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Male infertility is associated with altered treatment course of men with cancer

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SUMMARY

This study aims to evaluate whether cancer treatments differ in infertile men compared to men who have undergone vasectomy and age-matched controls. We analyzed subjects from the Truven Health MarketScan Claims database from 2001 to 2009. Infertile men were identified through diagnosis and treatment codes. Comparison groups included vasectomized men and an age-matched cohort who were not infertile and had not undergone vasectomy. We considered cancer types previously associated with infertility that were diagnosed after the diagnosis of infertility. The treatment regimens were determined based on the presence of claims with CPT codes for chemotherapy (CTX), radiation (RTX) or surgical treatment (ST) for each entity in all study groups. Cases with multimodal treatments were also identified. As a result, CTX was similarly distributed among the infertile, vasectomized, and control groups. In contrast, RTX treatment length was shorter in infertile men. The frequency of multimodal treatment (i.e., radiation and chemotherapy) was twofold lower in men with infertility compared to other men. By focusing on treatment patterns for each cancer type among these groups, the duration of RTX and CTX was shorter in infertile men diagnosed with NHL compared to controls. We conclude that Infertile men diagnosed with cancer and specific cancer types experience different treatment courses, with shorter RTX and less combined RTX/CTX compared to fertile and vasectomized men. These differences could reflect differences in stage at presentation, biological behavior, or treatment responses in infertile men.

INTRODUCTION

Recent studies have indicated an association between male infertility and tumor incidence (Moller & Skakkebaek, 1999; Jacobsen *et al.*, 2000; Eisenberg *et al.*, 2015). Moller *et al.* conducted a case–control study that demonstrated a higher risk of testis cancer in men with fewer children when paternity was used as a surrogate for fertility (Moller & Skakkebaek, 1999). Later, these findings were confirmed more directly in a cohort of infertile men by showing that men with impaired semen quality had a higher subsequent risk of testis cancer (Jacobsen *et al.*, 2000). More recently, Walsh *et al.*, (2009) evaluated a cohort of infertile couples in California and documented an increased risk of testicular cancer in men with male factor infertility.

Hodgkin's lymphoma (HL) mostly affects subjects of reproductive age, whereas non-Hodgkin's lymphoma (NHL) evolves in elderly patients. Chemotherapy and radiotherapy are treatment options in both diseases (Hennessy *et al.*, 2004; Ansell, 2016). Therefore, the semen cryoconservation is widely recommended prior treatment. A recent study on HL provided data that indicate an association between B symptoms and the semen quality prior treatment; however, no association between tumor stage and semen quality was found according to this study (Paoli *et al.*, 2016). A historical study from 1992 showed no differences in sperm quality between HL and NHL (Botchan *et al.*, 1997).

While the association between testis cancer and infertility has been demonstrated in several studies, the relationship between male fertility and other malignancies is less clear. Whereas some studies supported an increased risk of prostate cancer (CaP) and infertility (Rosenblatt *et al.*, 2001; Walsh *et al.*, 2010; Eisenberg *et al.*, 2011), others have failed to find an association or even showed a decreased risk of CaP in men with infertility (Ruhayel *et al.*, 2010; Mao *et al.*, 2016).

Despite some uncertainties of the relationship of male infertility with specific cancer types, infertile men have been shown to have a higher risk of all cancers (Eisenberg *et al.*, 2015). For

example, non-obstructive azoospermia, the most severe form of male infertility, has been associated with an increased risk of all cancers (Eisenberg *et al.*, 2013). Several investigators have hypothesized that the male infertility and cancer association could be driven by common biological features such as genetic, hormonal, environmental, lifestyle, or in utero factors (Matzuk & Lamb, 2008; Hotaling & Walsh, 2009; Hotaling & Carrell, 2014). However, it is difficult to study these etiologic factors due to the low incidence rate of cancers in men of reproductive age and the lack of centralized registries for reproductive outcomes. To address this challenge, we hypothesized that treatment course might reflect clinical or biological differences between cancers diagnosed in infertile and fertile men. We therefore investigated the treatment course and follow-up of infertile men with cancer and compared these to vasectomized and fertile controls using a large insurance claims database we have used previously to demonstrate a higher incidence of cancer in men with male factor infertility (Eisenberg *et al.*, 2015).

MATERIALS AND METHODS

Study cohort

We used the Truven Health MarketScan Commercial Claims and Encounters database for our study. This database is comprised of adjudicated, and paid insurance claims filed for the care of privately insured individuals with employment-based insurance through a participating employer. MarketScan provides claims data on 77 million covered lives since 1996. The number of individuals represented in the database varies over time; therefore, the data query was limited to the time span between 2001 and 2009, which included more than 30 million covered lives.

We identified a cohort of likely infertile men by selecting outpatient claims with an infertility diagnosis code (ICD-9 606.x, V26.21) or by the presence on any claim of a procedure code (CPT) for fertility testing or semen analysis/semen preparation (89300, 89310, 89320, 89321, 89322, 89325, 89329, 89330, 89331). We defined the first date of a relevant diagnosis or procedure code as the index date. Given the variation in infertility coding and reimbursement practices in the United States, we attempted to be as broad as possible with our definition.

As cancer diagnosis and treatment can lead to additional cancers, men having any claim with a diagnosis code for cancer before the index date or within one year after the index date were excluded from the study. We included only those subjects who had a plan covered by the database for at least one year before and for more than one year after the index date. We limited our cohort to men of reproductive age (between 18 and 50 years) on the index date.

A comparison group of men aged between 18 and 50 with claims containing a procedure code for vasectomy (CPT 55250 or 55450) as this group is likely to be enriched for fertile men with similar socioeconomic characteristics as infertile men (Eisenberg *et al.*, 2009; Hotaling *et al.*, 2015). In the vasectomy group, an index date was assigned at the earliest date of a claim with a vasectomy procedure code. All vasectomized men were enrolled in a plan covered by the database for at least 1 year before and 1 year after the index date. Finally, a control group was selected from men not included in the two previously described cohorts. Here, we selected ten men for each man in the infertile cohort, matched by age in the same year as the index date for the infertile men.

For each man, the number of outpatient visits after the index date was determined based on the presence of claims with CPT codes indicating new and follow-up office visits, consultations, or preventive medicine encounters. The follow-up duration was considered as the time from cancer diagnosis to the most recent office visit. Men with follow-up >2 or 3 years were identified, and their frequencies in the study groups were determined. Medical comorbidities were determined based on ICD-9 codes on any claim and included hypertension (401–405), obesity (278.0), smoking (305.1, V1582), and diabetes (250–250.93).

Diagnosis codes from inpatient and outpatient claims were applied to identify cancer diagnosis. Based on our previous study, we examined specific cancers based on highest and varied incidence between cases and controls for our analysis: melanoma (172.x), prostate (185.x), testis (186.x), bladder (188.x), thyroid (193.x), non-Hodgkin lymphoma (200.x, 202.x), Hodgkin's lymphoma (201.x), and leukemia (204.x, 205.x, 206.x, 207.x, 208.x). Treatment regimens were determined based on the presence of claims with CPT codes indicating chemotherapy (CTX), radiation (RTX), or surgical treatment (ST) for each cancer in the three patient groups (Table S1). The duration (in months) from cancer diagnosis to the first session of the treatment was calculated as median and range for CTX, RTX, and ST. The number of treatment sessions was assessed within or after six months from the index date depending on the therapy regimens for each cancer type, as we assumed that the primary treatment occurred within six months. Cases with multimodal treatment were identified using CPT codes, and the order of the treatment sequence was recorded. Further information regarding CPT codes for treatment regimens can be found in Table S1.

Statistical analysis

Men accrued at-risk time beginning one year after their index dates until cancer diagnosis or last day of enrollment in a health plan in the MarketScan database. As mentioned above, the first year after the index date was excluded. We compared the rates of cancer in infertile men to those in the vasectomy cohort and the control cohort. Differences in age at diagnosis were evaluated among groups using post hoc analyses. Office visits and treatment sessions were compared between these groups using X^2 test. The duration of follow-up and time from diagnosis to treatment were pairwise evaluated using Wilcoxon rank-sum test. p-values were two-sided with $p < 0.05$ considered statistically significant. Analyses were performed using SAS® (version 9.3; SAS Institute, Cary, NC, USA).

RESULTS

Of the 996,953 total men in the cohort with an average follow-up of 2.3 person-years, 5911 men (0.59%) developed cancer after the index date. The distribution of cancer types among the infertile, vasectomy, and control groups is shown in Table 1. Men with cancer in the infertility or vasectomy groups were followed longer and had more visits than men in the control group (Table 2). The number of men receiving chemotherapy was similar among the three groups. In contrast, radiation therapy was performed more frequently in infertile men compared to men who underwent vasectomy and controls. However, after adjusting for cancer type and comorbidities, the number of men

Table 1 Characteristics of control, infertile, and vasectomy groups

All cancers	Control	Infertile	Vasectomy	*p*-value (overall)	*p*-value*	*p*-value**
Population, *n*	3974	600	919			
Age, mean (SD)	41.7 (6.4)	40.5 (6.5)	43.3 (6.0)	<0.0001	<0.0001	<0.0001
Time from cancer diagnosis to censoring						
Mean (SD)	1.6 (1.4)	1.8 (1.6)	1.8 (1.5)	0.0002	0.0141	0.6684
Men with >2 years, *n* (%)	1164 (29.3)	219 (36.5)	335 (36.5)	<0.0001	0.0003	0.9851
Men with >3 years, *n* (%)	604 (15.2)	119 (19.8)	175 (19.04)	0.0009	0.0037	0.7029
Follow-up visits						
Mean (SD)	18.0 (17.6)	20.2 (21.1)	19.7 (18.4)	0.0005	0.0122	0.818
Median (range)	13 (0–348)	15 (0–248)	15 (0–191)			

*Infertility vs. control. **Infertility vs. vasectomy.

Table 2 Treatment characteristics of control, infertile, and vasectomy groups

All cancers	Control	Infertile (all diagnosis and treatment)	Vasectomy	*p*-value	Infertile vs. control	Infertile vs. vasectomy
Chemotherapy (CTX), *n*	574	50	120			
Time from diagnosis to CTX, median (range)	5.6 (0–189)	4.1 (0–235.4)	5.1 (0–256.3)	0.5363	0.3637	0.8028
CTX duration, median (range)	15.1 (0–283)	17.1 (0–132.1)	11.9 (0–224.7)	0.1959	0.9657	0.271
CTX duration (categorized)						
Men treated < 6 month, *n* (%)	408 (71.08)	36 (72.00)	85 (70.83)	0.9881	0.8905	0.8784
Men treated > 6 month, *n* (%)	166 (28.92)	14 (28.00)	35 (29.17)			
Radiotherapy (RTX), *n*	458	43	105			
Time from diagnosis to RTX, median (range)	6.6 (0–229.9)	4.3 (0.4–35.1)	5.4 (0–174.4)	0.229	0.893	0.1911
RTX duration, median (range)	6.4 (0–163.7)	4.7 (0–210.7)	7.4 (0–104.3)	0.0275	0.3223	0.0349
RTX duration (categorized)						
Men treated < 6 month, *n* (%)	443 (96.72)	40 (93.02)	97 (92.38)	0.0935	0.2124	0.8924
Men treated > 6 month, *n* (%)	15 (3.28)	3 (6.98)	8 (7.62)			
Stem cell transplantation (SCT), *n*	17	1	7			
Time from diagnosis to SCT, median (range)	38.1 (10.0–102)	48 (n.c.)	15.9 (0.4–102.3)	0.599	0.8472	0.6625
SCT duration (categorized)						
Men treated < 6 month, *n* (%)	17 (100)	1 (100)	7 (100)			
Treatment modality				*	*	*
Any treatment, *n* (%)	801 (20.16)	83 (13.83)	174 (18.93)	0.0009	0.0002	0.0009
CTX, *n* (%)	328 (40.95)	37 (44.58)	63 (36.21)	0.572	0.5876	0.2866
RTX, *n* (%)	203 (25.34)	32 (38.55)	46 (26.44)	0.224	0.1075	0.1104
ST, *n* (%)	0	0	0			
CT+RTX, *n* (%)	260 (32.46)	13 (15.66)	60 (34.48)	0.0536	0.0245	0.0129
CT+ST, *n* (%)	16 (2.00)	1 (1.20)	5 (2.87)	0.1389	0.3525	0.7884
RTX+ST, *n* (%)	8 (1.00)	0 (0)	3 (1.72)	0.3403	0.9421	0.9353
CT+RTX+ST, *n* (%)	8 (1.00)	0 (0)	2 (1.15)	0.115	0.7416	0.2885
Time from diagnosis to any treatment, median (range)	5 (0–205.3)	3.9 (0–144.1)	4.3 (0–174.4)	0.2214	0.1905	0.7752
Treatment duration, median (range)	0 (0–223.9)	0 (0–230.1)	0 (0–89.9)	0.0074	0.0042	0.0022
Treatment duration (categorized)						
Treated < 6 month, *n* (%)	733 (94.70)	77 (96.25)	150 (89.82)	0.0505	0.7903	0.1323
Treated > 6 month, *n* (%)	41 (5.30)	3 (3.75)	17 (10.18)			

**p*-values of multivariate models after adjusting to cancer types.

receiving radiation therapy was similar between the three groups. The duration of radiation therapy was significantly shorter in men with infertility compared to vasectomized men. In addition, the frequency of multimodal treatment (i.e., radiation and chemotherapy) was lower in men with infertility.

Men with non-Hodgkin lymphoma (NHL) showed differences in treatment patterns between the three groups. In men with NHL, the duration of radiation therapy was shorter in infertile men compared to vasectomized men and controls (Table 3). Similarly, the duration of chemotherapy was shorter in infertile men, and infertile men had fewer visits compared to the vasectomy group (1.7 vs. 4.3 visits per year). Infertile men received radiation therapy earlier than the other groups, where no differences were observed in other cancer types (Table 3). Looking at other individual cancer types, there were no significant differences in the duration of radiation and chemotherapy for infertile men compared to the other groups in prostate cancer, HL, leukemia, bladder cancer, testicular cancer, melanoma, and thyroid cancer (Table S2).

Table 3 Characteristics of the treatment course and the follow-up in men with non-Hodgkin lymphoma

	Control	Infertility	Vasectomy	*p*-value*	*p*-value**
Population, *n*	456	84	83		
Age (years), mean ± SD	40.4 ± 6.3	39.0 ± 6.0	41.3 ± 6.2	0.0741	0.0206
Time from diagnosis to censoring (years), mean ± SD	1.6 ± 1.4	2.0 ± 1.7	1.5 ± 1.1	0.0965	0.1109
Follow-up visits per person a year, mean ± SD	3 ± 6.8	1.7 ± 4.1	4.3 ± 11.7	0.3261	0.0399
Number of registered treatments, *n*	126	14	25		
Chemotherapy (CTX), *n* (%)	95 (73.6)	11 (78.6)	21 (77.8)		
Time from diagnosis to CTX (weeks), median (range)	4.9 (0–189)	3.6 (0–144.1)	2.7 (0–86.4)	0.4776	0.4152
Duration of CTX (weeks), median (range)	15 (0–150.1)	10.6 (0–45.1)	16.1 (0–84.1)	0.0084	0.0404
Treatment occurred < 6 month, *n* (%)	68 (71.6)	10 (90.9)	14 (66.7)		
Treatment occurred > 6 month, *n* (%)	27 (28.4)	1 (9.1)	7 (33.3)		
Radiotherapy (RTX), *n* (%)	32 (24.8)	3 (21.4)	4 (14.8)		
Time from diagnosis to RTX (weeks), median (range)	22.9 (0.1–205.3)	7.1 (5.7–9.9)	48.9 (35.9–60.6)	0.0271	0.0518
Duration of RTX (weeks), median (range)	4.4 (0–23.4)	2.7 (1–3.1)	5.7 (4.1–26.3)	0.1565	0.0518
Treatment occurred < 6 month, *n* (%)	32 (100)	3 (100)	3 (66.7)		
Treatment occurred > 6 month, *n* (%)	0	0	1 (33.3)		
Stem cell transplantation (SCT), *n* (%)	2 (1.6)	0 (0)	2 (7.4)		
Time from diagnosis to SCT (weeks), median (range)	61.6 (40.7–82.6)	0	69.1 (35.9–102.3)	n.c.	n.c.
Duration of SCT (weeks), median (range)	10.4 (0–20.7)	0	10.4 (0–20.7)	n.c.	n.c
Treatment occurred < 6 month, *n* (%)	2 (100)	0	2 (100)		
Treatment type				***p*-value (overall)**	
Any treatment	105 (22.9)	13 (15.5)	22 (26.5)	0.2025	
CTX only	65 (61.90)	10 (76.92)	15 (68.18)	0.5509	
RTX only	1 (0.95)	2	0	1.0000	
ST only	0	0	0	n.c.	
CTX+RTX	24 (22.86)	1 (7.69)	3 (13.64)	0.3932	
CTX+ST	2 (1.90)	0	2 (9.09)	0.1583	
RTX + ST	0	0	1 (4.55)	0.25	
CT+RTX+ST	0	0	1 (4.55)	0.25	

n.c., not calculable. *Infertility vs. control. **Infertility vs. vasectomy.

DISCUSSION

Using an insurance claims dataset, we observed different cancer treatment courses for infertile men compared to fertile and vasectomized counterparts. To our knowledge, ours is the first study to examine treatment types and duration in infertile men diagnosed with cancer. While the use and duration of chemotherapy were distributed similarly among the groups, radiation therapy was applied for a shorter duration in the infertile group. Moreover, multimodal therapy was used less commonly in infertile men.

When looking at specific tumor types, infertile men with NHL had shorter duration of chemotherapy or radiotherapy and had fewer follow-up visits despite a trend toward longer follow-up in the infertile men. Assuming that most men were treated in accordance with the NCCN Clinical Practice Guidelines in Oncology, we infer that the shorter duration of treatment and less frequent follow-up visits reflect that infertile men more commonly had less aggressive or earlier NHL. Treatment recommendations for early/indolent NHL usually entail six to eight cycles of R-CHOP without RT or three cycles of CHOP with RT, and is usually accomplished within 6 months of diagnosis or termination of active surveillance (Zelenetz, 2014). Thereafter, routine clinical follow-up is typically biannually one year after completing treatment. In advanced or aggressive NHL, the duration of chemotherapy is longer than 6 months and more frequently includes the addition of radiation therapy. Clinical follow-up visits for advanced and aggressive NHL occur usually three or four times a year for the 3 years following completion of therapy. Whether the shorter time of treatment we observed is due to biological features of the tumors, increased awareness of health concerns or increased healthcare contact in men with infertility cannot be determined. Several biological explanations have been put forward linking infertility and malignancy including exposure to toxins, defects in DNA repair, germline variations, and environmental exposures including diet and occupation. While each of these factors could affect the acquisition of cancer, they could also modify the risk of contracting subtypes of cancer that are correlated directly with clinical behavior.

While the etiology of the association between NHL and male infertility is unknown, several studies proposed the role of apoptosis regulation and DNA damage response in infertility development and aggressiveness of NHL (Furuchi *et al.*, 1996; Lenz *et al.*, 2008; Matzuk & Lamb, 2008). For instance, BCL-2 (B-cell lymphoma 2) is anti-apoptotic protein and a surrogate marker to predict clinical outcome of patients with a subtype of NHL called 'diffuse large B-cell lymphoma' (Lenz *et al.*, 2008). BCL-2 protein expression has been associated with poor prognosis in patients with diffuse large B-cell lymphoma due to resistance to chemotherapy (Reed, 1995; Hermine *et al.*, 1996; Pritchard *et al.*, 2011). BCL family plays a crucial role in regulating apoptosis during spermatogenesis, and its dysregulation was associated with the disturbance in spermatogenesis and development of azoospermia (Furuchi *et al.*, 1996; Yamamoto *et al.*, 2001; Bozec *et al.*, 2004). A recent study identified single nucleotide polymorphisms (SNP) variants of BCL-2 in azoospermia; a SNP variant of BCL-2 was sensitive against chemotherapy than the wild type of BCL-2 under in vitro condition (Makde *et al.*, 2010). These findings suggest a possible association between germline features in infertile men that might underlie the differences we observed in the treatment courses of infertile men. Much larger studies will be needed to test whether SNPs in BCL-2 or DNA repair genes are associated with infertility and response to cancer therapies.

The association between cancer treatment modalities and male infertility may reflect the biological behavior of cancers (tumor biology) developed in infertile men. However, the data may also be due to earlier access to health care, and as consequence, earlier discovery of cancer and thus more favorable treatment stage.

The current study exhibits some limitations that warrant mention. First, the length of follow-up was limited because it was not possible to track men once they had left the healthcare plans that are included in the database. Given the low rate of cancer in men of reproductive age, the number of incident cancer cases after identification of infertility was modest and affected the power of the study to find associations in individual tumor types. As with many analyses that rely on administrative data, detailed data regarding tumor grade and stage, chemotherapy regimens or radiation therapy were not available. The health insurance policy usually covers fertility testing and semen analysis as consequence of medical indication (e.g., infertility and unfulfilled desire to have children). However, information on each man regarding race, infertility diagnosis, and lifestyle factors was not included in the database. MarketScan represents only commercially insured individuals and may not be representative of all U.S. men. Finally, differences in care utilization can impact cancer diagnoses because of observational biases.

CONCLUSIONS

The current study suggests possible differences in treatment patterns among infertile men diagnosed with cancers in the years following a fertility evaluation compared to age-matched controls. If a relationship between infertility and cancer incidence, presentation, the course of treatment, and response to treatment is confirmed, additional work will be needed to elucidate the pathways that relate infertility and tumor biology.

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CONFLICT OF INTEREST

All authors state that there is no conflict of interests associated with this manuscript.

AUTHORS' CONTRIBUTIONS

OE, ME, and JB designed the study. SL and LB acquired study data and conducted the analyses. OE drafted the manuscript. ME and JB reviewed the manuscript. All authors reviewed and approved the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 List of CPT codes used to generate the cohorts and identify treatment course and follow-up.
Table S2 Treatment course by cancers type in Control, Infertility and Vasectomy groups.