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“IN-SITU” CARCINOMA OF THE GALLBLADDER: A SEER PERSPECTIVE

By

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Master of Public Health

EPIDEMIOLOGY

_____

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B.S., EMORY UNIVERSITY, 2008
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An abstract of

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of
Master of Public Health
in EPIDEMIOLOGY

2014

ABSTRACT

"IN-SITU" CARCINOMA OF THE GALLBLADDER: A SEER PERSPECTIVE

By KAJAL NILESH PATEL

Background: The etiology of gallbladder cancer remains unknown, treatment options are limited and prognosis dismal. Diagnosis of gallbladder carcinomas (GBCs) is often made incidentally and at later stages. While non-papillary (flat) carcinomas represent the most common histologic group (>75%) of this neoplasm, papillary (tumoral) variants have been recognized as a distinct morphologic variant. The distinct biologic behavior of the papillary GBC is thought to confer survival benefits.

Purpose: To conduct an analysis of GBC incidence, risk factors and survival with a primary focus histology and on the earliest (in-situ) stage.

Design: Retrospective analysis of primary GBC cases identified in the Surveillance Epidemiology and End Results (SEER) program from 1973-2010.

Methods: We examined cancer trends using Joinpoint regression. Kaplan-Meier and Cox proportional hazards regression methods were used to estimate clinical and demographic survival differences.

Results: Women, non-Hispanic whites and individuals 60 years of age or older represented >50% of cases. GBC in the distant stage was diagnosed roughly 9 times more than in-situ. Papillary tumors accounted for 5.6% of all GBC, but represented over 20% of in-situ cases.. Survival of all GBC cases was inversely related to age and stage, and non-papillary histology. Incidence of in–situ disease has not changed appreciably since 1973, while 5 and 10-year survival estimates for GBC at this stage were 87% and 79%, respectively.

Conclusion: We found that in situ GBC survival was lower than previously reported. The relatively low survival of in-situ disease suggests under-staging with missed invasive or more advanced carcinomas. In addition, deaths during the long-term follow-up period provide evidence of the occurrence of a field-effect/field defect phenomenon in the biliary tree. These findings indicate the need for reviewing the entire gallbladder specimen with non-invasive GBC findings to rule out more advanced disease. Relatively stable GBC in-situ rates indicate lack of earlier cancer detection mechanisms.

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ACKNOWLEDGEMENTS

I would like to express my gratitude to my thesis advisor, Dr. Michael Goodman, for his outstanding mentorship, patience, never-ending support and encouragement. I am very grateful for his invaluable expertise and advice throughout the completion of this thesis project.

My sincerest gratitude to Dr. Volkan, N. Adsay, Director of Anatomic Pathology, Emory University, for providing me with an incredible opportunity through the collaboration of this project. In addition to being an outstanding mentor, Dr. Adsay served as my faculty field advisor during the conduct of this study. His dedication and enthusiasm to the subject matter prompted inspiring discussions; and his wisdom, expertise and excellent guidance have been invaluable and instrumental throughout the thesis process.

I would especially like to acknowledge and express my deepest gratitude to Dr. Serdar Balci, who has served as my advisor, teacher, colleague and friend from the onset of the project. Dr. Balci was not only an excellent resource and collaborator, his support, excellent guidance and enthusiasm introduced me to the fascinating world of pathology. In addition to his invaluable contributions, his constant encouragement, thoughtful criticism, time and attention, guided me through the most difficult and trying times.

I would like to thank my family and friends for their support. I am so fortunate to have you all in my life.

Reflecting on the completion of this work, I am indebted to a very long list of generous and inspiring individuals, who have contributed to my development as a researcher.

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INTRODUCTION

Overview:

Malignant tumors of the biliary tract include cancers of the gallbladder (GB), ampulla of Vater, and intra- and extra-hepatic biliary tree. With respect to histology, most biliary tract neoplasms are carcinomas, with a very small proportion comprised of adenomas, and carcinoid and stromal tumors. [1 - 4]

Gallbladder carcinoma (GBC) originally described over 200 years ago, remains the most common form of biliary tract cancers (BTC). [5] It is the fifth or sixth most frequently diagnosed malignancy of the gastrointestinal (GI) tract. [2, 6, 7] GBC and other BTC are frequently regarded as highly lethal diseases with low 5-year survival estimates. Factors contributing to the poor prognosis of these malignant tumors include late presentation, aggressive biological behavior and unsatisfactory treatment. The only cure is complete resection, which is complicated by technical difficulties in achieving clear surgical margins. [8, 9] GBC presents with relatively non-specific symptoms, which seldom suggest cancer. Despite improved imaging techniques, most GBCs are diagnosed incidentally during laparoscopic procedures performed to confirm the presence of benign gallbladder disease. [1, 6]

The Gallbladder: Organ, Structure, Histology:

The GB is a pear shaped sac like structure, roughly 3-4 inches long and less than an inch wide, located under the right lobe of the liver. [10] It is an important component of the biliary system, where it receives, stores, modifies and secretes bile into the duodenum.

The GB wall is very thin and is made up of several layers. The innermost layer is a thin sheet of undulating epithelium, followed by loose connective tissue that forms the lamina propria; together the epithelium and lamina propria form the mucosa. Next is the muscularis - a smooth muscle layer, then perimuscular fibrous connective tissue and finally the serosa – the outer covering that does not have a sub mucosa layer. There is no muscularis mucosa to separate the epithelium/lamina propria complex from the outer structures; and the attachment to the liver along the hepatic surface does not have a serosa layer. [10 -13] These anatomic and histological features are believed to facilitate GB tumor invasion and contribute to the advanced local and regional disease usually present at the time of diagnosis. [12]

Risk Factors for GBC:

Genetic and environmental risk factors associated with chronic inflammation of the GB wall cause atypical and dysplastic changes, which are thought to lead the development of GBC. Gallstones are the most common risk factor. Other risk factors include older age, race, female gender, obesity, ethnicity and geography, porcelain gallbladder, choledochal cysts, bile duct anomalies, gallbladder polyps, primary sclerosing cholangitis, family history, smoking, chronic infections like *Salmonella typhi* and *S. paratyphi.* [6 - 10, 14, 15]

Given that most of the established risk factors of GBC are not modifiable, there are no known strategies for its primary prevention. For this reason, at the present time the more promising approaches towards improving GBC survival and prognosis include earlier detection, accurate staging, and appropriate management. [10]

GBC Clinical Features and Pathology:

GBC clinically mimics benign gallbladder diseases and often escapes detection until advanced stage. [10-17] Patients may present with non-specific signs and symptoms, which include right upper quadrant abdominal pain, jaundice, nausea, vomiting, anorexia, malaise, a palpable mass due to gallbladder enlargement. Most patients presenting with signs and symptoms caused by GBC have progressed to an advanced stage and at time of diagnosis are considered incurable due to direct extension into adjacent organs, local lymph node metastases or distant metastatic disease.

Like other cancers of the GI tract, including those arising in the stomach and colon, GBC appears to follow the metaplasia-dysplasia-carcinoma sequence. [13-16] GBC can originate from the fundus (60%), body (30%) or neck (10%) of the gallbladder. [8, 13] Most (80-90%) of GBC are adenocarcinomas, of which non-papillary (flat) adenocarcinomas represent the most common group while non-papillary (tumoral) types are much more rare. Other types include squamous cell carcinoma, small cell carcinoma and sarcoma, and are uncommon. [8, 10] GBC spreads via four modes: 1) local invasion to liver or adjacent organs; 2) lymphatic spread; 3) peritoneal dissemination; and 4) hematogenous spread. [8]

Molecular Pathology of GBC:

Most tumors of the GB are of epithelial cell origin. Epigenetic information from the study of precursor and invasive lesions of GBC has provided evidence of two distinct GB carcinogenesis models: the *metaplasia-dysplasia-carcinoma pathway* (for non-papillary 'flat' neoplasms) and the *adenoma-carcinoma pathway* (for papillary 'tumoral'

neoplasms). In the first model, the normal epithelium adapts (via metaplastic changes) to chronic irritation or inflammation. Dysplastic changes occur in the metaplastic epithelium, progressing to carcinoma in-situ (CIS) and eventually invasive cancer. In the second model, there is an initial benign glandular proliferation of the epithelium (forming a polyp or papillary lesion), malignant transformation occurs within this previously benign mass. [18]

Previously reported histologic studies identified 'papillary (tumoral) neoplasms' in 0.4% of cholecystectomies and 6-7% of invasive GBC cases. . While papillary neoplasms of the GBC are uncommon epidemiological evidence collected over the past few decades suggests they are associated with a better prognosis than their non-tumoral counterparts. [18 - 20] The favorable prognosis of papillary neoplasms is thought to be attributable to their outward growth forming a polyp/mass and delayed invasion into the GB wall. This structural feature potentially leads to early obstructive symptoms and thus earlier presentation.

GBC staging and challenges:

The main prognostic factor for GBC is the clinical or pathologic stage. [12, 14, 15] GBC is traditionally staged using TNM (Tumor, Nodes, Metastasis) classification, according to the American Joint Committee on Cancer (AJCC, Appendix Table A). [21] Under the TNM classification, there are 5 stages of tumor size: T1-T4 and a very early stage referred to as Tis or carcinoma in-situ (CIS).

CIS is the earliest possible stage of GBC with cancer cells only found inside the lining of the gallbladder wall. T1 stage means that the tumor has started to grow into the

gallbladder wall; T1 is further divided into T1a and T1b. In T1a stage the tumor invades the connective tissue layer underneath the inner lining of the GB wall, whereas a T1b tumor penetrates the connective tissue and invades the muscle. T2 tumors are still contained in the gallbladder, but they invade through the peri-muscular layer into the connective tissue that forms the outermost of the GB wall. Stage T3 tumors have grown through entire gallbladder wall and may show invasion of the liver or one other nearby organ. Stage T4 tumors show invasion of one of the main blood vessels to the liver, hepatic portal vein or hepatic artery or metastasis to non-regional lymph nodes and/or multiple distant organs. [9, 14, 15, 22, 23] T3 tumors are thought to be potentially resectable, while T4 tumors are considered inoperable. [10]

Despite medical advancements including the increased frequency of laparoscopic cholecystectomies, diagnosis of GBC remains a challenge. Certain pathologic features that make GBC difficult to diagnose include: 1) mistakenly making a diagnosis of a GBC instead of as benign lesions such as seen in deeply penetrating Rokitansky-Aschoff sinuses (over diagnosis), 2) misdiagnosing well-differentiated invasive carcinoma as benign (under diagnosis), and 3) under sampling of early, grossly occult disease. [16]

Survival of cancer patients after diagnosis, along with estimates of incidence and mortality, is a key indicator of cancer control. This information can be used to plan and evaluate health services, and make clinical recommendations. [24] Given the varying incidence of GBC around the world and the high level of subjectivity involved in grading dysplasia, there still remain inconsistencies in the diagnostic accuracy, which need to be considered in epidemiologic and clinicopathologic studies of this malignancy. [7, 25 - 26]

Epidemiology:

Frequency and distribution of GBC across population groups show prominent geographic, gender, and racial differences. Incidence of GBC peaks in the sixth and seventh decades of life, and it is two-to-three times higher in females compared to males. [6, 7, 13, 14, 15, 17] While the magnitude of gender disparity in GBC incidence varies by ethnicity, females are always at higher risk. [7]

The geographic variation of GBC incidence likely reflects genetic risk factors and racial/ethnic characteristics of the population. Worldwide GBC age-adjusted incidence rate is 2.0/100,000 and an age adjusted mortality rate of 1.5/100,000 each year. [27-29] Some of the highest GBC incidence rates are reported in India, Pakistan, Chile, and Ecuador while relatively low incidence is observed in Northern Europe, and in the USA and Canada. [6, 9, 11, 29, 30]

In the U.S, the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program is the main source of cancer statistics. The SEER program currently collects and publishes cancer incidence and survival data from population-based cancer registries. [26, 31] In the United States, GBC accounts for less than 1% of all cancer deaths with an age-adjusted mortality rate of 0.6/100,000 per year. The annual age-adjusted incidence estimate for GBC in the US is 1.7/100,000 persons with the highest rates highest rates noted in the Southwest, Midwest, and Appalachia. [27, 28, 30, 33] GBC rates are lowest among Non-Hispanic whites and highest among American Indians/Alaska Natives and Hispanics. [34]

Gall Bladder Carcinoma In-situ (GBCIS): What's special?

While it has been established that dysplasia and CIS precede most invasive GBCs, relatively little is known about the natural history of these precursor lesions. [11, 30] Since GBC is an uncommon disease in many countries, most pathologists do not have the opportunity to study its precursor lesions. Grading dysplasia based on the degree of cytologic and architectural atypia can be highly subjective with some using the terms 'high-grade dysplasia' and 'CIS' interchangeably. [35]

The neoplastic transformation in the biliary epithelium is a continuum, with low grade dysplasia at the lower end of the spectrum, high-grade dysplasia observed in more advanced lesions, and CIS representing complete malignant transformation of the cells and the uppermost end of the spectrum. [25] Extension of in situ or invasive carcinoma along preexisting normal epithelium-lined structures is not unique to the gallbladder. Recognition of this feature is important because invasive carcinomas that extend along the same epithelial structures may simulate in situ lesions. [36]

A major problem that arises is the misclassification of GBC staging with invasive stages classified as CIS or slightly lesser grade lesions being dismissed as clinically insignificant. This misclassification may affect the clinical management and survival after diagnosis. [25 - 26]

Trends in GBC:

Data from SEER program indicate a gradual decrease in GBC incidence over the last three decades in both males and females. [28] . Survival of GBC has also been reported to improve over time. [28] The decreasing incidence of gallbladder cancer and

improved survival are thought to be related to increasing use of cholecystectomy that is reported in many western countries. [34]

Most dysplasia and GB-CIS are discovered after cholecystectomy when the entire lesion is removed. With the advent of laparoscopic techniques, cholecystectomy has become a more commonly performed procedure and the number of incidentally discovered GB carcinomas increased. [11, 12, 36-39] In countries with high GBC incidence GBCIS can represent up to 15% of cancers diagnosed following cholecystectomies. [16]

Since most dysplasia and GB-CIS are discovered after cholecystectomy, trends in early stage GBC incidence should parallel the frequency of cholecystectomy procedures. Thus analysis of trends by stage for GBC can be a useful tool to evaluate the effectiveness of current diagnostic capabilities of a region in achieving higher rates of earlier-stage detection. [19, 26, 33-34]

Relevance:

While several population-based studies examined incidence and prognosis of GBC [21-26, 34 - 35] relatively few researchers have analyzed the data specifically for the earliest (in-situ) stage of this malignancy. Furthermore the relationship between histologic variants and survival is not well described. [27-29, 32-33]

With these information gaps in mind, the goals of the present study were to analyze national SEER data in order to 1) comprehensively review the across-population differences and time trends in GBC incidence and survival ; 2) Compare the survival in papillary (tumoral) and non-papillary (flat) tumors while taking into consideration other patient- and disease- related characteristics and 3) focus specifically on GBCIS.

MATERIALS AND METHODS

Data for most analyses were obtained from the 18 SEER registries, which together represent approximately 26 percent of the U.S. population. [38] Incidence rate calculations were based on the 9 original SEER registries, which allow assessing secular changes and trends since 1973. [39-40]

We used the *International Classification of Diseases for Oncology* (ICD-O-3 codes) to select all cases reported to the SEER program from 1973 to 2010 with gallbladder (C.23.9) recorded as the primary site. Cases were excluded from the analyses if they were of unknown age, identified from death certificates only, or were not microscopically confirmed. All patients with GBC reported during the study period were characterized according to sex, race, age at diagnosis, marital status, geographic region of residence, and tumor behavior, stage and grade. The GBC cases were categorized based on the World Health Organization (WHO) classification; [41] into the following five broad cytomorphologic groups (defined by ICD-O-3 codes): 1) non-papillary (8010, 8012, 8020-8022, 8030-8033, 8035, 8046, 8082, 8120, 8140-8145, 8160, 8162, 8170, 8180, 8190, 8255, 8310, 8323, 8340, 8430, 8470-8471, 8480-8481, 8490, 8500-8501, 8521, 8574, 8576, 8940, 8980); 2) papillary (8050, 8210-8211, 8221, 8260-8263, 8453, 8503-8504); 3) squamous (8070-8072, 8074-8075, 8560, 8570); 4) neuroendocrine (8013, 8041-8042, 8044-8045, 8154, 8240-8241, 8245-8246); and 5) other (8000-8001, 8720, 8800-8805, 8830, 8890, 8935, 8990, 9120).

Treatment information was available from 1983 onwards and only patients diagnosed from 1983 to 2010 were characterized with respect to tumor-directed surgery, which was expressed as a binary variable (any versus none). Vital status of each patient

through 2010 was classified into four main categories: alive or censored, dead due to GBC, dead due to pancreatic or biliary cancer, dead due to other causes.

The only consistently reported stage variable in SEER since 1973 that allows for the assessment of long-term secular trends is "SEER historic stage A". The SEER historic stage A classification scheme characterizes tumors as in situ, localized, regional, distant or unstaged based on the following definitions: [36, 42-45]

- **In situ cancer** is early cancer present only in the layer of cells in which it began;
- **Localized cancer** is cancer limited to the organ in which it began, without evidence of spread;
- **Regional cancer** is cancer that has spread beyond the original (primary) site to nearby lymph nodes or organs and tissues;
- **Distant cancer** is cancer that has spread from the primary site to distant organs or distant lymph nodes;
- **Unstaged cancer** is cancer for which there is not enough information to indicate a stage;

Marital status was classified into 3 categories: married (including common law), single (never married) and other (included separated, widowed or divorced). Race and ethnicity were combined using SEER variables Race recode (White, Black, Other) and the Origin recode NAACCR Hispanic Identification Algorithm (NHIA; Hispanic, Non-Hispanic). The new racio-ethnic variable was recoded into the following 4 categories:

Non-Hispanic White, Non-Hispanic Black, Hispanic, Other (Asian or Pacific Islander, American Indian, Alaskan Native, or any other). [46]

Age-adjusted incidence rates of GBC were calculated for the entire study period by sex, race and stage, and were expressed as the number of new cases per 1,000,000 individuals per year accompanied by 95% confidence intervals (CIs). The differences across population subgroups were examined by calculating the incidence rate ratios (IRRs) and corresponding 95% CIs.

Changes in incidence over time were expressed as the annual percentage change (APC) and were further examined using the Joinpoint Regression Program (Control and Population Sciences, National Cancer Institute, Bethesda, Md). Using the calendar year as the independent variable, a least-squares regression line was fitted to the natural logarithm of the rates to calculate the APC. Changes in trend, were tested using the Monte Carlo permutation method to identify inflexion points

Survival of patients with GBC was examined over a period of 10 years (120 months) after diagnosis using several measures. The first of those measures was observed survival (OS), which was defined as the proportion of GBD patients who survived beyond a given interval. [38] The relative survival (RS) was then estimated by dividing the OS among cancer patients by the expected survival (ES) of a cancer free cohort of the general population with the same age, race and sex characteristics. [19, 38, 49] Cause-specific survival (CS) was calculated by assessing the probability of dying specifically from GBC. [38] The 5- and 10-year OS, RS and CS estimates were evaluated overall and by sex, race, marital status and stage.

Kaplan-Meier curves were constructed and accompanied by log-rank tests to examine patient survival according to stage, sex, race, marital status, tumor-directed surgery, and histologic type. In addition, multivariable Cox proportional hazards (PH) models were used to further examine the association between survival and various patient-, tumor- and treatment-related characteristics. The results of these multivariable models were expressed as adjusted hazards ratios (HRs) and reported along with the corresponding 95% CIs. Proportional hazards assumptions were tested by examining log-minus-log plots for each variable. All models were examined for interactions and collinearity among covariates.

The analyses were performed using SPSS 21.0 for Windows (IBM Corp, Armonk, NY), SAS 9.3 for Windows (SAS Institute Inc., Cary, NC), SEER*Stat version 8.1.2 (National Cancer Institute, Bethesda, Md) statistical software packages.

RESULTS

From 1973 through 2010, 20,092 cases of GBC, including in situ carcinomas, were reported to SEER. Of these 17,441 cases were further identified as the first primary cancer and were used in the present analysis.

Table 1 shows the baseline descriptive characteristics of GBC by time period. The majority of GBC cases (72%) were women, about two thirds (64%) were Non-Hispanic whites, and over one-half (57%) were persons 70 years of age or older.

Table 2 lists the clinicopathologic characteristics of all tumors. The most common GBC histologic type was non-papillary (flat) representing 86.4% of all reported cases. Papillary tumors represented roughly 5.6% of all GBC cases. About 96% of GBC were invasive tumors. There were 685 cases of GBCIS, 4725 tumors were localized (within the GB wall), 4671 had regional lymph node metastases, 6402 had distant metastatic spread, and 957 cases were not staged. Additional surgery (i.e. re-resection of surrounding organs, liver, bile duct and nodes etc.) after diagnosis was performed in roughly 62% of cases. At the end of the study period 14.3% of patients were alive, 49.7% died due to their GBC, 13.9% died from cancers of the pancreatic and biliary tract, and the remaining patients died from other causes.

As shown in Table 3 the proportions of non-papillary (flat) GBC cases were similar across all stages. By contrast papillary (tumoral) cases were overrepresented among patients with early-stage diagnosis (22% for GBCIS and 12% for localized GBC), compared to those with more advanced malignancy (3% for regional and 0.5% for distant disease).

Table 4 presents the age-adjusted GBC incidence rates – overall and by gender, race and stage (9 SEER, 1973-2010). The average annual GBC incidence across the entire study period was 14.3 cases per 1,000,000 persons. Using men as the reference group, the IRR for GBC among women was 1.73 with the 95% CI from 1.66 to 1.80. The IRR (95% CI) estimates for blacks and other races relative to whites were 1.02 (0.95-1.10) and 1.38 (1.30-1.47) respectively. Incidence of GBCIS was 0.5 per 1,000,000 per year; and the corresponding estimates for localized, regional and distant disease were 3.9, 3.9 and 5.2, respectively.

The overall age-adjusted incidence rates for GBC declined throughout the period 1973-2010 with evidence of an inflexion point. Prior to 1997 the decline was more pronounced and statistically significant (APC -2.2; 95% CI: -2.5, -1.9); however the change was less apparent afterwards (-0.3; 95% CI: - 1.1, 0.5). In contrast to the overall GBC incidence, the rates of the in-situ disease remained fairly stable throughout the 1973-2010 time period (Figure 1-A). When the trends were examined by gender the results for women showed a similar pattern and the same joinpoint as those observed for overall GBC incidence (Fig. 1-B). As shown in Figures 1 C-D, age-adjusted GBC rates declined only among whites, but not among blacks, and not in other racial groups.

Table 5 lists the 5- and 10-year OS, RS and CS estimates by patient-related and clinicopathologic characteristics of GBC cases. RS estimates across all categories were 17.6% at 5 years and 14.8% at 10 years post-diagnosis. The 5-year RS rose from 11.6% in the first study decade (1973-1982) to 21.2% in the 2003-2010 interval. Both 5 and 10-year RS for GBC showed significant increases in survival from 1973 until mid- to late-1980s, followed by relatively flat trends thereafter *(see Figure 3 of the Appendix)*. There

were notable decreases in both 5- and 10-year RS with increasing disease stage. For example, 5-year RS for GBCIS was 87.4% compared to 39.8% for localized, 6.8% for regional and 2.0% for distant disease.

Among histology groups, papillary (tumoral) cases had better survival. At 5 years 54% of patients with papillary GBC were alive as compared to only 15.6% of persons diagnosed with non-papillary (flat) disease. Papillary GBCIS also showed better survival, compared to the non-papillary tumors of the same stage (Figures 2 A-C).

Kaplan-Meier curves comparing survival across various demographic and clinicopathologic GBC characteristics (Figures 3 A-E) demonstrate that survival clearly decreases with increasing stage and that patients with papillary (tumoral) cancers have a significantly better prognosis compared to those with non-papillary disease (log-rank test p-values < 0.0001).

Results for 10-year survival multivariate Cox-regression analysis are shown in Table 6. Age at diagnosis, gender, race and ethnicity, histology, surgery, stage and period of diagnosis met proportional hazards assumptions and were found to be significant independent prognostic factors.

Using in-situ cases as the reference category, mortality among patients diagnosed with GBC in the localized stage was 2.6 times higher while those with distant disease were 11.7 times more likely to die during follow up. Papillary (tumoral) cases had significantly better survival (HR: 0.60; 95% CI: 0.55, 0.66) than patients diagnosed with non-papillary GBC. Patients whose first course of treatment included tumor directed surgery had 40% lower mortality (HR: 0.6; 95% CI: 0.58-0.63) than those who were not

treated with surgery. Other important predictors of better survival were younger age and female gender, while differences by patient race/ethnicity were very small.[1]

Table 7 provides a detailed review of cause of death by stage of GBC. Over half (378 of 686) cases diagnosed with GB-CIS were alive at the end of the study period. While most patients died from non-cancer related causes, among malignancy related deaths roughly 4% died from pancreatic or other biliary cancers while only 2% died from GBC. In all other stages, especially with more advanced stage, death from GBC represented the most common cause of death. However, death from pancreatic and biliary cancers still formed a substantial proportion of deaths among these other stages.

[1] Results for 5 and 10-year survival from multivariable cox regression models for GBCIS are presented in Appendix, Table 8. Histology failed to meet the proportional hazards criteria required for long term survival analysis in the GB-CIS group with a clear time-dependent relationship observed in the later course of the disease.

DISCUSSION

The current study comprehensively examined incidence and survival of GBC at various stages, including CIS. Unlike previous SEER-based reports , the current study extended the follow up to the end of 2010 and performed several additional analyses including multivariable Cox regression and evaluation of incidence trends in search of inflexion points.

This study confirms previous reports [21, 24, 26, 30, 31, 51-56] indicating that GBC commonly presents at advanced stage and age with over a third of cases diagnosed at ages of 70 years or older and with evidence of distant spread. Also consistent with previous reports [53 - 56] were our findings that there was a significant decline in the overall incidence of GBC and that survival outcomes of this lethal disease have also improved over the last four decades. Our results showed that from the early 1970's with incidence rates leveling off and remaining fairly stable over the last decade.

Several studies have offered potential explanations to these recently observed trends. Carcinoma in-situ of the gallbladder presents with no symptoms and is almost invariably incidentally diagnosed by histologic examination. It has been postulated that since fewer cases of carcinoma confined to the gallbladder are correctly diagnosed preoperatively and as laparoscopic cholecystectomy becomes widely used pathologists can expect to see more cases of early gallbladder cancer. The declines in incidence trends and improved survival have been attributed to more widespread removal of premalignant lesions and early stage GBC through laparoscopic cholecystectomy. [2, 52, 57 - 59]

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Despite the greater number of laparoscopic cholecystectomies performed in the U.S, [55-56] we observed no increase in the incidence of early-stage GBC. While the incidence of distant disease showed a steady decline initially, trends for the past decade have shown a slight increase. [Appendix Figure 1] The latter observation may be due to improvements in imaging techniques, which are now more likely to pick up metastatic spread. [53-57]

While our findings demonstrate that survival following GBCIS diagnosis is high it appears to be different from previously reported estimates. [62-63] The 5- and 10-year RS estimates in our study were 89% and 79% respectively, as opposed to 100% and 70% as previously reported. [62]

The less than 100% survival following GBCIS diagnosis may have at least two explanations. As many GBCIS patients die from a variety of causes, including other primary cancers, it is possible that risk factors for GBC may also increase overall mortality due to seemingly unrelated conditions. In addition, it is possible that many GBCIS diagnoses represent under-staging of more advanced disease. The anatomical and histological features of GBC (mentioned in introduction) make the diagnosis of this malignancy particularly in the in-situ stage difficult. In the U.S, there is no standardized

method for gallbladder sampling and reporting and it is common for a 'random' sample of representative sections of the gallbladder specimen to be submitted for histological evaluated. This is in contrast to sampling methods of countries which experience a high incidence of this disease, where every specimen is submitted in entirety for evaluation. These countries also boast high survival rates of GBCIS with rates >90% at 10-years, likely because they are accurately diagnosing and staging the disease. Given the previously reported relatively high survival rates associated with GBCIS in the US, there has been no indication to change these sampling practices. Our results suggest that the phenomenon of under-sampling of gallbladder specimens leading to under-diagnosis to be at play in the SEER database.

International epidemiological studies have shown ethno-geographic difference of GBC incidence. For instance Chile has the highest rates of GBC in the world where it is the most significant contributor to mortality among women. In areas where GBC is endemic, the frequently diagnosed in-situ stage is associated with relatively good prognosis. [64] In a recent collaborative case-series analysis, the 10-year survival for 190 cases of completely sampled GB-CIS cases from Chile, was 90%. [65] In addition higher rates have been reported in several other case-series. In a separate analysis of 125 GB-CIS cases inclusive of both North American and Chilean cohorts, the 10-year survival rate was 86%. [66] The majority of deaths in that study population occurred in the North American patients, whose diagnosis more often relied on incomplete sampling of the gallbladder with fewer blocks submitted for review. These observations suggest missed invasive or more advanced carcinomas.

There is additional evidence suggesting that GBCIS reported to SEER may in fact represent more advanced cases. While the timeline for the gallbladder carcinogenesis not known, estimations have been made based on the mean ages of patients at each stage. [16, 67-68] In general the process for progression from in-situ to invasive carcinomas is thought to take roughly ten years, with a higher end estimate of 15 years. Our results demonstrate a gradient suggestive of the progression of these lesions to more advanced cases. In our analysis of SEER data the mean age of patients diagnosed with GBCIS is 64-69 years, which about 10 years higher than in corresponding mean age in case-based cohorts. [64-68]

Poor survival outcomes of invasive GBC can attributed to tumor recurrence, co-occurrence or other unknown factors. Recurrences of GBC have been well documented correlating with large numbers of retained micrometastases after simple resection of the gallbladder. [60, 69] Even in the absence of micrometastases, GBC tumors are found to recur and interestingly co-occurrences of carcinomas in the pancreas, gallbladder, ampulla of Vater and biliary system have been described. [70]

Tumors can recur because of the genetic changes that drive a cell towards malignancy. This is the premise behind the concept of field cancerization (field effect/field defect phenomenon). According to this theory genetic changes transform cells in a particular organ or tissue, such that they are genetically altered but appear histologically normal, these changes can predate the occurrence of neoplastic cells or coexist with malignant cells. Thus cancers can occur at disparate sites with similar histo-pathologic patterns resulting from a shared common pathway. [70-71]

An important contribution of the current study is the analyses of cause-specific survival among GBCIS patients. It is important to point out that many of the GBCIS

deaths were attributed to pancreatic and biliary tract cancers. This observation supports a field-effect/field-defect, indicating that even after the gallbladder is removed the remainder of the biliary mucosa and adjacent organs remain at risk for cancer. [72-73]

While Cox regression analyses confirmed that, in general, papillary histology was an independent predictor of GBC survival, we were unable to assess this association among GBCIS cases because of violation of proportional hazard assumptions. The time dependent nature of the association between histology and mortality among in-situ tumors is consistent with recent studies that have recognized the heterogeneity of papillary GBC.

The interpretation of our findings requires understanding of the strengths and limitations of the SEER data. As we previously noted elsewhere [37, 74] the large sample size enables SEER-based studies to study even rare cancers (e.g. GBCIS), allows sufficient power for detecting relatively moderate associations, and permits a variety of multivariable analyses. The population based, as opposed to institution-based, identification of cases increases the generalizability of findings and the active follow-up of cases improves the accuracy of survival analyses. While institutional studies often have more detailed information about each patient, those studies usually are confined to major referral centers and may not be representative of the cases treated in community hospitals and clinics.

The main limitations of this study pertain to the lack of data on certain important clinical and demographic variables. While SEER data on surgery and radiation are reasonably complete the information pertaining to systemic treatment such as chemotherapy is usually missing and is not included the public use files. [75] In addition,

SEER data do not contain information on such important predictors of survival as health insurance and socioeconomic status all of which may determine access to and utilization of health care. Another important data item that may need to be considered is the effect of provider- and facility-related characteristics, which cannot be addressed in the context of SEER-based research, but may be critical determinants of diagnostic (including pathology) quality. For all of the above reasons, both cancer registry-based and institution-based studies provide useful non-overlapping information that contributes to the evidence despite their strengths and limitations. [76]

CONCLUSION

Our data indicate that misinterpretation of subtle microscopic abnormalities, under-sampling of gallbladder specimens and lack of experience with this disease entity may contribute to deaths from early stage GBC including presumably in-situ disease. It is imperative for the pathologist to examine gallbladder specimens entirely to rule out advanced stage carcinomas and to accurately stage GBC. Clinicians should be aware of the risk factors and clinical history of GBC and maintain a high degree of suspicion particularly in high-risk groups.

In addition the evidence of GBC field-effect/field-defect phenomenon observed especially among GBCIS indicates the importance of clinician awareness and calls for patients diagnosed even in the earliest, curable stage, to be placed in long term follow-up. Future studies employing extended multivariable models with time-dependent variable should further examine the relation between tumor characteristics and survival among GBCIS patients.

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TABLE 1. Demographic Characteristics of Patients With Gallbladder Tumors by Decade: 18 SEER Registries, 1973-2010

Patient Characteristics	No. of Patients (%)				
	All Patients, N=17441	**1973-1982,** N=2807	**1983-1992,** N=2929	**1993-2002,** N=4979	**2003-2010,** N=6726
Gender					
Men	4899 (28.09)	772 (27.50)	778 (26.56)	1377 (27.66)	1972 (29.32)
Women	12542 (71.91)	2035 (72.50)	2151 (73.44)	3602 (72.34)	4754 (70.68)
Race					
Non-Hispanic White	11100 (63.64)	2231 (79.48)	2149 (73.37)	2935 (58.95)	3785 (56.27)
Hispanic	3006 (17.24)	252 (8.98)	294 (10.04)	1038 (20.85)	1422 (21.14)
Black	1497 (8.58)	129 (4.60)	183 (6.25)	422 (8.48)	763 (11.34)
Other[a]	1838 (10.54)	195 (6.95)	303 (10.34)	584 (11.73)	756 (11.24)
Age, years					
<50	1161 (6.66)	105 (3.74)	130 (4.44)	390 (7.83)	536 (7.97)
50-59	2278 (13.06)	325 (11.58)	325 (11.10)	609 (12.23)	1019 (15.15)
60-69	4004 (22.96)	675 (24.05)	689 (23.52)	1101 (22.11)	1539 (22.88)
70-79	5335 (30.59)	951 (33.88)	985 (33.63)	1576 (31.65)	1823 (27.10)
80+	4663 (26.74)	751 (26.75)	800 (27.31)	1303 (26.17)	1809 (26.90)
Marital Status*					
Married	8174 (48.70)	1267 (46.55)	1359 (47.62)	2321 (48.65)	3227 (50.12)
Single	1823 (10.86)	182 (6.69)	233 (8.16)	564 (11.82)	844 (13.11)
Other[b]	6788 (40.44)	1273 (46.77)	1262 (44.22)	1886 (39.53)	2367 (36.77)
Geographic Region					
Atlantic	2935 (16.83)	474 (16.89)	434 (14.82)	720 (14.46)	1307 (19.43)
Pacific/West	9001 (51.61)	1184 (42.18)	1350 (46.09)	2908 (58.41)	3559 (52.91)
MidWest	4008 (22.98)	1073 (38.23)	1021 (34.86)	950 (19.08)	964 (14.33)
South	1497 (8.58)	76 (2.71)	124 (4.23)	401 (8.05)	896 (13.32)

a Other races included Asian or Pacific Islander, American Indian, Alaska Native, or unspecified.

b Other Marital Status included Divorced, Widowed, Separated.

*** All unspecified or missing cases were excluded (N=656)**

TABLE 2. Clinicopathologic Characteristics of Gallbladder Tumors by Decade: 18 SEER Registries, 1973-2010

Clinicopathologic Characteristics	No. of Patients (%)				
	All Patients, N=17441	1973-1982, N=2807	1983-1992, N=2929	1993-2002, N=4979	2003-2010, N=6726
Histologic Type					
Non-papillary features [a]	15066 (86.38)	2482 (88.42)	2587 (88.32)	4321 (86.78)	5676 (84.39)
Papillary features [b]	976 (5.60)	161 (5.74)	164 (5.60)	246 (4.94)	405 (6.02)
Squamous features [c]	657 (3.77)	126 (4.49)	128 (4.37)	187 (3.76)	216 (3.21)
Neuroendocrine features [d]	278 (1.59)	11 (0.39)	20 (0.68)	78 (1.57)	169 (2.51)
Other [e]	464 (2.66)	27 (0.96)	30 (1.02)	147 (2.95)	260 (3.87)
Behavior					
Non-invasive [f]	686 (3.93)	67 (2.39)	118 (4.03)	198 (3.98)	303 (4.50)
Invasive	16755 (96.07)	2740 (97.61)	2811 (95.97)	4781 (96.02)	6423 (95.50)
Stage					
In-situ	686 (3.93)	67 (2.39)	118 (4.03)	198 (3.98)	303 (4.50)
Localized	4725 (27.09)	603 (21.48)	756 (25.81)	1426 (28.64)	1940 (28.84)
Regional	4671 (26.78)	880 (31.35)	849 (28.99)	1464 (29.40)	1478 (21.97)
Distant	6402 (36.71)	1091 (38.87)	1057 (36.09)	1598 (32.09)	2656 (39.49)
Unstaged	957 (5.49)	166 (5.91)	149 (5.09)	293 (5.88)	349 (5.19)
Grade					
Well Differentiated	1747 (10.02)	304 (10.83)	346 (11.81)	466 (9.36)	631 (9.38)
Moderately Differentiated	4076 (23.37)	341 (12.15)	687 (23.46)	1316 (26.43)	1732 (25.75)
Poorly Differentiated	4753 (27.25)	575 (20.48)	819 (27.96)	1544 (31.01)	1815 (26.98)
Undifferentiated	489 (2.80)	127 (4.52)	87 (2.97)	131 (2.63)	144 (2.14)
Unknown	6376 (36.56)	1460 (52.01)	990 (33.80)	1522 (30.57)	2404 (35.74)
Surgery					
Yes	10897 (62.48)	2746 (97.83)	2674 (91.29)	3621 (72.73)	1856 (27.59)
No	6544 (37.52)	61 (2.17)	255 (8.71)	1358 (27.27)	4870 (72.41)
Vital status					
Alive	2490 (14.28)	41 (1.46)	119 (4.06)	511 (10.26)	1819 (27.04)
Death due to Gallbladder Cancer	8673 (49.73)	1801 (64.23)	1678 (57.29)	2528 (50.77)	2664 (39.61)
Death due to Pancreatic or Biliary cancer	2432 (13.94)	274 (9.76)	356 (12.15)	735 (14.76)	1067 (15.86)
Death due to Other causes	3846 (22.05)	689 (24.55)	776 (26.49)	1205 (24.20)	1176 (17.48)

a Non-papillary: Adenocarcinoma, Carcinoma NOS with non-papillary f

b Papillary: Carcinoma arising from pre-invasive lesions, adenoma, with papillary features

c Squamous: Squamous cell carcinoma and adenosquamous carcinomas

d Neuroendocrine tumors

e Other: other malignant carcinomas and sarcomas

f Non-invasive features characterize in-situ behavior

TABLE 3. The Histopathologic Characteristics of Gallbladder Tumors by Stage; 18 SEER Registries, 1973-2010

	No. of Cases (%)					
	All GBC Cases	**In-Situ**	**Localized**	**Regional**	**Distant**	**Unstaged**
Clinicopathologic Characteristics	N=17441	N=686	N=4725	N=4671	N=6402	N=957
Histologic Type						
Non-papillary features [a]	15066 (86.38)	535 (77.99)	3871 (81.93)	4161 (89.08)	5827 (91.02)	672 (70.22)
Papillary features [b]	976 (5.60)	148 (21.57)	582 (12.32)	125 (2.68)	116 (1.81)	5 (0.52)
Squamous features [c]	657 (3.77)	2 (0.29)	143 (3.03)	258 (5.52)	231 (3.61)	23 (2.40)
Neuroendocrine features [d]	278 (1.59)	1 (0.15)	101 (2.14)	66 (1.41)	101 (1.58)	9 (0.94)
Other [e]	464 (2.66)	0 (0.00)	28 (0.59)	61 (1.31)	127 (1.98)	248 (25.91)

a Non-papillary: Adenocarcinoma, Carcinoma NOS with non-papillary features

b Papillary: Carcinoma arising from pre-invasive lesions, adenoma, with papillary features

c Squamous: Squamous cell carcinoma and adenosquamous carcinomas

d Neuroendocrine tumors

e Other: other malignant carcinomas and sarcomas

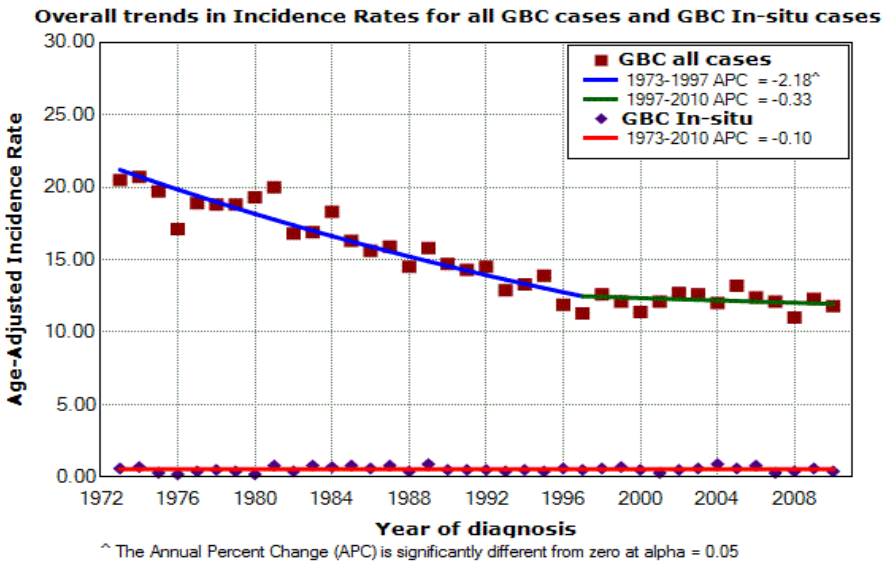
TABLE 4. Age-adjusted Incidence Rates & Incidence Rate Ratios of Gallbladder Tumors by Sex, Race & Stage.
(9 Surveillance, Epidemiology, and End Results Registries, 1973-2010)

Population Groups	Rate (95% CI)*	Rate ratio (95% CI, p.value)
All groups	14.30 (14.10, 14.60)	N/A
Gender		
Men (N=3440)	10.10 (9.80, 10.50)	Reference
Women (N=8415)	17.50 (17.10, 17.90)	1.73 (1.66, 1.80, 0.00)
Race		
White (N=9733)	13.90 (13.60, 14.10)	Reference
Black (N=888)	14.20 (13.20, 15.20)	1.02 (0.95, 1.10, 0.55)
Other[a] (N=1234)	19.20 (18.1, 20.3)	1.38 (1.30, 1.47, 0.00)
Stage		
In-situ (N=454)	0.5 (0.5, 0.6)	Reference
Localized (N=3179)	3.9 (3.7, 4.0)	7.12 (6.45, 7.88, 0.00)
Regional (N=3246)	3.9 (3.8, 4.1)	7.23 (6.55, 8.00, 0.00)
Distant (N=4307)	5.2 (5.0, 5.3)	9.57 (8.69, 10.57, 0.00)
Unstaged (N=669)	0.8 (0.8, 0.9)	1.52 (1.35, 1.72, 0.00)

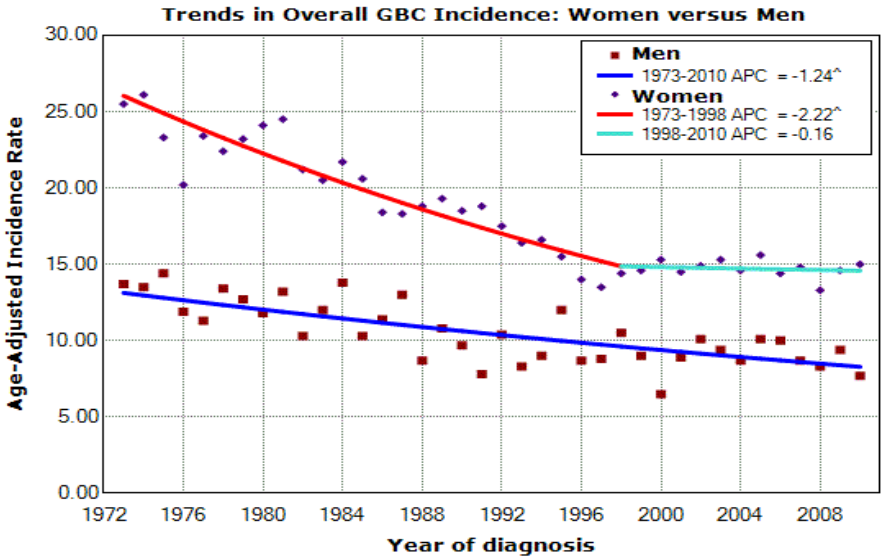
a Other races included Asian or Pacific Islander, American Indian, Alaska Native, or unspecified.

*** Rates are per 1,000,000 and age-adjusted to the 2000 US population**

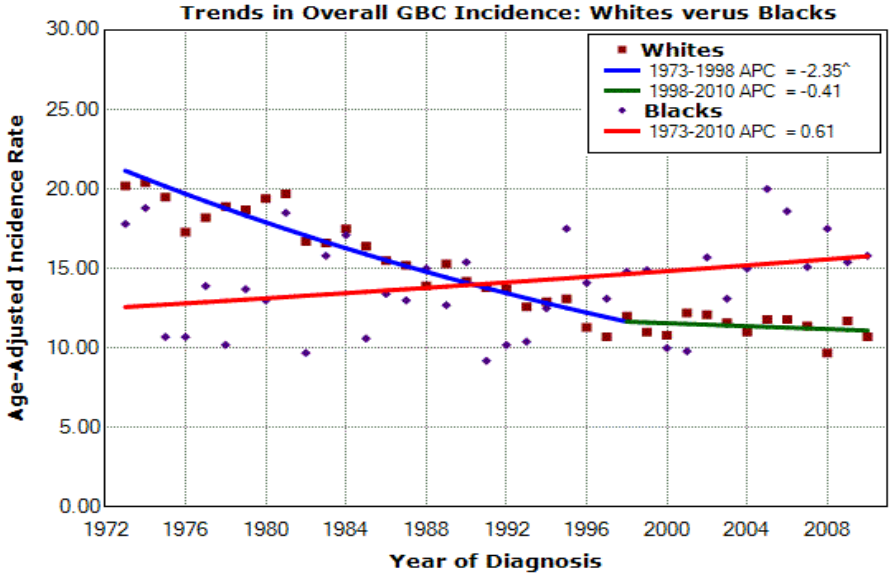
Figure 1 (A-D). Trends in observed Incidence of GBC tumors (1973-2010)



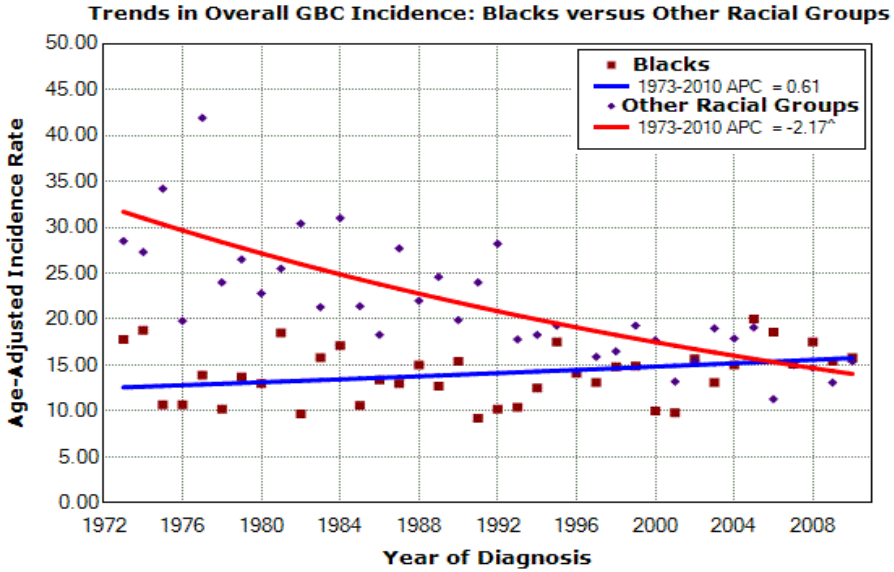
A. Trends in Overall GBC & GB-CIS Incidence (1973-2010)



B. Overall GBC Incidence in Men vs Women



C. GBC Incidence in Whites vs. Blacks



D. GBC Incidence in Blacks vs. Other Racial Groups

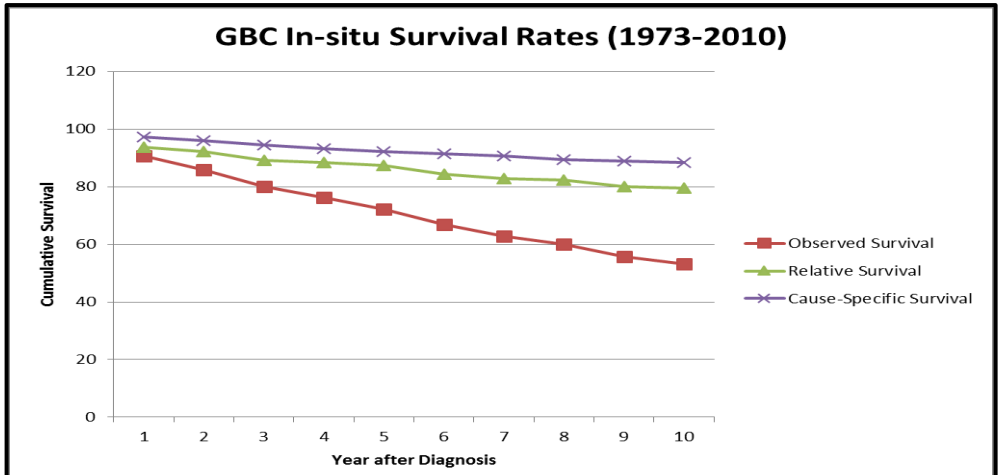
TABLE 5. The 5 and 10-year Survival or patients with Gallbladder Tumors by Sex, Race, Marital Status and Stage.
(18 Surveillance, Epidemiology, and End Results Registries, 1973-2010)

Patient & Clinical Characteristics	Survival Interval	OS (95% CI)*	RS (95% CI)**
All groups (N=17264)	5-year	14.50 (13.90, 15.10)	17.60 (17.00, 18.30)
	10-year	9.70 (9.20, 10.30)	14.80 (14.00, 15.60)#
Gender			
Men (N=4858)	5-year	13.70 (12.70, 14.80)	17.10 (15.80, 18.40)
	10-year	8.70 (7.80, 9.70)	13.60 (12.10, 15.10)#
Women (N=12406)	5-year	14.80 (14.10, 15.50)	17.90 (17.10, 18.70)
	10-year	10.10 (9.50, 10.80)	15.20 (14.30, 16.20)#
Race			
White (N=13921)	5-year	14.10 (13.40, 14.70)	17.30 (16.60, 18.10)
	10-year	9.50 (8.90, 10.00)	14.90 (12.00, 15.80)#
Black (N=1498)	5-year	13.20 (11.30 15.10)	15.80 (13.60, 18.10)
	10-year	7.50 (5.90, 9.40)	11.00 (8.60, 13.70)#
Other[a] (N=1845)	5-year	19.10 (17.20, 21.20)	21.30 (19.10, 23.50)#
	10-year	13.40 (11.60, 15.30)	16.90 (14.60, 19.20)#
Marital Status			
Married (N=8136)	5-year	16.70 (15.90, 17.60)	19.40 (18.40, 20.40)
	10-year	12.10 (11.30, 13.00)	16.90 (15.70, 18.00)#
Single (N=1812)	5-year	15.30 (13.50, 17.20)	17.30 (15.30, 19.50)
	10-year	10.40 (8.70, 12.30)	13.10 (11.0, 15.40)#
Other[b] (N=7316)	5-year	11.90 (11.10, 12.70)	15.70 (14.70, 16.80)
	10-year	7.00 (6.30, 7.70)	12.60 (11.40, 13.90)#
Histology			
Non-Papillary (N=14871)	5-year	12.80 (12.20, 13.40)	15.60 (14.90, 16.30)
	10-year	8.40 (7.90,9.00)	13.00 (12.20, 13.80)#
Papillary (N=972)	5-year	44.50 (27.30, 34.50)	54.00 (49.70,58.10)
	10-year	30.80 (27.30, 34.50)	46.50 (41.10, 56.70)#
Squamous Cell (N=656)	5-year	6.60 (4.70, 8.80)	7.30 (5.20, 9.70)#
	10-year	4.90 (3.30, 7.00)	6.10 (4.10, 8.60)#
Neuroendocrine (N=274)	5-year	31.70 (25.70, 37.80)	35.30 (28.60, 42.00)#
	10-year	24.40 (18.00, 31.50)	30.50 (22.30, 39.10)#
Other (N=381)	5-year	5.10 (3.10, 7.80)	6.60 (4.00,10.20)#
	10-year	3.00 (1.40, 5.40)	4.30 (2.00, 7.90)#
Stage			
In-situ (N=685)	5-year	72.10 (68.30, 75.60)	87.40 (82.20, 91.10)
	10-year	53.20 (48.50, 57.70)	79.40 (71.60, 85.30)#
Localized (N=4711)	5-year	32.30 (30.90, 33.80)	39.80 (38.00, 41.60)
	10-year	21.80 (20.40, 23.20)	33.90 (31.80, 36.10)#
Regional (N=4661)	5-year	5.80 (5.10, 6.50)	6.80 (6.00, 7.70)#
	10-year	3.40 (2.80, 4.00)	4.90 (4.00, 5.80)#
Distant (N=6346)	5-year	1.70 (1.30, 2.10)	2.00 (1.50, 2.40)#
	10-year	1.00 (0.70, 1.40)	1.50 (1.00, 2.00)#
Unstaged (N=860)	5-year	8.90 (6.90, 11.00)	11.40 (8.90, 14.10)
	10-year	4.30 (2.90, 6.20)	6.70 (4.50, 9.40)#

a Other races included Asian or Pacific Islander, American Indian, Alaska Native, or unspecified.
b Other Marital Status included Divorced, Widowed, Separated.
***OS = Observed Survival, percent of patients surviving beyond a given interval**
****RS = Relative Survival, OS of gallbladder cancer patients divided by the expected survival in population with the same age, race & gender characteristics.**
 # = Relative survival increased from a prior interval and has been adjusted.

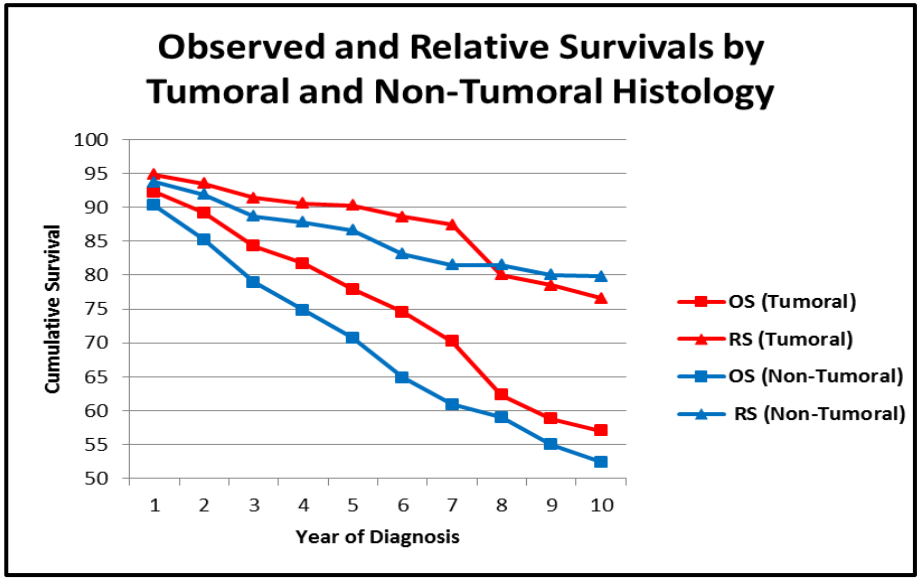
Figure 2 (A-C). Survival Rates for all GB-CIS cases, overall and by histology (1973-2010)

A.



Survival for all In-Situ GBC cases	1-year (%)	3-year (%)	5-year (%)	10-year (%)
Observed Survival (OS)	90.6	80	72.1	53.2
Relative Survival (RS)	93.8	89.2	87.4	79.4
Cause-Specific Survival (CS)	97.2	94.4	92.1	88.4

B.



C.

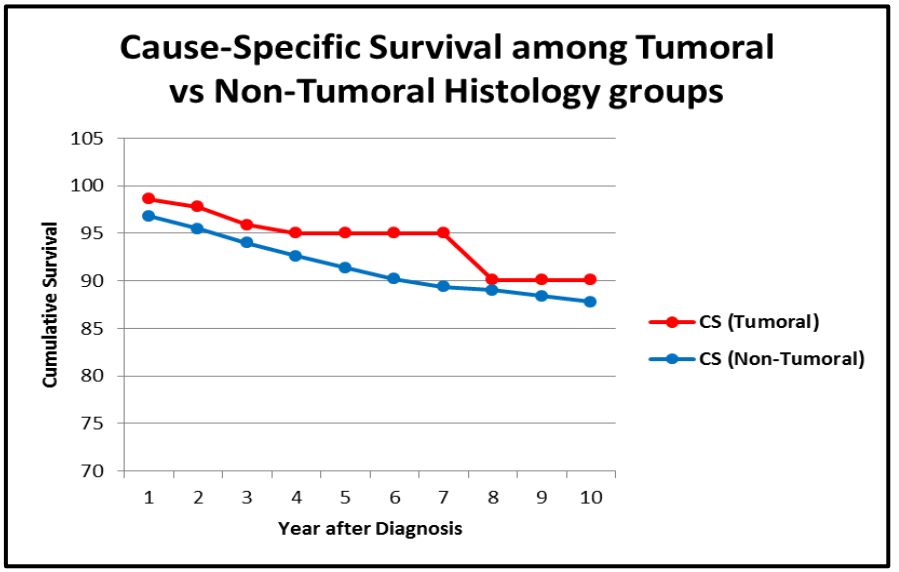
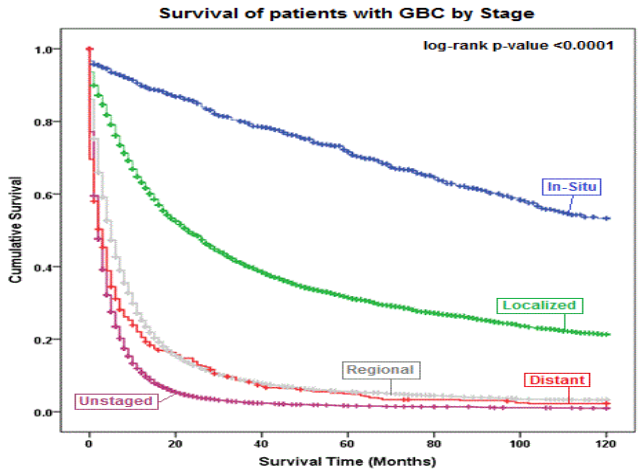
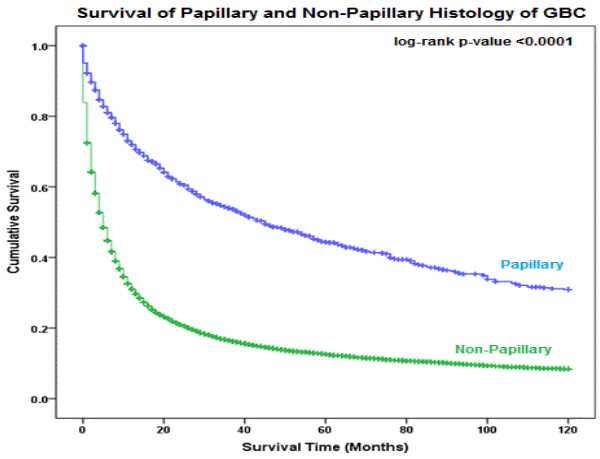


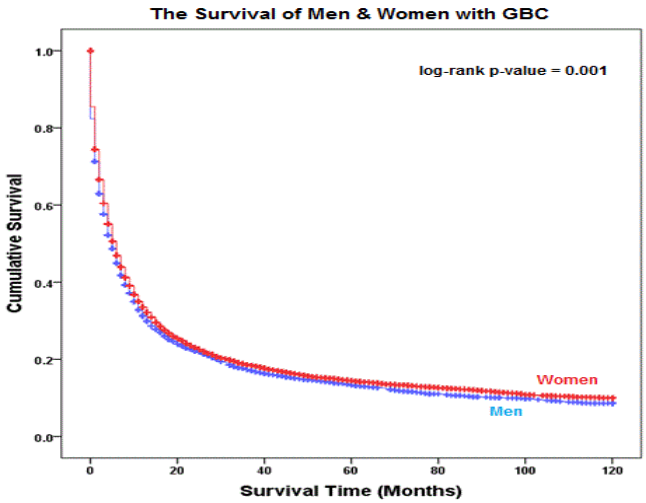
Figure 3 (A-E). Kaplan-Meier (K-M) Survival Curves for GBC cases (1973-2010)



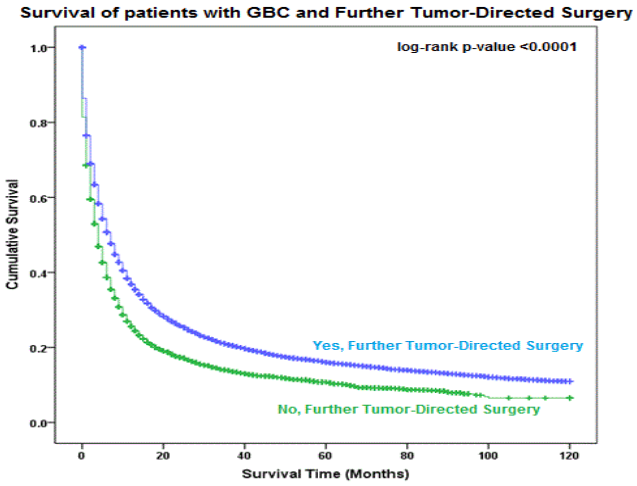
A. K-M Survival Curves for GBC cases by Stage



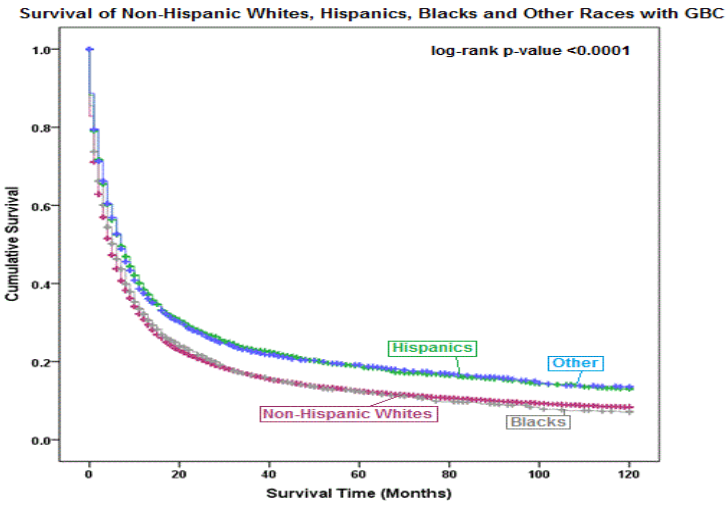
B. K-M Survival Curves for GBC cases by Histology



C. K-M Survival Curves for GBC cases by Gender



D. K-M Survival Curves for Further Surgery



E. K-M Survival Curves for GBC cases by Race/ethnicity

Table 6. 10-Year Survival Cox Multivariate Regression Parameters for all GBC tumors (1973-2010)

Covariate		Hazard Ratio (HR)	95% CI for HR Lower	Upper
Age[a]				
	50-59	1.22	1.12	1.34
	60-69	1.44	1.32	1.57
	70-79	1.73	1.59	1.88
	80+	2.42	2.22	2.64
Female Sex[b]		0.88	0.85	0.92
Race/Ethnicity[c]				
	Non-Hispanic Black	1.09	1.02	1.16
	Hispanic	0.95	0.9	1
	Other	0.91	0.85	0.96
Papillary (Tumoral) Histology[d]		0.6	0.55	0.66
Further Tumor Directed Surgery[e]		0.6	0.58	0.63
Stage[f]				
	Localized	2.64	2.31	3.02
	Regional	6.97	6.1	7.98
	Distant	11.17	9.76	12.77
	Unstaged	6.72	5.76	7.84
Period of Diagnosis[g]				
	1983-1992	0.79	0.74	0.83
	1993-2002	0.65	0.61	0.68
	2003-2010	0.44	0.41	0.46

Reference groups:
a: Ages <50 years
b: Male sex
c: Non-Hispanic Whites
d: Non-papillary (flat) histology
e: No Further Tumor Directed Surgery (re-resection)
f: In-situ stage
g: Time period 1973-1982

Table 7. Cause-specific death classification of Gallbladder Tumors by Stage: 18 Surveillance, Epidemiology, and End Results Registries, 1973-2010

	No. of Patients (%)					
Cause of Death	**All Patients,** N=17441	**In-Situ** N=686	**Localized** N=4725	**Regional** N=4671	**Distant** N=6402	**Unstaged** N=957
Alive	2490 (14.28)	378 (55.10)	1299 (27.49)	379 (8.11)	384 (6.00)	50 (5.22)
Accidents & Other Adverse Events [a]	482 (2.76)	40 (5.83)	234 (4.95)	99 (2.12)	79 (1.23)	30 (3.13)
Cardiovascular [b]	1072 (6.15)	113 (16.47)	545 (11.53)	198 (4.24)	161 (2.51)	55 (5.75)
Endocrine [c]	86 (0.49)	12 (1.75)	45 (0.95)	10 (0.21)	15 (0.23)	4 (0.42)
Female Reproductive Organs [d]	74 (0.42)	3 (0.44)	41 (0.87)	10 (0.21)	19 (0.30)	1 (0.10)
Gallbladder	8673 (49.73)	15 (2.19)	1575 (33.33)	2715 (58.12)	3777 (59.00)	591 (61.76)
Hematopoeitic cancers [e]	26 (0.15)	5 (0.73)	19 (0.40)	1 (0.02)	1 (0.01)	0 (0.00)
Infectious etiology [f]	156 (0.89)	18 (2.62)	66 (1.40)	31 (0.66)	30 (0.47)	11 (1.15)
Liver [g]	350 (2.01)	5 (0.73)	59 (1.25)	97 (2.08)	169 (2.64)	20 (2.09)
Malignancy, other [h]	671 (3.85)	11 (1.60)	92 (1.95)	133 (2.85)	404 (6.31)	31 (3.24)
Neurologic [i]	45 (0.26)	5 (0.73)	32 (0.68)	1 (0.02)	5 (0.08)	2 (0.21)
Other Digestive Organs [j]	241 (1.38)	15 (2.19)	69 (1.46)	45 (0.96)	98 (1.53)	14 (1.46)
Pancreas, Other Biliary [k]	2432 (13.94)	25 (3.64)	415 (8.78)	790 (16.91)	1081 (16.89)	121 (12.64)
Prostate	16 (0.09)	3 (0.44)	8 (0.17)	3 (0.06)	1 (0.01)	1 (0.10)
Pulmonary [l]	169 (0.97)	21 (3.06)	81 (1.71)	30 (0.64)	31 (0.48)	6 (0.63)
Renal-Urinary Tract [m]	164 (0.94)	6 (0.87)	60 (1.27)	38 (0.81)	53 (0.83)	7 (0.73)
State Death Certificate or Cause of Death not available	294 (1.69)	11 (1.60)	86 (1.82)	91 (1.95)	93 (1.45)	13 (1.36)

a Accidents & Adverse Events: Include suicides, self-inflicted injuries, signs & symptoms of an ill-defined condition, other causes of death.

b Cardiovascular: Aortic aneurysm & dissection, atherosclerosis, cerebrovascular diseases, other diseases of arterioles, arteries and capillaries, diseases of the heart, hypertension.

c Endocrine: Diabetes, thyroid and Other endocrine including thymus.

d Female Reproductive Organs: Breast, Cervix, Uterus & Ovary

e Hematopoeitic cancers: Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Chronic Lymphocytic Leukemia, Other acute leukemia, Non-Hodgkins Leukemia, Myeloma.

f Infectious etiology: Pneumonia, influenza, sepsis, Other infectious and parasitic etiology including HIV

g Liver: Chronic liver disease including cirrhosis and other liver etiology.

h Malignancy, other: In-situ, benign, or unknown behavior neoplasm, melanoma, other malignancies.

i Neurologic: Related to Head, neck, throat, includes Alzheimers, Other brain and nervous system disorders, gum-oropharynx and larynx.

j Other digestive organs: esophagus, stomach, stomach and duodenal ulcers, colon, rectosigmoid, peritoneum, omentum, mesentery and small intestine.

k Pancreas & Other Biliary: pancreas, other biliary and intra-hepatic bile ducts

l Pulmonary: COPD and other allied conditions, lung, bronchus.

m Renal/Urinary Tract: Kidney, renal pelvis, nephritis/nephrotic syndrome, urinary bladder, urinary tract, and ureter

Appendix: Table A. Adapted from the 7th edition of the AJCC staging system for gallbladder cancer. [22]

Primary Tumor (T)	TX	No description of tumor extent due to incomplete information.	Stage Grouping			
	T0	No evidence of primary tumor.	Stage 0	Tis	N_0	M_0
	Tis	Carcinoma in-situ, confined to epithelium of gallbladder	Stage IA	T_1	N_0	M_0
	T_1	Invades lamina propria (1a) or muscle layer (muscularis – 1b)	Stage IB	T_2	N_0	M_0
	T_2	Invades perimuscular connective tissue; no extension beyond serosa or into the liver	Stage IIA	T_3	N_0	M_0
	T_3	Perforates serosa (visceral peritoneum) and/or directly invades the liver and/or one adjacent organ or structure, such as stomach, duodenum, pancreas, colon or extra-hepatic bile ducts	Stage IIB	T_1	N_1	M_0
	T_4	Invades main portal vein or hepatic artery/invades multiple extra-hepatic organs or structures.		T_2	N_1	M_0
Regional Lymph Nodes (N)	N_X	No regional lymph node metastasis				
	N_0	No regional lymph node metastasis		T_3	N_1	M_0
	N_1	Regional lymph node metastasis				
	N_2	Non-Regional lymph node metastasis				
Distant Metastases (M)	M_0	No distant metastasis	Stage III	T_4	Any N	M_0
	M_1	Distant Metastasis	Stage IV	Any T	Any N	M_1

APPENDIX TABLE 1. CARCINOMA IN-SITU. Demographic Characteristics of Patients With In-Situ Gallbladder Cancer cases by Decade (18 Surveillance, Epidemiology, and End Results Registries, 1973-2010)

Patient Characteristics	No. of Patients (%)				
	All Patients, N=686	1973-1982, N=67	1983-1992, N=118	1993-2002, N=198	2003-2010, N=303
Sex					
Male	214 (31.20)	25 (37.31)	29 (24.58)	56 (28.28)	104 (34.32)
Female	472 (68.80)	42 (62.69)	89 (75.42)	142 (71.72)	199 (65.68)
Race					
Non-Hispanic White	404 (58.89)	45 (67.16)	79 (66.95)	112 (56.57)	168 (55.45)
Non-Hispanic Black	48 (7.00)	5 (7.46)	7 (5.93)	16 (8.08)	20 (6.60)
Hispanic	150 (21.87)	9 (13.43)	17 (14.41)	50 (25.25)	74 (24.42)
Other[a]	84 (12.24)	8 (11.94)	15 (12.71)	20 (10.10)	41 (13.53)
Age, years					
<50	108 (15.74)	11 (16.42)	13 (11.02)	33 (16.67)	51 (16.83)
50-59	101 (14.72)	12 (17.91)	15 (12.71)	30 (15.15)	44 (14.52)
60-69	144 (20.99)	13 (19.40)	27 (22.88)	42 (21.21)	62 (20.46)
70-79	180 (26.24)	13 (19.40)	37 (31.36)	52 (26.26)	78 (25.74)
80+	153 (22.30)	18 (26.87)	26 (22.03)	41 (20.71)	68 (22.44)
Marital Status*					
Married	324 (49.77)	33 (50.77)	60 (54.54)	96 (50.79)	135 (47.04)
Single	83 (12.75)	3 (4.62)	7 (6.36)	22 (11.64)	51 (27.27)
Other[b]	244 (37.48)	29 (44.61)	43 (39.10)	71 (37.57)	101 (35.19)
Geographic Region					
Atlantic	112 (16.33)	9 (13.43)	14 (11.86)	25 (12.63)	64 (21.12)
Pacific/West	393 (57.29)	39 (58.21)	64 (54.24)	128 (64.65)	162 (53.47)
MidWest	125 (18.22)	17 (25.37)	33 (27.97)	27 (13.64)	48 (15.84)
South	56 (8.16)	2 (2.99)	7 (5.93)	18 (9.09)	29 (9.57)
Grade					
Well Differentiated	69 (10.06)	4 (5.97)	16 (13.56)	21 (10.61)	28 (9.24)
Moderately Differentiated	17 (2.47)	1 (1.49)	0 (0.00)	6 (3.03)	10 (3.30)
Poorly Differentiated	5 (0.73)	0 (0.00)	0 (0.00)	2 (1.01)	3 (0.99)
Undifferentiated	17 (2.47)	0 (0.00)	0 (0.00)	6 (3.03)	11 (3.63)
Unknown	578 (84.27)	62 (92.54)	102 (86.44)	163 (82.32)	251 (82.84)
Surgery					
Yes	445 (64.87)	67 (100.00)	117 (99.15)	197 (99.49)	64 (21.12)
No	241 (35.13)	0 (0.00)	1 (0.85)	1 (0.51)	239 (78.88)
Vital status					
Alive	378 (55.10)	16 (23.88)	32 (27.12)	94 (47.47)	236 (77.89)
Death due to Gallbladder Cancer	15 (2.19)	2 (2.99)	2 (1.69)	7 (3.54)	4 (1.32)
Death due to Pancreatic or Biliary cancer	25 (3.64)	4 (5.97)	4 (2.29)	9 (4.55)	8 (2.64)
Death due to Other causes	268 (39.07)	45 (67.16)	80 (67.80)	88 (44.44)	55 (18.15)

a Other races included Asian or Pacific Islander, American Indian, Alaska Native, or unspecified.

b Other Marital Status included Divorced, Widowed, Separated.

*** All unspecified or missing cases were excluded (N=651)**

APPENDIX TABLE 2. LOCALIZED. Demographic Characteristics of Patients With Localized Gallbladder Cancer cases by Decade (18 Surveillance, Epidemiology, and End Results Registries, 1973-2010)

Patient Characteristics	No. of Patients (%)				
	All Patients, N=4725	1973-1982, N=603	1983-1992, N=756	1993-2002, N=1426	2003-2010, N=1940
Sex					
Male	1250 (26.46)	141 (23.38)	208 (27.51)	369 (25.88)	532 (27.43)
Female	3475 (73.55)	462 (76.62)	548 (72.49)	1057 (74.12)	1408 (72.58)
Race					
Non-Hispanic White	2914 (61.67)	465 (77.11)	552 (73.02)	844 (59.19)	1053 (54.28)
Non-Hispanic Black	395 (8.36)	31 (5.14)	46 (6.08)	105 (7.36)	213 (10.98)
Hispanic	876 (18.54)	60 (9.95)	83 (10.98)	296 (2.08)	437 (22.53)
Other[a]	540 (11.43)	47 (7.79)	75 (9.92)	181 (12.69)	237 (12.22)
Age, years					
<50	296 (6.26)	29 (4.81)	27 (3.57)	103 (7.22)	137 (7.06)
50-59	55 (1.16)	64 (10.61)	88 (11.64)	162 (11.36)	241 (12.42)
60-69	1007 (21.31)	143 (23.71)	159 (21.03)	302 (21.18)	403 (20.77)
70-79	1429 (30.24)	194 (32.17)	250 (33.07)	432 (30.29)	553 (28.51)
80+	1438 (30.43)	173 (28.69)	232 (30.69)	427 (29.94)	606 (31.24)
Marital Status*					
Married	2195 (48.79)	267 (46.03)	341 (46.84)	681 (50.22)	906 (49.37)
Single	476 (10.58)	32 (5.52)	51 (7.01)	151 (11.14)	242 (13.19)
Other[b]	1828 (40.63)	281 (48.45)	336 (46.15)	524 (38.64)	687 (37.44)
Geographic Region					
Atlantic	767 (16.23)	99 (16.42)	97 (12.83)	213 (14.93)	358 (18.45)
Pacific/West	2425 (51.32)	255 (42.29)	356 (47.09)	791 (55.47)	1023 (52.73)
MidWest	1066 (22.56)	228 (37.81)	262 (34.66)	297 (20.83)	279 (14.83)
South	467 (9.88)	21 (3.48)	41 (5.42)	125 (8.77)	280 (14.43)
Grade					
Well Differentiated	964 (20.40)	130 (21.56)	181 (23.94)	259 (18.16)	394 (20.31)
Moderately Differentiated	1682 (35.60)	104 (17.25)	233 (30.82)	581 (40.74)	764 (39.38)
Poorly Differentiated	1064 (22.52)	97 (16.09)	147 (19.45)	370 (25.95)	450 (23.20)
Undifferentiated	79 (1.67)	11 (1.82)	14 (1.85)	24 (1.68)	30 (1.55)
Unknown	936 (19.81)	261 (43.28)	181 (23.94)	192 (13.47)	302 (15.56)
Surgery					
Yes	3282 (69.46)	598 (99.17)	748 (98.94)	1394 (97.76)	542 (27.94)
No	1443 (30.54)	5 (0.83)	8 (1.06)	32 (2.24)	1398 (72.06)
Vital status					
Alive	1299 (27.49)	20 (3.32)	58 (7.67)	288 (20.20)	933 (48.09)
Death due to Gallbladder Cancer	1575 (33.33)	267 (44.28)	302 (39.95)	527 (36.96)	479 (24.69)
Death due to Pancreatic or Biliary cancer	415 (8.78)	48 (7.96)	63 (8.33)	150 (10.52)	154 (7.94)
Death due to Other causes	1436 (30.40)	268 (44.44)	333 (44.05)	461 (32.32)	374 (19.28)

a Other races included Asian or Pacific Islander, American Indian, Alaska Native, or unspecified.

b Other Marital Status included Divorced, Widowed, Separated.

*** All unspecified or missing cases were excluded (N=4499)**

APPENDIX TABLE 3. REGIONAL. Demographic Characteristics of Patients With Regional Gallbladder Cancer cases by Decade (18 Surveillance, Epidemiology, and End Results Registries, 1973-2010)

Patient Characteristics	No. of Patients (%)				
	All Patients, N=4671	1973-1982, N=880	1983-1992, N=849	1993-2002, N=1464	2003-2010, N=1478
Sex					
Male	1324 (28.35)	241 (27.39)	210 (24.73)	423 (28.89)	450 (30.45)
Female	3347 (71.65)	639 (72.61)	639 (75.27)	1041 (71.11)	1028 (69.55)
Race					
Non-Hispanic White	3018 (64.61)	717 (81.48)	592 (69.73)	851 (58.13)	858 (58.05)
Non-Hispanic Black	368 (7.88)	38 (4.32)	45 (5.30)	117 (7.99)	168 (11.37)
Hispanic	802 (17.17)	74 (8.41)	100 (11.78)	319 (21.79)	309 (20.91)
Other[a]	483 (10.34)	51 (5.79)	112 (13.19)	177 (12.09)	143 (9.68)
Age, years					
<50	282 (6.04)	23 (2.61)	45 (5.30)	115 (7.86)	99 (6.70)
50-59	630 (13.49)	112 (12.73)	94 (11.07)	186 (12.70)	238 (16.10)
60-69	1079 (23.10)	215 (24.43)	201 (23.67)	311 (21.24)	352 (23.82)
70-79	1516 (32.46)	301 (34.20)	292 (34.39)	514 (35.11)	409 (27.67)
80+	1164 (24.92)	229 (26.02)	217 (25.56)	338 (23.09)	380 (25.71)
Marital Status*					
Married	1164 (33.50)	229 (33.14)	217 (33.65)	338 (32.19)	380 (34.90)
Single	468 (13.47)	65 (9.41)	58 (8.99)	169 (16.10)	176 (16.16)
Other[b]	1843 (53.03)	397 (57.45)	370 (57.36)	543 (51.71)	533 (48.94)
Geographic Region					
Atlantic	787 (16.85)	172 (19.55)	115 (13.55)	218 (14.89)	282 (19.08)
Pacific/West	2460 (52.67)	355 (40.34)	451 (53.12)	884 (60.38)	770 (52.10)
MidWest	1029 (22.03)	326 (37.05)	252 (29.68)	230 (15.71)	221 (14.96)
South	395 (8.46)	27 (3.06)	31 (3.65)	132 (9.02)	205 (13.87)
Grade					
Well Differentiated	374 (8.00)	82 (9.32)	72 (8.48)	114 (7.78)	106 (7.17)
Moderately Differentiated	1192 (25.52)	118 (13.41)	229 (26.97)	397 (27.12)	448 (30.31)
Poorly Differentiated	1633 (34.96)	213 (24.20)	300 (35.34)	569 (38.87)	551 (37.28)
Undifferentiated	147 (3.15)	43 (4.89)	25 (2.94)	43 (2.94)	36 (2.44)
Unknown	1325 (28.37)	424 (48.18)	223 (26.27)	341 (23.29)	337 (22.80)
Surgery					
Yes	3371 (72.17)	867 (98.52)	781 (91.99)	1071 (73.16)	652 (44.11)
No	1300 (27.83)	13 (1.48)	68 (8.01)	393 (26.84)	826 (55.89)
Vital status					
Alive	379 (8.11)	3 (0.34)	19 (2.24)	77 (5.26)	280 (18.94)
Death due to Gallbladder Cancer	2715 (58.12)	646 (73.41)	553 (65.13)	859 (58.67)	657 (44.45)
Death due to Pancreatic or Biliary cancer	790 (16.91)	107 (12.16)	144 (16.96)	251 (17.14)	288 (19.49)
Death due to Other causes	787 (16.85)	124 (14.09)	133 (15.67)	277 (18.92)	253 (17.12)

a Other races included Asian or Pacific Islander, American Indian, Alaska Native, or unspecified.

b Other Marital Status included Divorced, Widowed, Separated.

*** All unspecified or missing cases were excluded (N=3475)**

APPENDIX TABLE 4. DISTANT. Demographic Characteristics of Patients With Distant Gallbladder Cancer cases by Decade (18 Surveillance, Epidemiology, and End Results Registries, 1973-2010)

Patient Characteristics	No. of Patients (%)				
	All Patients, N=6402	1973-1982, N=1091	1983-1992, N=1057	1993-2002, N=1598	2003-2010, N=2656
Sex					
Male	1790 (27.96)	310 (28.41)	285 (26.96)	423 (26.47)	772 (29.07)
Female	4612 (72.04)	781 (71.59)	772 (73.04)	1175 (73.53)	1884 (70.93)
Race					
Non-Hispanic White	4109 (64.18)	870 (79.74)	813 (76.92)	950 (59.45)	1476 (55.57)
Non-Hispanic Black	604 (9.43)	51 (4.67)	73 (6.91)	157 (9.82)	323 (12.16)
Hispanic	1061 (16.57)	88 (8.07)	83 (7.85)	329 (20.59)	561 (21.12)
Other[a]	628 (9.81)	82 (7.52)	88 (8.32)	162 (10.14)	296 (11.15)
Age, years					
<50	446 (6.97)	39 (3.57)	40 (3.78)	129 (8.07)	238 (8.96)
50-59	907 (14.17)	119 (10.91)	120 (11.35)	210 (13.14)	458 (17.24)
60-69	1611 (25.16)	274 (25.11)	273 (25.83)	397 (24.84)	667 (25.12)
70-79	1967 (30.72)	387 (35.47)	366 (34.63)	503 (31.48)	711 (26.77)
80+	1471 (22.98)	272 (24.93)	258 (24.41)	359 (22.47)	582 (21.91)
Marital Status*					
Married	1471 (21.08)	272 (21.60)	258 (21.59)	359 (21.01)	582 (20.67)
Single	3093 (44.32)	501 (39.80)	502 (42.01)	740 (43.30)	1350 (47.94)
Other[b]	2415 (34.60)	486 (38.60)	435 (36.40)	610 (35.69)	884 (31.39)
Geographic Region					
Atlantic	1054 (16.46)	175 (16.04)	169 (15.99)	197 (12.33)	513 (19.31)
Pacific/West	3271 (51.09)	453 (41.52)	424 (40.11)	947 (59.26)	1447 (54.48)
MidWest	1574 (24.59)	439 (40.24)	423 (40.02)	349 (21.84)	363 (13.67)
South	503 (7.86)	24 (2.20)	41 (3.88)	105 (6.57)	333 (12.54)
Grade					
Well Differentiated	315 (4.92)	83 (7.61)	70 (6.62)	64 (4.01)	98 (3.69)
Moderately Differentiated	1141 (17.82)	107 (9.81)	214 (20.25)	323 (20.21)	497 (18.71)
Poorly Differentiated	1971 (30.79)	245 (22.46)	354 (33.49)	578 (36.17)	794 (29.90)
Undifferentiated	237 (3.70)	69 (6.32)	45 (4.26)	56 (3.50)	67 (2.52)
Unknown	2738 (42.77)	587 (53.80)	374 (35.38)	577 (36.11)	1200 (45.18)
Surgery					
Yes	3298 (51.51)	1050 (96.24)	914 (86.47)	830 (51.94)	504 (18.98)
No	3104 (48.49)	41 (3.76)	143 (13.53)	768 (48.06)	2152 (81.02)
Vital status					
Alive	384 (6.00)	0 (0.00)	9 (0.85)	37 (2.32)	338 (12.72)
Death due to Gallbladder Cancer	3777 (59.00)	768 (70.40)	722 (68.31)	966 (60.45)	1321 (49.74)
Death due to Pancreatic or Biliary cancer	1081 (16.89)	105 (9.62)	130 (12.30)	283 (17.71)	563 (21.20)
Death due to Other causes	1160 (18.11)	218 (19.98)	196 (18.54)	312 (19.52)	434 (16.34)

a Other races included Asian or Pacific Islander, American Indian, Alaska Native, or unspecified.

b Other Marital Status included Divorced, Widowed, Separated.

*** All unspecified or missing cases were excluded (N=6979)**

APPENDIX TABLE 5. UNSTAGED. Demographic Characteristics of Patients With Distant Gallbladder Cancer cases by Decade (18 Surveillance, Epidemiology, and End Results Registries, 1973-2010)

Patient Characteristics	No. of Patients (%)				
	All Patients, N=957	1973-1982, N=166	1983-1992, N=149	1993-2002, N=293	2003-2010, N=349
Sex					
Male	321 (33.54)	55 (33.13)	46 (30.87)	106 (36.18)	114 (32.66)
Female	636 (66.46)	111 (66.87)	103 (69.13)	187 (63.82)	235 (67.34)
Race					
Non-Hispanic White	655 (68.44)	134 (80.72)	113 (75.84)	178 (60.75)	230 (65.90)
Non-Hispanic Black	82 (8.57)	4 (2.41)	12 (8.05)	27 (9.21)	39 (11.17)
Hispanic	117 (12.23)	21 (12.65)	11 (7.38)	44 (15.02)	41 (11.76)
Other[a]	103 (10.76)	7 (4.22)	13 (8.73)	44 (15.02)	39 (11.17)
Age, years					
<50	29 (3.03)	3 (1.81)	5 (3.36)	10 (3.41)	11 (3.15)
50-59	85 (8.88)	18 (10.84)	8 (5.37)	21 (7.17)	38 (10.89)
60-69	163 (17.03)	30 (18.07)	29 (19.46)	49 (16.72)	55 (15.76)
70-79	243 (25.40)	56 (33.74)	40 (26.84)	75 (25.60)	72 (20.63)
80+	437 (45.66)	59 (35.54)	67 (44.97)	138 (47.10)	173 (49.67)
Marital Status*					
Married	331 (37.40)	66 (42.04)	51 (35.66)	100 (38.02)	114 (35.40)
Single	96 (10.85)	11 (7.01)	14 (9.79)	25 (9.51)	46 (14.29)
Other[b]	458 (51.75)	80 (50.95)	78 (54.55)	138 (52.47)	162 (50.31)
Geographic Region					
Atlantic	215 (22.47)	19 (11.45)	39 (26.17)	67 (22.87)	90 (25.79)
Pacific/West	452 (47.23)	82 (49.40)	55 (36.92)	158 (36.92)	157 (44.98)
MidWest	214 (22.36)	63 (37.95)	51 (34.23)	47 (34.23)	53 (15.19)
South	76 (7.94)	2 (1.20)	4 (2.68)	21 (2.68)	49 (14.04)
Grade					
Well Differentiated	25 (2.61)	5 (3.01)	7 (4.70)	8 (2.73)	5 (1.43)
Moderately Differentiated	44 (4.60)	11 (6.63)	11 (7.38)	9 (3.07)	13 (3.73)
Poorly Differentiated	80 (8.36)	20 (12.05)	18 (12.08)	25 (8.54)	17 (4.87)
Undifferentiated	9 (0.94)	4 (2.41)	3 (2.01)	2 (0.68)	0 (0.00)
Unknown	799 (83.49)	126 (75.90)	110 (73.83)	249 (84.98)	314 (89.97)
Surgery					
Yes	501 (52.35)	164 (98.80)	114 (76.51)	129 (44.03)	94 (26.93)
No	456 (47.65)	2 (1.20)	35 (23.49)	164 (55.97)	255 (73.07)
Vital status					
Alive	50 (5.22)	2 (1.20)	1 (0.67)	15 (5.12)	32 (9.17)
Death due to Gallbladder Cancer	591 (61.76)	120 (72.30)	99 (66.44)	169 (57.68)	203 (58.17)
Death due to Pancreatic or Biliary cancer	121 (12.64)	10 (6.02)	15 (10.07)	42 (14.33)	54 (15.47)
Death due to Other causes	195 (20.38)	34 (20.48)	34 (22.82)	67 (22.87)	60 (17.19)

a Other races included Asian or Pacific Islander, American Indian, Alaska Native, or unspecified.

b Other Marital Status included Divorced, Widowed, Separated.

*** All unspecified or missing cases were excluded (N=885)**

Appendix: Table 6. The Histopathologic characteristics of Gallbladder Tumors for each Stage by Year of Diagnosis

Stage: In-Situ	No. of Patients (%)				
Histopathologic Characteristics	All Patients, N=686	1973-1982, N=67	1983-1992, N=118	1993-2002, N=198	2003-2010, N=303
Non-papillary features [a]	535 (77.99)	60 (89.55)	92 (77.97)	167 (84.34)	216 (71.29)
Papillary features [b]	148 (21.57)	7 (10.45)	26 (22.03)	29 (14.65)	86 (28.38)
Squamous features [c]	2 (0.29)	0 (0.00)	0 (0.00)	2 (1.01)	0 (0.00)
Neuroendocrine features [d]	1 (0.15)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)
Other [e]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Stage: Localized	**No. of Patients (%)**				
Histopathologic Characteristics	All Patients, N=4725	1973-1982, N=603	1983-1992, N=756	1993-2002, N=1426	2003-2010, N=1940
Non-papillary features [a]	3871 (81.93)	477 (79.10)	631 (83.47)	1193 (83.66)	1570 (80.93)
Papillary features [b]	582 (12.32)	101 (16.75)	87 (11.51)	152 (10.66)	242 (12.47)
Squamous features [c]	258 (5.46)	22 (3.65)	33 (4.37)	36 (2.52)	52 (2.68)
Neuroendocrine features [d]	101 (2.14)	0 (0.00)	2 (0.26)	37 (2.59)	62 (3.20)
Other [e]	28 (0.59)	3 (0.50)	3 (0.40)	8 (0.56)	14 (0.72)
Stage: Regional	**No. of Patients (%)**				
Histopathologic Characteristics	All Patients, N=4671	1973-1982, N=880	1983-1992, N=849	1993-2002, N=1464	2003-2010, N=1478
Non-papillary features [a]	4161 (89.08)	793 (90.11)	763 (89.87)	1294 (88.39)	1311 (88.70)
Papillary features [b]	125 (2.68)	24 (2.73)	25 (2.94)	41 (2.80)	35 (2.37)
Squamous features [c]	143 (3.06)	53 (6.02)	52 (6.12)	81 (5.53)	72 (4.87)
Neuroendocrine features [d]	66 (1.41)	4 (0.45)	5 (0.59)	21 (1.43)	36 (2.44)
Other [e]	61 (1.31)	6 (0.68)	4 (0.47)	27 (1.84)	24 (1.62)
Stage: Distant	**No. of Patients (%)**				
Histopathologic Characteristics	All Patients, N=6402	1973-1982, N=1145	1983-1992, N=1057	1993-2002, N=1598	2003-2010, N=2656
Non-papillary features [a]	5827 (91.02)	1006 (87.86)	973 (92.05)	1462 (91.49)	2386 (89.83)
Papillary features [b]	116 (1.81)	28 (2.45)	23 (2.18)	23 (1.44)	42 (1.58)
Squamous features [c]	231 (3.61)	42 (3.67)	39 (3.69)	60 (3.75)	90 (3.39)
Neuroendocrine features [d]	101 (1.58)	6 (0.52)	10 (0.95)	19 (1.19)	66 (2.48)
Other [e]	127 (1.98)	9 (0.79)	12 (1.14)	34 (2.13)	72 (2.71)
Stage: Unstaged	**No. of Patients (%)**				
Histopathologic Characteristics	All Patients, N=957	1973-1982, N=166	1983-1992, N=149	1993-2002, N=293	2003-2010, N=367
Non-papillary features [a]	672 (70.23)	146 (87.95)	128 (85.91)	205 (69.97)	193 (52.59)
Papillary features [b]	5 (0.52)	1 (0.60)	3 (2.01)	1 (0.34)	0 (0.00)
Squamous features [c]	23 (2.40)	9 (5.42)	4 (2.68)	8 (2.73)	2 (0.54)
Neuroendocrine features [d]	9 (0.94)	1 (0.60)	3 (2.01)	1 (0.34)	4 (1.09)
Other [e]	248 (25.91)	9 (5.42)	11 (7.38)	78 (26.62)	150 (40.87)

a Non-papillary: Adenocarcinoma, Carcinoma NOS with non-papillary features

b Papillary: Carcinoma arising from pre-invasive lesions, adenoma, with papillary features

c Squamous: Squamous cell carcinoma and adenosquamous carcinomas

d Neuroendocrine tumors

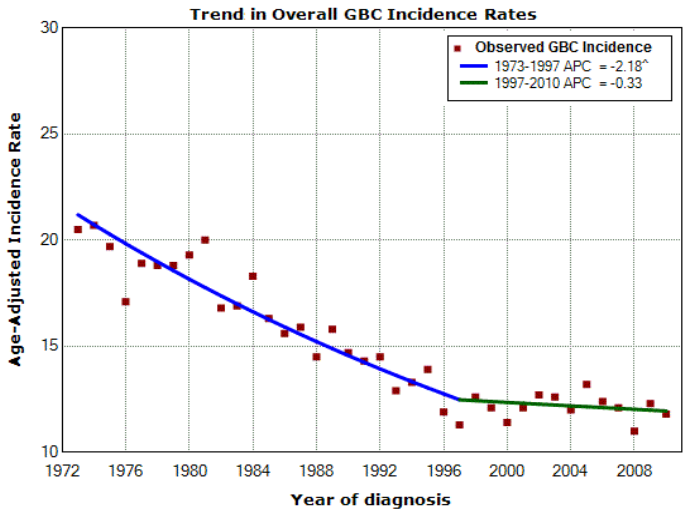
e Other: other malignant carcinomas and sarcomas

Appendix, Table 7. Cox Multivariate Regression parameters for GBC In-situ Cases (1973-2010)

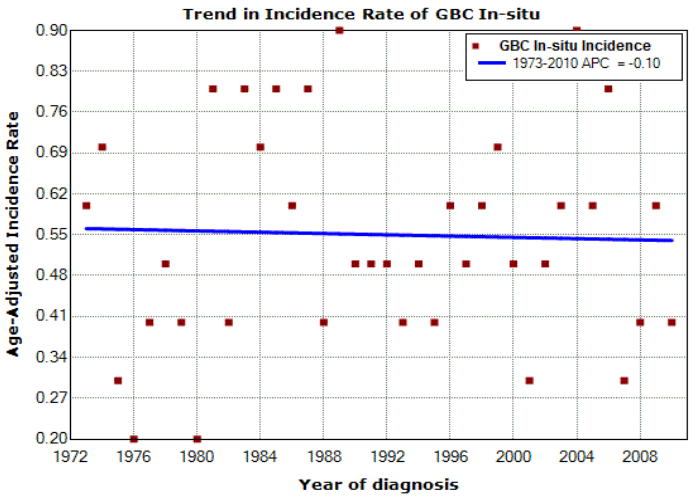
Covariate		Hazard Ratio (HR)	95% CI for HR Lower	Upper
10-Year survival regression parameters				
Age[a]				
	50-59	2	0.84	4.76
	60-69	4.39	1.06	9.37
	70-79	8.51	4.11	17.61
	80+	14	6.79	28.89
Female Sex[b]		0.71	0.54	0.92
Papillary (Tumoral) Histology[c]		0.95	0.67	1.34
5-Year survival regression parameters				
Age[a]				
	50-59	2.7	0.02	8.6
	60-69	5.47	0.09	15.65
	70-79	10.79	0.22	29.67
	80+	15.84	5.77	43.5
Female Sex[b]		0.7	0.51	0.96
Papillary (Tumoral) Histology[c]		0.84	0.57	1.27

Reference groups:
a: Ages <50 years
b: Male sex
c: Non-papillary (flat) histology

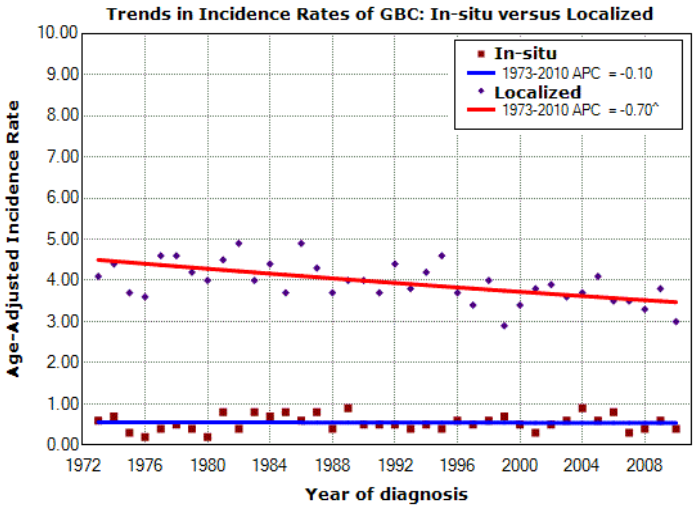
Appendix: Figure 1 (A-F). Trends in Observed Incidence of GBC Tumors by Stage (1973-2010)



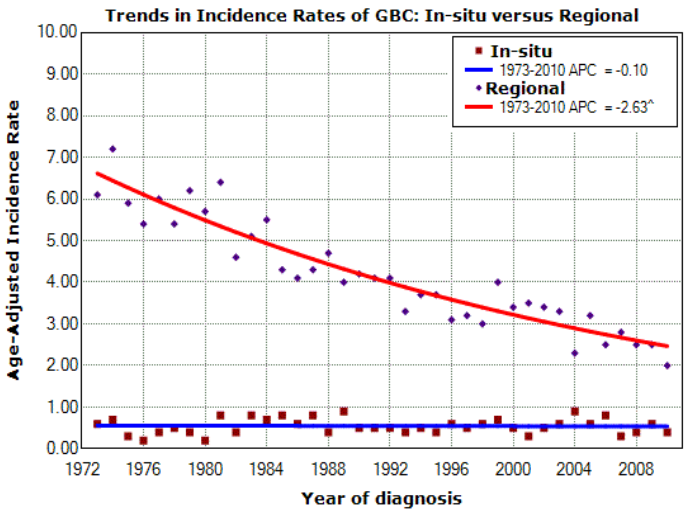
A. Trends in Overall GBC Incidence



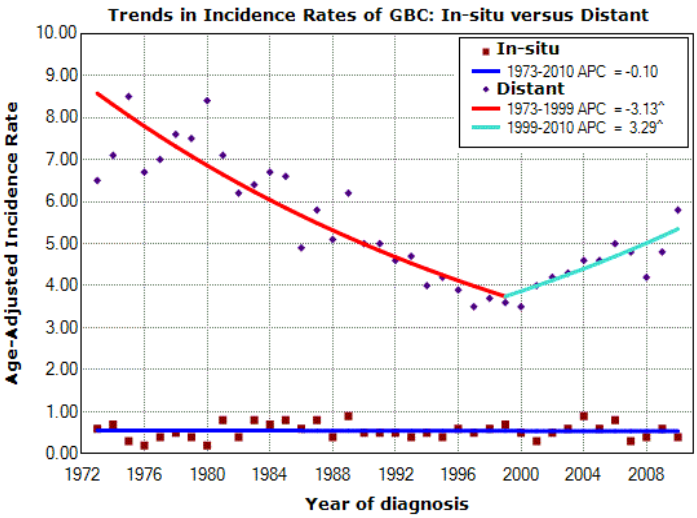
B. Trends in Overall GB-CIS Incidence



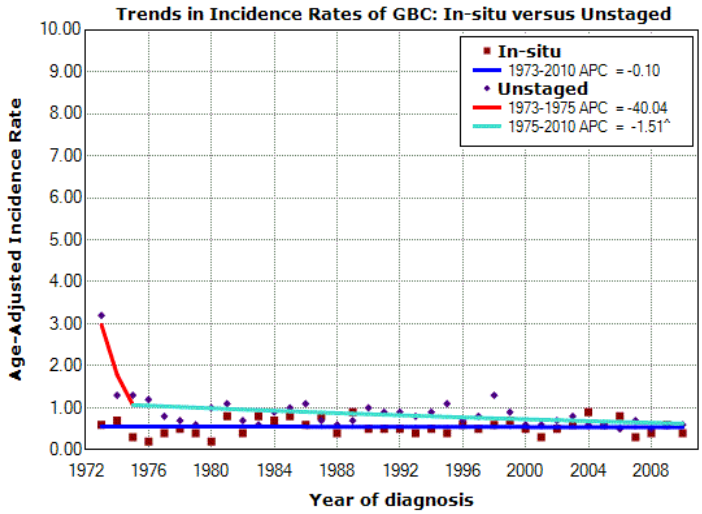
C. Trends in Overall GB-CIS and Localized stages



D. Trends in Overall GB-CIS and Regional stages

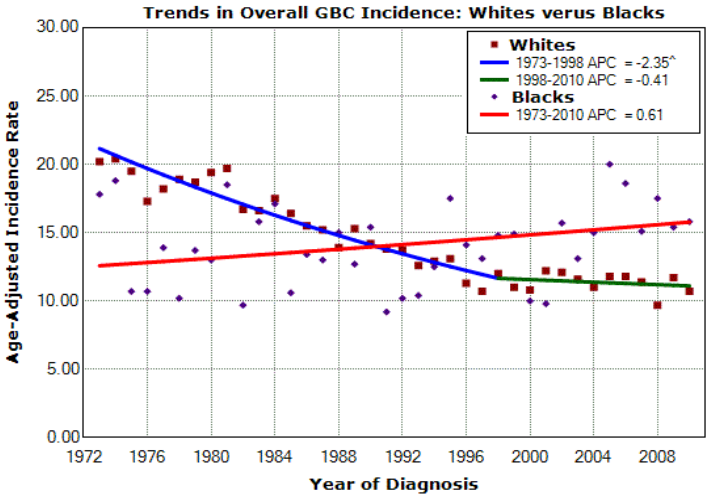


E. Trends in Overall GB-CIS and Distant stages

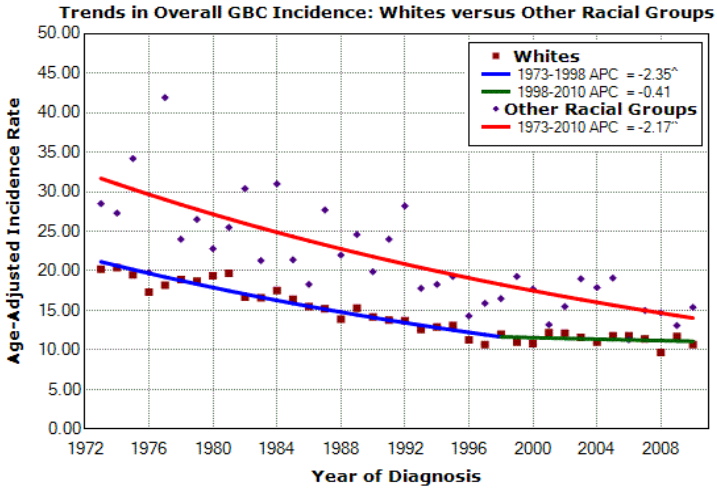


F. Trends in Overall Unstaged and GB-CIS stages

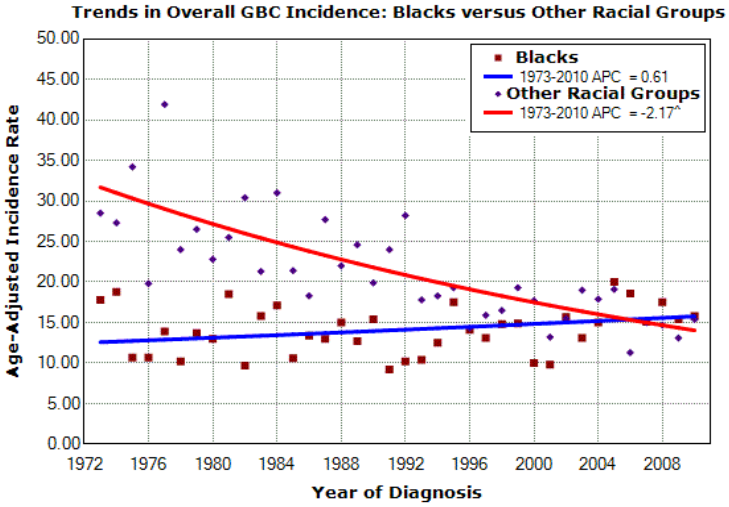
Appendix: Figure 2 (A-F). Trends in Observed Incidence of GBC Tumors by Race & Gender (1973-2010)



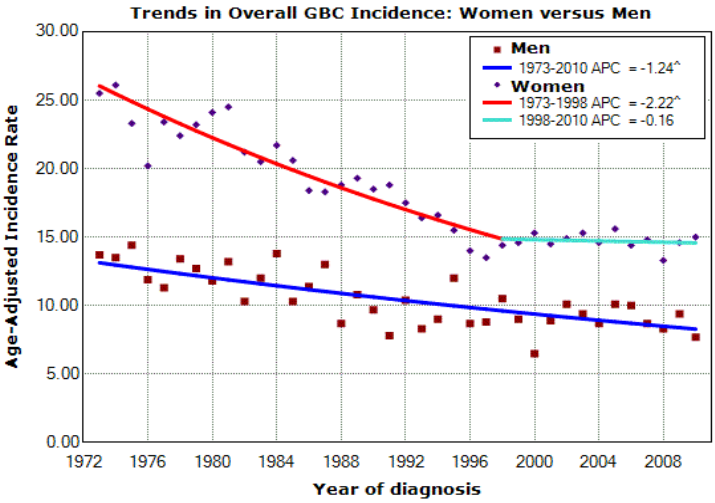
A. GBC Incidence among Whites vs. Blacks



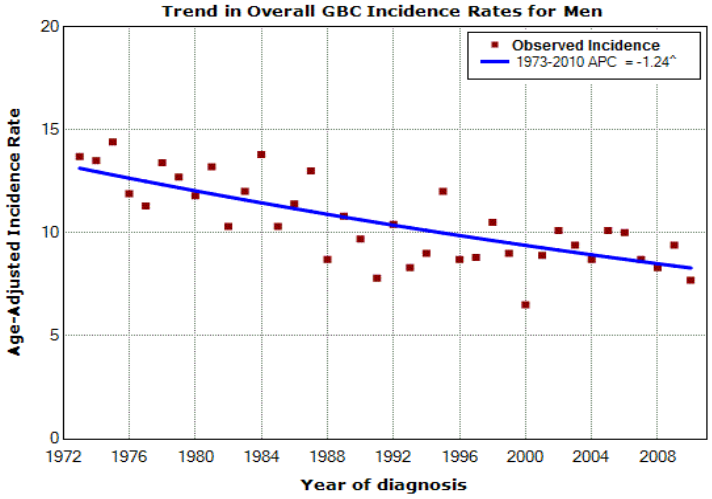
B. GBC Incidence among Whites vs. Other groups



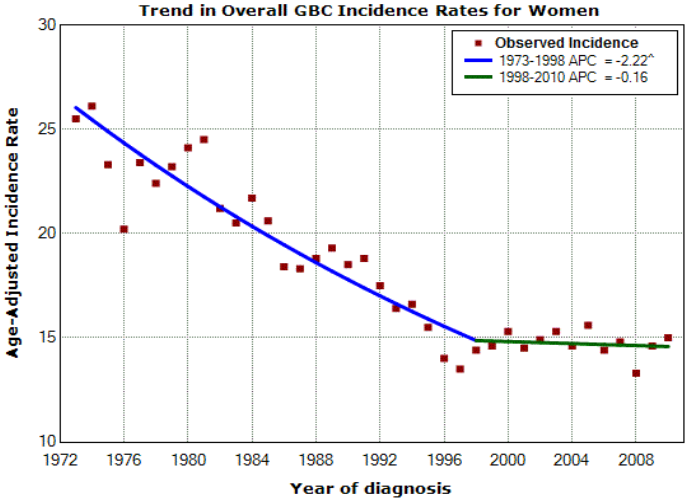
C. GBC Incidence among Blacks vs. Other groups



D. GBC Incidence by Gender groups

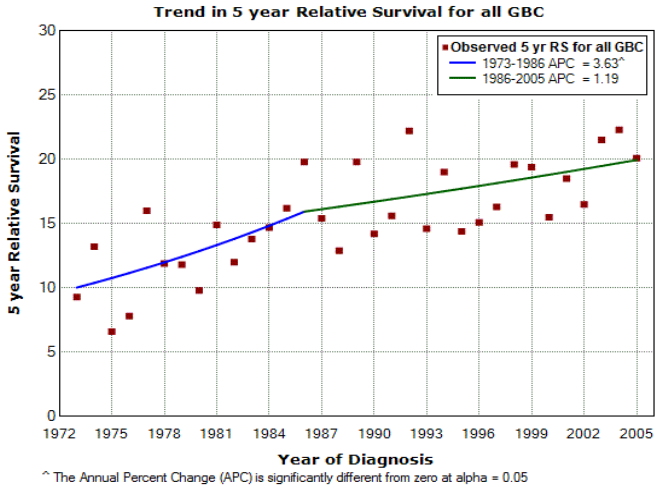


E. Overall GBC Incidence of men

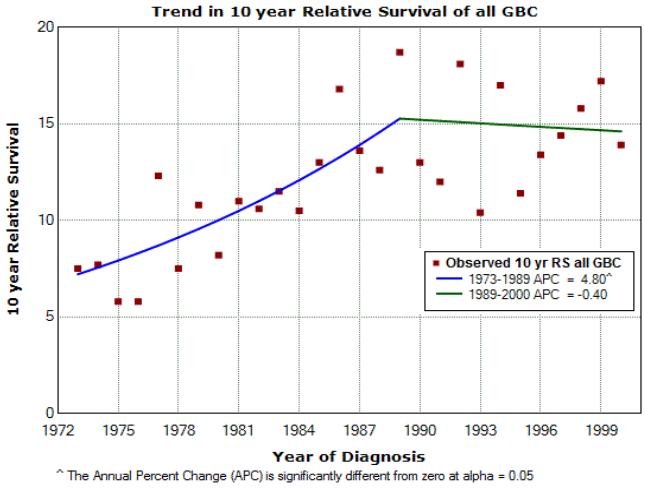


F. Overall GBC Incidence of women

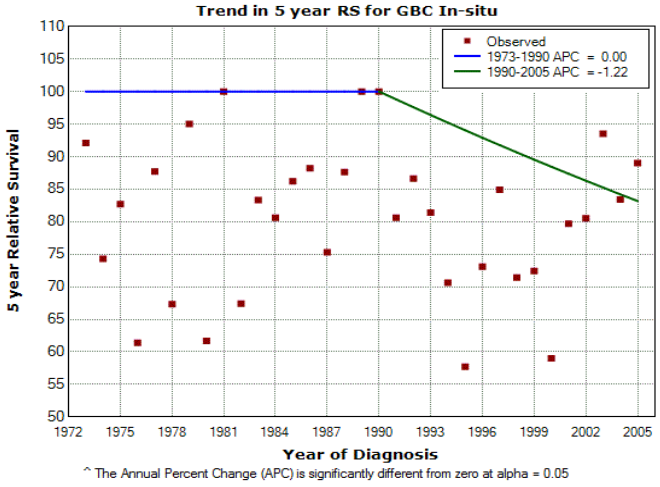
Appendix: Figure 3 (A-F). Trends in 5 and 10-year Relative Survival (RS) for all GBC and GB-CIS Tumors (1973-2010)



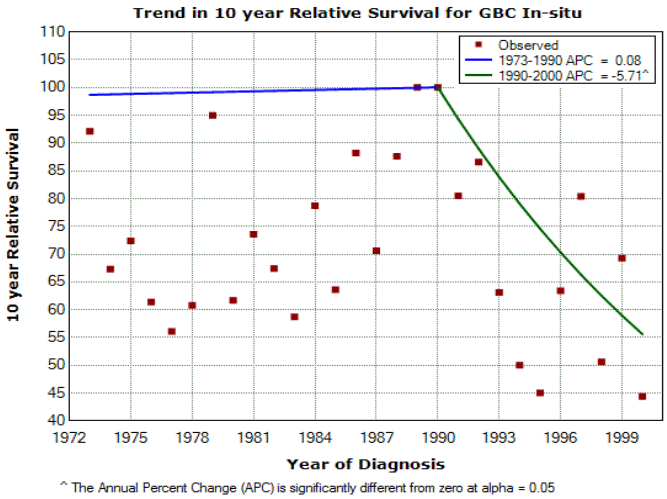
A. 5-year RS for all GBC Tumors



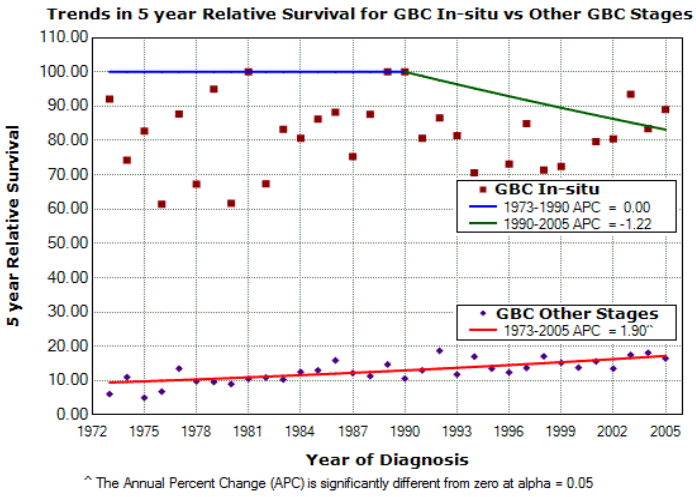
B. 10-year RS for all GBC Tumors



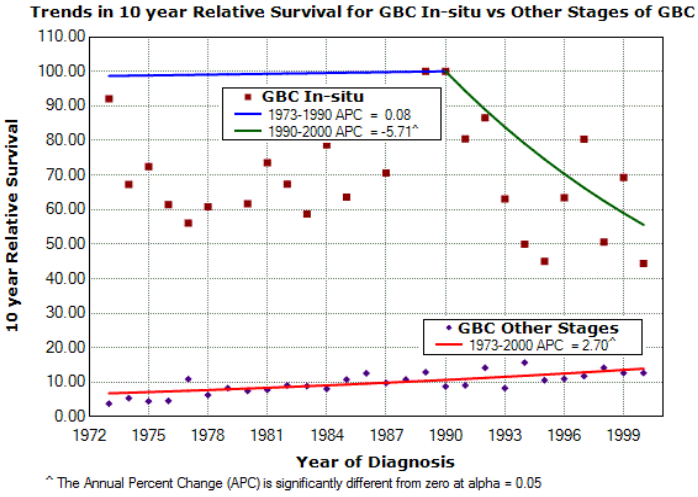
C. 5-year RS for GB-CIS Tumors



D. 10-year RS for GB-CIS Tumors

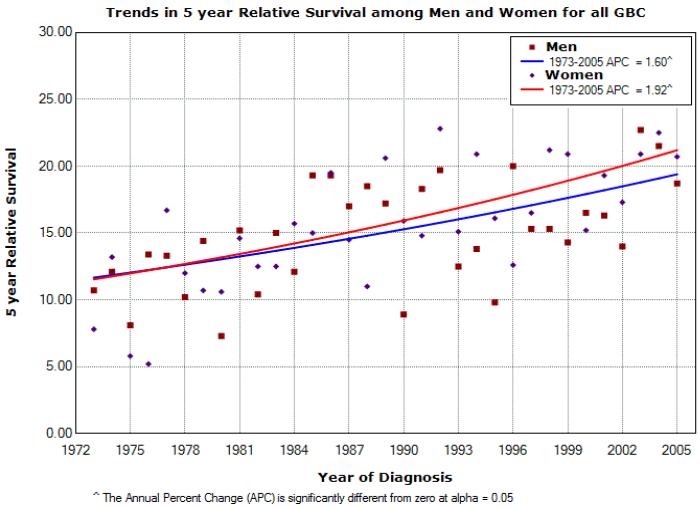


E. 5-year RS for GB and GB-CIS Tumors

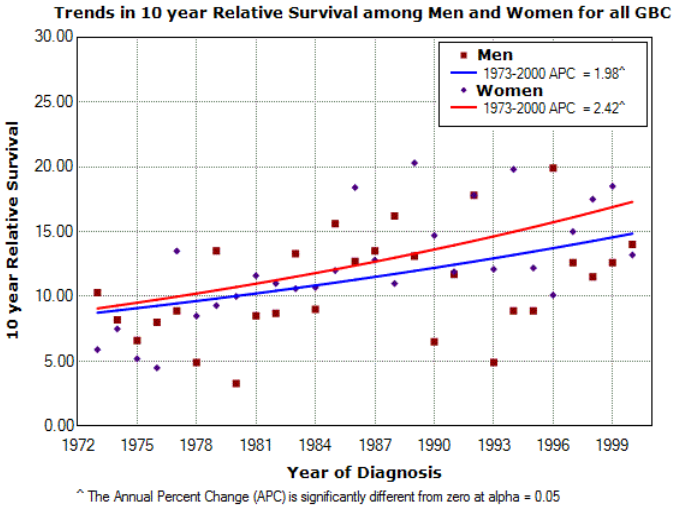


F. 10-year RS for GB and GB-CIS Tumors

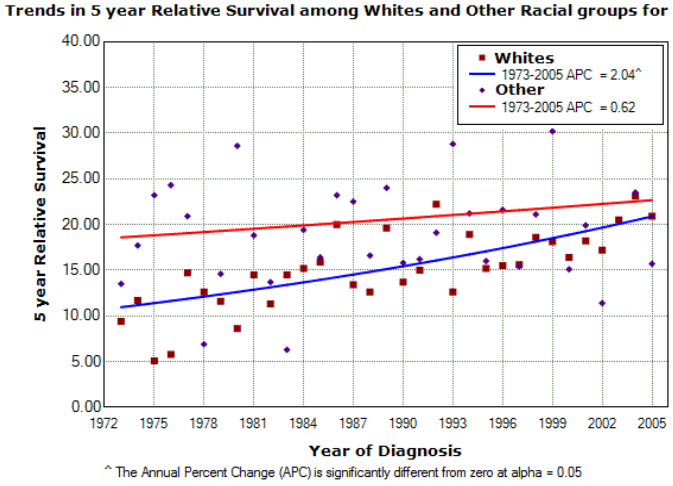
Appendix: Figure 4 (A-F). Trends in 5 & 10-year Relative Survival (RS) of GBC by Gender & Race/ethnicity (1973-2010)



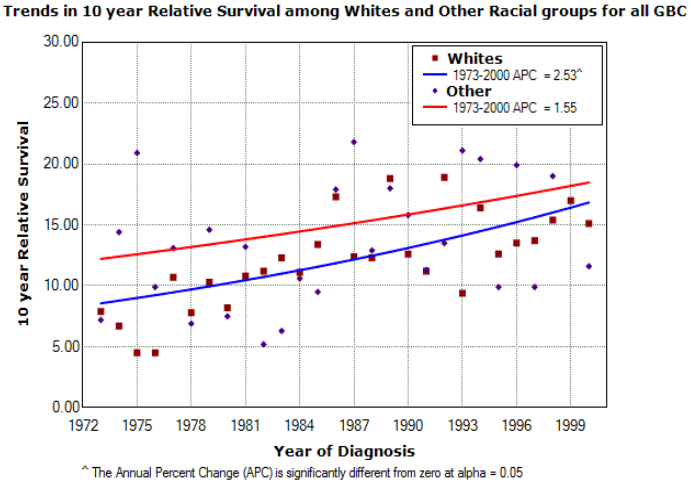
A. Trends in 5-year Relative Survival by Gender



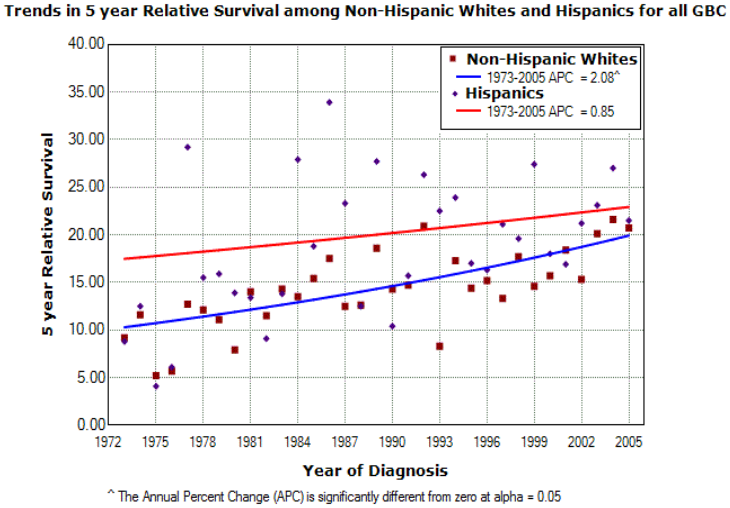
B. Trends in 10-year Relative Survival by Gender



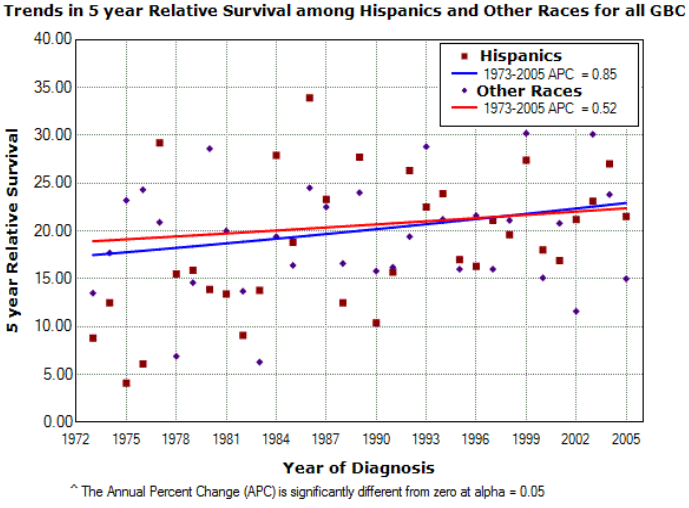
C. Trends in 5-year RS for Whites & Other Races



D. Trends in 10-year RS for Whites & Other Races

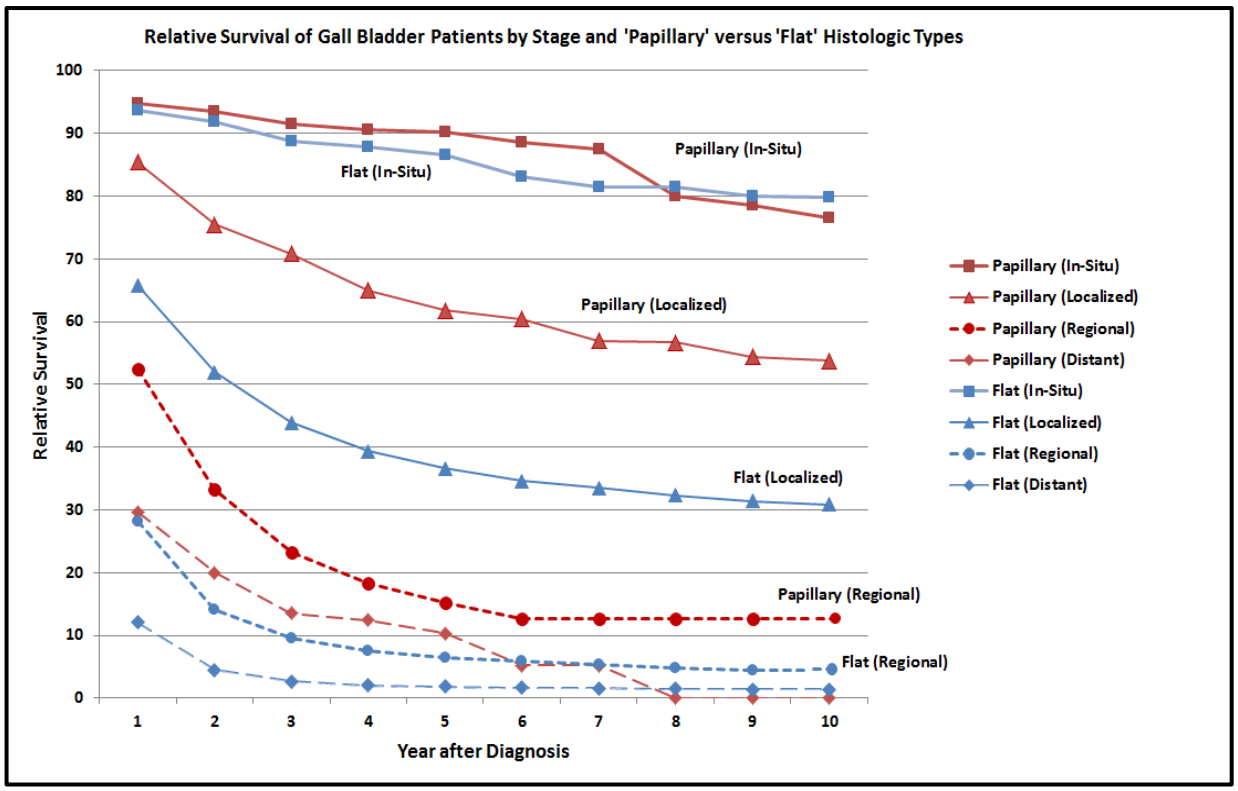


E. Trends in 5-yr RS: Non-Hispanic Whites & Other Races



F. Trends in 10-yr RS: Non-Hispanic Whites & Other Races

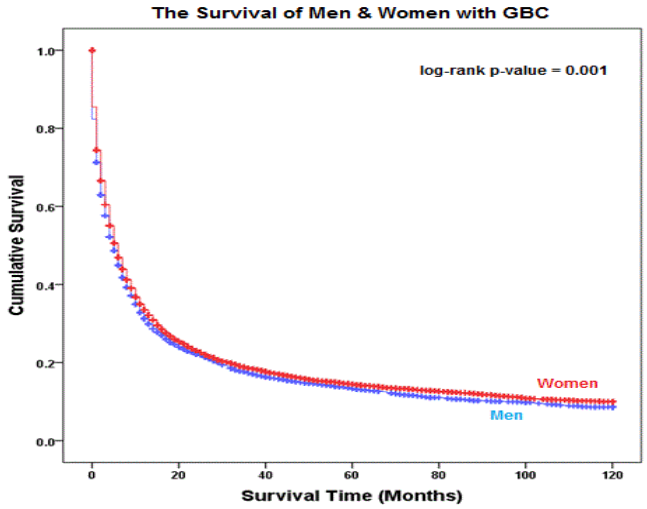
Appendix: Figure 5, Relative Survival of GBC cases by Histologic Types and Stage at Diagnosis.



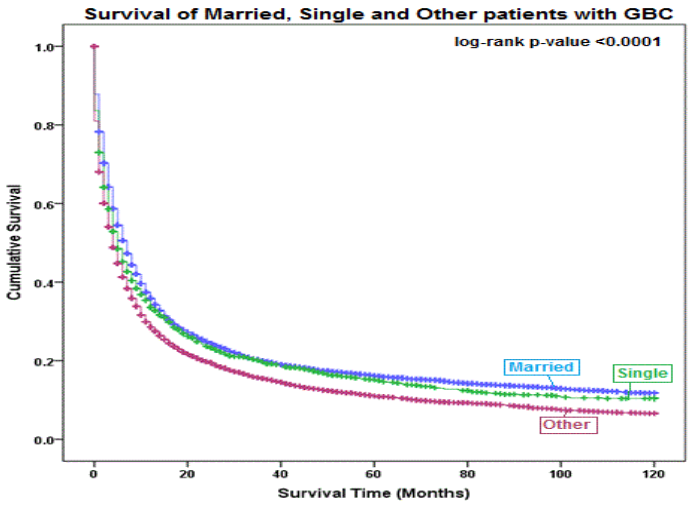
Relative Survival of GBC by Histology and Stage

	1yr (%)	2yr (%)	3yr (%)	4yr (%)	5yr (%)	6yr(%)	7 yr(%)	8yr (%)	9yr (%)	10yr (%)
Papillary (In-Situ)	94.8	93.5	91.4	90.6	90.3	88.6	87.4	80	78.5	76.6
Papillary (Localized)	85.4	75.5	70.8	65	61.8	60.4	57	56.7	54.4	53.8
Papillary (Regional)	52.5	33.3	23.2	18.3	15.2	12.7	12.7	12.7	12.7	12.7
Papillary (Distant)	29.7	20	13.5	12.4	10.3	5.2	5.2	0	0	0
Flat (In-Situ)	93.7	91.9	88.7	87.8	86.6	83.1	81.5	81.5	80	79.8
Flat (Localized)	65.8	51.9	43.9	39.3	36.6	34.6	33.5	32.3	31.4	30.9
Flat (Regional)	28.2	14.2	9.5	7.5	6.5	5.9	5.3	4.8	4.4	4.4
Flat (Distant)	12.1	4.5	2.7	2	1.8	1.7	1.6	1.5	1.4	1.4

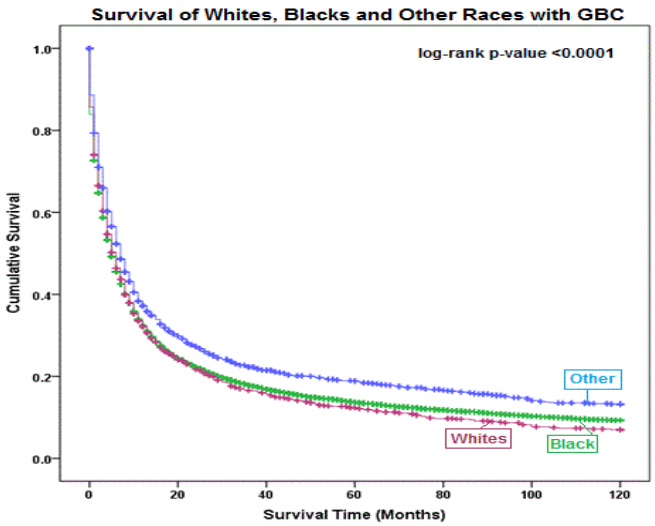
Appendix: Figure 6 (A-F). K-M Survival Curves for patients with GBC by Demographic characteristics



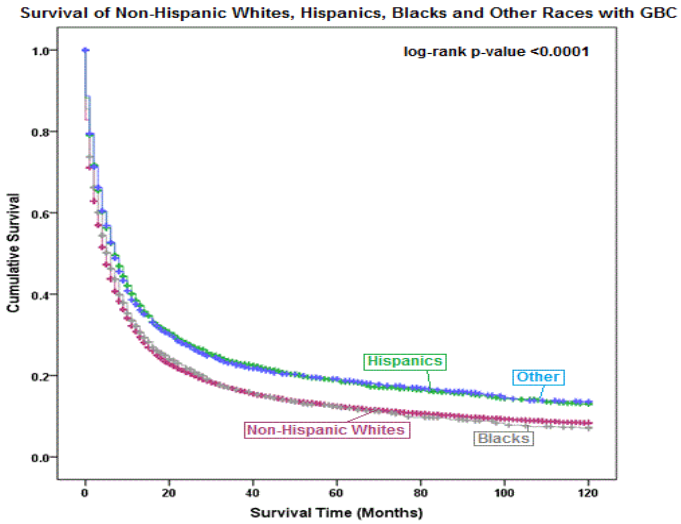
A. K-M Survival by Gender



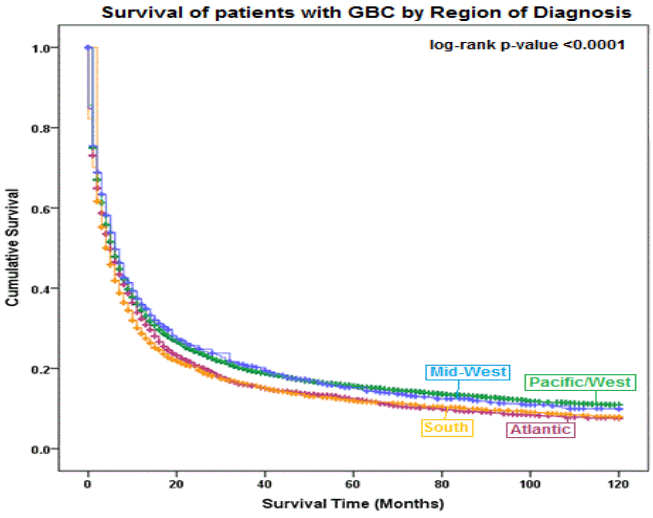
B. K-M Survival by Marital Status



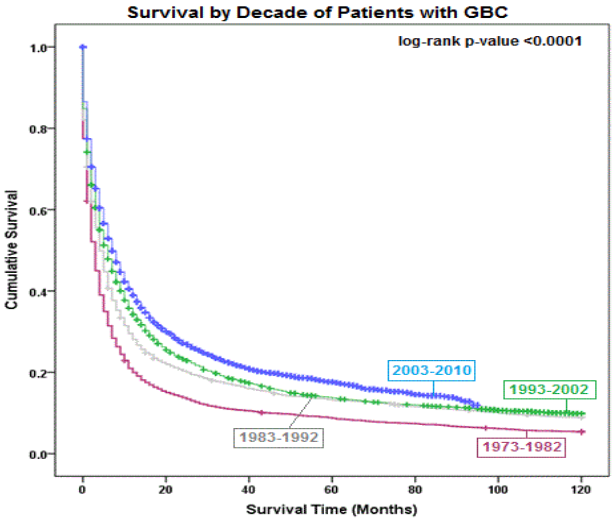
C. K-M Survival by Race



D. K-M Survival by Racio-ethnic groups

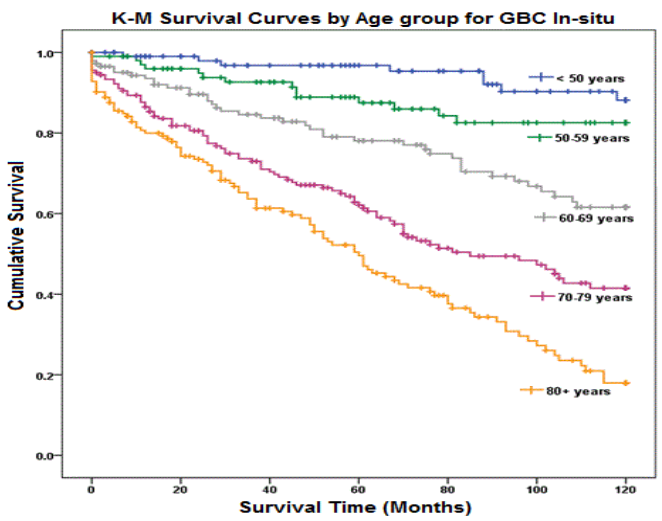


E. K-M Survival by Region of Diagnosis

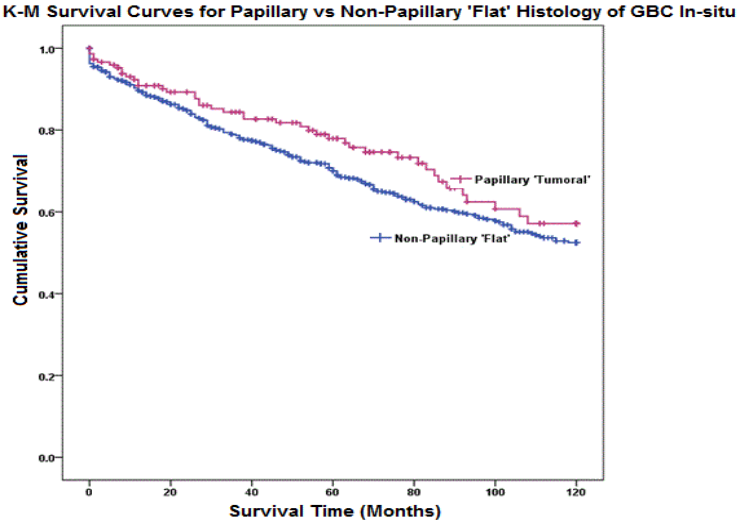


F. K-M Survival by Period of Diagnosis

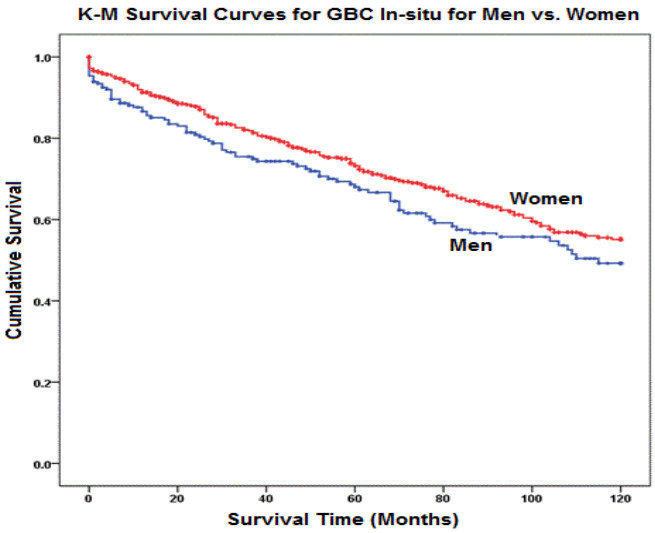
Appendix, Figure 7 (A-F). Kaplan-Meier (K-M) Survival Curves for GB-CIS cases (1973-2010)



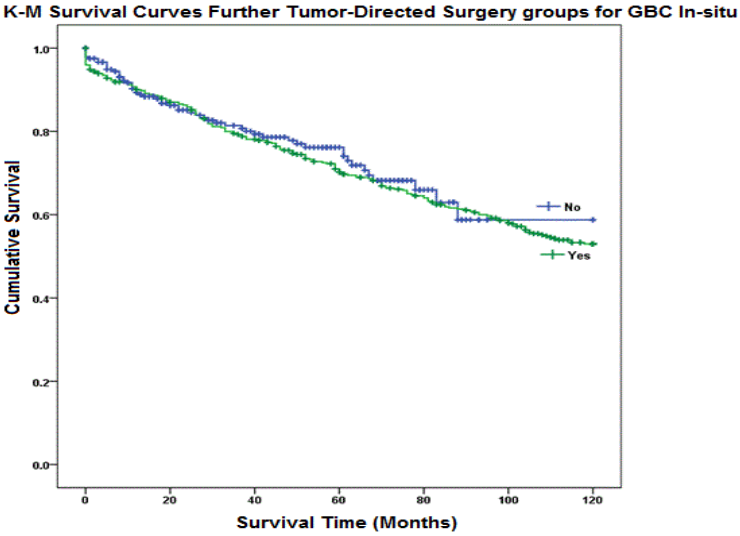
A. K-M Survival Curves for GB-CIS by age group



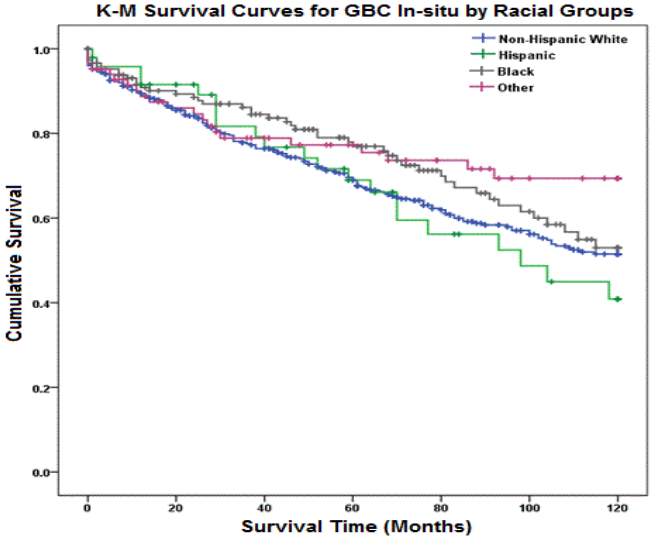
B. K-M Survival Curves for GB-CIS by Histology



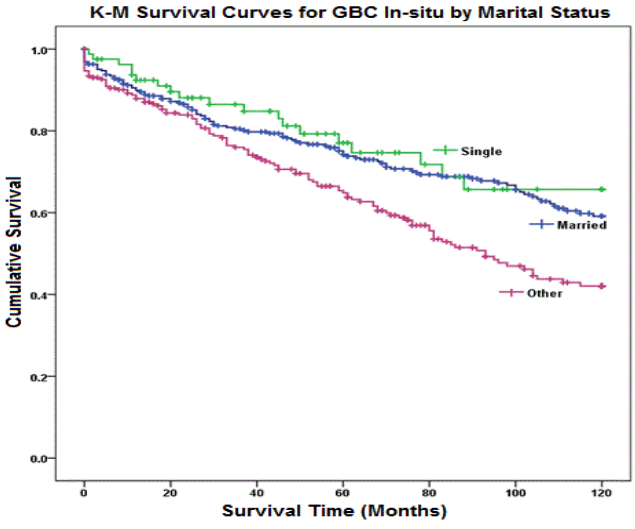
C. K-M Survival Curves for GB-CIS by Gender



D. K-M Survival Curves for Further Tumor Surgery



E. K-M Survival Curves for GB-CIS by Race/ethnicity



F. K-M Survival Curves for GB-CIS by Marital Status