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ORIGINAL ARTICLE ***Reproductive epidemiology***

Risk of infertility in female adolescents and young adults with cancer: a population-based cohort study

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STUDY QUESTION: Do female adolescents and young adults (AYAs) with cancer have a higher risk of subsequent infertility diagnosis than AYAs without cancer?

SUMMARY ANSWER: Female AYAs with breast, hematological, thyroid and melanoma cancer have a higher risk of subsequent infertility diagnosis.

WHAT IS KNOWN ALREADY: Cancer therapies have improved substantially, leading to dramatic increases in survival. As survival improves, there is an increasing emphasis on optimizing the quality of life among cancer survivors. Many cancer therapies increase the risk of infertility, but we lack population-based studies that quantify the risk of subsequent infertility diagnosis in female AYAs with non-gynecological cancers. The literature is limited to population-based studies comparing pregnancy or birth rates after cancer against unexposed women, or smaller studies using markers of the ovarian reserve as a proxy of infertility among female survivors of cancer.

STUDY DESIGN, SIZE, DURATION: We conducted a population-based cohort study using universal health care databases in the province of Ontario, Canada. Using data from the Ontario Cancer Registry, we identified all women 15–39 years of age diagnosed with the most common cancers in AYAs (brain, breast, colorectal, leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, thyroid and melanoma) from 1992 to 2011 who lived at least 5 years recurrence-free (Exposed, $n = 14{,}316$). Women with a tubal ligation, bilateral oophorectomy or hysterectomy previous to their cancer diagnosis were excluded. We matched each exposed woman by age, census subdivision, and parity to five randomly selected unexposed women ($n = 60{,}975$) and followed subjects until 31 December 2016.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Infertility diagnosis after 1 year of cancer was identified using information on physician billing codes through the Ontario Health Insurance Plan database (ICD-9 628). Modified Poisson regression models were used to assess the risk of infertility diagnosis (relative risk, RR) adjusted for income quintile and further stratified by parity at the time of cancer diagnosis (nulliparous and parous).

MAIN RESULTS AND THE ROLE OF CHANCE: Mean age at cancer diagnosis was 31.4 years. Overall, the proportion of infertility diagnosis was higher in cancer survivors compared to unexposed women. Mean age of infertility diagnosis was similar among cancer survivors and unexposed women (34.8 years and 34.9 years, respectively). The overall risk of infertility diagnosis was higher in cancer survivors (RR 1.30; 95% CI 1.23–1.37). Differences in infertility risk varied by type of cancer. Survivors of breast cancer (RR 1.46; 95% CI 1.30–1.65), leukemia (RR 1.56; 95% CI 1.09–2.22), Hodgkin lymphoma (RR 1.49; 95% CI 1.28–1.74), non-Hodgkin lymphoma (RR 1.42; 95% CI 1.14, 1.76), thyroid cancer (RR 1.20; 95% CI 1.10–1.30) and melanoma (RR 1.17; 95% CI 1.01, 1.35) had a higher risk of infertility diagnosis compared to women without cancer. After stratification by parity, the association remained in nulliparous women survivors of breast cancer, leukemia, lymphoma and melanoma, whereas it was attenuated in parous women. In survivors of thyroid cancer, the association remained statistically significant in both nulliparous and parous women. In survivors of brain or colorectal cancer, the association was not significant, overall or after stratification by parity.

LIMITATIONS, REASONS FOR CAUTION: Non-biological factors that may influence the likelihood of seeking a fertility assessment may not be captured in administrative databases. The effects of additional risk factors, including cancer treatment, which may modify the associations, need to be assessed in future studies.

WIDER IMPLICATIONS OF THE FINDINGS: Reproductive health surveillance in female AYAs with cancer is a priority, especially those with breast cancer, leukemia and lymphoma. Our finding of a potential effects of thyroid cancer (subject to over-diagnosis) and, to a lesser extent, melanoma need to be further studied, and, if an effect is confirmed, possible mechanisms need to be elucidated.

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Introduction

Adolescents and young adults (AYAs), aged 15–39 years at the time of cancer diagnosis, are a unique population in terms of both the biology of their cancers and the way they experience their cancer journey (Canadian Partnership Against Cancer 2017). This age range encompasses the majority of the reproductive life span, in which fundamental events in a woman's life occur. Improvements in cancer therapies have resulted in increasing survival rates. As survival improves, there is more emphasis on optimizing health and quality of life among survivors (Johnson *et al.*, 2016). Cytotoxic drugs, radiation therapy, surgery and the disease process itself can all result in infertility (Lee *et al.*, 2006). Continued surveillance is needed as the therapies and strategies for treating cancer are in constant evolution.

The literature on the risk of infertility in AYAs with cancer is limited to population-based studies comparing pregnancy or birth rates in women after treatment for cancer to women without cancer (unexposed). Using childbirth information in survivors of AYA cancers, studies from Finland (Madanat *et al.*, 2008) and Norway (Syse *et al.*, 2007, Stensheim *et al.*, 2011) show reduced childbirth rates as compared to the general population or matched controls. However, these studies include patients diagnosed over a long time period (as early as 1953), and reflect treatments that have changed over time. More recently, Baxter *et al.*, (2013) conducted a population-based matched cohort study to investigate childbirth in women diagnosed with non-gynecological malignancies at ages 20–34 years in Ontario between 1992 and 1999. Overall, survivors experienced a longer time to childbirth than controls, differing by cancer type and parity before cancer diagnosis. In Scotland, Anderson *et al.*, (2018) studied the impact of cancer in women diagnosed before the age of 40 years between 1981 and 2012 on subsequent pregnancies (miscarriage, termination of pregnancy, or delivery of a still or live born infant) compared to the number expected based on pregnancy rates in the general population. In general, cancer survivors had fewer pregnancies and the probability of having a first pregnancy was lower.

Pregnancy and childbirth rates are commonly used to study fertility rates at the population-based level. However, this study design fails to identify whether the childlessness is voluntary or due to infertility and, even among those who conceive, overall fertility rates do not identify the growing proportion of infants conceived through infertility treatment (Buck Louis 2011). The challenge is to identify markers of infertility at the population-level. Data linkage through health administrative databases provide an opportunity to address this issue, with landmark population-based studies on fertility and reproductive outcomes in the US, The Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART) (Declercq *et al.*, 2014), and Denmark (Jensen *et al.*, 2007), using ICD-9 or ICD-10 codes to identify infertility diagnosis at the population level.

Although female AYAs with cancer may experience decreased pregnancy and childbirth rates, the risk of infertility diagnosis after cancer has not been quantified at the population level. With this aim, we conducted a population-based cohort study in Ontario, Canada, to assess the risk of subsequent infertility diagnosis in female AYAs diagnosed with brain, breast, hematological, colorectal or thyroid cancer or melanoma: the most common non-gynecological cancers in this population (Canadian Partnership Against Cancer 2017).

Materials and methods

Data sources

We conducted a retrospective cohort study using linked administrative health care databases housed at ICES (www.ices.on.ca) using unique encoded identifiers. Data about incident cancers were obtained from the Ontario Cancer Registry (OCR), a provincially mandated registry that contains information on all incident cancer diagnoses in Ontario since 1964. The registry is over 95% complete. We also used the Ontario Health Insurance Plan (OHIP) database, which contains physician billing claims for services allowing identification of virtually all medical consults and diagnosis, the Registered Persons Database (RPDB), which provides demographic and eligibility information on all OHIP beneficiaries, and the Permanent Resident Database of Citizenship and Immigration Canada (CIC), which provides information about the immigrations status. In addition, we used the MOMBABY database, a validated database of pregnancy outcomes and mother-infant linkage that includes pregnancies >20 weeks gestation resulting in a hospital livebirth or stillbirth or pregnancy termination since 1988, and captures about 98% of all birth in Ontario (ICES).

Selection of female AYAs survivors of cancer

AYAs were identified using the OCR. All females aged 15-39 diagnosed with brain, breast, hematological, colorectal or thyroid cancer

or melanoma from 1992-2011 were eligible for inclusion. Women were excluded if they: had a diagnosis of infertility prior to a cancer diagnosis (OHIP ICD-9 billing code 628), died within 5 years of diagnosis, were not continuously eligible for provincial health insurance coverage for at least 5 years after diagnosis, had a cancer recurrence within 5 years of diagnosis, were missing census subdivision data from the RPDB, were registered in the OCR for a previous malignancy or had a tubal ligation, hysterectomy or bilateral oophorectomy at any point prior to cancer diagnosis or in the first year after their cancer diagnosis.

Cancer recurrence

The OCR does not include information on cancer recurrence, and therefore the algorithm created by Baxter *et al.*, (2013) was adapted and used to identify survivors with evidence of disease recurrence. Survivors with evidence of disease recurrence within 5 years of diagnoses were excluded from analysis.

Selection of controls (unexposed)

The female control population was identified using the RPDB. Women who were missing census subdivision data were excluded from the control population. As matching on parity was required, parity for each year of study (1992–2011) was determined as parity may have changed throughout the study period. A control was considered parous for a given year if they were recorded as having a delivery in the MOMBABY dataset at any point that year or in any of the years preceding the given year. Five controls were randomly selected from the full control population and matched to a given survivor on birth year, census subdivision and parity. The referent date for each control was assigned as the diagnosis date of the matched survivor. Controls were excluded if they had a diagnosis of infertility prior to the referent date, died within 5 years of the referent date, were recorded in the OCR as having a cancer diagnosis prior to the referent date, or were not continuously eligible for the OHIP in the 5 years after the referent date.

Covariates

Socioeconomic status was determined using the income quintile associated with the census dissemination area of the residence at the date of cancer diagnosis or referent date. Parity was identified using the MOMBABY dataset. Women were classified as parous if they had a record of a delivery in MOMBABY prior to their cancer diagnosis or the referent date.

Outcome

Infertility diagnosis, 1 year after a cancer diagnosis or referent date, was identified using information on claims billed by a physician through the OHIP database (ICD-9 628). Any woman with at least one billing record with a diagnosis of infertility was considered to have a diagnosis of infertility. Women were followed until 31 December 2016 to allow for a minimum of 5 years of follow-up for all women.

Statistical analyses

Baseline characteristics were compared using standardized differences. The standardized difference describes between-group differences in units of standard deviation and is not influenced by sample size (and thus is considered a better alternative to use of the p-value in large cohorts). Standardized differences greater than 0.10 are considered clinically meaningful (Austin 2009). Modified Poisson regression models, accounting for the matched pairs and follow-up time, were used to assess differences in infertility rates by cancer type and the relative risk of infertility, adjusting for income quintile. Unadjusted and adjusted RR were very similar; thus, only adjusted RR are presented. Models were also stratified by parity at the time of cancer diagnosis or the referent date, as parity influences seeking infertility assessment, with parous women consulting 60% less frequently compared to nulliparous women when faced with a delay in conception (Moreau *et al.*, 2010).

Data were analyzed using SAS version 9.4 (Cary, North Carolina) at ICES Queen's.

Ethical approval

The study was approved by the Queen's University Health Sciences and Affiliated Hospitals Research Ethics Board.

Results

Table I describes the characteristics of the population. AYAs survivors of cancer were similar to unexposed women without cancer in terms of age at cohort entry, parity, obesity, immigration status and income quintiles (as per matching criteria). Mean age at cancer diagnosis was 31.4 years. The median follow-up time was similar for cancer survivors and unexposed women (13.1 years and 13.6 years, respectively, standardized difference 0.08). A total of 5,144 women (35.9%) had thyroid cancer, 3,782 (26.4%) had breast cancer, and 2,181 (15.2%) had melanoma. Other types of cancer were less frequent. At the time of cancer diagnosis, 8,290 women (58%) were nulliparous.

Overall, the proportion of infertility diagnosis was higher in cancer survivors compared to unexposed women ranging from 8.9% in women with breast and colorectal cancer to 17.3% in women with Hodgkin lymphoma (Table II). Mean age of infertility diagnosis was similar among cancer survivors and unexposed women (34.8 and 34.9 years, respectively, standardized difference = 0.02). Among those with infertility (data not shown), the baseline characteristics at cohort entrance between cancer survivors and unexposed women were similar in terms of age, parity and income quintile.

The overall risk of infertility diagnosis was higher in cancer survivors (RR 1.30; 95% CI 1.23–1.37). Differences varied by type of cancer. Notably, AYAs with breast cancer (RR 1.46; 95% CI 1.30–1.65), leukemia (RR 1.56; 95% CI 1.09–2.22), Hodgkin lymphoma (RR 1.49; 95% CI 1.28–1.74), non-Hodgkin lymphoma (RR 1.42; 95% CI 1.14–1.76), thyroid cancer (RR 1.20; 95% CI 1.10–1.30), and melanoma (RR 1.17; 95% CI 1.01–1.35) had a higher risk of infertility diagnosis than women without cancer.

After stratification by parity, the association remained in nulliparous survivors of breast cancer (RR 1.63, 95% CI 1.43–1.87), leukemia (RR 1.67, 95% CI 1.14–2.44), Hodgkin lymphoma (RR 1.53, 95% CI 1.30–1.79), non-Hodgkin lymphoma (RR 1.52, 95% CI 1.20–1.91)

Table I Characteristics of the study population, Ontario, Canada 1992-2011

Characteristic		Survivors N = 14,316	Unexposed N = 60,975	Standardized Difference
Age at diagnosis*	Mean ± SD	31.4 ± 6.3	31.2 ± 6.4	0.04
	Median (IQR)	33 (27–37)	33 (27–37)	0.04
Age group	15–29	4,728 (33.0%)	21,327 (35.0%)	0.04
	30–39	9,588 (67.0%)	39,648 (65.0%)	0.04
Parity	Nulliparous	8,290 (57.9%)	36,164 (59.3%)	0.03
	Parous	6,026 (42.1%)	24,811 (40.7%)	0.03
Income quintile	1	2,542 (17.8%)	12,267 (20.1%)	0.06
	2	2,760 (19.3%)	12,298 (20.2%)	0.02
	3	2,928 (20.5%)	12,178 (20.0%)	0.01
	4	3,186 (22.3%)	12,466 (20.4%)	0.04
	5	2,856 (19.9%)	11,481 (18.8%)	0.03
	Missing	44 (0.3%)	285 (0.5%)	0.03
Obesity at baseline	No	13,734 (95.9%)	58,507 (96.0%)	0
	Yes	582 (4.1%)	2,468 (4.0%)	0
Immigration status	Immigrant	2,521 (17.6%)	11,547 (18.9%)	0.03
	Non-immigrant	11,795 (82.4%)	49,428 (81.1%)	0.03
Type of malignancy*	Brain	574 (4.0%)	2,517 (4.1%)	0.01
	Breast	3,782 (26.4%)	15,755 (25.8%)	0.01
	Colorectal	361 (2.5%)	1,510 (2.5%)	0
	Leukemia	292 (2.0%)	1,281 (2.1%)	0
	Hodgkin lymphoma	1,240 (8.7%)	5,516 (9.0%)	0.01
	Non-Hodgkin Lymphoma	742 (5.2%)	3,208 (5.3%)	0
	Thyroid	5,144 (35.9%)	21,846 (35.8%)	0
	Melanoma	2,181 (15.2%)	9,342 (15.3%)	0

*Values shown in the unexposed column correspond to number (%) of matched controls as evidence of the adequacy of the matching process.

Table II Proportion of infertility diagnosis among female AYA with cancer and unexposed women

	AYA with cancer N = 14,316	Unexposed N = 60,975	*P*-value*
All	1,649 (11.5%)	5,616 (9.2%)	<0.001
Brain cancer	61 (10.6%)	226 (9.0%)	0.06
Breast cancer	338 (8.9%)	1023 (6.5%)	<0.001
Colorectal cancer	32 (8.9%)	118 (7.8%)	0.43
Leukemia	40 (13.7%)	118 (9.2%)	0.01
Hodgkin lymphoma	215 (17.3%)	661 (12%)	<0.001
Non-Hodgkin lymphoma	109 (14.7%)	348 (10.9%)	0.001
Thyroid cancer	615 (12.0%)	2223 (10.2%)	<0.001
Melanoma	239 (11.0%)	899 (9.6%)	0.03

**P* values from unadjusted modified Poisson regression models.

and melanoma (RR 1.20, 95% CI 1.02–1.41), whereas it was no longer associated in parous women (Table III). In survivors of thyroid cancer, the association remained significant in both nulliparous (RR 1.18, 95% CI 1.07–1.31) and parous (RR 1.34, 95% CI 1.12–1.61) women. In survivors of brain or colorectal cancer, the association was not significant, overall or after stratification by parity (Table III).

Discussion

Our study indicates that young female survivors of non-gynecological cancer have a higher risk of subsequent infertility diagnosis, particularly those with breast, hematological, thyroid cancer and melanoma, as compared to age-matched controls without cancer. After stratification by parity, the association remained in nulliparous survivors of breast cancer, leukemia, lymphoma and melanoma, whereas it was attenuated in parous women. In survivors of thyroid cancer, the association remained statistically significant in both nulliparous and parous women. In survivors of brain or colorectal cancer, the association was not significant, overall or after stratification by parity.

To our knowledge, this is the first population-based matched-cohort study assessing the association between a cancer diagnosis and a subsequent infertility diagnosis using the ICD-9 code 628 as a proxy for infertility. Other population-based studies have used different definitions of infertility. In the Childhood Cancer Survivors Study, the risk of infertility, defined as more than one year of attempts at conception without success, was higher for survivors compared with their siblings

Table III Adjusted relative risk of infertility diagnosis in survivors of AYA cancer in Ontario, 1992–2011

	All women		Nulliparous		Parous	
Malignancy type	**RR (95% CI)**	***p*-value**	**RR (95% CI)**	***p*-value**	**RR (95% CI)**	***p*-value**
All	1.30 (1.23, 1.37)	<0.001	1.34 (1.26, 1.42)	<0.001	1.25 (1.10, 1.42)	<0.001
Brain cancer	1.32 (0.99, 1.76)	0.06	1.28 (0.93, 1.75)	0.13	1.72 (0.86, 3.42)	0.12
Breast cancer	1.46 (1.30, 1.65)	<0.001	1.63 (1.43, 1.87)	<0.001	1.07 (0.81, 1.40)	0.64
Colorectal cancer	1.14 (0.77, 1.69)	0.51	1.08 (0.69, 1.69)	0.73	1.50 (0.61, 3.72)	0.38
Leukemia	1.56 (1.09, 2.22)	0.01	1.67 (1.14, 2.44)	0.01	1.08 (0.33, 3.55)	0.90
Hodgkin lymphoma	1.49 (1.28, 1.74)	<0.001	1.53 (1.30, 1.79)	<0.001	1.32 (0.78, 2.24)	0.30
Non-Hodgkin lymphoma	1.42 (1.14, 1.76)	0.001	1.52 (1.20, 1.91)	<0.001	1.08 (0.58, 2.00)	0.82
Thyroid cancer	1.20 (1.10, 1.30)	<0.001	1.18 (1.07, 1.31)	0.001	1.34 (1.12, 1.61)	0.002
Melanoma	1.17 (1.01, 1.35)	0.03	1.20 (1.02, 1.41)	0.03	1.14 (0.80, 1.62)	0.46

(1.48, 95% CI 1.23–1.78) (Barton *et al.*, 2013). In the AYA population, other studies have reported pregnancy and birth rates as markers of subsequent fertility. Studies from Finland (0–34 years) (Madanat *et al.*, 2008) and Norway (16–45 years) (Syse *et al.*, 2007, Stensheim *et al.*, 2011) showed reduced fertility as compared to the general population or matched controls; however, these studies included patients diagnosed over a long time period (as early as 1953) and reflect treatments that have changed over time (Madanat *et al.*, 2008). More recently, in Ontario, Baxter *et al.*, (2013) studied birth rates in women 20–34 years old with a cancer diagnosis between 1992 and 1999. More recently Anderson *et al.*, (2018), studied pregnancy rates in women with a cancer diagnosis from ages 0–40 years between 1981 and 2012 in Scotland. We included female AYAs 15–39 years old with a cancer diagnosis between 1992 and 2011.

AYAs with breast cancer had a 46% higher risk of subsequent infertility diagnosis compared to women without cancer. Our results are in agreement with Baxter *et al.*, who reported decreased birth rates in women with breast cancer (Hazard Ratio-HR 0.74; 95% CI 0.61, 0.91) (Baxter *et al.*, 2013). In our study, the risk of subsequent infertility diagnosis increased by 63% in nulliparous women but became non-significant in parous women. Baxter *et al.*, (2013) reported lower birth rates after breast cancer in parous women (HR 0.45; 95% CI 0.29, 0.68), but not in nulliparous women (HR 0.90; 95% CI 0.72, 1.13). In that study, lower birth rates in parous women suggested that non-biological factors may influence childbirth rates in this group (motivation to conceive, for example), whereas a possible explanation for similar birth rates in nulliparous women could be that some of these pregnancies were conceived by infertility treatment, including oocyte donation. Anderson *et al.*, (2018), reported decreased overall pregnancy rates in women with breast cancer (standardized incidence ratio-SIR = 0.30, 95% CI 0.36, 0.42). The cumulative incidence of first pregnancy was decreased in nulliparous women with cancer compared to matched-controls (HR 0.30; 95% CI 0.26, 0.35), in agreement with our result of a higher infertility diagnosis in nulliparous women with breast cancer.

AYAs with hematological cancers had a higher risk of an infertility diagnosis compared to women without cancer (leukemia 56%, Hodgkin lymphoma 49%, non-Hodgkin lymphoma 42%). Our result differs with Baxter *et al.*, (2013) who reported no difference in overall birth rates in women with Hodgkin lymphoma or non-Hodgkin lymphoma. Leukemia was not included in this cohort. After stratification by parity, in our study the risk of infertility diagnosis slightly increased in nulliparous women (leukemia 67%, Hodgkin lymphoma 53%, non-Hodgkin lymphoma 52%) but disappeared in parous women. Baxter *et al.*, (2013) reported decreased birth rates in parous women with Hodgkin lymphoma (HR 0.57; 95% CI 0.36, 0.91) but no difference for women with non-Hodgkin lymphoma. In nulliparous women, birth rates were the same in those with Hodgkin lymphoma or non-Hodgkin lymphoma (Baxter *et al.*, 2013). Anderson *et al.*, (2018) reported an overall decreased pregnancy rate in women with leukemia (SIR 0.48; 95% CI 0.42, 0.54), Hodgkin lymphoma (SIR 0.67; 95% CI 0.62, 0.73) and non-Hodgkin lymphoma (SIR 0.67; 95% CI 0.58, 0.77). They also reported a decreased cumulative incidence of first pregnancy in nulliparous women with leukemia (HR 0.21; 95% CI 0.17, 0.25), Hodgkin lymphoma (HR 0.46; 95% CI 0.40 0.52) and non-Hodgkin lymphoma (HR 0.34; 95% CI 0.28, 0.43), in agreement with our results.

AYAs with thyroid cancer had a 20% increased risk of subsequent infertility diagnosis. After stratification by parity, the risk remained in nulliparous (18%) and parous women (34%). Baxter *et al.*, (2013) did not find lower birth rates in women with thyroid cancer overall or stratified by parity. Anderson *et al.*, (2018) reported a decreased overall pregnancy rate in women with thyroid cancer (SIR 0.79; 95% CI 0.72, 0.86) and a decreased cumulative incidence of first pregnancy in nulliparous women (HR 0.69; 95% CI 0.59, 0.81), in agreement with our results.

Leaders in oncofertility (Woodruff 2015) research have made a call to study the effect of melanoma and its treatments on infertility (Walter *et al.*, 2016). They reported that for female patients, 58% of systemic treatments for melanoma represent a fertility risk in animal or human studies, 33% have unknown risk, and one therapy (vemurafenib) did not show animal ovarian toxicity (Walter *et al.*, 2016). We reported a 17% risk of subsequent infertility in women with melanoma that remained in nulliparous women (20%) but was attenuated in

parous women. Baxter et al., (2013) observed similar birth rates in women with melanoma compared to matched-controls, independent of parity. Anderson et al., (2018) reported a decreased probability of pregnancy in women with skin cancer (melanoma and non-melanoma, SIR 0.87; 95% CI 0.84 0.90) and a decreased cumulative incidence of first pregnancy in nulliparous women (HR 0.66; 95% CI 0.62 0.72), in agreement with our results. Of note, melanoma has been associated with risk factors for infertility (e.g. late first pregnancy, endometriosis) (Melin et al., 2007, Hannibal et al., 2008, Kvaskoff et al., 2015). Thus, whether melanoma is an independent risk factor for infertility, or shares a common etiological pathway with causes of infertility, needs to be further investigated.

Finally, in survivors of brain or colorectal cancer, the association was not significant, either overall or after stratification by parity. Our results are in agreement with Baxter et al., (2013) who reported no difference in birth rates in women with brain cancer compared to matched controls, overall or stratified by parity. They did not include colorectal cancer as a separate type of cancer. Anderson et al., (2018) reported decreased pregnancy rates in women with brain/CNS cancer (SIR 0.42; 95% CI 0.36 0.48) and colorectal cancer (SIR 0.53; 95% CI 0.43, 0.64). They also reported a decreased cumulative incidence of first pregnancy in nulliparous women with brain/CNS cancer (HR 0.18; 95% CI 0.15, 0.22) and colorectal cancer (HR 0.26; 95% CI 0.18, 0.38). The different age ranges included in our study could explain these differences in our results. Although Anderson et al., included women from 0 to 40 years, we only included the AYA population (15–39 years). Also, we excluded women who had cancer recurrence within 5 years of cancer diagnosis as we hypothesize that the burden of their disease decrease the probability of seeking infertility assessment or pregnancy (as reported by Anderson et al. 2018).

Strengths of our study include our large sample size, the population-based matched cohort design, and the inclusion of the most prevalent non-gynecological cancers in female AYAs; however, we acknowledge some limitations that we attempted to address. First, the use of the ICD-9 code 628 to identify infertility diagnosis in health administrative databases has not been validated. Noteworthy, the same approach has been used in population-based studies on fertility and reproductive outcomes in the US, The Massachusetts Outcomes Study of Assisted Reproductive Technologies -MOSART- (Declercq et al., 2014), and in Denmark (Jensen et al., 2007). To decrease the probability of misclassifying fertility preservation counseling after cancer as an infertility diagnosis, we excluded diagnoses that occurred within 1 year after cancer. We also conducted a sensitivity analysis (data not shown) in which the outcome was based on a minimum of two consultation billings each with an infertility diagnosis, and the results were the same. In addition, we excluded women with a diagnosis of infertility before their cancer diagnosis to minimize the risk of reverse causality (i.e. infertility and/or its treatments as risk factors for selected cancers). Second, the ICD 9 code 628 was identified using information on physician billing codes through the Ontario Health Insurance Plan database. This database only records the first three digits of the ICD-9 code (628), excluding the etiology specific codes (628.0 anovulation, 628.1 pituitary-hypothalamic origin, 628.2 tubal origin, etc.).

We also acknowledge that our study only includes women who presented seeking care for infertility, rather than women who experienced infertility and did not seek medical attention. Indeed, non-biological factors, which may influence the likelihood of seeking a fertility assessment, may not be available in health administrative databases. For example, socioeconomic conditions may influence access to fertility care (Moreau et al., 2010). In Ontario, as in the rest of Canada, health care is publicly funded, including assessment of infertility. Thus, it is unlikely that health care cost affected our results. Sociodemographic and lifestyle factors including race/ethnicity, education, smoking and Body Mass Index (BMI) also affect in the use of infertility services. White/Caucasian women, those with higher levels of education, non-smokers or those with a normal BMI consult more frequently when faced with delay to conception compared with African American, Hispanic or Asian women, those with lower levels of education, smokers or those with a high BMI (Jain 2006, Moreau et al., 2010, Farland et al., 2016). Race/ethnicity, education, smoking and BMI were not available in our health administrative databases; however, we matched our sample according to census subdivision and adjusted our model by income quintile, which are variables correlated with these sociodemographic and lifestyle factors. Similarly, we lacked information on marital status. Cancer survivors are less likely to be married or co-habiting (Crom et al., 2007, Kirchhoff et al., 2012) and therefore even if their treatment has resulted in infertility they might be less likely to consult with infertility. It is also possible that cancer survivors (who have undergone extensive medical treatments with many visits and procedures over months/years) may be less inclined to seek additional elective medical care, even for something as important as suspected infertility. In addition, parity influences seeking infertility assessment, with parous women consulting 60% less frequently compared to nulliparous women when faced with a delay to conceive (Moreau et al., 2010). For that reason, we presented our results stratified by parity (parous and nulliparous women).

In conclusion, our results will inform counseling of female AYAs with cancer as they provide objective rates of subsequent infertility diagnosis at the population level. Although the risk of infertility varies depending on the type of cancer, our study reinforces the need of surveillance and fertility counseling in AYA women facing a new diagnosis of breast or hematological cancer (Loren et al., 2013). Although there are effective options for fertility preservation available (Woodruff 2015), referral rates continue to be low as we have recently documented in female AYAs with breast (Korkidakis et al., 2019) and hematological cancer (Coleman et al., 2020) in Ontario. Future studies need to assess the effect of specific cancer treatments, not assessed in our study, including new cancer therapies (e.g. immunotherapy). Our findings of potential effects of thyroid cancer and melanoma need to be further investigated.

Data availability

The data set from this study is held securely in coded form at ICES. Although data-sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS. The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros.

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Authors' roles

MPV was responsible for study design, analysis and drafting of the manuscript. HR participated in study design, analysis and critical discussion. NNB participated in study design, analysis and critical discussion. CMc was responsible for the statistical analysis. EG and RB participated as content experts and in critical discussion. MG participated in study design and critical discussion. All authors read and approved the final manuscript.

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Conflict of interest

None to declare.

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