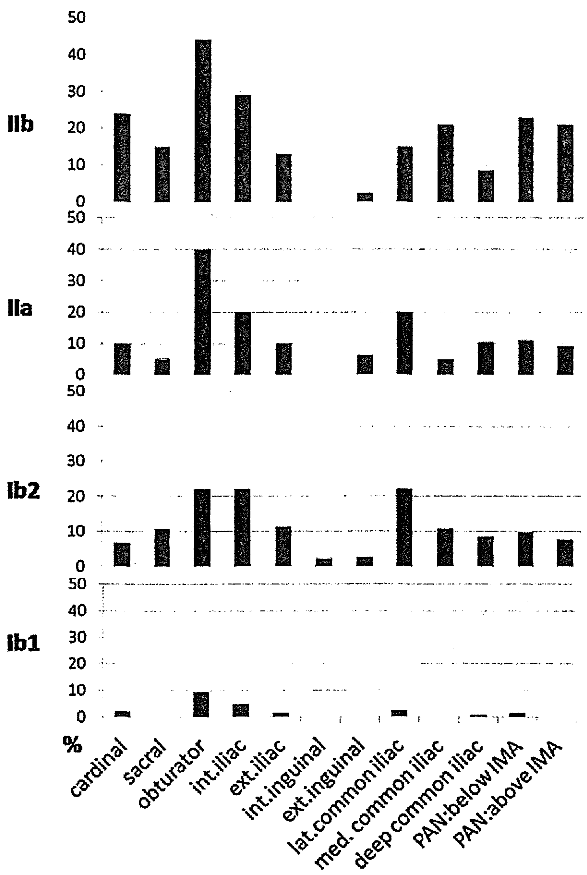

Figure 3 Distribution of lymph node metastasis. Lateral and medial common iliac nodes are combined as superficial common iliac nodes in the text. ext, external; IMA, inferior mesenteric artery; int, internal; lat, lateral; med, medial; PAN, para-aortic node.

Sentinel lymph node mapping

Fifty out of the 303 patients were subjected to sentinel lymph node navigation surgery (SLNN) for the clinical study, with patient consent. Thirty-six cases were assigned to stage Ib1, 6 to stage Ib2 and 8 to stage II. The successful detection rate (sensitivity) was 91.7% in stage Ib1, 50% in stage Ib2 and 50% in stage II. Stage Ib1 with a tumor size >2 cm (Ib1 bulky) and FIGO stages higher than Ib1 had unsatisfactory detection rates (Fig. 4). Then we analyzed the distribution pattern of the sentinel node in patients with stage Ib1 disease. Sentinel nodes were assigned only to obturator (Ob), inter-iliac (Ii), external iliac (Ei) and superficial common iliac (Sc) in stage Ib1 cases, but additionally to three other nodes in the upper stages (Fig. 5). All four lymph node stations detected by SLNN in stage Ib1

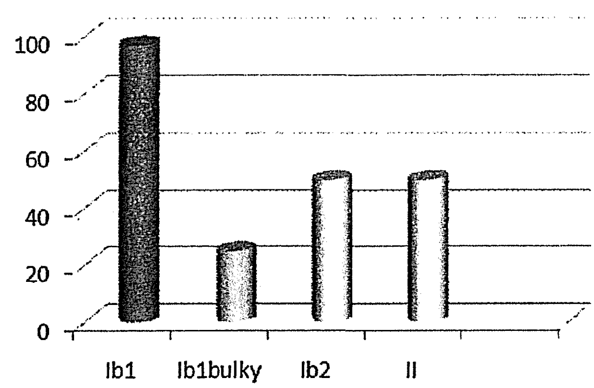

Figure 4 Detection rate of the sentinel nodes in each stage. Ib1bulky, tumor with size >2 cm in the longest diameter.

were included in the metastatic sites observed frequently by post-surgical, pathological examination.

Discussion

Type 4 (Okabyashi) radical hysterectomy and LA is widely adapted for early invasive cervical cancer in Japan; however, we have considered the concept that patients with stage Ib1 disease may benefit from curtailment of surgery, because of the less frequent occurrence of lymph node metastasis and parametrial involvement. There have been reports on lymph node metastasis showing rates of 11.5–21.7% in stage Ib, 10–26.7% in stage IIa and 34–43.4% in stage IIb.[1,18] In the present study, the rate was 15.7% in stage Ib (stages Ib1 and Ib2), 35.0% in stage IIa and 55.5% in stage IIb. The incidence in stage II was higher than that ever published in the literature, but the difference may be derived from the intensive LA in our hospitals. The number of lymph nodes removed in LA in the literature revealed 16–70 pelvic nodes plus para-aortic nodes,[1,18] but in this study the number was 71.7 in stage II disease. Concerning stage I disease, stage Ib1 had an incidence of 12.2%, whereas stage Ib2 had an incidence of 29.8%, indicating the significant difference between the two categories and the possibility of the curtailment of LA in stage Ib1 disease. On the other hand, due to the frequency and the wide distribution of metastasis (Fig. 3), LA should not be modified in disease stages higher than Ib1. The distribution pattern of lymph node metastasis in stage Ib1 was limited to Ob (9.5%), Ii (4.9%), Sc (2.3%), Cd (2.2%) and Ei (1.7%) nodes. Metastasis to deep common iliac and para-aortic nodes was also observed, but the frequency was quite

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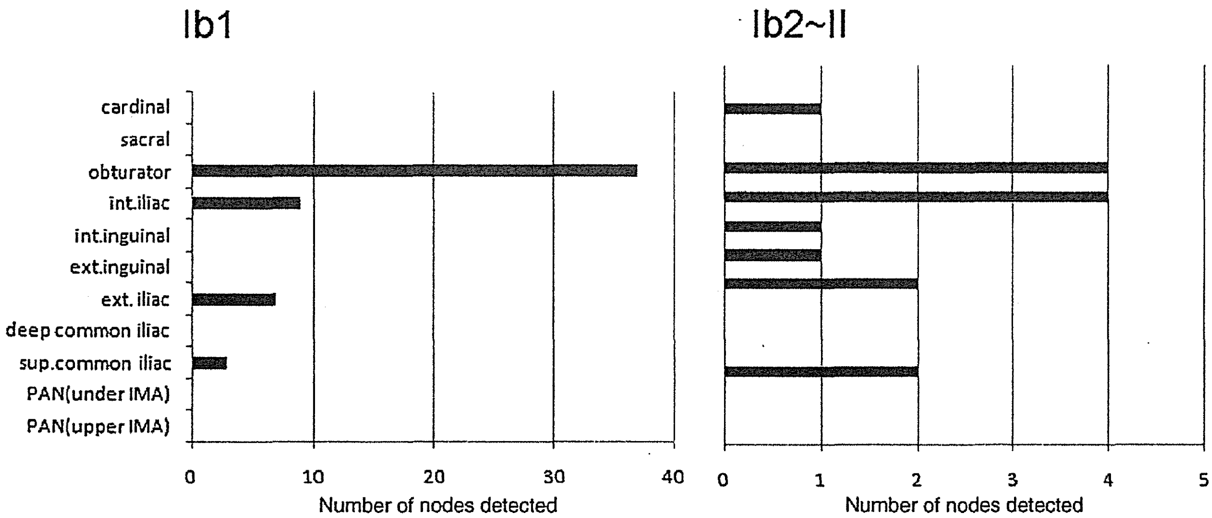

Figure 5 Number of sentinel lymph nodes detected in stage Ib1 versus stage Ib2 to stage II disease.

low (in 1 (0.8%) and 2 (1.34%) patients, respectively, of the 189 patients with stage Ib1 disease) and these three cases cover a wide range of metastasis in other pelvic nodes. No metastases were detected to the sacral or internal and external inguinal nodes, which corresponds with the report that the most distal circumflex iliac nodes were not found to be positive as isolated nodal metastases in early cervical cancer.[19]

Buchsbaum showed that, in the routes of lymphatic flow from the uterine cervix, the most crucial one is the channel directed laterally to the obturator, inter-iliac and common iliac nodes, the second is the anterior channels which terminate in the external iliac, and the third passes posteriorly to reach the common iliac, sacral and para-aortic nodes.[19] Reiffensthul *et al.* described that the routes can be divided into three main routes: the lateral trunk runs through the lateral parametrium to the obturator nodes, the anterior trunk through the vesicouterine ligament into the inter-iliac nodes and the posterior trunk through the sacrouterine ligament and ureter into the presacral and para-aortic nodes.[20] Benedetti-Panici *et al.* showed that all patients with pelvic lymph node metastasis showed parametrial invasion; the most frequent site was the lateral parametrium (27%) and the second was the cervicovesical ligament (6%); invasion into the sacrouterine ligament was quite a rare event in stage Ib1 disease.[3] These observations support the result in this study that most lymph node metastases in stage Ib1 converge into the Ob, Ii, Ei, Sc and Cd nodes. In addition, our finding that SLNN in stage Ib1 disease showed the limited involvement of metastasis into Ob, Ii, Ei and Sc, suggests that the first lymphatic drainage from the uterine cervix in early invasive cervical cancer runs into these nodes.

The most common strategy at present for the reduction of LA in cervical cancer is SLNN. In all the literature published, a detection rate of 79–100% with a negative predictive value of 87.5–100% has been found, which renders SLNN usable in routine clinical practice.[11,21] However, when the clinical FIGO stage exceeds Ib1, the detection rate becomes surprisingly low (Fig. 4). This observation may be derived from a disruption in the normal lymphatic flow, and presumably causes the change in the distribution pattern of the sentinel nodes (Fig. 5). It is possible that the original, anatomical sentinel node may be observed only with stage Ib1 disease. Frequently detected sentinel nodes have been reported in external, internal, superficial common iliac and obturator node stations.[11,21,22] Our study of SLNN was coincident with these data.

From the results of the present study, lymph node metastasis can be commonly observed in first drainage or original sentinel lymph node in stage Ib1 uterine cervical cancer, and the extent of LA could be routinely completed with the removal of Ob, Ii, Ei, Sc and Cd nodes. However, we have to consider micrometastases, which can be found in negative nodes with a certain frequency by ultrastaging. For example, 6.8% of all breast cancer patients treated at the John Wayne Cancer Institute showed micrometastases,[23] and 8.1–15% of early uterine cervical cancer patients with negative nodes had micrometastases.[24,25] Patients with

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micrometastases may later develop macrometastases in the secondary or downstream lymph nodes, and the impact on the prognosis has been discussed.[23–27] The existence of micrometastases in the nodes eliminated in this study and the effect of the removal of those nodes performed as part of conventional systemic lymphadenectomy on survival is unknown. Thus, the validity of the minimization of lymphadenectomy suggested in this study may have to be evaluated on the effect of prognosis by a prospective study. Alternatively, because the minimum lymph nodes suggested in this study are coincident with sentinel nodes, by more intensive pathological analysis (ultrastaging) on the nodes and by revealing micrometastases, we could identify the high-risk patients and adjuvant therapy may contribute to better survival. If this minimized lymphadenectomy is performed routinely, it may contribute to a higher quality of life for the patients. Especially, prevention of the removal of inguinal nodes will dramatically reduce lower extremity lymphedema and associated severe soft tissue infection.[28,29]

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INTRODUCTION TO REVIEW ARTICLES

Recent advances in research on epigenetic alterations and clinical significance of para-aortic lymphadenectomy in endometrial cancer: an introduction

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Endometrial cancer is the most frequent cancer of the female reproductive organs in industrialized countries. In 2012, the numbers of new cases and deaths from endometrial cancer in the US were estimated to be 47,130 and 8,010, respectively [1]. The incidence of endometrial cancer is also increasing steadily in Japan, where the estimated number of new cases in 2007 was 9,104 [2] and the number of deaths in 2011 was 2,034 [3]. Endometrial cancer is a surgically staged disease and post-operative therapy is offered to patients with a high risk of recurrence according to the extent and aggressiveness of the tumor. Current topics in endometrial cancer include: the therapeutic significance of lymphadenectomy, the role of epigenetic alterations, and revision of the International Federation of Gynecology and Obstetrics staging criteria (FIGO 2008) for this disease.

There was a paradigm shift in the treatment strategy for endometrial cancer after the introduction of a surgical staging system (FIGO 1988) that replaced the older clinical staging system. The newer paradigms of extended-surgical staging containing lymphadenectomy with more restricted use of adjuvant therapy and the older paradigm of simple hysterectomy bilateral salpingo-oophorectomy with more frequent use of adjuvant radiotherapy need to be compared prospectively in terms of survival benefits, quality of life, and cost of treatment [4]. Several issues regarding surgical staging need to be clarified. They include: how should suitable patients for complete lymphadenectomy be selected and what is the optimal extent of lymphadenenctomy?

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The therapeutic significance of lymphadenectomy has long been a matter of great debate. In 1964, Lewis suggested a therapeutic effect of pelvic lymphadenectomy in node-positive patients [5]. He employed pelvic lymphadenectomy because endometrial cancer often recurred at the pelvic side wall after conventional hysterectomy and bilateral salpingo-oophorectomy, which suggested inadequate primary surgery. Retrospective studies suggest a therapeutic significance for lymphadenectomy, which is a function of removed lymph node count (thoroughness) and area of dissection (pelvic only versus pelvic and para-aortic lymphadenectomy) [6–8]. However, two prospective randomized controlled trials (RCTs) that intended to prove the therapeutic role of pelvic lymphadenectomy failed to show any survival advantage of pelvic lymphadenectomy versus no lymphadenectomy [9, 10]. However, there has been some criticism about the design of these trials because para-aortic lymphadenectomy was not included in the study arm. A retrospective cohort study which compared pelvic lymphadenectomy with combined pelvic and para-aortic lymphadenectomy revealed survival improvement in the pelvic and para-aortic lymphadenectomy group if this treatment was offered to intermediate-/high-risk endometrial cancer patients [11]. Based on these findings, discussions have begun about the design of future clinical trials to validate the therapeutic significance of lymphadenectomy. Topics for discussion include the eligibility of patients (all patients or selected patients at some risk of nodal metastasis), extent of lymphadenectomy (area: pelvic alone versus pelvic plus para-aortic, thoroughness: number of nodes removed), and type of experimental design (RCT versus cohort study).

The difficulties and pitfalls of RCTs for validating surgical procedures have often been addressed [12–16]. These include the participating surgeons' expertise in experimental

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procedures and non-participation of experienced surgeons. Surgeons need to be conversant with both control arm procedures and study arm procedures. If a study arm includes a complex procedure that requires intensive training and if many of the participating surgeons are not familiar with the complex procedure, systemic bias may exist in favor of operations that are in wide use and may favor technically simple procedures [12]. Research in surgery is disadvantaged by the limited quality and quantity of randomized trials of surgical techniques [14]. A preliminary phase 2 surgery study before conducting a RCT or a well-designed prospective cohort study may be a possible solution for this problem [14–16].

Another important issue regarding endometrial cancer is the diversity of aggressiveness of the cancer and its underlying molecular alterations. Histological subtype of endometrial cancer is a strong prognostic factor. Based on the clinicopathological studies, the concept of two different pathogenetic types of endometrial cancer was proposed [17, 18]. Although there may be criticism that this model is an oversimplification, this concept is now widely accepted. Type 1 is represented by endometriod G1/G2 tumors and Type 2 is represented by serous adenocarcinoma and clear cell adenocarcinoma. Type 1 tumors have a relatively favorable prognosis, are related to unopposed estrogen, often coexist with endometrial hyperplasia, and are frequently associated with the phosphatase and tensin homolog (PTEN) mutation. Serous adenocarcinoma, the prototype of the Type 2 tumor, occurs among elderly women, is associated with a poor prognosis, exhibits no estrogen dependency, and is frequently (>90 %) associated with a p53 mutation. There is controversy regarding whether endometriod G3 tumors should be included in the Type 1 or Type 2 category [19, 20]. A p53 mutation has been suggested to be an independent prognostic factor for endometrial cancer and a dominant-negative mutation of the p53 tumor suppressor gene may play a critical role in the poor survival of patients irrespective of the histological subtype of the tumor [21, 22]. The expression profile of microRNA has been shown to be different between Type 1 and Type 2 tumors [23]. In clinical practice, these two types of tumors are treated with different treatment strategies [24, 25]. The malignant phenotypes, such as invasiveness, metastatic potential and resistance to therapy, are related to epithelial–mesenchymal transition (EMT) [26]. Recent studies have suggested that EMT may play an important role in the malignant behavior of endometrial cancer and is related to the invasive potential of endometrial cancer cells in vitro [27–29]. For future directions aimed at more personalized treatment strategies for endometrial cancer, further microRNA studies to establish a highly accurate method for diagnosing the aggressiveness of each tumor, as well as the development of novel molecular targeting therapies, are necessary [30].

In this issue, we have invited three distinguished experts to describe recent advances in research on epigenetic alterations and surgical therapy for endometrial cancer. We hope that this special review session will help oncological researchers and physicians from non-gynecological fields to comprehend some of the most important aspects of endometrial cancer.

Conflict of interest The author declares that he has no conflict of interest.

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Editorial

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Emerging concept of tailored lymphadenectomy in endometrial cancer

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See accompanying article on page 251.

Endometrial cancer is the most frequent cancer of female reproductive organs in western countries, and its incidence is steadily increasing in Japan. This type of tumor is generally regarded to be associated with relatively favorable prognosis because many patients have an early sign of genital bleeding that leads to early diagnosis. However, patients with lymph node metastasis are allocated to stage IIIC and have a 5-year survival rate of only ~50%. Endometrial cancer is a surgically staged disease, hence the diagnostic and prognostic significance of lymphadenectomy. In contrast, the therapeutic significance of lymphadenectomy has been a matter of debate for a long time. Treatment of endometrial cancer comprises local, regional and systemic control. Local control is achieved by removal of primary tumor by hysterectomy with sufficient surgical margins. Systemic control is achieved with systemic chemotherapy for clinical or occult hematogenous metastasis to distant organs. Regional control comprises eradication of cancer cells in regional lymph nodes, which is achieved by either lymphadenectomy or radiotherapy.

Two reports in *The Lancet* [1,2] strongly suggest that pelvic lymphadenectomy (PLX) has no therapeutic role in low-risk endometrial cancer, and complete pelvic and para-aortic lymphadenectomy (PLX+PALX) improves survival of patients with intermediate/high-risk endometrial cancer. The MRC ASTEC (A Study in the Treatment of Endometrial Cancer) trial [1] was a randomized controlled trial comparing standard treatment with total abdominal hysterectomy (TAH) plus bilateral salpingo-oophorectomy (BSO) and investigational treatment with TAH+BSO+PLX in early-stage endometrial cancer. PLX did not improve overall survival, and it is not recommended as a routine therapeutic procedure. In response to this recommendation, which contradicts the advice of some guidelines that do recommended PLX+PALX for patients with operable disease [2], Todo et al. [3] have reported the SEPAL (Survival Effect of Para-Aortic Lymphadenectomy) study, which is a retrospective cohort analysis of treatment of endometrial cancer in two tertiary center hospitals. One cohort was treated with PLX+PALX and the other with PLX alone, and the former improved survival of patients with surgically/pathologically defined intermediate/high-risk endometrial cancer. Notably, this survival effect was more significant in high-risk patients, 65% of whom had lymph node metastasis. In contrast, low-risk patients had no survival benefit from PLX+PALX, which suggests that lymphadenectomy itself has no survival benefit in surgically/pathologically determined low-risk endometrial cancer. It can be deduced from these two studies that lymphadenectomy does not have therapeutic effect in low-risk (low-risk of lymph node metastasis) endometrial cancer, and full lymphadenectomy for both pelvic and para-aortic areas has a therapeutic role in patients with intermediate/high-risk, especially node-positive, endometrial cancer.

In the post-ASTEC/SEPAL era, our discussion will be focused on tailoring lymphadenectomy in endometrial cancer in order to maximize the therapeutic effect of surgery and minimize its invasiveness and adverse effects. This will include: 1) preoperative assessment of the probability of lymph node metastasis in each patient to allocate only those with a certainty of lymph node metastasis to full lymphadenectomy; 2) standardization of type (PLX or PLX+PALX) and intensity (selective/sampling or systematic) of lymphadenectomy to optimize

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surgical therapy; 3) type of prospective study for validating usefulness of lymphadenectomy in patients with high risk of lymph node metastasis (randomized controlled trial or prospective comparative cohort study); and 4) identifying tumors with high potential of hematogenous systemic spread that are unlikely to benefit from formal lymphadenectomy. In this editorial, only the first point will be discussed in relation to an article by Kang et al. [4] in this issue. Diagnostic imaging using computed tomography, magnetic resonance imaging (MRI), and positron emission tomography are used for preoperative evaluation of lymph node metastasis. Positive predictive value is high, but sensitivity for detection of lymph node metastasis is not satisfactory [5-7]. Because of high positive predictive value, patients with positive diagnostic imaging should be candidates for formal lymphadenectomy. Among various histopathological factors, depth of myometrial invasion and tumor grade are well established risk factors for lymph node metastasis [8]. The former can be estimated preoperatively by MRI or intraoperatively by frozen section diagnosis or macroscopic evaluation. High-grade tumor, that is, G3 endometrioid or non-endometrioid tumor, can be diagnosed preoperatively by curettage and histopathological evaluation. The other predictive factor that is assessable in the preoperative settings includes serum CA-125 level [9,10]. Lymphovascular space invasion is a strong indicator of lymph node metastasis and patient survival. However, we do not have a reliable method to determine the presence and intensity of lymphovascular space invasion preoperatively or intraoperatively.

Patients with low probability of lymph node metastasis need not receive formal lymphadenectomy. Several investigators have proposed their own criteria for predicting lymph node metastasis, incorporating factors assessable in the preoperative setting [11-13]. The utility of these predicting or risk-scoring systems needs to be validated by large prospective studies. In such a circumstance, questions will be raised about what is a clinically acceptable cut-off value for accuracy of preoperative estimation of lymph node metastasis, which will be necessary in defining the endpoint of the validation study for the predicting system. In this issue of *J Gynecol Oncol*, Kang et al. [4] have tried to present a suggested false-negative rate as an index of the performance of a prediction model by analyzing three models for categorizing risk of lymph node metastasis by incorporating histopathological variables. They have proposed a false-negative rate <2% as an index of the usefulness of their prediction model, assuming that the prevalence of lymph node metastasis is 10% in the target patient cohort. This false-negative rate was obtained from postoperatively defined histopathological factors. Therefore, this value may not be directly applicable to preoperative predicting systems. However, their article provides us with the opportunity of discussing the index of reliability of a preoperative predicting system for lymph node metastasis in endometrial cancer. Acceptable false-negative rates for detecting lymph node metastasis using sentinel node biopsy are considered to be 5% for vulvar carcinoma [14] and 5% for breast cancer [15]. It would be acceptable to use those available predicting systems [11-13] in a prospective study to validate the survival effect of lymphadenectomy in order to exclude patients at low risk of lymph node metastasis.

CONFLICT OF INTEREST

No potential conflict of interests relevant to this manuscript was reported.

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Acceptance of and attitudes towards human papillomavirus vaccination in Japanese mothers of adolescent girls

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ABSTRACT

To better understand how to achieve high uptake rates of human papillomavirus (HPV) vaccination in Japan, we investigated acceptance of and attitudes towards HPV vaccination in 2192 mothers of girls aged 11–14 yrs. A school-based survey was conducted in five elementary and fourteen junior high schools in Sapporo, Japan. Responses from 862 participants were analyzed. Ninety-three percent of mothers would accept the vaccine for their daughter if free, but only 1.5% was willing to pay the minimum recommended price of ¥40,000. Vaccine acceptance was higher in mothers who had heard of HPV vaccine (adjusted odds ratio, aOR = 2.58, confidence interval, CI = 1.47–4.53), and who believed susceptibility to (aOR = 2.30, CI = 1.34–3.92) and severity of (aOR = 3.73, CI = 1.41–9.88) HPV to be high. Recommendations from a doctor (aOR = 12.60, CI = 7.06–21.48) and local health board (aOR = 27.80, CI = 13.88–55.86) were also positively associated with increased HPV vaccine acceptance. Concerns about side effects of both the HPV vaccine (aOR = 0.03, CI = 0.01–0.08) and routine childhood vaccines in general (aOR = 0.11, CI = 0.02–0.78) emerged as barriers to vaccination. Not participating in routine cervical screening also emerged as a deterrent (aOR = 0.49, CI = 0.27–0.91). While most mothers (66.8%) agreed that 10–14 yr was an appropriate age for vaccination, a further 30.6% believed >15 yr to be more appropriate.

In conclusion, attitudes of Japanese mothers toward HPV vaccination are encouraging. While lower vaccine acceptance in mothers who do not undergo regular cervical screening needs further investigation, this study indicates that high uptake may be possible in a publically funded HPV vaccination program if physicians actively address safety concerns and justify why the vaccine is needed at a particular age.
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1. Introduction

Cervical cancer, caused by persistent infection with an oncogenic human papillomavirus (HPV), is highly preventable, yet 275,100 women die from it annually [1]. Two highly effective prophylactic HPV vaccines have been developed [2,3]. Both contain antigens against HPV types 16 and 18, responsible for around 70% of cervical cancers worldwide.

HPV vaccines offer promising new options in future cervical cancer prevention programs. However, for the public health impact to be fully realized, high uptake is necessary. Since HPV is transmitted sexually, the vaccine should ideally be administered before sexual debut. Consequently, the primary target age group for vaccination is pre/adolescent girls. In this age group most countries require parental consent, so understanding parental attitudes towards HPV vaccine is essential. For this reason, many studies on parental attitudes towards and acceptance of HPV vaccination have taken place, both in Europe/North America [4–9] and Asia [10–14]. However, no such study has taken place in Japan.

One recent study reported the prevalence of HPV in Japanese women to be 22.5%; in young women aged 15–19 yrs it was 35.9% [15]. Eradication of cervical cancer began in the 1950s with a screening program that was initially successful. However, recent biennial screening rates have stagnated and are reported to be between 23.9% and 32.0% [16,17]. In women aged 20–29 yrs they are especially low at 23.1% [17]. Consequently, the incidence of cervical cancer is increasing – from 8.0 per 100,000 in 2002 to 9.8 per 100,000 in 2008 [1,18], and this increase is most pronounced in

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women aged ≤39 yrs [19]. Thus, despite Japan's being an economically developed country, cervical cancer is still a serious public health issue.

The bivalent and quadrivalent HPV vaccines were licensed in Japan in 2009 and 2011, respectively. In November 2010, the Japanese government decided to partially fund (50%) the HPV vaccine for girls aged 12–16 yrs if regional governments funded the remaining 50%. This funding has been extended to fiscal year 2012. Given the poor participation in cervical screening, HPV vaccination offers a unique opportunity to reduce morbidity and mortality associated with cervical cancer. However, for high uptake rates to be achieved, the vaccine must be both affordable and acceptable to those who influence uptake most. Since mothers in Japan are predominantly the main decision-makers for their child's healthcare, including vaccinations, this study was designed to: (i) determine acceptance of and preferences for HPV vaccine in Japanese mothers, (ii) examine mothers' attitudes to HPV and the HPV vaccine and (iii) identify socio-demographic and attitudinal predictors associated with HPV vaccine acceptance.

2. Materials and methods

2.1. Participants

At the time of implementation, three academic organizations recommended the primary target age group for HPV vaccination to be girls aged 11–14 yrs [20]. Consequently, 2192 primary caregivers (hereafter 'mothers') with daughters aged 11–14 yrs, attending 5 elementary ($n = 560$) and 14 junior high schools ($n = 1632$) in Sapporo were invited to participate in the study. Sapporo is Japan's fifth largest city and the capital of the Northern Island of Hokkaido. Since almost all elementary and junior high schools in Japan are public, it was necessary to consult with the Board of Education, who referred us to the Head Teachers' Association, for permission to carry out the study. As a result, randomization of schools was not possible; instead we had to rely on the Head Teachers Association and use convenience sampling. To obtain mothers from various socio-economic backgrounds, at least one school from each of Sapporo's 10 districts was chosen. Elementary schools were selected by the head of Sapporo Elementary Head Teachers' Association. For junior high school, schools with head teachers who were district representatives for health and physical education, a position that rotates every two years, were chosen. The Head Teachers' Association did not permit any material incentive being offered for participation in the study.

2.2. Survey instrument and measures

A 103-item survey instrument was developed based on previous research on vaccine acceptability [21,22]. It assessed mother's attitudes towards childhood vaccinations, socio-demographic factors, knowledge about and attitudes towards cervical cancer, HPV and the HPV vaccination, willingness to pay for HPV vaccine, as well as information on cervical screening history and HPV related diseases.

2.2.1. Vaccine preferences and acceptability

Since cost has been shown to be a significant barrier to HPV vaccination in previous studies [23–25] and it was likely the Japanese government would provide funding for the vaccine in the near future, vaccine acceptability was assessed by examining intentions to vaccinate if the vaccine was free, or at the minimum recommended price of ¥40,000 (around $400). The former was assessed by the question: 'If your daughters could have the HPV vaccine for free, how likely would you be to have her vaccinated'. Responses were on a 5-point scale ('very unlikely', 'unlikely', 'not sure', 'likely', 'very likely'). The latter was measured by the question, 'What is the most you would be willing to pay to have your daughter vaccinated against HPV'. Responses were on an 8-point scale: 'Nothing', '¥100–1999', '¥2000–4999', '¥5000–9999', '¥10,000–19,999', '¥20,000–29,999', '¥30,000–39,999' and '¥40,000 or more'. Furthermore, since the Japanese Immunization Act stipulates that all vaccinations be accomplished by private vaccination rather than school-based vaccination, and since there is no general practitioner (GP) system in Japan, we also investigated where mothers would prefer to have their daughters vaccinated and by whom.

2.2.2. Attitudes towards HPV and HPV vaccination

To assess participants' attitudes toward HPV and HPV vaccination, questions based on five concepts from the Health Belief Model [26]: perceived susceptibility to HPV infection; perceived severity of HPV infection; perceived benefits of HPV vaccination; perceived barriers to HPV vaccination and cues to action for HPV vaccination, such as recommendation from a doctor or local health board, were used. Perceived benefits and barriers were assessed with questions on vaccine efficacy and safety. For perceived susceptibility, perceived severity and perceived benefits, responses were dichotomized: a response of 'moderate(ly)', 'high', 'very high' or 'definitely' was categorized as 'Yes' and a response of 'low', 'very low' or 'not at all' was categorized as 'No'.

2.2.3. Socio-demographic characteristics

Socio-demographic factors included mother's age, number of children, marital status, educational background, annual household income and mother's monthly disposable income. Experience with HPV-associated conditions was assessed with 3 items that asked 'Have you ever been told you have HPV, genital warts, cervical cancer'. For screening history, the response to the question 'When was your most recent 'Pap smear' was assessed on a 6-point scale: 'Within the past 12 months', '13–24 months ago', '25–36 months ago', 'More than 37 months', 'Never', 'Don't know'. For statistical analyses, responses were divided into three categories: 'Within the past 24 months' (the recommended period for screening in Japan), 'More than 24 months' and 'Never/don't know'. History of an abnormal Pap smear was assessed on a 5-point scale, 'Never', 'Once', 'Twice', 'More than 3 times' and 'Not applicable'. Finally, we also asked whether participants had heard of the HPV vaccine.

2.3. Procedure

Between July and September 2010, the self-administered questionnaire, a stamp-addressed envelope and a letter explaining the purpose of the study were distributed through the schools and returned to the main investigator by post. Out of consideration for children who did not have, or were not living with their mother, the study was addressed to the primary caregiver. A reminder letter was also sent eight weeks after the questionnaires had been distributed. The study was approved by the Ethics Review Board for Epidemiological Studies at Hokkaido University Graduate School of Medicine. Since the survey was both voluntary and anonymous, completing the questionnaire was taken as consent to participate in the study.

2.4. Statistical analysis

Data were analyzed using IBM SPSS Statistics Version 19.0 (SPSS Inc., Chicago, USA). When analyzing vaccine acceptance, mothers indicating 'likely' or 'very likely' to have their daughter vaccinated were classified as 'acceptors', and those answering 'very unlikely', 'unlikely' or 'not sure' were classified as 'non-acceptors'. Logistic regression analysis was performed to investigate the association

Table 1
Selected characteristics of the sample population.

Characteristic	N[a] (%)	Characteristic	N (%)
Age (yrs)		Previous Pap smear	
30–34	32 (3.8)	Within 24 months	474 (55.1)
35–39	177 (20.8)	>24 months	208 (24.2)
40–44	368 (43.1)	Never/don't know	178 (20.7)
45–49	285 (27.5)	History of abnormal Pap smear	
≥50	41 (4.8)	Never	692 (87.7)
Education		Once	32 (4.1)
Junior high	21 (2.4)	Twice	16 (2.0)
High school	318 (37.0)	≥3 times	49 (6.2)
Vocational college/junior college	417 (48.5)	History of HPV infection	
University or more	103 (12.0)	Yes	13 (1.5)
Annual household income (¥[b])		No	797 (92.5)
<3 million	140 (16.4)	Don't know	43 (5.0)
3–<5 million	244 (28.5)	Diagnosis of genital warts	
5–<7 million	212 (24.8)	Yes	20 (2.3)
7–<10 million	174 (20.3)	No	801 (93.9)
≥10 million	86 (10.0)	Don't know	32 (3.8)
Mother's monthly disposable income (¥)		Diagnosis of cervical cancer	
<30,000	722 (84.3)	Yes	12 (1.4)
30,000–<50,000	76 (8.9)	No	828 (96.8)
50,000–<70,000	26 (3.0)	Don't know	15 (1.8)
≥70,000	32 (3.8)	Heard of HPV vaccine	
Marital status		Yes	557 (64.8)
Married/cohabiting	760 (88.2)	No	229 (26.7)
Separated/divorced/widowed/single	102 (11.8)	Don't know	73 (8.5)

[a] Numbers do not always add up to 862 due to missing data.
[b] 100 Japanese yen = 1 US Dollar.

between predictor variables and vaccine acceptance when provided for free. Three models were constructed: unadjusted, model 1 (adjusted for age) and model 2 (adjusted for age, education, household income and screening history) and odds ratios (ORs) and 95% confidence intervals (CI) calculated. Factors associated with having heard of HPV vaccine were determined by Pearson's chi-squared and Fisher's exact test. Statistical significance was defined as a 2-tailed p-value of <0.05.

3. Results

A total of 881 (40.2%) questionnaires were returned. Return rates by school type were 43.6% (n = 244) and 39.0% (n = 637), for elementary and junior high school, respectively, and ranged from 31.0% to 58.0%. Ten questionnaires were excluded because they were from fathers, eight were returned blank due to having two daughters in the study and one was excluded due to missing data for all socio-demographic factors. Thus, data from 862 participants were used in the final analysis.

3.1. Socio-demographics

Background characteristics of participants are shown in Table 1. The majority of participants were aged between 40 and 44 yrs (mean age 42.5 yrs; SD = 4.6), married or cohabiting (88.2%) and had attended junior or vocational college (48.5%). In all 474 (55.1%) had undergone cervical screening within the past 24 months and 97 (12.3%) had experienced an abnormal Pap smear. Twelve (1.4%) participants had been diagnosed with cervical cancer. In all 557 (64.8%) had heard of the HPV vaccine.

3.2. Vaccine preferences and acceptability

Preferences for HPV vaccination are shown in Table 2. If free, 92.6% of mothers said they were 'very likely' (66.2%) or 'likely' (26.3%) to have their daughter vaccinated, 5.9% were 'not sure' and 1.5% said it was 'very unlikely' or 'unlikely'. Only 1.5% of participants would pay the minimum recommended price of ¥40,000, with many (59.8%) only willing to pay up to ¥5000. While 66.8% of mothers agreed that 10–14 yrs was an appropriate age for vaccination, a further 24.3% did consider 15–18 yrs to be more appropriate. Preference for older vaccination was higher in non-acceptors, with 44.3% and 31.3% considering 15–18 yrs and ≥19 yrs, respectively, to be more appropriate (data not shown). Over half (55.6%) of respondents chose small neighborhood clinics (30.0%) or school (25.6%) as

Table 2
Preferences for and acceptance of HPV vaccination.

	N[a] (%)
Willing to vaccinate if free	
Yes	798 (92.6)
No	13 (1.5)
Don't know	51 (5.9)
Amount willing to pay if not free (¥[b])	
Won't pay	38 (4.4)
100–1999	159 (18.5)
2000–4999	355 (41.3)
5000–9999	248 (28.8)
10,000–39,999	47 (5.4)
≥40,000¥ (current price)	13 (1.5)
Preferred age for vaccination (yrs)	
0–9	22 (2.6)
10–14	571 (66.8)
15–18	208 (24.3)
≥19	54 (6.3)
Preferred person to vaccinate	
Gynecologist	320 (37.2)
Pediatrician	250 (29.0)
Internist	127 (14.8)
Nurse	158 (18.3)
Others	6 (0.7)
Preferred place for vaccination	
Small neighborhood clinic	257 (30.0)
School	220 (25.6)
General hospital	169 (19.7)
Local health centre	89 (10.4)
No preference	99 (11.5)
Others	24 (2.8)

[a] Numbers do not always add up to 862 due to missing data.
[b] 100 Japanese yen = 1 US Dollar.

Table 3
Attitudes towards HPV and HPV vaccination.

	N[a] (%)
Heard of HPV	
Yes	443(52.0)
No	299(35.1)
Don't know	110(12.9)
(Perceived susceptibility) What is the chance that your adolescent daughter will be infected with HPV in her lifetime?	
Moderate/high/definitely	629(73.1)
Low/no chance	231(26.9)
(Perceived susceptibility) What is the chance that your adolescent daughter will be diagnosed with cervical cancer in her lifetime?	
Moderate/high	608(70.7)
Low/no chance	252(29.3)
(Perceived seriousness) How serious a threat do you think an HPV infection would be to health?	
Moderate/high/very high	827(96.9)
No threat/very low/low	26(3.1)
(Perceived benefits) How effective do you think the HPV vaccine is in preventing HPV infection?	
Moderately/very/extremely	827(96.6)
Slightly/not at all	29(3.4)
(Perceived benefits) How effective do you think the HPV vaccine is in preventing cervical cancer?	
Moderately/very/extremely	778(98.2)
Slightly/not at all	14(1.8)
(Perceived barriers) Do you believe the HPV vaccine is safe?	
Yes	311(36.5)
No	76(8.9)
Not sure	467(54.7)
(Perceived barriers) Do you believe the HPV vaccine has serious side effects?	
Yes	150(17.5)
No	281(32.9)
Not sure	424(49.6)
(Cues to action)	
Recommendation from a doctor	
Yes	730(85.0)
No	129(15.0)
Recommendation from the local health board	
Yes	688(80.4)
No	168(19.6)
Hearing that daughter's friends are being vaccinated	
Yes	644(76.3)
No	200(23.7)

[a] Numbers do not always add up to 862 due to missing data.

the preferred place for vaccination, with gynecologists (37.2%) and pediatricians (29.0%) as the preferred healthcare professional.

3.3. Attitudes towards HPV and HPV vaccination

Overall, 52.0% of mothers had heard of HPV and many (73.1%) correctly believed their daughter had a lifetime risk of HPV infection (Table 3). However, almost all (96.9%) mistakenly believed HPV infection posed a great threat to health and many (70.7%) believed their daughter had a moderate to high chance of developing cervical cancer.

While most mothers were positive about vaccine efficacy, with 96.6% and 98.2% believing it would offer moderate to very high protection against HPV infection and cervical cancer, respectively, great uncertainty existed about vaccine safety. Over half (54.7%) answered they were unsure if the vaccine was safe and 49.6% said they were worried about serious side effects.

3.4. Predictors of HPV vaccine acceptability

Table 4 shows the relationship between free HPV vaccine acceptance and other covariates. Most socio-demographic predictors were not associated with acceptance. In a multivariate model adjusted for age (model 1), having a higher education (p-trend = 0.036) was related to increased vaccine acceptance. However, statistical significance disappeared when adjusted for screening history (model 2).

For gynecological predictors, mothers not undergoing regular screening were less likely to accept HPV vaccination (p-trend = 0.030). However, all respondents who had been diagnosed with an HPV infection, genital warts and cervical cancer stated they would vaccinate their daughter. Having heard of HPV vaccine also increased acceptance (adjusted odds ratio, aOR = 2.58, CI = 1.47–4.53). Variables associated with having heard of the HPV vaccine are shown in Table 5.

For attitudinal predictors, mothers who believed susceptibility to (aOR = 2.30, CI = 1.34–3.92) and severity of (aOR = 3.73, CI = 1.4–9.88) HPV infection to be high, were significantly more likely to accept HPV vaccination, as were those who believed the benefits of both HPV and routine childhood vaccinations to be great. As expected, mothers with safety issues, not only regarding HPV vaccine, but childhood vaccines in general, were significantly less likely to accept HPV vaccination for their daughters (see Table 4 for all relevant odds ratios and confidences intervals). For external factors, recommendation from a doctor, the local health board and believing one's daughter's friends were being vaccinated were significantly associated with increased HPV vaccine acceptance: (aOR = 12.60, CI = 7.06–21.48), (aOR = 27.80, CI = 13.83–55.86) and (aOR = 6.53, CI = 3.71–11.24), respectively.

4. Discussion

To better understand how to achieve high uptake rates of HPV vaccination in Japan, we investigate attitudes to and acceptance of HPV vaccine in mothers of adolescent daughters.

When offered for free, acceptance of the HPV vaccine was extremely high (92%). However, when vaccinating came at a cost, only 1.5% of mothers would pay the minimum recommended price. As a conceptually appropriate price, up to ¥5000 was considered by many to be reasonable. This is similar to the cost of vaccinating a child against influenza, the most common non-routine vaccination in Japan. One Korean study also reported that, while 78.6% of adult women would vaccinate their daughter against HPV, only 3.6% were willing to pay over US$300, with around 40% stating they would pay up to US$50 [23]. Both the present and Korean study reinforce the fact that price remains a significant barrier to HPV vaccine uptake, even in economically developed countries.

In line with many other studies, the majority of respondents considered 10–14 yrs to be appropriate for HPV vaccination [4,27,28]. However, 30.6% did prefer ≥15 yrs. Interim HPV vaccine uptake rates for Sapporo are around 74% (Table 6). This may indicate that some mothers are indeed waiting until their daughter is older to vaccinate and this is probably due to the fact that parents underestimate their children's sexual activity [29]. One 2005 survey found that by the age of 15 yrs, 9.8% of Japanese schoolgirls were sexually active and this increased to 44.3% by the age of 18 yrs [30]. More effective educational materials are needed to help parents understand that maximum benefits of HPV vaccine are obtained when administered to young adolescent before the onset of sexual activity.

Regarding socio-demographic predictors, unlike several studies from the UK and North America [7,28,31,32], higher education was not a barrier to HPV vaccine acceptance. The reasons for this may be that, while most Europeans/North Americans actively discuss treatment and medication with their doctors, in Japan the "leave it to the doctor" attitude prevails. And, regardless of educational background, most patients do just that. In this study, higher education seemed to be associated with higher vaccine acceptance, but this was due more to the fact that higher education was associated with undergoing regular screening (33.3%, 47.0% and 66.0% for

Table 4
Multiple logistic regression analyses of potential predictors of free HPV vaccine acceptance.

Variables	Acceptors N (%)	Unadjusted model OR (95% CI)	Model 1 adjusted[a] OR (95% CI)	Model 2 adjusted[b] OR (95% CI)
Socio-demographic predictors				
Age (yrs)				
30–34	30 (93.8)	0.77 (0.10–5.78)		0.97 (0.13–7.39)
35–39	166 (93.8)	0.77 (0.16–3.63)		0.76 (0.16–3.63)
40–44	347 (94.3)	0.85 (0.19–3.75)		0.75 (0.17–3.36)
45–49	211 (89.8)	0.45 (0.10–1.99)		0.39 (0.09–1.78)
≥50	39 (95.1)	1		1
		p-trend = 0.257		*p*-trend = 0.161
Education				
Junior high	18 (85.7)	1	1	1
High school	291 (91.5)	1.80 (0.50–6.49)	1.89 (0.52–6.89)	1.85 (0.50–6.81)
Vocational college/junior college	387 (92.8)	2.15 (0.60–7.71)	2.54 (0.70–9.22)	2.39 (0.63–8.99)
University/graduate school	99 (96.1)	4.12 (0.85–20.01)	4.62 (0.94–22.67)	4.61 (0.87–24.56)
		p-trend = 0.071	*p*-trend = 0.036	*p*-trend = 0.060
Annual household income (¥)				
<3 million	128 (91.4)	1		
3–<5 million	277 (93.0)	1.25 (0.58–2.70)	1.28 (0.58–2.80)	1.10 (0.49–2.43)
5–<7 million	198 (93.4)	1.33 (0.59–2.96)	1.56 (0.68–3.59)	1.16 (0.49–2.75)
7–<10 million	158 (90.8)	0.93 (0.42–2.03)	1.04 (0.47–2.31)	0.70 (0.30–1.65)
≥10 million	81 (94.2)	1.52 (0.52–4.47)	1.61 (0.55–4.77)	0.94 (0.30–3.00)
		p-trend = 0.858	*p*-trend = 0.618	*p*-trend = 0.517
Mother's monthly disposable income (¥)				
<30,000	671 (92.9)	1	1	1
30,000–<50,000	67 (88.2)	0.57 (0.27–1.20)	0.68 (0.30–1.56)	0.65 (0.27–1.54)
50,000–<70,000	23 (88.5)	0.58 (0.17–2.01)	0.57 (0.17–1.97)	0.49 (0.14–1.74)
≥70,000	31 (96.9)	2.36 (0.32–17.61)	2.25 (0.30–16.86)	1.53 (0.20–11.83)
		p-trend = 0.814	*p*-trend = 0.932	p-trend = 0.557
Marital status				
Married/cohabiting	702 (92.4)	1	1	1
Separated/divorced/widowed/single	93 (94.1)	1.32 (0.56–3.15)	1.20 (0.50–2.87)	1.37 (0.99–1.90)
Gynecological predictors				
Cervical screening history				
Within 24 months	445 (93.9)	1	1	
>24 months	194 (93.3)	0.90 (0.47–1.75)	0.84 (0.43–1.63)	0.88 (0.45–1.72)
Never/don't know	157 (88.2)	0.49 (0.27–0.88)	0.49 (0.27–0.91)	0.53 (0.28–1.00)
		p-trend = 0.024	*p*-trend = 0.030	*p*-trend = 0.063
History of abnormal Pap smear				
Never	638 (92.2)	1	1	1
Once	32 (96.9)	2.62 (0.35–19.59)	2.38 (0.23–17.85)	2.00 (0.26–15.27)
Twice or more	64 (98.5)	5.42 (0.74–39.81)	5.24 (0.71–38.60)	4.39 (0.59–32.67)
		p-trend = 0.061	*p*-trend = 0.070	*p*-trend = 0.059
Heard of HPV				
No	382 (91.2)	1	1	1
Yes	416 (93.9)	1.42 (0.89–2.50)	1.57 (0.92–2.69)	1.35 (0.78–2.35)
Heard of HPV vaccine				
No	266 (88.1)	1	1	1
Yes	530 (95.2)	2.26 (1.58–4.47)	2.83 (1.54–4.86)	2.58 (1.47–4.53)
Attitudinal predicators				
Believe daughter is susceptible to HPV infection				
No	201 (87.0)	1	1	1
Yes	595 (94.6)	2.61 (1.56–4.38)	2.42 (1.42–4.13)	2.30 (1.34–3.92)
Believe HPV infection is a serious health threat				
Yes	20 (76.9)	1	1	1
No	770 (93.1)	4.05 (1.57–10.49)	4.24 (1.63–11.03)	3.73 (1.41–9.88)
Believe HPV vaccine is effective against cervical cancer				
No	14 (58.3)	1	1	1
Yes	778 (93.8)	10.90 (4.61–25.74)	11.37 (4.79–26.99)	11.41 (4.71–27.63)
Believe HPV vaccine is not safe				
No	306 (98.4)	1	1	1
Yes	51 (67.1)	0.03 (0.01–0.09)	0.03 (0.01–0.08)	0.03 (0.01–0.08)
Don't know	435 (93.1)	0.22 (0.09–0.58)	0.18 (0.06–0.53)	0.19 (0.07–0.56)
Believe vaccines are necessary to protect children's health				
No	35 (66.0)	1	1	1
Yes	758 (94.4)	8.88 (4.55–16.48)	9.89 (5.10–19.03)	9.32 (4.82–18.04)
Believe childhood vaccines have dangerous side effects				
No	110 (98.2)	1	1	1
Yes	574 (91.8)	0.21 (0.05–0.85)	0.11 (0.02–0.82)	0.11 (0.02–0.78)
Don't know	113 (91.1)	0.19 (0.04–0.86)	0.09 (0.01–0.74)	0.09 (0.01–0.79)
Cues to action				
Recommendation from a doctor				
No	90 (69.8)	1	1	1
Yes	705 (96.6)	12.22 (7.06–21.14)	12.32 (6.98–21.75)	12.60 (7.06–21.48)

Table 4 (*Continued*)

Variables	Acceptors N (%)	Unadjusted model OR (95% CI)	Model 1 adjusted[a] OR (95% CI)	Model 2 adjusted[b] OR (95% CI)
Recommendation from local health board				
No	116 (69.0)	1	1	1
Yes	676 (98.3)	25.25 (13.08–48.76)	27.52 (13.88–54.88)	27.80 (13.83–55.86)
Believe daughter's friends are getting vaccinated				
No	161 (80.5)	1	1	1
Yes	621 (96.4)	6.54 (3.80–11.26)	6.33 (3.62–11.07)	6.53 (3.71–11.24)

[a] Model 1: multiple logistic regression model adjusted for age.
[b] Model 2: multiple logistic regression model adjusted for age, annual household income, education and screening history.

Table 5
Characteristics of participants who had heard about the HPV vaccine.

Characteristic	Yes		No		*p*-Value[a]
	N	(%)	N	(%)	
Age (yrs)					
30–34	14	(43.8)	18	(56.3)	
35–39	103	(58.2)	74	(41.8)	
40–44	234	(63.8)	133	(36.2)	
45–49	174	(74.7)	59	(25.3)	
≥50	25	(61.0)	16	(39.0)	<0.0001
Marital status					
Married/cohabiting	496	(65.5)	261	(34.5)	
Separated/divorced/widowed/single	61	(59.8)	41	(40.2)	0.270
Education					
Junior high	6	(28.6)	15	(71.4)	
High school	174	(54.9)	143	(45.1)	
Vocational college/junior college	295	(70.9)	121	(29.1)	
University or more	80	(78.4)	22	(21.6)	<0.0001
Annual household income (¥[b])					
<3 million	75	(53.6)	65	(46.4)	
3–<5 million	143	(58.6)	101	(41.4)	
5–<7 million	141	(66.5)	71	(33.5)	
7–<10 million	126	(72.8)	47	(27.2)	
≥10 million	68	(81.0)	16	(19.0)	<0.0001
Mother's monthly disposable income (¥)					
<30,000	459	(63.8)	260	(36.2)	
30,000–<50,000	52	(68.4)	24	(31.6)	
50,000–<70,000	16	(61.5)	10	(38.5)	
70,000–<100,000	9	(75.0)	3	(25.0)	
≥100,000	16	(80.0)	4	(20.0)	0.066
Screening history					
Within 24 months	333	(70.4)	140	(29.6)	
>24 months	143	(69.1)	64	(30.9)	
Don't know/never	81	(45.8)	96	(54.2)	<0.0001
History of abnormal Pap smear					
Yes	75	(77.3)	22	(22.7)	
No/don't know	449	(65.1)	241	(34.9)	0.021
History of HPV infection					
Yes	12	(64.4)	1	(35.6)	
No/don't know	539	(92.3)	298	(7.7)	0.040
Diagnosis of genital warts					
Yes	14	(70.7)	6	(29.3)	
No/don't know	537	(64.7)	30	(35.3)	0.649
Diagnosis of cervical cancer					
Yes	10	(83.3)	2	(16.7)	
No/don't know	543	(64.6)	297	(35.4)	0.232

[a] Pearson's chi squared or Fisher's exact test.
[b] 100 Japanese yen = 1 US Dollar.

Table 6
Interim HPV vaccine uptake rates[a] for Sapporo between April 2011 and February 2012.[b]

School year	Age (yrs)	Number of girls in Cohort	Number 1st dose	Uptake 1st dose (%)	Number 2nd dose	Uptake 2nd dose (%)
7	12	7924	5734	72.4	5704	72.0
8	13	7959	5940	74.6	5829	73.2
9	14	8108	6130	75.6	5999	74.0
10	15	8208	6099	74.3	6066	73.9
11	16	8563	6319	73.8	6160	71.9
Total		40,762	30,231	74.2	29,728	72.9

[a] Due to unexpectedly high demand after public funding was introduced, vaccine stock decreased drastically nationwide, and between March and August 2011 only those girls who had initiated the first dose t could be vaccinated. Thus most girls could not begin vaccination until after September 2011 and consequently have not completed the 3rd dose.
[b] Data provided by the Department of Infection Control of Sapporo Health Board.

9 yrs, 12 yrs and ≥16 yrs of education, respectively; data not shown) which in turn was associated with increased vaccine acceptance.

Attitudes to childhood vaccines in general were important predictors of HPV vaccine acceptance. Parents who believed vaccines were important to protect children's health were more likely to accept HPV vaccine, while having concerns about side effects was a barrier. Similar findings have been reported in several other studies [9,31–33] and illustrate the need for public health campaigns to not only reassure parents about the well-established safety profiles of HPV vaccines, but also about the safety and importance of childhood vaccinations in general. Japan has excellent uptake rates for traditional childhood vaccines. In 2010, Diphtheria/Tetanus/Pertussis (DTP), measles and polio vaccination rates were 99%, 97% and 98%, respectively [34]. However, many parents regard new vaccines with suspicion. This is partly due to irresponsible and sensationalist reporting by the Japanese media, but also due to the fact that many vaccine preventable diseases have been eradicated, so the focus has shifted from the morbidity and mortality caused by these diseases to the potential adverse effects associated with vaccinating a healthy child. Educational materials need to be developed to help parents contextualize HPV vaccine safety and risks with the risks and consequences of having an HPV-related condition, especially cervical cancer.

Another important predictor of HPV vaccine acceptance was physician recommendation. This is consistent with numerous other studies both in Asia [10,14] and Europe/North America [8,22,31]. Since there is no school-based vaccination system in Japan, recommendations from pediatricians and gynecologists will be crucial for increasing HPV vaccine uptake. In Japan, Pap smears are performed solely by gynecologists, and this study shows that women who have regular Pap smears are more likely to have heard about and be accepting of HPV vaccination. Gynecologists are also specialists in cervical cancer and more likely to emphasize the importance of vaccinating prior to sexual debut. Pediatricians, on the other hand, are specialist in childhood immunizations and see children regularly. Consequently, mothers may have a more familiar and trusting relationship with their child's pediatrician, so pediatricians may be more influential in reassuring parents about safety issues. However, one study of Asian physicians reported that 56% of pediatricians were not confident discussing HPV related issues and desired more knowledge or training [35]. Similar studies on physicians' attitudes must be carried out in Japan to identify any potential barriers to uptake.

One other potentially serious barrier to vaccine uptake which needs further investigation is mother's screening history. HPV vaccine is a promising public health intervention for decreasing morbidity and mortality caused by cervical cancer in women who do not undergo regular cervical screening. This represents around 75% of Japanese women. However, this study demonstrates that women who do not undergo regular screening are also less likely to vaccinate their daughters against HPV, even when the barrier of cost is removed. Furthermore, since mothers have a large influence on their children's health behavior [36], it is possible that daughters of non-screened mothers will be less likely to get screened as adults. Consequently, a significant subset of the population may remain at risk for cervical cancer and as a result the effectiveness of any subsided HPV vaccination program may be substantially decreased.

Our study has several limitations that must be addressed. Firstly, due to the relatively low response rate (40.2%) and schools from one city only, selection bias may exist and consequently, participants may not be representative of the Japanese population. Secondly, owning to ethical requirements for anonymity, we could not follow-up non-responders and thus, comparisons of socio-demographic characteristics between responders and non-responders could not be made. However, Japan is a very homogeneous society with almost no ethnic or religious variations. Thus, any socio-demographic differences would be in the form of educational background and household income. Since we assessed acceptance of HPV vaccine when offered for free in a publically funded program, the influence of differences in household income would have been minimal. Regarding education, statistics from the Japan National Statistics Office show that in 2010, 40.0% of Japanese women had graduated from high school and 14.6% had a university or post-graduate degree [37]. These figures do not differ greatly from those obtained in the present study at 37.0% and 12.0%, respectively. Thirdly, the percentage of responders who had undergone biennial screening was 55.1%, considerably higher than the national average, and indicates that women who do not attend for regular cervical screening may have been underrepresented in this study. However, Japan has no cut-off age for cervical screening, so even women aged >85 yrs are included in national statistics. Almost all respondents in this study were in the 30–55 yrs age group, with the majority in their early forties and the corresponding national screening rates for these age groups are 46.1% and 48.8%, respectively [17]. Finally, this study investigated acceptability (intention to vaccinate), which might overestimate eventual uptake rates. However, as well as preliminary uptake rates of around 74% in Sapporo, one Japanese city has reported final uptake rates of over 90%, which concurs with the results of this study [38].

In conclusion, the results of this first study investigating attitudes towards and acceptance of HPV vaccination in Japanese mothers of adolescent girls are encouraging. Acceptance is high, when cost is not a barrier. They suggest that if physicians actively address safety concerns and justify why vaccination is needed at a particular age, high uptake can be achieved in a publically funded HPV vaccination program. They do also indicate, however, that further research is needed to investigate whether lower vaccine acceptance in mothers who do not undergo regular cervical screening is also reflected in actual uptake rates, since widespread disparities in cervical cancer could result.

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Systematic lymphadenectomy in endometrial cancer

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Introduction

Endometrial cancer is the most common malignancy of the female genital tract in the USA, with an estimated number of 47 130 new cases in 2012.[1] The annual number of deaths has increased from 6000 in 1997[2] to 8010 in 2012.[1] Approximately 17% of patients with endometrial cancer eventually relapse and die of this disease.[1] From this viewpoint, improvements are needed in the treatment for endometrial cancer, especially patients at high risk of a poor prognosis. On the other hand, the International Federation of Gynecology and Obstetrics (FIGO) annual report demonstrated that the survival rates of endometrial cancer have continued to increase during recent decades.[3] This trend applies to all cases, including stage IIIC. Meanwhile, surgery has been playing the leading role in treatment of endometrial cancer, and there has been no paradigm shift except for the introduction of lymphadenectomy. Whether many patients with endometrial cancer can benefit from lymphadenectomy must be determined. Two recent randomized controlled trials showed negative effects of lymphadenectomy on prognosis,[4,5] and many gynecologists have since declared at conferences that standard surgery for endometrial cancer does not include lymphadenectomy. However, such a declaration is an overgeneralization of the results of the randomized studies. In the present manuscript, we tried to interpret the results of these two randomized controlled trials properly, and discussed pitfalls of randomized controlled trials in surgical intervention. A surgical field to be treated is proposed in a group of patients who require lymphadenectomy. In addition, a new strategy for preventing leg edema, the most frequent complication after lymphadenectomy, is introduced.

Therapeutic Role of Lymphadenectomy: Previous Discussion

Before 2008, all studies regarding the role of lymphadenectomy in endometrial cancer were retrospective. Some studies supported a survival benefit of lymphadenectomy,[6–13] and others did not.[14–17] Kilgore *et al.* showed a significant survival advantage for patients who underwent multiple-node sampling compared with patients who did not undergo node sampling regardless of risk of prognosis.[6] The mean number of nodes removed in the multiple-node sampling group was 11. Trimble *et al.* showed a survival benefit of lymph node sampling for patients with stage I, grade 3 disease based on data of more than 9000 women.[7] Fanning *et al.* showed a potential survival benefit of lymphadenectomy for patients with intermediate-risk endometrial cancer.[8] Cragun *et al.* showed a significant survival advantage for patients who had 11 or more lymph nodes removed compared with patients who did not.[9] Lutman *et al.* concluded that removal of 12 or more pelvic nodes is important to improve survival of patients with stage I–II and high-risk histologic disease.[10] Chan *et al.* reported that lymphadenectomy showed a survival benefit for patients with stage I, grade 3 as well as stage II–III endometrioid endometrial cancer from US nationwide cancer data on more than 39 000 cases.[11] That study suggested that lymphadenectomy has no survival benefit for patients with stage I, grade 1–2 endometrial cancer. Abu-Rustum *et al.* concluded that removal of more than 10 regional lymph nodes is associated with improved survival of older patients with lower-stage disease and no adjuvant therapy or brachytherapy only.[12] Regional lymph nodes in endometrial cancer are usually categorized into two sections: pelvic nodes and

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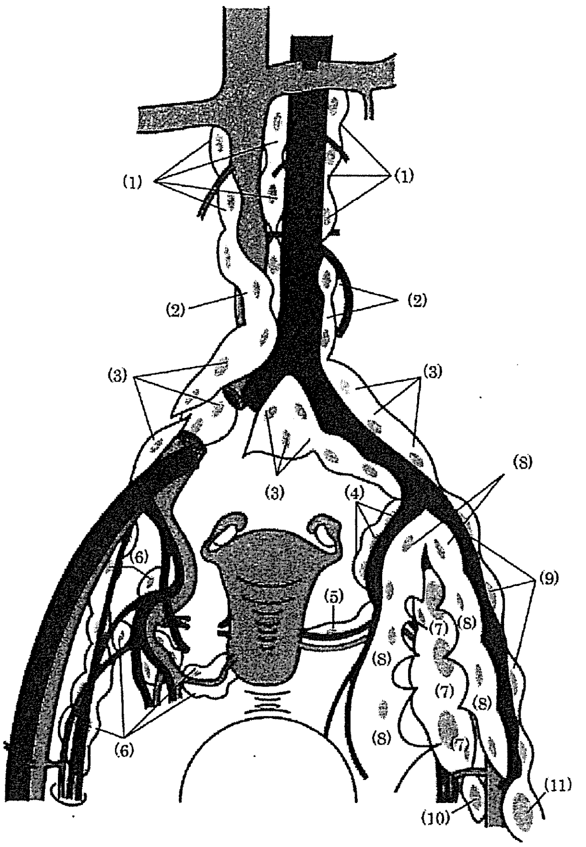

Figure 1 Regional lymph nodes of endometrial cancer. Para-aortic nodes: (1) the area above the inferior mesenteric artery (326b1); (2) the area below the inferior mesenteric artery (326b2). Pelvic nodes: (3) common iliac nodes; (4) sacral nodes; (5) para-uterine artery nodes; (6) cardinal ligament nodes; (7) obturator nodes; (8) internal iliac nodes; (9) external iliac nodes; (10) circumflex iliac nodes distal to the obturator nodes; and (11) circumflex iliac nodes distal to the external iliac nodes.

para-aortic nodes (Fig. 1). However, para-aortic lymphadenectomy has not been well valued. Mariani *et al.* focused on para-aortic nodes and showed a potential survival benefit of para-aortic lymphadenectomy in endometrial cancer.[13] They reported that removal of five or more para-aortic nodes is associated with improved survival of high-risk patients.

In 2008, Benedetti-Panici *et al.* conducted a randomized controlled trial to assess the therapeutic effect of lymphadenectomy for the first time.[4] In 2009, the results of the second randomized controlled trial to assess the therapeutic effect of lymphadenectomy were reported by A Study in the Treatment of Endometrial Cancer (ASTEC).[5] Because both randomized controlled trials showed negative effects of lymphadenectomy on prognosis, many gynecologists have declared at conferences that standard surgery for endometrial cancer does not include lymphadenectomy. However, there have been many arguments on the design of the studies. In both trials, para-aortic lymphadenectomy was not valued, and only a small number of cases underwent para-aortic lymphadenectomy (Benedetti-Panici's study, 26%; ASTEC trial, not available). Therefore, the median number of lymph nodes harvested was less than that in a Japanese study[18] (Benedetti-Panici's study, 30; ASTEC trial, 14; Japanese study, 82). Considering this limitation, appropriate interpretation of both trials would be as follows. Pelvic lymphadenectomy does not have therapeutic significance for low-risk clinical stage I endometrial cancer. Because clinical stage I includes not only low-risk patients but also intermediate- and high-risk patients, a conclusion that pelvic lymphadenectomy does not have therapeutic significance for clinical stage I endometrial cancer will cause some patients at high risk of lymph node metastasis to miss an opportunity to undergo lymphadenectomy. If lymphadenectomy has a survival benefit for intermediate- and high-risk patients, they would not be able to receive optimal treatment.

Therapeutic Role of Lymphadenectomy: Significance of Para-aortic Lymphadenectomy

In 2010, the author and colleagues presented the results of the survival effect of para-aortic lymphadenectomy (SEPAL) study in *The Lancet*[18]. The study showed no survival benefit of combined pelvic and para-aortic lymphadenectomy over pelvic lymphadenectomy alone for low-risk patients. However, a significant survival benefit of para-aortic lymphadenectomy combined with pelvic lymphadenectomy was confirmed for intermediate- and high-risk patients. In that study, the number of lymph nodes harvested was 36 in the pelvic lymphadenectomy group and 82 in the combined pelvic and para-aortic lymphadenectomy group. Surgery involving para-aortic lymphadenectomy was associated with a decreased incidence of death in patients with a hazard ratio of 0.44 (95% $CI = 0.30 - 0.64$, $P < 0.0001$) compared with surgery without para-aortic lymphadenectomy. Combined pelvic and para-aortic lymphadenectomy showed a

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