postage-paid envelope. The survey was sent out on 28 May 2010 and the mailed surveys postmarked by 31 July were included in the analysis. The consent from the participants was waived because of the anonymity of the survey. No honorarium was offered for completing the survey.

Data analysis

All analyses were conducted using IBM SPSS statistics version 18. Accuracy of knowledge about fertility was scored on the basis of four questions (A-1, 2, 3, 4, Table 1) concerning the standard knowledge about chemotherapy and the effect of chemotherapy on fertility. Respondents with appropriate knowledge were considered "accurate". Four questions (D-1, 2, 3, 5, Table 1) concerning the perspective and opinion about the fertility preservation were asked and scored as attitude score. Respondents were divided into "positive attitude group" and "negative attitude group" depending on the attitude score. Chi-square test was applied for correlation analysis between physician knowledge, attitude, and background. Physicians' background demographics, knowledge, and attitude regarding fertility issues were associated with physicians' practice behavior regarding fertility issues. Odds ratios (OR) and their 95% confidence interval (CI) were estimated to compare physician background factors, knowledge, and attitude with physician practice pattern, using simple and multivariable logistic regression models. All p values are two sided, and the statistical significance level was set at $p < 0.05$. No adjustments for multiple comparisons were considered because of the exploratory nature of this study.

Results

Response rate

The response rate was calculated as the number of breast oncologists completing the survey ($n = 434$) divided by the initial sample size minus undeliverable ($843 - 8 = 835$): this yielded a 52% response rate. This is higher than the previous survey on fertility preservation referral targeting oncology specialists in the USA [4].

Demographic and characteristics of responding breast oncologists

The background of respondents is shown in Table 2. A total of 16.6% of the respondents were female. More than 95% of the respondents were experienced physicians reflecting the requirement of basic board certification in general medicine, surgery, radiation oncology, or pathology in order to obtain JBCS Breast Oncologists certification. The majority was surgeons. Less than half responded that they have medical oncologists in their institutions. About 70% were the institutions in which they operated on less than five breast cancer patients per week (less than approximately 200 cases per year).

Association between knowledge, attitude, and physician background

Two hundred and seventy-nine (64%) respondents were considered to have accurate knowledge. Accuracy of knowledge about fertility was correlated with the number of young breast cancer patients treated ($p = 0.006$), presence of children of the physician ($p = 0.01$), age of the physician ($p = 0.019$), and the presence of female colleagues ($p = 0.019$).

The existence of a spouse/partner ($p = 0.011$), age ($p = 0.032$), and gender ($p = 0.023$) of the physician were the factors significantly correlated with a positive attitude toward fertility considerations of breast cancer patients. Physicians who have a spouse/partner, physicians who are younger than 50 years, and female physicians had more positive attitudes toward fertility issues for breast cancer patients.

Practice of fertility issues among breast oncologists

A total of 83% of the participants responded that they were positive in discussing fertility issues with young breast cancer patients.

Twenty-one percent responded that patients voluntarily bring up fertility issues in the clinic. Physicians who treat two or more young patients per week perceived that patients voluntarily express their concern in the clinic compared to physicians who treat fewer (OR 1.84, 95% CI 1.13–3.00, $p = 0.008$). Physicians who treat two or more young patients per week (OR 1.30, 95% CI 1.05–2.45, $p = 0.023$), who have board-certified nurse colleagues (OR 1.55, 1.19–2.03, $p < 0.001$) and have more than six breast surgeries per week (OR 1.20, 1.02–1.41, $p = 0.014$) responded that they perceived that patients talk to co-medical staff about their concerns about fertility. A total of 24% of the respondents consulted reproductive specialists when they encountered fertility problems in their patients and 42% referred patients to reproductive specialists when patients expressed concerns regarding fertility.

The association between physicians' behavior related to fertility issues and their knowledge, attitude, and background demographics are shown in Table 3. Fair knowledge had the strongest impact on physicians' positive behavior towards discussing fertility issue with patients. Positive attitude, presence of breast cancer-specialized CNS, young age, and female gender were also significant

Table 2 Demographic background of the responding physicians

	n	%
Total	434	100
Gender		
Female	72	16.6
Male	357	82.3
Unknown	5	1.2
Age		
20–29	1	0.2
30–39	52	12.0
40–49	183	42.2
50–59	148	34.1
60–69	41	9.4
70–	4	0.9
Unknown	5	1.2
Religion		
Buddhist	144	33.2
Christian	9	2.1
No special religion	276	63.5
Others	5	1.2
Year graduated from medical school		
–1994	347	80.0
1995–2000	76	17.5
2001–2005	6	1.4
Unknown	5	1.2
Specialty		
Surgery	412	94.9
Medical oncology	6	1.4
Radiation oncology	9	2.1
Gynecology	1	0.2
Others	6	1.4
Type of affiliation		
Cancer center	40	9.2
General hospital	190	43.8
University hospital	122	28.1
Private clinic	74	17.1
Unknown	8	1.8
Number of physicians		
1–3	164	37.8
4–7	137	31.8
8–	125	28.8
Unknown	8	1.8
Female physician colleague		
Present	276	63.6
Absent	150	34.6
Unknown	8	1.8
Medical oncologist		
Present	172	39.6
Absent	255	58.8
Unknown	7	1.6
Breast cancer specialized nurse		
Present	202	46.5
Absent	225	51.8
Unknown	7	1.6
Board-certified pharmacists		
Present	227	52.3
Absent	196	45.2
Unknown	11	2.5
Number of breast surgeries (per week)		
0–5	310	71.4
5–10	85	19.5
11–15	14	3.2
16–20	3	0.7
20–	14	3.2
Unknown	8	1.8
Number of patients aged <40 (per week)		
0–1	122	28.1
2–4	202	46.5
5–	103	23.7
Partner/spouse		
Present	401	92.4
Absent	25	5.8
Unknown	8	1.8
Children		
Present	351	80.9
Absent	64	14.7
Unknown	19	4.4

factors associated with positivity towards the discussion. Female oncologists and medical oncologists were more likely to take into account patients' social backgrounds such as history of childbirth, presence of a spouse/partner, and patients' economic status when discussing fertility issues.

Physicians with a positive attitude, physicians younger than 50 years, and female physicians were more likely to discuss fertility issues with patients with poorer prognoses. Positive attitude was the strongest factor related to consultation and referral to reproductive specialists.

Barriers for discussion with patients

High risk of disease recurrence (51%), lack of reproductive specialists or infertility clinic for referral (45%), and time constraints in the clinic (45%) were regarded as major barriers for discussing fertility issues. When only physicians who were negative in discussing fertility issues ($n = 69$) were analyzed, high risk of recurrence (57%), no signal of interest in fertility from patients (49%), and lack

Table 3 Factors associated with fertility-related practice behavior

	I discuss the impact of cancer treatment on future fertility with my patients				I do not feel comfortable discussing fertility issues with my patients				I take into account the history of childbirth when I discuss fertility issues with my patients			
	p	OR	95% CI		*p*	OR	95% CI		*p*	OR	95% CI	
			Min	Max			Min	Max			Min	Max
Knowledge												
Fair	0.000	1.717	1.321	2.231	0.063				0.799			
Not fair		1.000										
Attitude												
Conservative	0.012	1.000			0.180				0.697			
Aggressive		1.542	1.145	2.079								
Gender												
Female	0.005	1.166	1.080	1.258	0.807				0.022	1.130	1.041	1.227
Male		1.000								1.000		
Age												
<50	0.000	1.584	1.280	1.959	0.203				0.625			
>50		1.000										
Specialty												
Surgery	1.000				0.625				0.756			
Others												
Affiliation												
University hospital/cancer center	0.032	1.235	1.047	1.457	0.147				0.900			
General hospital/private hospital		1.000										
Female physician colleague												
Present	0.079				1.000				1.000			
Absent												
Medical oncologist colleague												
Present	0.432				0.366				0.043	1.190	1.003	1.141
Absent												
Breast cancer-specialized nurse												
Present	0.606				0.480				0.327			
Absent												
Board-certified cancer pharmacist												
Present	0.001	1.510	1.220	1.868	0.721				0.324			
Absent		1.000										
Number of breast surgeries per week												
1–5	0.884				0.692				0.495			
6–												
Number of young patients per week												
0–1	0.474				0.113				0.500			
2–												
Partner/spouse												
Present	0.281				0.008	1.000			0.193			
Absent						1.158	0.989	1.355				
Children												
Present	0.074				0.088				0.740			
Absent												

Table 3 continued

	I take into account whether she has a spouse/partner when I discuss fertility issues with my patients				I take into account economical status of the patient when I discuss fertility issues with my patients				I discuss fertility issues with breast cancer patients with high risk of recurrence			
	p	OR	95% CI		*p*	OR	95% CI		*p*	OR	95% CI	
			Min	Max			Min	Max			Min	Max
Knowledge												
Fair	0.839				0.609				0.910			
Not fair												
Attitude												
Conservative	0.601				0.694				0.001	1.000		
Aggressive										1.640	1.250	2.150
Gender												
Female	0.033	1.089	1.002	1.185	0.622				0.047	1.089	1.000	1.185
Male										1.000		
Age												
<50	0.326				0.267				0.003	1.391	1.131	1.712
>50												
Specialty												
Surgery	0.225				0.343				0.273			
Others												
Affiliation												
University hospital/cancer center	0.364				1.000				0.219			
General hospital/private hospital												
Female physician colleague												
Present	0.412				0.194				0.649			
Absent												
Medical oncologist colleague												
Present	0.022	1.206	1.032	1.408	0.043	1.261	0.996	1.596	1.000			
Absent		1.000				1.000						
Breast cancer specialized nurse												
Present	0.434				1.000				0.588			
Absent												
Board-certified cancer pharmacist												
Present	0.694				0.136				0.745			
Absent												
Number of breast surgeries per week												
1–5	0.125				0.262				0.903			
6–												
Number of young patients per week												
0–1	0.746				0.273				0.810			
2–												
Partner/spouse												
Present	0.299				0.192				1.000			
Absent												
Children												
Present	0.183				1.000				0.025	1.116	1.029	1.211
Absent										1.000		

Table 3 continued

	I ask co-medical staff if a patient has an interest in fertility				I provide my patients with educational material about fertility preservation				I use LHRH analogue to preserve fertility			
	p	OR	95% CI		*p*	OR	95% CI		*p*	OR	95% CI	
			Min	Max			Min	Max			Min	Max
Knowledge												
Fair	0.242				0.125				0.653			
Not fair												
Attitude												
Conservative	0.895				0.100				0.248			
Aggressive												
Gender												
Female	0.133				0.047	1.183	0.973	1.440	0.399			
Male												
Age												
<50	0.262				0.416				0.914			
>50												
Specialty												
Surgery	0.105				0.066				0.057			
Others												
Affiliation												
University hospital/cancer center	0.795				0.046	1.000			0.656			
General hospital/private hospital						1.671	0.959	2.911				
Female physician colleague												
Present	0.793				0.026	1.919	1.014	3.632	0.259			
Absent						1.000						
Medical oncologist colleague												
Present	0.443				0.407				0.381			
Absent												
Breast cancer-specialized nurse												
Present	0.316				0.871				0.516			
Absent												
Board-certified cancer pharmacist												
Present	0.900				0.325				0.663			
Absent												
Number of breast surgeries per week												
1–5	1.000				0.273				0.402			
6–												
Number of young patients per week												
0–1	0.583				0.721				1.000			
2–												
Partner/spouse												
Present	0.192				1.000				0.828			
Absent												
Children												
Present	0.614				1.000				0.156			
Absent												

Table 3 continued

	I consult a reproductive specialist with questions about fertility issues in my patients				I refer patients who have questions about fertility to reproductive specialists			
	p	OR	95% CI		*p*	OR	95% CI	
			Min	Max			Min	Max
Knowledge								
Fair	0.442				0.162			
Not fair								
Attitude								
Conservative	0.032	1.000			0.003	1.656	1.183	2.319
Aggressive		1.599	1.014	2.798		1.000		
Gender								
Female	0.039	1.121	0.995	1.277	0.001	1.176	1.062	1.302
Male		1.000				1.000		
Age								
<50	0.264				0.004	1.424	1.110	1.828
>50						1.000		
Specialty								
Surgery	1.000				0.795			
Others								
Affiliation								
University hospital/cancer center	0.007	1.349	1.067	1.706	0.012	1.243	1.047	1.474
General hospital/private hospital						1.000		
Female physician colleague								
Present	0.051	1.467	0.995	2.164	0.123			
Absent		1.000						
Medical oncologist colleague								
Present	0.103				0.042	1.212	1.011	1.453
Absent						1.000		
Breast cancer-specialized nurse								
Present	0.710				1.000			
Absent								
Board-certified cancer pharmacist								
Present	0.803				0.138			
Absent								
Number of breast surgeries per week								
1–5	0.785				1.000			
6–								
Number of young patients per week								
0–1	0.270				0.813			
2–								
Partner/spouse								
Present	0.807				0.670			
Absent								
Children								
Present	0.197				0.209			
Absent								

of reproductive specialists or infertility clinic for referral (38%) were the major causes for them not to discuss fertility with patients.

Discussion

This study describes the attitude of the main providers of breast cancer treatment in Japan towards fertility issues in young breast cancer patients. The high response rate to our survey in a relatively short time indicates the interest of breast oncologists in fertility issues. More than 80% of the participants responded that they had a positive attitude when discussing fertility issues in the clinic, but this result may be biased by the respondents' interest in fertility issues. The recent awareness of fertility issues among Japanese breast oncologists may be related to the publication of the ASCO guideline in 2006 and the inclusion of fertility-related contents in JBCS patient guideline 2009 [2, 9]. Indeed, the JBCS treatment guideline, the standard textbook for board certification of Breast Oncologists, updated its contents to cover fertility-related issues in July 2010 [10].

The physicians with a positive attitude and working in institutions with medical oncologists and/or female colleagues had a higher likelihood of consultation or referral to reproductive specialists. The likelihood of referring to reproductive specialists was slightly higher in female physicians, which was consistent with the results of the survey in the USA [4]. These results indicate that participation of female healthcare providers in the team and a multidisciplinary working environment might enhance physicians' awareness of and behavior toward fertility-related issues. Because knowledge and attitude seem to be influenced by gender, personal experience, and the working environment of the physicians, we think that outreach with educational materials and systematic learning opportunities for healthcare providers would be helpful in expanding knowledge and performance regarding fertility issues in young breast cancer patients.

High risk of disease recurrence was considered the greatest barrier for physicians, similar to the results of other studies [5, 6]. In our previous study, patients' with higher risk of disease recurrence did not voluntarily express their concerns regarding fertility when compared to patients of lower risk of disease recurrence [3]. Both patients and physicians may refrain from discussing future fertility when the estimation of prognosis of the cancer is poor. Although early referral to reproductive specialists might increase the patients' likelihood of receiving reproductive intervention and improve the fertility outcome [11, 12], fertility preservation techniques such as embryo preservation and oocyte preservation connote ethical issues especially in patients with poor prognosis [13]. Ethical and psychosocial support is necessary in the shared decision-making process among patients, families, and physicians.

A lack of reproductive specialists or infertility clinic for referral is a real problem. A survey in the USA showed that many breast cancer clinicians reported that they do not have knowledge of or resources for fertility preservation [8, 14]. Interdisciplinary communication between reproductive specialists and oncologists is necessary.

Early case–control studies suggest that pregnancy after primary treatment of breast cancer does not have a negative impact on cancer prognosis, although "healthy mother" bias might exist [15]. Because prognostication of breast cancer has become individualized using genetic biomarkers [16, 17], further investigations to clarify the impact of pregnancy after primary treatment on an individual basis is needed so that patients can personalize their decision-making regarding both cancer treatment and fertility.

In conclusion, Japanese breast oncologists were in general positive in discussing fertility issues with young breast cancer patients. Female and younger physicans as well as physicians working in a multidisciplinary environment had more positive attitudes and behavior towards fertility preservation. The development of multidisciplinary and interdisciplinary programs is necessary to meet the fertility needs of breast cancer patients.

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ORIGINAL ARTICLE

Paclitaxel-induced peripheral neuropathy in patients receiving adjuvant chemotherapy for breast cancer

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Abstract
Background The long-term outcomes and risk factors of paclitaxel-induced peripheral neuropathy (PIPN) have not yet been fully elucidated.
Methods We identified 219 breast cancer patients who received paclitaxel as adjuvant chemotherapy between 2002 and 2009. We retrospectively analyzed the incidence, time to onset, duration, and risk factors for PIPN by chart review.
Results Of the 219 patients, 212 developed PIPN (97%) during a median follow-up time of 57 months (range 5.3–95.5). Median time to PIPN onset was 21 days (range 11–101) for the entire patient population: 35 days (range 14–77) for weekly administration and 21 days (range 11–101) for tri-weekly administration. PIPN caused termination of paclitaxel treatment in 7 patients (4%). Median duration of PIPN was 727 days (range 14–2621 days). PIPN persisted in 64 and 41% of patients at 1 and 3 years after initiating paclitaxel, respectively. Age ≥60 years and severity of PIPN were significantly associated with PIPN duration.
Conclusions PIPN persists longer in older patients and in those who experience severe neuropathy. Further studies to identify the risk factors for PIPN are warranted.

Keywords Breast cancer · Paclitaxel · Peripheral neuropathy

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Introduction

Paclitaxel (PTX) is a key component of many therapeutic regimens in both early-stage and metastatic breast cancer [1–4]. PTX, a microtubule-stabilizing agent, binds to microtubules and abolishes their dynamic behavior, leading to inhibition of cell proliferation [5]. The agent is known to cause peripheral neurotoxicity (PN), which may result in discontinuation of treatment and poor quality of life.

The incidence of PTX-induced PN (PIPN) is known to depend on several factors, including dosages per cycle, treatment schedule, duration of infusion, cumulative dosage, and co-morbidity such as diabetes [6–11]. Although the clinical response of tumors to PTX is an important factor in selecting a chemotherapy regimen, it is also prudent to evaluate the risk of developing PN associated with each regimen, especially for patients already at high risk for neuropathy. The risk of sensory neuropathy is proportional to the dose of PTX administered. Grade 3 or 4 sensory neurotoxicity occurs in 20–35% of patients receiving 250 mg/m^2 every 3 weeks compared to 5–12% using doses ≤200 mg/m^2 every 3 weeks [12]. The weekly schedule is associated with higher neurotoxicity than the tri-weekly schedule. In a previous study, grade 3 neuropathy occurred significantly more often with the weekly regimen than with the tri-weekly regimen (24 vs. 12%) [13]. In another study, which compared weekly versus

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tri-weekly PTX dosages, it was reported that grade 2, 3, or 4 neuropathy occurred more frequently with weekly than with tri-weekly PTX administration (27 vs. 20%, respectively) [14].

The time to onset of PIPN was previously determined in a phase III trial of patients with metastatic breast cancer treated with PTX (175 mg/m^2) every 3 weeks; the mean total dose at the onset of grade 2 neurotoxicity was 715 mg/m^2 [15]. However, there are limited data available describing the outcome of PIPN and risk factors of severe PN. We therefore conducted a retrospective study to determine the duration of PIPN and to identify potential factors predicting severe or persistent PN.

Patients and methods

Data collection

This study included breast cancer patients treated with PTX as adjuvant chemotherapy at the National Cancer Center Hospital between 2002 and 2009. All patients met the following criteria: female gender; age >18 years; recipients of lumpectomy or mastectomy; and presentation of more than one axillary lymph node metastasis, as determined pathologically. The following patients were excluded from this study: those previously treated with PTX, those who presented with severe neuropathy before initiating PTX treatment, and those who discontinued PTX treatment after only 1 cycle for any reason.

We performed chart reviews for all patients to obtain the following information: age; gender; stage; hormonal status; human epidermal growth factor receptor-2 (HER2) status; previous surgical procedures (lumpectomy or mastectomy); adjuvant chemotherapy; adjuvant radiotherapy; PTX administration schedule; date of the first documentation of PIPN; maximum grade of PIPN; date of disappearance of PIPN symptoms. This study was approved by the local institutional review board.

Treatment schedule

Chemotherapy consisted of anthracycline followed by PTX regimens as generally recommended for high-risk breast cancer patients, according to the St. Gallen risk criteria at our division [16, 17]. However, therapeutic options could vary based on the physician's discretion. Patients received either 80 mg/m^2 of PTX on days 1, 8, and 15 of each 21-day interval for 4 cycles, following anthracycline plus cyclophosphamide (AC) (weekly administration schedule), or 175 mg/m^2 of PTX on day 1 of each 21-day interval for 4 cycles, following AC (tri-weekly administration schedule).

Grading of PIPN

Patients were evaluated during and after chemotherapy by medical oncologists. We graded PIPN retrospectively according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 [18]. Grade 1 PIPN had paresthesias including tingling, but not interfering with function, while grade 2 had sensory alterations or paresthesias interfering with function but not interfering with activities of daily living (ADL). Grade 3 had sensory alterations or paresthesias interfering with ADL. Patients were determined to have PIPN if their score for sensory neuropathy was grade 1 or higher. The severity of pain was not evaluated in this study because of insufficient data.

Statistical analysis

The time to onset of PIPN was defined as the time from the date of PTX administration to the date of the first documentation of PIPN. The duration of PIPN was defined as the time from the date of first documentation of PIPN to the date of disappearance of the PIPN symptoms described. The time to onset and duration of PIPN were estimated by the Kaplan–Meier method. We used multivariate Cox regression analysis to identify the variables associated with the time to onset and duration of PIPN. Furthermore, to identify the risk factors for PIPN above grade 2, we applied multivariate logistic regression analysis. A 2-sided $P < 0.05$ was considered statistically significant. All analyses were performed by SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Of the 227 patients initially identified, 2 were excluded due to severe neuropathy induced by combination chemotherapy with AC before being treated with PTX. Several patients discontinued systemic therapy before completion of 1 cycle due to the following adverse events: severe liver dysfunction (grade 3) ($n = 3$), acute renal failure (grade 3) ($n = 1$), allergic reaction (grade 3) ($n = 1$), and interstitial pneumonitis (grade 3) ($n = 1$). Finally, a total of 219 patients were included; 212 patients (97%) developed PIPN which was characterized by numbness and tingling, while 7 had no PIPN symptoms. The maximum severity of PIPN reached in each of the 212 patients was as follows: grade 1, 159 patients (75%); grade 2, 45 patients (21%); and grade 3, 9 patients (4%). Two patients needed dose modifications due to PIPN above grade 2. No patients postponed or skipped the scheduled PTX due to PIPN.

Baseline characteristics of the population are listed in Table 1. The median age of patients was 53 years (range 22–70). Eighteen patients had diabetes mellitus without neuropathy complications at baseline. Disease-free survival and overall survival were evaluated with a median follow-up time of 57.1 months (range 5.3–95.5). A total of 25 patients received weekly PTX: 23 following AC and 2 without AC. The remaining 194 patients received tri-weekly PTX: 182 following AC and 12 without AC. The mean dose intensity was 58 mg/week (range 16–80). Treatment cessation was deemed necessary in 9 patients (4%); reasons for cessation were PIPN (8 patients, 3 with grade 1, 1 with grade 2, and 5 with grade 3) and myelosuppression (1 patient).

Table 1 Patient characteristics

Variables	triPTX ($N = 188$)	wPTX ($N = 24$)	All ($N = 212$)
Age			
Median (range)	53 (22–70)	52 (32–68)	53 (22–70)
<60 (%)	141 (75.0)	17 (70.8)	158 (74.5)
≥60 (%)	47 (25.0)	7 (29.2)	54 (25.5)
Sex (%)			
Female	187 (99.5)	24 (100.0)	211 (99.5)
Male	1 (0.5)	0 (0.0)	1 (0.5)
Lymph (%)			
<4	118 (62.8)	12 (50.0)	130 (61.3)
≥4	70 (37.2)	12 (50.0)	82 (38.7)
Tumor size (%)			
<5 cm	153 (81.4)	18 (75.0)	171 (80.7)
≥5 cm	35 (18.6)	6 (25.0)	41 (19.3)
Surgery (%)			
Mastectomy	114 (60.3)	16 (66.7)	130 (61.3)
Lumpectomy	73 (39.2)	8 (33.3)	81 (38.2)
Excisional biopsy	1 (0.5)	0 (0.0)	1 (0.5)
Systemic therapy (%)			
Chemo	56 (29.8)	8 (33.3)	64 (30.2)
Chemo + endocrine	132 (70.2)	16 (66.7)	148 (69.8)
Radiation (%)			
No	69 (36.7)	8 (33.3)	77 (36.3)
Yes	119 (63.3)	16 (66.7)	135 (63.7)
Hormone (%)			
Negative	48 (25.5)	5 (20.8)	53 (25.0)
Positive	140 (74.5)	19 (79.2)	160 (75.0)
HER2 (%)			
Negative	156 (83.0)	16 (66.7)	172 (81.1)
Positive	32 (17.0)	8 (33.3)	40 (18.9)
Diabetes mellitus (%)			
No	171 (91.0)	23 (95.8)	194 (91.5)
Yes	17 (9.0)	1 (4.2)	18 (8.5)

triPTX tri-weekly paclitaxel, *wPTX* weekly paclitaxel, *chemo* chemotherapy

PIPN development time

The median time taken for the total patient group to develop PIPN was 21 days (range 11–101) (Fig. 1). With weekly administration of PTX, the median time taken to develop PIPN was also 21 days (range 11–101); the median time with tri-weekly administration was 35 days (range 14–77).

Cumulative dose

The mean cumulative dose at the onset of grade 1 or higher PIPN was 175 mg/m^2 for patients treated with PTX every 3 weeks and 320 mg/m^2 for weekly PTX patients.

Diabetes mellitus

Of 18 diabetic patients, all had PIPN and 3 had maximum grade 3 PIPN. Median time to PIPN onset was 21 days (range 20–21), and median duration of PIPN was 287 days (range 70–503). In patients without diabetes, median time to PIPN was 21 days (range 20–21), and median duration of PIPN was 231 days (range 190–271).

Risk factors correlated with PIPN

Multivariate analysis using a logistic regression model after stepwise selection revealed no significant correlations between time to PIPN onset and maximum PIPN severity (Table 2), while there were significant correlations between duration of PIPN and age (>60 years old) ($P = 0.027$) and between duration of PIPN and maximum PIPN severity ($P = 0.015$) (Table 3). Moreover, we could not identify

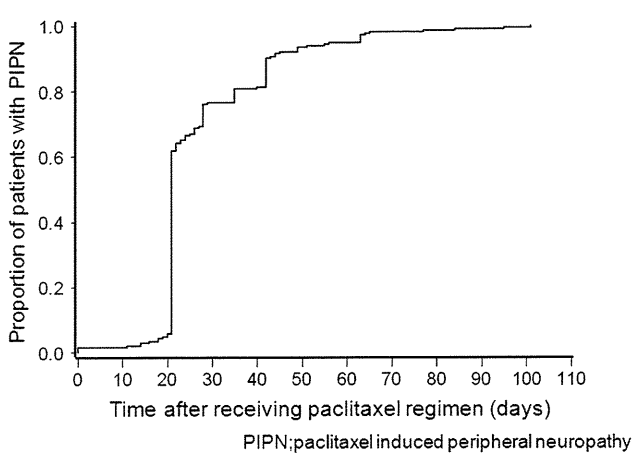

Fig. 1 Time taken for the total patient group to develop paclitaxel-induced peripheral neuropathy

Table 2 Multivariate analysis for factors associated with time to PIPN

Variables	HR	95% CI		*P* value
Regimen				
triPTX	1			
wPTX	0.66	0.43	1.03	0.070
Age				
<60				
≥60	0.99	0.72	1.37	0.960
Lymph				
<4				
≥4	1.20	0.82	1.77	0.341
Tumor size (cm)				
<5				
≥5	0.98	0.68	1.42	0.917
Radiation				
No				
Yes	0.78	0.51	1.20	0.259
Surgery				
Mastectomy				
Lumpectomy	1.08	0.75	1.56	0.666
Endocrine				
No				
Yes	0.87	0.65	1.18	0.366
Grade				
1				
2 or 3	1.35	0.97	1.87	0.073
Diabetes mellitus				
No				
Yes	1.34	0.81	2.21	0.260

PIPN paclitaxel-induced peripheral neurotoxicity, *triPTX* tri-weekly paclitaxel, *wPTX* weekly paclitaxel, *HR* hazard ratio, *CI* confidence interval

Table 3 Multivariate analysis for factors associated with duration of PIPN

Variables	HR	95% CI		*P* value
Regimen				
triPTX	1			
wPTX	0.48	0.19	1.21	0.119
Age				
<60				
≥60	0.55	0.32	0.94	0.027
Lymph				
<4				
≥4	0.86	0.46	1.59	0.621
Tumor size (cm)				
<5				
≥5	1.03	0.59	1.77	0.927
Radiation				
No				
Yes	1.05	0.52	2.12	0.900
Surgery				
Mastectomy				
Lumpectomy	0.67	0.36	1.26	0.213
Endocrine				
No				
Yes	1.10	0.70	1.73	0.668
Grade				
1				
2 or 3	0.53	0.32	0.88	0.015
Diabetes mellitus				
No				
Yes	0.66	0.28	1.56	0.345

PIPN paclitaxel-induced peripheral neurotoxicity, *triPTX* tri-weekly paclitaxel, *wPTX* weekly paclitaxel, *HR* hazard ratio, *CI* confidence interval

any correlation with grade 2/3 PIPN (Table 4). Based on the results of multivariate analyses, there were no significant associations between diabetes mellitus and time to PIPN onset ($P = 0.260$) or duration of PIPN ($P = 0.345$) or grade 2/3 PIPN ($P = 0.229$).

Duration of PIPN

The median duration of PIPN was 727 days for the total patient group (range 14–2621) (Fig. 2). With weekly administration, the median duration was not reached (range 14–1089); the median duration for patients with tri-weekly administration was 651 days (range 23–2621). One year after initiating PTX treatment, PIPN (all grades included) persisted in 64% of patients; 3 years after treatment initiation, this number had dropped to 41%.

Discussion

This is the first published report to our knowledge that investigates the time to onset and duration of PIPN among breast cancer patients and explores potential risk factors related to severe and/or persistent PIPN. The data from this study confirm that most patients (97%) developed PIPN with a severity of at least grade 1. Peripheral neuropathy persisted in 64% of patients at 1 year and 41% at 3 years after the first administration of PTX. Approximately half of the patients who received PTX and developed PN experienced recovery from PN within 9 months after cessation of PTX treatment. We found correlations between the maximum PIPN severity and both the time to onset of PIPN and the duration of PIPN. In addition, we observed that PN lasted significantly longer in patients >60 years of age.

Table 4 Multivariate analysis for factors associated with grade 2 or 3 PIPN

Variables	Odds ratio	95% CI		*P* value
Regimen				
triPTX	0.57	0.18	1.83	0.345
wPTX				
Age				
<60	1.65	0.81	3.36	0.171
≥60				
Lymph				
<4	0.98	0.40	2.41	0.968
≥4				
Tumor size (cm)				
<5	0.47	0.18	1.24	0.125
≥5				
Radiation				
No	0.98	0.35	2.77	0.975
Yes				
Surgery				
Mastectomy	0.73	0.29	1.82	0.499
Lumpectomy				
Endocrine				
No	0.72	0.36	1.45	0.360
Yes				
Diabetes mellitus				
No	2.05	0.69	6.09	0.197
Yes				
Dose intensity				
<58	1.00	0.50	2.01	1.000
≥58				
Cumulative dose				
<700	0.31	0.08	1.13	0.077
≥700	0.57	0.18	1.83	0.345

PIPN paclitaxel-induced peripheral neurotoxicity, *triPTX* tri-weekly paclitaxel, *wPTX* weekly paclitaxel, *CI* confidence interval

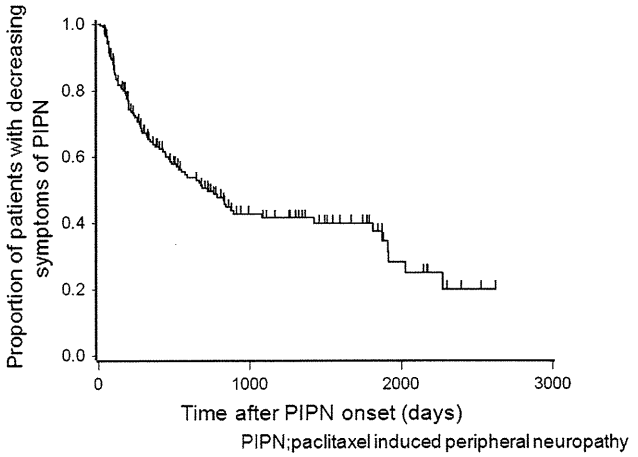

Fig. 2 Time to resolving PIPN from the time of developing paclitaxel-induced peripheral neuropathy

Previous studies have reported that the incidence of PIPN is related to several risk factors, including treatment schedule, doses per course, patient age, diabetes mellitus, and cumulative dose [6–11]. We found no association between the severity of PIPN and the PTX administration schedule including single dose, dose intensity, diabetes mellitus, or interval of administration. In our study, the mean cumulative dose at the onset of grade 1 or higher PN was 175 mg/m^2 for patients treated with PTX every 3 weeks and 320 mg/m^2 for weekly PTX patients. In contrast to an earlier study [14], our clinical outcomes indicated that tri-weekly administration of PTX was associated with more severe PIPN than weekly administration. However, this result may be attributed to frequent hospital visits and/or the relatively small number of patients treated by weekly PTX.

Previous reports suggest there are several risk factors for PIPN, including concurrent administration of cisplatin [19] and various genetic predispositions for neuropathy, such as *Wlds* (slow Wallerian degeneration gene) and *CYP3A* genotype [20, 21], but we did not examine any of those risk factors in this study.

Axonal microtubules are composed largely of β-tubulin. Neurotoxicity is caused by disruption of the microtubule structure, impairing axoplasmic transport and leading to dying-back neuropathy [22]. The most widely accepted mechanism of taxane neurotoxicity is a dying-back process that starts from distal nerve endings and progresses to affect Schwann cells, neuron bodies, or axons, resulting in transport changes that disturb cytoplasmic flow in the affected neurons [23]. Another possible cause of PIPN is that sensory nerves may be particularly vulnerable to the inhibition of tubulin assembly, as sensory nerves have long axons. However, motor neurons and C-neurons are not as sensitive to taxanes as are sensory nerves, despite the fact that these neurons are as long as sensory nerves. Some reports suggest that induction of Ca$\alpha 2\delta$-1 expression by PTX in the spinal root may be important, but further investigation is necessary to understand the mechanisms of PIPN [24].

There are no medications that prevent or relieve PIPN. Likewise, there are no laboratory tests that can predict the severity of PN. Management of PIPN is now based on early detection during chemotherapy to prevent its progression to grade 3 or 4. Clinical assessment, including a physical examination, is currently the most reliable method of assessing PIPN because we lack more reliable objective methods, and the symptoms of PIPN, such as numbness, sensory pain, fatigue, and weakness, are complicated [12, 25]. If grade 2 PN is diagnosed, it may be prudent to

withhold PTX until PN improves to at least grade 1; PTX administration can then be resumed at a reduced dose.

There were several limitations to our study. We used physician-based assessments, which relies on patients' report and examiners' interpretation and could have resulted in underestimation and under-reporting of the frequency and severity of PN [26]. In addition, physicians were more prone to quit following symptoms periodically once patients recovered from maximum PIPN. In fact, there were many censored cases in this study (Fig. 2). Therefore, features of PIPN such as location, presence of accompanying symptoms, and triggers for increase or decrease in severity were unclear. This study was retrospective, with censored data; the neurotoxicity corresponding to each grade of PIPN was unclear. In fact, time to onset of PIPN was faster for grades 2 and 3 than grade 1. In order to properly evaluate the correlation between severity and duration of PIPN, we will need further studies to determine whether or not the duration of PIPN is longer when the maximum severity increases from grade 1 to grade 2.

In conclusion, we analyzed the incidence and duration of PIPN and identified correlations between these and several risk factors. We found that the median time to onset of PIPN was 21 days, and the median duration of PIPN was 727 days. Patient age and PIPN severity were the independent risk factors significantly associated with longer PIPN duration. Urgent needs currently include identification of specific risk factors for PIPN, establishment of subjective methods for evaluating PIPN, and development of effective strategies for prevention and treatment of PIPN. To meet these ends, further investigation of the biological mechanisms leading to PIPN is warranted.

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Conflict of interest The authors have declared no conflicts of interest.

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● 原 著 ●

乳癌薬物治療に伴う妊孕性への影響に関する情報提供の実態調査

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Survey on Oncologists-Provided Information on Treatment-Related Infertility to Breast Cancer Patients: Akiko Kubo[*1], Keiichi Koido[*1], Mari Sawada[*1], Yasuaki Ryushima[*1], Chikako Shimizu[*2], Tomoyasu Kato[*3], Masashi Ando[*2], Takayuki Kinoshita[*2], Koji Murakoshi[*1], Nobuaki Yokote[*1], Yasuhiro Fujiwara[*2] and Hiroshi Yamamoto[*1] ([*1]*Dept. of Pharmacy*, [*2]*Dept. of Breast and Medical Oncology, and* [*3]*Dept. of Gynecology, National Cancer Center Hospital*)

Summary

Purpose: Treatment-related infertility is an important issue facing breast cancer survivors of childbearing age. A previous study at the National Cancer Center Hospital between 2000 and 2004 analyzed 136 postoperative breast cancer patients under 40 years old, and found that only 7% of them had been provided with information on fertility-related issues by their treating physicians. However, the way in which information is shared may have changed, given the recent publication of national and international guidelines on fertility issues in cancer patients, and we hypothesized that there will be an increase in the percentage of cases in which information about fertility-related issues is provided. Methods: We retrospectively analyzed patients 40 years old or younger who underwent surgery for primary breast cancer in this hospital between 2007 and 2009. We assessed patients' and oncologists' backgrounds, pathological stage, treatment plans, and whether or not oncologists provided explanations regarding fertility-related issues. Results: One hundred cases were analyzed. Five percent, 15%, and 80% of patients were＜30, 30-35, and＞35 years old, respectively. Sixty-one percent of patients had partners, while 29% had prior deliveries. Information on fertility-related issues was provided to 56% of patients. Significant factors influencing whether information was provided were patients' reproductive history (odds ratio (OR): 5.717, 95% confidence interval (CI): 1.752-18.66, p=0.004) and recommended treatment (OR: 24.22, CI: 3.150-186.2, p=0.017). By contrast, oncologists' background (specialty, gender, and duration of career as a physician) was not significant. The frequency with which treatment plans were changed did not correlate statistically with the provision of information on fertility-related issues. Conclusions: Information on treatment-related infertility is now provided much more frequently than in the past. We should encourage both patients and medical professionals to increase their awareness about this important issue. **Key words**: Breast cancer, Chemotherapy, Infertility (*Receive May 13, 2011/Accepted Jul. 6, 2011*)

要旨 背景: 薬物治療に関連した不妊は挙児希望を有する乳癌患者にとって重要な問題である。国立がん研究センター中央病院（以下，当院）における2000～2004年を対象期間とした調査では，40歳以下の乳癌患者に術前・術後薬物療法が妊孕性に及ぼす影響が伝えられていたのは7%だった。今回，われわれは2007～2009年における情報提供の実態調査を行った。方法: 2007～2009年に当院で手術を受けた40歳以下の女性乳癌患者を対象とした。診療録から，妊孕性に関する医師からの情報提供の有無，患者および担当医師の社会的背景，治療レジメンを後方視的に調査した。結果: 対象患者は100名。年齢［＜30歳/30～35歳/35歳≦］=［5/15/80］，病理病期［0/Ⅰ/Ⅱ/Ⅲ/Ⅳ］=［21/23/43/12/1］，パートナー［あり/なし］=［61/39］，出産歴［あり/なし］=［29/71］であった。情報提供［あり/なし］=［56/44］であった。情報提供の有無に影響する因子は，患者側の要因として出産歴〔odds ratio (OR): 5.717, 95% CI: 1.752-18.66, p=0.004〕や推奨される治療レジメン (OR: 24.22, 95% CI: 3.150-186.2, p=0.017) と関連がみられ，年齢やパートナーの有無は関連がみられなかった。また，医師側の背景因子（診療科，性別，医師経験年数）との関連はみられなかった。さらに，化学療法を含む治療方針からの変更割合は，情報提供の有無で差はみられなかった。結語: 2007～2009年においても，情報提供率は約60%にとどまり，癌治療に伴う妊孕性への影響について，医療者・患者双方の意識をさらに高める必要がある。

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はじめに

近年，診断技術や治療技術の進歩に伴い，がん患者の予後が改善されてきたことで，治療後のQOL向上が懸念されるようになった。その一つとして，治療に関連した不妊がある[1]。

乳癌の化学療法では卵巣機能障害が比較的高率に起きる。特にcyclophosphamide（CPA）は，治療後に永続的な無月経を惹起しやすい代表的な抗がん剤として報告されている[2]。乳癌は生殖年齢における罹患率が高く，挙児希望を有する乳癌患者にとって妊孕性への影響は重要な問題である。

2006年の米国臨床腫瘍学会（ASCO）の勧告では，医師は生殖能力を有する患者を治療する場合には，治療開始前に治療に伴う妊孕性の影響について十分に説明し，生殖医療の専門医への紹介を行うべきであるとしている。

しかし，国立がん研究センター中央病院（以下，当院）において2000～2004年を対象期間とした調査では，40歳以下の早期乳癌患者の術後補助療法を決定する際に，医師から患者に対し治療による妊孕性への影響について，積極的に説明が行われた頻度は7%にとどまった[3]。

本邦においても，2006年の日本乳癌学会の患者向けガイドラインに抗がん剤治療に伴う妊孕性への影響が明記される[4]など，患者を取り巻く情報環境に変化が現れはじめている。そこで今回，われわれは2006年以降における情報提供の実施状況の実態を明らかにするために調査・検討を行った。

Ⅰ．対象と方法

1．対象患者

2007年1月～2009年10月までの期間に当院乳腺外科で乳房切除術を施行した，手術時年齢が40歳以下の早期乳癌女性患者を対象とした。

2．調査方法および調査項目

調査は診療録を用いて後方視的に行った。調査項目は，妊孕性に関する情報提供の有無，対象患者における年齢，病理病期（pStage），パートナーの有無，出産歴の有無，医師から推奨された補助療法および実施された補助療法とした。なお，情報提供の有無はインフォームド・コンセント時の診療録に，不妊・早発閉経などの記載があった場合に，「情報提供あり」と判断した。

妊孕性に関する情報提供頻度の変化を調べるため，岡田らが報告した2000～2004年を対象期間とした症例をA群，今回調査を行った2007～2009年を対象期間とした症例をB群として比較を行った。患者背景における年齢の分類は，A群の調査に準じて行った。

情報提供の有無を決定する可能性のある背景因子として，患者側の要因（年齢，パートナーの有無，出産歴の有無，推奨された治療）および各対象患者における担当医師側の要因（診療科，性別および医師経験年数）の影響を検討した。

3．統計学的処理

2群間の比較にはχ^2検定を用いた。薬物治療に伴う妊孕性への影響に関する情報提供の有無にかかわる背景因子については，多重ロジスティック回帰分析により検討した。解析ソフトは，SPSS 15.0 J for Windowsを使用した。

Ⅱ．結　果

1．患者背景

B群の対象患者は100名であった。年齢中央値は37.5歳，年齢［<30歳/30～35歳/35歳≦］=［5/15/80］，パートナー［あり/なし］=［61/39］，出産歴［あり/なし］=［29/71］であった。情報提供［あり/なし］=［56/44］であった。また，術後に遠隔転移が発覚した患者（pStage Ⅳ）が1名認められた。

Table 1に両群の患者背景を示す。両群を比較すると，年齢層に差が認められ（$p<0.0001$），B群では35歳以上の患者が増加した。また，「出産歴あり」はA群が52.9%，B群が29%と有意に減少した（$p=0.0002$）。なお，pStage，パートナーの有無では両群間に有意な差は認めなかった。

2．妊孕性に関する情報提供の実施状況

担当医から患者に対し薬物治療に伴う妊孕性への影響に関する情報提供の実施頻度を示す（Fig. 1）。なお，B群で他の医療職種（看護師）から情報提供が行われていた症例が1例あったが，担当医からの説明の有無は不明であったため，「情報提供なし」と分類した。「情報提供あり」はA群が7%，B群が56%で8倍に増加した（$p<0.0001$）。

3．情報提供の有無に関連する背景因子

B群における情報提供の有無に関連する背景因子について解析した結果を示す（Table 2，3）。患者側の要因として，出産歴なし〔odds ratio(OR): 5.717, 95% CI: 1.752-18.66〕と推奨補助療法がホルモン治療（OR: 9.436, 95% CI: 1.219-73.05），化学療法（OR: 24.22, 95% CI: 3.150-186.2）が有意なリスク因子であることが明らかとなった。患者の年齢やパートナーの有無は関連性がみられなかった（Table 2）。また，担当医師側の要因として，診療科，性別，医師経験年数はいずれも情報提供の有無に影響しなかった（Table 3）。これらの結果から，情報提供

Table I　Patient characteristics

		Group A (2000-2004) n=136		Group B (2007-2009) n=100		p value (χ^2 test)
		n	%	n	%	
Age (years)	<30	13	9.6	5	5.0	<0.0001
	30～35	52	38.2	15	15.0	
	35<	72	52.9	80	80.0	
pStage	0	13	9.6	21	21.0	0.09
	I	27	19.9	23	23.0	
	II	73	53.7	43	43.0	
	III	23	16.9	12	12.0	
	IV	0	0	1	1.0	
Partner	Present	89	65.4	61	61.0	0.22
	Not present	47	34.6	39	39.0	
Prior delivery	Present	72	52.9	29	29.0	0.0002
	Not present	64	47.1	71	71.0	

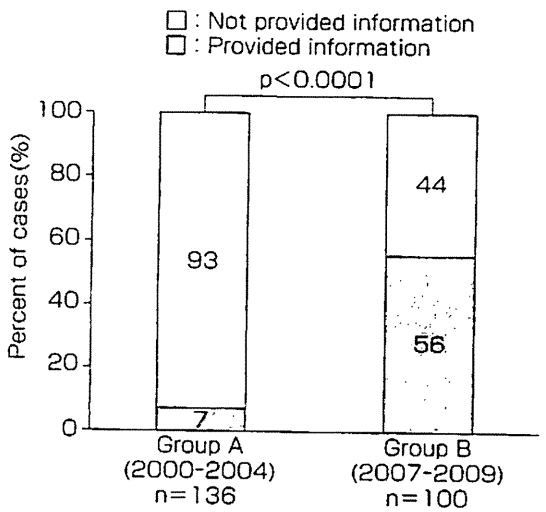

Fig. 1　The percentage of cases in which information on fertility-related issues was actively provided by treating physicians to primary breast cancer patients.
The percent of cases in which information was provided increased from 7 percent in Group A (2000-2004) to 56 percent in Group B (2007-2009).
p value: Chi square test

を「する」か「しない」かは，担当医師の背景に依存するのではなく，出産歴や提案する治療レジメンなどの患者背景に由来するものであることが示唆された。

4．補助療法の選択

医師が推奨した補助療法と，実際に実施された（≒患者が選択した）補助療法について示す（Table 4）。化学療法を含む治療から変更された割合は，「情報提供あり」群，「情報提供なし」群で差はみられなかった。つまり，妊孕性への影響に関して情報提供がされても治療方針の決定に影響がなかったことが示された。

Ⅲ．考　察

今回の調査結果から，2007年以降の症例において，医師から患者に対し妊孕性に関する情報提供が行われた頻度は56%と大幅に改善されていることがわかった。この理由として，2006年のASCOの勧告や日本乳癌学会の患者向けガイドラインの発表により，患者・医療者双方において，治療に伴う不妊のリスクに対する意識が高まった可能性がある。なお今回の調査は診療録を用いた後方視的調査であるため，診療録への記載不備などがあれば，結果に大きく影響する。つまり，以前よりも診療録への記載が徹底されるようになってきた可能性も考えられる。

両群の症例において，出産歴の有無が有意に異なるなど患者背景の違いが影響していることも考えられた。今回行った情報提供の有無に関連する背景因子の解析からは，出産歴のない患者に対してより積極的な情報提供が行われていることが示された。

また今回の検討では，不妊のリスクに関する情報提供の有無は，患者の治療選択に影響を与えなかった。しかし，情報提供は治療方針の内容にかかわらず，患者が納得して治療に取り組むために重要である。当院では薬剤師が患者指導に用いる術後化学療法のパンフレットに「卵巣機能障害」についての項目を作るなど，医師以外の医療職からも患者の潜在的なニーズを探りやすくするよう工夫している。

結論として，妊孕性に関する患者への情報提供は以前の調査よりも大幅に改善されていた。しかし，その割合は未だに約60%程度であり，妊娠可能年齢の全患者に対して情報提供が行われているわけではなく，医師は患者

Table 2 Background characteristics of Group B patients (2007-2009) who were or were not actively provided with information on fertility-related issues

		Physician actively provided information (n=56)		Physician did not actively provide information (n=44)		OR	95% CI	p value (χ^2 test)
		n	%	n	%			
Age (years)	Median	36.5		38				
	<30	4	7.1	1	2.3	1		0.063
	30~35	11	19.6	4	9.1	0.391	[0.022-0.693]	
	35<	41	73.2	39	88.6	0.092	[0.006-1.391]	
Partner	Present	34	60.7	27	61.4	1		0.152
	Not present	22	39.3	17	38.6	0.475	[0.171-1.317]	
Prior delivery	Present	11	19.6	18	40.9	1		0.004
	Not present	45	80.4	26	59.1	5.717	[1.752-18.66]	
Recommended adjuvant treatment	None	2	3.6	10	22.7	1		0.017
	Hormone therapy only	13	23.2	12	27.3	9.436	[1.219-73.05]	
	Treatment involving chemotherapy	36	64.3	22	50.0	24.22	[3.150-186.2]	
	Other (clinical trial)*	5	8.9	0	0	—	—	

OR: adjusted odds ratio, CI: confidence interval

*: Not applicable for calculating OR because all cases were provided with information on chemotherapy related-infertility

Table 3 Association between treating physicians' backgrounds and providing information on fertility-related issues

		OR	95% CI	p value (χ^2 test)
Specialty	Medical oncology (n=11)	1		0.269
	Breast surgery (n=5)	0.575	[0.216-1.534]	
Gender	Male (n=11)	1		0.684
	Female (n=5)	0.830	[0.339-2.033]	
Length of career	<15 years (n=9)	1		0.131
	≧15 years (n=7)	2.148	[0.796-5.792]	

OR: adjusted odds ratio, CI: confidence interval

Table 4 Patient selection of adjuvant treatment categorized by physician-provided information on fertility-related issues

	Physician actively provided information (n=56)		Physician did not actively provide information (n=44)	
	n	%	n	%
Treating physician's adjuvant treatment recommendation				
Chemotherapy-containing treatment	38	67.9	22	50.0
Patient's adjuvant treatment selection				
Chemotherapy-containing treatment	30	53.6	18	40.9

の背景に応じて選択的に情報提供を行っている可能性が示唆された。患者が納得して治療に取り組むためには，様々な状況を考慮しても情報提供は100%をめざすべきであると考える。癌治療に伴う妊孕性への影響について，医療者・患者双方の意識をさらに高められるよう働きかける必要がある。

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