骨系統疾患患児における歯科的問題点とその対応

大川玲奈　仲野和彦
大阪大学大学院歯学研究科小児歯科学教室

はじめに

平成24年度より厚生労働省科学研究費補助金難治性疾患克服事業「重症骨系統疾患の予後改善に向けての集学的研究（研究代表者：大阪大学医学系研究科小児科学　大薗恵一教授）」の研究分担者として、「骨系統疾患患児における歯科的問題点とその対応」というテーマの研究に従事している。本稿では、骨系統疾患患児における歯科的問題点とその対応についてまとめていきたい。

骨系統疾患とは、骨格に異常をきたす遺伝性疾患である。骨系統疾患を有する患児では歯科的な問題点を有することが多いが、日常臨床で遭遇する頻度が少なく、また臨床症状が多彩である。大阪大学歯学部附属病院小児歯科の現在の登録患者約2,000人から骨系統疾患を有する患児を抽出し、病名、歯科的症状およびそれらへの対応について調査した。その結果、36名の骨系統疾患患児の存在が確認された。内訳としては、骨形成不全症が18名と最も多く、次いで低フォスファターゼ症11名、X連鎖性低リン血症性ビタミンD抵抗性くる病4名と続き、その他は鎖骨頭蓋異形成症、脊椎骨端異形成症、軟骨無形成症が各1名であった（図1）。

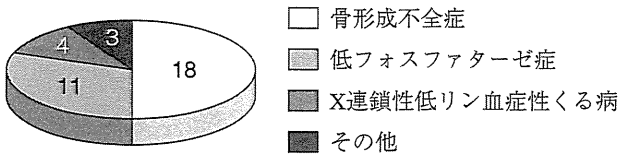


図1　本院小児歯科における骨系統疾患患児の内訳

今回は骨形成不全症、低フォスファターゼ症の歯科的問題点とその対応について述べたい。

骨形成不全症

骨形成不全症とは、Ⅰ型コラーゲンの形成異常によって骨の脆弱性をきたす疾患である。易骨折性、成長障害、青色強膜および聴力障害などの臨床症状を呈する。多くは常染色体優性遺伝であり、頻度は10万出生あたり4～6人だが、重症度は様々である[1)2)]。

歯科的症状としては象牙質形成不全が挙げられる。透過度の高いエナメル質を介して、形成不全の象牙質が見えるため、歯冠は半透明の琥珀色を呈する。また象牙質とエナメル質との接着が悪いため、エナメル質の剥離、著しい咬耗を認める（図2）。萌出前、直後の歯髄腔は広いが、象牙質が露出され、歯髄内

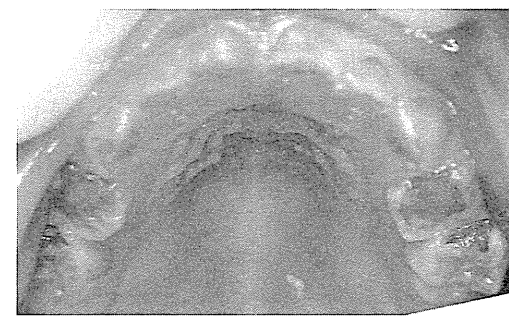


図2　骨形成不全症患児の口腔内写真（4歳3か月女児）

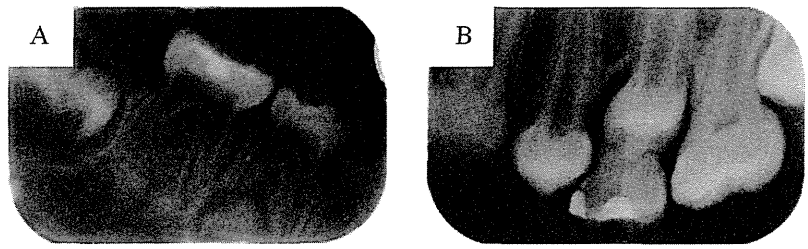


図3　骨形成不全症患児のデンタルエックス線像
A：下顎右側乳臼歯部（3歳4か月女児）、B：上顎左側臼歯部（12歳9か月男児）

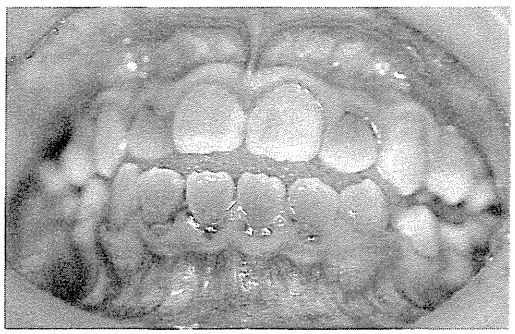


図4　骨形成不全症患児の口腔内写真（14歳7か月男児）

での象牙質の形成が起こり、歯髄腔の早期狭窄が起こる（図3）。この象牙質形成不全は、乳歯時と比較して永久歯での症状は軽度である（図4）。

乳歯において、エナメル質の剥離や咬耗が著しい場合、咬合高径を回復するために乳歯冠の装着を考慮する（図5）[3]。また、歯髄腔の狭窄は歯髄処置が困難となるため、う蝕の予防が重要である[4]。

骨吸収抑制剤であるビスフォスフォネート製剤の投与を受けている可能性がある場合、抜歯の際は医科への問い合わせが必要であるが、乳歯の交換期の抜歯で骨髄炎を誘発したという報告はない[4]。また、緊急性が高いものの低年齢であるなどの理由によって抑制下での治療が必要となった場合、易骨折性への配慮が重要である。

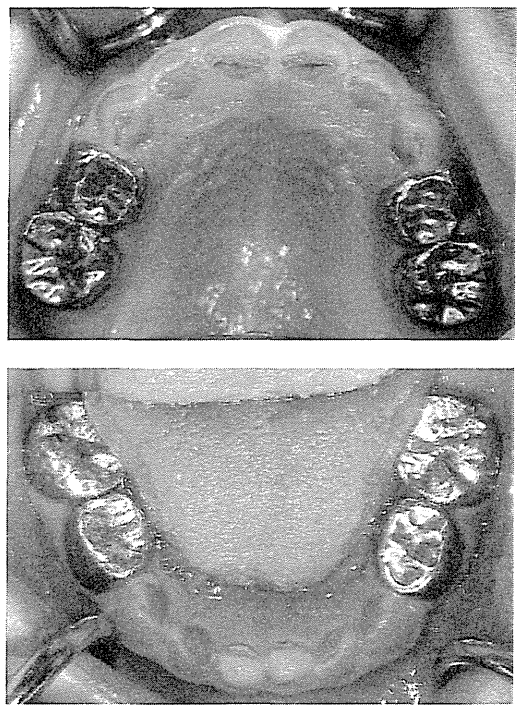


図5　骨形成不全症患児における乳歯冠による咬合の回復（5歳0か月女児）

低フォスファターゼ症

低フォスファターゼ症は組織非特異的アルカリフォスファターゼ（Alkaline phosphatase：ALP）遺伝子の異常により引き起こされる疾患である[5]。15万人に一人程度の発症といわれ、通常は常染色体劣性遺伝であるが、まれに常染色体優性遺伝もある[6]。ALPは

骨の石灰化に必要な酵素であるため、血清ALP値が低くなり、骨の石灰化が低下する。発生頻度は発症時期と症状によって、周産期型、良性周産期型、乳児型、小児型、成人型、歯限局型に分類されるが[7][8]、一般的に発症時期が早いほど重症である[9]。現在のところ、確立された治療法はない。

歯科的症状としては、セメント質の形成不全による乳歯の早期脱落がある（図6）[10]。永久歯の脱落に関する報告は極めて少ない。セメント質の形成不全のため歯根膜を介してのセメント質と歯槽骨との結合が弱く、咬合力に耐えることができずに乳歯が脱落するものと考えられる[10]。通常の歯周炎とは異なり炎症症状は軽度で、歯周病原性細菌の検出頻度も低い[11]。

平成21年度に全国29の大学歯学部および歯科大学の小児歯科学教室に本疾患罹患患児の有無を問い合わせ、該当者が存在する場合、病型、早期脱落乳歯および永久歯の有無とその時期について情報提供を依頼したところ、男児11名、女児8名の19症例の情報が得られた（表1）[10]。病型は小児型9名、歯限局型6名、良性周産期型3名、乳児型1名であった。乳歯の早期脱落は15名（約80％）において認めたが、永久歯の早期脱落を認めたケースはなかった。乳歯の早期脱落の好発部位は前歯部、とくに下顎前歯部であり、乳臼歯部では脱落を認めなかった。早期脱落の時期については、1歳から4歳にかけて集中していた（表2）。

早期脱落部への対応に関する報告はほとんどなく、歯周治療によって可及的な乳歯の保存を試みることが一般的な治療であろうと思われる。当科では、4歳5か月の時点で8本の乳前歯が早期脱落した良性周産期型の女児において、小児義歯の装着を試みた（図7）。以後、数回の義歯調整を行ったものの、残存乳歯の動揺や脱落はなく、経過は良好である。小児義歯の装着によって、咀嚼機能、発音機能および審美性の回復だけではなく、咬合力を分散させることによって残存歯の早期脱落を予防できるのではないかと考

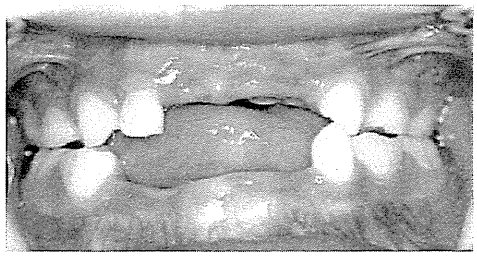


図6　低フォスファターゼ症患児の口腔内写真（4歳11か月女児）

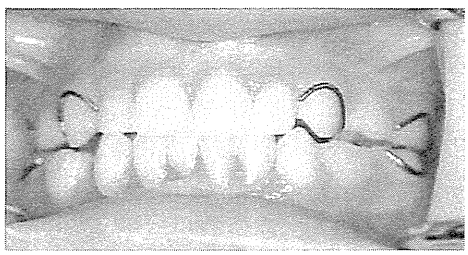
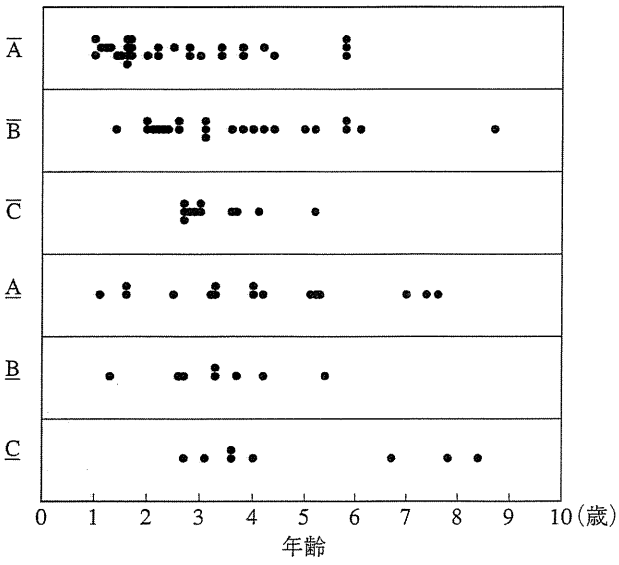


図7　低フォスファターゼ症患児における義歯の装着（4歳11か月女児）

表1　低フォスファターゼ症各分類における早期脱落歯の有無[10]

病型	性別	初診～最終診察時年齢	早期脱落乳歯	早期脱落永久歯
周産期型（良性）	女	2Y7M-14Y3M	2本	なし
周産期型（良性）	男	8Y8M-12Y4M	なし	なし
周産期型（良性）	女	1Y9M-4Y4M	3本	なし
乳児型	男	7Y8M-12Y8M	なし	なし
小児型	女	7Y0M-18Y0M	なし	なし
小児型	男	3Y0M-8Y9M	5本	なし
小児型	男	2Y2M-3Y9M	8本	なし
小児型	男	3Y10M-4Y8M	4本	なし
小児型	男	1Y5M-7Y	5本	なし
小児型	女	1Y7M-10Y2M	7本	なし
小児型	男	3Y5M-11Y	8本	なし
小児型	男	3Y2M-7Y3M	3本	なし
小児型	女	2Y7M-	6本	なし
歯限局型	男	3Y0M-8Y9M	2本	なし
歯限局型	男	2Y2M-3Y7M	4本	なし
歯限局型	女	4Y5M	1本	なし
歯限局型	女	2Y8M-15Y6M	6本	なし
歯限局型	男	5Y2M-23Y11M	なし	なし
歯限局型	女	4Y0M-8Y10M	7本	なし

表2　低フォスファターゼ症各症例における乳歯の脱落時期



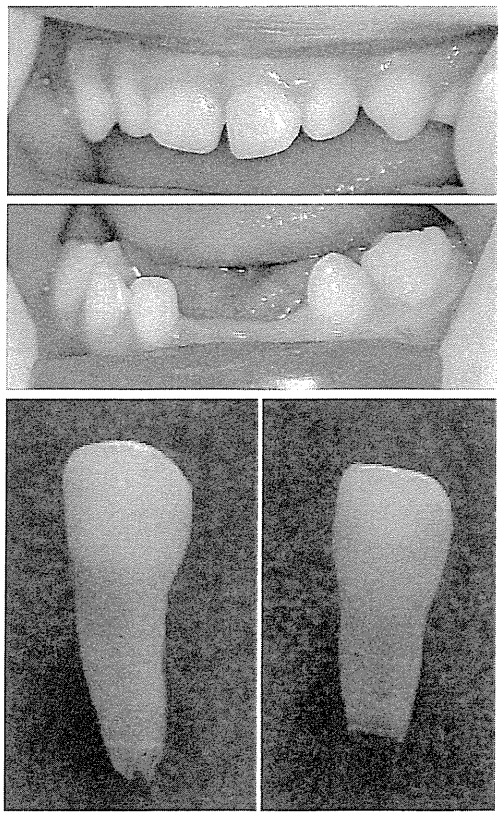


図8　低フォスファターゼ症患児の口腔内写真と持参された脱落歯（2歳3か月男児）

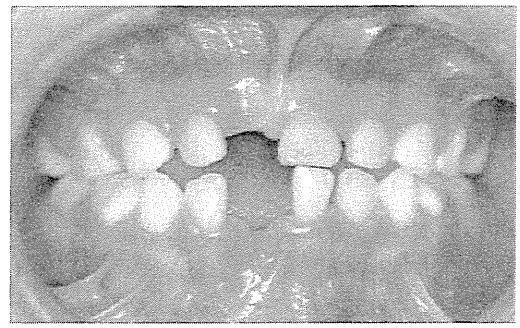


図9　低フォスファターゼ症患児の口腔内写真（4歳5か月女児）

えている。本疾患が平成20年度から小児義歯の保険適応に加わったことで、本症例への小児義歯の応用が普及することが期待される。

全身的な症状が軽度な場合、乳歯の早期脱落のため歯科を受診したことを機に、医科へと紹介され、低フォスファターゼ症と診断を受けることがある。当科においても初診時年齢1歳7か月の男児（図8）と4歳5か月の女児（図9）の2名が乳前歯の早期脱落のため当科を受診し、本学医学部附属病院へ紹介となり、歯限局型低フォスファターゼ症との診断を受けた。歯科領域における脱落歯を認める所見から医科領域へ紹介することで、低フォスファターゼ症の早期診断につながる可能性が上昇すると思われる。

おわりに

骨系統疾患の歯科的症状は様々であり、重症度も異なるために対応が困難である。また、骨系統疾患における歯科的問題に対応するためには小児科領域との連携が重要である。今後さらに症例を蓄積し、骨系統疾患を有する患児へのよりよい臨床的アプローチをエビデンスに基づいて構築していきたい。

なお、本研究班のホームページ（http://www.bone.med.osaka-u.ac.jp/skeleton/）を随時参照していただきたい。

謝　辞

難治性疾患克服事業における研究班の一員としてご指名いただき、重症骨系統疾患における歯科的問題点とその対処法に関する研究を行う機会を与えていただいた大阪大学医学系研究科小児科学　大薗恵一教授に厚くお礼申し上げます。また、研究の遂行にあたり、多くの症例提示や臨床的な助言をいただいた各大学小児歯科学教室の先生方に深く感謝申し上げます。本研究は、厚生労働省科学研究費補助金難治性疾患克服事業「重症骨系統疾患の予後改善に向けての集学的研究」に対する補助金を用いて行われました。

文　献

1) Hasegawa, K. : Osteogenesis imperfecta and genetic abnormalities. Clin Calcium 20 : 1190-1195, 2010
2) Tanaka, H. : Osteogenesis imperfecta. Clin Calcium 20 : 1245-1252, 2010
3) 大嶋　隆：小児の歯科治療　シンプルなベストを求めて，大阪大学出版会，吹田，2009
4) Shintani, S., Ooshima, T. : Dental management of patients with bone diseases. Clin Calcium 20 : 1259-1265, 2010
5) Rathbun, J. C. : Hypophosphatasia; a new developmental anomaly. Am J Dis Child 75 : 822-831, 1948
6) Ozono, K., Michigami, T. : Hypophosphatasia now draws more attention of both clinicians and researchers : a commentary on Prevalance of c. 1559delT in ALPL, a common mutation resulting in the perinatal (lethal) form of hypophosphatasias in Japanese and effects of the mutation on heterozygous carriers. J Hum Genet 56 : 174-176, 2011
7) Mornet, E. : Hypophosphatasia. Orphanet J Rare Dis 2 : 40, 2007
8) Mornet, E. : Hypophosphatasia. Best Pract Res Clin Rheumatol 22 : 113-127, 2008
9) Michigami, T., Uchihashi, T., Suzuki, A., Tachikawa, K., Nakajima, S. and Ozono, K. : Common mutations F310L and T1559del in the tissue-nonspecific alkaline phosphatase gene are related to distinct phenotypes in Japanese patients with hypophosphatasia. Eur J Pediatr 164 : 277-282, 2005
10) Okawa, R., Nakano, K., Matsumoto, M., Kawabata, K., Ooshima, T. : Oral manifestations of the patients with hypophosphatasia. Ped Dent J 22, 155-162, 2012
11) Miyamoto, E., Nakano, K., Tamura, K., Nomura, R., Sasaki, Y., Ooshima, T. : Clinical and microbiological evaluations of children with hypophosphatasia affected by periodontitis. Ped Dent J 17, 84-92, 2007

Int J Clin Oncol
DOI 10.1007/s10147-013-0649-z

ORIGINAL ARTICLE

Development of an integrated support system for hereditary cancer and its impact on gynecologic services

Mina Morii-Kashima · Hiroshi Tsubamoto · Chika Sato · Mariko Ushioda · Naohiro Tomita · Yasuo Miyoshi · Tomoko Hashimoto-Tamaoki · Kazuo Tamura · Hideaki Sawai · Hiroaki Shibahara

Received: 24 September 2013 / Accepted: 26 November 2013

Abstract
Objective Patients with hereditary cancer need an integrated support system. A recently launched project was evaluated in terms of its efficacy in screening patients with hereditary cancer at the gynecologic service.
Methods The project team comprised gynecologists, surgeons, medical geneticists, and certified genetic counselors (CGCs) in our hospital. At the gynecologic service, a newly developed self-administered family history questionnaire (SAFHQ) was given to patients with ovarian, endometrial, or breast cancer as well as a history of multiple cancers. After an interview, a CGC constructed a pedigree and evaluated the risk for hereditary cancer. Patients at risk were recommended by a gynecologist to receive further genetic counseling at the Department of Genetics according to the modified Bethesda criteria, Amsterdam II criteria, and National Comprehensive Cancer Network (NCCN) guidelines 2012 for breast–ovarian cancer syndrome (HBOC). The numbers of newly screened patients were compared before and after the project launch.
Results The SAFHQ was administered to 131 patients and 106 (81 %) pedigrees were constructed between August 2012 and July 2013. The number of newly screened patients according to the Bethesda criteria was 4 and 8 at 10 years before and 1 year after the project launch, respectively. Two and 31 patients met the NCCN criteria for HBOC excluding ovarian cancer alone, respectively, at these 2 time points. Of 54 patients who were recommended to undergo further counseling, 10 (19 %) visited the Department of Genetics.
Conclusion After the launch of an integrated support system, the number of patients with hereditary cancers who were screened increased. The gynecologic service played a pivotal role in patient and family care.

Keywords Gynecology · Lynch syndrome · Hereditary breast and ovarian cancer · Genetic counseling · PDSA cycle

M. Morii-Kashima · H. Tsubamoto (✉) · M. Ushioda · H. Sawai · H. Shibahara
Department of Obstetrics and Gynecology, Hyogo College of Medicine, Mukogawa 1-1, Nishinomiya, Hyogo 663-8501, Japan
e-mail: tsuba@hyo-med.ac.jp

C. Sato · T. Hashimoto-Tamaoki
Department of Genetics, Hyogo College of Medicine, Nishinomiya, Japan

N. Tomita · K. Tamura
Division of Lower GI, Department of Lower Gastrointestinal Surgery, Hyogo College of Medicine, Nishinomiya, Japan

Y. Miyoshi
Department of Breast and Endocrine Surgery, Hyogo College of Medicine, Nishinomiya, Japan

K. Tamura
Department of Life Science, Faculty of Science and Engineering, Kinki University, Higashiosaka, Japan

Introduction

Recently, a prominent celebrity underwent a preemptive double mastectomy because of a high familial propensity for breast cancer. This news garnered global media attention and heightened general population awareness of the importance of genetic screening based on family medical history. Approximately 2–5 % of uterine and 5–10 % of ovarian cancers are hereditary [1–4]. Lynch syndrome/hereditary non-polyposis colorectal cancer syndrome and breast–ovarian cancer syndrome (HBOC) are the main

Published online: 19 December 2013

hereditary gynecologic cancers. The incidences of Lynch syndrome and HBOC are similar in the Japanese population [5, 6]. However, the social and medical systems for caring for patients with hereditary cancer and their families are not widely accessible [7]. In 2011, the Japanese Clinical Practice Guideline of Breast Cancer announced that salpingo-oophorectomy reduces the risk of breast cancer, while the Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2012 for the Clinical Practice of Hereditary Colorectal Cancer were published in 2012. In addition, a guide to risk, prevention, and management of gynecologic cancers was translated into Japanese in 2011 [8].

In 2012, a project to support patients with hereditary cancers and their family members was launched at the teaching hospital of Hyogo College of Medicine. This report discusses the promotion and development of an integrated support system, from a gynecologic perspective, for the benefit of screening patients with hereditary cancer.

Methods

The project team comprised gynecologists, surgeons, medical geneticists, and certified genetic counselors (CGC) in our hospital. A self-administered family history questionnaire (SAFHQ) was developed (Table 1), and the manner in which pedigrees were drawn was made consistent. Genetic and clinical data were disseminated. Development of a support system was planned and conducted according to the Guidelines for Genetic Tests and Diagnoses in Medical Practice by the Japanese Association of Medical Sciences and the Guidelines of the Japanese Society for Familial Tumors.

Table 1 Self-administered family history questionnaire (Department of Obstetrics and Gynecology) (English version)

Self-administered Family History Questionnaire (Department of Obstetrics and Gynecology)

ID:	Name (Last, First):	Date of Birth:	Age:

Please answer the following questions.

【A】 About yourself

A-1	What is your current disease called? ( )	
A-2	Have you undergone any surgery in the past?	Yes No
	If yes, please mention the disease for which surgery was performed. ( )	
A-3	Please encircle the conditions below, for which you have a history. For encircled conditions, indicate the age at diagnosis.	
	Breast cancer (Age:) Ovarian cancer (Age:) Fallopian cancer (Age:) Endometrial cancer (Age:) Colorectal cancer (Age:) Gastric cancer (Age:)	
A-4	Do you have other types of cancer?	Yes No
	If yes, indicate the disease and the age at diagnosis.	( ) (Age:)
A-5	Did you receive/do you plan to receive hormone therapy for breast cancer?	Yes No
A-6	Did you undergo a genetic test for hereditary cancer?	Yes No
A-7	Do you wish to talk about the genetic disease or test, if you have a risk of hereditary cancer?	Yes No
A-8	We can provide integrated support with other doctors and co-medical professionals in our hospital if you have a risk of hereditary cancer. Do you wish to be introduced to other doctors at the related department?	Yes No

Please complete the reverse side of this form.

Table 1 continued

【B】About your family

B-1	Do you have a family history of any cancer or polyp on your maternal or paternal side?	Yes No Unknown

If yes, please list the relationship of the patientto you, the individual diagnosis, and the age at diagnosis.

Consider cancers as such colorectal cancer, gastric cancer, endometrial cancer, ovarian cancer, breast cancer, fallopian cancer, and brain cancer

Consider relationships as such father, mother, brother, grandparent, uncle, aunt, and niece

【Example】
Father, colorectal cancer, 55 years old
Paternal cousin, gastric cancer, 40 years old
Maternal aunt, breast cancer and ovarian cancer, 35 and 42 years old

B-2

Relationship	Cancer type	Age at diagnosis

B-3	Is there a male breast cancer patient in your family?	Yes No Unknown
B-4	Has any person in your family undergone genetic testing for hereditary cancer?	Yes No Unknown

Please hand over the completed form at the reception desk.

At the gynecologic service, a checklist was developed to guide recommendations for further genetic counseling including genetic testing. The revised Bethesda criteria as well as the Amsterdam criteria II were used for Lynch syndrome screening [9, 10]. Gastric cancer, atypical endometrial hyperplasia, and epithelial ovarian cancer were considered as Lynch-syndrome-related cancers. Non-obese women [body mass index (BMI) <25] <50 years old with regular menses who had endometrial cancer were included in the checklist [11]. For HBOC screening, a history of ovarian cancer alone was excluded from the criteria for further genetic risk evaluation by the National Comprehensive Cancer Network guidelines (NCCN) 2012 [12]. The checklist included patients with a history of two or more cancers except for cervical or hepatic cancer associated with viral infection.

After launching the project, inpatients and outpatients with ovarian, endometrial, or breast cancer as well as a history of multiple cancers were given the SAFHQ. After obtaining informed consent, the CGC interviewed the patients and constructed pedigrees. The gynecologist informed patients about hereditary cancers and recommended further genetic counseling on the basis of the checklist and pedigree results.

Cases of hereditary cancer have been recorded by gynecologists since 2001. The numbers of newly screened patients 10 years before and 1 year after the launch of the project were compared. After the project launch, the timing of information provision about hereditary cancer was recorded based on what treatment regimen or plan was administered to patients. The number of patients who visited the Department of Genetics was also recorded. The project was approved by our institutional review board, and written informed consent was obtained from patients to access their information recorded by the physicians or CGCs. Statistical analyses were performed using the software XLSTAT 2012 (Addinsoft, Paris, France) and P values were calculated using the χ^2 test.

Results

A CGC provided information to patients about hereditary cancer and the aim of the SAFHQ in simple language at the genetic service. Family history taking took 45–90 min, and almost half of the time was spent on relationship building. On the basis of a report on the risk of hereditary cancer, determined according to the checklist (Table 2) and constructed pedigree, gynecologists recommended patients with probable inherited disease for further genetic counseling or referred them to physicians at other departments. The genetic counselor acted as a patient advocate and liaison (Fig. 1). For young patients with non-gynecologic cancer, referred by other departments, fertility preservation was discussed, and patients diagnosed with HBOC were informed about risk-reducing bilateral salpingo-oophorectomy (RRSO) by a gynecologist.

The backgrounds of 131 patients who completed the SAFHQ between August 2012 and July 2013 are presented in Table 3. Eighty-six patients (66 %) had endometrial or ovarian cancers, and 5 with no cancer had a familial history of cancer. Seventeen patients were referred by the Department of Breast and Endocrine Surgery for construction of pedigrees and gynecologic screening. One patient with Cowden's disease was referred by the Department of Genetics for gynecologic screening. During the past 10 years, 279 endometrial cancer cases and 302 ovarian cancer cases were treated in our hospital. Ten years before and 1 year after the project launch, the number of newly screened patients with Lynch syndrome was 4 and 8 according to the revised Bethesda criteria and 4 and 3 according to the Amsterdam criteria, respectively, with gastric cancer included as a Lynch-syndrome-related cancer. The numbers of patients who met the NCCN criteria for HBOC excluding ovarian cancer alone were 2 and 31 at the 2 time points, respectively (Table 4). Among 31 patients who met the criteria for screening for HBOC according to the checklist, 1 patient had visited our clinic for annual cervical cancer screening for 3 years without being aware of her family history.

Data generated using the SAFHQ are presented in Fig. 2. Of 25 patients (19 %) who refused to disclose their family history to the CGC, 11 did not want to know their risk of hereditary cancer, 7 were not concerned about the risk, and 5 were open to discussing hereditary cancer after treatment ended. The proportion of patients who refused to be interviewed by a CGC was compared according to treatment status. Of 105 patients who were administered the SAFHQ before and during their treatment, 21 (20 %) refused an interview before treatment completion. On the other hand, of 21 patients administered the SAFHQ after their treatment, 4 (19 %) refused the interview ($p = 0.92$). Further genetic counseling at the Department of Genetics was recommended according to the checklist (Table 2). Of 8 patients who matched the revised Bethesda criteria and 31 who matched the modified NCCN criteria for HBOC, 10 (26 %) visited the Department of Genetics and 5 (13 %) underwent genetic testing. After the project was launched, RRSO was performed in 1 patient.

During the last year (2013), 2 patients with familial adenomatous polyposis (FAP) visited the gynecologic service for gynecologic neoplasms. A 31-year-old nulliparous woman was referred by the Department of Lower Gastrointestinal Surgery because routine surveillance by positron emission tomography/computed tomography detected uterine uptake of fluorodeoxyglucose. As a result, a grade 1 endometrioid tumor was diagnosed by endometrial curettage. The patient did not have known risk factors for endometrial cancer. Another 30-year-old woman was given consultation for mature cystic teratoma of the ovary. The patient and her mother did not understand the concept

Table 2 Checklist at the gynecologic service for recommending further genetic counseling

Individual matching all the following criteria:
Three or more relatives with an Lynch-syndrome-related cancer: colorectal cancer, EC, small bowel, ureter, or renal pelvis cancer, gastric cancer, atypical endometrial hyperplasia, and OC
One is a first-degree relative to the other two
At least two successive generations are affected
One or more diagnosed age <50 years
Individual with EC matching the following criteria
Diagnosed age ≤50 years
Non-obese with regular menses
Individual with one or more of the following:
☐ BC diagnosed age ≤50 years
☐ Triple negative BC (ER-, PR-, HER2-)
☐ Two BC primaries
☐ OC or BC at any age, and
≥1 close blood relative with BC diagnosed age ≤50 years
≥1 close blood relative with OC at any age
≥ 2 close blood relatives with BC or pancreatic cancer at any age
≥ 2 close blood relatives with male BC at any age
☐ A combination of OC or BC with one or more of the following on the same side of family:
OC, BC, thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, diffuse gastric cancer, dermatologic manifestations, leukemia and/or lymphoma
Individuals with ≥2 cancers
With the exception of cervical or hepatic cancer associated with viral infection

Close blood relatives include first-, second-, and third-degree relatives

EC endometrial cancer, *OC* epithelial ovarian cancer, *BC* breast cancer

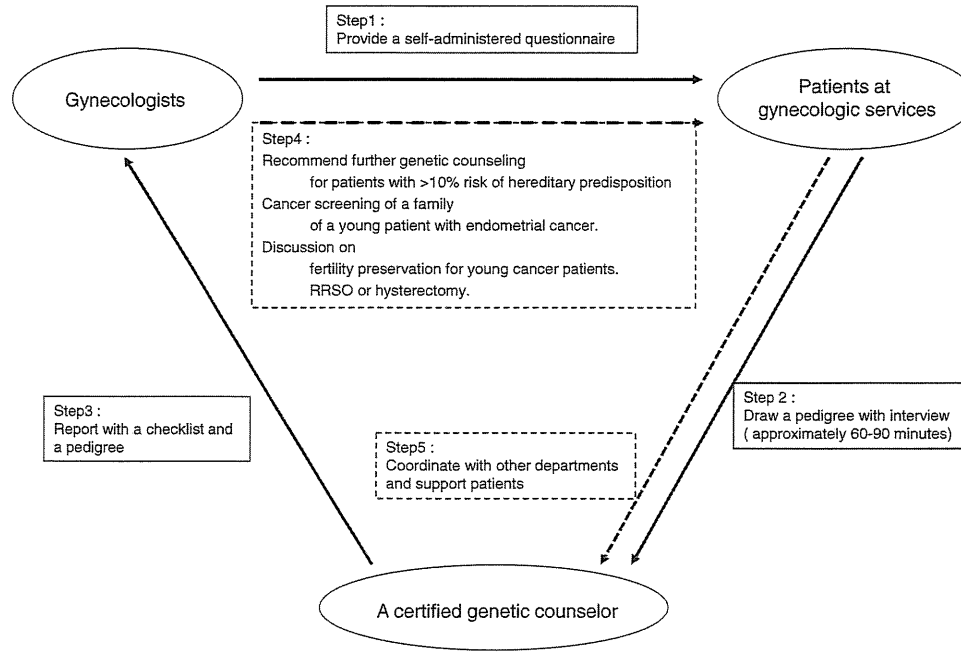


Fig. 1 Flowchart showing coordination between physicians and certified genetic counselors. *RRSO* risk-reducing bilateral salpingo-oophorectomy

Table 3 Characteristics of patients who were given a self-administered family history questionnaire ($n = 131$)

Total no. of patients	131
Age (years)	
Median	60
Range	27–82
Endometrial/ovarian cancer	86
Endometrial cancer or atypical endometrial hyperplasia only	35
Ovarian, fallopian, or primary peritoneal cancer only	44
Endometrial cancer and colon cancer	3
Ovarian cancer and breast cancer	4
Non-endometrial/ovarian cancer	40
Breast cancer only	17
≥ 2 cancers	21
Colon cancer only	2
No diagnosis of cancer	5
Treatment status	126
Before the initial treatment	6
During the initial treatment	99
After the initial treatment	
Recurrence	20
No recurrence	1

Treatment included chemotherapy and surgery

Breast cancer, breast cancer and cervical cancer; *≥2 cancers*, history of two or more cancers excluding cervical or hepatic cancer associated with viral infection

of FAP-related cancer, the appropriate follow-up, or genetic testing results. According to her medical chart, she had undergone counseling 7 years previously.

Discussion

Patients with hereditary cancers, including Lynch syndrome and HBOC, are at risk of developing other cancers [8]. However, management of related cancers is not fully recognized by physicians. Several reports have documented that patients with Lynch syndrome and their families are mostly unaware of associated cancers [13–16]. Over 50 % of women with Lynch syndrome had been previously diagnosed with endometrial or ovarian cancers [17]. Morgan et al. reported that, of 69 women with at least a 10 % predicted likelihood of carrying a BRCA1/2 mutation or a documented BRCA1/2 mutation, only 4 % were referred by gynecologists for genetic counseling [18]. Hereditary cancer can affect young patients who may wish to have children in the future. The recent revised guidelines for fertility preservation by the American Society of Clinical Oncology recommend explaining options for fertility preservation to this class of patients [19]. Gynecologic services play an important role in identifying women with a hereditary predisposition, and cooperation with physicians treating patients with Lynch syndrome and HBOC is essential. The present project was therefore established in our hospital.

The project team comprised 2 CGCs (genetic counselors other than medical doctors), one belonging to the Department of Obstetrics and Gynecology, and the other to the Department of Genetics. The CGC at the gynecologic service assisted with taking patients' histories and collating data using the completed SAFHQs. She then presented checklists and pedigrees to the gynecologist, while patient care during and after collecting genetic information was provided by the

Table 4 New patients with hereditary cancer predisposition cared for at the gynecologic service

Time before and after launching the integrative system in 2012	10 years before	1 year after
Lynch syndrome		
Bethesda criteria	4	8
Amsterdam II criteria[a] including GC	4	3
Amsterdam II criteria	2	0
Genetic diagnosis	2	0
HBOC		
Criteria for further genetic risk evaluation[b]		
Excluding ovarian cancer only	2	31
Genetic diagnosis	1	1

During the past 10 years, 279 endometrial cancer and 302 ovarian cancer cases were treated in our hospital

GC gastric cancer

[a] Amsterdam criteria including gastric cancer as a Lynch-syndrome-related cancer

[b] Criteria for further genetic risk evaluation of National Comprehensive Cancer Network guidelines 2012 excluding ovarian cancer alone

gynecologist. The patients felt less stressed if they learnt about hereditary risks from their physicians in the presence of the CGCs. Compared with the written SAFHQ findings alone, 33 % more patients were identified as matching the checklist after the interview by the CGC. Thus, CGCs were essential during the screening process by helping to identify patients who would benefit from further assessment [20]. In addition, physicians have limited time to take precise familial histories during daily examinations; thus, CGCs help free up some time for physicians to perform other duties.

Wood et al. [21] reported that, in the United States, screening of patients with hereditary cancers by oncologists is not fully utilized. Given the low incidence of taking family histories at gynecologic services [22, 23], Vogel et al. [24] and Ooseto et al. [25] reported the efficacy of SAFHQs for hereditary cancers in gynecologic services. Among 131 patients, 19 % refused family history taking and pedigree constructions. Before treatment initiation or during the treatment, patients were stressed and anxious

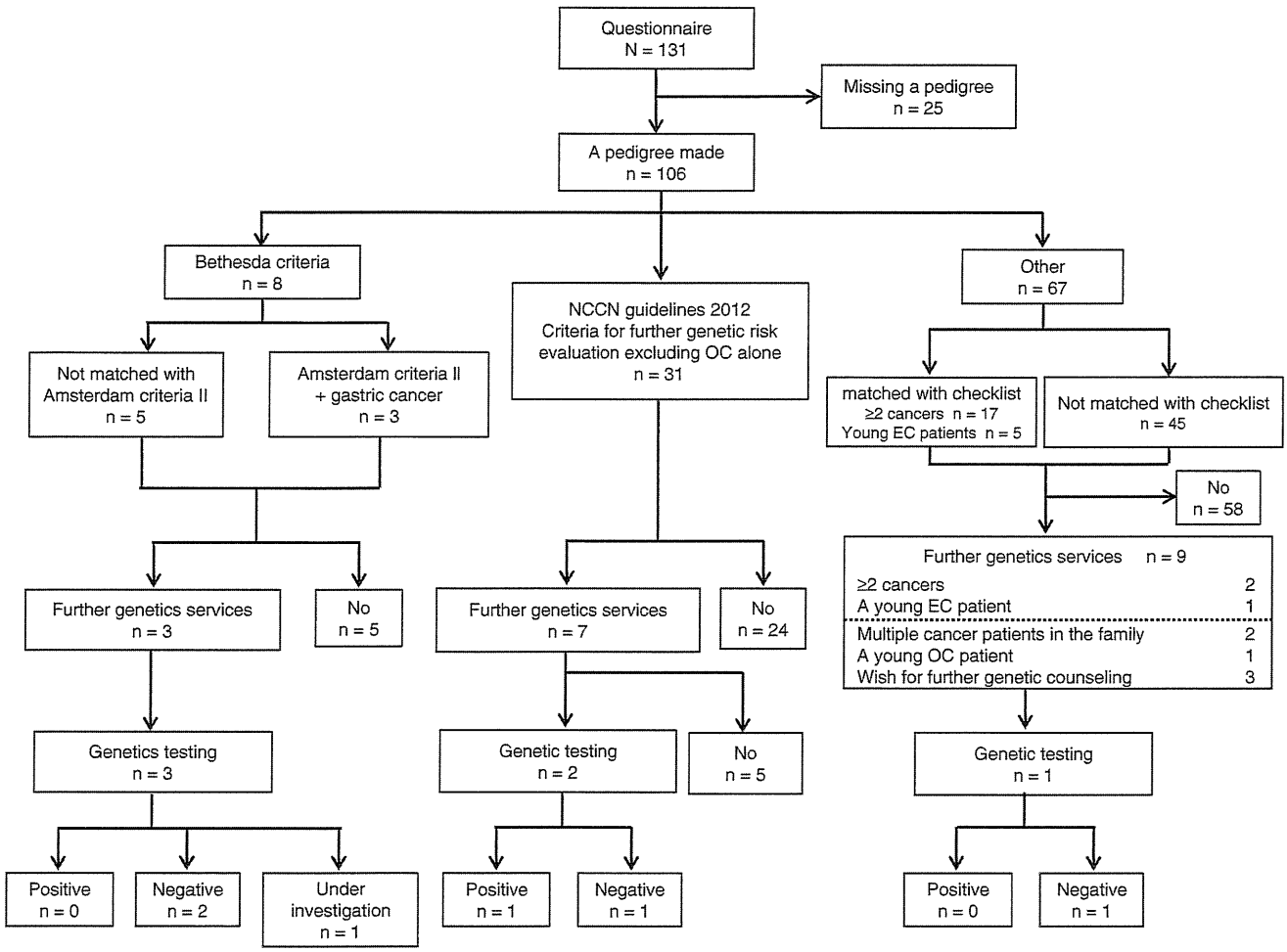


Fig. 2 Flowchart of patients after self-administered questionnaires were obtained ($n = 131$). *EC* endometrial cancer, *OC* epithelial ovarian cancer, *≥2 cancers* history of two or more cancers excluding cervical or hepatic cancer associated with viral infection, *young EC patients* those diagnosed at age ≤50 years, with a body mass index of <25, and with regular menses

about the treatment and the cancer itself. Although the proportion of patients who were interviewed depending on their treatment status was not significantly different in this study, continuous support and care for those with genetic predispositions seemed necessary [26].

Our experience with one FAP case with a benign ovarian tumor emphasized the importance of continuous efforts to inform patients and their families about familial cancers. Although genetic testing was conducted after obtaining informed consent and the results according to the medical chart were explained to the patient and her family, 7 years later they did not recollect this discussion and the news of FAP caused anxiety. The patient and her mother were informed again about FAP and were provided with the patient's medical records.

The purpose of the checklist given to gynecologists was to identify patients who would benefit from genetic counseling—in particular, those with a >10 % chance of having an inherited cancer predisposition [27, 28]. Both the Amsterdam II criteria and the revised Bethesda criteria were initially generated for patients with colon cancers. However, for a gynecologic cancer population, the sensitivity is inadequate [3, 29]. In a 2006 study of more than 500 endometrial cancers, 70 % of the patients who carried a germ-line Lynch mutation did not meet either the Amsterdam II or Bethesda criteria [3, 30–34]. Gastric cancer was included in the Lynch-syndrome-related cancers in the Bethesda criteria, the Society of Gynecologic Oncologists Education Committee statement [28], and the JSCCR Guidelines 2012 for the Clinical Practice of Hereditary Colorectal Cancer. In the checklist used in the present study, the Amsterdam II criteria were modified to include gastric cancer, atypical endometrial hyperplasia, and epithelial ovarian cancer as Lynch-syndrome-related cancers. The checklist excluded patients with ovarian cancer alone, all of whom were informed of familial cancer by a gynecologist and a CGC at the gynecologic service. Further genetic counseling or genetic testing was not routinely recommended.

Women <50 years old with endometrial cancers are at a 5–10 % risk of carrying germ-line mutations, meriting referral for genetic counseling and testing. Approximately 9 % of these women are Lynch syndrome carriers, compared with 2–6 % of all patients with endometrial cancers [3, 30]. In Japan, Aoki et al. [6] reported that the mean age at diagnosis of endometrial cancer with Lynch syndrome was 49.9 years, which is 7 years younger than that for sporadic cancers. Therefore, young women <50 years old without classical risk factors such as diabetes, obesity, nulliparity, hypertension, or unopposed estrogen exposure were included in our checklist and were carefully examined for family histories of cancer [35]. The following case was encountered before the present system was introduced and is a good example of why families of young patients diagnosed with endometrial cancers should undergo gynecologic cancer screening.

A 41-year-old woman with endometrial cancer presented to the clinic with her 66-year-old mother. Her BMI was 19.9 kg/m^2, her menses were regular, and she had no history of diabetes or cancer. She had not experienced sexual intercourse. She and her mother were interviewed regarding their familial history of endometrial cancers or colon cancers, but no history was noted. She underwent complete curative surgery. Three years later, her mother presented with genital bleeding and was diagnosed as having grade 3 endometrial cancer. Colonoscopy revealed stage I colon cancer. Complete surgery was not possible because the tumor had invaded her pelvic wall, and she died 12 months after surgery.

Until recently, only 2 cases of endometrial cancer with FAP had been reported: they were in patients over 55 years of age, which is the susceptible age for endometrial cancer [36, 37]. Generally, FAP is not related to gynecologic cancers. The patient described here was young and did not have any known risk factors for endometrial cancer. Iwama et al. [38] reported that 4 (0.8 %) out of 482 FAP patients died of uterine cancers (including cervical or endometrial cancers). Thus, the possibility of endometrial cancers should not be disregarded in FAP cases.

Despite an enormous effort, there is no proof that routine screening for ovarian cancer using serum markers, sonography, or pelvic examinations in the high-risk or general population decreases mortality [27, 39]. Despite a rigorous follow-up of patients with Lynch syndrome, some have been diagnosed with advanced-stage endometrial cancers [40]. We have encountered a patient in whom occult ovarian carcinoma in situ was detected in specimens obtained by hysterectomy and bilateral salpingo-oophorectomy for atypical endometrial hyperplasia [41]. These facts highlight the importance of genetic counseling and information about risk-reducing salpingo-oophorectomy or hysterectomy [42–46]. Given that not all physicians address the NCCN guidelines on BRCA1/2 [45], gynecologists should cooperate in caring for patients.

In the present study, following the launch of an integrated support system, the number of patients cared for at the gynecologic service increased. Among 8 patients who met the revised Bethesda criteria and 31 who met the modified NCCN criteria for HBOC, 10 (26 %) were seen for further genetic counseling and 5 (13 %) underwent genetic testing. The majority of patients declined referral because of financial reasons. Further genetic counseling at the Department of Genetics, genetic testing, and prophylactic surgery are not covered by medical insurance in Japan. In Ontario, where BRCA1 and BRCA2 genetic testing has been available free of charge for patients with serous ovarian carcinomas, only 23 % availed themselves

of genetic counseling [47]. The main reason was noted as a lack of patient interest. In a study of 237 women diagnosed with ovarian cancers, 89 % indicated that they would undergo genetic testing if it influenced their treatment [48]. In this study, SAFHQs were administered before and during the initial treatment to 105 (80 %) patients. Although the proportion of patients who refused CGC interviews was not significantly different among patients with different treatment statuses, some patients might have been overwhelmed by coping with their cancer and the initial treatment at the time. Anxiety may be attributed to patient compliance with further genetic counseling. Giving information about possible preventative strategies in an appropriate manner would improve patient compliance [49].

The integrated support system described here was planned in accordance with the *Plan–Do–Study–Act* [PDSA, or *Plan–Do–Check–Act* (PDCA)] cycle, which was first introduced in Japan in the 1950s by Edwards Deming to improve manufacturing processes efficiently and continuously [50]. Recently, the PDSA cycle was applied to the medical field for quality management as well as system development [51–54]. The concept of the PDSA cycle was first introduced to our gynecologic service for developing regional coordination for late-stage or terminal cancer patients in 2008 and was considered effective [55]. The advantages of the PDSA cycle include a clear indication of required improvements and promotion of an effective communication network that results in increased consciousness among the team members. This study was conducted in accordance with the Study of the first PDSA cycle to improve the quality of care for hereditary cancer patients and their families. The next Plan of the second PDSA cycle is to enhance regional coordination for patients with hereditary cancers and their families. SAFHQs and checklists have been introduced in a regional hospital to evaluate their efficacy in a non-teaching hospital without any CGCs.

Acknowledgments Production of the self-administered questionnaire was supported by the following certified genetic counselors: Kumiko Oseto from Nagoya City University, Keika Kaneko from Shikoku Cancer Center, and Chieko Tamura from Juntendo University.

Conflict of interest The authors have no conflicts of interest to disclose.

References

1. Pal T, Permuth-Wey J, Betts JA et al (2005) BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. Cancer 104:2807–2816
2. Lu KH (2008) Hereditary gynecologic cancers: differential diagnosis, surveillance, management and surgical prophylaxis. Fam Cancer 7:53–58
3. Hampel H, Frankel W, Panescu J et al (2006) Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. Cancer Res 66:7810–7817
4. Dinh TA, Rosner BI, Atwood JC et al (2011) Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. Cancer Prev Res (Phila) 4:9–22
5. Komata D, Yahata T, Kodama S et al (2009) The prevalence of hereditary breast/ovarian cancer risk in patients with a history of breast or ovarian cancer in Japanese subjects. Obstet Gynecol Res 35:912–917
6. Aoki D, Udagawa Y, Ohwada M et al (2009) A report of Fujinka-Shuyo-Iinnkai. Acta Obstet Gynaecol Jpn 61:1540–1541
7. Kaneko K, Ohsumi S, Aogi K et al (2013) Genetic counseling and practice of hereditary cancers at Shikoku Cancer Center. Gan To Kagaku Ryoho 40:139–142
8. Lu KH (2008) Hereditary gynecologic cancer: Risk, prevention, and management. Informa Healthcare
9. Umar A, Boland CR, Terdiman JP et al (2004) Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 96:261–268
10. Vasen HF (2000) Clinical diagnosis and management of hereditary colorectal cancer syndromes. J Clin Oncol 18(21 Suppl):81–92
11. Masuda K, Banno K, Hirasawa A et al (2012) Relationship of lower uterine segment cancer with Lynch syndrome: a novel case with an hMLH1 germline mutation. Oncol Rep 28:1537–1543
12. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#detection. Accessed 1 July 2012
13. Yang K, Allen B, Conrad P et al (2006) Awareness of gynecologic surveillance in women from hereditary non-polyposis colorectal cancer families. Fam Cancer 5:405–409
14. Domanska K, Carlsson C, Bendahl PO et al (2009) Knowledge about hereditary nonpolyposis colorectal cancer; mutation carriers and physicians at equal levels. BMC Med Genet 10:30
15. Ketabi Z, Mosgaard BJ, Gerdes AM et al (2012) Awareness of endometrial cancer risk and compliance with screening in hereditary nonpolyposis colorectal cancer. Obstet Gynecol 120:1005–1012
16. Salemink S, Dekker N, Kets CM et al (2013) Focusing on patient needs and preferences may improve genetic counseling for colorectal cancer. J Genet Couns 22:118–124
17. Soliman PT, Oh JC, Schmeler KM et al (2005) Risk factors for young premenopausal women with endometrial cancer. Obstet Gynecol 105:575–580
18. Morgan D, Sylvester H, Lucas FL et al (2010) Hereditary breast and ovarian cancer: referral source for genetic assessment and communication regarding assessment with nongenetic clinicians in the community setting. Genet Med 12:25–31
19. Loren AW, Mangu PB, Beck LN et al (2013) Fertility preservation for patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 31:2500–2510
20. Shulman LP (2010) Hereditary breast and ovarian cancer (HBOC): clinical features and counseling for BRCA1 and BRCA2, Lynch syndrome, Cowden syndrome, and Li-Fraumeni syndrome. Obstet Gynecol Clin N Am 37:109–133
21. Wood M, Kadlubek P, Lu KH et al (2012) Quality of cancer family history and referral for genetic counseling and testing among oncology practices: a pilot test of quality measures as part of the ASCO Quality Oncology Practice Initiative (QOPI). J Clin Oncol 30 (suppl; abstr CRA1505)

22. Murff HJ, Spigel DR, Syngal S (2004) Does this patient have a family history of cancer? An evidence-based analysis of the accuracy of family cancer history. JAMA 292:1480–1489
23. Mai PL, Garceau AO, Graubard BI et al (2011) Confirmation of family cancer history reported in a population-based survey. J Natl Cancer Inst 103:788–797
24. Vogel TJ, Stoops K, Bennett RL et al (2012) A self-administered family history questionnaire improves identification of women who warrant referral to genetic counseling for hereditary cancer risk. Gynecol Oncol 125:693–698
25. Ooseto K, Arakawa A, Ando M et al (2012) Usefulness of the family career hearing in the interview vote with Lynch syndrome. Tokai Sanka Fujinka Gakkai Zasshi 49:303–307
26. Patenaude AF (2005) Genetic testing for cancer: psychological approaches for helping patients and families. American Psychological Association, Washington, DC
27. Rosenthal AN, Fraser L, Manchanda R et al (2013) Results of annual screening in phase I of the United Kingdom familial ovarian cancer screening study highlight the need for strict adherence to screening schedule. J Clin Oncol 31:49–57
28. Lancaster JM, Powell CB, Kauff ND et al (2007) Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. Gynecol Oncol 107:159–162
29. Resnick KE, Hampel H, Fishel R et al (2009) Current and emerging trends in Lynch syndrome identification in women with endometrial cancer. Gynecol Oncol 114:128–134
30. Lu KH, Schorge JO, Rodabaugh KJ et al (2007) Prospective determination of prevalence of lynch syndrome in young women with endometrial cancer. J Clin Oncol 25:5158–5164
31. Matthews KS, Estes JM, Conner MG et al (2008) Lynch syndrome in women less than 50 years with endometrial cancer. Obstet Gynecol 111:1161–1166
32. Shih KK, Garg K, Levine DA et al (2011) Clinicopathologic significance of DNA mismatch repair protein defects and endometrial cancer in women 40 years of age and younger. Gynecol Oncol 123:88–94
33. Ring KL, Connor EV, Atkins KA et al (2013) Women 50 years or younger with endometrial cancer: the argument for universal mismatch repair screening and potential for targeted therapeutics. Int J Gynecol Cancer 23:853–860
34. Cohn DE, Frankel W, Resnick KE et al (2006) Improved survival with an intact DNA mismatch repair system in endometrial cancer. Obstet Gynecol 108:1208–1215
35. Kauff ND (2007) How should women with early-onset endometrial cancer be evaluated for lynch syndrome? J Clin Oncol 25:5143–5146
36. Günther K, Horbach T, Hohenberger W et al (2000) Colonic late-onset familial adenomatous polyposis combined with severe duodenal polyposis and familial endometrial cancer. Am J Med 108:681–683
37. Oshima S, Miyake Y, Ikeda M et al (2007) A case of an uterine and pancreatic cancer with familial adenomatous polyposis detected by FDG-PET (in Japanese). Surgery 69:237–240
38. Iwama T, Tamura K, Morita T et al (2004) A clinical overview of familial adenomatous polyposis derived from the database of the Polyposis Registry of Japan. Int J Clin Oncol 9:308–316
39. Schorge JO, Modesitt SC, Coleman RL et al (2010) SGO White Paper on ovarian cancer: etiology, screening and surveillance. Gynecol Oncol 119:7–17
40. Auranen A, Joutsiniemi T (2011) A systematic review of gynecological cancer surveillance in women belonging to hereditary nonpolyposis colorectal cancer (Lynch syndrome) families. Acta Obstet Gynecol Scand 90:437–444
41. Inoue K, Tsubamoto H, Hao H et al (2013) Ovarian carcinoma in situ of presumable fallopian tube origin in a patient with Lynch syndrome: a case report. Gynecol Oncol Case Rep 5:61–63
42. Kuppermann M, Wang G, Wong S et al (2013) Preferences for outcomes associated with decisions to undergo or forgo genetic testing for Lynch syndrome. Cancer 119:215–225
43. Domchek SM, Friebel TM, Neuhausen SL et al (2006) Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. Lancet Oncol 7:223–229
44. Grann VR, Jacobson JS, Thomason D et al (2002) Effect of prevention strategies on survival and quality-adjusted survival of women with BRCA1/2 mutations: an updated decision analysis. J Clin Oncol 20:2520–2529
45. Schmeler KM, Lynch HT, Chen LM et al (2006) Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med 354:261–269
46. Dhar SU, Cooper HP, Wang T et al (2011) Significant differences among physician specialties in management recommendations of BRCA1 mutation carriers. Breast Cancer Res Treat 129:221–227
47. Demsky R, McCuaig J, Maganti M et al (2013) Keeping it simple: genetics referrals for all invasive serous ovarian cancers. Gynecol Oncol 130:329–333
48. Lacour R, Daniels M, Westin S et al (2008) What women with ovarian cancer think and know about genetic testing. Gynecol Oncol 111:132–136
49. Backes FJ, Mitchell E, Hampel H et al (2011) Endometrial cancer patients and compliance with genetic counseling: room for improvement. Gynecol Oncol 123:532–536
50. Deming WE (1986) Out of the crisis, 1st edn. MIT Press, Cambridge
51. Nakayama DK, Bushey TN, Hubbard I et al (2010) Using a Plan-Do-Study-Act cycle to introduce a new or service line. AORN J 92:335–343
52. Vogel P, Vassilev G, Kruse B et al (2011) Morbidity and mortality conference as part of PDCA cycle to decrease anastomotic failure in colorectal surgery. Langenbecks Arch Surg 396: 1009–1015
53. Oh HC, Toh HG, Giap Cheong ES (2011) Realization of process improvement at a diagnostic radiology department with aid of simulation modeling. J Healthc Qual 33:40–47
54. Michael M, Schaffer SD, Egan PL et al (2013) Improving wait times and patient satisfaction in primary care. J Healthc Qual 35:50–60
55. Honda O, Tsubamoto H, Ito Y et al (2013) Regional coordination for end-of-life care in our department. Jpn J Gynecol Oncol 1:1–8

J Genet Counsel (2013) 22:795–804
DOI 10.1007/s10897-013-9632-0

GENETIC COUNSELING: A GLOBAL PERSPECTIVE

The Current State of Genetic Counseling Before and After Amniocentesis for Fetal Karyotyping in Japan: A Survey of Obstetric Hospital Clients of a Prenatal Testing Laboratory

Miyuki Nishiyama · Hideaki Sawai · Shinji Kosugi

Received: 2 November 2012 / Accepted: 15 July 2013 / Published online: 24 August 2013

Abstract Pregnant women undergoing prenatal genetic testing should receive genetic counseling so they can make informed decisions. We examined the current state of providing genetic counseling in Japan to pregnant women before they elected amniocentesis for prenatal diagnosis of chromosome abnormalities and after test results were completed, and explored the opportunity for expanding access to certified genetic counselors (CGC) at clinical practices offering amniocentesis. An anonymous survey was mailed to the 298 hospitals that referred amniotic fluid specimens to LabCorp Japan in 2009. Most genetic counseling was provided by the obstetrician alone; 73.8 % (76/103) of pre-amniocentesis, 82.5 % (85/103) if normal results, and 49.4 % (44/89) if abnormal results. Respondents spent limited time in genetic counseling; 57.3 % spent <10 min for pre-amniocentesis, 88.3 % spent <10 min for normal results, and 54.0 % spent <20 min for abnormal results. While 45.8 % indicated that CGC do not have an essential role in clinical practice, responses that supported employment of CGC were more likely to come from hospitals that submitted more than ten specimens annually ($p<0.0001$), university hospitals ($p<0.0001$), and MD geneticists ($p=0.020$). Currently, there is limited genetic counseling available in Japan. This indicates there are opportunities for the employment of CGC to improve the quality of genetic counseling.

Keyword Prenatal diagnosis · Amniocentesis · Fetal chromosome analysis · Genetic counseling · Genetic counselor

Introduction

Since the early 1970s, amniocentesis for prenatal diagnosis of chromosome abnormalities was offered to women considered to be at increased risk of carrying a fetus with Down syndrome or other chromosomal abnormalities. Prenatal maternal serum screening (MSS) provided individualized risk estimates for Down syndrome and trisomy 18 that could be used to decide whether or not to proceed with invasive diagnostic testing. In Japan, based on the population distribution of maternal age and assuming no prenatal diagnosis or termination of pregnancy, the projected frequency of Down syndrome was 1.79 per 1,000 (or 1/566) live births in 2006 (Kajii 2008). Although both invasive diagnostic testing and prenatal MSS are performed in Japan, the uptake rate of each test is extremely low compared with other advanced countries; less than 2 % of all pregnant women in Japan received prenatal MSS, and less than 2 % had invasive diagnostic testing (Sasaki et al. 2011).

The lack of information provided by physicians regarding prenatal diagnosis is thought to be one of the reasons why relatively few pregnant women in Japan receive prenatal testing. Japan Society of Obstetrics and Gynecology (JSOG) and Genetic-Medicine-Related Societies (GMRS)

Miyuki Nishiyama is an employee of LabCorp Japan. Other authors do not have conflicts to report. This manuscript is submitted solely to this journal and was not published elsewhere.

Electronic supplementary material The online version of this article (doi:10.1007/s10897-013-9632-0) contains supplementary material, which is available to authorized users.

M. Nishiyama (✉)
LabCorp Japan, G.K., 2F, Tsukiji MT Building, 2-11-9 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: miyukin0119@gmail.com

M. Nishiyama · S. Kosugi
Kyoto University School of Public Health, Ethics/Medical Genetics, Kyoto, Japan

H. Sawai
Hyogo College of Medicine, Obstetrics and Gynecology, Nishinomiya, Hyogo, Japan

including the Japan Society of Human Genetics (JSHG) and the Japanese Society for Genetic Counseling (JSGC) stated in their guidelines that advanced maternal age (AMA) is an appropriate indication for referral for prenatal diagnostic testing (JSOG 2007; GMRS 2003). However, the guidelines do not require physicians to inform AMA pregnant women of diagnostic testing options. Prenatal MSS is not commonly offered to women based on the 1999 statement by the Expert Committee on Prenatal Diagnosis of the Sciences Council for Evaluating Advanced Medical Techniques of Japan (1999). This stated that physicians were not required to give information about MSS to pregnant women and should not even recommend this test. In 2011, the JSOG updated their earlier position regarding MSS indicating that obstetricians can offer the option of MSS and that discussion should include appropriate and sufficient genetic counseling (JSOG 2011).

Another deterrent to pregnant women receiving prenatal diagnosis in Japan may be related to issues surrounding abortion which is not permitted legally for fetal abnormalities. Based on the statement from the Ministry of Health, Labor and Welfare in 1990, artificial abortions before 22 weeks gestation are permitted for certain indications. The maternal health protection law from 2011 permits artificial abortions with the following two conditions; 1) if maternal health may be seriously affected by continuation of the pregnancy or childbirth due to medical or economic problems, and 2) conception from rape. Although artificial abortions because of fetal abnormalities are performed with maternal economic or health problems given as the reason, many people in Japan believe that artificial abortions are unethical even if a fetus has serious abnormalities (Sasaki et al. 2011).

The National Society of Genetic Counselors (NSGC) and the Japanese Association of Medical Sciences (JAMS) state that genetic counseling is a process to help people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease (NSGC 2006; JAMS 2011). Genetic counseling regarding amniocentesis for fetal chromosome analysis should provide accurate and clear information about the risks, benefits and limitations of testing that allows pregnant women to make informed decisions about testing. Genetic counselors have a unique skill set that allows them to play a role in both providing information about prenatal testing and helping patients understand how this information applies to their own experiences and concerns (Farrelly et al. 2012). Thus, their interactions with patients can be especially helpful when it occurs before prenatal testing by facilitating informed decision making (Farrelly et al. 2012). In Japan, in order to improve the use of medical geneticists who get involved in clinical genetics, the Japanese Board of Medical Genetics was established in 1991, and a total of 968 clinical geneticists were qualified by 2012 (Japanese Board of Medical Genetics 2012). As of November 2012, JSGC and the JSHG have certified 139 genetic counselors who are not medical doctors since the certification system was established in 2004 (Japanese Board of Certified Genetic Counselors 2012). According to one survey, 52.7 % of certified genetic counselors (CGC) worked at hospitals, and this was followed by work at a company (14.9 %), education or research institution (13.5 %) and students of doctoral courses (13.5 %). Among CGC who worked at hospitals, 35.8 % were employed as CGC, and the rest of them (64.2 %) were employed as healthcare professionals such as nurses and midwives (Yamanouchi et al. 2010; Yamanouchi, personal communication, February 4, 2013).

This study explored the current state in Japan of providing genetic counseling to pregnant women before electing amniocentesis for prenatal diagnosis of chromosome abnormalities and after test results were completed, and also looked at the opportunity for expanding access to CGC at clinical practices offering amniocentesis.

Methods

A self-administered anonymous survey was mailed to the 298 hospitals and private clinics that are LabCorp Japan clients which referred amniotic fluid specimens for fetal chromosome analysis in 2009. The address of each hospital and the name of person in charge of prenatal testing were obtained from customer registration data at LabCorp Japan. LabCorp Japan is a Laboratory Corporation of America Holdings company and offers testing services for reproductive and genetic medicine, specifically prenatal testing. Chorionic villi sampling (CVS) was not included as this is rarely performed in Japan. This study was approved by the Ethical Committee of Kyoto University.

Data Collection

The survey instrument (Appendix 1) was developed by the investigator, based on preliminary conversations with multiple obstetricians who provided genetic counseling for pregnant women before they elected amniocentesis for prenatal diagnosis of chromosome abnormalities and after test results were completed. Multiple drafts of the content of the questionnaire were reviewed by medical geneticists, CGC, and students enrolled in a Master's level genetic counseling program.

The instructions specified that the survey should be completed by the person most familiar with the current process for providing information regarding amniocentesis for prenatal diagnosis and results of fetal chromosome analysis. The

survey asked a total of 39 questions: five related to practice demographics; seven to the characteristics of the hospital; five about genetic counseling before electing amniocentesis for prenatal diagnosis of chromosome abnormalities; 13 about the genetic counseling after test results were completed; two about the understanding of two relevant professional guidelines (Guidelines for Prenatal Diagnosis for Congenital Fetal Abnormalities (JSOG 2007) and Guidelines for Genetic Testing (GMRS 2003)); five related to the employment opportunity for CGC at clinical practices offering amniocentesis for prenatal diagnosis; and two about opinions of the employer providing prenatal diagnostic testing.

Table 1 Characteristics of survey respondents

Characteristic of respondent	Count	
	#	%
Practice setting		
Private clinic	49	47.6 %
General hospital	25	24.3 %
University Hospital	17	16.5 %
Obstetrics and gynecology hospital[a]	10	9.7 %
Other	2	1.9 %
Age		
20–29 years	0	0.0 %
30–39 years	9	8.7 %
40–49 years	39	37.9 %
50–59 years	37	35.9 %
60–69 years	14	13.6 %
≥70 years	4	3.9 %
Years of experience providing pre-/post-amniocentesis counseling		
< 5 years	3	2.9 %
5–9 years	12	11.7 %
10–14 years	27	26.2 %
15–19 years	29	28.2 %
≥20 years	32	31.1 %
Annual number of amniocenteses performed at facility		
< 10	52	50.5 %
10–29	24	23.3 %
30–49	13	12.6 %
50–99	6	5.8 %
≥100	8	7.8 %
Profession		
Obstetrician	84	81.6 %
Obstetrician certified as MD geneticist	15	14.6 %
Other MD geneticist	1	1.0 %
Nurse or midwife	2	1.9 %
CGC	0	0.0 %
Other	1	1.0 %
Number of full-time obstetricians at the facility		
1	25	24.3 %
2	22	21.4 %
3–4	15	14.6 %
5–9	25	24.3 %
≥10	16	15.5 %

[a] Obstetrics and Gynecology hospitals may include other smaller departments

Respondents were asked to complete the survey and return their completed, anonymous responses in an enclosed, stamped envelope. Collection of survey responses was closed in August 2010.

Data Analysis

Responses were analyzed by SPSS version 11.5 software using descriptive analysis, chi-square test as a univariate analysis, and logistic regression as a multivariate analysis. In this study, a p value <0.05 was considered statistically significant.

Results

Of the 298 mailed surveys, 37.2 % (110) were returned with a valid response rate of 93.6 % (103/110). Baseline data for these respondents are given in Table 1. The largest proportion of practice settings was private clinics, 47.6 %. Approximately 75 % of respondents were from 40 to 59 years of age. The annual number of amniocenteses performed at the facilities ranged from less than 10 to greater than 100, with 50.5 % submitting less than ten specimens annually. Over 80 % of respondents were obstetricians not certified as MD geneticists. A total of 16 respondents (15.6 %) were MD geneticists; 15 of these were obstetricians certified as MD geneticists. There were no CGC among the respondents. Over half of the hospitals had more than three full-time obstetricians; 24.3 % had only one obstetrician.

Among the 103 surveys with valid responses, 89 respondents (86.4 %) answered that they had provided genetic counseling prior to amniocentesis and, when results became available for both normal and abnormal results. The remaining 14 respondents had experience with providing genetic counseling prior to amniocentesis and afterwards only if there were normal results. Regarding the individual(s) providing genetic counseling, the data revealed that pre-amniocentesis genetic counseling was usually provided by the obstetrician alone (73.8 %), by MD geneticists (18.4 %), including obstetricians certified as MD geneticists (12.6 %) and MD geneticists with other specialties (5.8 %), and by an obstetrician and nurse/midwife (7.8 %) (Table 2). After results became available, normal fetal chromosome results were most frequently communicated by the obstetrician alone (82.5 %), by MD geneticists in 15.5 % of cases, including obstetricians certified as MD geneticists (14.6 %) and MD geneticists with other specialties (0.9 %), and by obstetricians and nurse/midwives or CGC's for the remaining 2.0 %. Although the obstetrician alone provided genetic counseling for almost half (49.4 %) of abnormal results, MD geneticists (23.6 %), including obstetricians certified as MD geneticists (18.0 %) and MD geneticists with other specialties (5.6 %), and referrals to other professional facilities that have an MD geneticist and/or CGC (23.6 %) combined to provide genetic counseling for most of the remaining abnormal cases. Obstetricians with CGC provided genetic counseling for only 3.4 % of abnormal cases (Table 2).

With regards to the amount of time spent in genetic counseling (Table 3), 57.3 % spent less than 10 min for pre–amniocentesis genetic counseling. For discussion of the chromosome results, 88.3 % spent less than 10 min when informing patients of normal results compared with 69.7 % who spent ≥10 min for abnormal results. Respondents who spent more time in genetic counseling, ≥10 min for pre-amniocentesis (38.8 %) or ≥20 min for abnormal results (41.6 %), were significantly correlated with hospitals that submitted over ten specimens annually ($p<0.001$, $p=0.001$), MD geneticists ($p=0.001$, $p<0.001$), and facilities with more than three full-time obstetricians ($p=0.033$, $p=0.012$) (Table 4). Respondents who spent ≥5 min discussing normal results (47.5 %) were more likely to have an understanding of the JSOG guideline for prenatal testing ($p=0.021$), to be MD geneticists ($p=0.017$), or to have over 15 years experience providing such information ($p=0.046$) (Table 4).

The survey questions regarding difficulties experienced with discussion of amniocentesis results were completed by 12/103 (11.7 %) of respondents with normal results and 25/89 (28.1 %) with abnormal results. Responses were grouped based on respondent experiences of normal versus abnormal results and content areas specific to each type of test result were evaluated (Table 5). All respondents encountered difficulties when pregnant women lacked an understanding of the limitations of chromosome analysis with normal results. For normal results, 25.0 % reported a dilemma regarding disclosure of fetal sex when the woman expressed a strong desire to know. Based on the 2007 JSOG guideline for prenatal testing, except for prenatal diagnosis for a severe X-linked disorder, gender of the fetus should not be disclosed. For abnormal results, 60.0 % expressed genetic counseling difficulties regarding the prognosis for abnormal results, and 20.0 % had dilemmas related to a discussion of abortion. These were followed by recurrence risk (16.0 %), limitations of chromosome analysis (8.0 %), and the limited amount of time for decision making due to the advanced gestational age at time of results disclosure (8.0 %).

Figure 1 shows the respondents' answers regarding the employment opportunity for CGC at clinical practices offering amniocentesis for prenatal diagnosis. Among the 103 respondents, 93(90.3 %) were familiar with CGC, and 54 (58.1 %) indicated that CGC have an essential role in providing information regarding prenatal testing. Among the ten respondents who answered that they were not familiar with CGC, two indicated that such professionals would provide a

Table 2 Providers of genetic counseling services

Individual(s) providing genetic counseling	Before electing amniocentesis		After the results were completed			
			Normal		Abnormal	
	#	%	#	%	#	%
OB alone	76	73.8 %	85	82.5 %	44	49.4 %
MD geneticists	19	18.4 %	16	15.5 %	21	23.6 %
OB and nurse/midwife	8	7.8 %	1	1.0 %	0	0.0 %
OB and CGC	0	0.0 %	1	1.0 %	3	3.4 %
Referral to other professional facilities	–	–	–	–	21	23.6 %
Total	103	100.0 %	103	100.0 %	89	100.0 %

critical role in clinical practices offering amniocentesis for prenatal diagnosis. In total, 56 of the 103 respondents (54.2 %) indicated that CGC have an essential role in clinical practice. Examining the factors that correlate with these 56 respondents revealed that those less than 50 years old and hospitals that submitted more than ten specimens annually were significantly correlated factors (p=0.002, p=0.013) (Table 6). Among the 56 respondents who indicated that CGC have an essential role, 41 respondents (73.2 %) did not support the employment of CGC. The reasons for these negative attitudes toward CGC employment included: the practice had a small number of amniotic fluid samples and few abnormal results (65.9 %), patients were referred to a facility with an MD geneticist and/or CGC as needed (34.1 %), lack of understanding of the CGC role at hospitals (17.1 %), and the high cost for genetic counseling service (9.8 %). Since some respondents provided more than one reason, total responses were over 100 %. The remaining 15 (26.8 %) answered that they already employ CGC or want to employ CGC. Among the positive responses that supported CGC employment or employed a CGC, more were likely to have come from hospitals that submitted more than ten specimens annually (p<0.0001), university hospitals (p<0.0001), and MD geneticists (p=0.020) (Table 7).

Discussion

The guidelines of the JSOG and the GMRS including JSHG and JSGC recommend that pregnant women undergoing prenatal genetic testing should receive genetic counseling (JSOG 2007; GMRS 2003). However, the current study showed that the majority of genetic counseling regarding amniocentesis and subsequent results was provided by the obstetrician alone with limited time in genetic counseling. Most respondents spent <10 min for pre-amniocentesis genetic counseling and to discuss normal results, and <20 min for abnormal results, with limited involvement of CGC's. These findings might be attributed to the limited recognition of the importance of genetic counseling in obstetric practices offering prenatal genetic testing.

In examining who provided the genetic counseling, most genetic counseling was provided by the obstetrician alone in all situations, including pre-amniocentesis genetic counseling, discussion of normal results, and reporting of abnormal results.

Table 3 Length of genetic counseling sessions

Time spent in counseling	Before electing amniocentesis		After the results were completed			
			Normal		Abnormal	
	#	%	#	%	#	%
<5 min	17	16.5 %	54	52.4 %	3	3.4 %
5–9 min	42	40.8 %	37	35.9 %	20	22.5 %
10–19 min	23	22.3 %	9	8.7 %	25	28.1 %
20–29 min	10	9.7 %	2	1.9 %	17	19.1 %
≥30 min	7	6.8 %	1	1.0 %	20	22.5 %
Other	3	2.9 %	0	0.0 %	3	3.4 %
No response	1	1.0 %	0	0.0 %	1	1.1 %
Total	103	100 %	103	100 %	89	100 %

Table 4 Correlations between length of genetic counseling sessions and varied provider characteristics

Factor	Before electing amniocentesis ≥10 min (38.8 %)		After results were completed			
			Normal results ≥5 min (47.5 %)		Abnormal results ≥20 min (41.6 %)	
	Odds	p value	Odds	p value	Odds	p value
Private clinic	0.606	0.220	0.696	0.361	0.462	0.079
# of patient visits: ≥ 50 daily	2.444	0.032	1.341	0.474	2.040	0.111
Full-time obstetricians: ≥ 3	2.435	0.033	1.058	0.887	3.150	0.012
Experience: ≥ 15 years	1.250	0.590	2.267	0.046	1.644	0.267
MD geneticist	6.321	0.001	4.054	0.017	14.292	<0.001
Aminiocentesis: ≥ 10 annually	4.913	<0.001	1.122	0.771	4.603	0.001
Aminiocentesis: ≥ 30 annually	4.909	0.001	2.338	0.062	2.645	0.037
Understanding of the JSOG guideline	1.853	0.156	2.658	0.021	3.638	0.008

For abnormal fetal chromosome results, genetic counseling was more likely to be performed by MD geneticists or a referral was made to facilities that have an MD geneticist and/or CGC having more expertise regarding prenatal diagnostic testing. In this study, the most frequently reported difficulty that the respondents encountered in genetic counseling of abnormal cases involved providing information regarding prognosis for the abnormal result. Thus, for smaller facilities that do a small number of amniocentesis procedures without an MD geneticist, it is reasonable to refer pregnant women with abnormal results to the genetic professionals at large facilities. Establishing the coordination with such professional facilities enables the obstetricians to refer the pregnant women with abnormal results within the limited time frame of prenatal diagnosis. This would be especially important for abnormal results, since information about prognosis is essential for women to make informed decisions regarding whether or not to continue a pregnancy.

With regards to the amount of time spent in genetic counseling, over 50 % spent <10 min for pre-amniocentesis, over 80 % spent <10 min for a discussion of normal results, and over 50 % spent <20 min for reporting abnormal results. This suggests that these respondents more likely provided information-giving consultations, rather than genetic counseling. MD geneticists spent more time in providing counseling compared to obstetricians in all situations. Therefore, the amount and the quality of the information provided by MD geneticists could be different from that provided by others. An additional survey that would examine the specific information provided to pregnant women by providers of genetic counseling would allow us to evaluate this assumption. This differentiation by genetic counseling providers is important since most women prefer to be fully informed regarding prenatal testing with unbiased, comprehensive information delivered in a timely manner that supports the decision making process (Bhogal and Brunger 2010).

Table 5 Difficulties encountered in genetic counseling were grouped into two categories, informing of normal fetal chromosome test results and informing of abnormal fetal chromosome test results

	#	% cited
Normal results		
Lack of understanding regarding limitations of chromosome analysis	12	100.0 %
Disclosure of fetal sex	3	25.0 %
Other	1	8.3 %
Abnormal results		
Prognosis for abnormal results	15	60.0 %
Issues related to abortion	5	20.0 %
Recurrence risk	4	16.0 %
Limitations of chromosome analysis	2	8.0 %
Advanced gestational age at time of results disclosure	2	8.0 %
Other	3	12.0 %