Department of Clinical Epidemiology

Threatened abortion and risk of cancer

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Abstract

The objective of the study was to investigate an association between TA and the woman's subsequent increased risk of cancer. We conducted a nationwide cohort study of 105,277 women with a first-time threatened abortion (TA) diagnosis in Denmark (1978-2013) with up to 33 years of follow-up. We used indirectly-standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) calculated by dividing the observed by the expected number of cases to estimate the association between TA and cancer. During the follow-up, 6571 women with TA had a cancer diagnosis. The SIR for any cancer in women with TA was 1.01 (95% CI: 0.98–1.03). TA diagnosis did not increase risk of any cancer at 6 months, 12 months or more than 12 months of follow-up. TA was not associated with an increased risk of cancer of breast, uterine cervix, ovary or uterus. In conclusion, having a TA diagnosis did not increase risk of any or site-specific cancers when compared with women from the general population.

Background

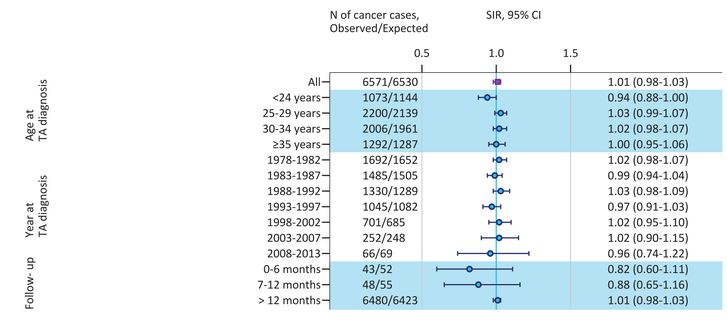
- Threatened abortion (TA) is a vaginal bleeding occurring before the 20th week of gestation in a woman with a viable intrauterine pregnancy.
- In pregnancies with TA the abortogenic Th1 immunity arm with elevated levels of proinflammatory and coagulation-activating cytokines (TNF-α, IL-1-β and IL-6) is overrepresented. Hypercoagulability, in turn, causes venous thromboembolism (VTE).
- VTE is indicative of occult cancer.
- We hypothesised that TA, mediated by cytokine-activated inflammation and hypercoagulability, may be associated with the woman's subsequent increased risk of cancer.

Methods

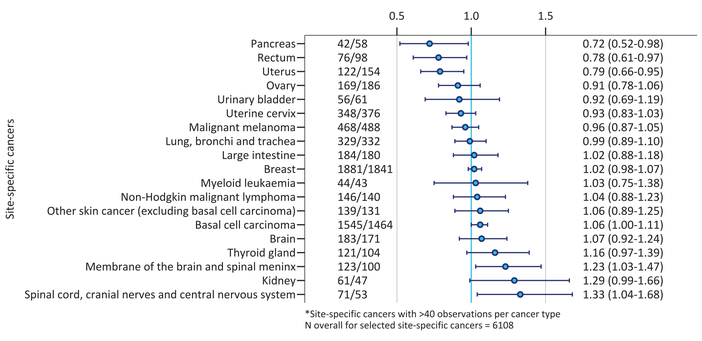
- We conducted a nationwide cohort study using the Danish National Patient Registry to identify all women with a first-time hospital diagnosis of TA from 1 January 1978 through 30 November 2013.
- We followed the cohort of women from TA diagnosis until the earliest of:
  - an incident primary cancer diagnosis as registered in the Danish Cancer Registry
  - death or emigration as registered in the Danish Civil Registration System
  - the study end (30 November 2013).
- We linked the data from different registries on individual level via unique personal identifier.
- To estimate the association between TA and cancer, we calculated indirectly-standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) by dividing the observed by the expected number of cases.
- Expected number of cancer cases was based on cancer incidence rates of women from the general population.

Figure 1 SIRs of cancers in women with TA, Denmark, 1978-2013

A. SIRs of all cancers in women with TA by age at TA diagnosis, year of TA diagnosis and duration of follow-up



B. SIRs of various cancers* in women diagnosed with TA



*Site-specific cancers with >40 observations per cancer type
N overall for selected site-specific cancers = 6108

Table 1 Standardized Incidence Ratios (SIRs) of site-specific cancer among women with threatened abortion (TA) by follow-up duration, Denmark, 1978-2013. Only malignancies with more than 40 observations overall were included (N = 6108)

Cancer type	Follow-up duration					
	<6 months		6-12 months		>12 months	
	N of cancer cases, observed/ expected	SIR (95% CI)	N of cancer cases, observed/ expected	SIR (95% CI)	N of cancer cases, observed/ expected	SIR (95% CI)
Pancreas	0	–	0	–	42/57.8	0.73 (0.52-0.98)
Rectum	0	–	1/0.4	2.52 (0.06-14.05)	75/97.2	0.77 (0.61-0.97)
Uterus	1/0.4	2.68 (0.07-14.91)	0	–	121/152.9	0.79 (0.66-0.95)
Ovary	3/1.6	1.84 (0.38-5.36)	2/1.7	1.18 (0.14-4.28)	164/82.5	0.90 (0.77-1.05)
Urinary bladder	0	–	1/0.3	3.43 (0.09-19.10)	55/60.5	0.91 (0.68-1.18)
Uterine cervix	9/8.2	1.10 (0.50-2.08)	3/8.5	0.35 (0.07-1.04)	336/358.9	0.94 (0.84-1.04)
Malignant melanoma	4/7.7	0.52 (0.14-1.33)	10/7.9	1.27 (0.61-2.33)	454/472.4	0.96 (0.87-1.05)
Lung, bronchi and trachea	0	–	1/0.8	1.31 (0.03-7.32)	328/ 330.3	0.99 (0.89-1.11)
Large intestine	0	–	1/0.8	1.26 (0.03-6.99)	183/178.1	1.03 (0.88-1.19)
Breast	5/9.3	0.54 (0.17-1.25)	11/10.1	1.09 (0.54-1.94)	1865/1821.5	1.02 (0.98-1.07)
Myeloid leukaemia	1/0.7	1.50 (0.04-8.36)	0	–	43/41.4	1.04 (0.75-1.40)
Non-Hodgkin malignant lymphoma	0	–	1/1.2	0.81 (0.02-4.52)	145/137.3	1.06 (0.89-1.24)
Other skin cancer (excluding basal cell carcinoma)	1/0.8	1.29 (0.03-7.16)	1/0.8	1.23 (0.03-6.83)	137/129.2	1.06 (0.89-1.25)
Basal cell carcinoma	9/8.1	1.11 (0.51-2.10)	12/8.7	1.11 (0.51-2.10)	1524/1447.2	1.05 (1.00-1.11)
Brain	2/3.1	0.64 (0.08-2.30)	2/3.2	0.63 (0.08-2.26)	179/164.8	1.09 (0.93-1.26)
Thyroid gland	1/1.7	0.58 (0.01-3.22)	0	–	120/100.4	1.19 (0.99-1.43)
Membrane of the brain and spinal meninx	0	–	1/0.7	1.40 (0.04-7.77)	122/98.3	1.24 (1.03-1.48)
Kidney	0	–	0	–	61/46.8	1.30 (1.00-1.68)
Spinal cord, cranial nerves and central nervous system	2/0.7	2.79 (0.34-10.08)	0	–	69/51.9	1.33 (1.03-1.68)

Results

- We identified 105,277 women with a first-time TA diagnosis:
  - median age at TA = 28.7 years (interquartile range 25.1–32.5 years)
  - median follow-up = 16.9 years (interquartile range 10.5–24.4 years)
  - 6,571 women with TA had a cancer diagnosis during the follow-up.
- The SIR for any cancer in women with TA was 1.01 (95% CI: 0.98–1.03).
- TA diagnosis did not increase risk of any cancer at the follow-up of:
  - 6 months (SIR = 0.82, 95% CI: 0.60–1.11)
  - 12 months (SIR = 0.88, 95% CI: 0.65–1.16)
  - more than 12 months (SIR = 1.01, 95% CI: 0.98–1.03).

→ see Figure 1A

- TA was not associated with an increased risk of cancer of:
  - breast (SIR = 1.02, 95% CI: 0.98–1.07)
  - uterine cervix (SIR = 0.93, 95% CI: 0.83–1.03)
  - ovary (SIR = 0.91, 95% CI: 0.78–1.06)
  - uterus (SIR = 0.79, 95% CI: 0.66–0.95).

→ see Figure 1B
Results did not vary by women's age or calendar year of TA diagnosis.

- Few site-specific cancer cases were observed over the first 6 and 12 months of follow-up, with SIRs being moderately increased for certain cancers, however, the estimates were imprecise (see Table 1).

Discussion

- Our study has several key features:
  - population-based design
  - long and virtually complete follow-up of the cohort
  - availability of nation-wide prospectively collected data
- Since we compared cancer incidence rates in women diagnosed with TA vs. cancer incidence rates in women from the general population, we cannot rule out that the association of TA and cancer was confounded by pregnancy.
- If the comparison of women diagnosed with TA would be made with a population of pregnant women, higher SIRs of cancer could be observed.

Conclusion

- Our study showed that having a TA diagnosis did not increase risk of any or site-specific cancers when compared with women from the general population.

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