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Determinants of Access to Fertility Preservation in Women with Breast Cancer

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Abstract

OBJECTIVE—Evaluation of socio-economic, demographic, and medical factors that influence the referral pattern either before cancer treatment to fertility preservation (FP, early referral) or post-chemotherapy to assisted reproduction (PCART, delayed referral).

DESIGN—Secondary analysis.

SETTING—Academic medical centers.

PATIENT(S)—Three hundred fourteen patients with breast cancer who were counseled for FP (n=218) or PCART (n=96) from June 1999 to July 2009.

INTERVENTION(S)—None

MAIN OUTCOME MEASURE(S)—Factors favoring early referrals

RESULT(S)—Mean age at diagnosis was higher in FP vs PCART (35.3±4.5 vs 33.9±4.7, p<0.01). Ninety percent presented with cancer stage 1 or 2. From 2000 to 2009 the proportion of referrals for FP increased continually. In 2009, nearly all (95.5%) were for FP. The majority (63.8%) was referred from an academic center. Patients with a family history of breast cancer were more likely to consult for FP (75.2% vs 64.3% without, p=0.04). There was no association with occupation, income, race, ethnicity, obstetrical history, and prior infertility treatment. Only 22.9% of those counseled in PCART compared to 45.0% in the FP group proceeded with a procedure (p<0.001).

CONCLUSION(S)—There has been an increasing trend within the last 10 years for early referral of breast cancer patients to FP. Factors favoring early referrals are older age, early stage cancer,

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This is the first and largest study provides detailed information on early referral to fertility preservation compared to delayed referral to post-chemotherapy to assisted reproduction in women with breast cancer.

family history of breast cancer, and an academic center involvement. Those seen before cancer treatment are more likely to receive an intervention.

Keywords

Breast Cancer; Fertility Preservation; Access; Chemotherapy; Referral

Introduction

Fertility preservation is an emerging discipline that now has a key place in the care of young people with cancer.^{1,2} Early referral is critical for fertility preservation as more established techniques such as embryo freezing takes around two weeks from the beginning of menstruation.³ While under ideal circumstances the patients should be referred to fertility preservation before chemotherapy, many of those who did not have this opportunity may develop infertility and referred for post-chemotherapy assisted reproduction (PCART).⁴

Because likelihood of ART success post-chemotherapy is significantly diminished,⁵ it is extremely important to understand the factors that determine the access to fertility preservation and early referral. This information would reveal any barriers to accessing early FP care. Here we evaluated the socio-economic, demographic, and medical factors that influence early referral before cancer treatment to FP versus delayed referral to PCART.

Materials and Methods

The data were evaluated by the secondary analysis of the prospective deidentified database from June 1999 to July 2009.^{2,3,6-10} Only patients who were diagnosed with breast cancer that required chemo- and/or radiotherapy and under the age of 45 were included. Patients were also excluded when information on the time period between the date of cancer diagnosis and the date of initial consultation was not available. Of the 672 patients who were in the database, a total of 314 patients met the inclusion criteria. Of those, 218 were counseled for FP group and 96 were counseled for PCART (figure 1).

Referral sources included university hospitals, community hospitals, private practices, and some were self-referred. The distance to our fertility treatment center was calculated using Google Maps according to individual patients' address. The 2000 Standard Occupational Classification (SOC) System of Federal Statistical Agencies was modified and used to classify patients into occupational categories. Race, ethnicity, and family history of cancer as well as prior obstetrical history were determined. Household income estimates were generated from a public database (www.zipwho.com) based on zip codes.

Statistical analysis was performed with the SPSS 17 for Windows package (SPSS Inc., Chicago, IL). Normal distribution of the parameters was evaluated using the Kolmogorov-Smirnov test ($\alpha=0.01$) to choose the appropriate statistical test. Correlations were analyzed with Spearman's test. Averages of multiple groups of continuous data were compared with Kruskal-Wallis test followed by multiple comparisons with the Mann Whitney U test. Categorical data was evaluated with Chi-square or Fisher's exact test when appropriate. The α level was set at 0.05. In this retrospective screening of the patient's databases no adjustment for multiple comparisons was performed to avoid throwing out interesting effects and to obtain preliminary measures of association.¹¹

Results

Demographic and clinical characteristics of subjects that met the inclusion criteria are presented in Table 1. Mean age at diagnosis was higher (35.3 ± 4.5 vs. 33.9 ± 4.7 , $p < 0.01$) in the FP (early referral) group than the PCART (delayed referral) group (range: 21 to 45). The proportion of women less than thirty-five years of age was lower (63.6% vs. 76.8%, FP vs. PCART, $p = 0.01$) in the FP group compared to the PCART group. A plausible explanation to these findings is that older patients were more likely to become menopausal after chemotherapy and were less likely to be candidates for PCART.

The year of diagnosis with breast cancer ranged from 1990 to 2009 in this study. Before the year 2000, all were referred for infertility treatment after chemo- and/or radiotherapy (PCART). From 2000 to 2009 the proportion of early referrals for FP increased continually while PCART referrals decreasing. In 2009 nearly all (95.5%) were referred for FP before cancer treatment (figure 2).

The cancer stage was available for 273 women. Of those 90.4% presented with stage 1 and 2 breast cancer. Moreover, 87.5% of all women with stage 0 cancer were in the FP group. There was statistically significant negative association between breast cancer stage and the proportion of early referrals for FP ($p < 0.01$, Fisher's exact test) (figure 3).

The information on the referral source was available for 276 patients. The majority (63.8%) was referred from an academic center, 27.9% from a local oncologist, 2.5% from a community hospital and 5.8% were self-referred. A home address was available for 294 patients. Distance from home to clinic was divided into 4 groups: <10 miles, 10-<100 miles, 100-<1000 miles, and 1000 miles. There was no significant difference in the distance groups between FP and PCART ($p = 0.72$).

We also analyzed the impact of occupation on referrals. After using the modified 2000 SOC system, fifteen groups were created. Occupation was defined as the job classification at the time of the first visit. No association was detected with occupation and family income within or between the early FP referral and the PCART groups.

Of the total number of patients, 69.7% were White, 8.2% were African-American, 9.2% were Asian, and 6.1% were Hispanic. There were no patients with the background of American Indian/Alaska Native. Race and ethnicity appeared to have no influence on the referral pattern.

Family history of cancer up to second degree relatives was documented in 297 out of 314 women. Patients with a family history of breast cancer, but no other type of cancer, were more likely to consult for FP before chemotherapy compared to those without (75.2% vs. 64.3%, $p = 0.04$). A total of 129 out of 297 patients (43.4%) had a family history of breast cancer, and 97 out of 129 patients (75.2%) were in the FP group.

Information on prior obstetrical history was available for 290 patients. Overall 238 (82.0%) did not have a child. One hundred and seventy five patients had never been pregnant, and the remaining experienced at least one pregnancy loss. There was no difference with prior obstetrical history between the FP and the PCART groups. Data for prior infertility treatment was documented in 281 patients, and 34 patients had a history of infertility treatment prior to cancer treatment. The presence of prior infertility treatment had no influence on the referral pattern between the FP and the PCART groups.

Only 22.9% in the PCART compared to 45.0% in the FP group undertook a procedure ($p < 0.01$). There was no difference between household income and treatment decision

between groups ($p=0.72$ vs. $p=0.66$, FP vs. PCART) who underwent a FP or PCART procedure. In the FP group, 5.1% ($n=5/98$) of patients underwent ovarian tissue cryopreservation, 12.2% ($n=12/98$) oocyte cryopreservation, 74.5% ($n=73/98$) had embryo cryopreservation performed, and 8.2% ($n=8/98$) underwent a combination of two treatments.

Discussion

The clinical guidelines of American Society of Clinical Oncology (ASCO) have outlined the key discussion elements between cancer patient and physician regarding referral and fertility preservation methods.¹ Fertility preservation options are dependent on several factors, including age, type of treatment, diagnosis, presence or absence of a partner, time availability and the potential for metastasis of the primary cancer to the ovaries.^{2,12,13} According to ASCO guidelines, embryo freezing is the most established method of fertility preservation when there is a partner available.¹ Evidence has been accumulating that oocyte freezing success and safety may be similar to embryo freezing.¹⁴⁻¹⁶ At least two weeks are required to complete an ovarian stimulation cycle. Because ovarian stimulation is begun with the onset of menstruation, the delay before cancer treatment can be as long as 5-6 weeks depending on when in the cycle a patient is referred. In a typical adjuvant chemotherapy setting this time period is available in women with breast cancer, while such a delay may not be acceptable in other settings. When time is insufficient to allow embryo or oocyte freezing, ovarian tissue freezing is the only option, as it does not require pre-treatment. The latter is the most experimental of all three. Thus early referral also favors more established fertility preservation procedures.

Oncologists play a key role in understanding the patients' concerns regarding fertility. Despite our encouraging data indicating increased referral for FP, most recent studies indicate that still less than half of physicians routinely refer cancer patients of childbearing age to reproductive specialists.¹⁷ Another recent study reported that most oncologists recognize the importance of discussing infertility risks after cancer treatment, but few actually bring up FP with their patients.¹⁸ Primary importance may be placed on discussing issues regarding immediate or life-threatening complications instead of discussing possible infertility issues in the patient-physician setting. Additionally emotional discomfort regarding fertility issue discussions by physicians may be problematic.¹⁹ The importance of fertility to cancer survivors may go unrecognized by some oncologists.²⁰

Our results suggested several factors favoring early referrals. Older age affects early referral, perhaps because these women are perceived as more likely to have ovarian failure post-chemotherapy. Early stage cancer also favors early referral to FP. A possible explanation for the latter finding is that in early stage breast cancer, oncologists may be more open to delaying chemotherapy or any perceived risks of undergoing fertility treatments. Receiving academic center cancer also increases the likelihood of referral to FP. It is possible that the oncologists at academic centers may be better informed about FP options and may have easier access to investigation of fertility preservation protocols.

A family history of breast cancer is another factor influencing early referral to FP. Patients with a family history of breast cancer may be more aware of fertility issues associated with chemotherapy because of personal involvement in the subject. It is also possible that because younger women are more likely to have BRCA mutations, and impending decision for risk-reducing salpingo-oophorectomy might have influenced favorable decision towards FP. Another possible explanation is that, those who are BRCA-positive are more likely to be childless, as we have recently shown that some women with those mutations may have compromised ovarian function.¹² Nevertheless, our database did not suggest a significant

influence of parity on the referrals. We also did not have sufficient information on the BRCA status to test this hypothesis from this database.

From the analysis of our database, we did not find any impact of distance from patient's residence to the center, type of occupation, race, ethnicity or household income. These data suggest that fertility preservation is important among people regardless of their distance to the specialists, occupation, race, ethnicity and family income. Notably, given the racial mix in our area, non-whites were under-represented in FP referrals. Gravida, parity, abortion, childbearing, and infertility treatment history did not affect the referral pattern. However, the study size might have limited the detection of possible subtle differences between categories.

To our knowledge this is the first and largest study that provides detailed information on early referral to FP compared to delayed referral to PCART. The insight gained from our data may help us improve patient access to FP. Nevertheless, a secondary analysis of a database poses some limitations. As a retrospective study, some data such as the socioeconomic status, educational level, and medical insurance information were not available. Fertility preservation procedures are in general excluded under the infertility coverage as these patients do not meet the classical definition of infertility. Because we did not have precise information on socioeconomic status (SES), we could not directly analyze the impact of SES on access to FP. Instead, we examined as a surrogate for SES, an indirect measure of the median household income based on the postal code of the patients' residence. Based on this indirect assessment, income had no significant influence on referral patterns.

Our data suggests that younger patients may experience further delay in referral presumably because of the belief that their fertility may not be affected by cancer treatments. Further research on the impact of cancer treatments on young cancer patients are needed, and some are under way.²¹⁻²² However, the concept of chemotherapy-induced diminished reserve must be better conveyed to patients as many will experience early menopause. Given that information and especially if the patient desires a large family, even the youngest women with cancer may consider FP before chemotherapy.¹²

The importance of early referral to FP cannot be overstated. In a recent study we quantified the benefit of early referral.³ We found that those who were referred late in the process were less likely to cryopreserve as many oocytes and embryos, and would experience 3-4 weeks of delay in the initiation of chemotherapy. The current study identified some important factors influencing delay in access to FP, which can be used to improve the delivery of the care.

Acknowledgments

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Figure 1.
Flow of study participants

Figure 2.

Proportion of referral for FP increased continually from 2000 to 2009.

FP: Fertility preservation (early referral)

PCART: Post-chemotherapy assisted reproduction (delayed referral)

Figure 3. Proportion of referral for FP inversely associated with the stage of breast cancer.
FP: Fertility preservation (early referral)
PCART: Post-chemotherapy assisted reproduction (delayed referral)

Table 1

Patient demographic and clinical characteristics

	FP (n=218)		PCART (n=96)		P	
	No. of patients	%	No. of patients	%		
Age (years)	Mean	35.3±4.5	33.9±4.7		<0.01	
	Range	23-45	21-44			
Referral Hospital	University hospital	132	75	44	25	0.02
	Community hospital	5	71.4	2	28.6	
Distance	Private practice	54	70.1	23	29.9	
	Self-referral	8	50	8	50	
	Total	199	72.1	77	27.9	
	<10 miles	95	72.5	36	27.5	NS
	10-<100 miles	79	69.9	34	30.1	
	100-<1000 miles	21	70	9	30	
Occupation	1000 miles	12	60	8	40	
	Total	207	70.4	87	29.6	
	Management	20	83.3	4	16.7	NS
	Business and Financial Operations	11	57.9	8	42.1	
	Architecture and Engineering	3	60	2	40	
	Life, Physical, and Social Science	1	33.3	2	66.7	
	Community and Social Services	4	57.1	3	42.9	
	Legal	14	70	6	30	
	Education, Training, and Library	11	73.3	4	26.7	
	Arts, Design, Entertainment, Sports, and Media	20	71.4	8	28.6	
Healthcare Practitioner and Technical	12	70.6	5	29.4		
Food Preparation and	1	100	0	0		

	FP (n=218)		PCART (n=96)		P	
	No. of patients	%	No. of patients	%		
Household income	Serving Related					
	Personal Care and Service	0	0	2	100	
	Sales and Related	4	57.1	3	42.9	
	Office and Administrative Support	8	61.5	5	38.5	
	Student	6	66.7	3	33.3	
	Housewife	3	42.9	4	57.1	
	Total	118	66.7	59	33.3	
	<50,000	45	63.4	26	36.6	
	50,000-80,000	119	74.4	41	25.6	
	80,000	29	67.4	14	32.6	
Race and Ethnicity	Total	193	70.4	81	29.6	
	White	154	70.3	65	29.7	
	NS					
	African-American	17	65.4	9	34.6	
	Asian	18	62.1	11	37.9	
	Hispanic	13	68.4	6	31.6	
	N/A	16	76.2	5	23.8	
	Total	218	69.4	96	30.6	
	Gravida	0	117	66.9	58	33.1
	1	47	74.6	16	25.4	
Parity	2	25	69.4	11	30.6	
	3	8	61.5	5	38.5	
	4	2	100	0	0	
	5	1	100	0	0	
	Total	200	69	90	31	
	0	164	68.9	74	31.1	
	1	28	70	12	30	
	2	7	63.6	4	36.4	
	NS					

		FP (n=218)		PCART (n=96)		P
		No. of patients	%	No. of patients	%	
Abortion	3	1	100	0	0	
	Total	200	69	90	31	
	0	141	68.4	65	31.6	NS
	1	39	69.6	17	30.4	
	2	14	63.6	8	36.4	
	3	4	100	0	0	
	4	2	100	0	0	
Family history of breast cancer	Total	200	69	90	31	
	No family history of breast cancer	108	64.3	60	35.7	0.04
	Family history of breast cancer	97	75.2	32	24.8	
Prior Infertility Treatment	Total	205	69	92	31	
	No history of infertility	174	70.4	73	29.6	NS
	History of infertility	19	55.9	15	44.1	
Treatment for FP or PCART	Total	193	68.7	88	31.3	
	No treatment	120	61.9	74	38.1	<0.01
	Treatment	98	81.7	22	18.3	
	Total	218	69.4	96	30.6	

FP: Fertility preservation (early referral)

PCART: Post-chemotherapy assisted reproduction (delayed referral)