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A retrospective analysis of incidence trends, socio-demographic, and clinical characteristics in adolescents and young adults with pancreatic cancer in the United States using the SEER Database, 2004-2015

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2011

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An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

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Abstract

A retrospective analysis of incidence trends, socio-demographic, and clinical characteristics in adolescents and young adults with pancreatic cancer in the United States using the SEER Database, 2004-2015

By Meredith A. Renfroe

Background: Pancreatic cancer is one of the deadliest malignant neoplasms worldwide. Age-adjusted incidence has increased from 11.85 per 100,000 in 2000 to 14.7 per 100,000 in 2014. Similarly, the cancer incidence of adolescents and young adults (AYA) for all sites is also increasing. Despite the vulnerable nature of young cancer patients, research on AYAs with pancreatic cancer is limited. The purpose of this descriptive study was to determine trends in incidence as well as compare demographics, stage at presentation, treatment patterns, and survival with older individuals between 2004 and 2015.

Methods: Publicly available data was obtained from the Surveillance, Epidemiology, and End Results (SEER) Database. SEER*Stat was used to calculate incidence rates and trends, percent change, annual percentage change, and survival statistics of AYA with pancreatic cancer. Distributions of age, sex, marital status, race, and median household income were also generated for all cases. Chi square analyses were used to conduct descriptive statistics between age groups (15-39 vs 40+).

Results: The incidence rate of pancreatic cancer in AYA has not increased significantly since 2004 (0.358 per 100,000 in 2004, 0.426 per 100,000 in 2015). Significant differences in race, marital status, stage at diagnosis, and treatment were present between age groups ($p<0.0001$). AYA had higher cause-specific survival rates than older individuals. Notable gains in cause-specific survival rates were seen in this population over time, specifically those with advanced disease.

Conclusions: Prospective research on this population is needed to determine possible differences in tumor biology as well as those at increased risk for decreased health-related quality of life.

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Chapter I: Introduction

Problem Statement

Pancreatic cancer is one of the deadliest malignant neoplasms worldwide (Ilic, 2016). Incidence rates continue to increase in the United States: the age-adjusted incidence rates increased from 11.85 per 100,000 in 2000 to 14.7 per 100,000 in 2014 (Wu, 2018). Similarly, cancer incidence among adolescents for all sites is also increasing. Between 2008 and 2012, the overall incidence rate was 22.9 per 100,000 for male teens and 21.3 per 100,000 for female teens. This represents an increase in incidence for all sites combined of more than 25% since 1975 (Burkhamer, 2017). The cancers with the highest incidence in young people are non-Hodgkin's lymphoma, thyroid cancer, acute myeloid leukemia, and testicular cancer. While the increasing incidence of cancer in both adolescents and pancreatic cancer is well known, the incidence trends, stage at presentation, treatment patterns, and survival of adolescents and young adults (AYA) with pancreatic cancer is not well described.

Pancreatic cancer among AYA accounts for less than 1% of all new pancreatic cancer cases (Cancer Stat Facts: Pancreatic Cancer, 2018). As a result, research on this population is limited. While some studies show an increase in the incidence of pancreatic cancer in young patients, few papers have examined incidence trends specifically in adolescents and young adults (Zhang, 2007; National Cancer Intelligence Network, 2011). Given the varying definitions of this patient population, this project uses the National Cancer Institute's definition of adolescents and young adults (AYA), which is individuals between 15 and 39 years old (Adolescent, 2006). Research on individuals under 40 years old with pancreatic cancer is scarce, with limited sample sizes in most analyses. Because cancer in AYA has unique genetic features and biologic characteristics, presentation and outcomes of AYA with some types of cancer differ considerably

from pediatric and adult cancers (Bleyer, 2008). As such, there is a need to better understand the burden of disease, treatment patterns, and outcomes as well as the demographic characteristics of AYA patients with pancreatic cancer in the United States.

Theoretical Framework

A purely descriptive approach is used to describe the burden of disease (incidence) over time as well as the demographic and clinical characteristics of the AYA pancreatic cancer population. Basic statistical analyses were conducted to first examine the annual percent change in the incidence of disease and then to compare demographic characteristics, stage at disease presentation, treatment patterns, and survival between the AYA population and older adults (individuals 40 years old and older) with pancreatic cancer. These results may contribute to a better understanding of pancreatic cancer in this important population and inform the direction of future analytic studies.

Purpose Statement

The purpose of this project is to determine trends in incidence and to compare the socio-demographic characteristics, stage at presentation, treatment patterns, and cause-specific survival of AYA pancreatic cancer cases with older individuals in the United States. The hypotheses are listed as follows.

Hypotheses

H_0: There is no difference in the incidence trends over time in AYA with pancreatic cancer.

H_a: There is a difference in the incidence trends over time in AYA with pancreatic cancer.

H_0: There is no difference in the sociodemographic and clinical characteristics of AYA compared to older adults with pancreatic cancer.

H_a: There is a difference in the sociodemographic and clinical characteristics of AYA compared to older adults with pancreatic cancer.

Significance Statement

Cancer in AYA is unique for several reasons. First, AYA are a vulnerable population and have significant challenges that are different than older patients. A cancer diagnosis within this age range is particularly devastating due to life stage and social circumstances. Young people experience disruptions to their education, career, social groups and support system. They often have young children and limited economic resources (Zebrack, 2014). In research on breast cancer survivors, older patients experience more positive interpersonal relationships, and younger patients often report the worst outcomes in quality of life compared to older patients (Stava, Lopez, & Vassilopoulou-Sellin 2006).

In addition to AYA being a particularly vulnerable population, cancer in AYA has a different biology. In 2006, the Adolescent and Young Adult Oncology Progress Review Group of the National Cancer Institute issued recommendations that included investigating the potential biological basis of differences related to age in AYA cancer (Bleyer, 2008). A growing body of evidence has emerged that supports taking a unique approach to treating cancer in AYA. AYA with acute lymphoblastic leukemia experience superior outcomes when treated with pediatric treatment protocols (Muffly, 2016). Similarly, young women with breast cancer often have higher grade disease, larger tumor size, greater lymph node positivity, and higher ERBB2 expression. Biological differences are also seen in AYA in colorectal cancer. Almost 50% of

AYA with colorectal cancer have mucinous adenocarcinoma, which is often associated with a worse prognosis. This is compared with approximately 4% in older adults (Bleyer, 2008). If there are differences in the demographics and cancer-related outcomes between AYA and older patients, it may also be true that AYA pancreatic cancer patients will benefit from a tailored treatment approach. Results of this project may help to support an argument for further prospective research.

Finally, cancer in AYA is an important population to study given the societal impact of "years of potential life lost" (YPLL). YPLL is a measurement of premature mortality (early death) and represents the number of years lived by individuals who die before reaching a pre-determined age, often 75 in the U.S. (General Health Status, 2018). The Office of Disease Prevention and Health Promotion (ODPHP) monitors YPLL along with many other measures to assess the health status of the U.S. population, and deaths among young individuals contribute more to YPLL than death among older individuals.

Definition of Terms

1. Adolescents and young adults (AYA) – Adolescents and young adults is defined by the National Cancer Institute as individuals between the ages of 15 and 39 years old (AYA, n.d.).
2. Pancreatic Cancer – Pancreatic cancer is cancer that originates in the pancreas, which is an organ positioned behind the stomach. Two types of cells are present in the pancreas: exocrine cells, which make enzymes to help with food digestion, and endocrine cells, which make hormones like insulin. SEER Registries collect only new diagnoses of this disease where the primary cancer originated in the pancreas (SEER, 2018). The following diagnoses were included in this analysis: C25.0 Malignant Neoplasm of head of pancreas, C25.1 Malignant Neoplasm of

body of pancreas, C25.2 Malignant Neoplasm of tail of pancreas, C25.3 Malignant Neoplasm of pancreatic duct, C25.7 Malignant Neoplasm of other specified part of pancreas, C25.8 Malignant Neoplasm of overlapping lesions of pancreas, and C25.9 Malignant Neoplasm of Pancreas, NOS (Topography, 2013).

3. Staging System – Staging is the process of determining the amount of cancer present and where it is located. The system used in this analysis is the Sixth Edition of the AJCC Cancer Staging Manual and an explanation of each stage group with regards to pancreatic cancer is listed below (AJCC Cancer Staging Manual, 2002).

Stage		**Primary Tumor (T)**	**Regional Lymph Nodes (N)**	**Distant Metastasis (M)**
Stage I Localized, resectable disease	Stage IA	T1	N0	M0
	Stage IB	T2	N0	M0
Stage II Localized, resectable disease	Stage IIA	T3	N0	M0
	Stage IIB	T1-T3	N1	M0
Stage III Locally Advanced Disease	-	T4	Any N	M0
Stage IV Metastatic	-	Any T	Any N	M1

Primary Tumor (T)

T1: Tumor limited to the pancreas, 2 cm or less in greatest dimension

T2: Tumor limited to the pancreas, more than 2 cm in greatest dimension

T3: Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery

T4: Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

Regional Lymph Nodes (N)

N0: No regional lymph node metastasis

N1: Regional lymph node metastasis

Distant Metastasis (M)

M0: No distant Metastasis

M1: Distant Metastasis

4. Treatment Patterns – SEER registries collect the first course of treatment (SEER Program Coding and Staging Manual, 2006). Pancreatic cancer is typically treated with chemotherapy, radiation, or surgery, and the type of treatment chosen depends on the staging of a patient's disease. In this analysis, treatment includes only surgery given the amount of chemotherapy and radiation data that was unknown in the registries. The following surgeries are included: Local excision of tumor, NOS; Partial pancreatectomy, NOS; Local or partial pancreatectomy and duodenectomy (includes with and with partial gastrectomy); Total pancreatectomy; Total pancreatectomy and subtotal gastrectomy or duodenectomy; Extended pancreatoduodenectomy; Pancreatectomy, NOS; and Surgery, NOS.

5. Cause-specific survival is a net survival measure. It is the probability of surviving pancreatic cancer in the absence of other causes of death (NCI 2018).

Chapter 2: Review of the Literature

Pancreatic cancer among patients less than 39 years old accounts for less than 1% of all new pancreatic cancer cases. As a result, research on this population is limited, and few papers examine incidence trends in this population. Thirteen papers evaluate differences in pancreatic

cancer cases between age groups. Of those, eight papers reported data from the United States, two from Japan, with the remaining on data from various countries such as Italy, Canada, France, and England. Of the four papers on younger patients with pancreatic cancer in the United States, only one analysis focuses on individuals 39 years old and younger.

Incidence

Zhang et al. published a paper evaluating temporal trends in pancreatic cancer incidence using SEER data from 1973 to 2002 (Zhang, 2007). Age was categorized into individuals less than 60 (N=13,983) and 60 or greater (N=56, 535). The analysis included only African Americans and Caucasians. Overall incidence decreased in most sex-, race-, and age-specific groups, however an increase in incidence was noted in younger individuals in specific areas. For example, the incidence rate in Connecticut in individuals less than 60 years old increased from 1977 to 2001. Similarly, the incidence rate in Detroit increased significantly (1.86% per year) from 1988 to 2002. The estimated annual percent change (EAPC) was 0.86 in individuals less than 60 years old in the U.S. from 1994 to 2002. A strength in this analysis was the large sample size of young patients, which included 13, 983 patients less than 60 years old. A limitation is the exclusion of races other than White and Black.

The National Cancer Intelligence Network published a data briefing on incidence of pancreatic cancer in young people in England. 53,265 patients were diagnosed with pancreatic cancer between 1998 and 2006, and 1.5% were diagnosed at 39 years old or younger (National Cancer Intelligence Network, 2011). There was no significant change in incidence in males younger than 50 over this time period (National Cancer Intelligence Network, 2011). There was a slight significant increase in incidence in females 20 to 39 years old (National Cancer Intelligence Network, 2011).

Wu et. al. evaluated trends in incidence of pancreatic cancer using the SEER database from 2000-2014 (2018). The average annual percent change (AAPC) for all cases was 1.9, which was statistically significant. Looking at individual age groups, the AAPC was 5.3 in individuals ages 20-29 and 2.1 for ages 30-39 years old. Both were statistically significant ($p<0.05$).

Socio-demographics in AYA compared to Older Patients

There is some discord in the literature regarding demographic differences between age groups: Wheeler et al. and Nakai et al. found no difference in gender or race of young patients compared to older patients with pancreatic cancer. Young patients were defined as those 50 or younger and less than 75 years old respectively (Wheeler, 2014; Nakai, 2011). In contrast, there were gender differences in young patients (ages 10-39) in Japan compared to older patients. There were significantly more males among AYA, although the sample size of AYA was limited to 526 (Eguchi, 2016).

Clinical Characteristics in AYA compared to Older Patients

Staging

Based on most of the literature, younger patients tend to be diagnosed with more advanced stage pancreatic cancer than older patients (Baxter, 2007; Piciucchi, 2015; Eguchi, 2016). However, Wheeler found no difference in tumor location, stage at diagnosis, surgery, or survival months of younger (50 or less) compared to older patients (2014). The sample size of younger patients was limited.

Treatment

Multiple studies have documented that pancreatic cancer patients who are younger in age have higher rates of cancer-directed surgery and radiation (Wheeler, 2014; Baxter, 2007; Gagliardi, 2016; Amin, 2013). Nancy Baxter from the University of Toronto and colleagues published a retrospective analysis in 2007 of SEER data from 1988 through 2002. Baxter found differences in treatment between age groups. Individuals 49 years old or younger had significantly higher rates of cancer-directed surgery and radiation than patients 80 and older.

In 2013, Amin et al. published a retrospective review of treatment disparities by age using the SEER registry from 1983 to 2007. Age was stratified as follows: younger than 50, 50-70, and older than 70. Kaplan Meier curves and Cox's proportional hazards models were used to evaluate survival differences and logistic regression to compare treatment disparities. Younger patients tended to receive more treatment. The prevalence of surgical resection was 21% among individuals less than 50 years old, compared to 13% among those older than 70. Similarly, the prevalence of radiation among younger patients was 28%, compared to 17% among older patients.

In contrast, a retrospective study of Ellis Fischel Cancer Center's database in Missouri found no difference in rates of surgery between individuals 50 years old and younger compared those older than 50 (Wheeler, 2014). This is a unique population given that Missouri cancer data is not reflected in SEER data. The limited sample size of patients under the age of 50 is the major weakness of this study.

Survival

Baxter et al. evaluated overall survival between age groups and found that individuals diagnosed with pancreatic cancer at age 49 years old or younger were 25% more likely to survive

for two years than patients diagnosed at 80 and older (Baxter, 2007). Notably, this analysis was limited to patients with nonmetastatic disease. Given that more than half of the patients captured in the SEER database since 1988 were metastatic at diagnosis, this limits the comprehensiveness of this analysis for the outcomes of younger patients. In this study, young age was defined as less than 49 years old, which differs from the definition currently utilized by the NCI and in this research project.

He et al. also found differences in survival between age groups. Median overall survival (19 months vs. 16 months) of resectable patients as well as 5- and 10- year observed survival was longer for younger patients (He, 2013). Similarly, risk of mortality increased, and median survival decreased as age at diagnosis increased (Fesinmeyer, 2005; Amin, 2013; Gagliardi, 2016). In contrast, the rate of overall survival for younger patients with pancreatic cancer in Japan was worse than the rate for older patients (Eguchi, 2016). These results should be interpreted with caution given the small sample size of patients under the age of 40.

Amin et al. reported that younger patients had slightly better overall survival with 10.4 months for younger than 50 versus 6.4 months for those older than 70 (Amin, 2013). A strength of this paper is the large sample size of young patients: 2, 845 patients younger than 50 years old were included.

In 2017, Alese et al. reported an abstract evaluating treatment, outcomes, and impact of race in young adults with pancreatic cancer using the National Cancer Database (NCDB) from 2004 to 2013 (Alese, 2017). Significant survival differences were observed in individuals between ages 18 and 34 compared to individuals between 35 and 50 years, with better survival rates in younger patients. The 5-year overall survival rates showed significant improvement, with major differences among American Indians and Asian/Pacific Islanders, African Americans, and

Hispanics. Sample sizes per age group were not available, however Alese's analysis included 9,657 patients in total.

Summary of Literature

Few papers examine incidence trends in AYA patients with pancreatic cancer. Young patients are typically diagnosed with metastatic disease and treated more aggressively with chemotherapy, radiation, and surgery than older patients. Overall survival rates are low for pancreatic cancer cases, and survival rates in this population are poorly understood.

Chapter 3: Methodology

Introduction

Eligible cases for this study included all individuals contained in the National Cancer Institute's SEER 18 database who were diagnosed with pancreatic cancer between 2004 and 2015 (SEER Program, 2018) and were greater than 14 years old. SEER is a system of population-based cancer registries covering more than 34% of the U.S. population. The design of the study was a retrospective review of the pancreatic cancer case data including demographics, incidence rates, treatment patterns, and survival statistics.

SEER*Stat software was used to select patients with pancreatic tumors based on diagnosis codes C25.0-C25.9, excluding C25.4 (SEER*Stat Software, n.d.). Cases with diagnosis code of C25.4, which is endocrine pancreas cancer, were excluded because this disease is considered biologically different from exocrine pancreatic cancer; accordingly, endocrine pancreas cancer is treated with different regimens and has very different outcomes. A case listing session was created including the following variables: age, race, sex, primary site, surgery, marital status, median household income, and stage at diagnosis. Data was exported from SEER*Stat and imported into SAS Studio where variables were recoded. Patients were stratified

into groups based on age at diagnosis (15-39, ≥40). Marital status initially included the following categories: single (never married), married (including common law), separated, unmarried or domestic partner, divorced, widowed, and unknown. The "separated" and "unmarried or domestic partner" categories were combined into one group to maintain confidentiality of individuals due to small cell sizes. Median household income was assigned to groups mirroring the U.S. Census Bureau definitions (U.S. Census Bureau, 2016). Two categories of median household income ("$19,000-24,999" and "$25,000-34,999") were combined as well to maintain confidentiality of individuals. Staging was classified into the major stage groups including Stage I, II, III, IV, and Unknown. Individual surgical procedures are captured in SEER but for the purpose of these analyses, surgery was recoded as either None, Surgery performed, or Unknown. Charts and figures were created in Microsoft Excel. No data collection instruments were used in this project as this was a secondary data analysis.

SEER*Stat software was used to calculate incidence rates and trends, percent change, annual percent change, and survival statistics. Percent change was calculated by taking the difference between the initial and ending rates and subsequently dividing the difference by the initial rate then multiplying it by 100 to convert it to a percentage (SEER Stat Web Help, n.d.). To calculate the annual percent change, a least squares regression line was fitted to the natural logarithm of the rates. SAS Studio was used to recode variables and conduct descriptive statistics, including chi square analyses. This study did not conduct human research. Institutional Review Board (IRB) submission was required but deemed exempt by the Emory University IRB.

Chapter 4: Results

Key Findings

Incidence

Table 1 shows incidence trends in this population since 2004. The incidence rate of AYA with pancreatic cancer was 0.426 per 100,000 in 2015, compared to 0.358 per 100,000 in 2004. The annual percent change (APC) was 1.6% per year, and the percent change (PC) in the rate over the entire 12-year period was 18.8%.

Socio-demographics in AYA compared to Older Patients

As shown in Table 2, a total of 127,580 eligible pancreatic cancer cases were reported to SEER from 2004 to 2015. 1,274 (1%) of those cases were AYA, and 126,306 cases were individuals diagnosed at 40 years old or older. Approximately half all cases in both age groups were male and the majority were white. The age groups were significantly different by race with the AYA population comprising a larger proportion of minorities (27.3% vs 19.5%). There were also differences in marital status between age groups ($p<0.0001$), as would be expected, with 41.6% of AYA cases classified as single (never married) compared to only 12.1% of older patients. Significant differences were not observed in median household income or gender between the age groups. Over half of the cases across both age groups had a median household income between $50,000 and $74,999.

Clinical Characteristics and Outcomes in AYA compared to Older Patients

Differences in clinical characteristics between age groups are shown in Tables 2. While almost half of both age groups were diagnosed with Stage IV disease at diagnosis, (48.3% AYA, 47.2% Older Age), significant differences were observed in the stage distribution between the age groups with a higher percentage of AYA having Stage I disease at diagnosis (18.2% vs

7.2%) and a higher percentage of older patients having unstaged disease (16.0% vs. 7.2%). In keeping with the literature, most pancreatic cases were not treated with surgery (59.4% AYA, 79.5% Older Age) but a significantly higher percentage of AYA patients did receive some type of surgical procedure for their disease compared to older patients (38.8% vs 16.3%; $p<0.0001$). Cause-specific survival rates of AYA cases in 2010 have improved substantially since 2004. The 5 year survival rate in this population was 48.8% in 2010, compared to 25.5% in 2004. Also, rates were considerably higher than those reported for older patients at 1, 3, and 5 years. 1 year survival was 72.1% for AYA in 2010 compared to 28.4% for older individuals. These stark differences were seen at 3 and 5 years as well.

Other findings

Additional findings of interest include differences in outcomes among AYA cases. As seen in Table 4, females have higher cause-specific survival at 12, 36, and 60 months regardless of race, except in AI/AN where rates are equal at 36 and 60 months. The most notable difference was observed in Black females, whose 5-year survival rates was 48.9% (95% CI: 37.8-59.1) compared to 22.5% (95% CI: 13.1-33.4) in males.

Cause-specific survival rates appear to have increased across most stage groups. As seen in Table 5, the five-year survival rate for patients diagnosed with Stage I disease was 90.9% in 2010, compared to 83.9% in 2004. Given that a higher percentage of AYA are diagnosed with Stage I disease than older patients, these results are important. Rates are increasing for patients with Stage II and IV disease as well. Rates were not able to be determined for Stage III due to a limited sample size. The most notable gains are seen in Stage IV survival rates. Rates for 1 and 3-year survival were 57.8% (95% CI: 42.2-70.7) and 31.5% (95% CI: 18.4-45.5) in 2010, compared to 22.1% (95% CI: 11.9- 34.2) and 8% (95% CI: 2.6-17.6) in 2004. Cause-specific

survival rates in this table should be interpreted with caution. Given the small sample size there is a wide range in confidence intervals. There were differences in stage at diagnosis between sexes among AYA cases, as seen in Figure 1. The most notable difference was in cases diagnosed with Stage I disease where 73.3% of AYA cases were female ($p<0.0001$).

Finally, there were significant differences in treatment patterns between sexes among AYA cases ($p<0.0001$). 60.8% of patients that were treated with surgery were female (Figure 2).

Chapter 5: Conclusions, Implications and Recommendations

Summary of Study

Given the significant increase in the incidence of pancreatic cancer, the high mortality associated with the disease, and the increase in cancer of all sites in AYA patients, it was important to more fully describe the burden of disease in this vulnerable population. While descriptive in nature, this study has highlighted pancreatic cancer incidence trends, sociodemographic and disease characteristics, and survival outcomes in the AYA population and has generated some findings that likely warrant further investigation.

Discussion of Key Results

The results of the study indicate that although the incidence of pancreatic cancer in the AYA population is increasing, the trend is not significant. Differences in race, marital status, stage, and treatment patterns were significant, however, between this population and older individuals. A higher percentage of AYA cases were Black, AIAN, and API compared to older cases. There has been a growing body of literature citing biological factors as contributors to increased cancer incidence and mortality in some races. For example, African Americans have significantly higher incidence of and mortality due to prostate cancer compared to Caucasians.

Even after adjustment for differences in environmental factors, access to healthcare, and socioeconomic status, African Americans were still at higher risk of developing and dying from prostate cancer (Henderson, et. al., 2012). It is thought that these differences in incidence and survival may be a result of inherent biological factors. Differences in tumor biology between African Americans and European Americans has been documented in non-small cell lung cancer as well (Mitchell, 2017).

Superior survival outcomes in AYA compared to older individuals were not surprising given the differences in staging seen in this analysis and the differences in treatment between age groups found in the literature. There were major advances in chemotherapy treatment during the time period under study: combination therapy with Gemcitabine and Tarceva was approved in 2005, FOLFIRINOX in 2010, and combination therapy with Gemcitabine and Abraxane in 2013 (NCI, 2018). Younger patients also have historically higher participation in clinical trials with promising investigational treatments (Burkhamer, 2017).

Social differences also exist in this population. A significantly higher proportion of AYA were single at diagnosis compared to older individuals (41.8% vs 12.1%, $p<0.0001$). While not surprising given the lower ages included in the AYA definition, these differences are important because AYA have distinctive supportive care and psychosocial needs compared to older patients. Factors, such as untimely confrontation with mortality, fluctuations in physical appearance, potential loss of reproductive capability, increased dependence on others, and disruptions in education, social life, and employment, have significant negative impacts on the quality of life of this population (Kaal, 2017). Social support is a well-known predictor of health (Eskander, 2016). Rates of surgery and treatment with radiation or chemotherapy were

significantly higher in married patients (Eskander, 2016; Shapiro, 2016). Married patients also had higher overall survival (Eskander, 2016).

In addition to the findings directly related to the main hypotheses, there were interesting findings related to outcomes of this vulnerable population. Huge gains in cause-specific survival were seen in AYA over a short period of time. Further investigation is needed to determine the causality of these major survival gains. Gains may be attributed to early diagnosis and/or more aggressive treatment. Survival differences could also be attributable to differences in etiology/biology. The improvements in survival of this population, specifically in those diagnosed with advanced disease, is promising and warrants further study.

Most pancreatic cancer cases documented globally are male (Are, 2016). While the gender distribution among all AYA cases was evenly divided (50.5% female), 73% of AYA cases diagnosed with Stage I disease were female. Accordingly, a higher percentage of females undergo surgery than males (54% vs 36%), and females have higher cause-specific survival than males at 1, 3, and 5 years regardless of race (excluding AI/AN where 3 and 5 year survival is the same for both groups).

Limitations

Due to difficulties in capturing complete data on adjuvant therapies by population-based registries, chemotherapy and radiation data were not included in this analysis. Given the advanced stage and inoperability of most pancreatic cancer cases, chemotherapy and radiation are an important insight into possible differences between this population and older patients. This limited the conclusions and scope of this analysis.

In addition, conclusions based on this analysis should be made with caution given the descriptive statistical approach. A multivariate approach to these questions would enable further investigation into the differences seen between groups and would allow for more robust conclusions.

Implications

Adolescents and young adults are different than older individuals (those at least 40 years old) in terms of stage at presentation, treatment patterns, and cause-specific survival. Research focusing specifically on AYAs with pancreatic cancer is warranted to determine if the disease has different biology than the disease in older adults. If the biology of these cancers differs then optimal treatment may also. This is particularly true for newer molecularly targeted agents. (Bleyer, 2008)

Gender disparities among AYA in staging, treatment, and survival were the most notable results outside of the two main hypotheses. Similar results were found in a retrospective review of all cancers in SEER registries between 2003 and 2012 (Najari, 2013). Across all non-sex specific cancers during this time period, men are diagnosed with and die more often from cancers that should affect both genders equally. The mortality rate for men is more than 12% higher than women after controlling for higher male incidence. The disparity may be attributed to many factors, such as differences in biology, health care utilization, and modifiable risk factors. This gender disparity is poorly understood in pancreatic cancer specifically.

Recommendations and Conclusion

In keeping with the recommendations by the Adolescent and Young Adult Oncology Progress Review Group, we recommend more robust research efforts to better understand the tumor biology and microenvironment that contribute to differences in incidence, treatment

response and survival in AYAs. Advancements in understanding of tumor biology in AYA with ALL have led to improvements in outcomes, however very little is known about genetic variability by age in other cancers (Muffly, 2016; AYAO, 2016). These recommendations were published more than a decade ago, however little research focused in this population has been done. While pancreatic cancer in AYA is rare, the increasing incidence and high mortality warrant the need for further investigation to improve outcomes. Improvements in survival noted in this analysis are encouraging. To make further improvements, it is important to determine the etiology (aggressive treatment, tumor biology, etc.) behind differences noted in this analysis. In addition, multivariate analyses of this data could shed light on the survival differences, specifically differences within stages, between age groups.

In addition to additional research on the tumor biology in this population, additional research is needed to determine if subsets of this population may benefit from support interventions. Given the vulnerability and uniqueness of a cancer diagnosis between ages 15 and 39 years old, it is important to target individuals at higher risk of decreased health-related quality of life, such as those that are single (not married).

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Table 1. Trends in Incidence over Time in AYA with Pancreatic Cancer

		95% CI	
	Incidence Rate[1]	Lower CI	Upper CI
2004	0.358	0.291	0.435
2005	0.362	0.293	0.441
2006	0.364	0.296	0.442
2007	0.317	0.254	0.391
2008	0.354	0.287	0.431
2009	0.471	0.393	0.558
2010	0.372	0.303	0.452
2011	0.372	0.303	0.452
2012	0.422	0.347	0.507
2013	0.396	0.325	0.478
2014	0.4	0.329	0.481
2015	0.426	0.353	0.509

	Percent Change	Lower CI	Upper CI
2004-2015 PC	18.858		
2004-2015 APC	1.615	-0.134	3.395

[1]Rates are per 100,000 and age-adjusted to the 2000 US Std Population

Table 2. Socio-demographic and clinical characteristics of Pancreatic Cancer Cases by Age: SEER 2004-2015

Case Characteristics	All Cases (n=127,580)		Age Groups AYA (n=1,274)		Older Pts (n=126,306)		P Value
	N	%	N	%	N	%	
Gender							0.99
Male	64,060	50.2	640	50.2	63,420	50.2	
Female	63,520	49.8	634	49.8	62,886	49.8	
Race							<0.0001
White	102,441	80.3	921	72.3	101,520	80.4	
Black	15,203	11.9	196	15.4	15,007	11.9	
American Indian/ Alaska Native	727	0.6	15	1.2	712	0.6	
Asian or Pacific Islander	8,923	7.0	136	10.7	8,787	7.0	
Unknown	286	0.2	6	0.5	280	0.2	
Marital Status							<0.0001
Single	15,813	12.4	530	41.6	15,283	12.1	
Married	66,297	52.0	597	46.9	65,700	52.0	
Separated, Unmarried, or Domestic Partner	1,530	1.2	30	2.3	1,500	1.2	
Divorced	12,398	9.7	64	5.0	12,334	9.8	
Widowed	26,118	20.5	7	0.5	26,111	20.7	
Unknown	5,424	4.3	46	3.6	5,378	4.3	
Median Household Income							0.07
$0 to 34,999	4,556	3.6	46	3.6	4,510	3.6	
$35,000 to 49,999	27,488	21.5	270	21.2	27,218	21.5	
$50,000 to 74,999	68,325	53.5	723	56.7	67,602	53.5	
$75,000 to 99,999	25,523	20.0	227	17.8	25,296	20.0	
$100,000 to 149,999	1,677	1.3	8	0.6	1,669	1.3	
$150,000-700,000	11	0.0	0	0.0	11	0.0	

Table 2 (continued). Socio-demographic and clinical characteristics of Pancreatic Cancer Cases by Age: SEER 2004-2015

Case Characteristics	All Cases (n=127,580)		Age Groups AYA (n=1,274)		Older Pts (n=126,306)		P Value
	N	%	N	%	N	%	
Stage at Diagnosis							<0.0001
Stage I	9,267	7.3	232	18.2	9,035	7.2	
Stage II	28,143	22.1	259	20.3	27,884	22.1	
Stage III	9,563	7.5	76	6.0	9,487	7.5	
Stage IV	60,252	47.2	615	48.3	59,637	47.2	
Unknown	20,355	16.0	92	7.2	20,263	16.0	
Treatment							<0.0001
Surgery	101,187	79.3	494	38.8	20,634	16.3	
No Surgery	21,128	16.6	757	59.4	100,430	79.5	
Unknown	5,265	4.1	23	1.8	5,242	4.2	

Table 3. Cause-specific Survival of Pancreatic Cancer Cases by Age: SEER 2004-2015

	Age Groups					
	AYA			Older Pts		
	Rate	Lower CI	Upper CI	Rate	Lower CI	Upper CI
2004 - 1 year	42.7%	32.5%	52.5%	23.6%	22.6%	24.7%
2004 - 3 year	29.1%	20.1%	38.7%	7.7%	7.1%	8.4%
2004 - 5 year	25.5%	17.0%	34.8%	5.4%	4.8%	5.9%
2010 - 1 year	72.1%	61.8%	80.0%	28.4%	27.4%	29.3%
2010 - 3 year	54.4%	43.7%	63.9%	10.4%	9.8%	11.1%
2010 - 5 year	48.8%	38.2%	58.6%	7.0%	6.5%	7.6%

Table 4. Cause-specific survival by Sex and Race among AYA, 2004-2015

		Male			Female		
		Rate	Lower CI	Upper CI	Rate	Lower CI	Upper CI
White	12 month	54.3%	49.3%	59.0%	71.0%	66.1%	75.3%
	36 month	33.6%	28.7%	38.5%	52.9%	47.3%	58.2%
	60 month	29.5%	24.7%	34.4%	46.6%	40.7%	52.2%
Black	12 month	49.5%	37.8%	60.2%	64.3%	53.4%	73.3%
	36 month	28.5%	18.3%	39.4%	51.7%	40.6%	61.7%
	60 month	22.5%	13.1%	33.4%	48.9%	37.8%	59.1%
AI/AN	12 month	33.3%	4.6%	67.6%	50.0%	15.2%	77.5%
	36 month	33.3%	4.6%	67.6%	33.3%	5.6%	65.8%
	60 month	33.3%	4.6%	67.6%	33.3%	5.6%	65.8%
API	12 month	53.2%	39.8%	64.9%	70.0%	56.6%	80.0%
	36 month	39.6%	26.9%	52.1%	55.8%	41.6%	67.8%
	60 month	32.5%	20.2%	45.4%	55.8%	41.6%	67.8%

Table 5. Cause-Specific Survival among AYA by Stage at Diagnosis

	Stage I					
	2004	Lower CI	Upper CI	2010	Lower CI	Upper CI
12 month	100.0%	*	*	95.50%	71.9%	99.3%
36 month	92.3%	56.6%	98.9%	90.9%	68.3%	97.6%
60 month	83.9%	49.4%	95.7%	90.9%	68.3%	97.6%
	Stage II					
	2004	Lower CI	Upper CI	2010	Lower CI	Upper CI
12 month	67.0%	37.9%	84.7%	81.0%	56.9%	92.4%
36 month	46.9%	21.4%	68.9%	61.9%	38.1%	78.8%
60 month	46.9%	21.4%	68.9%	52.2%	29.4%	70.8%
	Stage III					
	2004	Lower CI	Upper CI	2010	Lower CI	Upper CI
12 month	25.2%	3.7%	56.1%	~	~	~
36 month	12.6%	0.7%	42.5%	~	~	~
60 month	12.6%	0.7%	42.5%	~	~	~
	Stage IV					
	2004	Lower CI	Upper CI	2010	Lower CI	Upper CI
12 month	22.1%	11.9%	34.2%	57.8%	42.2%	70.7%
36 month	8.0%	2.6%	17.6%	31.5%	18.4%	45.5%
60 month	6.0%	1.6%	14.9%	24.3%	12.7%	37.8%

* Statistic could not be calculated

~ Value could not be calculated

Figure 1. Stage at Diagnosis by Sex Among AYA with Pancreatic Cancer, 2004-2015

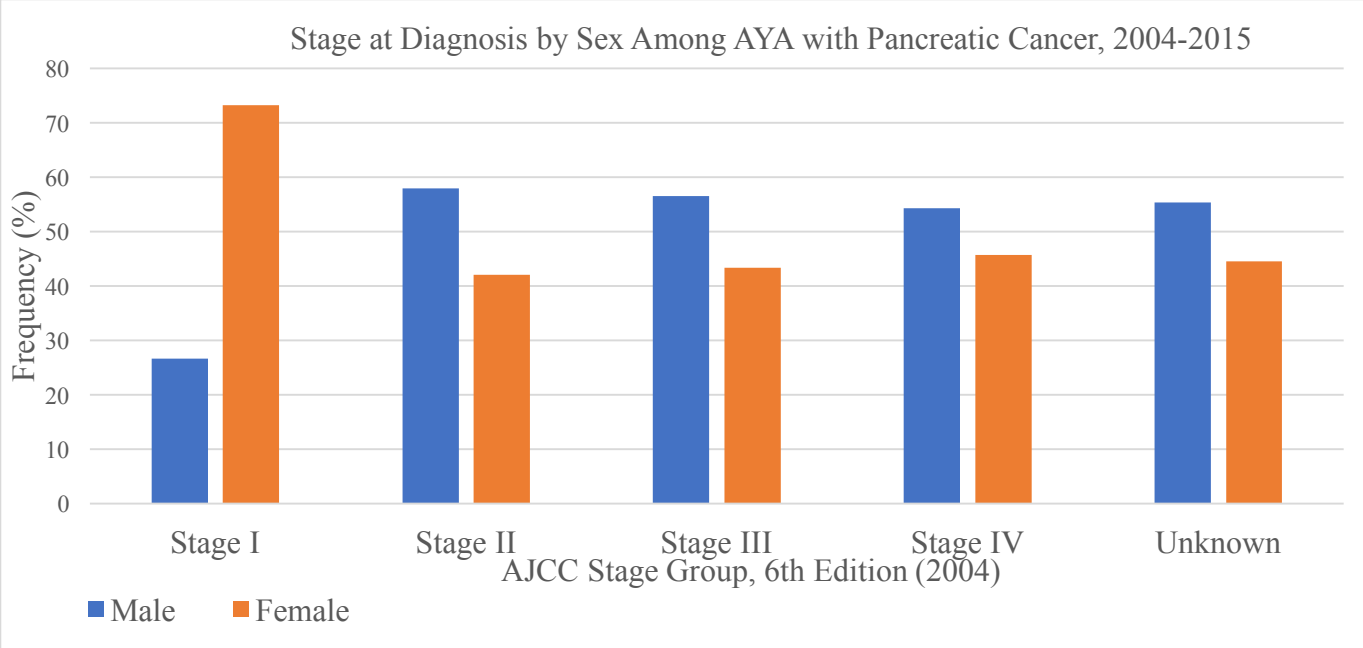

Figure 2. Treatment Patterns (Surgery to Primary Site) by Sex among AYA with Pancreatic Cancer, 2004-2015