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Current Status of Endocrine Therapy for Prostate Cancer in Japan—Analysis of Primary Androgen Deprivation Therapy on the Basis of Data Collected by J-CaP

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Background: Based on the data of current status of endocrine therapy for prostate cancer registered in the Japan Study Group of Prostate Cancer (J-CaP), we conducted an analysis of primary androgen deprivation therapy (PADT) and an interim analysis of the prognosis.
Methods: Of the 26 272 cases registered in the server of J-CaP, the 19 409 cases initially receiving PADT were included in this study. The initial therapy was divided into eight categories according to its features.
Results: Of the 19 409 patients, 1513 (7.8%) were given anti-androgen monotherapy, 955 patients (4.9%) surgical castration only, 1001 patients (5.2%) surgical castration + anti-androgen, 3015 patients (15.5%) LHRH monotherapy, 1658 patients (8.5%) LH-RH + short-term anti-androgen, 10 434 patients (53.8%) LH-RH + anti-androgen, 37 patients (0.2%) watchful waiting and 796 patients (4.1%) other therapy. In progression-free survival, the prognosis was slightly better following maximum androgen blockade (MAB) in each stage.
Conclusions: The pattern of PADT is more typical in Japan compared with that in the United States. Patients who received MAB accounted for 59.0% of all the patients. MAB tends to be more often selected for patients who are rated as being at high risk on the basis of high Gleason score or PSA level upon diagnosis in each clinical stage of the disease. Investigations of the outcome are on-going and they will make clear the significance of this trend in Japan.

Key words: primary androgen deprivation therapy – prostate cancer – J-CaP

INTRODUCTION

Endocrine therapy for prostate cancer takes a more important position in Japan compared with in Europe and the United States (1). The Japan Study Group of Prostate Cancer (J-CaP) conducted an analysis of the registration status of the patients and their background variables as of October 2003, and the result has been reported previously (2). The program completed the registration of the patients in 2004, and is performing a prognosis investigation. This analysis is revealing the current status of endocrine therapy for prostate cancer in Japan.

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PATIENTS AND METHODS

J-CaP surveillance is a nationwide longitudinal observational study of patients newly starting hormone therapy for

prostate cancer from January 2001 to December 2003 (2). Institutions participating in this program registered individual cases, with entry of information pertaining to endocrine therapy via secure server over the Internet. After registration, information on the prognosis of individual registered cases and changes in treatment, if any, were entered periodically.

As of 1 August 2006, 26 272 cases were registered in the J-CaP server. Of these cases, 26 170 cases were diagnosed by biopsy as having prostate cancer and began to receive treatment between 1 January 2001 and 31 December 2003. Among these cases, the number of cases who initially received primary androgen deprivation therapy (PADT) after diagnosis of prostate cancer and on whom detailed information on the endocrine therapy given was available was 19 409 (the year of starting treatment: 2001, 5921cases; 2002, 6424 cases; and 2003, 7064 cases). The present study analyzed these 19 409 cases for the type of PADT.

Definition of Initial Endocrine Therapy

Initial endocrine therapy was defined as follows.

(1) Drugs used:
- Therapies using bicalutamide, flutamide, chrolmadinone acetate (CMA) or diethyl stilbestrol (DES) as anti-androgens.
- Therapies using 1-month or 3-month preparations of goserelin or leuprolide as LHRH agonists.

(2) Timing of starting drug treatment; definition of 'initial therapy':
- In the patients receiving monotherapy with anti-androgen, or LH-RH agonist, or castration, if combined treatment with some other drug (anti-androgen or LH-RH agonist, or vice versa), started within 120 days, such combination therapy was deemed to be initial therapy.
- In cases where the drugs were added or modified for reasons of PSA failure, clinical failure, etc., the therapy given before the addition or modification was deemed to be initial therapy.
- In cases where some other drugs were added or the ongoing drug therapy was discontinued 120 days after the start of original treatment but earlier than the occurrence of failure, the original treatment given before the addition the drugs or discontinuation was deemed to be initial therapy.
- Anti-androgen therapy given during the period between 30 days before and 60 days after the start of LH-RH agonist therapy was defined as anti-androgen therapy for the purpose of flare prevention, and was classified as short-term anti-androgen therapy.

(3) Watchful waiting:
- Patients reported as watchful waiting cases at the time of starting treatment were assigned to the category 'watchful waiting'.

(4) Others:
- Patients who received therapies other than bicalutamide, flutamide, CMA, DES, goserelin, leuprolide and surgical castration within 120 days after the start of treatment were assigned to the category 'others'.

In this way, initial therapy was divided into eight categories:

(1) anti-androgen monothreapy;
(2) surgical castration only;
(3) LHRH agonist monotherapy;
(4) LH-RH agonist + short-term anti-androgen;
(5) surgical castration + anti-androgen;
(6) LH-RH agonist + anti-androgen;
(7) watchful waiting;
(8) other.

The categories (5) and (6) are defined as maximal androgen blockade (MAB). The categories 'watchful waiting' and 'others' were excluded from part of this interim analysis of prognosis because the number of patients assigned to these two categories was too small.

Analysis of Prognosis

Although the data are still immature for complete analysis, the interim analyses of prognosis on progression-free survival and overall survival were done. When calculating the progression-free survival, the first day of endocrine therapy was counted as the starting point. Events taken into account in calculation of the progression-free survival were PSA failure, clinical failure and death. If multiple events occurred in the same patient, the time of appearance of the first of these events was deemed as the time of event in this patient. In calculation of overall survival, the first day of endocrine therapy was counted as the starting point. Death (from cancer or other causes) was the event taken into account in calculation of overall survival, and the number of days until the event occurred was calculated. Cases where no event occurred were censored at the time of the final evaluation of the prognosis for both the progression-free survival and overall survival.

Statistical analysis was performed using JMP5.1.2 (3). Trends of hormonal therapy were tested by chi-square test and the Cochran–Mantel–Haenszel test. Prognosis analyses were performed using Kaplan–Meier methods. Survival analysis was tested by the log-rank test. Microsoft Excel was employed for depicting survival curves.

RESULTS

Of the 19 409 patients who initially received PADT after diagnosis of prostate cancer, 1513 patients (7.8%) were initially treated with anti-androgen monotherapy, 955 patients (4.9%) with surgical castration only, 3015 patients (15.5%) with LHRH monotherapy, 1658 patients (8.5%)

with LHRH + short-term anti-androgen, 1001 patients (5.2%) with surgical castration + anti-androgen, 10 434 patients (53.8%) with LHRH + anti-androgen, 37 patients (0.2%) with watchful waiting and 796 patients (4.1%) with other therapy (Fig. 1). Thus, 11 435 patients (59.0%) of all cases received MAB therapy. Table 1 shows the distribution type of institution, age at diagnosis, PSA at the time of diagnosis and Gleason score. Table 2 shows the distribution of T category, N category, M category (according to UICC, *TNM Classification of the Malignant Tumors*, 5th edn (4)) and clinical stage.

When analyzed by T category (Fig. 2), the percentage of cases receiving LHRH agonist + anti-androgen or surgical castration + anti-androgen rose as the T category advanced ($P < 0.0001$). A similar trend was also noted as the clinical stage (rated on the basis of not only T category but also N and M categories) advanced ($P < 0.0001$; Fig. 2). When the endocrine therapy for T1-T2N0M0 cases was analyzed in relation to risk category according to the classification of D'Amico et al. (5) (Fig. 2), the percentage of cases treated with LHRH + anti-androgen or castration + anti-androgen (MAB) increased as the risk became higher ($P < 0.0001$).

When the relationship between the age at the time of diagnosis and endocrine therapy was analyzed for each clinical stage (Fig. 3), the percentage of cases receiving MAB tended to decrease slightly as the age became higher, irrespective of the clinical stage. Among patients over 80 years of age, the percentage of cases receiving surgical castration tended to rise slightly. According to a previously reported study in the United States on the selection of endocrine therapy for prostate cancer, treatment of localized prostate cancer with LHRH agonists was often selected for patients over 80 years of age irrespective of disease stage and histological features (6). Therefore, although direct comparison between Japan and the United States is not possible, there seems to be some differences in the selection of therapy for prostate cancer between the two countries. When the relationship between PSA level at the time of diagnosis and endocrine therapy was analyzed for each clinical stage of prostate cancer (Fig. 4), the percentage of cases treated with LHRH agonist + anti-androgen or surgical castration + anti-androgen tended to be higher in cases with PSA over 20, irrespective of disease stage ($P < 0.05$ in all stages). Also in the analysis in relation to Gleason score (Fig. 5), the percentage of cases treated with LHRH agonist + anti-androgen or surgical castration + anti-androgen became higher as the Gleason score rose irrespective of clinical stage of the disease in the cases with Gleason score of 5 or more ($P < 0.001$ in stages II and III). Combined together, these results indicate that patients with high risk (rated on the basis of PSA level at the time of diagnosis and Gleason

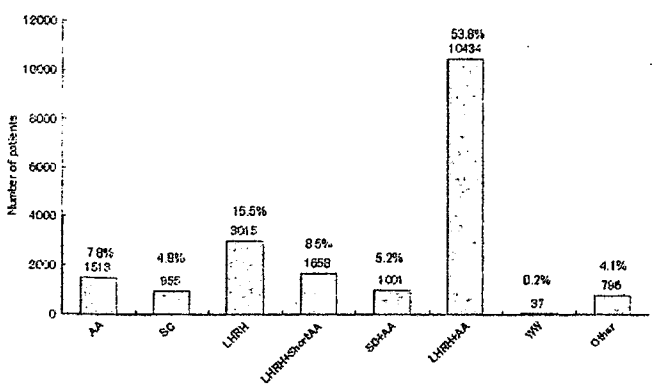

Figure 1. Initial endocrine therapy. AA, anti-androgen monotherapy; SC, surgical castration only; SC + AA, surgical castration + anti-androgen; LHRH, LH-RH agonist monotherapy; LHRH + shortAA, LH-RH agonist + short-term anti- androgen; LHRH + AA, LH-RH agonist + anti-androgen; WW, watchful waiting.

Table 1. The distribution of type of institution, age at the diagnosis, PSA at the time of diagnosis and Gleason score at the time of diagnosis by year of registration

	2001	2002	2003	Total	%
Type of institution					
University Hospital	1180	1221	1185	3586	18.5
Public Hospital	4179	4501	5139	13819	71.2
Private Hospital	562	702	740	2004	10.3
Total	5921	6424	7064	19409	100.0
Age at Diagnosis					
<60	171	183	164	518	2.7
60–64	334	381	410	1125	5.8
65–70	713	776	822	2311	11.9
70–74	1476	1578	1757	4811	24.8
75–79	1625	1831	2124	5580	28.7
≥80	1602	1675	1787	5064	26.1
Total	5921	6424	7064	19409	100.0
PSA at Diagnosis					
0–4	220	243	258	721	3.7
4–10	1108	1340	1620	4068	21.0
10–20	1050	1223	1454	3727	19.2
>20	3532	3607	3718	10857	55.9
No description	11	11	14	36	0.2
Total	5921	6424	7064	19409	100.0
Gleason score					
2–4	502	407	415	1324	6.8
5–6	1262	1506	1832	4600	23.7
7	1246	1634	1967	4847	25.0
8–10	1541	2139	2421	6101	31.4
No description	1370	738	429	2537	13.1
Total	5921	6424	7064	19409	100.0

PSA, prostate specific antigen.

Table 2. The distribution of T category, N category, M category and clinical stage by year of registration

	2001	2002	2003	Total	%
T stage					
T1a,b	193	171	133	497	2.6
T1c	946	1122	1455	3523	18.2
T2a	912	1047	1198	3157	16.3
T2b	900	1009	1222	3131	16.1
T3	2302	2352	2399	7053	36.3
T4	636	687	621	1944	10.0
No description	32	36	36	104	0.5
Total	5921	6424	7064	19409	100.0
N factor					
N0	4507	4982	5717	15206	78.3
N1	969	977	929	2875	14.8
NX	413	429	382	1224	6.3
No description	32	36	36	104	0.5
Total	5921	6424	7064	19409	100.0
M factor					
M0	3829	4303	5112	13244	68.2
M1	145	128	92	365	1.9
M1a	78	81	67	226	1.2
M1b	1504	1546	1367	4417	22.8
M1c	99	76	105	280	1.4
Mx	234	254	285	773	4.0
No description	32	36	36	104	0.5
Total	5921	6424	7064	19409	100.0
Clinical Stage					
II	2370	2719	3390	8479	43.7
III	998	1088	1215	3301	17.0
IV	2043	2079	1905	6027	31.1
No description	510	538	554	1602	8.3
Total	5921	6424	7064	19409	100.0

score) at each clinical stage of disease were more frequently treated with MAB therapy rather than LH-RH agonist or anti-androgen monotherapy.

An interim analysis on the prognosis was performed using the data on 19 327 cases on whom prognosis data were available for at least one point of evaluation. The number of events was 5723 and the median follow-up period was 1441 days in the progression-free survival analysis. In the overall survival analysis, the number of events was 2330.

Data on prognosis was best following treatment with castration + anti-androgen for stage II cases, and was best following treatment with castration + anti-androgen or LHRH agonist + anti-androgen for stage III cases in the

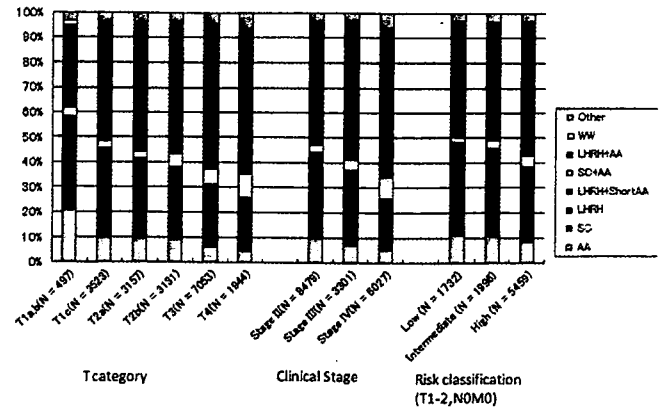

Figure 2. Initial endocrine therapy trends according to T category, clinical stage and D'Amico's risk classification. (Abbreviations as in Fig. 1.)

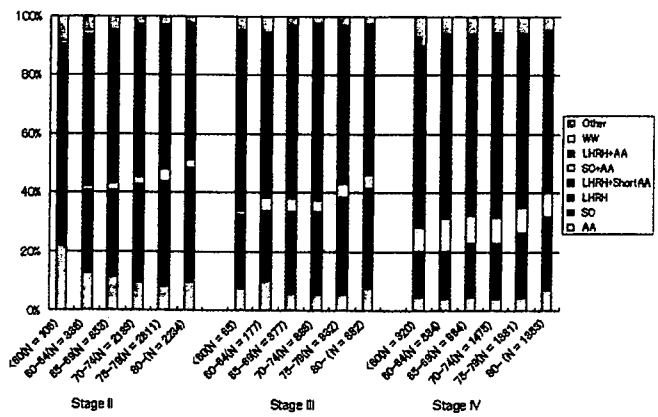

Figure 3. Initial endocrine therapy according to age in clinical stages II, III and IV. (Abbreviations as in Fig. 1.)

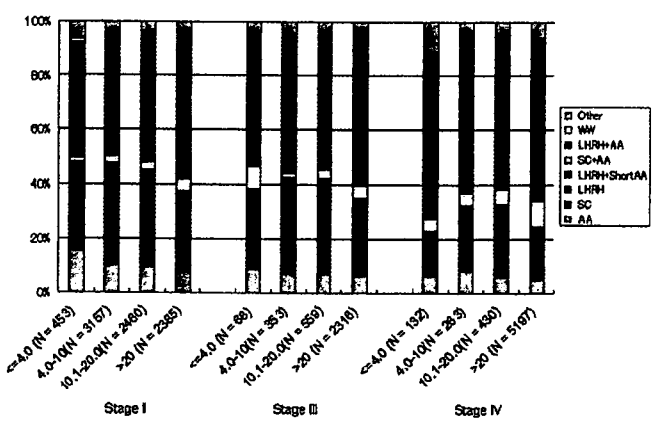

Figure 4. Initial endocrine therapy according to PSA level at the time of diagnosis in clinical stages II, III and IV. (Abbreviations as in Fig. 1.)

period until about 3 years after the start of treatment in progression-free survival (Fig. 6). As described above, MAB therapy tends to be selected more frequently for high-risk

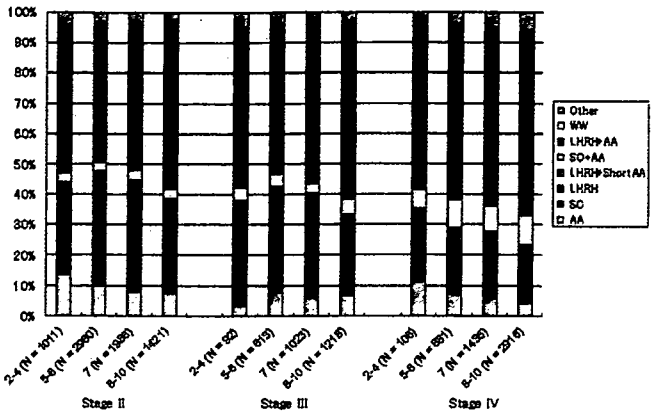

Figure 5. Initial endocrine therapy according to Gleason score at the time of diagnosis in clinical stages II, III and IV. (Abbreviations as in Fig. 1.)

patients at each clinical stage of the disease, but in stage II and III cases, MAB therapy exerts an efficacy which is high enough to offset the influence of background variables ($P < 0.0001$, log-rank test, MAB vs not MAB). In stage IV cases, no evident difference in prognosis was noted among different methods of endocrine therapy. In the overall survival, the prognosis was slightly better following MAB therapy in stage III ($P = 0.006$) and stage IV cases ($P = 0.001$), but the number of events was too small to allow any definite conclusion, and further prognosis investigation is needed (Fig. 7).

DISCUSSION

J-CaP surveillance was started to investigate the current status of endocrine therapy for prostate cancer in Japan by collecting data on many cases of prostate cancer registered across Japan (2). The data collected in this program reflect the current status of the clinical practice on adoption and modification of the strategy for treatment of prostate cancer in Japan based on the therapeutic policy at individual medical facilities. The Japanese Urological Association (JUA) strongly recommends that diagnosing prostate cancer and taking records of its diagnosis should be based on the 'General Rule for Clinical and Pathological Studies on Prostate Cancer' (7). Therefore, there seems to be little difference in the method of diagnosis and records of prostate cancer among different facilities. As shown in Table 1, 18.5% of all cases analyzed were patients treated at university hospitals. This distribution of data in this study differs from that in CaPSURE in which 9.1% of all cases were registered at academic institutions (8). We may therefore say that the cases analyzed in this study reflect the current status of treatment of prostate cancer throughout Japan, including cases treated at academic institutions as well.

The present study was a survey of the actual state of treatment and not a randomized comparison within an experimental frame. The survey revealed that, when a method of treatment was selected, various background variables were

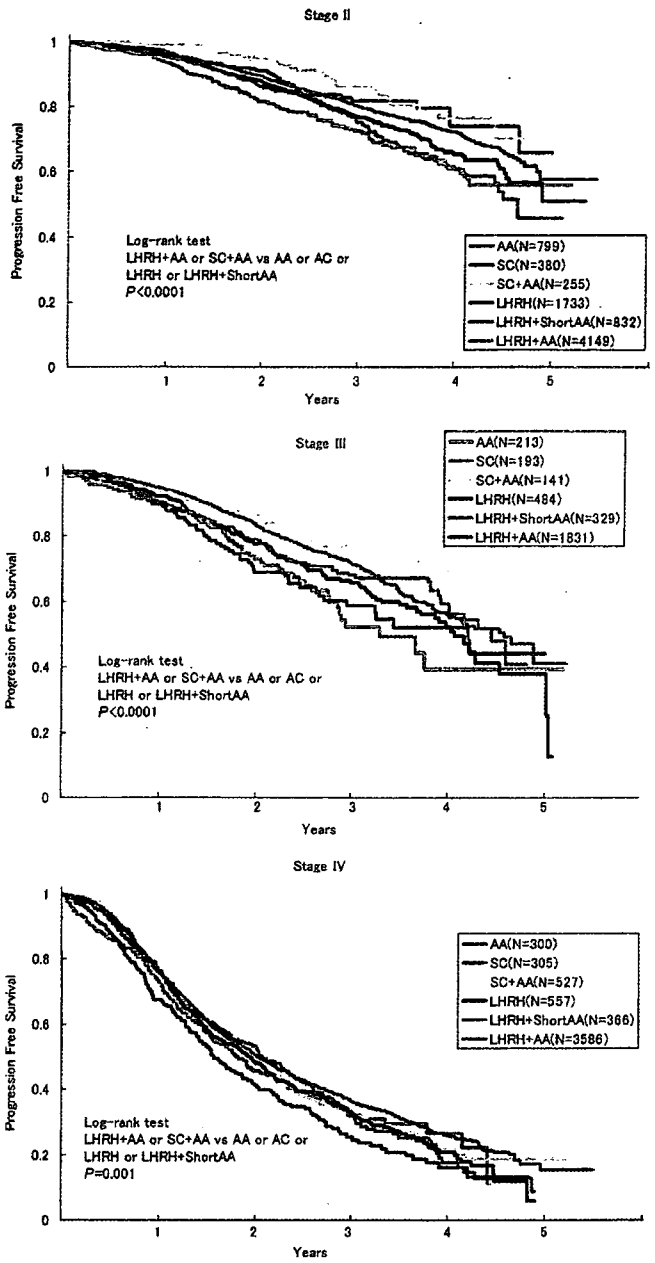

Figure 6. Progression-free survival in (a) clinical stage II, (b) clinical stage III and (c) clinical stage IV. (Abbreviations as in Fig. 1.)

taken into account, and MAB therapy tended to be often selected for high-risk patients, as stated above. It is difficult, therefore, to make any conclusion about responses to endocrine therapy corrected for the influence from background variables. To our knowledge, no previous study has analyzed data from so many cases registered from a given district as in the present study. No previous report examined so detailed a characterization of individual methods of treatment and dealt with analysis of endocrine therapy divided into such small categories as in the present study. If the data collected by this study group are summarized, we may say that MAB therapy is possibly superior in terms of progression-free

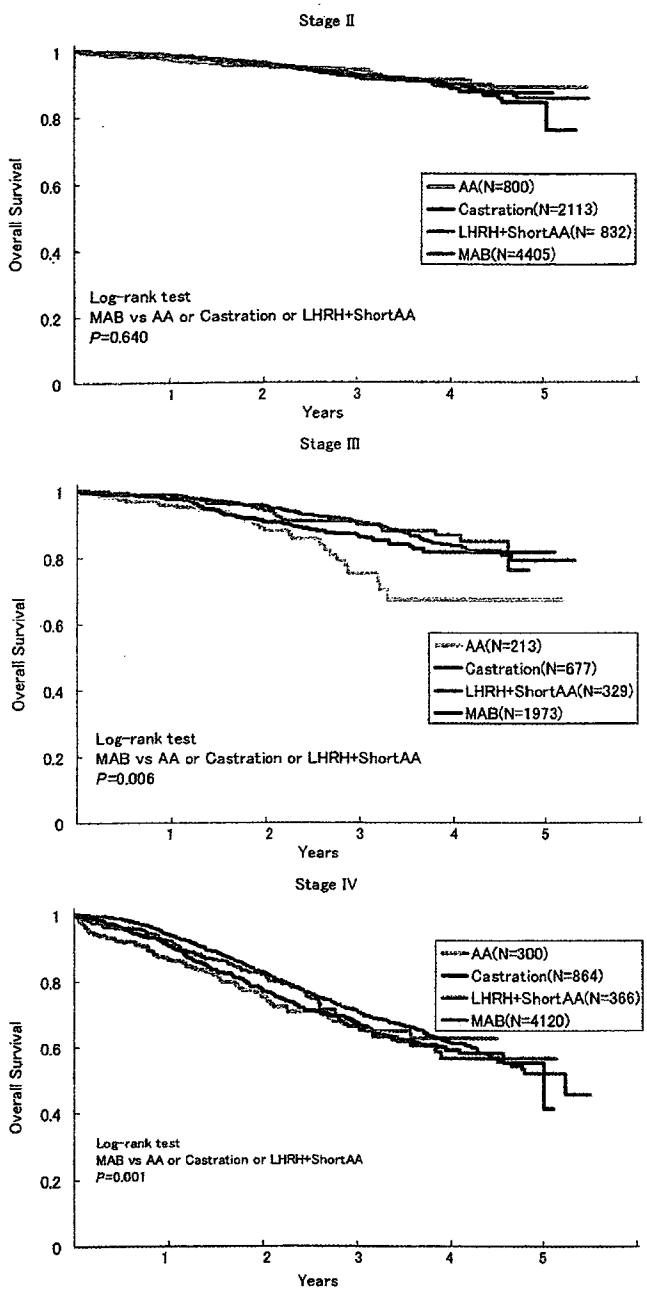

Figure 7. Overall survival in (a) clinical stage II, (b) clinical stage III and (c) clinical stage IV. (Abbreviations as in Fig. 1.)

survival for stage II and III cases and overall survival for stage IV cases. The *Guidelines on Diagnosis and Treatment of Prostate Cancer*, edited by JUA, and published in May 2006 (9), also quote the results of Japanese randomized controlled trials, suggesting the effectiveness of endocrine therapy alone for localized prostate cancer (10). Endocrine therapy has been often selected for the treatment of localized prostate cancer relatively extensively in Japan. Accumulation of data on outcomes of this kind of treatment will facilitate review of the clinical stages of prostate cancer indicated for endocrine therapy (1). When such a review is made, the usefulness of MAB needs to be evaluated on the basis of a general assessment of efficacy, adverse events, QOL and economic aspects.

J-CaP now plans to conduct a survey of adverse events, with a goal of evaluating the efficacy of endocrine therapy for prostate cancer in more detail while taking into account adverse events and QOL. J-CaP also plans to conduct a further long-term prognosis survey and an investigation of cause of death of the patients who died. If the data from these surveys are collected and analyzed, it will be possible for us to make more detailed reports on the advantages and disadvantages of endocrine therapy alone, not only for advanced prostate cancer but also for localized prostate cancer. At that time, we must discuss the economic aspect of how long the endocrine therapy should be continued.

The role played by endocrine therapy for localized prostate cancer in Japan differs markedly from that in Europe and the United States. According to the prostate registry operated by JUA (11), which included 4529 registered patients who were diagnosed with prostate cancer in 2000, PADT was selected as an initial treatment for 45.9% of the 2671 patients with stage T1c-T3N0M0 prostate cancer. In the United States, the number of cases with localized prostate cancer treated with PADT has also been increasing, according to the CaPSURE report and the SEER data, but the number in the United States is less than half of that in Japan (6,8). A recent analysis made by CaPSURE yielded a noteworthy finding as to the background variables of patients for whom PADT was selected (12).

In the existing guidelines pertaining to the treatment of localized prostate cancer, especially in the United States, there is hardly any statement that recommends the use of PADT. This may be explained by the following factors: (1) PADT is viewed only as a means of conservative treatment of advanced cancer; and (2) there is concern over androgen deprivation syndrome appearing as an adverse reaction to PADT (1). In Europe and the United States, few high-quality clinical studies have been carried out on PADT used for the treatment of localized prostate cancer, and clinical evidence is absent.

Then, why has the use of PADT for the treatment of localized prostate cancer been increasing in the United States in recent years? Shahinian et al. viewed selection of PADT as a Wennberg's practice style hypothesis and explained that it is primarily dependent on the view of individual urologists (13). A Wennberg's hypothesis is that, when there is uncertainty about the optimal treatment course, use of medical interventions is determined by the characteristics of the physician. In other words, the treatment provided depends more on the physician who is treating the patient than on specific characteristics of the patient's disease. However, the analysis made by Kawakami et al., cited above, involved a comparison between radical therapy and palliative therapy and suggested that the selection of PADT was based on the relatively evident features of patient's background and the results of recent clinical studies demonstrating the efficacy of this

therapy, rather than being dependent on the personal preference of individual urologists (12). We expect that discussions over the involvement of PADT in the treatment of localized prostate cancer will increase in the future.

Conflict of interest statement
None declared.

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ORIGINAL ARTICLE

Bicalutamide 80 mg combined with a luteinizing hormone-releasing hormone agonist (LHRH-A) versus LHRH-A monotherapy in advanced prostate cancer: findings from a phase III randomized, double-blind, multicenter trial in Japanese patients

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To compare combination therapy with bicalutamide 80 mg and a luteinizing hormone-releasing hormone agonist (LHRH-A) versus LHRH-A alone in Japanese men with untreated advanced prostate cancer. A total of 205 patients with stage C/D prostate cancer were randomized to either LHRH-A + once-daily oral bicalutamide 80 mg or placebo. Primary study variables have been reported previously. Secondary variables included: time to achieve prostate-specific antigen ≤ 4 ng/ml, time-to-treatment failure (TTTF), time-to-disease progression (TTP), overall survival (OS), adverse events and adverse drug reactions. Following combination therapy with bicalutamide 80 mg, there were significant ($P<0.001$) advantages over LHRH-A alone in terms of TTTF and TTP, but the difference in the interim OS was not statistically significant. First-line combination therapy with bicalutamide 80 mg in Japanese patients with advanced prostate cancer offers significant benefits over LHRH-A alone, with respect to TTTF and TTP. Follow-up for OS continues.
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Keywords: clinical trials; advanced prostate cancer; hormone therapy; LHRH-A; bicalutamide

Introduction

Combined androgen blockade (maximum androgen blockade), consisting of an antiandrogen plus either a luteinizing hormone-releasing hormone agonist (LHRH-A) or orchiectomy, is standard care in Japan for patients with advanced prostate cancer.[1,2]

Although the rationale for administering combination therapy is strong, results from individual clinical studies have been mixed.[3] The Prostate Cancer Trialists' Collaborative Group (PCTCG) conducted a meta-analysis of all available randomized trials (27 studies) of combination therapy versus castration alone.[4] The results of this large analysis ($n=8275$) demonstrated a small but statistically significant survival benefit, with the addition of a nonsteroidal antiandrogen (nilutamide or flutamide), to castration monotherapy ($P=0.005$). Conversely, combination therapy with the steroidal antiandrogen cyproterone acetate was associated with a 13% increase in the risk of death ($P=0.04$).

First approved in 1995, bicalutamide is a nonsteroidal antiandrogen. A Phase III study to assess the efficacy of bicalutamide 50 mg combination therapy was initiated in Caucasian men using a flutamide combination regimen, which was considered standard care at that time, as the active comparator.[5] The results demonstrated that bicalutamide 50 mg combination therapy was at least as effective as flutamide combination therapy. In addition, the bicalutamide regimen was better tolerated, with a significantly lower rate of diarrhea ($P<0.001$) and fewer withdrawals due to adverse events.

Using data from the study conducted by Schellhammer *et al.*,[5] together with findings from the PCTCG meta-analysis,[4] a retrospective analysis was recently conducted to indirectly assess the efficacy of bicalutamide 50 mg combination therapy with that of castration alone. This analysis demonstrated that bicalutamide 50 mg combined with castration results in a 20% reduction in the risk of mortality compared with castration alone.[3]

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This estimated benefit is larger than that observed with the other antiandrogens in the PCTCG analysis.

To date, only three studies have investigated combination hormonal therapy in Japanese men with advanced prostate cancer. Two of these studies assessed combination therapy using the steroidal antiandrogen chlormadinone acetate, and one used the nonsteroidal antiandrogen flutamide. Neither of the steroidal antiandrogen studies showed an improvement in overall survival (OS) with combination therapy compared with LHRH-A alone.[6,7] The use of the nonsteroidal antiandrogen flutamide combined with an LHRH-A was studied in 161 Japanese patients.[8] In this unblinded study, combination therapy was superior to LHRH-A monotherapy in terms of reduction of prostate-specific antigen (PSA) level and time to PSA progression.

To further elucidate the effect of adding an antiandrogen to LHRH-A, we initiated a randomized, double-blind, multicenter study. As bicalutamide has good compliance and tolerability findings, it was selected for investigation in this study.[9] In most countries, bicalutamide is given at a dose of 50 mg when used in combination with an LHRH-A. However, based on pharmacokinetic and pharmacodynamic data, the approved dose of bicalutamide in Japanese men is 80 mg per day. We had previously conducted a pilot study of LHRH-A in combination with bicalutamide 80 mg per day, which identified no significant safety concerns.[10] Therefore, we selected the 80 mg dose for our phase III study in Japanese men.[11,12]

Primary efficacy findings (median follow-up 66 weeks) from this phase III study have previously been reported in an interim publication.[9] At 12-weeks following treatment initiation, bicalutamide 80 mg combination therapy significantly improved the proportion of patients achieving PSA levels of $\leqslant 4$ ng/ml compared with LHRH-A alone (79.4 versus 38.6%, respectively; $P<0.001$). Bicalutamide also improved 12-week overall tumor-response rates compared with LHRH-A alone (77.5 versus 65.3%, respectively; $P=0.063$). Importantly, safety was not compromised with the addition of a second therapy (withdrawal rate due to adverse drug reactions 8.8% bicalutamide versus 10.9%, LHRH-A alone).

This is the first double-blind, controlled clinical trial to assess bicalutamide combination therapy versus castration alone, in men with prostate cancer. Here, we report a longer-term analysis of the secondary outcome variables from this study, at a median of 127 weeks. We discuss time to achieve a PSA level of $\leqslant 4$ ng/ml, time-to-treatment failure (TTTF), time-to-disease progression (TTP), OS and the incidence of adverse events and adverse drug reactions. These results were first presented in brief at the American Society of Oncology (ASCO) annual meeting in 2005. Treatment responses subsequent to disease progression, including antiandrogen withdrawal syndrome and responses to second-line bicalutamide 80 mg treatment are also discussed.

Patients and methods

Study design and treatment

Financial sponsorship for this trial was provided by AstraZeneca. The design of this randomized, double-blind, multicenter trial has been reported previously.[9] All patients received LHRH-A (goserelin acetate 3.6 mg or leuprorelin acetate 3.75 mg) by subcutaneous depot injection every 4 weeks. Patients were randomized 1:1 to either oral bicalutamide 80 mg or matching placebo, once daily, using a double-blind method. As the minimum duration of follow-up time exceeded 6 months, the code was broken in September 2002 for ethical reasons. Subsequently, patients in the LHRH-A only group discontinued placebo and received LHRH-A alone, and patients in the bicalutamide 80 mg combination therapy group continued combination therapy in an open-label manner. Combination therapy was continued until November 2003, or until either disease progression or other withdrawal criterion occurred.

If a patient in the combined therapy group experienced disease progression during open-label treatment, bicalutamide was discontinued and the patient was monitored for antiandrogen withdrawal syndrome. Any subsequent therapy was initiated at the investigator's discretion. Patients in the LHRH-A only group who had disease progression were treated at the investigator's discretion, with addition of bicalutamide 80 mg being an option.

Patients

Patients with histologically confirmed, previously untreated advanced (stage C/D) prostate cancer were recruited, February 2000–December 2001, at 49 Japanese centers. Inclusion and exclusion criteria have been described previously.[9] All patients provided written, informed consent before enrolment.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice requirements. The protocol was approved at all participating institutions by an Institutional Review Board. An Independent Data Monitoring Committee was established to conduct annual interim assessments of findings from the study.

Assessments

The primary lesion and metastatic sites were assessed clinically and by appropriate imaging techniques (scintigraphy, computed tomography, magnetic resonance imaging, ultrasound, X-ray) at baseline, 12 weeks and as appropriate. Efficacy assessments were performed, as described previously,[9] and were measured at baseline, weeks 1, 4, 5, 8 and 12 after the start of treatment, and then every 4 weeks until either disease progression or treatment withdrawal. Following this, patients were evaluated annually for progression and survival. Outcome variables were established using the Japanese Urological Association Criteria, edition 2.[13]

Details of adverse events were recorded at each visit and up to 4 weeks after treatment withdrawal. Events for which a causal relationship to the study drug(s) could not be excluded were classified as adverse drug reactions.

Outcome variables and statistical analysis

All patients who received at least one dose of study medication were included in the safety and primary efficacy analyses (intention-to-treat analysis).

The primary study variables were the PSA normalization rate (defined as the proportion of patients with a normal (≤4 ng/ml) PSA level) and overall tumor-response rate (defined as the proportion of patients with a partial response or better) at 12 weeks and the rate of withdrawals due to adverse drug reactions at the time of data cutoff (January 22, 2004). Calculations on the sample size required assumed that these variables would be similar to those observed in previous studies.[9] The percentage of withdrawals due to adverse drug reactions in the combined androgen blockade (CAB) group was considered clinically acceptable if the upper limit of the 95% confidence interval (CI) for the difference between the two treatment groups was <12.5%. Based on these assumptions, the required sample size (90% power, two-sided significance level of 0.05) was 200 patients (100 in each treatment group).

Secondary variables were: time to achieve PSA levels of ≤4 ng/ml; TTTF; TTP; OS; quality-of-life (to be reported elsewhere); and the incidence of adverse events/adverse drug reactions. TTTF was defined as the number of days between the first dose of the study treatment (earliest of LHRH-A or randomized therapy) and the earliest of study treatment withdrawal, disease progression or death. TTP was defined as the number of days between the first dose of study treatment and either disease progression or prostate cancer death. The relapse of primary lesion and/or metastatic sites assessed by imaging techniques, and/or PSA relapse (e.g. increases at three consecutive measurements) were judged to be disease progression.

Following disease progression and discontinuation of bicalutamide in the combination group, no change in PSA or reduced PSA levels were described as antiandrogen withdrawal responses. Among patients who had disease progression following LHRH-A alone, and were subsequently given bicalutamide 80 mg in an open-label fashion, a ≥50% reduction in PSA levels constituted a response to second-line combination treatment.

The Cox proportional hazards model was used to analyze the time-to-event data. In addition, time to achieve PSA ≤4 ng/ml, TTTF and TTP were compared between the treatment groups using the log-rank test.

Results

Patient demographics and dispositions

Patients ($n=205$) were randomized to either bicalutamide 80 mg combination therapy ($n=102$) or LHRH-A alone ($n=103$). Two patients in the LHRH-A only arm withdrew before therapy. As reported previously, patient demographics for the two treatment groups were well matched (Table 1).

Treatment was discontinued early in 54/102 patients who received bicalutamide 80 mg combination therapy, and in 78/101 of the patients who received LHRH-A alone (Figure 1). Only one patient, who received combination therapy, could be not followed-up for efficacy.

Efficacy variables

Here, we report the effect of bicalutamide on the secondary efficacy variables of the study at a median follow-up of 127 weeks (Table 2).

Table 1 Patient demographics at baseline

Characteristic	*Bicalutamide 80 mg combination therapy*, n (%)	*LHRH-A alone*, n (%)
N	102 (100)	101 (100)
Age (years)		
<75	53 (52.0)	50 (49.5)
≥75	49 (48.0)	51 (50.5)
PSA (ng/ml)		
<60	40 (39.2)	37 (36.6)
≥60	62 (60.8)	64 (63.4)
Histopathological class		
Well	3 (2.9)	6 (5.9)
Moderate	52 (51.0)	55 (54.5)
Poor	47 (46.1)	40 (39.6)
Clinical stage		
C/D1	59 (57.8)	57 (56.4)
D2	43 (42.2)	44 (43.6)
Disease stage		
T2	3 (2.9)	1 (1.0)
T3	83 (81.4)	77 (76.2)
T4	16 (15.7)	23 (22.8)
Nodal stage		
N0	74 (72.5)	63 (62.4)
N1	28 (27.5)	38 (37.6)
Metastatic status		
M0	59 (57.8)	58 (57.4)
M1	43 (42.2)	43 (42.6)
Lesion of metastases		
Bone	40 (39.2)	40 (39.6)
Lymph node	28 (27.5)	38 (37.6)
Other	2 (2.0)	3 (3.0)
LHRH-A		
Goserelin acetate	77 (75.5)	79 (78.2)
Leuprorelin acetate	25 (24.5)	22 (21.8)
Performance status		
0, 1	99 (97.1)	99 (98.0)
2	3 (2.9)	2 (2.0)

Abbreviations: LHRH-A, luteinizing hormone-releasing hormone agonist; PSA, prostate-specific antigen.

Time to achieve a prostate-specific antigen level of ≤4 ng/ml. Time to achieve a PSA level of ≤4 ng/ml was significantly shorter with bicalutamide 80 mg combination therapy than with LHRH-A alone (8.1 weeks versus 24.1 weeks, respectively; hazard ratio (HR) 3.96; 95% CI 2.77–5.66; $P<0.001$) and occurred in 96/102 (94.1%) patients in the combination therapy arm and 59/101 (58.4%) patients in the LHRH-A only arm ($P<0.001$).

Time-to-treatment failure. Time-to-treatment failure was significantly longer with bicalutamide 80 mg combination therapy than with LHRH-A alone (Figure 2). Treatment failure occurred in 54/102 (52.9%) patients at a median of 117.7 weeks in the combination therapy group and in 78/101 (77.2%) patients at a median of 60.3 weeks in the LHRH-A only group (HR 0.54; 95% CI 0.38–0.77; $P<0.001$).

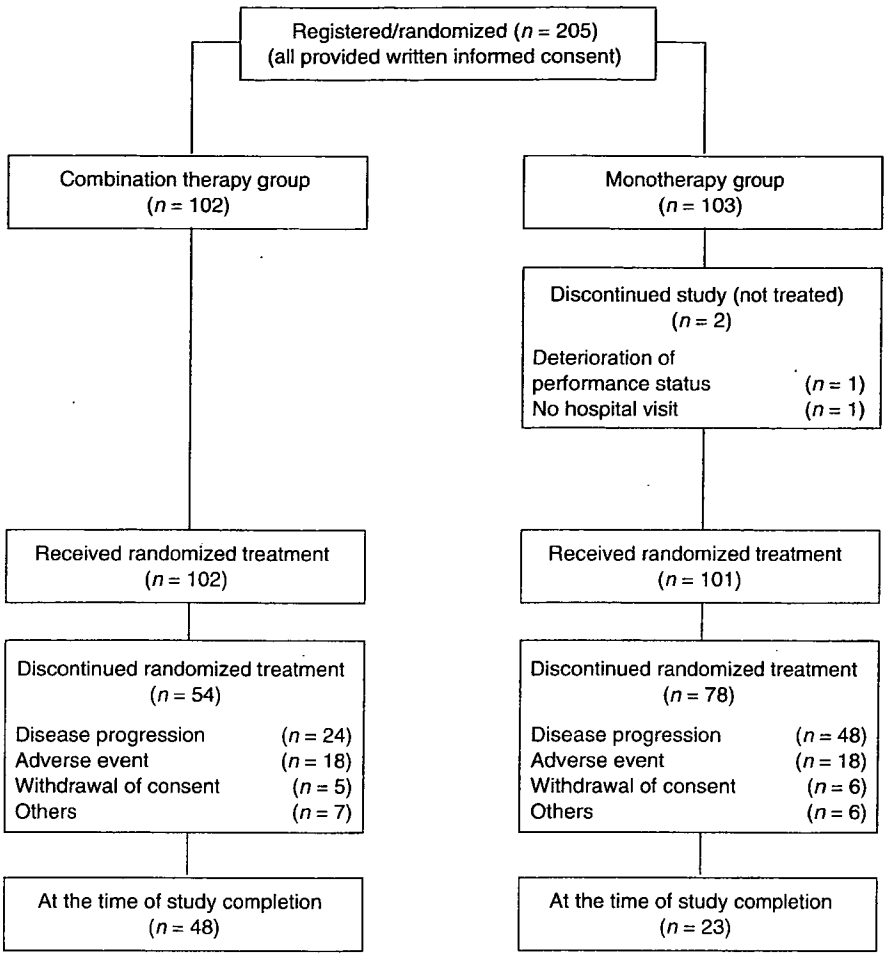

Figure 1 Outline of trial.

Table 2 Efficacy findings: bicalutamide 80 mg in combination with LHRH-A

Secondary efficacy variable	*Bicalutamide 80 mg combination therapy*	*LHRH-A alone*	*Log-rank test (P-value)*
N	102	101	
No. of patients with PSA ⩽ 4 ng/ml	96	59	
Median time to PSA ⩽ 4 ng/ml, weeks (range)	8.1 (2.9–91.6)	24.1 (3.1–119.7)	<0.001
No. of patients with treatment failure	54	78	
Median time to treatment failure, weeks (range)	117.7 (2.9–186.9)	60.3 (3.1–185.1)	<0.001
No. of progression events	30	57	
Time to progression, weeks (range)	Not yet reached (0.1–188.1)	96.9 (7.1–190.1)	<0.001
No. of deaths	13	18	
Time to mortality, weeks (range)	Not yet reached (8.3–202.0)	Not yet reached (8.1–190.1)	Not significant

Abbreviations: LHRH-A, luteinizing hormone-releasing hormone agonist; PSA, prostate-specific antigen.

Time to disease progression. Overall, disease progression occurred in 30/102 (29.4%) and 57/101 (56.4%) patients in the combination therapy and LHRH-A only groups, respectively. Patients in the combination therapy group benefited from a significantly longer TTP than patients in the LHRH-A alone group (HR 0.40; 95% CI 0.26–0.63; $P<0.001$; Figure 3). The median TTP in the LHRH-A group was 96.9 weeks; the median TTP has yet to be reached in the combination group.

Time-to-disease progression among patients with different stages of prostate cancer was investigated as part of an exploratory analysis. A greater effect was seen in bicalutamide 80 mg combination therapy versus LHRH-A alone in the 99 patients with stage C locally advanced disease (134.1 weeks versus median TTP not yet reached, $P<0.001$; Figure 4).

Overall survival. To date, 13/102 (12.7%) patients in the bicalutamide 80 mg combination group and 18/101 (17.8%) in the LHRH-A only group have died. The disease-specific survival findings were similar for the treatment groups (Figure 5).

Exploratory analysis of combined PSA data from the treatment groups demonstrated a significantly lower disease-specific mortality rate among patients who

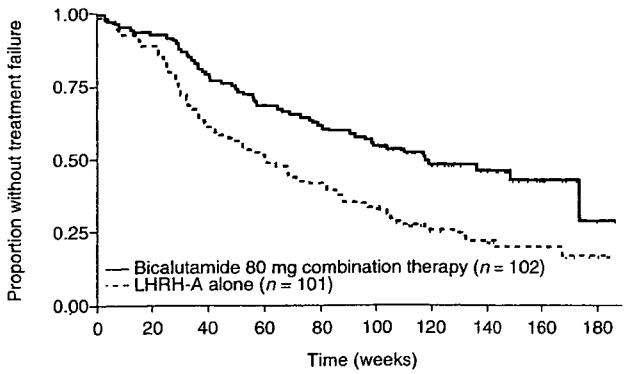

Figure 2 Time-to-treatment failure in patients receiving bicalutamide 80 mg combination therapy or LHRH-A alone. Median follow-up: 127 weeks; hazard ratio 0.54; 95% CI 0.38–0.77; $P<0.001$; bicalutamide 80 mg combination therapy events = 54 (52.9%); LHRH-A alone events = 78 (77.2%); LHRH-A, luteinizing hormone-releasing hormone agonist.

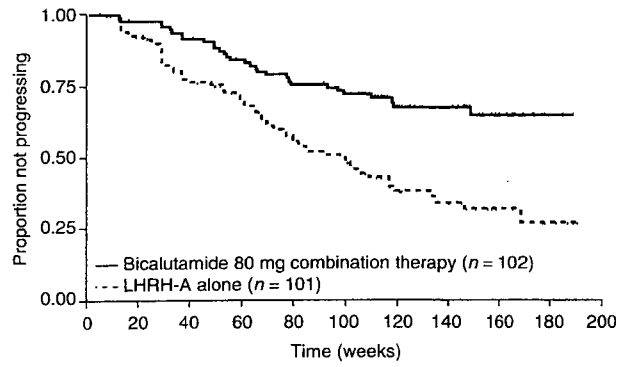

Figure 3 Time to disease progression in patients receiving bicalutamide 80 mg combination therapy or LHRH-A alone. Median follow-up: 127 weeks; hazard ratio 0.40; 95% CI 0.26–0.63; $P<0.001$; bicalutamide 80 mg combination therapy events = 30 (29.4%); LHRH-A alone events = 57 (56.4%); LHRH-A, luteinizing hormone-releasing hormone agonist.

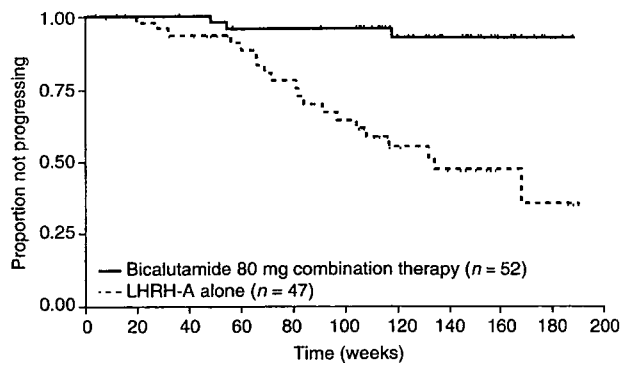

Figure 4 Time to disease progression among patients with stage C prostate cancer. $P<0.001$; bicalutamide 80 mg combination therapy events = 3 (5.8%); LHRH-A alone events = 20 (42.6%); LHRH-A, luteinizing hormone-releasing hormone agonist.

achieved a PSA level ⩽4 ng/ml at 12 weeks, compared with patients who did not (HR 0.15; 95% CI 0.06–0.38; $P<0.001$; Figure 6).

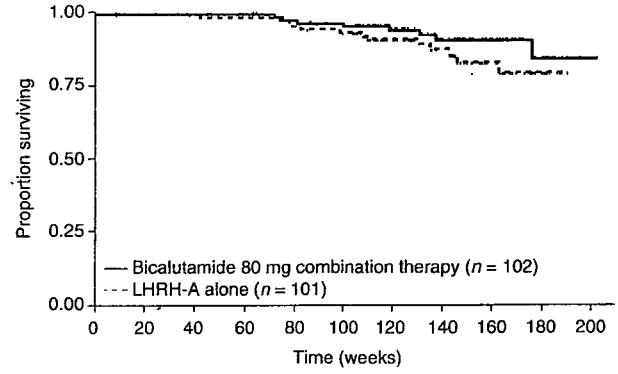

Figure 5 Disease-specific survival in patients receiving bicalutamide 80 mg combination therapy or LHRH-A alone. Median follow-up: 127 weeks; hazard ratio 0.63; 95% CI 0.26–1.54; $P=0.314$; bicalutamide 80 mg combination therapy events = 8 (7.8%); LHRH-A alone events = 13 (12.9%); LHRH-A, luteinizing hormone-releasing hormone agonist.

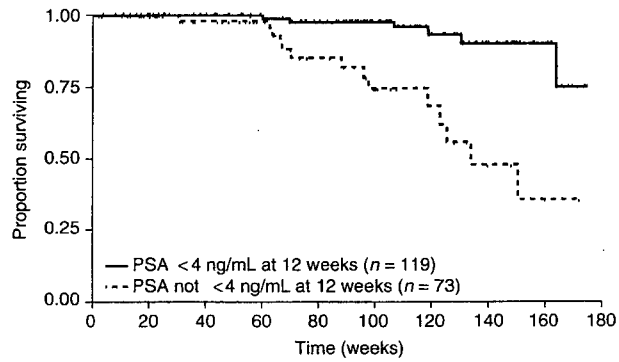

Figure 6 Disease-specific survival for patients achieving PSA levels of ⩽4 ng/ml at 12 weeks versus those not achieving PSA levels of ⩽4 ng/ml at 12 weeks. Hazard ratio 0.15; 95% CI 0.06–0.38; $P<0.001$; PSA, prostate-specific antigen.

Responses subsequent to disease progression

Eighteen patients consented to undergo follow-up for antiandrogen withdrawal syndrome: seven (38.9%) had a reduced/unchanged PSA after discontinuing bicalutamide. The median time to response in these seven patients was 6.9 weeks and the effect lasted for a median of 58.1 weeks.

Among patients who received LHRH-A only, before relapse, 31/40 (77.5%) experienced decreased PSA levels after adding bicalutamide 80 mg (i.e. ⩾50% reduction in PSA following relapse). The median times to, and duration of, response with second-line bicalutamide 80 mg combination therapy were 4.1 weeks and 39.6 weeks, respectively.

Tolerability

Bicalutamide 80 mg combination therapy had a tolerability profile similar to LHRH-A alone (Table 3). Withdrawals due to adverse drug reactions were comparable: 8.8% (9/102) of patients in the combination therapy group withdrew, whereas 10.9% (11/101) in the LHRH-A only group (95% CI on difference: −10.7–6.4).

Table 3 Incidence of most common (>10% in either group) adverse events (AEs) and adverse drug reactions (ADRs) among patients with advanced prostate cancer receiving either bicalutamide 80 mg combination therapy or LHRH-A alone

	Bicalutamide 80 mg combination therapy (n = 102)		*LHRH-A alone (n = 101)*	
	AEs (%)	*ADRs (%)*	*AEs (%)*	*ADRs (%)*
Any	93.1	66.7	93.1	65.3
Any serious	29.4	2.0	25.7	8.9
Nasopharyngitis	28.4	1.0	25.7	1.0
Hot flushes	17.6	16.7	33.7	32.7
Back pain	15.7	2.0	12.9	3.0
Increased blood LDH	11.8	6.9	7.9	3.0
Anemia	10.8	8.8	6.9	5.9
Increased blood ALP	10.8	10.8	5.9	5.0
Increased blood ALT	7.8	2.9	13.9	9.9
Increased blood AST	7.8	3.9	12.9	10.9
Constipation	6.9	1.0	11.9	1.0

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; LHRH-A, luteinizing hormone-releasing hormone agonist.
Two patients in the bicalutamide 80 mg combination therapy group had an adverse drug reaction of breast pain and one patient in this arm had nipple swelling.

Discussion

This trial is the world's first double-blind controlled study to directly compare bicalutamide plus LHRH-A versus LHRH-A alone in men with prostate cancer.

Once-daily bicalutamide 80 mg in combination with LHRH-A provided superior efficacy to LHRH-A alone in terms of time to achieve PSA levels of ⩽4 ng/ml, TTTF and TTP. Notably, the median TTP has still not been reached among patients receiving bicalutamide 80 mg combination therapy, but was 96.9 weeks among men in the LHRH-A only arm. Additionally, the differences in TTTF and TTP between the two treatment groups were greater than those observed in an earlier analysis,[9] indicating that the advantage seen with bicalutamide 80 mg combination therapy has become more pronounced with increased follow-up.

These findings are supported by those reported in an earlier interim analysis from this study, which showed that at 12 weeks, patients receiving bicalutamide 80 mg combination therapy are significantly more likely to achieve PSA levels of ⩽4 ng/ml and have higher overall tumor-response rates than those receiving LHRH-A alone.[9]

An exploratory analysis revealed that the effect of bicalutamide 80 mg therapy on TTP is most pronounced in patients with locally advanced disease (stage C). The baseline characteristics of the two treatment groups were well balanced among patients with stage C disease. This suggests that although combination therapy using bicalutamide 80 mg has the potential to benefit all patients with advanced/locally advanced disease, the benefit over castration alone is greatest for patients with locally advanced tumors without spread to the lymph nodes or elsewhere.

There was no significant difference between the bicalutamide 80 mg combination therapy arm and the LHRH-A only arm in terms of OS/disease-specific survival at this analysis. This was not unexpected, as the mortality rates remain low in both treatment arms. Long-term follow-up of patients will be continued to show if there is any correlation between the choice of treatment and a reduced risk of death. Findings from an additional exploratory analysis of this data suggest that this is likely to be the case. The exploratory analysis revealed an association between levels of PSA ⩽4 ng/ml at 12 weeks and a lower risk of death caused by prostate cancer. This, taken alongside the primary trial finding that bicalutamide 80 mg combination therapy significantly improves the proportion of patients achieving PSA levels of ⩽4 ng/ml at 12 weeks relative to LHRH-A alone, demonstrates that bicalutamide 80 mg combination therapy has strong potential to improve survival. The likelihood that bicalutamide 80 mg combination therapy can improve OS versus castration alone is further supported by the findings from a recent indirect analysis by Klotz *et al*.[3] In this analysis, bicalutamide 50 mg plus LHRH-A was associated with a 20% reduction in mortality risk compared with LHRH-A alone.

Most patients with advanced prostate cancer who initially respond to combination therapy with an antiandrogen plus castration will, ultimately, experience disease progression. However, following subsequent withdrawal of antiandrogen therapy, some patients will experience a decrease in serum PSA levels and develop an antitumor response. This well-recognized phenomenon is referred to as the antiandrogen withdrawal syndrome and has also been described for patients who have received other nonsteroidal antiandrogens.[14–16] Indeed, a PSA response following withdrawal of nonsteroidal antiandrogen therapy (including with bicalutamide) typically occurs in approximately 15–36% of patients, and is characterized by a ⩾50% decrease in PSA for 4–7 months.[17,18] In this trial, 39% of patients had a PSA response (no change or a decrease in PSA levels) following discontinuation of bicalutamide 80 mg, and responses lasted for a median of 58 weeks. One explanation of why the PSA response rate following bicalutamide withdrawal was higher in this study, than in others, is that our definition of response was different to that used in other studies.

In those men who experienced disease progression following first-line LHRH-A alone, 78% (31/40) responded to the addition of bicalutamide 80 mg treatment. The efficacy of second-line bicalutamide 80 mg combination therapy in men with prostate cancer could suggest that combination therapy should only be used following initial therapy with castration alone. However, the median duration of response to second-line bicalutamide 80 mg was 40 weeks, and the median TTP following LHRH-A alone was 97 weeks, indicating a combined total TTP of 137 weeks. In contrast, based on current findings, the median TTP in patients receiving first-line bicalutamide 80 mg combination therapy is expected to be greater than the median TTP of 137 weeks calculated for patients receiving delayed bicalutamide 80 mg combination therapy (to date, <50% of patients have experienced progression). Therefore, we would expect bicalutamide 80 mg combination to be more effective as a first-line approach than as a second-line approach.

Importantly, in our trial, combination of bicalutamide 80 mg with LHRH-A did not lead to a rise in toxicity or withdrawals compared with LHRH-A alone. The rates of

withdrawal due to adverse drug reactions were also similar for the two treatment groups. As in the earlier analysis, the most common adverse events, occurring with similar incidence in both treatment arms, were nasopharyngitis and hot flushes. Although the reason for the relatively high incidence of nasopharyngitis is not clear, the incidence of nasopharyngitis that was attributed to adverse drug reactions was very low (1.0% in both groups). Less than 7% of patients in the bicalutamide 80 mg combination therapy group had gastrointestinal symptoms (constipation 6.9%, nausea 5.9% and diarrhea 4.9%), which was comparable to that observed in the LHRH-A only arm (11.9, 3.0 and 4.0%, respectively). The incidence of gastrointestinal adverse events among patients receiving bicalutamide 80 mg was lower than predicted from studies with bicalutamide 50 mg combination therapy in Caucasians,[5] but reflected the low incidence reported in the earlier analysis of our study.[5,9] As expected from previous studies of hormonal combination therapy,[19] the incidences of breast pain and gynecomastia were also low, occurring in only three men in the bicalutamide 80 mg combination group, and in no men in the LHRH-A alone group.

The tolerability profile of bicalutamide makes it an attractive agent for use in hormonal combination regimens, particularly as the profile is favorable compared with other antiandrogens.[17,20] Compared with bicalutamide, flutamide carries a higher risk of gastrointestinal events and hepatotoxicity; nilutamide is associated with delayed adaptation to darkness, alcohol intolerance and interstitial pneumonitis; and steroidal antiandrogens carry a risk of hepatotoxicity, cardiovascular events, reduced sexual potency and adverse serum lipid changes.

In summary, among Japanese men with advanced prostate cancer, first-line treatment with a combination of bicalutamide 80 mg and an LHRH-A provides significant efficacy benefits over LHRH-A alone, without increasing the incidence of adverse events or reducing tolerability. Patients continue to be followed for OS.

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Harasanshin Hospital (22); Kansai Medical University Hospital (nine); Shimane University Hospital (eight); Nishi-Kobe Medical Center (seven); Okayama University Hospital (seven); Fujieda Municipal General Hospital (six); Kurashiki Central Hospital (six); Nihon University Itabashi Hospital (six); Shikoku Cancer Center (six); Showa University Hospital (six); Tokushima University Hospital (six); Gifu University Hospital (five); Kanazawa University Hospital (five); Kobe University Hospital (five); Kyushu University Hospital (five); Nagasaki Medical Center (five); Nara University of Medical Science Hospital (five); Tokyo Medical University Hospital (five); Hirosaki University School of Medicine and Hospital (four); Hiroshima University Hospital (four); Kawasaki Medical School Hospital (four); Keio University Hospital (four); Kyoto University Hospital (four); Nagasaki University Hospital (four); Osaka University Hospital (four); Sasebo Municipal General Hospital (four); Tokyo Women's Medical University Hospital (four); Kitasato University Hospital (three); Osaka City University Hospital (three); The University of Tokyo Hospital (three); Teikyo University Ichihara Hospital (three); University Hospital, Kyoto Prefectural University of Medicine (three); Yamagata University Hospital (three); Asahi Central Hospital (two); Jikei University School of Medicine Hospital (two); Kochi Medical School Hospital (two); Nagoya City University Hospital (two); Nagoya Daini Red Cross Hospital (two); Niigata Cancer Center Hospital (two); Niigata University Medical and Dental Hospital (two); Sapporo Medical University Hospital (two); Tohoku University Hospital (two); Tsukuba University Hospital (two); Yokohama City University Hospital (two); Chiba University Hospital (one); Hokkaido University Hospital (one); Osaka Medical Center for Cancer and Cardiovascular Diseases (one); Toranomon Hospital (one); Tottori University Hospital (one).

*Values in parentheses represent the number of enrolled patients.

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Dietary Isoflavones May Protect against Prostate Cancer in Japanese Men[1,2]

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Abstract

We examined associations between nutritional and other lifestyle factors and the prevalence of prostate cancer in a case-control study of Japanese men. Two hundred patients and 200 age-matched controls (±5 y) were selected from 3 geographic areas of Japan. BMI, physical activity, occupation, family history of prostate cancer, and medical history were not associated with prostate cancer risk. Isoflavones and their aglycones (genistein and daidzein) were significantly associated with decreased risk. The odds ratio for the highest category (≥89.9 mg/d) compared with the lowest category (<30.5 mg/d) of isoflavone intake was 0.42 (95% CI = 0.24–0.72) and the linear trend was significant ($P < 0.01$). PUFA, (n-6) fatty acids, and magnesium were significantly associated with decreased risk but not after adjustment for isoflavone intake. Isoflavone intake was correlated with the intake of PUFA ($r = 0.68$, $P < 0.001$), (n-6) fatty acids ($r = 0.69$, $P < 0.001$), and magnesium ($r = 0.56$, $P < 0.001$), because soy products contain high levels of these nutrients. On the other hand, isoflavone significantly decreased the risk of prostate cancer regardless of adjustment by PUFA, (n-6) fatty acids or magnesium. In conclusion, our findings indicate that isoflavones might be an effective dietary protective factor against prostate cancer in Japanese men. J. Nutr. 137: 1974–1979, 2007.

Introduction

The age-standardized incidence rate of prostate cancer is lower in Japan (9.2/100,000 in Osaka prefecture in 1993–1997) than in other countries (e.g. 50.7/100,000 in Saarland, Germany, between 1993 and1997 and 44.4/100,000 in Oxford, England, during the same period) (1). However, the rates associated with Japanese immigrants in Hawaii is 62.1/100,000, which is ~6-fold higher than that in Japan (1) and the incidence of prostate cancer in Japan is gradually increasing. Thus, environmental factors such as dietary habits might play a major role in prostate cancer. The Japanese diet is high in soy products and fish. Soy includes substantial amounts of isoflavones, which are phytoestrogens. This case-control study evaluated the effects of isoflavones, fatty acids, vitamins, and minerals in the Japanese diet on prostate cancer risk. In addition, we examined whether physical activity, occupation, family history of prostate cancer, and medical history are associated with prostate cancer risk, because such associations in Japan had not been reported.

Materials and Methods

Participants. Surveys for this case-control study were performed in the Ibaraki, Nara, and Hokkaido areas. Two hundred cases with a confirmed histological diagnosis of adenocarcinoma of the prostate by prostate-specific antigen testing, digital rectal examination, and biopsies between 1996 and 2003 were used for analysis. A total of 80 cases from the Department of Urology of Tsukuba University Hospital in Ibaraki, 28 cases from the Department of Urology of Nara Medical College Hospital in Nara, and 92 cases from the Department of Urology of Sapporo Medical University Hospital in Hokkaido were included. The age range was 59–73 y. The stage distribution was as follows: 1 case of Stage 1, 131 cases of Stage 2, 44 cases of Stage 3, and 24 cases of Stage 4. The median and mode time between diagnosis and interview for this study were 3 and 2 mo, respectively.

A total of 200 controls were selected from the urology, oral surgery, ophthalmology, orthopedics, and dermatology departments of the same hospitals (or clinics in the same area as cases) and matched to each case by age (±5 y). Disease categories were benign kidney disorder, oral diseases, cataract, otitis media, and dermatosis. Exclusion criteria for controls were clinical history of benign prostatic hypertrophy, other prostatic diseases, malignant tumors, dietary restriction, or a serum prostate-specific antigen concentration of >4.0 μg/L.

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The total sample size was 400, which was sufficient to detect an OR of 0.5 or 2.0 with 80% statistical power or more at 5% significance.

This study was approved by the ethics committee of each university. Physicians obtained informed consent from all subjects.

Questionnaire. Fully trained staff interviewed both case and control participants in hospitals. The questionnaire included the following information: height, weight, cigarette smoking, physical activity, employment history, medical history, family (first and second degree) history of prostate cancer, and food items consumed. We used participants' height and weight to calculate their mean BMI from age 40 to 45 y and 1 y before diagnosis. Information on smoking habits included age when participant started, duration in years, and number of cigarettes smoked per day. Employment history included occupation 1 y before diagnosis and the job at which the participant worked for the longest period. Physical activity other than during working time included the type, period, mean frequency per month, and hours per occasion from age 40 to 45 y and 1 y before diagnosis. Employment history included the occupation held 1 y before diagnosis and the job at which the participant worked for the longest period. Medical history included questions about hypertension, diabetes, tuberculosis, heart disorder, stroke, sexually transmitted diseases, other infectious or lifestyle-related diseases, and vasectomy.

Interviewers questioned the participants in detail about their habitual diets, showing photographs of types and amounts of meals. The mean daily intakes of beverages and various foods including 11 soybean products during the 5 y before diagnosis was assessed using a semiquantitative FFQ that was a modification (with the authors' permission) of the questionnaire used in the Takayama study (2) in the Gifu prefecture. The validity of the Takayama study questionnaire was verified by Shimizu et al. (2). For men, the Pearson correlation coefficient for macronutrients between the questionnaire and 3-d records ranged from 0.45 to 0.51 in the Takayama study (2). We added 4 soy products to soybean items of the Takayama study. The following 12 food items were included in the questionnaire: tofu (soybean curd), natto (fermented soybeans), miso soup (soybean paste soup), okara (bean curd refuse), aburaage (fried bean curd), ganmodoki (fried bean curd with vegetables), kinako (soy flour), yuba (dried bean curd), tonyu (soybean milk), soy sauce, green soybeans, and bean sprouts.

Most participants in this study consumed a traditional Japanese diet consisting of fish, soy products, rice, and a little meat. Control subjects consumed 92.4 ± 79.8 g fish/d, 145.4 ± 94.8 g soy products/d, 279.3 ± 140.3 g rice/d, and 43.6 ± 30.1 g meat/d. Case subjects consumed 87.6 ± 63.0 g fish/d, 119.0 ± 75.6 g soy products/d, 299.6 ± 147.0 g rice/d, and 46.0 ± 28.7 g meat/d.

Data analysis. We categorized BMI as <23.0 (normal), 23.0–24.9 (overweight), and ≥25.0 (obese). For physical activity, metabolic equivalent (MET) hours per week (MET-h/wk) were calculated for each participant. One MET equals ~3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ of oxygen consumed, the cost of sitting at rest, with higher activity levels represented in multiples of this value. The various MET values provided by Ainsworth et al. (3) were used to estimate physical activity. The MET-h/wk were categorized into tertiles. Occupation was summarized in 4 categories based on major groups of the 2002 Census Occupational Classification (4). The OR of each occupation 1 y before diagnosis of prostate cancer and for the longest duration of employment was calculated using all other occupations and no employment as a reference category. Estimates of age-adjusted OR and 95% CI were calculated by conditional logistic regression models with adjustment for pack-years of smoking [cigarettes/(d × 20) × years of smoking] as a potential confounding factor, because some controls were selected from patients with smoking-related diseases, such as cataract (5) and oral disease (6,7).

The quantity of each nutrient included in each food item was obtained from the Standard Tables of Food Composition in Japan 2002. The nutrients we investigated were total isoflavones and their aglycones (genistein and daidzein), protein, carbohydrates, fatty acids (total fatty acids, SFA, monounsaturated fatty acids, PUFA, (n-6) fatty acids, and (n-3) fatty acids as a subcategory of PUFA), lycopene, vitamins (all carotenes, folate, vitamin K, thiamin, riboflavin, vitamin B-6, vitamin B-12, niacin, pantothenic acid, vitamin C, vitamin D, and vitamin E), and minerals (sodium, potassium, calcium, magnesium, selenium, zinc, and iron). Daily intake of each nutrient was calculated by adding the intake of food items and multiplying the portion size (in grams) by food frequency per day and was classified into quartiles (Q1–Q4) or other suitable categories on the basis of the distribution among control subjects. Estimates of age-adjusted OR, 95% CI, and linear trends of nutrient intake were calculated by conditional logistic regression models with adjustment for total energy intake, tobacco pack-years, and also isoflavone intake. Furthermore, total isoflavones and their aglycones were adjusted with PUFA, (n-6) fatty acids, or magnesium intakes. Median values in each category were entered into models for the linear trend tests.

The lowest category, with an OR of 1.00, was the reference category throughout the analyses. Analyses were performed with SPSS release 11.5.

Results

The OR for BMI, physical activity, industries, and family history of prostate cancer were not significant (all P-values > 0.1)(**Table 1**). Two of the 13 cases with family history of prostate cancer were both a father and a brother of prostate cancer patients. There was no association between medical history and prostate cancer risk (data not presented).

Total isoflavones, genistein, and daidzein were significantly associated with decreased risk of prostate cancer (**Table 2**). The OR for the fourth (Q4) vs. the first (Q1) category were 0.42 (95% CI = 0.24–0.72) for total isoflavones, 0.58 (95% CI = 0.34–0.97) for genistein, and 0.55 (95% CI = 0.32–0.93) for daidzein. Each linear trend also showed significantly decreasing risk ($P < 0.05$). The PUFA-adjusted OR and linear trend of total isoflavones showed significantly decreased risk (Table 2). The adjusted OR and linear trend of total isoflavones by (n-6) fatty acids and magnesium were similar (data not presented).

PUFA and (n-6) fatty acids were significantly associated with decreased risk (**Table 3**). The OR for Q4 vs. Q1 was 0.44 (95% CI = 0.22–0.86) for PUFA and 0.53 (95% CI = 0.29–0.98) for (n-6) fatty acids. Each linear trend was significant ($P < 0.05$). The isoflavone-adjusted OR and linear trend of PUFA and (n-6) fatty acids did not show decreased risk (Table 3). Total, monounsaturated, and (n-3) fatty acids, SFA, and the ratio of (n-6): (n-3) fatty acids were not associated with prostate cancer risk (Table 3).

Magnesium was significantly associated with decreased risk (**Table 4**). The OR for Q4 vs. Q1 was 0.32 (95% CI = 0.16–0.66) and the P-value of the linear trend was <0.01. The isoflavone-adjusted OR and linear trend for magnesium showed no association (Table 4). Lycopene, vitamins (all carotenes, folate, vitamin B-12, vitamin C, vitamin D, and vitamin E), and selenium were not associated with prostate cancer risk (Table 4). The following other nutrients also were not associated with risk of prostate cancer: energy, protein, carbohydrates, sodium, potassium, vitamin K, thiamin, riboflavin, vitamin B-6, niacin, pantothenic acid, vitamin C, calcium, zinc, and iron (data not presented). Beverages (alcohol, coffee, black tea, and green tea) showed no association (data not presented).

Discussion

Although it has been suggested that obesity and physical activity are associated with circulating testosterone levels (8,9), epidemiological studies have not provided strong evidence in prostate cancer (10). In this study, the prevalence of obesity may not have had enough statistical power for risk evaluation, because the frequency of obesity (BMI ≥25.0) in the Japanese

TABLE 1 Risk of prostate cancer associated with BMI, physical activity, occupation, and family history in Japanese men

Characteristics	Cases	Controls	OR (95% CI)[1]
n	200	200	
BMI at age 40–45 y, *kg/m²*			
<23.0	107	94	1.00
23.0–24.9	53	55	0.89 (0.61–1.31)
≥25.0	40	50	0.80 (0.53–1.20)
P for trend			0.27
BMI before 1 y of diagnosis, *kg/m²*			
<23.0	81	92	1.00
23.0–24.9	60	47	1.28 (0.87–1.87)
≥25.0	59	61	1.06 (0.72–1.55)
P for trend			0.65
Physical activity at age 40–45 y, *MET-h/wk*			
0	141	150	1.00
0.1–97.1	29	25	1.12 (0.71–1.78)
≥97.2	30	25	1.13 (0.72–1.77)
P for trend			0.61
Physical activity 1 y before diagnosis, *MET-h/wk*			
0	105	124	1.00
0.1–122.4	46	39	1.21 (0.81–1.80)
≥122.5	49	37	1.29 (0.87–1.91)
P for trend			0.19
Occupation for the longest period			
Management, professional, and related occupations	45	36	1.21 (0.83–1.78)
Sales, office, and service	92	79	1.14 (0.83–1.57)
Natural resources, construction, and maintenance	34	48	0.76 (0.51–1.15)
Production, transportation, and material moving	29	37	0.86 (0.55–1.32)
Occupation 1 y before diagnosis			
Management, professional, and related occupations	37	30	1.18 (0.79–1.77)
Sales, office, and service	49	43	1.08 (0.75–1.55)
Natural resources, construction, and maintenance	26	27	0.98 (0.61–1.59)
Production, transportation, and material moving	19	18	1.04 (0.60–1.81)
No employment	68	81	1.19 (0.85–1.65)
Family history of prostate cancer			
No	187	192	1.00
Yes	13	6	1.60 (0.82–3.11)

[1] Adjusted for cigarette smoking.

population is low, with only 29.9% of controls having a BMI ≥25.0 1 y before diagnosis.

Occupational associations with prostate cancer are inconclusive except for farming (11). Positive associations between prostate cancer and farming were found in meta-analyses, although the excess risk was slight (12).

Many case-control studies (13–16) and cohort studies (17,18) have suggested that a family history of prostate cancer is associated with an increased risk of prostate cancer. In this study, a family history of prostate cancer showed no association. Our study may have had insufficient power to detect such an association, because the number of participants was relatively small and the age-adjusted incidence of prostate cancer is low in Japan. The required sample size would be 1600 for both cases and controls in this study.

The traditional Japanese diet includes many soy products, especially tofu and natto, which are rich in isoflavones (509 μg/g tofu and 1273 μg/g natto) (19) and, thus, the dietary isoflavone intake of the Japanese population is high. Serum phytoestrogen concentrations are higher among Japanese men and women than among those in Western countries. For example, the mean serum concentration of genistein in Japanese men is 492.7 nmol/L compared with 33.2 nmol/L in men from the UK) (20) and urinary excretion of phytoestrogens by Japanese is also high (21). In this study, control subjects consumed 67.0 mg isoflavone/d, which is ~200 times that in Sweden (22). Some epidemiological studies in Japan have suggested that the intake of soybean products may protect against prostate cancer (23,24). In the present study, the OR of ≥89.9 mg/d for <30.5 mg/d of isoflavone intake was 0.42 (95% CI = 0.24–0.72) and the linear trend was significant. These findings indicate that isoflavones indeed confer a protective effect against prostate cancer. Genistein and daidzein, which are aglycones of isoflavones, were associated with significant reductions in prostate cancer risk. However, the PUFA-adjusted OR and linear trend for genistein and daidzein did not show significant associations. The amounts of these aglycones compared with the amounts of total isoflavones in soy products may have been insufficient for risk evaluation. The proportion of aglycones in the isoflavones in each soybean product is different. The proportions of aglycones are below 15.0% in tofu, natto, aburaage, kinako, yuba, and tonyu, substantial amounts of which are consumed daily in Japan, but over 60% in miso and soy sauce, both of which are also consumed on a daily basis but in small amounts.

TABLE 2 Risk of prostate cancer associated with isoflavone and aglycone intakes in Japanese men

Nutrient[1]	Cases	Controls	OR (95% CI)[2]	OR (95% CI)[3]
n	200	200		
Isoflavones, *mg/d*				
<30.5 (Q1)	69	50	1.00	1.00
30.5–59.3 (Q2)	62	50	0.92 (0.62–1.37)	0.91 (0.59–1.41)
59.4–89.8 (Q3)	46	50	0.73 (0.47–1.12)	0.72 (0.44–1.17)
≥89.9 (Q4)	23	50	0.42 (0.24–0.72)	0.48 (0.25–0.93)
P for trend			< 0.01	0.02
Genistein, *mg/d*				
<1.1 (Q1)	57	49	1.00	1.00
1.1–1.8 (Q2)	58	51	1.05 (0.68–1.61)	1.04 (0.67–1.62)
1.9–2.4 (Q3)	55	50	0.95 (0.62–1.48)	0.97 (0.61–1.55)
≥2.5 (Q4)	30	50	0.58 (0.34–0.97)	0.68 (0.39–1.20)
P for trend			0.04	0.19
Daidzein, *mg/d*				
<0.8 (Q1)	58	50	1.00	1.00
0.8–1.3 (Q2)	64	50	1.14 (0.75–1.72)	1.12 (0.73–1.72)
1.4–1.8 (Q3)	49	49	0.88 (0.56–1.39)	0.90 (0.55–1.48)
≥1.9 (Q4)	29	51	0.55 (0.32–0.93)	0.64 (0.36–1.17)
P for trend			0.02	0.12

[1] Quartile distribution based on controls.
[2] Adjusted for cigarette smoking and energy intake.
[3] Adjusted for cigarette smoking and energy and PUFA intakes.

Many experimental studies have reported anticancer effects of isoflavones, and aglycones in particular, against prostate cancer; the mechanisms are thought to involve induction of apoptosis of prostate cancer cells (25–27) and growth inhibition by cell cycle arrest (28–30). In an intervention study, Dalais et al. (31) showed that men whose diets were high in phytoestrogens had reduced risks of prostate cancer development and progression. Recently, an adverse effect of isoflavones on normal hormone-related tissue was demonstrated; isoflavones promoted endometrial hyperplasia (32,33). In June 2006, the Food Safety Investigation Council in Japan (34) established an upper limit of isoflavone intake except from food sources at 30 mg/d for both men and women. The council contends that the Japanese population consumes sufficient isoflavones daily and does not need additional sources beyond the normal diet; in particular, the sensitivity of men to isoflavones may be higher than that of women, although adverse effects on the prostate have not been reported.

PUFA was mainly contained in the following foods in Japan: soy products, fish (mackerel, sardines, pacific saury, and horse mackerels, etc.), and vegetable oils. PUFA are classified into (n-3) and (n-6) fatty acids, with the former being found in fish, especially mackerel, sardines, and pacific saury. These are daily staples among Japanese people; the intake of fish per day among controls in this study was 92.4 g. MacLean et al. (35) noted that a large body of literature spanning numerous cohorts from many countries and with different demographic characteristics does not provide evidence to suggest a significant association between (n-3) fatty acids intake and prostate cancer incidence. In our study, the OR and the linear trend for (n-3) fatty acids were not significant. PUFA and (n-6) fatty acids are present in substantial amounts in soy, >10.0 g and >8.0 g, respectively, per 100 g of dried Japanese soy (Standard Tables of Food Composition in Japan) (36). Isoflavone intake was correlated with the intake of (n-6) fatty acids ($r = 0.69$; $P < 0.001$) and PUFA ($r = 0.68$; $P < 0.001$); therefore, the isoflavone-adjusted OR and linear trend of

TABLE 3 Risk of prostate cancer associated with fatty acid intakes in Japanese men

Nutrient[1]	Cases	Controls	OR (95% CI)[2]	OR (95% CI)[3]
n	200	200		
Total fatty acids, *g/d*				
<25.1 (Q1)	39	50	1.00	1.00
25.1–35.2 (Q2)	67	50	1.47 (0.90–2.39)	1.64 (0.99–2.70)
35.3–47.3 (Q3)	63	50	1.27 (0.73–2.21)	1.49 (0.84–2.65)
≥47.4 (Q4)	31	50	0.78 (0.41–1.51)	1.02 (0.51–2.04)
P for trend			0.35	0.91
SFA,[4] *g/d*				
<9.1 (Q1)	50	49	1.00	1.00
9.1–12.1 (Q2)	50	51	0.94 (0.58–1.51)	0.99 (0.61–1.60)
12.2–16.4 (Q3)	58	49	1.00 (0.60–1.64)	1.06 (0.64–1.76)
≥16.5 (Q4)	42	51	0.81 (0.46–1.45)	0.89 (0.49–1.62)
P for trend			0.53	0.76
MUFA, *g/d*				
<9.2 (Q1)	47	49	1.00	1.00
9.2–12.8 (Q2)	59	50	1.13 (0.70–1.83)	1.24 (0.76–2.01)
12.9–17.6 (Q3)	62	51	1.08 (0.64–1.83)	1.21 (0.71–2.06)
≥17.7 (Q4)	32	50	0.70 (0.38–1.31)	0.86 (0.45–1.62)
P for trend			0.23	0.56
PUFA, *g/d*				
<7.1 (Q1)	50	49	1.00	1.00
7.1–10.2 (Q2)	68	51	1.04 (0.66–1.64)	1.20 (0.72–1.98)
10.3–13.5 (Q3)	56	50	0.80 (0.47–1.38)	1.09 (0.58–2.05)
≥13.6 (Q4)	26	50	0.44 (0.22–0.86)	0.74 (0.33–1.68)
P for trend			0.01	0.38
(n-6) fatty acids, *g/d*				
<5.8 (Q1)	54	50	1.00	1.00
5.8–8.1 (Q2)	64	50	1.03 (0.66–1.60)	1.18 (0.73–1.92)
8.2–10.2 (Q3)	49	50	0.73 (0.43–1.24)	1.00 (0.55–1.82)
≥10.3 (Q4)	33	50	0.53 (0.29–0.98)	0.91 (0.43–1.93)
P for trend			0.03	0.75
(n-3) fatty acids, *g/d*				
<1.3 (Q1)	45	49	1.00	1.00
1.3–1.9 (Q2)	65	51	1.22 (0.76–1.95)	1.39 (0.86–2.27)
2.0–2.5 (Q3)	55	49	1.04 (0.62–1.75)	1.37 (0.77–2.43)
≥2.6 (Q4)	35	51	0.71 (0.38–1.33)	1.11 (0.55–2.22)
P for trend			0.20	0.94
(n-6):(n-3) ratio of fatty acids				
<3.6 (Q1)	53	50	1.00	1.00
3.6–4.4 (Q2)	52	48	1.00 (0.65–1.54)	1.05 (0.68–1.65)
4.5–5.2 (Q3)	54	51	0.98 (0.63–1.54)	1.01 (0.65–1.59)
≥5.3 (Q4)	41	51	0.79 (0.49–1.26)	0.77 (0.48–1.25)
P for trend			0.33	0.29

[1] Quartile distribution based on controls.
[2] Adjusted for cigarette smoking and energy intake.
[3] Adjusted for cigarette smoking and energy and isoflavone intakes.
[4] SFA, saturated fatty acids; MUFA, monounsaturated fatty acids.

(n-6) fatty acids and PUFA showed no association. It was suggested that PUFA and (n-6) fatty acids were the insignificant risk factors depending on the intake of isoflavones in soy products.

Magnesium is present in substantial amounts in tofu, a type of soy product (>30 mg/100 g tofu according to by the Standard Tables of Food Composition in Japan) (36). Isoflavone intake was correlated with the intake of magnesium ($r = 0.56$; $P < 0.001$); therefore, the isoflavone-adjusted OR and linear trend for magnesium showed no association. Few reports have noted

TABLE 4 Risk of prostate cancer associated with lycopene, vitamin, and mineral intakes in Japanese men

Nutrient[1]	Cases	Controls	OR (95% CI)[2]	OR (95% CI)[3]
n	200	200		
Lycopene, *mg/d*				
<1.3 (Q1)	45	49	1.00	1.00
1.3–2.5 (Q2)	43	50	0.96 (0.60–1.54)	0.94 (0.59–1.51)
2.6–6.0 (Q3)	71	51	1.32 (0.85–2.04)	1.36 (0.87–2.14)
≥6.1 (Q4)	41	50	0.88 (0.54–1.44)	0.89 (0.53–1.49)
P for trend			0.49	0.53
All carotenes, *mg/d*				
<1.6 (Q1)	49	50	1.00	1.00
1.6–2.4 (Q2)	63	50	1.09 (0.70–1.71)	1.13 (0.72–1.78)
2.5–3.5 (Q3)	43	50	0.84 (0.51–1.38)	0.96 (0.58–1.59)
≥3.6 (Q4)	45	50	0.90 (0.54–1.50)	1.03 (0.61–1.73)
P for trend			0.51	1.00
Folate, *μg/d*				
<236 (Q1)	55	50	1.00	1.00
236–344 (Q2)	58	50	0.95 (0.60–1.48)	1.05 (0.67–1.66)
345–472 (Q3)	53	50	0.82 (0.50–1.33)	0.92 (0.55–1.55)
≥473 (Q4)	34	50	0.64 (0.36–1.14)	0.87 (0.47–1.59)
P for trend			0.10	0.54
Vitamin B-12, *μg/d*				
<5.2 (Q1)	48	49	1.00	1.00
5.2–7.3 (Q2)	59	51	1.04 (0.65–1.65)	1.08 (0.67–1.73)
7.4–10.8 (Q3)	56	49	1.00 (0.60–1.66)	1.08 (0.65–1.81)
≥10.9 (Q4)	37	51	0.73 (0.40–1.32)	0.87 (0.47–1.63)
P for trend			0.24	0.60
Vitamin D, *μg/d*				
<5.2 (Q1)	48	50	1.00	1.00
5.2–8.4 (Q2)	60	50	1.18 (0.76–1.84)	1.22 (0.78–1.92)
8.5–13.4 (Q3)	47	50	0.98 (0.60–1.60)	1.07 (0.65–1.75)
≥13.5 (Q4)	45	50	0.98 (0.57–1.70)	1.08 (0.62–1.90)
P for trend			0.75	0.98
Vitamin E, *mg/d*				
<5.1 (Q1)	57	49	1.00	1.00
5.1–7.0 (Q2)	49	50	0.83 (0.52–1.32)	0.90 (0.56–1.46)
7.1–9.5 (Q3)	54	51	0.76 (0.46–1.26)	0.94 (0.55–1.58)
≥9.6 (Q4)	40	50	0.68 (0.39–1.18)	0.88 (0.48–1.58)
P for trend			0.18	0.71
Magnesium, *mg/d*				
<222 (Q1)	59	50	1.00	1.00
222–286 (Q2)	51	50	0.74 (0.45–1.22)	0.81 (0.49–1.35)
287–387 (Q3)	69	50	0.76 (0.44–1.30)	0.98 (0.53–1.80)
≥388 (Q4)	21	50	0.32 (0.16–0.66)	0.48 (0.22–1.08)
P for trend			<0.01	0.11
Selenium, *μg/d*				
<59.5 (Q1)	43	50	1.00	1.00
59.5–83.2 (Q2)	55	50	1.20 (0.73–2.00)	1.28 (0.76–2.13)
83.3–113.3 (Q3)	69	50	1.24 (0.73–2.13)	1.33 (0.76–2.31)
≥113.4 (Q4)	33	50	0.81 (0.42–1.59)	0.84 (0.42–1.68)
P for trend			0.41	0.42

[1] Quartile distribution based on controls.
[2] Adjusted for cigarette smoking and energy intake.
[3] Adjusted for cigarette smoking, energy, and isoflavone intakes.

an association between magnesium intake and prostate cancer risk.

Other nutrients and beverages did not show significant associations with prostate cancer risk in this study. Many epidemiological studies have evaluated possible inverse associations of prostate cancer risk with lycopene (37), β-carotene (38,39), vitamin E (40–42), and selenium (43,44), although epidemiologic evidence is still inconsistent.

We cannot deny the possibility of recall bias, because our study was retrospective in design. However, in conclusion, isoflavones might be an effective dietary protective factor against prostate cancer in Japanese men.

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