Mean (SD)	57.4 (13.1)	56.2 (13.5)	59.0 (12.5)	56.9 (13.4)	62.0 (13.7)
Median	57.0	56.0	58.0	56.0	62.0
Age at diagnosis. N (%)					
< 45	666 (17.3%)	454 (22.6%)	192 (10.9%)	456 (19.0%)	35,984 (10.7%)

45-54	1,043 (27.2%)	501 (25.0%)	523 (29.7%)	650 (27.0%)	72,805 (21.6%)
≥ 55	2,132 (55.5%)	1,053 (52.4%)	1,046 (59.4%)	1,299 (54.0%)	228,821 (67.8%)
Stage at diagnosis. N (%)					
In-situ	595 (15.5%)	304 (15.1%)	290 (16.5%)	349 (14.5%)	52,374 (15.5%)
Localized	1,863 (48.5%)	929 (46.3%)	901 (51.2%)	1,122 (46.7%)	184,496 (54.6%)
Non-Localized	1,383 (36.0%)	775 (38.6%)	570 (32.4%)	934 (38.8%)	100,760 (29.8%)
Year at diagnosis. N (%)					
1988-1992	411 (10.7%)	321 (16.0%)	66 (3.8%)	298 (12.4%)	59,662 (17.7%)
1993-1997	561 (14.6%)	410 (20.4%)	140 (8.0%)	408 (17.0%)	62,727 (18.6%)
1998-2002	856 (22.3%)	522 (26.0%)	319 (18.1%)	499 (20.8%)	71,795 (21.3%)
2003-2007	884 (23.0%)	414 (20.6%)	461 (26.2%)	568 (23.6%)	66,572 (19.7%)
2008-2013	1,129 (29.4%)	341 (17.0%)	775 (44.0%)	632 (26.3%)	76,874 (22.8%)
ER. N (%)					
ER positive	2,462 (64.1%)	1,154 (57.5%)	1,268 (72.0%)	1,517 (63.1%)	194,418 (57.6%)
ER negative	514 (13.4%)	281 (14.0%)	226 (12.8%)	337 (14.0%)	43,872 (13.0%)
ER unknown	865 (22.5%)	573 (28.5%)	267 (15.2%)	551 (22.9%)	99,340 (29.4%)
PR. N (%)					
PR positive	2,067 (53.8%)	991 (49.4%)	1,040 (59.1%)	1,255 (52.2%)	162,337 (48.1%)
PR negative	818 (21.3%)	407 (20.3%)	400 (22.7%)	540 (22.5%)	69,122 (20.5%)
PR unknown	956 (24.9%)	610 (30.4%)	321 (18.2%)	610 (25.4%)	106,171 (31.5%)
Tumor grade. N (%)					
Well differentiated	544 (14.2%)	242 (12.1%)	294 (16.7%)	318 (13.2%)	58,650 (17.4%)
Moderately well differentiated	1,437 (37.4%)	709 (35.3%)	704 (40.0%)	829 (34.5%)	117,972 (34.9%)
Poorly differentiated	1,180 (30.7%)	624 (31.1%)	539 (30.6%)	798 (33.2%)	83,986 (24.9%)
Undifferentiated/ anaplastic	138 (3.6%)	86 (4.3%)	48 (2.7%)	103 (4.3%)	11,231 (3.3%)
Unknown if differentiated	542 (14.1%)	347 (17.3%)	176 (10.0%)	357 (14.8%)	65,791 (19.5%)
Histologic type. N (%)					
Ductal	2,415 (62.9%)	1,281 (63.8%)	1,084 (61.6%)	1,545 (64.2%)	220,543 (65.3%)
Lobular	308 (8.0%)	150 (7.5%)	156 (8.9%)	178 (7.4%)	30,153 (8.9%)
Ductal/lobular	370 (9.6%)	197 (9.8%)	165 (9.4%)	208 (8.7%)	23,796 (7.1%)
Mucinous	68 (1.8%)	45 (2.2%)	21 (1.2%)	39 (1.6%)	6,492 (1.9%)

Others	680 (17.7%)	335 (16.7%)	335 (19.0%)	435 (18.1%)	56,646 (16.8%)
Surgery. N (%)					
No	153 (4.0%)	66 (3.3%)	84 (4.8%)	122 (5.1%)	14,032 (4.2%)
Yes	3,687 (96.0%)	1,941 (96.7%)	1,677 (95.2%)	2,283 (94.9%)	323,508 (95.8%)
Unknown	1 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	90 (0.0%)
Chemotherapy. N (%)					
No	2,376 (61.9%)	1,211 (60.3%)	1,134 (64.4%)	1,429 (59.4%)	239,355 (70.9%)
Yes	1,399 (36.4%)	763 (38.0%)	599 (34.0%)	943 (39.2%)	93,176 (27.6%)
Unknown	66 (1.7%)	34 (1.7%)	28 (1.6%)	33 (1.4%)	5,099 (1.5%)

Abbreviations: ME: Middle Eastern immigrants; NHW: Non-Hispanic Whites; N (%): Sample size (percentage); SES: Socio-Economic Status; SD: Standard Deviation; ER: Estrogen Receptor; PR: Progesterone Receptor

Percentages may not be equal to 100 because of rounding

*72 cases in first generation ME immigrants have missing duration of residence

Table 4.2: Odds Ratios (ORs) and 95% confidence intervals (CIs) for in-situ breast cancer stage compared to localized stage among the 3 population groups: California Cancer Registry, 1988-2013.

	In-situ vs. localized	
	OR	**95% CI**
First generation ME immigrants compared to NHW		
Model 0	0.98	0.89, 1.08
Model 1: SES	0.97	0.89, 1.07
Model 2: model 1 + health insurance	0.98	0.89, 1.07
Model 3: model 2 + marital status	0.97	0.87, 1.07
Second or subsequent generations ME immigrants compared to NHW		
Model 0	0.98	0.87, 1.11
Model 1: SES	0.99	0.88, 1.12
Model 2: model 1 + health insurance	0.99	0.88, 1.12
Model 3: model 2 + marital status	0.99	0.88, 1.12
First generation ME immigrants compared to second or subsequent generations ME immigrants		
Model 0	1.01	0.84, 1.22
Model 1: SES	1.01	0.84, 1.22
Model 2: model 1 + health insurance	1.01	0.84, 1.21
Model 3: model 2 + marital status	1.00	0.83, 1.21

Abbreviations: OR: Odds Ratio; CI: Confidence Interval; ME: Middle Eastern; NHW: Non-Hispanic Whites; SES: Socio-Economic Status
Localized stage serves as the baseline stage
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by SES
Model 2: adjusted by SES and health insurance
Model 3: adjusted by SES, health insurance, and marital status

Table 4.3: Risk of advanced breast cancer stage at diagnosis (non-localized compared to localized stage), among the 3 population groups: California Cancer Registry, 1988-2013.

	Non-localized vs. localized	
	OR	**95% CI**
First generation ME immigrants compared to NHW		
Model 0	**1.28**	**1.19, 1.37**
Model 1: SES	**1.29**	**1.20, 1.39**
Model 2: model 1 + health insurance	**1.28**	**1.19, 1.37**
Model 3: model 2 + marital status	**1.28**	**1.20, 1.38**
Second or subsequent generations ME immigrants compared to NHW		
Model 0	**1.42**	**1.30, 1.55**
Model 1: SES	**1.41**	**1.09, 1.54**
Model 2: model 1 + health insurance	**1.40**	**1.28, 1.53**
Model 3: model 2 + marital status	**1.41**	**1.29, 1.54**
First generation ME immigrants compared to second or subsequent generations ME immigrants		
Model 0	0.88	0.77, 1.01
Model 1: SES	0.91	0.79, 1.04
Model 2: model 1 + health insurance	0.91	0.79, 1.04
Model 3: model 2 + marital status	0.90	0.79, 1.03

Abbreviations: ME: Middle Eastern; NHW: Non-Hispanic Whites; OR: Odds Ratio; CI: Confidence Interval; SES: Socio-Economic Status
Significant results are bolded
Localized stage serves as the baseline stage
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by SES
Model 2: adjusted by SES and health insurance
Model 3: adjusted by SES, health insurance, and marital status

Table 4.4: Association between duration of residence and risk of advanced breast cancer stage at diagnosis (non-localized compared to localized stage), in first generation ME immigrants: California Cancer Registry, 1988-2013.

	< 20 years compared to ≥ 20 years N=3,175	
	OR	**95% CI**
Model 0	1.18	0.97, 1.44
Model 1: SES	1.15	0.95, 1.40
Model 2: model 1 + health insurance	1.15	0.94, 1.40
Model 3: model 2 + marital status	1.14	0.94, 1.40

Abbreviations: ME: Middle Eastern; OR: Odds Ratio; CI: Confidence Interval; SES: Socio-Economic Status
Localized stage serves as the baseline stage
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by SES
Model 2: adjusted by SES and health insurance
Model 3: adjusted by SES, health insurance, and marital status

Table 4.5: Ten-year overall and breast cancer specific survival for primary female invasive breast cancers for stages combined and stratified by breast cancer stage in the 3 population groups: California Cancer Registry, 1988-2013.

	Nº of patients	10-year overall survival		10-year breast cancer-specific survival	
		Nº of deaths	Survival% (95% CI)	Nº of deaths from breast cancer	Survival% (95% CI)
Stages combined					
First generation ME immigrants	3,246	937	60.0% (57.9, 62.1)	531	77.4% (75.6, 79.2)
Second or subsequent generations ME immigrants	2,056	746	51.7% (49.1, 54.4)	417	72.7% (70.3, 75.1)
NHW	285,256	123,617	45.0% (44.7, 45.2)	46,898	78.2% (78.0, 78.4)
Log-rank test		<0.0001		<0.0001	
Localized stage					
First generation ME immigrants	1,863	354	71.0% (68.4, 73.6)	119	90.4% (88.6, 92.1)
Second or subsequent generations ME immigrants	1,122	293	62.3% (58.8, 65.9)	89	87.9% (85.5, 90.4)
NHW	184,496	69,779	50.0% (49.7, 50.2)	14,200	88.9% (88.7, 89.1)
Log-rank test		<0.0001		0.1808	
Non-localized stage					
First generation ME immigrants	1,383	583	45.5% (42.3, 48.7)	412	59.9% (56.7, 63.1)
Second or subsequent generations ME immigrants	934	453	39.0% (35.2, 42.8)	328	54.2% (50.3, 58.2)
NHW	100,760	53,838	35.8% (35.5, 36.2)	32,698	58.6% (58.2, 58.9)
Log-rank test		<0.0001		0.0234	

Abbreviations: CI: Confidence Interval; ME: Middle Eastern; NHW: Non-Hispanic Whites

Table 4.6: Hazard Ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality and breast cancer-specific mortality in the different generations of ME immigrants compared to NHW: California Cancer Registry, 1988-2013.

	First generation ME immigrants compared to NHW N=288,502		Second or subsequent generations ME immigrants compared to NHW N=287,312	
	HR	**95% CI**	**HR**	**95% CI**
All-cause mortality				
Model 0	**0.91**	**0.86, 0.97**	**1.14**	**1.06, 1.23**
Model 1: stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, and cancer histology	**0.86**	**0.80, 0.92**	1.05	0.98, 1.13
Model 2: model 1 + SES	**0.87**	**0.82, 0.93**	1.03	0.96, 1.11
Model 3: Model 2 + health insurance	**0.86**	**0.80, 0.92**	1.02	0.95, 1.10
Model 4: Model 3 + marital status	**0.86**	**0.80, 0.92**	1.02	0.95, 1.10
Breast cancer-specific mortality				
Model 0	1.09	1.00, 1.19	**1.35**	**1.23, 1.49**
Model 1: stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, and cancer histology	0.98	0.90, 1.07	**1.14**	**1.04, 1.26**
Model 2: model 1 + SES	0.99	0.91, 1.08	**1.12**	**1.02, 1.24**
Model 3: Model 2 + health insurance	0.96	0.88, 1.05	1.10	1.00, 1.21
Model 4: Model 3 + marital status	0.97	0.89, 1.06	1.11	1.00, 1.22

Abbreviations: HR: Hazard Ratio; CI: Confidence Interval; ME: Middle Eastern; NHW: Non-Hispanic Whites; ER: Estrogen Receptor; PR: Progesterone Receptor; SES: Socio-Economic Status

Significant results are bolded

Age at diagnosis and year at diagnosis were controlled as strata

Model 0: unadjusted

Model 1: adjusted by stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, and cancer histology

Model 2: adjusted by stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, cancer histology, and SES

Model 3: adjusted by stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, cancer histology, SES, and health insurance

Model 4: adjusted by stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, cancer histology, SES, health insurance, and marital status

Table 4.7: Association between duration of residence and all-cause and breast cancer-specific mortality in first generation ME immigrants: California Cancer Registry, 1988-2013.

	< 20 years compared to ≥ 20 years N=3,175	
	HR	**95% CI**
All-cause mortality		
Model 0	0.97	0.78, 1.20
Model 1: stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, and cancer histology	1.02	0.79, 1.31
Model 2: model 1 + SES	1.01	0.78, 1.29
Model 3: Model 2 + health insurance	0.99	0.77, 1.28
Model 4: Model 3 + marital status	1.02	0.79, 1.32
Breast cancer-specific mortality		
Model 0	0.96	0.74, 1.26
Model 1: stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, and cancer histology	1.01	0.72, 1.41
Model 2: model 1 + SES	1.01	0.72, 1.41
Model 3: Model 2 + health insurance	1.01	0.72, 1.41
Model 4: Model 3 + marital status	1.02	0.73, 1.44

Abbreviations: HR: Hazard Ratio; CI: Confidence Interval; ME: Middle Eastern; ER: Estrogen Receptor; PR: Progesterone Receptor; SES: Socio-Economic Status

Age at diagnosis and year at diagnosis were controlled as strata

Model 0: unadjusted

Model 1: adjusted by stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, and cancer histology

Model 2: adjusted by stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, cancer histology, and SES

Model 3: adjusted by stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, cancer histology, SES, and health insurance

Model 4: adjusted by stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, cancer histology, SES, health insurance, and marital status

CHAPTER 5

PROSTATE CANCER CHARACTERISTICS IN MIDDLE EASTERN MEN IMMIGRANTS COMPARED TO NON-HISPANIC WHITE MEN IN CALIFORNIA

5.1. Introduction

Prostate cancer is the second most common cancer in men worldwide[50] and is the most common cancer in men in the United States (US)[164] with 161,360 new cancer cases and 26,730 deaths from prostate cancer estimated in 2017[31]. In the US, prostate cancer death rates have been declining with 5-year survival rising from 66.0% in 1975 to 99.3% in 2009[51]. The rise in survival has been associated with treatment improvement and the increase in screening rates[46,165]. Prostate cancer cases detected at an earlier stage have better 5-year survival rates with 100.0% for localized and regional prostate cancers compared to 29.8% for distant prostate cancers[51].

Studies have been conducted to identify predictors of prostate cancer screening in the US. Factors that have been identified include older age, higher income, having a current employment, perception of self-health control, belief in screening efficacy, and presence of social support[166–169]. Previous studies have shown that immigrants present with more advanced stage of prostate cancer when compared with non-immigrant Non-Hispanic Whites (NHW)[85,170,171]. Different barriers have been suggested to explain the delay in prostate screening among immigrants, which might lead to an advanced stage in diagnosis. These barriers included language barriers, different cultural beliefs, physical modesty, and acculturation[172–174].

Immigrants from the Middle East (ME) are among the growing immigrant populations in the US. To our knowledge, no previous studies have investigated prostate cancer stage at diagnosis and survival in ME immigrants to the US. The dearth of studies can be explained by the lack of classification of ME immigrants as a separate ethnicity within the NHW in the US census. NHW race is defined as any person from European, North African, and Middle Eastern ancestry[70]. A study conducted in Norway has not shown any significant differences in prostate cancer stage at diagnosis distribution between first generation ME immigrants and native Norwegians[175]. Another study conducted in Sweden has shown that first generation ME immigrants had lower prostate cancer mortality when compared with native Swedes[176].

Immigrant studies can evaluate the impact of acculturation by investigating cancer outcomes by place of birth (different generations of immigrants) and duration of residence in the host country[79,80,128]. Shorter duration of residence in immigrants has been shown to be an important indicator in not receiving guideline-concordant cancer screening[129]. This study aims to analyze the association between ME immigration status and prostate cancer stage at diagnosis and all-cause and prostate cancer-specific mortality in different generations of ME immigrants and NHW in California between 1988 and 2013. It also aims to investigate the association between the duration of residence and prostate cancer stage and all-cause and prostate cancer-specific mortality in first generation ME immigrants. First generation ME immigrants are defined as having a ME last name[91] and born in the Middle East. While second or subsequent generations ME immigrants are defined as having a ME last name[91] but not born in the Middle East.

5.2. Methods

5.2.1. Study populations

Prostate cancer patients were identified using the California Cancer Registry (CCR). CCR is a population-based cancer registry that collects information on cancer cases diagnosed in California since 1988. This study cohort consisted of all patients who: 1) were diagnosed in California between January 1st, 1988 and December 31st, 2013 with a primary invasive prostate cancer (N=452,869), 2) were adults aged 85 years old or younger at diagnosis (N=434,577), 3) had an available social security number (SSN) at diagnosis (N=411,607), 4) were part of the 3 population groups of interest (first generation ME immigrants, second or subsequent generations ME immigrants, and NHW) (N=280,595), and 5) had a known prostate cancer stage at diagnosis (N=262,489). The final sample in this study included 2,874 first generation ME immigrants, 1,304 second or subsequent generations ME immigrants, and 258,311 NHW men **(figure 5.1)**.

The 3 population groups of interest in this study are: first generation ME immigrants, second or subsequent generations ME immigrants, and NHW. If the patient had a Middle Eastern last name[91], did not have a Hispanic nor an Asian last name, and was born in one of the Middle Eastern countries, he was considered first generation ME immigrant. If the patient had a Middle Eastern last name[91], did not have a Hispanic nor an Asian last name, was not born in one of the Middle Eastern countries, did not have a missing birth country, he was considered second or subsequent generations ME immigrant. If the patient did not have a ME nor Hispanic nor Asian last name and was identified as White in the CCR database, he was considered NHW in our analysis.

5.2.2. Stage at diagnosis and survival

Summary stage at diagnosis (SEER summary stage) from CCR was used in this study. Localized stage corresponds to tumors confined to the prostate gland. Regional stage includes prostate cancers that have spread to areas near the prostate, such as lymph nodes. Remote or distant stage describes prostate cancers that have spread to distant lymph nodes, bones, or other organs. We categorized prostate cancer stage in our analysis into localized and non-localized. Localized stage was considered an early cancer stage and was used as the referent stage. Regional and remote prostate cancer stages were combined into the non-localized stage which was considered the advanced stage at diagnosis.

CCR contains the patient's underlying cause of death, vital status, and follow-up time in months. In this study, the last date of follow-up was December 31st, 2013. The survival end-points were overall death and death from prostate cancer. Prostate cancer specific deaths were classified as code 185 of the International Classification of Diseases (ICD) ninth revision for deaths that occurred between 1988 and 1998 and C61 of the ICD tenth revision for deaths occurred in 1999 and beyond.

5.2.3. Other study variables

The socio-economic status (SES) variable was created from 2 different variables already existing in CCR: "quinyost" available till the end of 2005 and "quinyang" available from 2006 forward. Both variables were categorized into quintiles with the lowest quintile corresponds to the lowest SES. Health insurance was categorized into 3

categories: having insurance, not having insurance, and unknown. Duration of residence in the US was calculated for first generation ME immigrants by using year at diagnosis and year of issue of SSN (duration of residence=year at diagnosis - year of issue of SSN). A categorical variable was created with duration of residence less than 21 years and duration or residence equal to 21 years or more. This cutoff point was selected based on the median duration of residence for first generation ME immigrants. Age at diagnosis was used as a continuous measurement, in addition to being categorized into 4 quartile groups: < 62, 62-67, 68-73, and $\geq$ 74 years old. Year at diagnosis, ranging from 1988 to 2013, was categorized into five groups: 1988-1992, 1993-1997, 1998-2002, 2003-2007, and 2008-2013. Tumor grade was defined as: well differentiated, moderately differentiated, poorly differentiated, undifferentiated/anaplastic, and unknown if differentiated. Lastly, a treatment variable that incorporated surgery, hormonal, and radiation therapy was created.

5.2.4. Statistical analysis

Descriptive data was stratified and presented by the 3 population groups of interest (first generation ME immigrants, second or subsequent generations ME immigrants, and NHW) and by duration of residence for first generation ME immigrants. Means ± standard deviations and medians were used for continuous variables and numbers (percentages) for categorical variables.

Unconditional logistic regression was performed with odds ratios (ORs) and 95% confidence intervals (CIs) calculated. This regression was applied to evaluate the risk of

non-localized (advanced) prostate cancer stage in comparison with localized cancer (referent stage) between the different generations of ME immigrants and NHW. It was also applied to evaluate the risk of advanced prostate cancer stage in first generation ME immigrants residing in the US for less than 21 years (shorter duration) compared to first generation ME immigrants residing in the US for 21 years or more (longer duration). We started with a model (model 0) containing the main exposure variable (population group or duration of residence). We then added each of the covariates selected a priori: SES to model 1, health insurance to model 2, and marital status to model 3. The time of this study is large (1988 to 2013) and there are differences in prostate cancer screening practices and guidelines among these years in the US and the Middle East. Therefore, in the multivariate analyses of risk of advanced stage, age and year at diagnosis were controlled as strata.

Cox proportional hazard models were applied to calculate the hazard ratios (HRs) with their 95% CIs for all-cause mortality and prostate cancer specific mortality between the different generations of ME immigrants and NHW. They were also applied to evaluate the risk of all-cause or prostate cancer-specific death in first generation ME immigrants with shorter duration of residence compared to first generation ME immigrants with longer duration of residence in the US. We began with a model (model 0) containing the main exposure variable (population group or duration of residence). We then added summary stage at diagnosis, tumor grade, and cancer treatment to model 1, SES to model 2, health insurance to model 3, and marital status to model 4. In the multivariate analyses of risk of death (overall or prostate cancer specific death), age and year at diagnosis were controlled as strata. The proportional hazard assumption

was examined by testing the interaction of time with the covariates. There was no violation for this assumption. All data analyses were completed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

5.3. Results

Table 5.1 shows the descriptive characteristics for invasive prostate cancer cases for localized and non-localized stages combined, stratified by the 3 populations groups. Most of the patients had the highest quintile of SES and had health insurance with first generation ME immigrants having the highest proportion (SES 44.4% and health insurance 82.2%). Prostate cancer proportions were much lower in the first two-time segments (1988-1997) compared to later years in all 3 population groups. NHW were slightly older at diagnosis compared to the different generations of ME immigrants. Prostate cancer patients in the 3 population groups were diagnosed the most at a localized stage (77.0%-80.3%). Over 50.0% of the prostate tumors were moderately differentiated with most of the patients (41.6%-47.3%) having surgery alone as a prostate cancer treatment. This table also shows the characteristics of first generation ME immigrants stratified by duration of residence. A higher percentage of first generation ME immigrants residing in the US for 21 years or more had the highest SES (52.3% vs. 36.6%) and had health insurance (90.6% vs. 74.5%) compared to immigrants who have been residents for less than 21 years. First generation ME immigrants with a longer duration of residence also were younger at diagnosis and were more likely to be diagnosed in a more recent year (33.7% vs. 11.3% from 2008 to 2013) compared to first generation ME immigrants with a shorter duration of residence.

Results from the stratified logistic regression are displayed in **table 5.2**. After controlling for age and year at diagnosis as strata and adjusting for SES, health insurance, and marital status, first generation ME immigrants were at higher odds of being diagnosed with more advanced (non-localized vs. localized) prostate cancer stage when compared to NHW (OR=1.22 with 95% CI: 1.11, 1.33). Second or subsequent generations ME immigrants also had higher odds of being diagnosed with a non-localized stage when compared with NHW (OR=1.25 with 95% CI: 1.09, 1.43).

Analyses conducted to evaluate the risk of advanced prostate cancer stage in first generation ME immigrants residing in the US for less than 21 years (shorter duration) compared to first generation ME immigrants residing in the US for 21 years or more (longer duration) are illustrated in **table 5.3.** There were no significant differences in the risk of advanced prostate cancer stage between first generation ME immigrants with shorter duration of residence compared to first generation ME immigrants with longer duration of residence (OR=1.10 with 95% CI: 0.86, 1.42).

After controlling for age and year at diagnosis as strata and adjusting for stage at diagnosis, tumor grade, cancer treatment, SES, health insurance, and marital status, first generation ME immigrants had a 23% (HR=0.77 with 95% CI: 0.72, 0.82) lower risk for all-cause mortality and second or subsequent generations ME immigrants had a 11% (HR=0.89 with 95% CI: 0.82, 0.97) lower mortality risk than NHW. The estimated prostate cancer specific mortality risk among first generation ME immigrants was 10% lower than that of NHW, although the association was not statistically significant (HR=0.90 with 95% CI: 0.80, 1.02). No significant differences existed in prostate cancer-

specific mortality between second or subsequent generations ME immigrants and NHW (HR=1.03 with 95% CI: 0.88, 1.21) **(table 5.4)**.

Table 5.5 shows the risk of all-cause and prostate cancer-specific death in first generation ME immigrants with shorter duration of residence compared to longer duration of residence in the US. No significant differences were detected in all-cause and prostate cancer specific death between the 2 groups of first generation ME immigrants.

5.4. Discussion

The present study shows that ME immigrants had significantly higher risk of advanced prostate cancer stage at diagnosis and lower all-cause mortality when compared to NHW. No significant differences were detected in prostate cancer-specific mortality between the different generations of ME immigrants and NHW. Furthermore, there were no statistical differences in the risk of advanced prostate cancer stage and mortality in first generation ME immigrants by duration of residence in the US.

Studies conducted in the US have shown that immigrants were more likely to be diagnosed with more advanced prostate cancer stage in comparison with NHW[85,170,171]. Our results are similar with first and second or subsequent generations ME immigrants having higher odds of being diagnosed with advanced stage when compared to NHW. Multiple factors have been previously associated with advanced prostate cancer stage in immigrants. These factors include lower prostate cancer screening rates and not having health insurance[177]. The risk of having a higher risk of advanced prostate cancer

stage did not significantly change after adjusting for health insurance with using age at diagnosis and year at diagnosis as strata in the logistic regression. In addition, ME immigrants had higher rates of health insurance compared to NHW. Therefore, we believe that the higher risk of advanced stage might be related to prostate cancer screening non-compliance behavior in ME immigrants.

The lower screening rates leading to late prostate cancer detection in immigrants were previously explained by language barriers and cultural differences[172]. A report from a tertiary care center in Saudi Arabia has shown 64.0% of the patients having extra-prostatic disease[178]. However, this report was conducted on 76 men only. Another study was conducted on a cohort of healthy population in Saudi Arabia where participants were subjected to Prostate Specific Antigen (PSA) blood testing and digital rectal examination (DRE). This study reported 21.1% of the prostate cancer patients diagnosed at a locally advanced stage and 26.9% at a metastatic stage[179]. Another study conducted in three ME countries and assessed the knowledge and attitude of men aged 40 years and older towards prostate cancer detection and screening[180]. The study illustrated that ME men had a poor knowledge concerning prostate cancer screening which can lead to lower prostate cancer screening rates. Another study carried out in Jordan aimed to assess the predictors of prostate cancer screening[181]. They found that Jordanian men who had health motivation, knew the benefits of PSA, and had lower levels of cost barriers to PSA were more likely to participate in prostate cancer screening. Additional predictors for prostate cancer screening participation were having a family history of prostate cancer, presence of urinary symptoms, being older, and having prostate cancer knowledge[181].

This study also shows the different generations of ME immigrants having lower all-cause mortality when compared with NHW. Studies have shown that a greater adherence to the Mediterranean diet is associated with lower overall mortality after prostate cancer diagnosis[182] and that a greater adherence to the Westernized diet is positively associated with higher mortality[161]. We believe that the lower mortality in ME immigrants is related to their lifestyle behavior such as adopting a Mediterranean diet[156,157]. We speculate that the higher overall HR estimates in second or subsequent generations ME immigrants, are related to patients being less adherent to the Mediterranean diet and them adopting more of a Westernized diet.

First generation ME immigrants also had lower prostate cancer-specific mortality compared to NHW. However, this association was not significant after adjustment. We believe that the lower mortality is not related to the tumor itself but to lifestyle factors which can explain the differences in the results between overall and prostate cancer specific mortality.

Acculturation was assessed in our study by looking at place of birth (different generations of ME immigrants) and duration of residence for first generation ME immigrants. No significant differences were detected in the risk of advanced prostate stage and the mortality risk by duration of residence. In addition, same cancer outcome pattern was shown between first generation ME immigrants and NHW and second or subsequent generations ME immigrants and NHW. Therefore, acculturation is unlikely to be the main reason for the advanced diagnosis stage in ME immigrants.

To our knowledge, this is the first study in the US to investigate prostate cancer stage and survival in ME immigrants while taking the duration of residence into

consideration. Our study is based on data from the CCR, which is California's statewide cancer registry that captures cancer incidence and characteristics among all Californians since 1988. We examined prostate cancer stage and survival in different generations of ME immigrants and by the duration of residence in the US for first generation ME immigrants. Our study also bares a few limitations. Data regarding prostate cancer screening measurements was not available in this study. We also did not have information on lifestyle behaviors including diet, alcohol consumption, and smoking. ME immigrants with missing ME last name or patients with missing place of birth were not captured in this study. Huge differences exist in the sample sizes of the 3 population groups of interest, limiting the comparability of our groups. Lastly, data on other co-morbid conditions were not available in the CCR dataset. These co-morbidities might be important confounders for the associations investigated in this study.

In summary, ME immigrants have a significantly higher risk of advanced prostate cancer stage at diagnosis and a lower all-cause mortality when compared to NHW. Our findings are novel but need to be replicated in different states such as Michigan where there is a very big community of ME immigrants. Future interventions to increase awareness on the importance of prostate cancer screening need to be designed for ME immigrants. This will likely increase early detection and reduce the risk of advanced stage at diagnosis among ME immigrants.

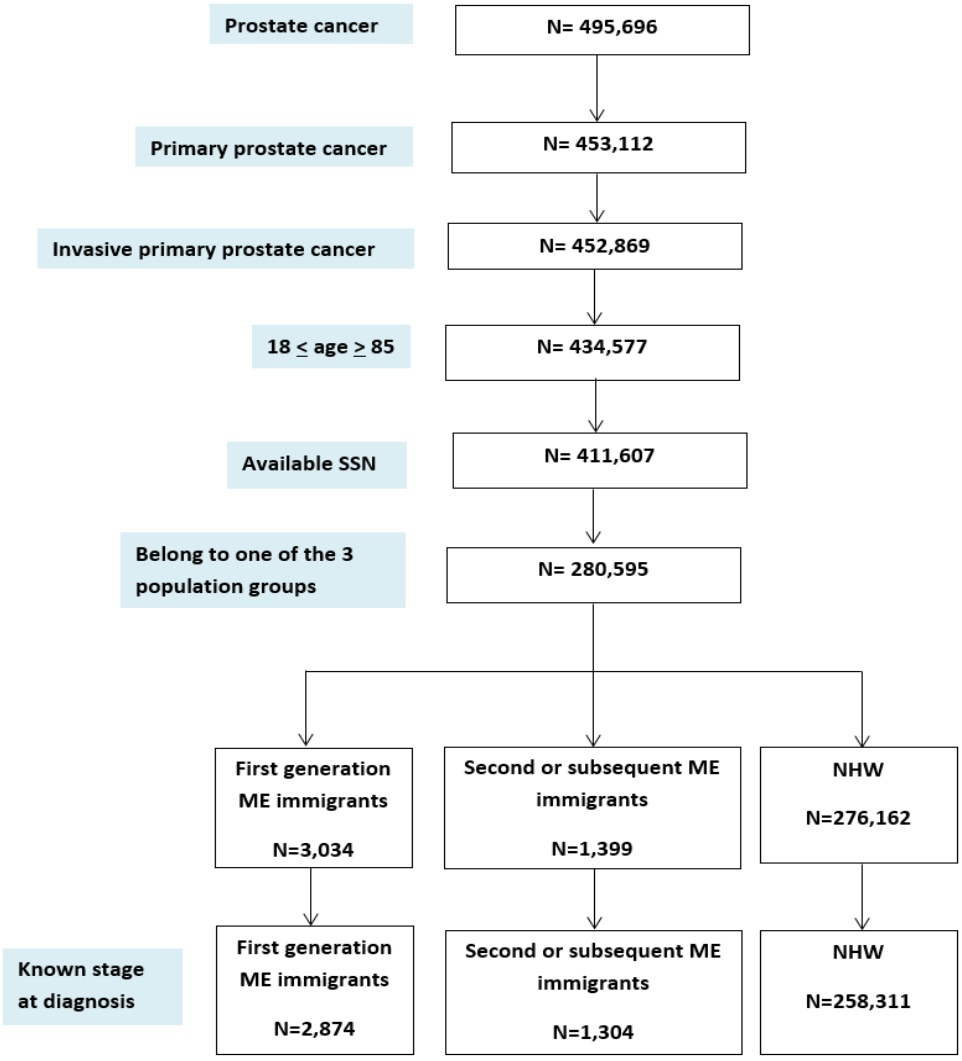

Figure 5.1: Inclusion criteria for study participants with prostate cancers: California Cancer Registry, 1988-2013.
Abbreviations: SSN: Social Security Number; ME: Middle Eastern; NHW: Non-Hispanic Whites.

Table 5.1: Descriptive characteristics of male patients with primary invasive prostate cancer stratified by population groups and by duration of residence for first generation ME immigrants: California Cancer Registry, 1988-2013.

Characteristics	First generation ME immigrants			Second or subsequent generations ME immigrants	NHW
	Total	Duration of residence			
		< 21 years	≥ 21 years		
	N=2,874*	N=1,351	N=1,462	N=1,304	N=258,311
Marital status. N (%)					
Single	139 (4.8%)	52 (3.9%)	84 (5.8%)	111 (8.5%)	21,652 (8.4%)
Married	2,354 (81.9%)	1,124 (83.2%)	1,181 (80.8%)	997 (76.5%)	193,440 (74.9%)
Separated/Divorced	145 (5.1%)	46 (3.4%)	97 (6.6%)	75 (5.8%)	15,276 (5.9%)
Widowed	113 (3.9%)	68 (5.0%)	41 (2.8%)	76 (5.8%)	13,757 (5.3%)
Unknown	123 (4.3%)	61 (4.5%)	59 (4.0%)	45 (3.5%)	14,186 (5.5%)
Quintile of SES. N (%)					
Lowest SES	184 (6.4%)	113 (8.4%)	64 (4.4%)	150 (11.5%)	19,411 (7.5%)
Lower-Middle SES	326 (11.3%)	191 (14.1%)	118 (8.1%)	220 (16.9%)	38,650 (15.0%)
Middle SES	431 (15.0%)	233 (17.3%)	186 (12.7%)	239 (18.3%)	51,808 (20.1%)
Higher-Middle SES	656 (22.8%)	320 (23.7%)	329 (22.5%)	276 (21.2%)	63,752 (24.7%)
Highest SES	1,277 (44.4%)	494 (36.6%)	765 (52.3%)	419 (32.1%)	84,690 (32.8%)
Health insurance. N (%)					
Yes	2,363 (82.2%)	1,007 (74.5%)	1,324 (90.6%)	1,010 (77.5%)	189,682 (73.4%)
No	53 (1.8%)	30 (2.2%)	20 (1.4%)	19 (1.5%)	1,485 (0.6%)
Unknown	458 (15.9%)	314 (23.2%)	118 (8.1%)	275 (21.1%)	67,144 (26.0%)
Age at diagnosis, years					
Mean (SD)	67.1 (8.2)	68.4 (7.8)	65.8 (8.3)	67.0 (8.3)	67.7 (8.6)
Median	67	69	66	67	68
Quartile of age, years. N (%)					
< 62	688 (23.9%)	250 (18.5%)	434 (29.7%)	330 (25.3%)	62,174 (24.1%)

62-67	754 (26.2%)	325 (24.1%)	412 (28.2%)	328 (25.2%)	60,318 (23.4%)
68-73	775 (27.0%)	416 (30.8%)	340 (23.3%)	338 (25.9%)	66,100 (25.6%)
≥ 74	657 (22.9%)	360 (26.7%)	276 (18.9%)	308 (23.6%)	69,719 (27.0%)
Stage at diagnosis. N (%)					
Localized	2,267 (78.9%)	1,074 (79.5%)	1,151 (78.7%)	1,004 (77.0%)	207,307 (80.3%)
Non-Localized	607 (21.1%)	277 (20.5%)	311 (21.3%)	300 (23.0%)	51,004 (19.8%)
Year at diagnosis. N (%)					
1988-1992	275 (9.6%)	182 (13.5%)	74 (5.1%)	202 (15.5%)	47,373 (18.3%)
1993-1997	535 (18.6%)	390 (28.9%)	131 (9.0%)	239 (18.3%)	50,120 (19.4%)
1998-2002	684 (23.8%)	372 (27.5%)	292 (20.0%)	282 (21.6%)	54,426 (21.1%)
2003-2007	734 (25.5%)	255 (18.9%)	473 (32.4%)	278 (21.3%)	53,643 (20.8%)
2008-2013	646 (22.5%)	152 (11.3%)	492 (33.7%)	303 (23.2%)	52,749 (20.4%)
Tumor grade. N (%)					
Well differentiated	178 (6.2%)	122 (9.0%)	51 (3.5%)	109 (8.4%)	20,242 (7.8%)
Moderately differentiated	1,649 (57.4%)	801 (59.3%)	816 (55.8%)	694 (53.2%)	145,529 (56.3%)
Poorly differentiated	949 (33.0%)	383 (28.4%)	547 (37.4%)	454 (34.8%)	81,659 (31.6%)
Undifferentiated/anaplastic	6 (0.2%)	4 (0.3%)	2 (0.1%)	11 (0.8%)	1,050 (0.4%)
Unknown if differentiated	92 (3.2%)	41 (3.0%)	46 (3.2%)	36 (2.8%)	9,831 (3.8%)
Treatment. N (%)**					
None of the three treatments	300 (10.6%)	128 (9.6%)	166 (11.4%)	157 (12.1%)	36,184 (14.1%)
Radiation only	365 (12.8%)	173 (13.0%)	183 (12.6%)	185 (14.2%)	49,449 (19.3%)
Hormone only	189 (6.7%)	88 (6.6%)	94 (6.5%)	103 (7.9%)	19,122 (7.5%)
Radiation + hormone	336 (11.8%)	178 (13.4%)	155 (10.7%)	140 (10.8%)	25,982 (10.1%)
Surgery	1,345 (47.3%)	602 (45.2%)	723 (49.8%)	593 (45.6%)	106,715 (41.6%)
Surgery + radiation	73 (2.6%)	33 (2.5%)	35 (2.4%)	41 (3.2%)	7,307 (2.9%)
Surgery + hormone	197 (6.9%)	106 (8.0%)	83 (5.7%)	68 (5.2%)	9,018 (3.5%)
Three treatments together	38 (1.3%)	24 (1.8%)	12 (0.8%)	14 (1.1%)	2,630 (1.0%)
Missing	31	19	11	3	1,904

Abbreviations: ME: Middle Eastern; NHW: Non-Hispanic Whites; N (%): Sample size (percentage); SES: Socio-Economic Status; SD: Standard Deviation.

Percentages may not be equal to 100 because of rounding

* 61 cases in first generation ME immigrants had missing duration of residence

**Treatment includes surgery, radiation therapy, or hormonal therapy

Table 5.2: Risk of advanced prostate cancer stage at diagnosis (non-localized vs. localized), in the different generations of ME immigrants compared to NHW: California Cancer Registry, 1988-2013.

	First generation ME immigrants compared to NHW		Second or subsequent generations ME immigrants compared to NHW	
	OR	**95% CI**	**OR**	**95% CI**
Model 0	**1.22**	**1.11, 1.33**	**1.27**	**1.11, 1.45**
Model 1: SES	**1.22**	**1.11, 1.34**	**1.27**	**1.11, 1.44**
Model 2: model 1 + health insurance	**1.21**	**1.11, 1.33**	**1.26**	**1.10, 1.44**
Model 3: model 2 + marital status	**1.22**	**1.11, 1.33**	**1.25**	**1.09, 1.43**

Abbreviations: ME: Middle Eastern; NHW: Non-Hispanic Whites; OR: Odds Ratio; CI: Confidence Interval; SES: Socio-Economic Status.
Localized stage serves as the baseline stage
NHW serves as the referent population group
Significant results are bolded
Age at diagnosis and year at diagnosis were controlled as strata.
Model 0: unadjusted
Model 1: adjusted by SES
Model 2: adjusted by SES and health insurance
Model 3: adjusted by SES, health insurance, and marital status

Table 5.3: Association between duration of residence and risk of advanced prostate cancer stage at diagnosis in first generation ME immigrants: California Cancer Registry, 1988-2013.

	< 21 years compared to ≥ 21 years N=2,813	
	OR	**95% CI**
Model 0	1.13	0.89, 1.44
Model 1: SES	1.13	0.88, 1.44
Model 2: model 1 + health insurance	1.12	0.87, 1.43
Model 3: model 2 + marital status	1.10	0.86, 1.42

Abbreviations: ME: Middle Eastern; OR: Odds Ratio; CI: Confidence Interval; SES: Socio-Economic Status.
Localized stage serves as the baseline stage
Age at diagnosis and year at diagnosis were controlled as strata.
Model 0: unadjusted
Model 1: adjusted by SES
Model 2: adjusted by SES and health insurance
Model 3: adjusted by SES, health insurance, and marital status

Table 5.4: Hazard Ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality and prostate cancer-specific mortality in the different generations of ME immigrants compared to NHW: California Cancer Registry, 1988-2013.

	First generation ME immigrants compared to NHW		Second or subsequent generations ME immigrants compared to NHW	
	HR	**95% CI**	**HR**	**95% CI**
All-cause mortality				
Model 0	**0.75**	**0.70, 0.79**	0.92	0.84, 1.00
Model 1: stage at diagnosis, tumor grade, and cancer treatment	**0.75**	**0.70, 0.79**	**0.90**	**0.83, 0.98**
Model 2: model 1 + SES	**0.77**	**0.72, 0.81**	**0.89**	**0.82, 0.96**
Model 3: Model 2 + health insurance	**0.76**	**0.72, 0.81**	**0.89**	**0.82, 0.97**
Model 4: Model 3 + marital status	**0.77**	**0.72, 0.82**	**0.89**	**0.82, 0.97**
Prostate cancer-specific mortality				
Model 0	0.92	0.82, 1.03	1.13	0.97, 1.32
Model 1: stage at diagnosis, tumor grade, and cancer treatment	**0.88**	**0.78, 0.99**	1.04	0.89, 1.22
Model 2: model 1 + SES	0.90	0.80, 1.02	1.04	0.89, 1.22
Model 3: Model 2 + health insurance	0.89	0.79, 1.00	1.04	0.89, 1.21
Model 4: Model 3 + marital status	0.90	0.80, 1.02	1.03	0.88, 1.21

Abbreviations: HR: Hazard Ratio, CI: Confidence Interval; ME: Middle Eastern; NHW: Non-Hispanic Whites; SES: Socio-Economic Status.
NHW serves as the referent population group
Significant results are bolded
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by stage at diagnosis, tumor grade, and cancer treatment
Model 2: adjusted by stage at diagnosis, tumor grade, cancer treatment, and SES
Model 3: adjusted by stage at diagnosis, tumor grade, cancer treatment, SES, and health insurance
Model 4: adjusted by stage at diagnosis, tumor grade, cancer treatment, SES, health insurance, and marital status

Table 5.5: Association between duration of residence and all-cause and prostate cancer-specific mortality in first generation ME immigrants: California Cancer Registry, 1988-2013.

	< 21 years compared to ≥ 21 years N=2,813	
	HR	**95% CI**
All-cause mortality		
Model 0	0.91	0.76, 1.09
Model 1: stage at diagnosis, tumor grade, and cancer treatment	0.89	0.73, 1.07
Model 2: model 1 + SES	0.86	0.71, 1.05
Model 3: Model 2 + health insurance	0.86	0.71, 1.05
Model 4: Model 3 + marital status	0.87	0.72, 1.06
Prostate cancer-specific mortality		
Model 0	1.28	0.91, 1.81
Model 1: stage at diagnosis, tumor grade, and cancer treatment	1.32	0.84, 2.09
Model 2: model 1 + SES	1.38	0.87, 2.20
Model 3: Model 2 + health insurance	1.45	0.90, 2.33
Model 4: Model 3 + marital status	1.52	0.93, 2.49

Abbreviations: ME: Middle Eastern; HR: Hazard Ratio, CI: Confidence Interval; SES: Socio-Economic Status.
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by stage at diagnosis, tumor grade, and cancer treatment
Model 2: adjusted by stage at diagnosis, tumor grade, cancer treatment, and SES
Model 3: adjusted by stage at diagnosis, tumor grade, cancer treatment, SES, and health insurance
Model 4: adjusted by stage at diagnosis, tumor grade, cancer treatment, SES, health insurance, and marital status

CHAPTER 6

DIFFERENCES IN COLORECTAL CANCER STAGE AND SURVIVAL BETWEEN MIDDLE EASTERN IMMIGRANTS AND NON-HISPANIC WHITES IN CALIFORNIA

6.1. Introduction

Colorectal cancer (CRC) is a slowly developing cancer that starts as a polyp on the wall of the colon or rectum[183,184]. It takes 10 years for polyps to develop to cancer. That is why CRC is highly preventable and ideal for screening[185].

In the United States (US), CRC is the third leading cause of cancer death in both males and females[164,186] with an estimation of 50,260 Americans dying from CRC in 2017[52]. Age-adjusted death rates for all races have been declining from 28.09 per 100,000 in 1975 to 13.99 per 100,000 in 2015[187]. The mortality decline has been associated with treatment improvement and the increase in screening rates.

Screening prevents CRC from developing by detecting and allowing for the removal of pre-cancerous polyps[188]. It can also detect CRC at an early stage improving CRC survival. Five-year survival rates drop from 89.9% for localized CRC stage, to 71.3% for regional CRC stage, to 13.9% for distant CRC stage[58]. Studies from the US have showed racial/ethnic differences in CRC stage and survival[189,190]. Immigrants from the Middle East (ME) are among the growing immigrant populations in the US. To our knowledge, only one study investigated CRC in ME immigrants. This study was limited to one single center in Illinois and described solely CRC stage at diagnosis[191]. It showed

50% of the ME immigrants being diagnosed at stage II cancer, 11.1% at stage III, and 11.1% at stage IV CRC. The dearth of studies can be explained by the lack of classification of ME immigrants as a separate ethnicity within the NHW in the US census[70].

Distint genetic, immunological, and molecular differences exist between proximal colon and distal colorectal cancers[192,193]. A review article has shown that proximal or right-sided colon cancers manifest at a more advanced stage and have worse overall survival compared to distal or left-sided colorectal cancers[192]. This study aims to analyze the association between ME immigration status and CRC cancer stage at diagnosis and all-cause and CRC-specific mortality in different generations of ME immigrants and NHW in California between 1988 and 2013. It also aims to investigate if this association is modified by gender and CRC tumor location.

6.2. Methods

6.2.1. Study populations

CRC patients were identified using the California Cancer Registry (CCR). CCR is a population-based cancer registry that collects information on cancer cases diagnosed in California since 1988. This study cohort consisted of all patients who: 1) were diagnosed in California between January 1st, 1988 and December 31st, 2013 with a primary invasive CRC, 2) had an available social security number (SSN) at diagnosis, 3) had a known CRC stage at diagnosis, and 4) were part of the 3 population groups of interest (first generation ME immigrants, second or subsequent generations ME

immigrants, and NHW) (N=174,828). The final sample in this study included 1,980 first generation ME immigrants (1,138 males & 842 females), 1,209 second or subsequent generations ME immigrants (597 males & 612 females), and 171,639 NHW (87,334 males & 84,305 females) **(figure 6.1)**.

The 3 population groups of interest in this study are: first generation ME immigrants, second or subsequent generations ME immigrants, and NHW. If the patient had a Middle Eastern last name[91], did not have a Hispanic nor an Asian last name, and was born in one of the Middle Eastern countries, he/she was considered first generation ME immigrant. If the patient had a Middle Eastern last name[91], did not have a Hispanic nor an Asian last name, was not born in one of the Middle Eastern countries, did not have a missing birth country, he/she was considered second or subsequent generations ME immigrant. If the patient did not have a ME nor Hispanic nor Asian last name and was identified as White in the CCR database, he/she was considered NHW in our analysis.

6.2.2. Stage at diagnosis and survival

The outcomes of interest in this study were stage at diagnosis and overall and CRC-specific mortality. Summary stage at diagnosis (SEER summary stage) from CCR was used in this study. We categorized CRC stage in our analysis into localized and non-localized tumors. Localized stage corresponds to tumors confined to the colon or rectum. Non-localized stage includes cancers that have spread to regional or distant lymph nodes, bones, or other organs[188]. Localized stage was considered an early

cancer stage and was used as the referent stage. Non-localized stage was considered the advanced stage at diagnosis.

CCR contains the patient's underlying cause of death, vital status, and follow-up time in months. In this study, the last day of follow-up was December 31st, 2013. The survival end-points were death from all causes and death from CRC. CRC specific deaths were classified as codes 153 and 154 of the International Classification of Diseases (ICD) ninth revision for deaths that occurred between 1988 and 1998 and codes C18 and C21 of the ICD tenth revision for deaths occurred in 1999 and beyond.

6.2.3. Other study variables

The marital status was categorized as single, married, separated/divorced, widowed, and unknown status. The socio-economic status (SES) variable was created from 2 different variables already existing in CCR: "quinyost" available till the end of 2005 and "quinyang" available from 2006 forward. Both of these variables were categorized into quintiles with the lowest quintile corresponds to the lowest SES. Health insurance was categorized into 3 categories: having insurance, not having insurance, and unknown. Age at diagnosis was used as a continuous measurement. In addition, age was categorized into 2 groups: patients with less than 50 years of age at diagnosis and 50 years and older at diagnosis. This age cutoff point was selected based on CRC recommended age for screening[61]. Year at diagnosis, ranging from 1988 to 2013, was categorized into five groups: 1988-1992, 1993-1997, 1998-2002, 2003-2007, and 2008-2013. The third edition of the ICD for Oncology (ICD-O-3)[194] was used to define the

tumor location. It was categorized as proximal, distal, and not specified (large intestine, NOS). The proximal or right-sided colon cancer included tumors arising from the cecum, ascending colon, hepatic flexure, and transverse colon. The distal or left-sided colorectal cancer included tumors arising from the splenic flexure, descending colon, sigmoid, and rectum & rectosigmoid junction. The tumor grade was defined as: well differentiated, moderately differentiated, poorly differentiated, undifferentiated/anaplastic, and unknown if differentiated. Lastly, a treatment variable that incorporated surgery, chemotherapy, and radiation therapy was created.

6.2.4. Statistical analysis

Descriptive data was stratified and presented by the 3 population groups of interest (first generation ME immigrants, second or subsequent generations ME immigrants, and NHW) and by tumor location, with the exception of large intestine, NOS. Means ± standard deviations and medians were used for continuous variables and numbers (percentages) for categorical variables.

The association between ME immigration status and stage at diagnosis was estimated using unconditional logistic regression. Localized CRC stage was used as the referent stage. We obtained the estimated odds ratios (ORs) and 95% confidence intervals (CIs) for non-localized CRC stage at diagnosis for the different generations of ME immigrants compared to NHW while controlling for potential confounding variables. We started with a model (model 0) containing the main exposure variable (population groups). We then added the following covariates selected a priori: SES and health

insurance to model 1, marital status and gender to model 2, and tumor location to model 3. The time of this study is large (1988 to 2013) and there are differences in CRC screening practices and guidelines among these years in the US and the Middle East. Therefore, in the multivariate analyses of risk of advanced stage, age and year at diagnosis were controlled as strata. Additional analyses stratified by gender, tumor location (with the exception of large intestine, NOS), and age at diagnosis as a categorical variable were conducted.

Cox proportional hazard models were applied to calculate the hazard ratios (HRs) with their 95% CIs for all-cause mortality and CRC-specific mortality between the different generations of ME immigrants and NHW. We began with a model (model 0) containing the main exposure variable (population groups). We then added the stage at diagnosis, tumor grade, cancer treatment, and tumor location to model 1. We also added SES, health insurance, marital status, and gender to model 2. Age and year at diagnosis were controlled as strata. We performed additional cox proportional hazards models stratified by gender, tumor location (with the exception of large intestine, NOS), and age at diagnosis as categorical to explore the potential differences in overall mortality and CRC-specific mortality between the different generations of ME immigrants and NHW. The proportional hazard assumption was examined by testing the interaction of time with the covariates. There was no violation for this assumption.

All data analyses were completed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

6.3. Results

Table 6.1 shows the descriptive characteristics of patients with primary invasive CRC stratified by the 3 population groups. The percentage of males with CRC was higher in the 3 population groups with the highest percentage being in first generation ME immigrants (57.5%). Most of the patients with CRC were married (56.4%-67.1%), had the highest quintile of SES (with the exception of second or subsequent generations ME immigrants), and had health insurance with first generation ME immigrants having the highest proportion of SES and health insurance (SES 34.3% and health insurance 81.5%). NHW were older at diagnosis compared to the different generations of ME immigrants. Although most patients were diagnosed at age 50 or higher, 12.7% of first generation ME immigrants and 13.2% of second or subsequent generations ME immigrants were younger than 50 years old at diagnosis compared to 7.5% of NHW. First generation ME immigrants were diagnosed the most at recent years while the highest percentage of NHW was diagnosed between 1988 and 1992. Patients in the 3 population groups were diagnosed the most at a more advanced CRC stage (non-localized) with 63.2% in first generation, 66.0% in second or subsequent generations, and 61.1% in NHW. Most of the tumors were distal colorectal tumors with different proportions in the 3 population groups (66.2% for first generation, 61.4% for second or subsequent generations ME immigrants, and 57.7% for NHW). More than 60% of the tumors were moderately well differentiated. Lastly, most of the patients received surgery as the only treatment with a highest percentage in NHW (62.0%).

The descriptive characteristics of patients with primary invasive CRC stratified by the 3 population groups and by the tumor location (proximal and distal) are shown in **table**

6.2. Of the main differences between the 2 tumor locations, patients with distal CRC were younger at diagnosis and had a highest percentage under the age of 50 years old (14.3% vs. 9.0% for first generation ME immigrants, 16.3% vs. 8.4% for second or subsequent generations ME immigrants, and 9.4% vs. 4.9% for NHW). The percentages of non-localized tumors were lower in distal colorectal cancers compared to proximal colon cancers. More patients with distal CRC were treated with a combination of the 3 treatments: surgery, chemotherapy, and radiation therapy.

Results from the logistic regression are illustrated in **table 6.3**. First generation ME immigrants had higher odds of being diagnosed with a non-localized stage (vs. localized stage) when compared with NHW [OR=1.16 with 95% CI (1.06, 1.28)] after adjusting by SES, health insurance, marital status, gender, and tumor location and controlling for age and year at diagnosis as strata. Second or subsequent generations of ME immigrants also had higher odds of being diagnosed with a non-localized stage (vs. localized stage) when compared with NHW [OR=1.26 with 95% CI (1.12, 1.42)].

In males **(table 6.4)**, there were no significant differences between first generation ME immigrants and NHW after adjusting for SES, health insurance, and marital status. After adding the tumor location, the OR increased to reach a significance [OR=1.15 with 95% CI (1.02, 1.31)]. However, second or subsequent generations ME immigrants had higher odds of being diagnosed with a more advanced CRC stage when compared with NHW (OR=1.24 in males and OR=1.29 in females) regardless of the adjustments. Same pattern was shown in females as in males for the risk of advanced CRC stage in the different generations of ME immigrants in comparison with NHW **(table 6.5)**.

Additional stratification by tumor location was conducted in **table 6.6**. For proximal colon cancers, there were no statistical differences between first generation ME immigrants and NHW [OR=1.05 with 95% CI (0.88, 1.24)]. However, first generation ME immigrants with distal colorectal tumors had a higher risk of advanced stage when compared to NHW [OR=1.23 with 95% CI (1.10, 1.38)]. Regardless of the tumor location, second or subsequent generations ME immigrants had a higher risk of advanced cancer stage when compared with NHW (OR=1.28 for proximal colon cancers and OR=1.22 for distal colorectal cancers).

Results from the logistic regression for patients younger than 50 years old at diagnosis are illustrated in **table 6.7**. In proximal and distal cancers, there were no significant differences in the risk of advanced CRC stage between the different generations of ME immigrants and NHW.

For patients 50 years and older at diagnosis, in proximal colon cancers, there were no statistical differences between first generation ME immigrants and NHW [OR=1.04 with 95% CI (0.87, 1.24)]. However, first generation ME immigrants with distal colorectal tumors had a higher risk of advanced stage when compared to NHW [OR=1.21 with 95% CI (1.07, 1.37)]. Regardless of the tumor location, second or subsequent generations ME immigrants had a higher risk of an advanced CRC stage when compared with NHW (OR=1.28 for proximal colon cancers and OR=1.23 for distal colorectal cancers) **(table 6.8)**.

After adjusting for stage at diagnosis, tumor grade, cancer treatment, tumor location, SES, health insurance, marital status, and gender, and controlling for age and

year at diagnosis as strata, first generation ME immigrants were 19% less likely to die than NHW [HR=0.81 with 95% CI (0.76, 0.87)]. They also were 13% less likely to die from CRC then NHW [HR=0.87 with 95% CI (0.80, 0.95)]. There were no significant differences in overall mortality or CRC-specific mortality between second or subsequent generations ME immigrants and NHW **(table 6.9)**.

In males and after full adjustments, first generation ME immigrants were 23% less likely to die than NHW [HR=0.77 with 95% CI (0.71, 0.84)]. There were no significant differences in all-cause mortality or CRC-specific mortality between second or subsequent generations ME immigrants and NHW. Furthermore, no significant difference was shown in the risk of dying from CRC between first generation ME immigrants and NHW after full adjustments [HR=0.89 with 95% CI (0.79, 1.00)] **(table 6.10)**.

In females, first generation ME immigrants were 13% less likely to die than NHW [HR=0.87 with 95% CI (0.79, 0.96)]. They also were 15% less likely to die from CRC then NHW [HR=0.85 with 95% CI (0.74, 0.99)]. There were no significant differences in all-cause mortality or CRC-specific mortality between second or subsequent generations ME immigrants and NHW females **(table 6.11)**.

The risk of overall death stratified by the tumor location is shown in **table 6.12**. In both proximal and distal tumors, first generation ME immigrants were at lower risk of dying than NHW (HR=0.75 for proximal colon cancers and HR=0.85 for distal colorectal cancers). No statistical differences were shown between second or subsequent generations ME immigrants and NHW.

For patients with proximal or right-sided tumors, first generation ME immigrants were 25% less likely to die from CRC than NHW [HR=0.75 with 95% CI (0.64, 0.88)]. No statistical differences were shown between second or subsequent generations ME immigrants and NHW for all locations or between first generation ME immigrants and NHW for distal CRC **(table 6.13)**.

For CRC-specific mortality, no statistical differences were shown between the different generations of ME immigrants and NHW regardless of the tumor location for patients younger than 50 years old at diagnosis **(table 6.14)**. Furthermore, for patients 50 years and older at diagnosis, no statistical differences were shown between the different generations of ME immigrants and NHW with the exception of proximal cancers where first generation ME immigrants were less likely to die from CRC than NHW [HR=0.76 with 95%CI (0.64, 0.90)] **(table 6.15)**.

6.4. Discussion

This study found that first generation ME immigrants had lower all-cause and CRC-specific mortality despite being diagnosed at a non-localized CRC stage when compared with NHW. Second or subsequent generations ME immigrants also had higher risk of advanced CRC stage at diagnosis when compared with NHW but no statistical differences were shown for overall and CRC-specific mortality.

Previous studies conducted in the US have shown that immigrants are diagnosed at a more advanced CRC stage when compared to NHW[189,195,196]. Same results were illustrated in our study with the different generations of ME immigrants being diagnosed

at a more advanced stage in comparison with NHW. A study conducted in Northwestern Iran has shown that Iranians presented with a more advanced CRC stage in comparison with the developed countries[197]. In addition to the lack of population-based screening programs in most of the countries of the Middle East, multiple barriers prevent the people of the Middle East from being screened. These barriers can be economic, cultural, religious, or personal in nature[198]. The non-adherence to the CRC screening recommendations can lead to the advanced stage shown in the different generations of ME immigrants when compared to NHW in our study. A few studies were conducted in Michigan, the location of many Middle Eastern immigrants. A survey has shown that the screening rates for CRC in ME immigrants of Michigan were exceptionally lower than the general population (45.6 vs. 60.8) for men and women aged 50 or older[199]. Another study identified the potential barriers for CRC screening in ME immigrants. These barriers included feeling a discomfort or intimidation, being unaware of the screening procedure, screening not being recommended by their primary physician, and having a limited English proficiency[200]. The most common reported barrier was the misconception that screening is not needed for CRC in a survey conducted on ME immigrants from Lebanon and Yemen who were 50 years and older[201]. The risk of advanced CRC stage is higher in second or subsequent generations ME immigrants compared to NHW. Second or subsequent generations ME immigrants might be reluctant to the CRC screening in addition to having additional lifestyle risk factors leading to the higher OR estimates when compared with first generation ME immigrants.

Our study shows that first generation ME immigrants had a lower all-cause and CRC-specific mortality risk when compared to NHW. The differences in mortality can be multifactorial. Healthier people from the Middle East tend to immigrate to the US (healthy migrant effect). First generation ME immigrants are more likely to adopt a Mediterranean diet. A meta-analysis of cohort studies has shown that an adherence to high-quality diet was inversely associated with overall mortality[161]. A cohort of CRC patients has shown that physical activity and having a normal weight were related to lower overall and CRC-specific mortality[202]. There were no significant differences in mortality between second or subsequent generations of ME immigrants and NHW. We speculate that second or subsequent generations ME immigrants are adopting the same lifestyle behaviors as NHW.

There is a general consensus that the anatomic site plays a role in CRC stage and survival. A review article, that included studies published between 1947 and 2014, has shown that right-sided or proximal colon cancers have a more advanced stage at diagnosis and worse overall survival compared to left-sided or distal colorectal cancers[203]. Our analysis shows that for patients diagnosed with distal colorectal cancers, there is a higher risk of advanced stage in first generation ME immigrants compared with NHW. This pattern was not shown in patients diagnosed with proximal colon cancers. This can be explained by colonoscopy and sigmoidoscopy being more effective in capturing the distal cancers. Additional analysis stratified by age at diagnosis shows no difference in the risk of advanced stage for patients younger than 50 years old at diagnosis for any of the tumor locations. In contrast, first generation ME immigrants aged 50 years or older with distal colorectal cancers were at higher risk of

advanced stage when compared with NHW. No significant differences were shown for first generation ME immigrants who were 50 years or older with proximal cancers and NHW with same age and same tumor location. Our findings highlight the impact of CRC screening recommended for adults 50 years and older[60]. Second or subsequent generations ME immigrants who were 50 years or older at diagnosis were at higher risk of advanced CRC stage compared to NHW regardless of the tumor location. Furthermore, regardless of the tumor location, first generation ME immigrants were at lower risk of death from all causes compared to NHW. However, they were at lower risk of death from CRC only if the tumor was right-sided or proximal. It is possible that this difference in CRC-specific mortality is related to different genetic, epigenetic, or molecular pathways[203]. A meta-analysis has shown that positive microsatellite instability tumors (MSI positive) have better survival and right-sided colon cancers are more likely to be MSI positive[204]. Further research is needed to confirm our findings and explain the patterns seen in this study.

To our knowledge, this is the first study in the US to investigate colorectal cancer stage and survival in different generations of ME immigrants to California. Our study is based on data from the CCR, which is California's statewide cancer registry that captures cancer incidence and characteristics among all Californians since 1988. We also examined if our associations are modified by tumor locations. Our study also bares a few limitations. We excluded missing stage at diagnosis which can be a source of bias if the proportion of cases with an unknown stage varied by ME immigration status. ME immigrants with missing ME last name or patients with missing place of birth were not captured in this study. Data on access to health care, adherence to CRC screening, and

certain lifestyle factors such as diet, smoking, and physical activity were not available in this study. We also did not have information on body composition. Information on family history of CRC, cultural practices and beliefs, and comorbid diseases were not available. We used the cause of death on the birth certificate. A certain degree of misclassification can occur for cancer-related deaths when using this variable[205]. Lastly, huge differences exist in the sample sizes of the 3 population groups of interest, limiting the comparability of our groups.

In summary, ME immigrants had a significantly higher risk of advanced CRC stage at diagnosis when compared to NHW. However, first generation ME immigrants had lower all-cause and CRC-specific mortality. With CRC being highly preventable, it is good to understand why ME immigrants are diagnosed at advanced stage. Future interventions to increase awareness on the importance of CRC screening need to be designed for ME immigrants.

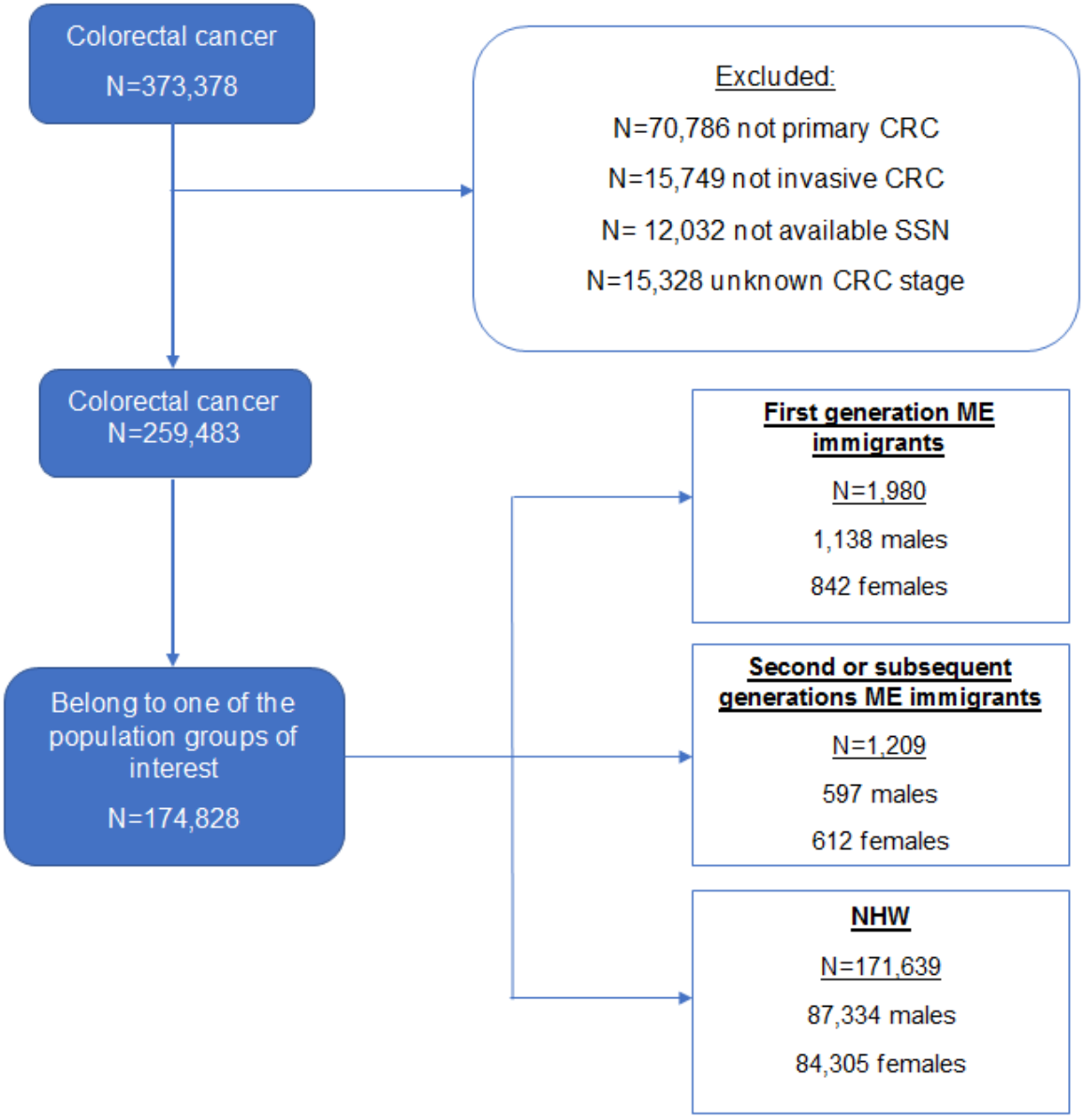

Figure 6.1: Inclusion criteria for study participants with colorectal cancers: California Cancer Registry, 1988-2013.
Abbreviations: CRC: Colorectal Cancer; SSN: Social Security Number; ME: Middle Eastern; NHW: Non-Hispanic Whites.

Table 6.1: Descriptive characteristics of patients with primary invasive colorectal cancer stratified by population groups: California Cancer Registry, 1988-2013.

Characteristics	First generation ME immigrants	Second or subsequent generations ME immigrants	NHW
	N=1,980	N=1,209	N=171,639
Gender. N (%)			
Male	1,138 (57.5%)	597 (49.4%)	87,334 (50.9%)
Female	842 (42.5%)	612 (50.6%)	84,305 (49.1%)
Marital status. N (%)			
Single	165 (8.3%)	121 (10.0%)	19,003 (11.1%)
Married	1,329 (67.1%)	777 (64.3%)	96,839 (56.4%)
Separated/Divorced	132 (6.7%)	87 (7.2%)	14,591 (8.5%)
Widowed	323 (16.3%)	206 (17.0%)	37,143 (21.6%)
Unknown	31 (1.6%)	18 (1.5%)	4,063 (2.4%)
Quintile of SES. N (%)			
Lowest SES	150 (7.6%)	159 (13.2%)	17,450 (10.2%)
Lower-Middle SES	315 (15.9%)	286 (23.7%)	31,155 (18.2%)
Middle SES	383 (19.3%)	245 (20.3%)	38,313 (22.3%)
Higher-Middle SES	452 (22.8%)	249 (20.6%)	41,563 (24.2%)
Highest SES	680 (34.3%)	270 (22.3%)	43,158 (25.1%)
Health insurance. N (%)			
Presence	1,614 (81.5%)	952 (78.7%)	117,172 (68.3%)
Absence	30 (1.5%)	22 (1.8%)	1,422 (0.8%)
Unknown	336 (17.0%)	235 (19.4%)	53,045 (30.9%)
Age at diagnosis, years			
Mean (SD)	65.4 (13.4)	65.8 (13.6)	69.6 (13.0)
Median	67	67	71
< 50	251 (12.7%)	160 (13.2%)	12,896 (7.5%)
≥ 50	1,729 (87.3%)	1,049 (86.8%)	158,743 (92.5%)

Year at diagnosis. N (%)			
1988-1992	200 (10.1%)	166 (13.7%)	37,867 (22.1%)
1993-1997	293 (14.8%)	211 (17.5%)	34,781 (20.3%)
1998-2002	460 (23.2%)	307 (25.4%)	34,642 (20.2%)
2003-2007	488 (24.7%)	239 (19.8%)	31,720 (18.5%)
2008-2013	539 (27.2%)	286 (23.7%)	32,629 (19.0%)
Stage at diagnosis. N (%)			
Localized	729 (36.8%)	411 (34.0%)	66,750 (38.9%)
Non-Localized	1,251 (63.2%)	798 (66.0%)	104,889 (61.1%)
Tumor location. N (%)			
Proximal	622 (31.4%)	443 (36.6%)	68,600 (40.0%)
Distal	1,311 (66.2%)	742 (61.4%)	99,060 (57.7%)
Large intestine, NOS	47 (2.4%)	24 (2.0%)	3,979 (2.3%)
Tumor grade. N (%)			
Well differentiated	133 (6.7%)	82 (6.8%)	16,639 (9.7%)
Moderately well differentiated	1,284 (64.9%)	758 (62.7%)	102,922 (60.0%)
Poorly differentiated	355 (17.9%)	250 (20.7%)	30,622 (17.8%)
Undifferentiated/ anaplastic	27 (1.4%)	10 (0.8%)	1,642 (1.0%)
Unknown if differentiated	181 (9.1%)	109 (9.0%)	19,814 (11.5%)
Treatment. N (%)†			
None of the three treatments	66 (3.5%)	46 (4.0%)	9,312 (5.6%)
Radiation only	3 (0.2%)	3 (0.3%)	697 (0.4%)
Chemotherapy only	45 (2.4%)	40 (3.4%)	3,558 (2.1%)
Radiation + chemotherapy	24 (1.3%)	24 (2.1%)	2,349 (1.4%)
Surgery	990 (52.0%)	644 (55.3%)	103,360 (62.0%)
Surgery + radiation therapy	24 (1.3%)	10 (0.9%)	2,614 (1.6%)
Surgery + chemotherapy	488 (25.6%)	273 (23.4%)	31,383 (18.8%)
Three treatments together	263 (13.8%)	125 (10.7%)	13,533 (8.1%)
Missing	77	44	4,833

Abbreviations: ME: Middle Eastern; NHW: Non-Hispanic Whites; N (%): Sample size (percentage); SES: Socio-Economic Status; SD: Standard Deviation.

Percentages may not be equal to 100 because of rounding

†Treatment includes surgery, chemotherapy, and radiation therapy

Table 6.2: Descriptive characteristics of patients with primary invasive colorectal cancer stratified by population groups and by tumor location (only proximal and distal): California Cancer Registry, 1988-2013.

Characteristics	Proximal colon			Distal colorectal		
	First generation ME immigrants	Second or subsequent generations ME immigrants	NHW	First generation ME immigrants	Second or subsequent generations ME immigrants	NHW
	N=622	N=443	N=68,600	N=1,311	N=742	N=99,060
Gender. N (%)						
Male	344 (55.3%)	202 (45.6%)	31,015 (45.2%)	770 (58.7%)	383 (51.6%)	54,373 (54.9%)
Female	278 (44.7%)	241 (54.4%)	37,585 (54.8%)	541 (41.3%)	359 (48.4%)	44,687 (45.1%)
Marital status. N (%)						
Single	50 (8.0%)	49 (11.1%)	6,815 (9.9%)	106 (8.1%)	69 (9.3%)	11,690 (11.8%)
Married	411 (66.1%)	270 (61.0%)	36,936 (53.8%)	892 (68.0%)	494 (66.6%)	57,985 (58.5%)
Separated/Divorced	47 (7.6%)	30 (6.8%)	5,481 (8.0%)	83 (6.3%)	56 (7.6%)	8,748 (8.8%)
Widowed	104 (16.7%)	92 (20.8%)	18,024 (26.3%)	209 (15.9%)	107 (14.4%)	18,056 (18.2%)
Unknown	10 (1.6%)	2 (0.5%)	1,344 (2.0%)	21 (1.6%)	16 (2.2%)	2,581 (2.6%)
Quintile of SES. N (%)						
Lowest SES	50 (8.0%)	58 (13.1%)	6,772 (9.9%)	96 (7.3%)	97 (13.1%)	10,215 (10.3%)
Lower-Middle SES	104 (16.7%)	103 (23.3%)	12,352 (18.0%)	204 (15.6%)	177 (23.9%)	17,996 (18.2%)
Middle SES	99 (15.9%)	96 (21.7%)	15,461 (22.5%)	274 (20.9%)	147 (19.8%)	21,971 (22.2%)
Higher-Middle SES	145 (23.3%)	84 (19.0%)	16,808 (24.5%)	300 (22.9%)	159 (21.4%)	23,768 (24.0%)
Highest SES	224 (36.0%)	102 (23.0%)	17,207 (25.1%)	437 (33.3%)	162 (21.8%)	25,110 (25.4%)
Health insurance. N (%)						
Presence	504 (81.0%)	347 (78.3%)	48,444 (70.6%)	1,069 (81.5%)	587 (79.1%)	65,971 (66.6%)
Absence	14 (2.3%)	8 (1.8%)	483 (0.7%)	15 (1.1%)	13 (1.8%)	900 (0.9%)
Unknown	104 (16.7%)	88 (19.9%)	19,673 (28.7%)	227 (17.3%)	142 (19.1%)	32,189 (32.5%)
Age at diagnosis, years						
Mean (SD)	67.4 (13.1)	68.8 (13.3)	72.6 (12.3)	64.5 (13.4)	63.9 (13.5)	67.4 (13.0)
Median	69	70	74	66	65	68
< 50	56 (9.0%)	37 (8.4%)	3,350 (4.9%)	188 (14.3%)	121 (16.3%)	9,266 (9.4%)
$\geq$ 50	566 (91.0%)	406 (91.7%)	65,250 (95.1%)	1,123 (85.7%)	621 (83.7%)	89,794 (90.7%)
Year at diagnosis. N (%)						

1988-1992	59 (9.5%)	68 (15.4%)	13,992 (20.4%)	138 (10.5%)	96 (12.9%)	23,200 (23.4%)
1993-1997	88 (14.2%)	75 (16.9%)	13,676 (19.9%)	200 (15.3%)	130 (17.5%)	20,366 (20.6%)
1998-2002	141 (22.7%)	112 (25.3%)	14,054 (20.5%)	308 (23.5%)	188 (25.3%)	19,788 (20.0%)
2003-2007	146 (23.5%)	85 (19.2%)	13,205 (19.3%)	326 (24.9%)	151 (20.4%)	17,618 (17.8%)
2008-2013	188 (30.2%)	103 (23.3%)	13,673 (19.9%)	339 (25.9%)	177 (23.9%)	18,088 (18.3%)
Stage at diagnosis. N (%)						
Localized	211 (33.9%)	125 (28.2%)	23,485 (34.2%)	510 (38.9%)	285 (38.4%)	42,754 (43.2%)
Non-Localized	411 (66.1%)	318 (71.8%)	45,115 (65.8%)	801 (61.1%)	457 (61.6%)	56,306 (56.8%)
Tumor grade. N (%)*						
Well differentiated	35 (5.6%)	32 (7.2%)	5,794 (8.5%)	95 (7.3%)	49 (6.6%)	10,632 (10.7%)
Moderately well differentiated	384 (61.7%)	267 (60.3%)	39,825 (58.1%)	879 (67.1%)	480 (64.7%)	61,995 (62.6%)
Poorly differentiated	150 (24.1%)	113 (25.5%)	16,565 (24.2%)	199 (15.2%)	134 (18.1%)	13,418 (13.6%)
Undifferentiated/ anaplastic	11 (1.8%)	5 (1.1%)	982 (1.4%)	15 (1.1%)	5 (0.7%)	607 (0.6%)
Unknown if differentiated	42 (6.8%)	26 (5.9%)	5,434 (7.9%)	123 (9.4%)	74 (10.0%)	12,408 (12.5%)
Treatment. N (%)†						
None of the three treatments	23 (3.9%)	19 (4.5%)	3,003 (4.5%)	33 (2.6%)	22 (3.1%)	4,728 (4.9%)
Radiation only	0 (0.0%)	0 (0.0%)	46 (0.1%)	2 (0.2%)	3 (0.4%)	619 (0.6%)
Chemotherapy only	17 (2.9%)	16 (3.8%)	1,166 (1.8%)	23 (1.8%)	23 (3.2%)	1,943 (2.0%)
Radiation + chemotherapy	0 (0.0%)	1 (0.2%)	89 (0.1%)	23 (1.8%)	23 (3.2%)	2,220 (2.3%)
Surgery	359 (60.6%)	252 (59.0%)	45,944 (69.0%)	615 (48.6%)	384 (53.6%)	56,222 (58.3%)
Surgery + radiation therapy	0 (0.0%)	1 (0.2%)	195 (0.3%)	24 (1.9%)	9 (1.3%)	2,402 (2.5%)
Surgery + chemotherapy	177 (29.9%)	134 (31.4%)	15,507 (23.3%)	300 (23.7%)	132 (18.4%)	15,383 (16.0%)
Three treatments together	16 (2.7%)	4 (0.9%)	605 (0.9%)	246 (19.4%)	121 (16.9%)	12,885 (13.4%)
Missing	30	16	2,045	45	25	2,658

Abbreviations: ME: Middle Eastern; NHW: Non-Hispanic Whites; N (%): Sample size (percentage); SES: Socio-Economic Status; SD: Standard Deviation.

Percentages may not be equal to 100 because of rounding

*Difference not significant for proximal colon cancer (p-value=0.1162)

†Treatment includes surgery, chemotherapy, and radiation therapy

Table 6.3: Risk of advanced colorectal cancer stage at diagnosis (non-localized vs. localized), in the different generations of ME immigrants compared to NHW: California Cancer Registry, 1988-2013.

	First generation ME immigrants compared to NHW		Second or subsequent generations ME immigrants compared to NHW	
	OR	**95% CI**	**OR**	**95% CI**
Model 0	**1.11**	**1.01, 1.22**	**1.25**	**1.11, 1.41**
Model 1: SES + health insurance	**1.12**	**1.02, 1.23**	**1.23**	**1.09, 1.39**
Model 2: Model 1 + marital status + gender	**1.13**	**1.03, 1.24**	**1.24**	**1.10, 1.40**
Model 3: Model 2 + tumor location	**1.16**	**1.06, 1.28**	**1.26**	**1.12, 1.42**

Abbreviations: ME: Middle Eastern; NHW: Non-Hispanic Whites; OR: Odds Ratio; CI: Confidence Interval; SES: Socio-Economic Status.
Localized stage serves as the baseline stage
NHW serves as the referent population group
Significant results are bolded
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by SES and health insurance
Model 2: adjusted by SES, health insurance, marital status, and gender
Model 3: adjusted by SES, health insurance, marital status, gender, and tumor location

Table 6.4: Risk of advanced colorectal cancer stage at diagnosis (non-localized vs. localized), in the different generations of ME immigrants' **males** compared to NHW **males**: California Cancer Registry, 1988-2013.

	First generation ME immigrants compared to NHW		Second or subsequent generations ME immigrants compared to NHW	
	OR	**95% CI**	**OR**	**95% CI**
Model 0	1.10	0.98, 1.25	**1.23**	**1.03, 1.46**
Model 1: SES + health insurance	1.11	0.98, 1.26	**1.21**	**1.02, 1.44**
Model 2: Model 1 + marital status	1.13	1.00, 1.27	**1.22**	**1.03, 1.45**
Model 3: Model 2 + tumor location	**1.15**	**1.02, 1.31**	**1.24**	**1.04, 1.47**

Abbreviations: ME: Middle Eastern; NHW: Non-Hispanic Whites; OR: Odds Ratio; CI: Confidence Interval; SES: Socio-Economic Status.
Localized stage serves as the baseline stage
NHW serves as the referent population group
Significant results are bolded
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by SES and health insurance
Model 2: adjusted by SES, health insurance, and marital status
Model 3: adjusted by SES, health insurance, marital status, and tumor location

Table 6.5: Risk of advanced colorectal cancer stage at diagnosis (non-localized vs. localized), in the different generations of ME immigrants' **females** compared to NHW **females**: California Cancer Registry, 1988-2013.

	First generation ME immigrants compared to NHW		Second or subsequent generations ME immigrants compared to NHW	
	OR	**95% CI**	**OR**	**95% CI**
Model 0	1.12	0.97, 1.29	**1.28**	**1.08, 1.52**
Model 1: SES + health insurance	1.12	0.97, 1.30	**1.27**	**1.07, 1.51**
Model 2: Model 1 + marital status	1.13	0.98, 1.31	**1.27**	**1.07, 1.51**
Model 3: Model 2 + tumor location	**1.16**	**1.01, 1.35**	**1.29**	**1.09, 1.54**

Abbreviations: ME: Middle Eastern; NHW: Non-Hispanic Whites; OR: Odds Ratio; CI: Confidence Interval; SES: Socio-Economic Status.
Localized stage serves as the baseline stage
NHW serves as the referent population group
Significant results are bolded
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by SES and health insurance
Model 2: adjusted by SES, health insurance, and marital status
Model 3: adjusted by SES, health insurance, marital status, and tumor location

Table 6.6: Risk of advanced colorectal cancer stage at diagnosis (non-localized vs. localized), in the different generations of ME immigrants compared to NHW and stratified by tumor location: California Cancer Registry, 1988-2013.

	First generation ME immigrants compared to NHW		Second or subsequent generations ME immigrants compared to NHW	
	OR	**95% CI**	**OR**	**95% CI**
Proximal colon				
Model 0	1.03	0.87, 1.22	**1.28**	**1.04, 1.59**
Model 1: SES + health insurance	1.04	0.87, 1.23	**1.27**	**1.03, 1.58**
Model 2: Model 1 + marital status	1.05	0.88, 1.24	**1.28**	**1.03, 1.58**
Model 3: Model 2 + gender	1.05	0.88, 1.24	**1.28**	**1.03, 1.58**
Distal colorectal				
Model 0	**1.20**	**1.07, 1.35**	**1.22**	**1.05, 1.42**
Model 1: SES + health insurance	**1.21**	**1.08, 1.36**	**1.21**	**1.04, 1.41**
Model 2: Model 1 + marital status	**1.23**	**1.09, 1.37**	**1.23**	**1.05, 1.43**
Model 3: Model 2 + gender	**1.23**	**1.10, 1.38**	**1.22**	**1.05, 1.42**

Abbreviations: ME: Middle Eastern; NHW: Non-Hispanic Whites; OR: Odds Ratio; CI: Confidence Interval; SES: Socio-Economic Status.
Localized stage serves as the baseline stage
NHW serves as the referent population group
Significant results are bolded
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by SES and health insurance
Model 2: adjusted by SES, health insurance, and marital status
Model 3: adjusted by SES, health insurance, marital status, and gender

Table 6.7: Risk of advanced colorectal cancer stage at diagnosis (non-localized vs. localized), in the different generations of ME immigrants compared to NHW for patients younger than 50 years of age at diagnosis and stratified by tumor location: California Cancer Registry, 1988-2013.

	First generation ME immigrants compared to NHW		Second or subsequent generations ME immigrants compared to NHW	
	OR	**95% CI**	**OR**	**95% CI**
Proximal colon				
Model 0	1.16	0.58, 2.31	1.14	0.47, 2.78
Model 1: SES + health insurance	1.15	0.57, 2.29	1.15	0.47, 2.80
Model 2: Model 1 + marital status	1.16	0.58, 2.30	1.18	0.48, 2.87
Model 3: Model 2 + gender	1.15	0.58, 2.30	1.18	0.49, 2.89
Distal colorectal				
Model 0	1.28	0.92, 1.79	1.17	0.78, 1.74
Model 1: SES + health insurance	1.31	0.94, 1.83	1.15	0.77, 1.72
Model 2: Model 1 + marital status	1.33	0.95, 1.86	1.16	0.78, 1.74
Model 3: Model 2 + gender	1.33	0.95, 1.86	1.17	0.78, 1.75

Abbreviations: ME: Middle Eastern; NHW: Non-Hispanic Whites; OR: Odds Ratio; CI: Confidence Interval; SES: Socio-Economic Status.
Localized stage serves as the baseline stage
NHW serves as the referent population group
Significant results are bolded
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by SES and health insurance
Model 2: adjusted by SES, health insurance, and marital status
Model 3: adjusted by SES, health insurance, marital status, and gender

Table 6.8: Risk of advanced colorectal cancer stage at diagnosis (non-localized vs. localized), in the different generations of ME immigrants compared to NHW for patients 50 years and older at diagnosis and stratified by tumor location: California Cancer Registry, 1988-2013.

	First generation ME immigrants compared to NHW		Second or subsequent generations ME immigrants compared to NHW	
	OR	**95% CI**	**OR**	**95% CI**
Proximal colon				
Model 0	1.02	0.86, 1.22	**1.29**	**1.04, 1.61**
Model 1: SES + health insurance	1.03	0.86, 1.23	**1.28**	**1.03, 1.60**
Model 2: Model 1 + marital status	1.04	0.87, 1.24	**1.29**	**1.03, 1.60**
Model 3: Model 2 + gender	1.04	0.87, 1.24	**1.28**	**1.03, 1.60**
Distal colorectal				
Model 0	**1.19**	**1.06, 1.35**	**1.23**	**1.05, 1.45**
Model 1: SES + health insurance	**1.20**	**1.06, 1.36**	**1.22**	**1.04, 1.43**
Model 2: Model 1 + marital status	**1.21**	**1.07, 1.37**	**1.24**	**1.05, 1.45**
Model 3: Model 2 + gender	**1.21**	**1.07, 1.37**	**1.23**	**1.05, 1.45**

Abbreviations: ME: Middle Eastern; NHW: Non-Hispanic Whites; OR: Odds Ratio; CI: Confidence Interval; SES: Socio-Economic Status.
Localized stage serves as the baseline stage
NHW serves as the referent population group
Significant results are bolded
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by SES and health insurance
Model 2: adjusted by SES, health insurance, and marital status
Model 3: adjusted by SES, health insurance, marital status, and gender

Table 6.9: Hazard Ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality and colorectal cancer-specific mortality in the different generations of ME immigrants compared to NHW: California Cancer Registry, 1988-2013.

	First generation ME immigrants compared to NHW		Second or subsequent generations ME immigrants compared to NHW	
	HR	**95% CI**	**HR**	**95% CI**
All-cause mortality				
Model 0	**0.82**	**0.77, 0.87**	1.00	0.93, 1.08
Model 1: stage at diagnosis + tumor grade + cancer treatment + tumor location	**0.80**	**0.76, 0.86**	0.95	0.89, 1.03
Model 2: Model 1 + SES + health insurance + marital status + gender	**0.81**	**0.76, 0.87**	0.95	0.88, 1.03
Colorectal cancer-specific mortality				
Model 0	**0.89**	**0.82, 0.97**	1.09	0.99, 1.21
Model 1: stage at diagnosis + tumor grade + cancer treatment + tumor location	**0.86**	**0.79, 0.94**	1.01	0.91, 1.12
Model 2: Model 1 + SES + health insurance + marital status + gender	**0.87**	**0.80, 0.95**	1.01	0.91, 1.12

Abbreviations: HR: Hazard Ratio, CI: Confidence Interval; ME: Middle Eastern; NHW: Non-Hispanic Whites; SES: Socio-Economic Status.
NHW serves as the referent population group
Significant results are bolded
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by stage at diagnosis, tumor grade, cancer treatment, and tumor location
Model 2: adjusted by stage at diagnosis, tumor grade, cancer treatment, tumor location, SES, health insurance, marital status, and gender

Table 6.10: Hazard Ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality and colorectal cancer-specific mortality in the different generations of ME immigrants' **males** compared to NHW **males**: California Cancer Registry, 1988-2013.

	First generation ME immigrants compared to NHW		Second or subsequent generations ME immigrants compared to NHW	
	HR	**95% CI**	**HR**	**95% CI**
All-cause mortality				
Model 0	**0.78**	**0.72, 0.85**	0.98	0.89, 1.09
Model 1: stage at diagnosis + tumor grade + cancer treatment + tumor location	**0.75**	**0.69, 0.81**	0.92	0.83, 1.02
Model 2: Model 1 + SES + health insurance + marital status	**0.77**	**0.71, 0.84**	0.92	0.82, 1.02
Colorectal cancer-specific mortality				
Model 0	0.92	0.82, 1.02	1.09	0.94, 1.26
Model 1: stage at diagnosis + tumor grade + cancer treatment + tumor location	**0.86**	**0.76, 0.97**	0.98	0.84, 1.14
Model 2: Model 1 + SES + health insurance + marital status	0.89	0.79, 1.00	0.98	0.85, 1.14

Abbreviations: HR: Hazard Ratio, CI: Confidence Interval; ME: Middle Eastern; NHW: Non-Hispanic Whites; SES: Socio-Economic Status.
NHW serves as the referent population group
Significant results are bolded
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by stage at diagnosis, tumor grade, cancer treatment, and tumor location
Model 2: adjusted by stage at diagnosis, tumor grade, cancer treatment, tumor location, SES, health insurance, and marital status

Table 6.11: Hazard Ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality and colorectal cancer-specific mortality in the different generations of ME immigrants' **females** compared to NHW **females**: California Cancer Registry, 1988-2013.

	First generation ME immigrants compared to NHW		Second or subsequent generations ME immigrants compared to NHW	
	HR	**95% CI**	**HR**	**95% CI**
All-cause mortality				
Model 0	**0.86**	**0.78, 0.95**	1.02	0.92, 1.13
Model 1: stage at diagnosis + tumor grade + cancer treatment + tumor location	**0.86**	**0.78, 0.95**	0.97	0.87, 1.08
Model 2: Model 1 + SES + health insurance + marital status	**0.87**	**0.79, 0.96**	0.97	0.87, 1.08
Colorectal cancer-specific mortality				
Model 0	**0.86**	**0.74, 0.98**	1.08	0.94, 1.25
Model 1: stage at diagnosis + tumor grade + cancer treatment + tumor location	**0.85**	**0.73, 0.98**	1.00	0.86, 1.16
Model 2: Model 1 + SES + health insurance + marital status	**0.85**	**0.74, 0.99**	1.00	0.86, 1.16

Abbreviations: HR: Hazard Ratio, CI: Confidence Interval; ME: Middle Eastern; NHW: Non-Hispanic Whites; SES: Socio-Economic Status.
NHW serves as the referent population group
Significant results are bolded
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by stage at diagnosis, tumor grade, cancer treatment, and tumor location
Model 2: adjusted by stage at diagnosis, tumor grade, cancer treatment, tumor location, SES, health insurance, and marital status

Table 6.12: Hazard Ratios (HRs) and 95% confidence intervals (CIs) for **all-cause mortality** in the different generations of ME immigrants compared to NHW and stratified by tumor location: California Cancer Registry, 1988-2013.

	First generation ME immigrants compared to NHW		Second or subsequent generations ME immigrants compared to NHW	
	HR	**95% CI**	**HR**	**95% CI**
Proximal colon				
Model 0	**0.80**	**0.71, 0.89**	1.00	0.89, 1.12
Model 1: stage at diagnosis + tumor grade + cancer treatment	**0.74**	**0.66, 0.84**	0.94	0.83, 1.06
Model 2: Model 1 + SES + health insurance + marital status + gender	**0.75**	**0.67, 0.85**	0.93	0.82, 1.05
Distal colorectal				
Model 0	**0.84**	**0.78, 0.91**	1.00	0.91, 1.10
Model 1: stage at diagnosis + tumor grade + cancer treatment	**0.84**	**0.77, 0.90**	0.95	0.87, 1.05
Model 2: Model 1 + SES + health insurance + marital status + gender	**0.85**	**0.78, 0.92**	0.96	0.87, 1.06

Abbreviations: HR: Hazard Ratio, CI: Confidence Interval; ME: Middle Eastern; NHW: Non-Hispanic Whites; SES: Socio-Economic Status.
NHW serves as the referent population group
Significant results are bolded
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by stage at diagnosis, tumor grade, and cancer treatment
Model 2: adjusted by stage at diagnosis, tumor grade, cancer treatment, SES, health insurance, marital status, and gender

Table 6.13: Hazard Ratios (HRs) and 95% confidence intervals (CIs) for **colorectal cancer-specific mortality** in the different generations of ME immigrants compared to NHW and stratified by tumor location: California Cancer Registry, 1988-2013.

	First generation ME immigrants compared to NHW		Second or subsequent generations ME immigrants compared to NHW	
	HR	**95% CI**	**HR**	**95% CI**
Proximal colon				
Model 0	**0.78**	**0.67, 0.92**	1.11	0.95, 1.30
Model 1: stage at diagnosis + tumor grade + cancer treatment	**0.74**	**0.63, 0.87**	0.99	0.84, 1.16
Model 2: Model 1 + SES + health insurance + marital status + gender	**0.75**	**0.64, 0.88**	0.99	0.84, 1.16
Distal colorectal				
Model 0	1.00	0.89, 1.10	1.08	0.94, 1.24
Model 1: stage at diagnosis + tumor grade + cancer treatment	0.95	0.85, 1.10	1.01	0.88, 1.17
Model 2: Model 1 + SES + health insurance + marital status + gender	0.96	0.86, 1.08	1.01	0.88, 1.17

Abbreviations: HR: Hazard Ratio, CI: Confidence Interval; ME: Middle Eastern; NHW: Non-Hispanic Whites; SES: Socio-Economic Status.
NHW serves as the referent population group
Significant results are bolded
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by stage at diagnosis, tumor grade, and cancer treatment
Model 2: adjusted by stage at diagnosis, tumor grade, cancer treatment, SES, health insurance, marital status, and gender

Table 6.14: Hazard Ratios (HRs) and 95% confidence intervals (CIs) for **colorectal cancer-specific mortality** in the different generations of ME immigrants compared to NHW for patients younger than 50 years of age at diagnosis and stratified by tumor location: California Cancer Registry, 1988-2013.

	First generation ME immigrants compared to NHW		Second or subsequent generations ME immigrants compared to NHW	
	HR	**95% CI**	**HR**	**95% CI**
Proximal colon				
Model 0	0.78	0.45, 1.35	0.79	0.40, 1.55
Model 1: stage at diagnosis + tumor grade + cancer treatment	0.64	0.35, 1.19	0.74	0.35, 1.53
Model 2: Model 1 + SES + health insurance + marital status + gender	0.65	0.35, 1.21	0.77	0.37, 1.60
Distal colorectal				
Model 0	0.98	0.72, 1.33	0.97	0.67, 1.41
Model 1: stage at diagnosis + tumor grade + cancer treatment	0.88	0.62, 1.23	0.75	0.50, 1.11
Model 2: Model 1 + SES + health insurance + marital status + gender	0.90	0.64, 1.26	0.75	0.50, 1.12

Abbreviations: HR: Hazard Ratio, CI: Confidence Interval; ME: Middle Eastern; NHW: Non-Hispanic Whites; SES: Socio-Economic Status.
NHW serves as the referent population group
Significant results are bolded
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by stage at diagnosis, tumor grade, and cancer treatment
Model 2: adjusted by stage at diagnosis, tumor grade, cancer treatment, SES, health insurance, marital status, and gender

Table 6.15: Hazard Ratios (HRs) and 95% confidence intervals (CIs) for **colorectal cancer-specific mortality** in the different generations of ME immigrants compared to NHW for patients 50 years and older at diagnosis and stratified by tumor location: California Cancer Registry, 1988-2013.

	First generation ME immigrants compared to NHW		Second or subsequent generations ME immigrants compared to NHW	
	HR	**95% CI**	**HR**	**95% CI**
Proximal colon				
Model 0	**0.78**	**0.67, 0.92**	1.14	0.97, 1.34
Model 1: stage at diagnosis + tumor grade + cancer treatment	**0.75**	**0.63, 0.88**	1.01	0.85, 1.19
Model 2: Model 1 + SES + health insurance + marital status + gender	**0.76**	**0.64, 0.90**	1.01	0.85, 1.19
Distal colorectal				
Model 0	0.99	0.88, 1.11	1.10	0.95, 1.28
Model 1: stage at diagnosis + tumor grade + cancer treatment	0.96	0.85, 1.08	1.06	0.91, 1.24
Model 2: Model 1 + SES + health insurance + marital status + gender	0.97	0.86, 1.10	1.06	0.91, 1.24

Abbreviations: HR: Hazard Ratio, CI: Confidence Interval; ME: Middle Eastern; NHW: Non-Hispanic Whites; SES: Socio-Economic Status.
NHW serves as the referent population group
Significant results are bolded
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by stage at diagnosis, tumor grade, and cancer treatment
Model 2: adjusted by stage at diagnosis, tumor grade, cancer treatment, SES, health insurance, marital status, and gender

CHAPTER 7

SUMMARY AND CONCLUSIONS

7.1. Summary

This dissertation project highlighted the cancer characteristics in Middle Eastern immigrants to the US. It aimed to analyze the association between ME immigration status and cancer stage at diagnosis and overall and cancer-specific incidence and mortality in different generations of ME immigrants and NHW.

First generation ME immigrants were more likely to be at increased risk of stomach and hepatobiliary cancers in females and thyroid and stomach cancers in males in comparison with NHW. Second or subsequent generations ME immigrants were at increased risk of thyroid cancer in comparison with NHW, and malignant melanoma cancer in comparison with first generation ME immigrants. The risk levels of breast, thyroid, and bladder cancers in first generation ME immigrants were significantly higher compared to NHW regardless of time spent in the US suggesting the role of genetic predisposition, and/or cultural characteristics associated with these cancers. The results suggested that differences in cancer risk between ME first generation immigrants and NHW change in second or subsequent generations, approaching the risk level of NHW and indicating the impact of acculturation in this immigrant population.

First generation ME immigrants had higher odds of being diagnosed with an advanced breast cancer stage compared to NHW. Second or subsequent generations ME immigrants also had higher odds of being diagnosed with an advanced breast cancer stage than NHW. First generation ME immigrants were 14% less likely to die

cancer than NHW. No significant differences were seen in breast cancer-specific mortality between first generation ME immigrants and NHW. The risk of overall death or breast cancer-specific death was not significantly different between second or subsequent generations ME immigrants and NHW.

The different generations of ME immigrants had significantly higher risk of advanced prostate cancer stage at diagnosis and lower overall mortality when compared to NHW. No significant differences were detected in prostate cancer-specific mortality between the different generations of ME immigrants and NHW. Furthermore, there were no statistical differences in the risk of advanced prostate cancer stage and mortality in first generation ME immigrants by duration of residence in the US.

First generation ME immigrants had lower overall and CRC-specific mortality despite being diagnosed at a non-localized CRC stage when compared with NHW. Second or subsequent generations ME immigrants also had higher risk of advanced CRC stage at diagnosis when compared with NHW but no statistical differences were shown for overall and CRC-specific mortality.

7.2. Strengths and limitations

There are strengths and limitations to each of the aims and they are discussed in the previous chapters. The main strength is using CCR which is California's statewide population-based cancer registry, capturing cancer incidence in Californians since 1988 with a high completeness rate. This dissertation is the first of its kind to investigate the different cancer characteristics in different generations of ME immigrants to California in

comparison with NHW. This dissertation is one of few to use the year of issue of SSN as an estimate for year of immigration for ME immigrants and therefore calculate the duration of stay in the US from immigration to cancer diagnosis. The impact of acculturation was investigated by looking at the different generations of ME immigrants and by investigating the duration of residence for first generation ME immigrants.

Although the limitations were discussed in the previous chapters, some of them are worth mentioning again. It was impossible to differentiate between second and subsequent generations of ME immigrants. Therefore, they were grouped together in the analysis. More than 40% of the birth country was missing in CCR which can lead to a misclassification bias. Maiden name is not accessible for Health Insurance Portability and Accountability Act reasons. ME females who changed their last name after marriage or children born to ME females but not ME males (given that the children usually take the father's last name in the Middle Eastern culture) were not captured in the analysis. Immigrants with missing ME last name were not captured either. Information on body composition, cancer screening behaviors, diet, smoking, and other lifestyle factors were missing in CCR. The population groups of interest are Middle Eastern immigrants, so results cannot be generalized to other immigrants. Lastly, healthier people (healthy migrant effect) with higher SES and education tend to immigrate; therefore, results of this dissertation project cannot be generalized to people still residing in the Middle East.

7.3. Conclusion

Our results from a population-based sample quantify the disparities in cancer stage at diagnosis for first generation ME immigrants. Our novel study highlights on the importance of adapting screening interventions tailored to the ME immigrant population in the US with using an appropriate language and taking into consideration the ME immigrants' specific cultural and religious beliefs.

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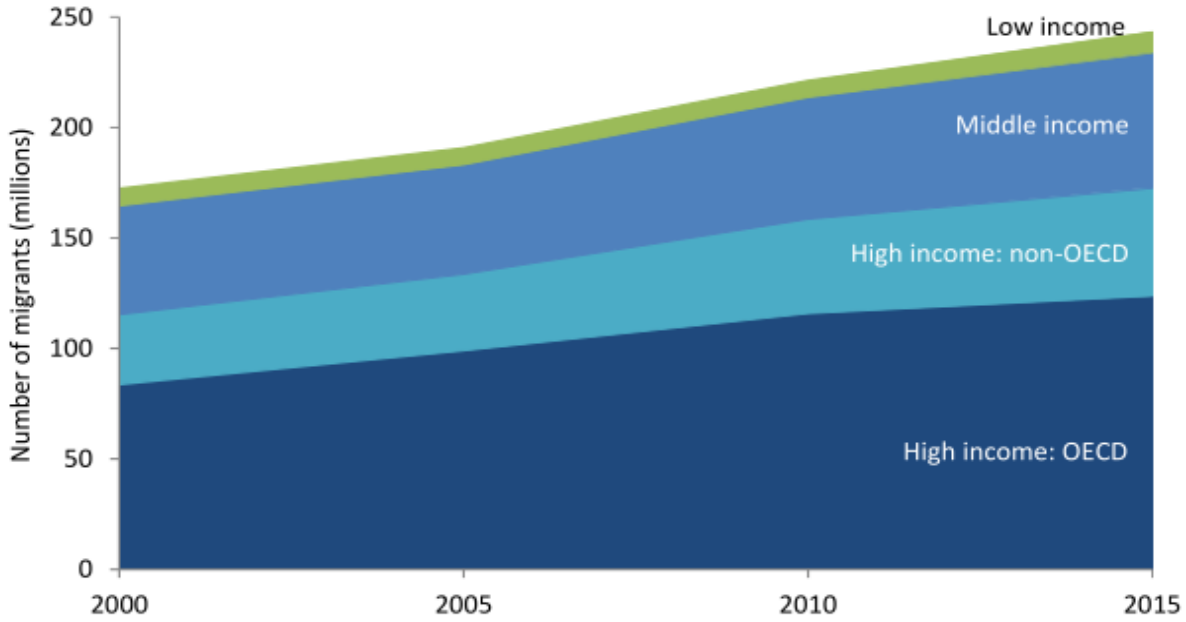
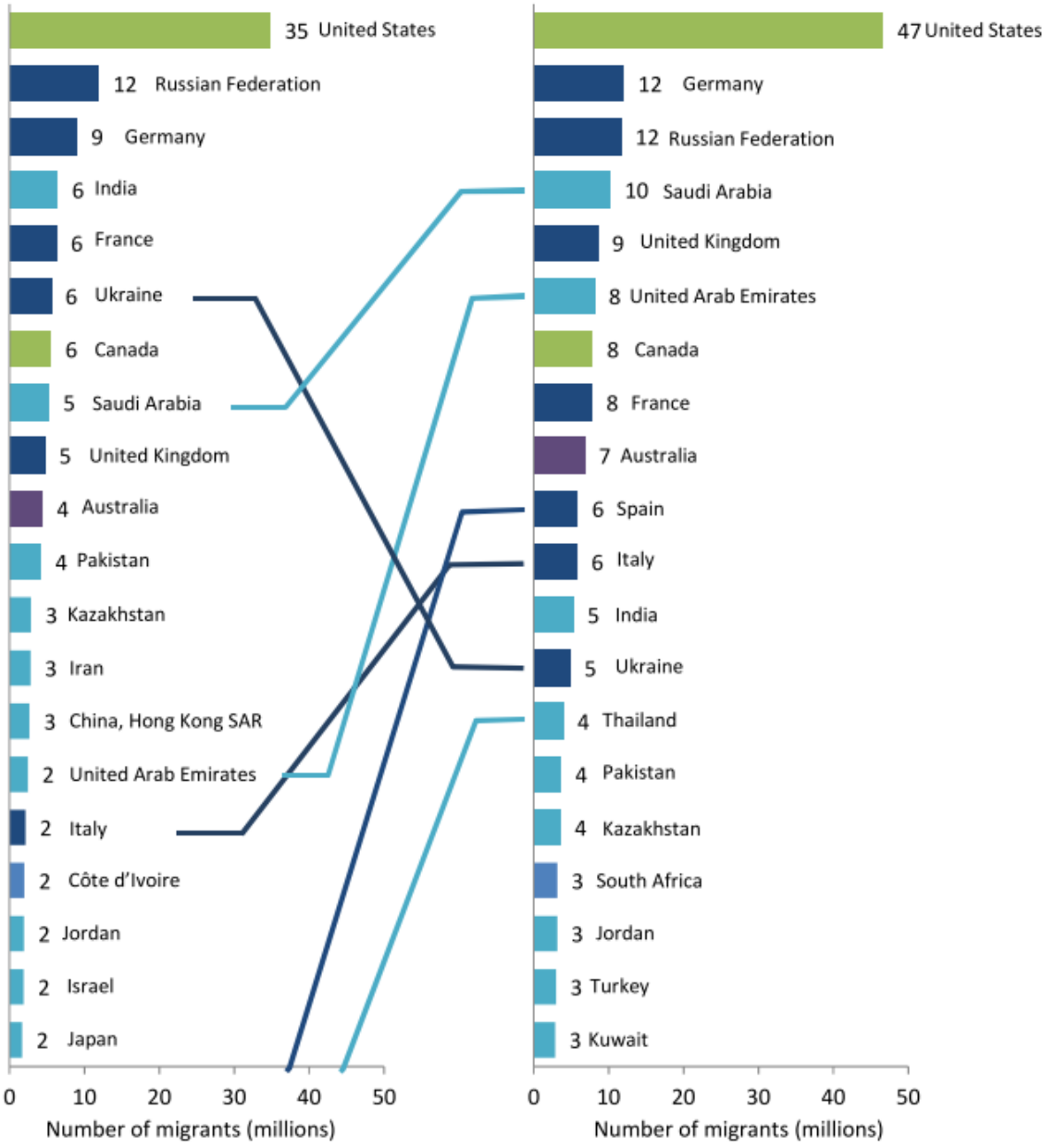
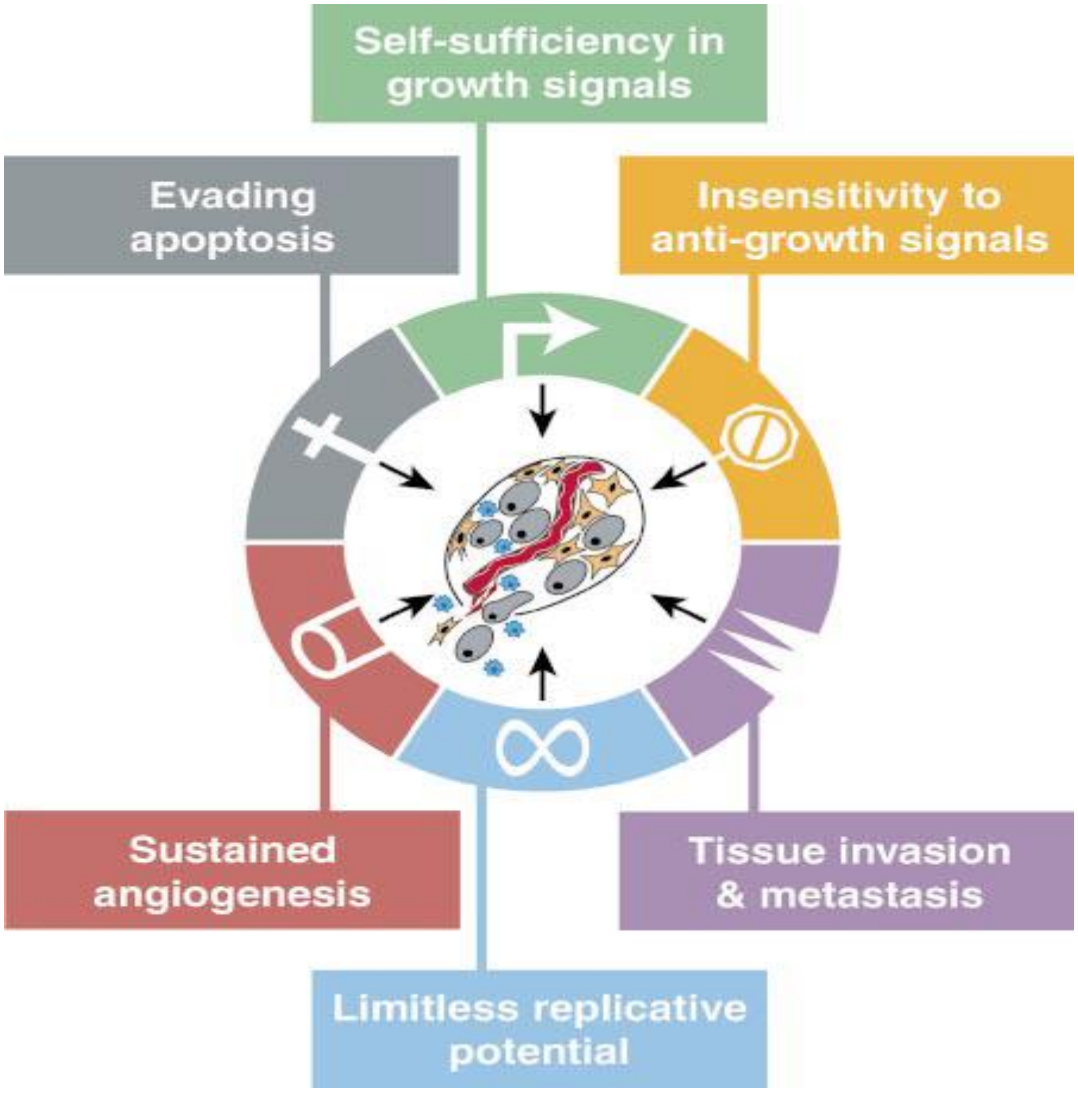
Appendix A: Number of international migrants by income group of country or area of destination, 2000 to 2015[3].



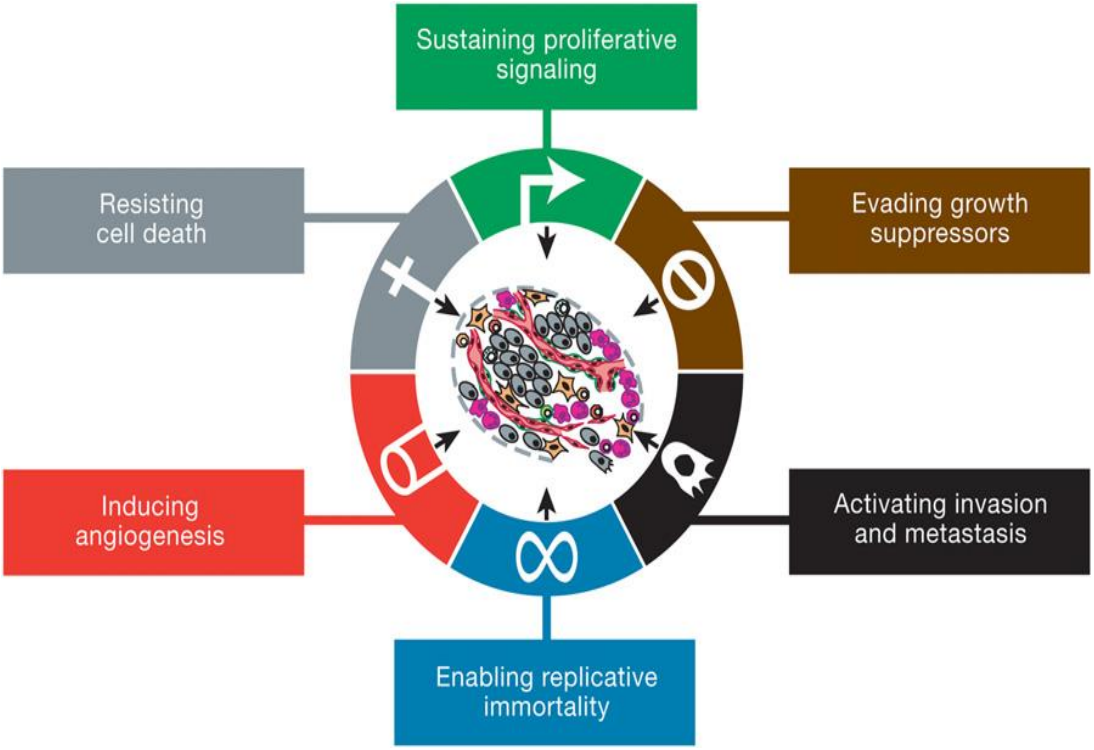
Appendix B: Twenty countries or areas hosting the largest numbers of international migrants, 2000 and 2015[3].



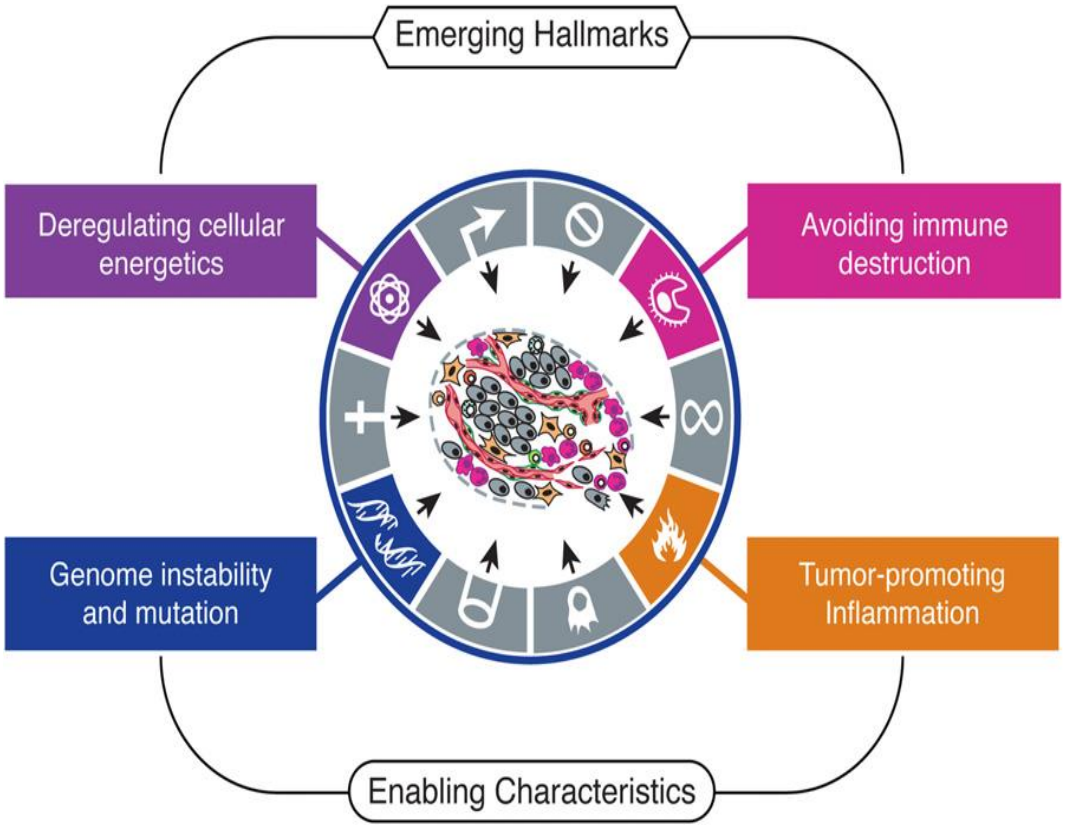
Appendix C: Acquired Capabilities of Cancer[11].



Appendix D: The hallmarks of Cancer[13].



Appendix E: Emerging Hallmarks and Enabling Characteristics[13].



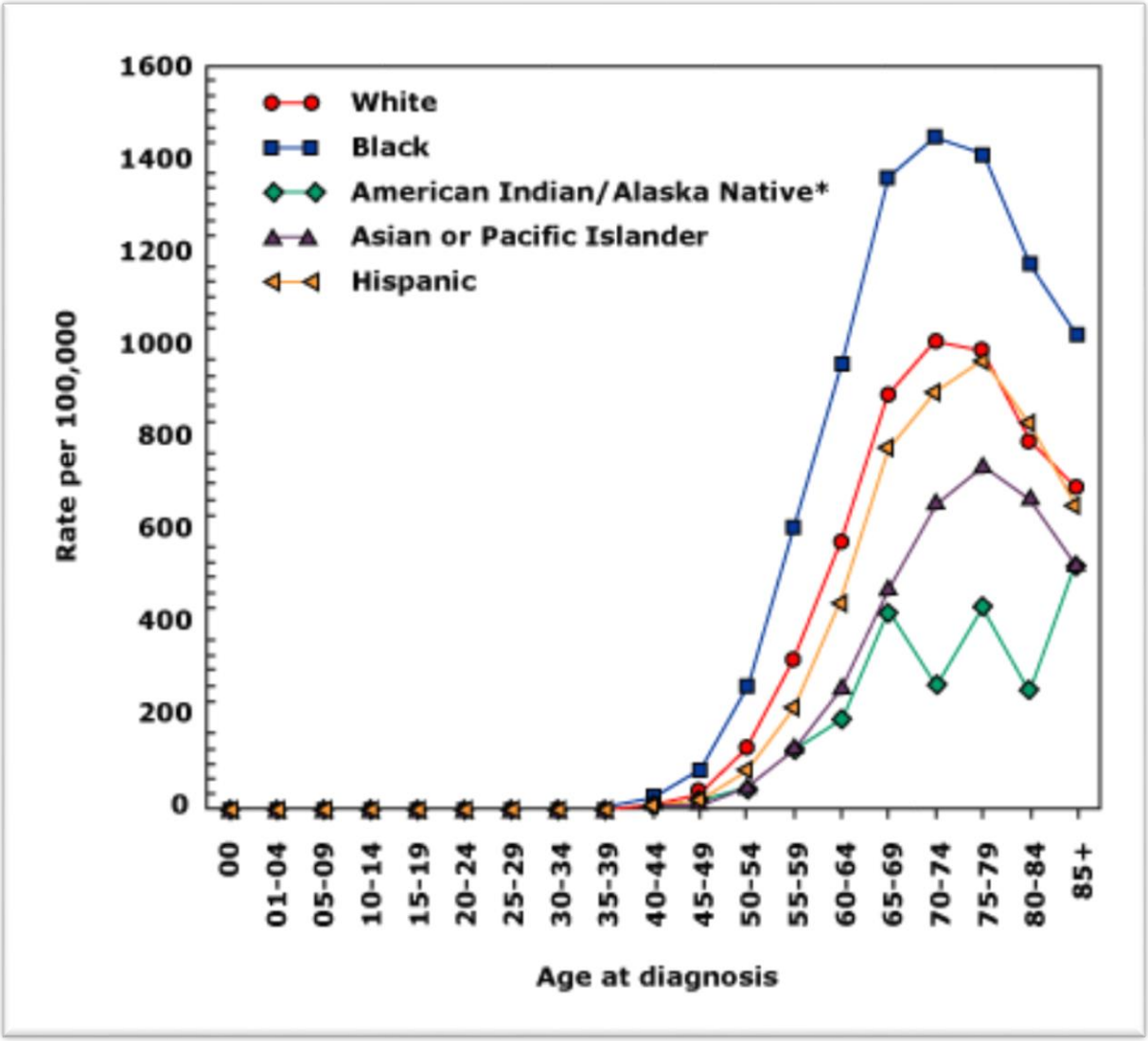
Appendix F: American Cancer Society recommendations for early detection of cancer in average-risk asymptomatic people[21].

American Cancer Society Recommendations for the Early Detection of Cancer in Average-risk Asymptomatic People*

Cancer Site	Population	Test or Procedure	Recommendation
Breast	Women, ages 40-54	Mammography	Women should undergo regular screening mammography starting at age 45 years. Women ages 45 to 54 should be screened annually. Women should have the opportunity to begin annual screening between the ages of 40 and 44.
	Women, ages 55+		Transition to biennial screening, or have the opportunity to continue annual screening. Continue screening as long as overall health is good and life expectancy is 10+ years.
Cervix	Women, ages 21-29	Pap test	Screening should be done every 3 years with conventional or liquid-based Pap tests.
	Women, ages 30-65	Pap test & HPV DNA test	Screening should be done every 5 years with both the HPV test and the Pap test (preferred), or every 3 years with the Pap test alone (acceptable).
	Women, ages 66+	Pap test & HPV DNA test	Women ages 66+ who have had ≥3 consecutive negative Pap tests or ≥2 consecutive negative HPV and Pap tests within the past 10 years, with the most recent test occurring in the past 5 years should stop cervical cancer screening.
	Women who have had a total hysterectomy		Stop cervical cancer screening.
Colorectal†	Men and women, ages 50+	Guaiac-based fecal occult blood test (gFOBT) with at least 50% sensitivity or fecal immunochemical test (FIT) with at least 50% sensitivity, **OR**	Annual testing of spontaneously passed stool specimens. Single stool testing during a clinician office visit is not recommended, nor are "throw in the toilet bowl" tests. In comparison with guaiac-based tests for the detection of occult blood, immunochemical tests are more patient-friendly and are likely to be equal or better in sensitivity and specificity. There is no justification for repeating FOBT in response to an initial positive finding.
		Stool DNA test, **OR**	Every 3 years
		Flexible sigmoidoscopy (FSIG), **OR**	Every 5 years alone, or consideration can be given to combining FSIG performed every 5 years with a highly sensitive gFOBT or FIT performed annually.
		Double-contrast barium enema, **OR**	Every 5 years
		Colonoscopy, **OR**	Every 10 years
		CT Colonography	Every 5 years
Endometrial	Women at menopause		Women should be informed about risks and symptoms of endometrial cancer and encouraged to report unexpected bleeding to a physician.
Lung	Current or former smokers ages 55-74 in good health with 30+ pack-year history	Low-dose helical CT (LDCT)	Clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should initiate a discussion about annual lung cancer screening with apparently healthy patients ages 55-74 who have at least a 30 pack-year smoking history, and who currently smoke or have quit within the past 15 years. A process of informed and shared decision making with a clinician related to the potential benefits, limitations, and harms associated with screening for lung cancer with LDCT should occur before any decision is made to initiate lung cancer screening. Smoking cessation counseling remains a high priority for clinical attention in discussions with current smokers, who should be informed of their continuing risk of lung cancer. Screening should not be viewed as an alternative to smoking cessation
Prostate	Men, ages 50+	Prostate-specific antigen test with or without digital rectal examination	Men who have at least a 10-year life expectancy should have an opportunity to make an informed decision with their health care provider about whether to be screened for prostate cancer, after receiving information about the potential benefits, risks, and uncertainties associated with prostate cancer screening. Prostate cancer screening should not occur without an informed decision-making process.

CT-Computed tomography. *All individuals should become familiar with the potential benefits, limitations, and harms associated with cancer screening. †All positive tests (other than colonoscopy) should be followed up with colonoscopy.

Appendix G: Age-specific (crude) SEER incidence rates by 'expanded' race for prostate cancer, males SEER 17 registries for 2000-2003[47].



Appendix H: Ten leading cancer types for the estimated new cancer cases and deaths by gender, United States, 2017[31].

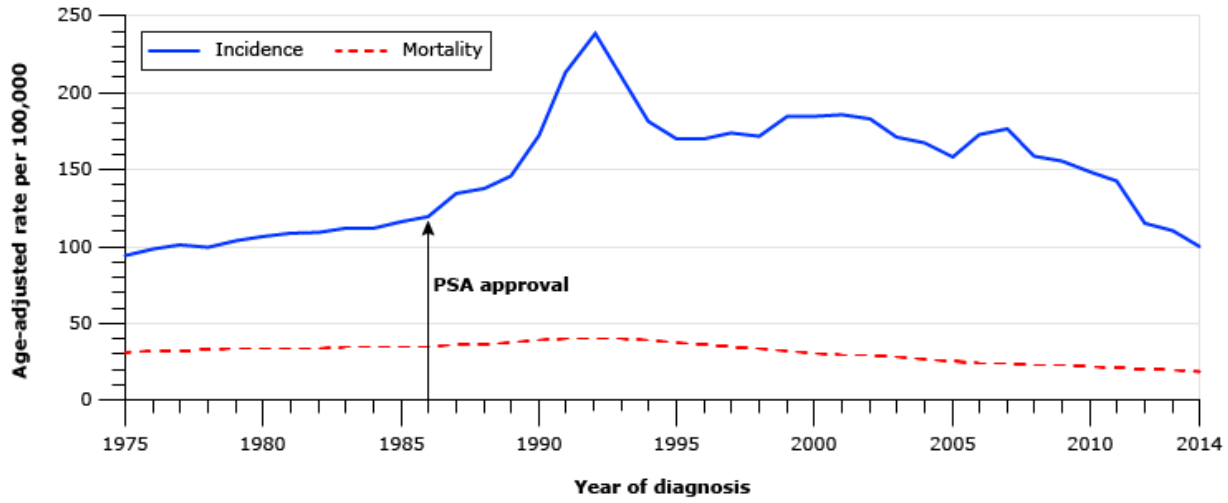
Estimated New Cases

Males				Females		
Prostate	161,360	19%		Breast	252,710	30%
Lung & bronchus	116,990	14%		Lung & bronchus	105,510	12%
Colon & rectum	71,420	9%		Colon & rectum	64,010	8%
Urinary bladder	60,490	7%		Uterine corpus	61,380	7%
Melanoma of the skin	52,170	6%		Thyroid	42,470	5%
Kidney & renal pelvis	40,610	5%		Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	40,080	5%		Non-Hodgkin lymphoma	32,160	4%
Leukemia	36,290	4%		Leukemia	25,840	3%
Oral cavity & pharynx	35,720	4%		Pancreas	25,700	3%
Liver & intrahepatic bile duct	29,200	3%		Kidney & renal pelvis	23,380	3%
All Sites	**836,150**	**100%**		**All Sites**	**852,630**	**100%**

Estimated Deaths

Males				Females		
Lung & bronchus	84,590	27%		Lung & bronchus	71,280	25%
Colon & rectum	27,150	9%		Breast	40,610	14%
Prostate	26,730	8%		Colon & rectum	23,110	8%
Pancreas	22,300	7%		Pancreas	20,790	7%
Liver & intrahepatic bile duct	19,610	6%		Ovary	14,080	5%
Leukemia	14,300	4%		Uterine corpus	10,920	4%
Esophagus	12,720	4%		Leukemia	10,200	4%
Urinary bladder	12,240	4%		Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	4%		Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%		Brain & other nervous system	7,080	3%
All Sites	**318,420**	**100%**		**All Sites**	**282,500**	**100%**

Appendix I: Prostate cancer: Changes over time in average annual age-adjusted incidence and mortality rates in the United States, 1975-2014[52].



Appendix J: American Cancer Society Guidelines on Screening and Surveillance for the Early Detection of Colorectal Adenomas and Cancer in People at Increased Risk or High Risk[61].

Risk category	When to test	Recommended test(s)	Comment
INCREASED RISK – People who have a history of polyps on prior colonoscopy			
People with small rectal hyperplastic polyps	Same age as those at average risk	Colonoscopy, or other screening options at same intervals as for those at average risk	Those with hyperplastic polyposis syndrome are at increased risk for adenomatous polyps and cancer and should have more intensive follow-up.
People with 1 or 2 small (no more than 1 cm) tubular adenomas with low-grade dysplasia	5 to 10 years after the polyps are removed	Colonoscopy	Time between tests should be based on other factors such as prior colonoscopy findings, family history, and patient and doctor preferences.
People with 3 to 10 adenomas, or a large (at least 1 cm) adenoma, or any adenomas with high-grade dysplasia or villous features	3 years after the polyps are removed	Colonoscopy	Adenomas must have been completely removed. If colonoscopy is normal or shows only 1 or 2 small tubular adenomas with low-grade dysplasia, future colonoscopies can be done every 5 years.
People with more than 10 adenomas on a single exam	Within 3 years after the polyps are removed	Colonoscopy	Doctor should consider possible genetic syndrome (such as FAP or Lynch syndrome).
People with sessile adenomas that are removed in pieces	2 to 6 months after adenoma removal	Colonoscopy	If entire adenoma has been removed, further testing should be based on doctor's judgment.

INCREASED RISK – People who have had colorectal cancer

People diagnosed with colon or rectal cancer	At time of colorectal surgery, or can be 3 to 6 months later if person doesn't have cancer spread that can't be removed	Colonoscopy to look at the entire colon and remove all polyps	If the tumor presses on the colon/rectum and prevents colonoscopy, CT colonoscopy (with IV contrast) or DCBE may be done to look at the rest of the colon.
People who have had colon or rectal cancer removed by surgery	Within 1 year after cancer resection (or 1 year after colonoscopy to make sure the rest of the colon/rectum was clear)	Colonoscopy	If normal, repeat in 3 years. If normal then, repeat test every 5 years. Time between tests may be shorter if polyps are found or there's reason to suspect Lynch syndrome. After low anterior resection for rectal cancer, exams of the rectum may be done every 3 to 6 months for the first 2 to 3 years to look for signs of recurrence.

INCREASED RISK – People with a family history

Colorectal cancer or adenomatous polyps in any first-degree relative before age 60, or in 2 or more first-degree relatives at any age (if not a hereditary syndrome).	Age 40, or 10 years before the youngest case in the immediate family, whichever is earlier	Colonoscopy	Every 5 years.
Colorectal cancer or adenomatous polyps in any first-degree relative aged 60 or older, or in at least 2 second-degree relatives at any age	Age 40	Same test options as for those at average risk.	Same test intervals as for those at average risk.

HIGH RISK

Familial adenomatous polyposis (FAP) diagnosed by genetic testing, or suspected FAP without genetic testing	Age 10 to 12	Yearly flexible sigmoidoscopy to look for signs of FAP; counseling to consider genetic testing if it hasn't been done	If genetic test is positive, removal of colon (colectomy) should be considered.
Lynch syndrome (hereditary non-polyposis colon cancer or HNPCC), or at increased risk of Lynch syndrome based on family history without genetic testing	Age 20 to 25 years, or 10 years before the youngest case in the immediate family	Colonoscopy every 1 to 2 years; counseling to consider genetic testing if it hasn't been done	Genetic testing should be offered to first-degree relatives of people found to have Lynch syndrome mutations by genetic tests. It should also be offered if 1 of the first 3 of the modified Bethesda criteria is met.
Inflammatory bowel disease: -Chronic ulcerative colitis -Crohn's disease	Cancer risk begins to be significant 8 years after the onset of pancolitis (involvement of entire large intestine), or 12-15 years after the onset of left-sided colitis	Colonoscopy every 1 to 2 years with biopsies for dysplasia	These people are best referred to a center with experience in the surveillance and management of inflammatory bowel disease.

Appendix K: Cancer type by SEERWHO[a] code.

Cancer type	SEERWHO codes	Description
Oral	20010,20020,20030, 20040,20050,20060, 20070,20080,20090, 20100	Oral cavity and Pharynx: Lip, tongue, salivary gland, floor of mouth, gum and other mouth, nasopharynx, tonsil, oropharynx, hypopharynx, and other oral cavity and pharynx
Esophagus	21010	Esophagus
Stomach	21020	Stomach
Small Intestine	21030	Small Intestine
Colorectal	21041,21042,21043, 21044,21045,21046, 21047,21048,21049, 21051,21052	Cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, large intestine NOS, recto-sigmoid junction, and rectum
Anus	21060	Anus, anal canal, and anorectum
Liver	21071	Liver
Biliary & Gallbladder	21072, 21080, 21090	Intrahepatic bile duct, Gallbladder, and other biliary
Pancreas	21100	Pancreas
Other digestive	21110, 21120, 21130	Retroperitoneum, peritoneum, omentum and mesentery, and other digestive organs
Respiratory system	22010,22050,22060	Nose, nasal cavity and middle ear, pleura, and trachea, mediastinum and other respiratory organs
Larynx	22020	Larynx

Lung	22030	Lung and Bronchus
Bones	23000	Bones and joints
Soft tissue	24000	Soft tissue including heart
Melanoma	25010	Skin Melanoma
Skin non Melanoma	25020	Other non-epithelial skin
Breast	26000	Breast
Cervix	27010	Cervix Uteri
Endometrium	27020,27030	Corpus Uteri and Uterus NOS
Ovary	27040	Ovary
Other female genitals	27050,27060,27070	Vagina, vulva, and other female genital organs
Prostate	28010	Prostate
Testis	28020	Testis
Other male genitals	28030,28040	Penis and other male genital organs
Bladder	29010	Urinary bladder
Kidney	29020	Kidney and Renal Pelvis
Other Urinary system	29030,29040	Ureter and other urinary organs

Eye	30000	Eye and Orbit
Brain	31010	Brain
Cranial Nerves	31040	Cranial nerves other nervous system
Thyroid	32010	Thyroid
Other endocrine	32020	Other endocrine including thymus
Hodgkin Lymphoma	33011, 33012	Hodgkin nodal and extra nodal
Non-Hodgkin Lymphoma	33041, 33042	NHL nodal and extra nodal
Myeloma	34000	Multiple Myeloma
Leukemia	35011,35012,35013, 35021,35031,35022, 35023,35041,35043	Acute lymphocytic leukemia, chronic lymphocytic leukemia, other lymphocytic leukemia, myeloid and monocytic leukemia, acute myeloid leukemia, acute monocytic leukemia, chronic myeloid leukemia, other myeloid/monocytic leukemia, other acute leukemia, and aleukemic, subleukemic and NOS
Mesothelioma	36010	Mesothelioma
Kaposi Sarcoma	36020	Kaposi Sarcoma
Miscellaneous	37000	Miscellaneous

[a] SEERWHO: Surveillance, Epidemiology, and End Results Program World Health Organization.

Appendix L: Odds Ratios (ORs) and 95% confidence intervals (CIs) in first generation ME immigrants compared to NHW for non-localized (advanced) breast cancer stage compared to localized stage, stratified by duration of residence for first generation ME immigrants: California Cancer Registry, 1988-2013.

	Duration of residence			
	< 20 years		≥ 20 years	
	OR	95% CI	OR	95% CI
Model 0	**1.40**	**1.27, 1.55**	**1.13**	**1.01, 1.25**
Model 1: SES	**1.41**	**1.28, 1.55**	**1.15**	**1.03, 1.28**
Model 2: model 1 + health insurance	**1.39**	**1.26, 1.53**	**1.14**	**1.03, 1.27**
Model 3: model 2 + marital status	**1.40**	**1.27, 1.54**	**1.15**	**1.03, 1.28**

Abbreviations: OR: Odds Ratio; CI: Confidence Interval; ME: Middle Eastern; NHW: Non-Hispanic Whites; SES: Socio-Economic Status
Age at diagnosis and year at diagnosis were controlled as strata
Significant results are bolded
Model 0: unadjusted
Model 1: adjusted by SES
Model 2: adjusted by SES and health insurance
Model 3: adjusted by SES, health insurance, and marital status

Appendix M: Hazard Ratios (HRs) and 95% confidence intervals (CIs) for all-cause and breast cancer-specific mortality in first generation ME immigrants compared to NHW stratified by duration of residence for first generation ME immigrants: California Cancer Registry, 1988-2013.

	Duration of residence			
	< 20 years		**≥ 20 years**	
	HR	**95% CI**	**HR**	**95% CI**
All-cause mortality				
Model 0	**0.90**	**0.83, 0.98**	0.92	0.83, 1.03
Model 1: stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, and cancer histology	**0.84**	**0.78, 0.92**	**0.88**	**0.79, 0.98**
Model 2: model 1 + SES	**0.85**	**0.78, 0.93**	0.91	0.81, 1.00
Model 3: Model 2 + health insurance	**0.84**	**0.77, 0.91**	0.90	0.80, 1.00
Model 4: Model 3 + marital status	**0.84**	**0.77, 0.91**	0.90	0.81, 1.00
Breast cancer specific mortality				
Model 0	1.08	0.97, 1.21	1.08	0.94, 1.25
Model 1: stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, and cancer histology	0.98	0.87, 1.09	1.00	0.86, 1.15
Model 2: model 1 + SES	0.98	0.88, 1.10	1.01	0.88, 1.17
Model 3: Model 2 + health insurance	0.95	0.85, 1.06	1.00	0.87, 1.16
Model 4: Model 3 + marital status	0.96	0.85, 1.07	1.01	0.87, 1.16

Abbreviations: HR: Hazard Ratio; CI: Confidence Interval; ME: Middle Eastern; NHW: Non-Hispanic Whites; ER: Estrogen Receptor; PR: Progesterone Receptor; SES: Socio-Economic Status

Age at diagnosis and year at diagnosis were controlled as strata

Significant results are bolded

Model 0: unadjusted

Model 1: adjusted by stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, and cancer histology

Model 2: adjusted by stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, cancer histology, and SES

Model 3: adjusted by stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, cancer histology, SES, and health insurance

Model 4: adjusted by stage at diagnosis, tumor grade, surgery, chemotherapy treatment, ER, PR, cancer histology, SES, health insurance, and marital status

Appendix N: Descriptive characteristics of patients with primary invasive colorectal cancer stratified in first generation ME immigrants stratified by duration of residence: California Cancer Registry, 1988-2013.

Characteristics	First generation ME immigrants		
		Duration of residence	
	Total	< 20 years	≥ 20 years
	N=1,980*	N=917	N=1,028
Gender. N (%)			
Male	1,138 (57.5%)	500 (54.5%)	622 (60.5%)
Female	842 (42.5%)	417 (45.5%)	406 (39.5%)
Marital status. N (%)			
Single	165 (8.3%)	70 (7.6%)	92 (9.0%)
Married	1,329 (67.1%)	616 (67.2%)	691 (67.2%)
Separated/Divorced	132 (6.7%)	43 (4.7%)	88 (8.6%)
Widowed	323 (16.3%)	173 (18.9%)	141 (13.7%)
Unknown	31 (1.6%)	15 (1.6%)	16 (1.6%)
Quintile of SES. N (%)			
Lowest SES	150 (7.6%)	74 (8.1%)	73 (7.1%)
Lower-Middle SES	315 (15.9%)	159 (17.3%)	145 (14.1%)
Middle SES	383 (19.3%)	191 (20.8%)	187 (18.2%)
Higher-Middle SES	452 (22.8%)	208 (22.7%)	236 (23.0%)
Highest SES	680 (34.3%)	285 (31.1%)	387 (37.7%)
Health insurance. N (%)			
Presence	1,614 (81.5%)	686 (74.8%)	908 (88.3%)
Absence	30 (1.5%)	14 (1.5%)	15 (1.5%)
Unknown	336 (17.0%)	217 (23.7%)	105 (10.2%)
Age at diagnosis, years			
Mean (SD)	65.4 (13.4)	64.9 (14.4)	66.0 (12.4)
Median	67	68	66
< 50	251 (12.7%)	144 (15.7%)	100 (9.7%)
≥ 50	1,729 (87.3%)	773 (84.3%)	928 (90.3%)
Year at diagnosis. N (%)			
1988-1992	200 (10.1%)	133 (14.5%)	59 (5.7%)
1993-1997	293 (14.8%)	202 (22.0%)	84 (8.2%)
1998-2002	460 (23.2%)	254 (27.7%)	197 (19.2%)
2003-2007	488 (24.7%)	190 (20.7%)	292 (28.4%)
2008-2013	539 (27.2%)	138 (15.1%)	396 (38.5%)
Stage at diagnosis. N (%)			
Localized	729 (36.8%)	340 (37.1%)	379 (36.9%)

Non-Localized	1,251 (63.2%)	577 (62.9%)	649 (63.1%)
Tumor location. N (%)			
Proximal	622 (31.4%)	257 (28.0%)	358 (34.8%)
Distal	1,311 (66.2%)	642 (70.0%)	642 (62.5%)
Large intestine, NOS	47 (2.4%)	18 (2.0%)	28 (2.7%)
Tumor grade. N (%)			
Well differentiated	133 (6.7%)	61 (6.7%)	69 (6.7%)
Moderately well differentiated	1,284 (64.9%)	604 (65.9%)	663 (64.5%)
Poorly differentiated	355 (17.9%)	167 (18.2%)	179 (17.4%)
Undifferentiated/ anaplastic	27 (1.4%)	10 (1.1%)	16 (1.6%)
Unknown if differentiated	181 (9.1%)	75 (8.2%)	101 (9.8%)
Treatment. N (%)**			
None of the three treatments	66 (3.5%)	34 (3.9%)	30 (3.0%)
Radiation only	3 (0.2%)	2 (0.2%)	1 (0.1%)
Chemotherapy only	45 (2.4%)	14 (1.6%)	31 (3.1%)
Radiation + chemotherapy	24 (1.3%)	11 (1.3%)	12 (1.2%)
Surgery	990 (52.0%)	460 (52.3%)	512 (51.8%)
Surgery + radiation therapy	24 (1.3%)	16 (1.8%)	8 (0.8%)
Surgery + chemotherapy	488 (25.6%)	218 (24.8%)	264 (26.7%)
Three treatments together	263 (13.8%)	124 (14.1%)	131 (13.3%)
Missing	77	38	39

Abbreviations: ME: Middle Eastern; NHW: Non-Hispanic Whites; N (%): Sample size (percentage); SES: Socio-Economic Status; SD: Standard Deviation.

Percentages may not be equal to 100 because of rounding

* 35 cases in first generation ME immigrants had missing duration of residence

**Treatment includes surgery, chemotherapy, and radiation therapy

Appendix O: Association between duration of residence and risk of advanced colorectal cancer stage at diagnosis in first generation ME immigrants: California Cancer Registry, 1988-2013.

	< 20 years compared to ≥ 20 years N=1,980	
	OR	**95% CI**
Model 0	0.85	0.65, 1.13
Model 1: SES + health insurance	0.86	0.65, 1.14
Model 2: Model 1 + marital status + gender	0.89	0.67, 1.19
Model 3: Model 2 + tumor location	0.91	0.68, 1.22

Abbreviations: ME: Middle Eastern; OR: Odds Ratio; CI: Confidence Interval; SES: Socio-Economic Status.
Localized stage serves as the baseline stage
First generation ME immigrants with longer duration of residence (≥ 20) serve as the referent group
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by SES and health insurance
Model 2: adjusted by SES, health insurance, marital status, and gender
Model 3: adjusted by SES, health insurance, marital status, gender, and tumor location

Appendix P: Association between duration of residence and all-cause mortality in first generation ME immigrants with invasive primary colorectal cancers stratified by tumor location: California Cancer Registry, 1988-2013.

	< 20 years compared to ≥ 20 years N=1,980	
	HR	**95% CI**
Proximal colon		
Model 0	**0.54**	**0.30, 0.97**
Model 1: stage at diagnosis + tumor grade + cancer treatment	0.58	0.27, 1.24
Model 2: Model 1 + SES + health insurance + marital status + gender	1.04	0.40, 2.69
Distal colorectal		
Model 0	0.77	0.57, 1.05
Model 1: stage at diagnosis + tumor grade + cancer treatment	0.89	0.62, 1.27
Model 2: Model 1 + SES + health insurance + marital status + gender	0.85	0.59, 1.23

Abbreviations: ME: Middle Eastern; HR: Hazard Ratio, CI: Confidence Interval; SES: Socio-Economic Status.
First generation ME immigrants with longer duration of residence (≥ 20) serve as the referent group
Significant results are bolded
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by stage at diagnosis, tumor grade, cancer treatment, and tumor location
Model 2: adjusted by stage at diagnosis, tumor grade, cancer treatment, tumor location, SES, health insurance, and marital status

Appendix Q: Association between duration of residence and colorectal cancer-specific mortality in first generation ME immigrants with invasive primary colorectal cancers stratified by tumor location: California Cancer Registry, 1988-2013.

	< 20 years compared to ≥ 20 years N=1,980	
	HR	**95% CI**
Proximal colon		
Model 0	0.57	0.22, 1.52
Model 1: stage at diagnosis + tumor grade + cancer treatment	0.60	0.10, 3.60
Model 2: Model 1 + SES + health insurance + marital status + gender	1.19	0.04, 35.81
Distal colorectal		
Model 0	**0.65**	**0.43, 0.98**
Model 1: stage at diagnosis + tumor grade + cancer treatment	0.66	0.37, 1.17
Model 2: Model 1 + SES + health insurance + marital status + gender	0.69	0.37, 1.27

Abbreviations: ME: Middle Eastern; HR: Hazard Ratio, CI: Confidence Interval; SES: Socio-Economic Status.
First generation ME immigrants with longer duration of residence (≥ 20) serve as the referent group
Significant results are bolded
Age at diagnosis and year at diagnosis were controlled as strata
Model 0: unadjusted
Model 1: adjusted by stage at diagnosis, tumor grade, cancer treatment, and tumor location
Model 2: adjusted by stage at diagnosis, tumor grade, cancer treatment, tumor location, SES, health insurance, and marital status