Improved Fertility Preservation Care for Male Patients With Cancer After Establishment of Formalized Oncofertility Program

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Purpose: Survival to reproductive age among men with cancer has steadily increased and yet cancer therapy and cancer itself may carry the risk of infertility. Since 2006, we have used a formalized fertility preservation program with expedited fertility care at our institution. We assessed the impact of this program by comparing the frequency of sperm cryopreservation and patient characteristics before and after its implementation.

Materials and Methods: Men 18 to 55 years old diagnosed with cancer at our institution from 2002 to 2010 were included in our study. We retrospectively reviewed patient charts to identify those who were offered and subsequently used fertility preservation services before and after program formalization.

Results: From 2002 to 2010 at our institution 4,818 men 18 to 55 years old were diagnosed with cancer, of whom 411 were offered fertility preservation consultation and 249 underwent sperm cryopreservation. Since program implementation, the annual number of men receiving fertility preservation consultation and undergoing sperm cryopreservation increased by 2.4 and 2.7-fold, respectively, while the total number diagnosed with cancer remained fairly constant. Upon substratifying patients into the more conventional reproductive age range of 18 to 40 years 23.4% of all men with cancer in this group were offered consultation before formalization vs 43.3% after formalization ($p < 0.05$). The overall sperm use and discard rates were 8.4% and 14.8%, respectively.

Conclusions: A formalized institutional fertility preservation program significantly increased the overall number and percent of male patients with cancer who received fertility preservation consultation and pursued sperm cryopreservation. These increases were seen in men with all types of cancer and across all demographics assessed at our institution.

Key Words: testis; neoplasms; infertility, male; sperm; cryopreservation

Abbreviation and Acronym

SCP = sperm cryopreservation

Submitted for publication July 25, 2011.

Study received Northwestern University institutional review board approval.

* Financial interest and/or other relationship with Lilly, American Medical Systems, Coloplast, Abbott, Agilent and Medtronic.

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Approximately 44% of all men face a cancer diagnosis during their lifetime.[1] Improved cancer treatment regimens have increased the patient survival rate,[1] revealing many long-term deleterious effects of cancer and cancer therapy. Previous studies have shown that underlying disease processes may impact fertility even before cancer diagnosis.[2,3] As a result, survivorship issues have become an area of rapidly expanding interest.

Known deleterious effects of oncogenesis and cancer progression can

0022-5347/12/1873-0987/0
THE JOURNAL OF UROLOGY®

Vol. 187, 987-994, March 2012
Printed in U.S.A.
DOI:10.1016/j.juro.2011.10.154

include interruption of the hypothalamic-pituitary-gonadal axis,[4,5] immunological and cytological responses to cancer that injure the germinal epithelium,[6,7] systemic processes (fever, malnutrition and immunosuppression) that impact spermatogenesis[8,9] and psychological issues that affect male sexual performance.[10] Cancer therapy can further worsen this already compromised state. Such treatments include radiation therapy,[11] chemotherapy,[11] surgical procedures and opioid treatments for pain management.[12]

As the cancer survival rate increases and emphasis is placed on long-term quality of life, the possibility of future fatherhood emerges as a pressing concern.[13–15] A survey of males 14 to 40 years old who were newly diagnosed with cancer revealed that at diagnosis 51% of all study subjects and 77% of childless subjects desired to father children in the future.[16] The population of cancer survivors desiring future paternity is expanding as an increasing number of men pursues fatherhood later in life due to factors such as divorce, educational and professional demands or the death of a spouse. Thus, cancers thought of as predominately affecting men beyond the reproductive age, such as lung, colon and prostate cancer, are increasingly seen in men who desire future paternity.[13] In turn these societal changes influence the target patient population for fertility preservation. However, while fertility preservation is often a concern for patients with cancer, providers are sometimes more reluctant or unable to provide adequate counseling due to time constraints, perceived high cost and lack of accessible facilities.[17–19]

At our institution SCP services have been available to patients since 1999. However, no formalized institutional fertility preservation program was in place for men diagnosed with cancer. In late 2005 a formalized oncofertility program was established at our institution.[20,21] Numerous in service educational seminars were held to teach and train oncology physicians and nurses about fertility preservation options and procedures. Oncology grand rounds were held to highlight the male and female fertility preservation programs at our institution, and to increase physician awareness. A prompt was also added to our electronic medical record system that asks the treating physician whether fertility preservation options were discussed with new oncology patients.

The final components of our oncofertility program were added in early 2006, including a patient navigator, a patient facing website in English and Spanish (http://myoncofertility.org/) with e-mail accessibility to providers and a fertility preservation hotline. We assessed the efficacy of implementing a formalized institutional fertility preservation program for men with cancer.

MATERIALS AND METHODS

In this institutional review board approved study we evaluated the use of fertility preservation services (fertility preservation consultations and sperm or testicular tissue cryopreservation) by male patients with cancer at our institution between 2002 and 2010. Enterprise Data Warehouse (http://edw.berkeley.edu/) and EpicCare (Epic, Verona, Wisconsin) chart review software were used to access the medical records and demographic information of patients who met study criteria. Patients with cancer, excluding skin cancer, were identified using ICD-9 codes 140-209.9, indicating malignant neoplasm. Patients were then sorted by the primary cancer site, including blood/lymph, testis, brain, lung, gastrointestinal tract, bone/soft tissue, head/neck and other. The text of all notes on patients with cancer was electronically searched for terms to identify those offered a fertility preservation consultation, usually by an oncologist or surgeon, and those who went on to a fertility preservation consultation.

Our institutional policy requires that any patient with cancer who banks sperm undergo an initial fertility preservation consultation, defined as an encounter by a urologist or a urology physician assistant to discuss sperm or testicular tissue storage opportunities. Notes were manually screened to verify that the selected patients had received a fertility preservation consultation.

Only men 18 to 55 years old at diagnosis were included in study. Patients who had previously completed cancer treatment and who subsequently presented with infertility complaints were excluded. Consulted patients who pursued fertility preservation services at our tertiary care institution were further categorized by the encounter outcome as refusing to proceed with fertility preservation, agreeing to proceed with preservation, which was unsuccessfully attempted, and agreeing to proceed with successful storage of sperm or testicular tissue. Laboratory records were accessed to confirm cryopreservation and disposition of the stored specimen(s).

Standard descriptive statistics were used to analyze all data. The unpaired Student t test was used to compare means and the chi-square test was used to compare frequencies between groups as needed.

RESULTS

From 2002 to 2010 at our institution 4,881 men 18 to 55 years old were diagnosed with cancer, excluding skin cancer. A total of 411 male patients with cancer were offered fertility preservation consultations by their oncologists or cancer care providers, of whom 306 (74.5%) proceeded to a formal consultation. Of these consultations 73.6% were provided by the same urologist or urology physician assistant, each of whom subspecialized in male reproduction. The remaining patients were counseled about fertility preservation options by their primary urologist.

These urologists were members of our department and are familiar with our departmental fertility preservation options and procedures. A total of 266 patients agreed to bank sperm with cryopreservation successfully achieved by 249 (238 by ejaculation and 11 by testicular tissue extraction). Attempts failed in 17 patients (fig. 1).

The 411 patients offered fertility preservation consultation had an average ± SD age of 33.1 ± 9.1 years, 44.8% were married and 65.2% described themselves as white (table 1). Patients who proceeded with a fertility preservation consultation were significantly younger than those who refused consultation (31.9 vs 36.5 years, $p < 0.01$). Of those offered consultation marital status was not significantly different between those who accepted and those who refused consultation ($p = 0.22$). Further analysis of consulted patients revealed that only 57.0% with 2 or more children agreed to bank sperm compared with 90.2% of patients with no children (table 2). The mean age of patients who accepted vs refused SCP was not significantly different (31.6 vs 33.4 years, $p = 0.22$).

At our institution there was annual growth in the raw number and percent of patients with cancer who used fertility preservation services from 2002 to 2010 (fig. 2). There was a marked increase in use after 2006, when the oncofertility program was formally implemented. During the 2002 to 2010 interval the annual number of male patients diagnosed at

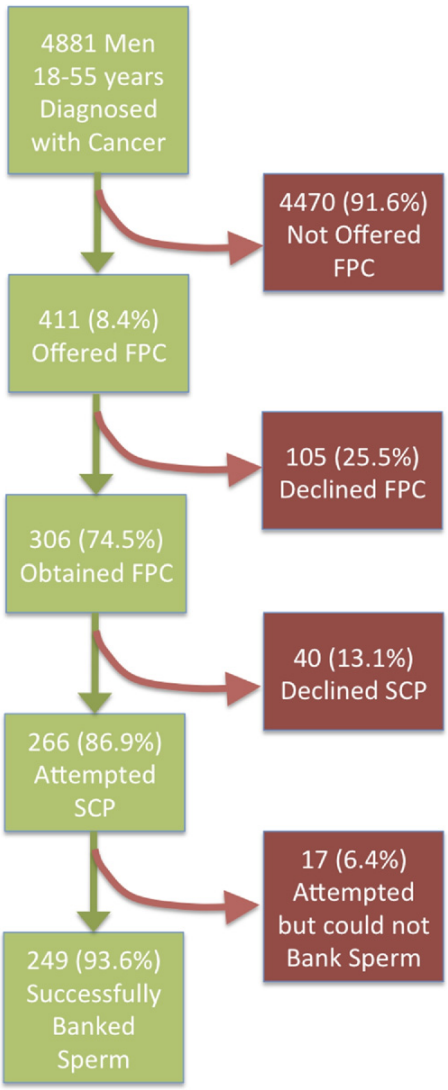

Figure 1. Algorithm to preserve fertility after cancer diagnosis in men 18 to 55 years old at our institution. Green arrows indicate path to successful preservation. *FPC,* fertility preservation consultation.

Table 1. *Marital status and ethnicity of 411 patients with cancer offered fertility preservation consultation at our institution from 2002 to 2010*

	No. Accepting (%)	No. Refusing (%)	Total No.
Marital status:			
Single	170 (77.6)	49 (22.4)	219
Married	133 (72.3)	51 (26.4)	184
Subtotals	303 (75.2)	100 (24.8)	403
Ethnicity:			
White	208 (77.6)	60 (22.4)	268
Hispanic	29 (80.6)	7 (19.4)	36
Black	17 (68.0)	8 (32.0)	25
Asian	10 (90.9)	1 (9.1)	11
Other	14 (60.9)	9 (39.1)	23
Subtotals	278 (76.6)	85 (23.4)	363
Totals	306 (74.5)	105 (25.5)	411

Table 2. *Demographics of 306 patients who accepted fertility preservation consultation*

	No. SCP (%)	No. No SCP (%)	Total No.
Marital status:			
Single	145 (85.3)	25 (14.7)	170
Married	118 (88.7)	15 (11.3)	133
Subtotals	263 (86.8)	40 (13.2)	303
Ethnicity:			
White	189 (90.9)	19 (9.1)	208
Hispanic	23 (79.3)	6 (20.7)	29
Black	10 (58.8)	7 (41.2)	17
Asian	9 (90.0)	1 (10.0)	10
Other	11 (78.6)	3 (21.4)	14
Subtotals	242 (87.1)	36 (12.9)	278
No. children:			
0	194 (90.2)	21 (9.8)	215
1	24 (88.9)	3 (11.1)	27
2+	12 (57.1)	9 (42.9)	21
Subtotals	230 (87.5)	33 (12.5)	263
Totals	266 (86.9)	40 (13.1)	306

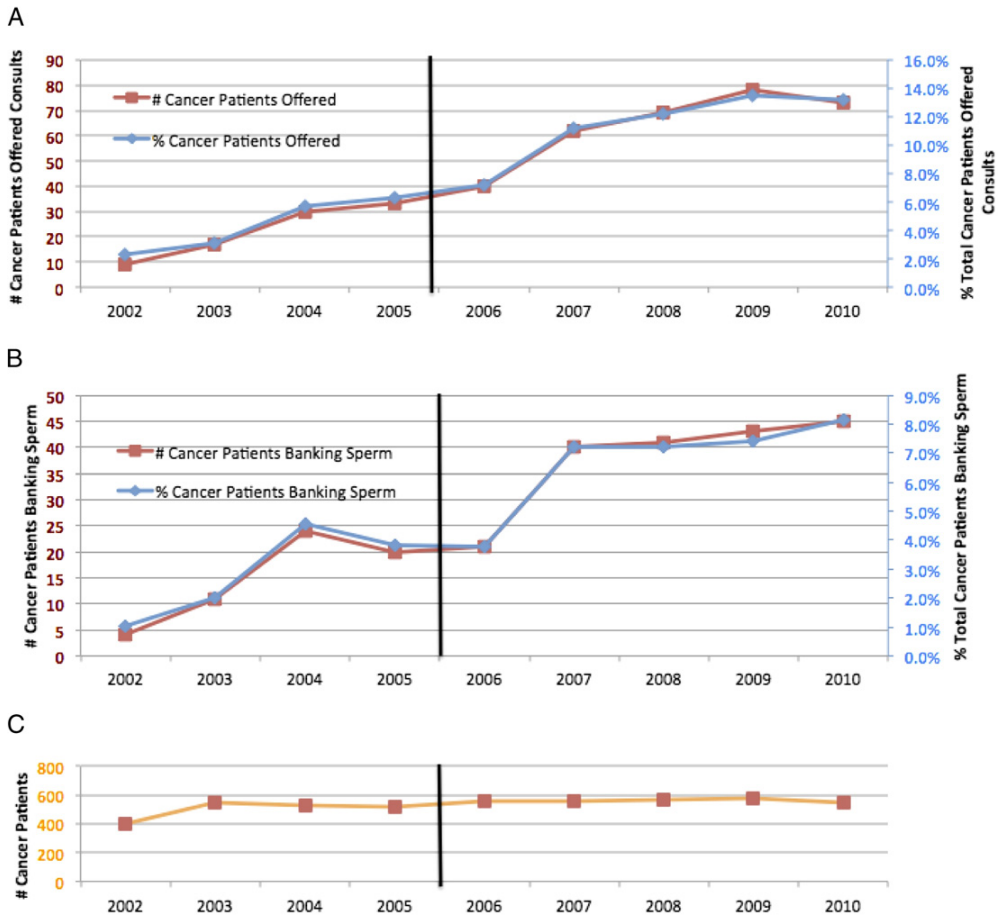

Figure 2. Fertility preservation use in men 18 to 55 years old before and after establishing formalized oncofertility program. *A*, men offered fertility consultation. Note increase after program formalization in 2006 (vertical line). *B*, men who banked sperm. Note increase after formalization. *C*, number of men 18 to 55 years old diagnosed with cancer.

our institution with cancer who were 18 to 55 years old remained fairly constant. Before formalization (2002 to 2005) an average of 22.3 male patients with cancer annually were offered fertility preservation consultation compared to 64.4 after formalization in 2006 to 2010 ($p < 0.01$). After formal implementation of the program the annual number of patients who accepted consultation and the number who agreed to SCP increased by 2.4-fold and 2.7-fold, respectively. The percent of consulted patients who agreed to SCP increased from 77.9% before 2006 to 90.0% after 2006.

Subgroup analysis of patients in the commonly cited reproductive age range of 18 to 40 years revealed an increase in the annual percent of those who were offered consultation (23.4% to 43.3%, $p = 0.035$) and proceeded to SCP (15.2% to 27.9%, $p = 0.046$) after program formalization (fig. 3). In contrast, the annual percent of patients with cancer who were 41 to 55 years old, and were offered consultation and successfully banked sperm remained low even after our program was implemented (3.5% vs 1.5%, table 3). The number of patients 41 to 55 years old with cancer was more than 4 times the number in the 18 to 40-year-old range. The percentage of men offered fertility preservation consultation who proceeded to sperm bank use increased substantially in each age group.

When all patients were stratified by cancer type, a similar increase in SCP was consistently seen across all neoplasms after program formalization (fig. 4). The fold increase in the annual SCP rate was highest for malignancy of the brain (14.4 times), gastrointestinal tract (7.6 times), head and neck (6.4 times), prostate (4.0 times) and bone/soft tissue (3.5 times). Among patients who agreed to SCP leukemia/lymphoma and testicular neoplasms were the most common oncological diagnoses. We also observed an increase in the number of patients with cancer from various demographic groups who agreed to SCP before and after the institution of our formalized oncological fertility program (table 4). In-

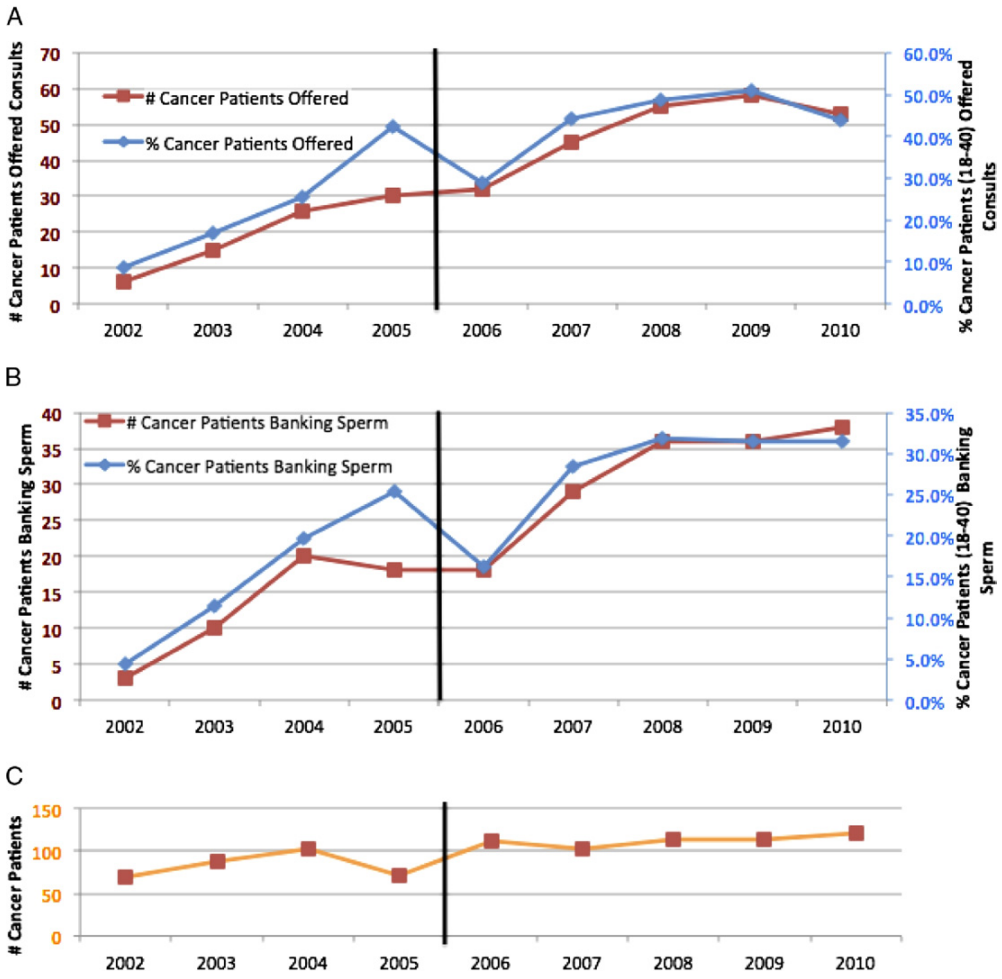

Figure 3. Fertility preservation use in men 18 to 40 years old before and after establishing formalized oncofertility program. *A* and *B*, number of patients increased after program was formalized in 2006 (vertical line). *C*, number of men 18 to 40 years old diagnosed with cancer.

creased program use was noted for each demographic. Data on all demographic parameters were not available for each patient.

Of the 249 patients who successfully banked sperm from 2002 to 2010 at our institution 21 (8.4%) transferred the sperm for assisted reproduction and 37 (14.8%) discarded the sperm. Six of the 37 patients had sperm discarded due to death. Sperm samples were transferred for use after an average of 25.8 months and discarded after an average of 31.1 months of storage.

Table 3. *Fertility preservation by age of patients with cancer*

Pt Age	Av 2002–2005/Yr	Av 2006–2010/Yr	p Value
18–40:			
No. Ca	82.5	112.2	
% Offered consultation	23.4	43.3	0.036
% SCP/yr	15.2	27.9	0.047
41–55:			
No. Ca	414.75	450.0	
% Offered consultation	0.72	3.5	<0.01
% SCP/yr	0.48	1.5	0.03

DISCUSSION

The improved fertility preservation care resulting from a formalized oncofertility program is evidenced by the significant increase in male patients with cancer who were offered consultation, received consultation and ultimately underwent SCP. Before our program was implemented the occasional men whom we saw for sperm cryopreservation tended to be younger, namely those with testicular or blood/lymph cancer. After implementing our program oncologists at our institution began to refer patients more consistently, and across broader oncological diagnostic categories and age groups. This paradigm shift

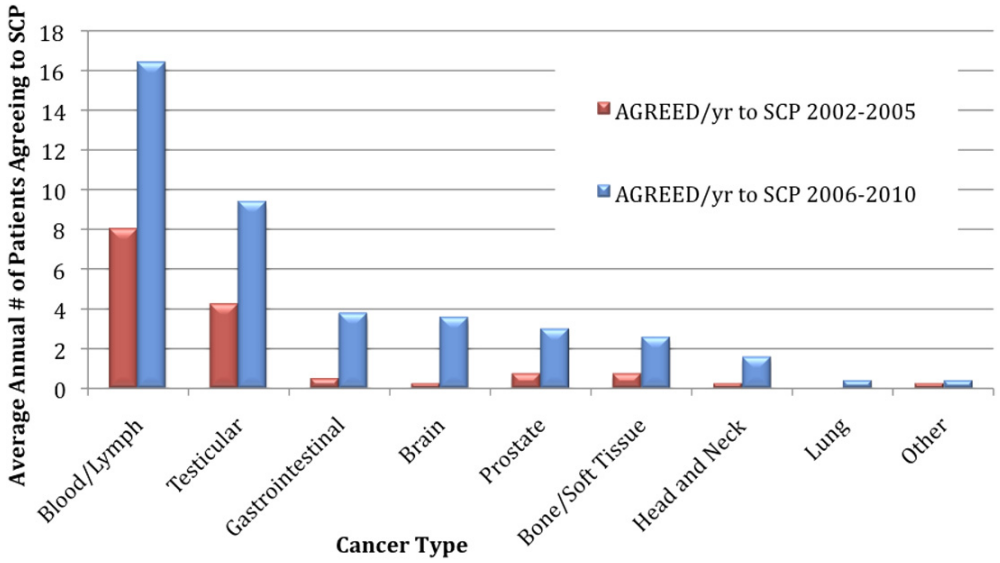

Figure 4. Average annual number of patients who agreed to SCP by cancer type from 2002 to 2005 vs 2006 to 2010. Average number increased after program formalization.

among our oncologists yielded a greater fold increase in consultation for men with other neoplasms compared to those with testicular or blood/lymph cancer.

Previous groups identified barriers to male fertility preservation resulting from provider knowledge deficits, logistical constraints and financial concerns.[22–25] As described, the establishment of our formal oncofertility program addressed many of these potential hurdles to sperm cryopreservation.

Prominent barriers to care include knowledge gaps and discomfort voiced by oncology physicians and nurses in discussing fertility preservation options.[18] In addition to a lack of adequate awareness and understanding of the available fertility preservation techniques and facilities, oncological health care providers report that they often find it difficult to raise the topic of fertility preservation in the midst of acute cancer treatment.[22–25] However, the 2006 American Society of Clinical Oncology recommendations stress the importance of discussing fertility preservation efforts with potentially interested patients shortly after the cancer diagnosis.[26]

Table 4. *Patient fertility preservation by demographics before and after program formalization*

	Av No. SCP/Yr			Av No. Consultation/Yr		
	2002–2005	2006–2010	p Value	2002–2005	2006–2010	p Value
Cumulative rate	15.0	41.2	<0.01	19.3	45.8	<0.01
Marital status:						
Single	8	22.6	<0.01	10.3	25.8	<0.01
Married	6.8	18.2	<0.01	8.8	19.6	0.01
Age category:						
18–25	4	10.6	0.02	5.3	11.6	0.01
26–35	6.3	19.4	<0.01	7.8	21	0.01
36–45	4	7.8	0.16	4.8	9	0.15
46–55	0.8	3.4	0.11	1.5	4.2	0.11
Ethnicity:						
White	11.8	28.4	0.01	13.8	30.6	0.02
Hispanic	0.5	4.2	0.053	1	5	0.053
Black	0.5	1.6	0.13	1	2.6	0.13
Asian	0.8	1.2	0.58	1	1.2	0.83
Other	0.8	1.6	0.50	1.3	1.8	0.65
No. children:						
0	8.3	32.2	<0.01	11	34.2	<0.01
1	1	4	0.10	1.3	4.4	0.08
2+	0.8	1.8	0.22	1.5	3	0.06

Along these lines, our program targeted oncology nurses through educational in service seminars on fertility preservation options and the need for timely consultation. Grand rounds presentations were delivered to increase physician knowledge of fertility preservation services available in the context of routine and acute oncological care. Also, automated physician prompts in the electronic medical record reminded physicians to consider patient referral to a urologist for fertility preservation evaluation.

Even after educating and training medical staff the timely initiation of fertility preservation care remains a lingering issue.[22–25] To address such logistical concerns a patient navigator position was created to guide the patient from the initial oncology encounter to successful fertility preservation.[27] Navigator responsibilities include arranging fertility preservation consultations with the urology staff, coordinating sperm banking appointments and serving as patient liaison.

During the urology consultation the oncological treatment plan is discussed along with the potential impact of the therapy on reproductive and sexual health. The patient is also counseled on the use of cryopreserved sperm in the setting of assisted reproduction. The patient navigator follows each patient throughout the whole process up to the completion of his fertility preservation care. We believe that the streamlined, comprehensive care provided by the subspecialized urology staff and the patient navigator are key factors accounting for much of the increase in the use of fertility preservation services.

In addition to knowledge gaps and logistical barriers, several studies suggest that financial concerns may pose a potential barrier to fertility preservation care in patients with cancer.[22,23] In contrast, a recent survey of patients showed that cryopreservation fees were not an important consideration for patients in the decision to bank sperm.[28] However, the latter study may have suffered from selection bias since it only surveyed men who had agreed to and presented for SCP.

Given the lack of clarity in the existing literature, further studies are needed to elucidate how much of an obstacle the cost of sperm banking poses to oncology patients. This point is particularly relevant since insurance plans typically do not cover SCP.[29] Although we could not specifically assess patient concerns with cost in this study, the fees for sperm banking at our institution have remained constant since 2002. Nonetheless, further studies are required to help define the effects of cost on patient decision making.

Despite the significant increase in the use of fertility preservation services observed in our study only an average of 43.3% of new male patients with cancer who were of reproductive age (18 to 40 years) were offered fertility preservation consultation annually after the program was implemented. Oncology health care providers serve as gatekeepers for the fertility preservation process. It is likely that various factors led to the decision not to offer consultation to the remaining 56.7% of patients. At one end of the spectrum oncologists may view some patients as at low risk for infertility resulting from cancer therapy. At the other end, oncologists may regard some patients as having a poor prognosis and, thus, not being appropriate candidates for referral. We suspect that between these extremes there are still many patients who would desire and benefit from the offer of fertility preservation. Persistent knowledge gaps, logistical constraints and other barriers that interfere with the optimal delivery of fertility preservation care to these patients must be further characterized.

Men 41 to 55 years old appear to be an especially vulnerable population. After implementing our program only 3.5% of these men were offered consultation, of whom 41.7% proceeded to bank sperm. This potentially indicates an unfulfilled demand for fertility preservation among the remaining 96.5% of these patients not offered consultation. Hence, we advise against using age as a sole indicator to judge patient interest in fertility preservation.

Our study has several limitations. The retrospective design carries inherent limitations in data collection and the possibility of introducing bias. Furthermore, while the increased use of fertility preservation services is significant, it is possible that these increases may have been due at least in part to factors other than the implementation of our program. For instance, increased public awareness of fertility preservation may account for some of our findings. Thus, the lack of a comparative control prevented us from specifically quantifying increases in use due to the implementation of our program.

Finally, while we addressed the delivery of fertility preservation care, the ultimate aim of sperm cryopreservation is to safeguard future male reproduction. As shown by our sperm disposition rates, at our institution the use of fertility preservation is similar to that in the literature.[30] Long-term followup of fertilization and pregnancy rates will serve as a final measure of our efforts.

CONCLUSIONS

After introducing a formal oncofertility program the annual fertility preservation consultation and SCP use rates increased significantly. Our program implemented numerous targeted measures to help overcome barriers to fertility preservation in male patients with cancer. Specifically the education and training of oncology providers, the addition of a patient navigator model and the streamlined delivery of oncofertility care optimized the environment for

successful fertility preservation. This comprehensive model offers a solution to help bridge the gap between current fertility preservation recommendations and the challenge of actual fertility preservation care in patients newly diagnosed with cancer.

ACKNOWLEDGMENTS

Dr. Stacy Tobin assisted with manuscript revision. Valerie Gillis contributed to the oncofertility program. Dr. Anthony J. Schaeffer supported the program.

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