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ORIGINAL PAPER

Obstetrical and infant outcomes among women with neoplasms during pregnancy

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Abstract

Purpose One in 1,000 pregnancies is complicated by malignancies. Prevalence is greater for benign neoplasms. Adverse outcomes among women with malignancies have been reported. Less is known of postpartum outcomes for infants, or outcomes among women with benign neoplasms.

Methods We conducted a population-based cohort study using Washington State-linked vital-hospital discharge records. Women with neoplasms (707 malignant; 13,156 benign) with deliveries in 1987–2012 were identified, and a randomly selected comparison cohort. Obstetrical/infant outcomes and rehospitalization < 2 years post-delivery were compared separately for each group by multivariable regressions to estimate risk ratios (RR) and 95% confidence intervals (CI).

Results Women with either condition had increased anemia, cesarean, and preterm delivery; their infants were more often < 2,500 g or jaundiced. Women with benign conditions had increased gestational diabetes (RR = 1.20; 95% CI 1.12–1.28) and preeclampsia (RR = 1.27; 95% CI 1.18–1.36); their infants had increased malformations (RR = 1.29; 95% CI 1.19–1.38). Women with neoplasms more often were hospitalized seven or more days or rehospitalized; their infants' hospitalizations were also longer.

Conclusion Malignant and benign neoplasms were associated with several adverse outcomes. Reasons for relationships of benign neoplasms with gestational diabetes, preeclampsia, and congenital malformations merit further study.

Keywords Cancer · Pregnancy-related cancer · Pregnancy outcomes · Infant outcomes

Introduction

Cancer during pregnancy is uncommon. However, given the current trend toward delayed childbearing [1] and the greater cancer risk associated with aging [2], increasing incidence of cancer during pregnancy may be expected [3]. It is estimated that approximately 1 in 1,000 pregnancies is complicated by a concurrent cancer diagnosis [4, 5].

Pregnancies with concurrent cancer diagnosis are complicated because of the need to balance the welfare of the fetus with that of the mother. Treatments are often delayed or avoided during pregnancy due to possible toxic effects on fetal development [6–8]. Suboptimal therapies or delaying cancer treatment to preserve fetal health may worsen cancer prognosis for the mother [9]. For patients with some low-grade neoplasms, doctors and patients may be concerned that hormone changes, immunological suppression, and increased vascularization from pregnancy may increase the risk of progression [10].

An increasing number of studies of malignancy during pregnancy have observed greater risks of adverse obstetrical and neonatal complications among pregnant patients including congenital malformation, small size for gestational age, preterm delivery, or premature rupture of membranes [11, 12]. However, most studies focus on malignancies only, and few are population-based. There is limited information on the distribution of benign neoplasms during pregnancy and their impact on pregnancy and infant outcomes. Uterine

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leiomyoma is one of the most common benign neoplasms during pregnancy [13], yet little is known about its possible consequences during pregnancy [14] or for offspring. Few studies have examined the possible postpartum effects of maternal neoplasms (benign or malignant) during pregnancy for both the mother and infant. We used 26 years of population-based data from Washington State to compare the relative occurrence of selected adverse obstetrical and infant outcomes (including rehospitalizations < 2 years after delivery) among women with and without neoplasm diagnoses (benign and malignant separately) at the time of delivery.

Materials and methods

Study design and data sources

We conducted a retrospective population-based cohort study using linked birth/fetal death certificate-hospital discharge records for all deliveries 1987–2012 in Washington State. Details of the linkage have been described elsewhere [15]. Birth and fetal death (≥ 20 weeks gestation) records of deliveries in Washington State are routinely linked to hospital discharge data for both the mother and child for the delivery/birth hospitalization. Information on the mothers' demographic characteristics, reproductive history, pregnancy course, and outcome is present on the birth/fetal death certificates. The hospital discharge records include all hospitalizations in non-federal facilities in the state, with information about the length of hospital stay, type of medical insurance, and multiple fields of ICD-9 (International Classification of Diseases, 9th revision) diagnosis/procedure codes that can identify maternal/infant conditions and comorbidities. Rehospitalization information (non-pregnancy-related only) for the mother and infant and infant mortality < 2 years of life was obtained for this analysis via additional linkage to hospital discharge and death records for the 2 years after delivery.

Identification of women with neoplasms

Women with neoplasms during pregnancy were identified by screening all available diagnosis fields in the hospital discharge records of women with live birth or fetal death deliveries (five fields available for 1987–1991; nine fields for 1992–2012) for ICD-9 codes indicating the presence of neoplasm (ICD-9 140–239). These women were further classified into two subgroups: malignancies (ICD-9 140–209) and benign neoplasms/carcinoma in situ (CIS) (ICD-9 210–239) (Supplemental Table S1; Supplementary Figure S1). For every woman with a neoplasm code during pregnancy, 10 women without these codes were randomly selected from the remaining women, matched on the delivery year. A total of 14,194 women with neoplasms and 141,940 comparison women were identified. Because characteristics of multiple and singleton pregnancies differ, we excluded women with multiple gestations (328 cases, 2,152 comparison women) or missing plurality data (two cases, 20 comparison women). Four comparison women with missing maternal age were also excluded, leaving 13,862 women with neoplasm codes (13,156 benign; 707 malignancies) and 139,765 comparison women for analyses.

Obstetrical and neonatal outcomes

Gestational diabetes, preeclampsia/eclampsia, maternal anemia during pregnancy, oligohydramnios, polyhydramnios, prolonged/precipitous/obstructed labor, *placenta previa*, *abruptio placenta*, Cesarean delivery, and use of forceps/vacuums (among women with vaginal deliveries only) were examined as maternal outcomes. Infant outcomes included preterm delivery (< 37 weeks of gestation), low birthweight (< 2,500 g), 5-min Apgar score < 7, breech delivery, fetal distress, infant jaundice, congenital malformations, and death at < 2 years. Small size for gestational age (SGA), indicating the lowest 10%, was calculated based on sex-specific birthweight distributions from population-based Washington State birth data.

With the exception of SGA, assessed from the birth certificate only, we used a capture–recapture method to identify the obstetrical and infant outcomes in the linked data. These variables were first identified in the birth certificate. To improve accuracy, we also screened all diagnosis/procedure fields in the linked hospital discharge records for relevant ICD-9 codes. We assumed the presence of an outcome if relevant codes (Supplemental Table S2) were observed in either source, and absence of it if not identified from either source. This method has been demonstrated to result in greater accuracy of identification of obstetric conditions [16]. Infant mortality < 2 years of birth was based on linkage to death records. We also assessed mothers' and infants' length of delivery hospitalization (< 7; 7 + days) and occurrence of non-pregnancy-related rehospitalization (0; 1 +) during the 2 years after delivery/birth.

Statistical analysis

We used frequencies, means, and proportions to characterize women with benign and malignant neoplasm codes and comparison women. Levels of missing data ranged from 0.01% to 3.5% of all variables and were similar across the three groups. Analyses were restricted to subjects with non-missing information for the variables relevant to each analysis.

Logistic regression and recycled predictions [17] were used to estimate risk ratios (RR); 95% confidence intervals

(CI) were calculated using the delta method. We used causal diagrams with a priori knowledge and previous literature to identify potential confounders, including maternal age (< 19, 19–24, 25–29, 30–34,35–39, 40 + years); marital status; race/ethnicity (White, African American, Hispanic, Asian, other); prenatal smoking (yes/no); parity and gravidity (each as 0, 1, 2 +); education (< 12, 12, 13–16, 17 + years); and health insurance billed at discharge (private, Medicaid, self-paid, other, unknown). Fetal death deliveries (671 comparison; 67 benign; eight malignancies) were excluded from analyses of delivery type, use of instrumentation among women with vaginal deliveries, and any infant outcomes. Maternal and infant deaths were excluded from analyses of rehospitalization. Unless otherwise indicated, all estimates are adjusted for delivery year, maternal age, marital status, health insurance, and parity. Small numbers precluded the analyses of separate malignancies, although sub-analyses restricted to leiomyoma were conducted.

Analyses were conducted in Stata 14 software (StataCorp. 2015. Stata Statistical Software: release 14. College Station, TX: StataCorp LP). The study was approved by all relevant Institutional Review Boards prior to study conduct.

Results

Neoplasm distribution

Breast cancer (15%), Hodgkin's lymphoma (13%), and leukemia (11%) were the most common malignancies identified at delivery (Supplementary Table S1). Leiomyomas (58%), skin neoplasms (14%), and ovarian neoplasms (10%) were the most common benign conditions identified.

A greater proportion (68%) of women with benign neoplasms were > 30 years old than among women with malignancies (54%) or comparison women (39%) (Table 1). Women with benign neoplasms were more likely to be married, have private insurance and no prior births than women with malignancies or comparison women. Race/ethnicity, education levels, prenatal smoking, and gravidity were generally similar across all groups.

Obstetrical outcomes

Compared to women without neoplasms, modestly increased risks were observed for most pregnancy outcomes among women with malignancies including maternal anemia (RR = 1.42, 95% CI 1.11–1.74), preterm premature rupture of membranes (RR = 3.24, 95% CI 1.71–4.78), oligohydramnios (RR = 1.68, 95% CI 1.02–2.34), and cesarean delivery (RR = 1.30, 95% CI 1.15–1.44). Women with malignancies had decreased risk of obstructed labor (RR = 0.74, 95% CI 0.52–0.97).

Women with benign neoplasms, compared to women without neoplasms, were more likely to experience gestational diabetes (RR = 1.20, 95% CI 1.12–1.28), preeclampsia/eclampsia (RR = 1.27, 95% CI 1.18–1.36), maternal anemia (RR = 1.33, 95% CI 1.25–1.41), *placenta previa* (RR = 2.32, 95% CI 1.90–2.74), and *abruptio placenta* (RR = 1.56, 95% CI 1.30–1.81) (Table 2). Similar to women with malignancies, they had increased risks of oligohydramnios (RR = 1.36, 95% CI 1.21–1.50) and polyhydramnios (RR = 1.58, 95% CI 1.30–1.85). They also had increased risks of obstructed labor (RR = 1.43, 95% CI 1.35–1.50) and cesarean delivery (RR = 2.18, 95% CI 2.14–2.22). However, they were less likely to experience prolonged (RR = 0.78, 95% CI 0.71–0.85) or precipitous labor (RR = 0.42, 95% CI 0.37–0.48) than the comparison group. RRs from sub-analyses restricted to leiomyoma were generally slightly greater than those for benign neoplasms overall, although the pattern was similar (results not shown).

Infant outcomes

Infants of women with malignancies were more likely to be preterm (RR 3.38, 95% CI 2.88-3.88), have low birthweight (RR = 3.65, 95% CI 2.87–4.43), or be SGA (RR = 1.30, 95% CI 0.99–1.60) (Table 3). They were more likely to be jaundiced (RR = 1.77, 95% CI 1.44–2.10) or to have low Apgar scores (RR = 1.93, 95% CI 1.02–2.84). Risk estimates for low birthweight (RR = 1.59, 95% CI 1.22–1.97) and jaundice (RR = 1.32, 95 CI 1.06–1.57) remained increased even after additional adjustment for gestational age (data not shown). They were not, however, more likely to have a congenital malformation identified at delivery.

Compared to infants of women without neoplasms, infants whose mother had benign conditions were also more likely to be preterm (RR = 1.38, 95% CI 1.29–1.46), low birthweight (RR = 1.56, 95% CI 1.43–1.69), or jaundiced (RR = 1.45, 95% CI 1.37–1.52). However, unlike infants of women with malignancies, we also observed increased risks of breech malpresentation (RR = 2.49, 95% CI 2.33–2.66), fetal distress (RR = 1.32, 95% CI 1.23–1.40), or having a congenital malformation (RR = 1.29, 95% CI 1.19–1.38). Their risk of death within 2 years was 1.30 (95% CI 0.94–1.79).

Length of delivery hospitalization–rehospitalizations

Women with benign neoplasms were more likely to have delivery hospitalizations of 7 days or longer, even after adjustment for method of delivery (RR = 1.28, 95% CI 1.09–1.47); this similarly adjusted risk among women with malignancies was RR = 7.00 (95% CI 5.03–8.99) (Table 4). The risks of having longer delivery hospitalizations persisted

Table 1 Characteristics of women with benign neoplasms, malignancies, and without neoplasms who had singleton deliveries in Washington State 1987–2012

Characteristics	No cancer[a] $n=139,765$		Benign[a] $n=13,156$		Malignant[a] $n=707$	
	n	(%)	*n*	(%)	*n*	(%)
Age (years)						
Mean (SD)	*27.74 (5.99)*		*32.05 (5.70)*		*30.14 (6.13)*	
< 19	7,365	5.27	114	0.87	15	2.12
19–24	37,423	26.78	1,254	9.53	135	19.09
25–29	40,782	29.18	2,820	21.44	178	25.18
30–34	34,363	24.59	4,287	32.59	186	26.31
35–39	16,297	11.66	3,505	26.64	150	21.22
40 +	3,535	2.53	1,176	8.94	43	6.08
Race/ethnicity						
White	100,117	73.30	9,532	74.12	556	80.70
African American	5,966	4.37	827	6.43	23	3.34
Hispanic	14,830	10.86	829	6.45	38	5.52
Asian	11,534	8.45	1,460	11.35	46	6.68
Others	4,129	3.02	212	1.65	26	3.77
Marital status						
Married	96,547	69.27	10,647	81.12	544	77.60
Unmarried	42,839	30.73	2,478	18.88	157	22.40
Smoked prenatally						
No	117,724	88.04	11,577	91.96	595	89.07
Yes	15,994	11.96	1,011	8.04	73	10.93
Education (years)[b]						
< 12	34,000	25.24	2,020	15.82	110	16.39
12	31,880	23.67	2,138	16.74	132	19.67
13–16	57,096	42.39	6,537	51.19	341	50.82
17 +	11,708	8.96	2,074	16.24	88	13.11
Medical insurance						
Private	79,257	56.71	9,637	73.25	440	62.23
Medicaid	55,972	40.05	3,120	23.72	248	35.08
Self-pay	2,179	1.56	172	1.31	10	1.41
Other	2,344	1.68	226	1.72	9	1.27
No. prior births						
0	57,474	41.89	6,565	50.85	282	40.87
1	43,886	31.99	3,868	29.96	192	27.83
2 +	35,830	26.12	2,477	19.19	216	30.30
No. prior pregnancies						
0	44,465	32.54	4,672	36.35	218	31.82
1	38,310	28.03	3,600	28.01	158	23.07
2 +	53,879	39.43	4,581	35.64	309	45.11

SD standard deviation

[a]Numbers may not add to totals due to missing values

[b]Data available since 1992 (138,684 comparison women; 12,769 women with benign neoplasms; 671 women with malignancies)

for both neoplasm groups regardless of delivery method. Infants born to both groups of women also had increased risks of longer birth hospitalizations, which persisted after adjusting for the length of their mothers' hospital stay or gestational length (data not shown).

Infants of women with benign neoplasms had an RR for rehospitalization of 1.08 (95% CI 1.01–1.16) compared to infants of comparison women, which was slightly attenuated after additional adjustment for gestational age (RR = 1.06, 95% CI 0.98–1.13; data not shown), or restriction to infants

Table 2 Obstetrical outcomes among singleton deliveries of women with benign neoplasms, malignancies, and without neoplasms in Washington State, 1987–2012

Obstetrical outcomes	No cancer $n=139,765$		Benign $n=13,156$				Malignant $n=707$			
	n	%	*n*	%	RR[a]	95% CI	*n*	%	RR[a]	95% CI
Gestational diabetes										
Yes	8,296	5.94	1,200	9.12	1.20	1.12–1.28	51	7.21	0.99	0.68–1.29
No	131,469	94.06	11,956	90.88			656	92.79	(Ref)	
Preeclampsia/eclampsia										
Yes	8,577	6.14	1,112	8.45	1.27	1.18–1.36	48	6.79	1.15	0.80–1.51
No	131,188	93.86	12,044	91.55	(Ref)		659	93.21	(Ref)	
Maternal anemia										
Yes	14,315	10.24	1,586	12.06	1.33	1.25–1.41	103	14.57	1.42	1.11–1.74
No	125,450	89.76	11,570	87.94	(Ref)		604	85.43	(Ref)	
Preterm premature rupture of membranes										
Yes	1,432	1.02	169	1.28	1.15	0.94–1.36	24	3.39	3.24	1.71–4.78
No	138,333	98.98	12,987	98.72	(Ref)		683	96.61	(Ref)	
Oligohydramnios										
Yes	3,788	2.71	560	4.26	1.36	1.21–1.50	29	4.10	1.68	1.02–2.34
No	135,977	97.29	12,596	95.74	(Ref)		678	95.90	(Ref)	
Polyhydramnios										
Yes	1,126	0.81	199	1.51	1.58	1.30–1.85	10	1.41	1.60	0.49–2.71
No	138,639	99.19	12,957	98.49	(Ref)		697	98.59	(Ref)	
Prolonged labor										
Yes	6,216	4.45	609	4.63	0.78	0.71–0.85	25	3.54	0.87	0.52–1.23
No	133,549	95.55	12,547	95.37	(Ref)		682	96.46	(Ref)	
Precipitous labor										
Yes	8,242	5.90	274	2.08	0.42	0.37–0.48	28	3.96	0.73	0.45–1.02
No	131,523	94.10	12,882	97.92	(Ref)		679	96.04	(Ref)	
Obstructed labor										
Yes	12,713	9.10	1,960	14.90	1.43	1.35–1.50	52	7.36	0.74	0.52–0.97
No	127,052	90.90	11,196	85.10	(Ref)		655	92.64	(Ref)	
Placenta previa										
Yes	721	0.52	211	1.60	2.32	1.90–2.74	6	0.85	1.45	0.18–2.72
No	139,044	99.48	12,945	98.40	(Ref)		701	99.15	(Ref)	
Abruptio placenta										
Yes	1,610	1.15	240	1.82	1.56	1.30–1.81	9	1.27	1.34	0.41–2.27
No	138,155	98.85	12,916	98.18	(Ref)		698	98.73	(Ref)	
Cesarean delivery[b]										
Yes	38,108	27.40	8,641	66.02	2.18	2.14–2.22	273	39.06	1.30	1.15–1.44
No	100,986	72.60	4,448	33.98	(Ref)		426	60.94	(Ref)	
Use of instrumentation among women with vaginal delivery[b]										
Forceps assisted										
Yes	2,731	2.70	190	4.27	1.17	0.99–1.35	12	2.82	0.96	0.38–1.53
No	98,255	97.30	4,258	95.73	(Ref)		421	97.18	(Ref)	
Vacuum assisted										
Yes	10,230	10.07	564	12.53	0.98	0.90–1.08	55	12.70	1.05	0.75–1.36
No	91,312	89.93	3,937	87.47	(Ref)		378	87.30	(Ref)	

Ref reference, *RR* risk ratio, *CI* confidence interval

[a]All risk ratios adjusted for delivery year, maternal age, marital status, insurance, and parity

[b]Women with fetal deaths excluded (671 comparison; 67 benign; eight malignancies)

Table 3 Outcomes among singleton infants of women with, and without neoplasms

Neonatal outcomes	No Cancer $n=139,765$		Benign $n=13,156$				Malignant $n=707$			
	n	%	*n*	%	RR[a]	95% CI	*n*	%	RR[a]	95% CI
Birthweight (g)										
< 2500	6,437	4.63	960	7.33	1.56	1.43–1.69	108	15.45	3.65	2.87–4.43
2500 +	132,657	95.37	12,129	92.67	(Ref)		591	84.55	(Ref)	
Gestational length (weeks)										
< 37	11,743	8.44	1,476	11.28	1.38	1.29–1.46	182	26.04	3.38	2.88–3.88
37 +	127,351	91.56	11,613	88.72	(Ref)		517	73.96	(Ref)	
Small for gestational age										
Yes	123,86	9.00	1,244	9.60	1.09	1.03–1.16	72	10.45	1.30	0.99–1.60
No	125,214	91.00	11,710	90.40	(Ref)		617	89.55	(Ref)	
Breech delivery										
Yes	5,199	3.74	1,431	10.93	2.49	2.33–2.66	30	4.29	0.97	0.56–1.38
No	133,895	96.26	11,658	89.07	(Ref)		669	95.71	(Ref)	
Fetal distress										
Yes	9,065	6.52	1,346	10.28	1.32	1.23–1.40	53	7.58	1.13	0.79–1.47
No	130,029	92.48	11,743	89.72	(Ref)		646	92.42	(Ref)	
Infant jaundice[b]										
Yes	14,604	10.50	2,087	15.94	1.45	1.37–1.52	127	18.17	1.77	1.44–2.10
No	124,490	89.50	11,002	84.06	(Ref)		572	81.83	(Ref)	
Apgar score < 7[c]										
Yes	2,448	1.76	278	2.12	0.98	0.83–1.13	28	4.01	1.93	1.02–2.84
No	136,645	98.24	12,811	97.88	(Ref)		671	95.99	(Ref)	
Congenital anomalies										
Yes	8,377	6.02	1,075	8.21	1.29	1.19–1.38	46	6.58	0.98	0.64–1.31
No	130,717	93.98	12,014	91.79	(Ref)		653	93.42	(Ref)	
Infant death < 2 years										
Yes	664	0.48	74	0.57	1.30	0.94–1.79	3	0.43		
No	138,430	99.52	13,015	99.43	(Ref)		696	99.57		

Ref reference, *RR* risk ratio, *CI* confidence interval

[a]All risk ratios adjusted for delivery year, maternal age, marital status, and parity. Fetal deaths excluded (671 comparison; 67 benign; eight malignancies)

[b]Adjusted additionally for mothers' race

[c]Adjusted additionally for method of delivery

without congenital malformations (RR = 1.06, 95% CI 0.98–1.14; data not shown). The RR for infants of women with malignancies was 1.23 (95% CI 0.91–1.54). Similar to results of obstetrical outcomes, RRs from sub-analyses restricted to leiomyoma for infant outcomes were generally slightly greater than those for benign neoplasms (results not shown).

Discussion

Although we lacked treatment information, large population-based observational studies are important because they include persons often underrepresented in clinical studies [18, 19] and may support results of clinical studies. We observed that women with either a malignant or benign neoplasm during pregnancy had increased risks of several pregnancy conditions and outcomes, including anemia, oligohydramnios, and cesarean delivery relative to women without a neoplasm. We also observed increased risks of preterm delivery, low birthweight, infant jaundice, and low Apgar score among infants born to women with either type of neoplasm. Infants of affected women also had longer birth hospitalizations but were no more likely to be re-admitted < 2 years after delivery, compared to infants of women without neoplasms.

Table 4 Length of delivery hospitalization and occurrence of rehospitalization < 2 years for women with, and without neoplasms and their infants

Hospitalization	No cancer $n = 139{,}765$		Benign $n = 13{,}156$				Malignant $n = 707$			
	n	%	*n*	%	RR[a]	95% CI	*n*	%	RR[a]	95% CI
Mother										
Delivery hospitalization (days)[b]										
< 7	138,219	98.89	12,804	97.32	(Ref)		647	91.51	(Ref)	
7+	1,546	1.11	352	2.68	1.28	1.09–1.47	60	8.49	7.00	5.03–8.99
Rehospitalized[d]										
No	116,194	87.22	10,737	85.66	(Ref)		416	66.56	(Ref)	
Yes	17,026	12.78	1,797	14.34	1.21	1.15–1.28	209	33.44	2.96	2.61–3.31
Infant										
Delivery hospitalization (days)[c]										
< 7	128,361	96.63	11,799	94.41	(Ref)		573	88.15	(Ref)	
7+	4,473	3.37	698	5.59	1.58	1.43–1.73	77	11.85	3.69	2.74–4.64
Rehospitalized[c,e]										
No	125,691	90.84	11,900	91.44	(Ref)		622	89.37	(Ref)	
Yes	12,675	9.16	1,114	8.56	1.08	1.01–1.16	74	10.63	1.23	0.91–1.54

Ref reference, *RR* risk ratio, *CI* confidence interval

[a]All risk ratios adjusted for delivery year, maternal age, marital status, insurance, and parity

[b]Adjusted additionally for delivery method

[c]Fetal deaths excluded (671 comparison; 67 benign; eight malignancies)

[d]Maternal deaths excluded (73 comparison; seven benign; 57 malignancies)

[e]Infant deaths (664 comparison; 74 benign; three malignancies) and children discharged alive but died < 2 years after delivery (64 comparison; one benign; zero malignancies) excluded

Neoplasm distribution

Breast cancer was the most frequent malignancy during pregnancy observed, consistent with most reports from studies of women with newly diagnosed cancer during pregnancy [4, 20] but different from studies of cancer survivors who later became pregnant, in which prior malignant skin cancer (melanoma) was the most common neoplasm diagnosis [21, 22]. This suggests that cancer diagnoses as measured by ICD-9 codes in our data are more likely to be newly diagnosed during gestation, rather than indication of pre-pregnancy diagnoses, although we lacked information about the specific timing.

Obstetrical conditions and outcomes

Despite a growing number of studies on pregnant women with malignancies, there is relatively little information on the distribution of benign neoplasms complicating pregnancy. In our population-based data, there were approximately 18 times more women with benign neoplasms than with malignancies. Pregnant women with benign neoplasms generally receive different and less onerous (typically non-systemic) treatments than women with malignancies and likely have fewer concerns about their own or their infants' health. However, prior research has demonstrated increased risks of several adverse pregnancy outcomes (e.g., cesarean sections, preterm births, breech presentation) among women with benign neoplasms [23, 24], relative to women without these conditions. Our results support these findings and suggest that women with benign neoplasms during pregnancy may also have modestly increased risk of gestational diabetes, preeclampsia, and anemia.

Increased maternal anemia in women with malignancies might be due to the burden of cancer; however, reasons for the observed increased risk among women with benign tumors are unclear. It is possible that submucosal fibroids (the majority of women in our study with benign neoplasm codes having leiomyomas) cause heavier menstrual bleeding that may lead to anemia [25]. Reasons for the observed modest increased gestational diabetes and preeclampsia risks in women with benign neoplasms are unclear, although an association of endometrial hyperplasia with gestational diabetes has been reported [26], possibly due to excess levels of circulating insulin. An association of leiomyoma with preeclampsia has been reported in some [27] but not all [28] prior studies; possible mechanisms to explain such an association may include shared microRNA expression pathways [29] or characteristics related to apoptosis and cell proliferation [30]. Both neoplasm groups were more likely to have cesarean deliveries than comparison women, the risk for benign

neoplasm likely because of the association of leiomyoma with cesarean delivery [28].

Closer monitoring of women with neoplasms may result in more frequent reporting of at least some of the adverse outcomes for which we observed increased risks. One might expect this especially among women with malignancies; however, we also observed increased RRs among women with benign neoplasms for selected outcomes. Increased cesarean deliveries among women with malignancies may be due to a need to reduce the burden of labor in women with cancer, or to increased elective cesarean deliveries in order to initiate therapy as soon as possible, whereas increased cesarean delivery among women with benign neoplasms is likely driven by the fact that the majority had leiomyomas that may have obstructed normal placental placement and the course of labor.

Infant outcomes

Similar to other studies, we observed greater risk of preterm delivery among pregnancies complicated by malignancies [9, 22]. We also found a 38% increased risk of preterm delivery among infants born to women with benign neoplasms, similar to a prior study of women with leiomyoma [28].

Women with benign neoplasms are less likely to be treated during pregnancy than are women with malignancies. Iatrogenic/elective preterm deliveries to hasten the diagnostic process and initiate cancer treatment were suggested as an important factor for the fivefold increased risk of preterm delivery among women with malignancies observed in a previous study [22]. Compared with the threefold increased risk of preterm delivery in our study, this earlier study included fewer types of malignancies and was not population-based, which may explain the slight difference in these risk estimates.

Greater risk of other adverse neonatal outcomes such as low birthweight is documented among preterm births [31]. We observed increased low birthweight and jaundice among both groups of infants born to women with neoplasms even after conditioning on infants' gestational age. Newborns of women with neoplasms were more likely to have low birthweight or to be jaundiced than comparison infants of the same gestational age. This implies that maternal neoplasms might have other pathways than through preterm deliveries to affect infants' uterine growth. Women with benign or malignant neoplasms both were also more likely to have anemia during pregnancy. Maternal anemia could result in intrauterine malnourishment and subsequently restrict fetal growth [32].

We observed 6% prevalence of congenital malformations among live born infants of women without neoplasms; slightly greater than the US average prevalence of 3–5% [33, 34], possibly because of varying inclusion criteria and case ascertainment methods across studies. We included all congenital malformations within the range of relevant ICD codes instead of a limited number of major structural defects or chromosomal anomalies, as is the practice of many birth defects registries. We also ascertained cases from hospital discharge records to improve the completeness of identifying malformations from birth certificates. In comparison to infants of women without neoplasms, infants of women with malignancies were not more likely to have congenital malformations. Although we lacked cancer treatment information, our findings support prior studies indicating no greater risks of severe problems among fetuses of women who received chemotherapy after the first/second trimester [11, 35]. The observed 29% greater risk of malformations among infants of women with benign neoplasms is perhaps due to the majority of these cases having leiomyoma, a condition previously associated with increased infant malformations [28]. Fibroids may compress and distort the intrauterine cavity leading to limb reduction, caudal dysplasia, and head deformation [36]. Little is known about infant outcomes in relation to other benign neoplasms; however, no increased malformation, low birthweight, or mortality were noted in a prior study of women with benign ovarian cysts [37].

Hospitalization

Women with benign or malignant neoplasms had increased risks of having delivery hospitalizations of 7 days or longer, regardless of delivery method. The 28% increased risk of longer hospitalization may have been due to additional rest or monitoring needed because of the greater occurrence of adverse obstetrical conditions, although the sevenfold risk of longer hospitalizations among women with malignancies may also be related to initiation of cancer treatment after delivery. Additional studies with cancer treatment information are needed to elucidate this.

We also observed longer hospitalizations for infants of mothers with neoplasms, a result that persisted after adjustment for the maternal length of hospitalization. However, it is reassuring that infants of mothers with benign or malignant neoplasms did not have markedly greater rehospitalization risks, suggesting no serious morbidity in the first 2 years of life due to gestational exposure to maternal neoplasm. This is consistent with prior findings that maternal cancer and therapies after the second trimester may not greatly affect the long-term health of infants [38].

Limitations

We could not identify rehospitalizations among women who migrated out of Washington State after delivery. This could introduce bias if women with cancer diagnoses were more or less likely to move out of state than comparison

women. However, it seems unlikely that this would have led to a twofold higher risk for readmission among women with malignancies. It is also unlikely that benign neoplasms are related to more/less frequent migration. Outmigration bias is not a concern for infant mortality, as death certificates for State residents who die in other states or countries are obtained through intra-agency agreements. Another limitation is the lack of disease severity and treatment information. Cancer stage or the severity of benign neoplasms, as well as the type/timing of treatment, may greatly affect obstetrical and neonatal outcomes. Underdiagnoses may occur for asymptomatic women or those with very mild disease at delivery. Misclassification of cases into the comparison group would have biased our estimates toward the null. As women with more advanced neoplasms may be less likely to attempt pregnancy or to conceive, we may have only included women with less serious disease in our case groups. This could have made it more difficult to detect increased risk for some outcomes.

Only linked vital records-hospital discharge data were available for this project; we were unable to verify neoplasm status in medical records or to access treatment information. Although the neoplasm distribution we observed based on ICD-9 codes is more consistent with that of women newly diagnosed during pregnancy than of women with prior diagnoses, we cannot be certain when diagnosis occurred. Identification of incident breast cancer (most common malignancy in our data) by ICD-9 codes is improved in combination with cancer registry data [39], a resource not available for this project. In previous assessments of the identification of breast [40–42] and lung [42] cancer using ICD-9 codes, proportions of cases with these malignancies identified by codes who were found to truly have disease (positive predictive value, or PPV) were 68%–88% [41–43] and 93% [42] for breast and lung cancer, respectively. These studies were not restricted to pregnant women (or even to women for non-breast cancer sites) and included all ages. The extent to which inclusion of procedure codes might have improved our ability to identify neoplasms is unclear, as operations and treatments are often delayed during pregnancy. Unfortunately, we could not extend our observation window to include subsequent rehospitalizations or outpatient treatments.

For benign neoplasms, an earlier study with data from our state compared hospital discharge records of women with leiomyoma to medical records; a PPV of 95% was calculated [28], consistent with similar data from California (PPV 100%) [44]. Small or asymptomatic fibroids or other benign neoplasms were probably less likely to have been identified; if no complications occurred, these may not have been identified in our data, which would have biased our results toward the null.

Outcome measures also relied on linked vital-hospital discharge data, with PPVs in earlier studies assessed as quite high for delivery type, birthweight, and preterm delivery (87%–100%) [44–49]; gestational diabetes (PPV 72%–91%) [16, 45, 46]; preeclampsia (91%–100% in U.S. studies) [44, 45] poly- (100%) or oligohydramnios (68%–96%) [44, 46]; *placenta previa* (75%–100%) [16, 44, 46]; *abruptio placenta* (82%–100%) [16, 44, 46, 48] breech/malpresentation (67%–99%) [44, 46–48]; use of instrumentation/forceps (90%–99%) [44, 50]; and Apgar score [46, 48]. Lower PPVs were reported for preterm rupture of membranes, anemia, precipitous or prolonged labor, and fetal distress (lowest being anemia 14%–36%) [44–48]. The PPV for identification of major malformations using birth and hospital discharge data overall is 68%, with variation by organ system [51]. Misclassification of outcomes not well measured in our data would have biased our estimates, e.g., if monitoring of women with neoplasms was enhanced, it is possible that some adverse outcomes among women in the comparison group were not recorded; this would have biased our results toward the null.

Small numbers also hampered our ability to evaluate risks for specific tumor types. Finally, as information about earlier pregnancy loss or terminations was unavailable, we only included women with live singleton births and fetal deaths $\geq$ 20 weeks and could not examine earlier or other outcomes.

Conclusions

Our results support prior studies suggesting that women with malignant neoplasms have increased risks of many adverse obstetrical outcomes compared to women without neoplasm codes. Their infants also are more likely to have selected adverse neonatal outcomes than their counterparts. Effects of benign neoplasms on pregnancy have rarely been studied. Some of our results (e.g., association with gestational diabetes, preeclampsia) have not been reported and suggest areas for future study. These findings emphasize the need for close surveillance and management for pregnant women with benign, as well as malignant neoplasms and their infants. Further studies with detailed clinical and treatment information are warranted to elucidate associations with adverse obstetrical outcomes.

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Compliance with ethical standard

Conflicts of interest The authors declare that they have no conflicts of interest.

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