**In-hospital complications in pregnant women with current or historical cancer diagnoses**

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**Abstract**

*Objective*

To assess the temporal trends, patient characteristics and comorbidities, and in-hospital cardiovascular and obstetric complications and outcomes of pregnant women with current or historical cancer diagnosis at the time of admission for delivery.

*Patients and Methods*

We analysed delivery hospitalisations with or without current or historical cancer between January 1, 2004 and December 31, 2014 from the United States National Inpatient Sample database.

*Results*

We included 43,132,097 delivery hospitalisations with no cancer, 39,118 with current cancer and 67,336 with historical diagnosis of cancer. The five most common types of current cancer were haematological, thyroid, cervical, skin and breast cancer. Women with current and historical cancer were older (29 and 32 vs. 27 years) and incurred higher hospital costs ($4,131 and $4,078 vs. $3,521), compared to women without cancer. Most of the cancer types were associated with preterm birth (haematological: adjusted odds ratio (aOR) 1.48, 95% confidence interval (CI) 1.35-1.62; cervical: aOR 1.47, 95% CI 1.32-1.63; breast: aOR 1.93, 95% CI 1.72-2.16). Current haematological cancer was associated with the highest risk of peripartum cardiomyopathy (aOR 12.19, 95% CI 7.75-19.19), all-cause mortality (aOR 6.50, 95% CI 2.22-19.07), arrhythmia (aOR 3.82, 95% CI 2.04-7.15) and postpartum haemorrhage (aOR 1.31, 95% CI 1.11-1.54). Having current or historical cancer diagnosis did not confer additional risk for stillbirth; however metastases increased the risk of maternal mortality and preterm birth.

*Conclusion*

Women with current or historical diagnosis of cancer at delivery have more comorbidities compared to women without cancer. Clinicians should communicate the risks of multi-system complications to this complex patient group.

**Abbreviations**

AHRQ Agency for Healthcare Research and Quality

CI Confidence intervals

DRG Delivery related procedures and diagnosis-related group

HCUP Healthcare Cost and Utilization Project

ICD-90 CM International Classification of Diseases, Ninth Revision, Clinical Modification NIS National Inpatient Sample

ORs Odds ratios

US United States

**Introduction**

Cancer is the second commonest cause of mortality in women of reproductive age in the United States (U.S.).1 Although still uncommon, the increase in cancer prevalence during pregnancy has been in part attributed to older maternal age.2, 3 In addition to maternal health concerns, there are fears of adverse impact on fetal development due to in-utero exposure to malignancy and cancer treatment.4-7 Women who have been diagnosed with cancer either during pregnancy, or before they have completed childbearing, need appropriate counselling so they can make informed choices.8 However, due to limited clinical experience and expertise, management of cancer in pregnancy remains a challenge for clinicians, the expectant mothers and their families.

Current evidence, albeit limited, suggest that pregnancies in women with active diagnosis of cancer do not have worse perinatal outcomes, except for preterm birth.2-4, 9 Though much of the literature comprises of case series or studies on cohorts from decades ago,3, 10, 11 a recent study indicated women with current cancer more often experienced death, ventilation or sepsis at delivery.12 However, this study lacked granularity as all cancers were combined. A meta-analysis showed that cancer survivors had increased risk of preterm birth, Caesarean section and postpartum haemorrhage.13

Whilst cardiovascular disease is the leading cause of maternal mortality in the U.S.,14 there are no data on cardiovascular outcomes, such as arrythmia, myocardial infarction and peripartum cardiomyopathy, following pregnancies affected by current or historical cancer. We aimed to assess the temporal trends, patient characteristics and comorbidities, and in-hospital cardiovascular and obstetric complications and outcomes of pregnant women with current or historical cancer diagnosis at the time of admission for delivery.

**Methods**

*Data source*

We obtained data from the U.S. National Inpatient Sample (NIS) database containing hospital discharges between 2004 and 2014. As the largest all-payer inpatient health care database in the U.S., the NIS was developed by the Agency for Healthcare Research and Quality (AHRQ) as part of the Healthcare Cost and Utilization Project (HCUP). The NIS approximates a 20% stratified sample of all discharges from U.S. hospitals and contains information on 7 to 8 million hospital discharges each year.

*Study design*

We included all women admitted for delivery between January 2004 and December 2014 using a validated protocol.15 Briefly, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes of 650 (normal delivery), V27 (outcome of delivery e.g. singleton or multiple birth), selected delivery related procedures and diagnosis-related group (DRG) delivery codes were used to identify delivery hospitalisation episodes. To assess temporal trends, we chose an 11-year study period. This ended in 2014 to allow code consistency as ICD-10 coding was used in the NIS from 2015 onwards. Due to the design of the NIS database, we were only able to conduct hospitalisation-specific rather than patient-specific analyses. As some women have more than one pregnancy, one woman may have multiple delivery hospitalisations during our study period. However, the number of these cases are likely to be low for women with cancer due to subfertility following cancer, even with fertility preservation and assisted reproductive technology.16

The NIS includes sampling weights which can be used to calculate national estimates. There has been a change in the sampling design in 2012. Prior to 2012 the NIS retained all discharges from a sample of hospitals, however since 2012 the NIS was created using a sample of discharges from all hospitals participating in HUCP, which approximates 20% of all discharges from U.S. community hospitals, excluding rehabilitation and long-term acute care hospitals. In order to ensure the data were comparable across all years of the study period, AHRQ developed a new discharge trend weight (TRENDWT) for data prior to 2012, which were calculated in the same way as the weights for the redesigned 2012 NIS. Therefore, we applied the trend weight in all our analyses.

Cancer was the exposure of interest and divided into current or historical cancer diagnosis. We considered the 20 most common types of cancer in our study cohort, using clinical classifications software or ICD-9-CM diagnosis codes (Supplemental Table 1). Selected maternal (acute kidney injury, arrhythmia, all-cause mortality, myocardial infarction, peripartum cardiomyopathy, stroke) and delivery (Caesarean section, fetal distress, placental abruption, postpartum haemorrhage, preterm birth, stillbirth) complications and outcomes were identified from the dataset using ICD-9-CM codes in previous literature (Supplemental Table 2A).17-21 The maternal complications have been previously reported in the general population following cancer,22-25 while the delivery complications have been included in maternity research core outcome sets.26, 27 Cost outcomes (length of stay, total billed hospitalisation charge) were extracted. As the total charge in the NIS database is not representative of the actual cost of hospital services, a charge to cost conversion ratio provided by AHRQ was used to convert the reported charge into actual cost for the payer.

We extracted covariate information on demographics, obstetric factors, and comorbidities including all AHRQ Elixhauser comorbidity measures, except for blood loss, which is deemed too common during a delivery hospitalisation. The ICD-9-CM codes have been previously published and are included in Supplemental Table 2B.17 All extracted data, including historical cancer diagnosis, comorbidities complications and outcomes, are based on information from the same delivery hospitalisation episode.

*Statistical analysis*

All analyses were conducted using Stata/MP version 14.0 statistical package. Continuous variables are presented as median and interquartile range, while categorical data are presented as numbers and percentages. For variables with <10% missing data overall, hospitalisation episodes with missing data were removed and assumed to be missing at random. For variables with >10% missing data (ethnicity, median ZIP code income), a missing category was used. Additional sensitivity analyses were performed to assess the effect of excluding observations with missing ethnicity or median ZIP code income.

We used sampling weights per discharge provided by AHRQ to calculate national estimates and correct variances.28 As recommended by AHRQ, NIS population survey weights (*svy* prefix in Stata) were applied to all analyses, since this process reduces the margin of error of the national estimates as well as provides more stable estimates. In the temporal trend analyses, the years were divided into 2004-2007, 2008-2011 and 2012-2014 groups.

Chi-square and t-tests were used to determine statistical difference between the groups for categorical and continuous variables, respectively. Binary logistic regression analyses were conducted to examine the impact of cancer diagnosis on in-hospital complications and outcomes (as listed in Supplemental Table 2). The odds ratios (ORs) are presented with the corresponding 95% confidence intervals (CI). We adjusted for the following potential confounders: year of admission, age, ethnicity, median ZIP code income quartile and the comorbidities listed in Table 1. For the cancer-specific models, the other cancer-associated deliveries were categorised as other cancer.

**Results**

*Prevalence of cancer*

We included 43,238,551 delivery hospitalisation episodes between 2004 and 2014 (Figure 1). There was an increase over time in the prevalence of women admitted with a historical cancer diagnosis (2004-2014: 0.12%-0.22%) with a smaller increase in women with a current diagnosis of cancer (2004-2014: 0.07%-0.12%) (Supplemental Figure 1).

*Current and historical cancer diagnoses*

The characteristics of our study population stratified into no cancer, current cancer and historical cancer groups are presented in Table 1. The prevalence of current cancer and historical cancer diagnoses among pregnant women were 0.09% (weighted *n*=39,118) and 0.15% (weighted *n*=67,336), respectively. Women with current and historical cancers were older (median ages 29 and 32 vs. 27 years), had higher proportion of White ethnicity (51% and 62% vs. 44%), and had more admissions to urban teaching hospitals (62% and 59% vs. 48%). Women with current and historical cancers had higher prevalence of most comorbidities, including previous myocardial infarction (0.09% and 0.07% vs. 0.01%), heart failure (0.31% and 0.23% vs. 0.05%) and previous stroke (0.14% and 0.15% vs. 0.03%). There were more smokers in current (12.54%) and historical (9.29%) cancer groups compared with the no cancer (6.08%) group.

Compared with the historical cancer group, the current cancer group had a higher proportion of younger women, women of Black and Hispanic ethnicity and women residing in the wealthiest quartile of household income. Women with current cancer had more comorbidities compared with women with historical cancer, including HIV and AIDS (0.24% vs. 0.03%), peripheral vascular disease (0.05% vs. 0.02%) and pulmonary circulation disorders (0.15% vs. 0.07%). However, the prevalence for hypothyroidism was significantly higher in those with historical cancer compared to those with current cancer.

*In-hospital complications and outcomes*

The prevalence of most maternal complications and outcomes was highest in women with current cancer, compared to women with historical cancer or no cancer (Table 2). These included mortality (0.30% vs. 0.02% and 0.01%), acute kidney injury (0.45% vs. 0.21% and 0.07%) and stroke (0.12% vs. 0.06% and 0.02%). Similarly, delivery outcomes such as preterm birth (13.63% vs. 9.97% and 7.88%) and postpartum haemorrhage (4.29% vs. 3.18% and 2.91%) were most prevalent in the current cancer group. Between 2004 and 2014, the prevalence of postpartum haemorrhage in both the current and historical cancer groups increased steadily over the years (Supplemental Table 3).

In the multivariable regression models, women with current cancer diagnoses had increased odds of maternal mortality (OR 16.34, 95% CI 9.44-28.26), peripartum cardiomyopathy (OR 3.92, 95% CI 2.22-6.93), arrhythmia (OR 2.84, 95% CI 1.72-4.71), acute kidney injury (OR 1.88, 95% CI 1.18-2.99), preterm birth (OR 1.67, 95% CI 1.56-1.79) and postpartum haemorrhage (OR 1.22, 95% CI 1.09-1.37), but reduced odds of fetal distress (OR 0.86, 95% CI 0.79- 0.93) compared to women without cancer (Table 3). Women with historical cancer diagnoses also had increased odds of peripartum cardiomyopathy (OR 5.32, 95% CI 3.67-7.69), acute kidney injury (OR 1.71, 95% CI 1.09-2.68) and preterm birth (OR 1.25, 95% CI 1.18-1.33), and in addition increased odds of Caesarean section delivery (OR 1.13, 95% CI 1.09-1.18). There were increased odds of myocardial infarction in both current and historical cancer groups. However due to the wide confidence intervals, these did not reach statistical significance. The presence of metastases increased the odds of mortality, Caesarean section, preterm birth and stillbirth in the current cancer group (Supplemental Table 4). Over the 11-year study period, the increased risk of preterm birth (2004-2007: OR 1.89, 95% CI 1.69-2.10 vs. 2012-2014: OR 1.48, 95% CI 1.30-1.69) reduced in the current cancer group, but remained stable in the historical cancer group (Supplemental Figure 2A). No other complications or outcomes changed over time (Supplemental Figure 2B).

For the cost outcomes, women with cancer had similar lengths of hospital stay but slightly higher hospital costs (current cancer: median $4,131, IQR $2,784-$6,610 and historical cancer: median $4,078, IQR $2,847-$5,939) compared to women without cancer (median $3,521, IQR $2,479-$5,096) (Table 1). There were no temporal changes in the length of stay and total cost outcomes (Supplemental Table 3). Additional sensitivity analyses on complications and outcomes were conducted to examine for the effects of excluding records with missing data (data not shown) and revealed no important changes in the ORs.

*Five most prevalent cancer diagnoses*

The prevalence of the cancers we examined in our cohort and the proportion of records that had either a current or historical diagnosis of these cancer are presented in Supplemental Table 5. The commonest current cancer diagnosis was haematological cancer (lymphoma and leukaemia), followed by thyroid cancer and cervical cancer, whereas the commonest historical cancer diagnosis was thyroid cancer. During the study period, there was an increase in current thyroid cancer (2004-2014: 0.03%-0.07%), while haematological cancer (2004-2014: 0.04%-0.06%) and cervical cancer (2004-2014: 0.03%-0.04%) remained stable (Supplemental Figure 3). Supplemental Table 6 shows the characteristics of patients with the five most prevalent current cancer diagnoses. Women with breast cancer were older, while women with haematological cancer had more comorbidities. More women resided in the poorest quartile of household income for majority of the cancer types, except for cervical cancer where more women resided in the wealthiest quartile.

Out of the five cancers we evaluated, the prevalence of all maternal complications and outcomes were the highest in women with haematological cancers (Table 2), for example, peripartum cardiomyopathy (1.09% vs. 0.05% for no cancer), acute kidney injury (0.47% vs. 0.07% for no cancer) and arrhythmia (0.36% vs. 0.05% for no cancer). Furthermore, the prevalence of postpartum haemorrhage (4.60% vs. 2.91%) and placental abruption (1.27% vs. 1.08%) were also the highest in haematological cancers.

In the multivariate models, current haematological, cervical and breast cancers were associated with preterm birth (Table 3). Compared to no cancer, haematological cancer was associated with the highest odds of peripartum cardiomyopathy (OR 12.19, 95% CI 7.75-19.19), maternal mortality (OR 6.50, 95% CI 2.22-19.07), arrhythmia (OR 3.82, 95% CI 2.04-7.15) and postpartum haemorrhage (OR 1.31, 95% CI 1.11-1.54). The highest increased odds for stroke (OR 4.11, 95% CI 1.27-13.32) was in the skin cancer group, while the highest increased odds for acute kidney injury (OR 2.49, 95% CI 1.07-5.80) and preterm birth (OR 1.93, 95% CI 1.72-2.16) occurred in women with cervical cancers and breast cancers, respectively. Having cancer did not confer additional risks for stillbirth and placental abruption. For the mortality, myocardial infarction and stroke outcomes which had low number of cases per each type of cancer, we also performed limited models adjusting only for demographics, previous myocardial infarction and previous stroke to reduce potential issues of sparse data or over-fitting. We did not find significant changes to our findings, except that the highest increased odds for stroke in the limited model was in the haematological cancer group rather than the skin cancer group.

**Discussion**

Our study based on over 43 million delivery hospitalisation episodes is the first to examine cardiovascular complications in women with cancer presenting for delivery. We show that 0.24% of delivery hospitalisations have a current or historical cancer diagnosis, with haematological, thyroid and cervical cancers being the three most prevalent current cancer diagnosis. In-hospital complications differed depending on the type of cancer, while metastases increased the risk of mortality and preterm birth. After adjusting for baseline risk profile, most of the cancer types were associated with preterm birth, while haematological cancers were associated with particular high risks of in-hospital complications including maternal mortality and peripartum cardiomyopathy.

To our knowledge, we are the first to assess cardiovascular complications in the context of pregnant women with current and historical cancer diagnoses. We show that women with cancer have an increased risk of peripartum cardiomyopathy, compared to women without cancer. The increased risk of peripartum cardiomyopathy in women with historical cancer diagnoses may be because they were previously exposed to cancer treatment modalities known to be associated with cardiomyopathy, such as chest irradiation and high-dose anthracycline.29, 30

In keeping with previous cohort studies on cancer in pregnancy,11, 12, 31-33 we show increased risk of preterm birth in women with current cancer compared to women without cancer. We quantified the preterm birth risk to a 1.7-fold increase in odds, which is similar to the 1.8-fold increase in relative risk reported in a population-based study of Denmark and Sweden,34 but lower than the 2.7-fold risk demonstrated in a study using NIS from 2011-2013.12 This may be due to our comprehensive approach to adjusting for confounding factors or difference in study period. Previous research has shown that the majority of preterm birth in women with invasive cancer diagnosed in pregnancy were iatrogenic.9 Elective early delivery may have been planned to allow earlier start of cancer therapy, or due to fetal growth restriction. Other possible mechanisms for preterm birth include: metabolic disturbances, local inflammatory environment, fever, malnutrition, reduced oxygen supply to fetus and hormone distribution in female-specific cancers, as these may affect fetal development and growth.5, 32, 35-37 Radiotherapy or chemotherapy may adversely affect fetal growth through vascular or pulmonary impairments. Finally, psychological stress relating to cancer diagnosis and treatment may be another factor as stress has been associated with preterm delivery previously.38

Our prevalence of pregnancy-associated cancer is in keeping with previous literature,12, 39 though others have suggested a lower incidence of 0.04%.11 During the study period, there was an increase of deliveries from women with prior or active cancer, mainly driven by an increase of the prior cancer group. The five most common current cancers in this study were haematological, thyroid, cervical, skin and breast cancers. This is consistent with prior literature on pregnant women,3, 9, 12, 40, 41 and mirrors the pattern of leading cancers in females aged between 20 and 39 years in the U.S.42 We found the prevalence of these cancers increased over the study period. This is in keeping with the general temporal trend of increasing incidence rates in the overall female population women for breast, thyroid and skin cancers.43 The incidence of thyroid cancer has increased over the past four decades in US men and women,44 which has been partly attributed to overdiagnosis and overtreatment.45-47 This phenomenon may explain our finding of a high prevalence of hypothyroidism amongst women with prior and current cancer.

Women with prior cancer had increased odds of mortality, though this was not statistically significant due to the lack of power from a low number of cases. However, previous research show that women who survive cancer and subsequently conceive have similar or better survival than women matched for age and stage of cancer who do not subsequently conceive, possibility due to selection bias contributing to the ’healthy mother effect’.48 We found cancer survivors had reduced risks of fetal distress, which may be due to closer monitoring and earlier Caesarean section intervention. This is further supported by our findings of increased risks of Caesarean section delivery and preterm birth which are likely to be iatrogenic in women with historical cancer diagnoses.

Women with active cancers in pregnancy are likely to be undergoing treatment during pregnancy. Women with breast cancers had the highest odds of preterm birth but did not have increased risks of other complications. Anthracyclines are one of the few chemotherapies for breast cancer frequently prescribed during the second and third trimester of pregnancy.49 As anthracyclines are not known to cause spontaneous preterm birth,9, 50 it is likely that women had iatrogenic preterm birth. We found that patients with haematological cancers had the highest odds of mortality, peripartum cardiomyopathy, arrhythmia and postpartum haemorrhage. These complications may reflect the impact of both cancer itself and treatment for cancer.51 It is reassuring to find that having active cancer was inversely associated with risk of fetal distress and not associated with stillbirth. This is in keeping with previous studies on cervical cancer stillbirths,52, 53 but in contrast to a Swedish study that examined all cancers which found increased risk of small-for-gestational-age stillbirths.54 Our study showed that metastases increased the odds of mortality, Caesarean section, preterm birth and stillbirth. Coupled with previous research showing that pregnant women are more likely to be diagnosed with advanced disease, this implies that pregnant women with newly diagnosed cancer have poor prognoses.55

In pregnant patients, it is pertinent to be aware of maternal and neonatal risks associated with current and historical cancer diagnosis so these can be monitored. Furthermore, the risks of preterm birth should be noted as there are short-term and long-term health implications, such as perinatal morbidity and mortality, and neurodevelopmental problems in childhood.56, 57 Clinicians should communicate the risks of multi-system complications to this complex patient group.

The strengths of this study include the sample size and the comprehensive capture of delivery hospitalisations, which enabled us to have the statistical power to examine patterns of rare diseases, such as cancer, in pregnancy. We are the first to evaluate comorbidities and in-hospital complications and outcomes based on types of cancer. Most of the previous studies either combined all cancers and lacked granularity, or only focused on one specific type of cancer.

There are several limitations to our study, mainly attributable to the database. The NIS does not capture timing of diagnosis, cause of mortality, or long-term follow-up. As such, we were unable to perform analyses on time to events or duration of comorbidities. As we were limited to in-hospital events, one woman could have had multiple deliveries during the study period. Due to lack of pharmacotherapy information, we could not consider current or past medication, radiation dose or chemotherapeutics in our study. Coding errors and underreporting of secondary diagnoses are known potential sources of bias in database studies. For example, the lack of medical record information on comorbidity or historical cancer diagnosis could have been misclassified as not having the comorbidity or prior cancer. As our results are national estimates based on sampling weights, and some unweighted events are low for each cancer type, some of the calculated odds ratios in the subgroup analyses have wide confidence intervals. Furthermore, some of the statistically significant results may have arisen by chance as we did not adjust for multiple testing. Finally, the accuracy may have improved over time in the temporal analyses, due to improved diagnosis or coding through incentives or changes in practice guidelines.

**Conclusion**

In conclusion, women with current or historical diagnosis of cancer at delivery have more comorbidities compared to women without cancer. Disparities exist in the in-hospital complications between different cancer types. Haematological cancer was the most common cancer type and associated with worse mortality as well as more in-hospital complications. Clinicians should communicate the risks of multi-system complications to this complex patient group.

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Table 1. Patient characteristics stratified by subgroups of cancer.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | No cancer | Historical cancer | Current cancer | P-valuea | P-valueb |
| Delivery hospitalisation | 99.76% | 0.15% | 0.09% | --- | --- |
| Number of deliveries, weighted | 43,132,097 | 67,336 | 39,118 | --- | --- |
| Age (years), median (IQR) | 27 (23-32) | 32 (28-36) | 29 (24-34) | **<.001** | **<.001** |
| Race and ethnicity:  White | 43.55% | 61.67% | 51.08% | **<.001** | **<.001** |
| Black | 11.58% | 6.46% | 11.61% |  |  |
| Hispanic | 18.91% | 8.74% | 15.15% |  |  |
| Asian / Pacific Islander | 3.99% | 3.61% | 2.33% |  |  |
| Native American | 0.67% | 0.41% | 0.50% |  |  |
| Other | 4.03% | 3.11% | 3.04% |  |  |
| Missing | 17.27% | 16.00% | 16.29% |  |  |
| Median ZIP code income (quartile):  1st | 22.09% | 15.22% | 23.66% | **<.001** | **<.001** |
| 2nd | 20.30% | 17.82% | 19.97% |  |  |
| 3rd | 19.49% | 22.75% | 19.87% |  |  |
| 4th | 17.65% | 28.31% | 19.64% |  |  |
| Missing | 20.47% | 15.91% | 16.86% |  |  |
| Admission type:  Elective admission | 49.28% | 52.28% | 47.10% | .097 | **<.001** |
| Admission day:  Weekday | 80.78% | 82.17% | 82.86% | **<.001** | .202 |
| Length of stay (days), median (IQR) | 2 (2-3) | 3 (2-3) | 3 (2-3) | **<.001** | **<.001** |
| Total cost ($), median (IQR) | 3,521  (2,479-5,096) | 4,078  (2,847-5,939) | 4,131  (2,784-6,610) | **<.001** | **<.001** |
| Expected primary payer:  Medicare | 0.64% | 1.92% | 1.74% | **<.001** | **<.001** |
| Medicaid | 43.43% | 22.89% | 42.50% |  |  |
| Private insurance | 49.74% | 70.47% | 49.98% |  |  |
| Self-pay | 3.26% | 1.65% | 2.55% |  |  |
| No charge | 0.20% | 0.12% | 0.26% |  |  |
| Other | 2.73% | 2.95% | 2.97% |  |  |
| Hospital location / teaching status:  Rural | 11.13% | 7.77% | 9.08% | **<.001** | **<.001** |
| Urban nonteaching | 40.69% | 33.18% | 28.64% |  |  |
| Urban teaching | 48.18% | 59.05% | 62.28% |  |  |
| Hospital size:  Small | 11.48% | 10.61% | 9.18% | **<.001** | **.030** |
| Medium | 26.77% | 23.33% | 22.72% |  |  |
| Large | 61.75% | 66.06% | 68.10% |  |  |
| Comorbidities | | | |  |  |
| Alcohol abuse | 0.11% | 0.20% | 0.33% | **<.001** | .072 |
| Chronic pulmonary disease | 3.16% | 6.28% | 6.36% | **<.001** | .807 |
| Coagulopathy | 1.24% | 2.26% | 3.18% | **<.001** | **<.001** |
| Congenital heart disease | 0.11% | 0.27% | 0.18% | **<.001** | .174 |
| Deficiency anaemia | 7.02% | 8.34% | 12.31% | **<.001** | **<.001** |
| Depression | 1.82% | 4.05% | 4.46% | **<.001** | .160 |
| Diabetes mellitus | 1.02% | 1.65% | 1.64% | **<.001** | .943 |
| Drug abuse | 1.45% | 1.66% | 2.59% | **<.001** | **<.001** |
| Dyslipidaemia | 0.08% | 0.30% | 0.43% | **<.001** | .116 |
| Fluid and electrolyte disorders | 0.50% | 1.02% | 2.51% | **<.001** | **<.001** |
| Heart failure | 0.05% | 0.23% | 0.31% | **<.001** | .282 |
| HIV and AIDS | 0.03% | 0.03% | 0.24% | **<.001** | **<.001** |
| Hypothyroidism | 1.99% | 19.48% | 4.98% | **<.001** | **<.001** |
| Liver disease | 0.13% | 0.34% | 0.30% | **<.001** | .603 |
| Obesity | 3.52% | 4.81% | 5.50% | **<.001** | **.050** |
| Other neurological disorders | 0.51% | 1.53% | 2.05% | **<.001** | **.006** |
| Paralysis | 0.03% | 0.07% | 0.03% | **<.001** | **<.001** |
| Peptic ulcer disease | 0.00046% | 0% | 0% | .785 | NA |
| Peripheral vascular disease | 0.01% | 0.02% | 0.05% | **.004** | .349 |
| Previous MI | 0.01% | 0.07% | 0.09% | **<.001** | .680 |
| Previous stroke | 0.03% | 0.15% | 0.14% | **<.001** | .815 |
| Psychoses | 0.68% | 1.12% | 1.62% | **<.001** | **.002** |
| Pulmonary circulation disorders | 0.03% | 0.07% | 0.15% | **<.001** | .078 |
| Renal failure | 0.04% | 0.23% | 0.14% | **<.001** | .162 |
| Rheumatoid arthritis/collagen vascular diseases | 0.23% | 0.66% | 0.59% | **<.001** | .547 |
| Smoker | 6.08% | 9.29% | 12.54% | **<.001** | **<.001** |
| Valvular disease | 0.44% | 1.34% | 0.76% | **<.001** | **<.001** |
| Weight loss | 0.03% | 0.10% | 0.59% | **<.001** | **<.001** |

aComparison of no cancer vs. cancer group.

bComparison of current cancer vs. historical cancer group.

cAIDS, acquired immunodeficiency syndrome. HIV, human immunodeficiency virus. IQR, interquartile range. MI, myocardial infarction.

Table 2. In-hospital maternal and delivery complications and outcomes according to timing of cancer diagnosis and types of cancer.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Variable | | No cancer  *n*=43,132,097 | Any cancer | | |  |  | Current cancer | | | | |
| Historical cancer  *n*=67,336 | | Current cancer  *n*=39,118 | P-valuea | P-valueb | Haematological  *n*=20,755 | Thyroid  *n*=17,295 | Cervix  *n*=15,998 | Skin  *n*=15,133 | Breast  *n*=12,972 |
|  |  | | | **Maternal** | | | | | | | | |
| Mortality | | 0.01% | 0.02% | | 0.30% | **<.001** | **<.001** | 0.12% | 0% | 0% | 0.03% | 0.04% |
| Acute kidney injury | | 0.07% | 0.21% | | 0.45% | **<.001** | **.002** | 0.47% | 0.09% | 0.26% | 0.03% | 0.22% |
| Arrhythmia | | 0.05% | 0.10% | | 0.26% | **<.001** | .011 | 0.36% | 0.14% | 0.15% | 0.10% | 0.13% |
| Myocardial infarction | | 0.003% | 0.01% | | 0.03% | **<.001** | .513 | 0.03% | 0% | 0% | 0% | 0% |
| Peripartum cardiomyopathy | | 0.05% | 0.41% | | 0.42% | **<.001** | .885 | 1.09% | 0.03% | 0.12% | 0.10% | 0.23% |
| Stroke | | 0.02% | 0.06% | | 0.12% | **<.001** | .106 | 0.10% | 0.05% | 0% | 0.08% | 0.08% |
|  |  | | | **Delivery** | | | | | | | | |
| Caesarean section | | 31.51% | 39.54% | | 35.51% | **<.001** | **<.001** | 37.68% | 35.99% | 31.27% | 39.68% | 40.96% |
| Fetal distress | | 9.93% | 9.15% | | 8.45% | **<.001** | .082 | 9.43% | 8.81% | 7.29% | 10.12% | 8.85% |
| Placental abruption | | 1.08% | 1.09% | | 1.10% | .912 | .932 | 1.27% | 1.21% | 0.90% | 0.87% | 0.90% |
| Postpartum haemorrhage | | 2.91% | 3.18% | | 4.29% | **<.001** | **<.001** | 4.60% | 2.90% | 3.10% | 3.26% | 2.99% |
| Preterm birth | | 7.88% | 9.97% | | 13.63% | **<.001** | **<.001** | 11.99% | 8.37% | 12.25% | 7.88% | 14.39% |
| Stillbirth | | 0.62% | 0.59% | | 0.60% | .714 | .761 | 0.66% | 0.61% | 0.76% | 0.21% | 0.48% |

aComparison of no cancer vs. cancer group.

bComparison of current cancer vs. historical cancer group.

Table 3. Association between history of any cancer, any current cancer, the top five most prevalent cancer sites in the study cohort and in-hospital maternal and delivery complications and outcomes.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Any Cancer | | Current Cancer | | | | |
| Historical | Current | Haematological | Thyroid | Cervical | Skin | Breast |
| MATERNAL | | | | | | | |
| Mortality | | | | | | | |
| Unadjusted | 2.72  (0.87, 8.57) | 40.38  (27.55, 59.21) | 15.56  (6.46, 37.46) | NA | NA | 4.33  (0.61, 30.86) | 4.87  (0.68, 34.72) |
| Limited adjustment | --- | --- | 15.80 d  (6.55, 38.14) | NA | NA | 4.74d  (0.66, 33.77) | 3.26 d  (0.46, 23.07) |
| Fully adjusted | 2.12  (0.63, 7.16) | 16.34  (9.44, 28.26) | 6.50  (2.22, 19.07) | NA | NA | 5.66  (0.77, 41.54) | 2.87  (0.38, 21.43) |
| Acute kidney injury | | | | | | | |
| Unadjusted | 3.07  (2.13, 4.41) | 6.57  (4.73, 9.11) | 6.89  (4.46, 10.63) | 1.25  (0.40, 3.88) | 3.80  (1.88, 7.68) | 0.47  (0.07, 3.37) | 3.20  (1.43, 7.15) |
| Fully adjusted | 1.71  (1.09, 2.68) | 1.88  (1.18, 2.99) | 2.16  (1.17, 3.99) | 0.95  (0.31, 2.94) | 2.49  (1.07, 5.80) | 0.44  (0.06, 3.35) | 2.13  (0.89, 5.13) |
| Arrhythmia | | | | | | | |
| Unadjusted | 2.15  (1.25, 3.69) | 5.30  (3.34, 8.41) | 7.56  (4.41, 12.94) | 2.90  (1.20, 6.99) | 3.18  (1.31, 7.70) | 1.96  (0.64, 6.00) | 2.72  (0.87, 8.46) |
| Fully adjusted | 1.16  (0.67, 2.02) | 2.84  (1.72, 4.71) | 3.82  (2.04, 7.15) | 1.72  (0.71, 4.16) | 2.12  (0.86, 5.27) | 1.25  (0.41, 3.85) | 1.60  (0.51, 5.01) |
| Myocardial infarction | | | | | | | |
| Unadjusted | 4.33  (1.07, 17.49) | 8.26  (2.06, 33.13) | 8.11  (1.14, 57.52) | NA | NA | NA | NA |
| Limited adjustment | --- | --- | 6.84d  (0.96, 48.92) | NA | NA | NA | NA |
| Fully adjusted | 1.69  (0.40, 7.11) | 2.44  (0.39, 15.23) | 2.08  (0.17, 26.12) | NA | NA | NA | NA |
| Peripartum cardiomyopathy | | | | | | | |
| Unadjusted | 7.91  (6.04, 10.36) | 8.17  (5.70, 11.72) | 21.18  (15.68, 28.60) | 0.51  (0.07, 3.63) | 2.34  (0.88, 6.20) | 1.86  (0.60, 5.80) | 4.47  (2.01, 9.95) |
| Fully adjusted | 5.32  (3.67, 7.69) | 3.92  (2.22, 6.93) | 12.19  (7.75, 19.19) | 0.39  (0.04, 3.89) | 1.18  (0.21, 6.74) | 1.74  (0.62, 4.86) | 2.41  (0.89, 6.56) |
| Stroke | | | | | | | |
| Unadjusted | 2.95  (1.37, 6.36) | 6.53  (3.55, 12.04) | 5.18  (1.94, 13.84) | 2.67  (0.38, 18.95) | NA | 4.50  (1.42, 14.33) | 4.34  (1.09, 17.27) |
| Limited adjustment | --- | --- | 4.34d  (1.60, 11.75) | 2.27d  (0.32, 16.32) |  | 3.88d  (1.20, 12.50) | 2.94d  (0.75, 11.47) |
| Fully adjusted | 1.86  (0.84, 4.12) | 1.78  (0.79, 3.99) | 3.00  (1.04, 8.64) | 2.16  (0.27, 17.38) | NA | 4.11  (1.27, 13.32) | 2.16  (0.48, 9.76) |
| DELIVERY | | | | | | | |
| Caesarean section | | | | | | | |
| Unadjusted | 1.42  (1.37, 1.48) | 1.20  (1.14, 1.26) | 1.31  (1.24, 1.40) | 1.22  (1.14, 1.31) | 1.16  (1.08, 1.25) | 1.43  (1.32, 1.54) | 1.51  (1.39, 1.64) |
| Fully adjusted | 1.13  (1.09, 1.18) | 1.03  (0.98, 1.09) | 1.14  (1.07, 1.22) | 0.91  (0.85, 0.97) | 1.04  (0.96, 1.12) | 1.18  (1.09, 1.27) | 1.07  (0.99, 1.16) |
| Fetal distress | | | | | | | |
| Unadjusted | 0.91  (0.86, 0.97) | 0.84  (0.77, 0.91) | 0.94  (0.85, 1.05) | 0.88  (0.78, 0.99) | 0.71  (0.62, 0.82) | 1.02  (0.91, 1.15) | 0.88  (0.77, 1.01) |
| Fully adjusted | 0.95  (0.90, 1.01) | 0.86  (0.79, 0.93) | 0.96  (0.86, 1.07) | 0.90  (0.80, 1.02) | 0.74  (0.64, 0.85) | 1.08  (0.96, 1.22) | 0.96  (0.84, 1.10) |
| Placental abruption | | | | | | | |
| Unadjusted | 1.00  (0.86, 1.18) | 1.02  (0.81, 1.27) | 1.18  (0.90, 1.54) | 1.12  (0.83, 1.51) | 0.83  (0.57, 1.21) | 0.80  (0.55, 1.17) | 0.83  (0.56, 1.23) |
| Fully adjusted | 0.92  (0.78, 1.07) | 0.85  (0.68, 1.06) | 1.04  (0.80, 1.36) | 1.09  (0.81, 1.48) | 0.67  (0.46, 0.99) | 0.78  (0.54, 1.14) | 0.74  (0.50, 1.10) |
| Postpartum haemorrhage | | | | | | | |
| Unadjusted | 1.10  (0.99, 1.21) | 1.50  (1.33, 1.68) | 1.61  (1.36, 1.90) | 1.00  (0.82, 1.22) | 1.07  (0.88, 1.30) | 1.13  (0.93, 1.37) | 1.03  (0.83, 1.29) |
| Fully adjusted | 1.04  (0.94, 1.15) | 1.22  (1.09, 1.37) | 1.31  (1.11, 1.54) | 1.00  (0.82, 1.21) | 1.00  (0.82, 1.21) | 1.10  (0.91, 1.35) | 0.98  (0.77, 1.23) |
| Preterm birth | | | | | | | |
| Unadjusted | 1.29  (1.22, 1.37) | 1.84  (1.72, 1.97) | 1.59  (1.45, 1.75) | 1.07  (0.95, 1.20) | 1.63  (1.48, 1.81) | 1.00  (0.87, 1.15) | 1.96  (1.75, 2.20) |
| Fully adjusted | 1.25  (1.18, 1.33) | 1.67  (1.56, 1.79) | 1.48  (1.35, 1.62) | 1.03  (0.92, 1.16) | 1.47  (1.32, 1.63) | 1.07  (0.94, 1.23) | 1.93  (1.72, 2.16) |
| Stillbirth | | | | | | | |
| Unadjusted | 0.95  (0.75, 1.19) | 0.97  (0.73, 1.29) | 1.05  (0.71, 1.56) | 0.97  (0.64, 1.49) | 1.22  (0.81, 1.84) | 0.34  (0.15, 0.80) | 0.77  (0.45, 1.33) |
| Fully adjusted | 0.94  (0.75, 1.19) | 0.87  (0.65, 1.15) | 0.98  (0.66, 1.46) | 1.04  (0.68, 1.58) | 1.12  (0.74, 1.70) | 0.39  (0.17, 0.90) | 0.71  (0.41, 1.22) |

aData expressed as odds ratios and 95% confidence intervals, reference group is no cancer.

bHaematological cancer includes lymphoma and leukaemia.

cFull adjustment include year of admission, age, race/ethnicity, median ZIP code income quartile, smoker, congenital heart disease, dyslipidaemia, previous stroke, previous myocardial infarction and selected Elixhauser comorbidity measures (heart failure, valvular disease, pulmonary circulation disorders, peripheral vascular disease, paralysis, other neurological disorders, chronic pulmonary disease, diabetes mellitus, hypothyroidism, chronic renal failure, liver disease, peptic ulcer disease, HIV and AIDS, rheumatoid arthritis/collagen vascular diseases, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, deficiency anaemias, alcohol abuse, drug abuse, psychoses and depression).

dModels adjusted for demographics (year of admission, age, race/ethnicity, median ZIP code income quartile), previous stroke and previous myocardial infarction only.

eNA, not applicable as too few cases to determine odds ratio.

Figure 1. Flow diagram of included/excluded records.

Age – 6,423 missing

Weekend admission – 5 missing

Primary payer – 16,176 missing

Length of stay – 25 missing

Death – 1,887 missing

Total cost – 216,825 missing

Elective admission – 40,712 missing

Hospital location – 47,156 missing

Radiotherapy/chemotherapy treatment without cancer diagnosis – 99 removed

All records taken from NIS database

from 2004 - 2014

Excluded records with less than 10% missing covariate information or obvious errors

(*n* = 9,039,509 unweighted)

Unweighted 9,368,817 records were identified with delivery hospitalisation

Identified all delivery hospitalisations using published algorithm

Records with a delivery included in analysis

(*n* = 43,238,551 weighted)