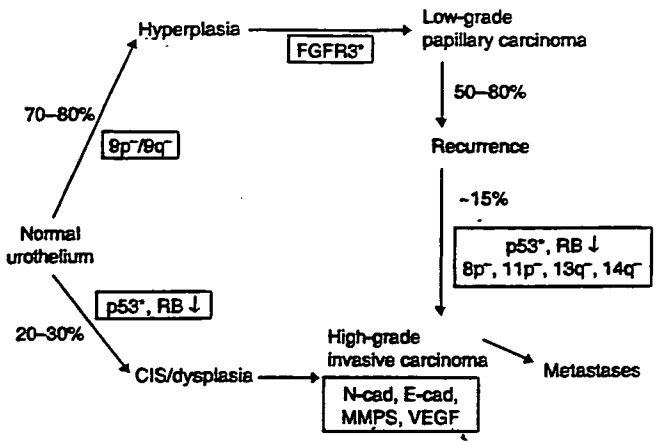

Fig. 9. Presumed molecular pathways of development of papillary and nodular carcinoma. (Modified from Wu.[38]) CIS, carcinoma *in situ*; FGFR3, fibroblast growth factor receptor 3; MMPS, matrix metal proteinases; RB, retinoblastoma gene; VEGF, vascular endothelial growth factor.

tract carcinomas occur infrequently after transurethral management of bladder carcinomas, the incidence is much greater in patients with vesico-ureteral reflux,[10] suggesting seeding or implantation of primary urothelial carcinoma cells after spread via the urine rather than field cancerization. In addition, recent molecular analyses using X-chromosome inactivation,[23] p53 mutation,[24–28] LOH[27,28] and comparative genomic hybridization[29] have provided compelling evidence that multifocal urothelial carcinomas are monoclonal in origin, despite some discrepancies.[30,31]

Comparing the basic morphological patterns of urothelial carcinomas, namely low-grade, superficial papillary carcinomas and high-grade, invasive nodular carcinomas, these two patterns of urothelial carcinomas are clearly separated in rats[32] and mice.[33] However, in dogs,[34] papillary carcinomas and nodular carcinomas can both be induced, depending on the concentration and period of carcinogen administration. In humans, papillary carcinomas and nodular carcinomas may originally develop separately, but coexistence of the two types is occasionally observed in a single bladder together with dysplasia and carcinoma *in situ*.[35] During the process of repeated recurrence, progression from papillary carcinoma to nodular carcinoma may be observed and molecular analysis of bladder carcinogenesis indicates the presence of two pathways: LOH of 9p/9q loss and FGFR3 mutation resulting in papillary carcinoma, and if p53 mutation occurs, nodular carcinoma. If p53 mutations occur initially, nodular carcinoma develops via dysplasia and carcinoma *in situ*. The available data clearly indicate that multiple genetic alterations are associated with the development and progression of bladder cancer.[36–38]

In the normal-appearing mucosa of the renal pelvis, ureter and bladder, dysplasia and carcinoma *in situ* may be frequently observed.[46] As mucosal dysplasia is not malignant, a derivation by implantation from primary carcinomas is not conceivable. In normal-appearing mucosa in remote areas from tumors, p53 mutation may be observed.[27] Intraepithelial spread[27,28] has been proposed as an explanation but this would appear unlikely. The phenomenon of coexistence of dysplasia, carcinoma *in situ* and p53 mutation in normal-appearing mucosa can be far more readily explained by the field cancerization theory. Differences in growth patterns of papillary and nodular carcinomas, and carcinoma *in situ*, as well as in cellular polarity and grade of malignancy make a single origin by seeding unreasonable. Finally, on detailed analysis of recurrent patterns of papillary carcinomas after TUR with or without intravesical instillation therapy, Akaza *et al.* concluded that recurrence patterns are biphasic, with an initial peak due to seeding or implantation of cancer cells during therapy and a second peak due to a new tumor occurrence from a background of field changes.[47] Thus, multifocal bladder recurrence of urothelial carcinomas is due to a combination of seeding and field changes. This is directly relevant to the condition for reconstruction of the urinary tract after cystectomy, inhibition and control of multiple recurrences after TUR, and the frequency and timing of follow-up for upper tract malignancies after treatment of bladder carcinoma. However, such clinical issues will be covered elsewhere.

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Comparison of Observed and Expected Numbers of Detected Cancers in the Research Center for Cancer Prevention and Screening Program

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Background: The Research Center for Cancer Prevention and Screening program is a one-arm prospective study designed to evaluate the effect of multiple modalities for cancer screening. Basic programs consist of screening tests for cancer of the lung, esophagus, stomach, colon, rectum, liver, gall bladder, pancreas and kidneys, in addition to prostate cancer screening for males and breast, cervical, endometrial and ovarian cancer screenings for females.
Objective: To investigate the possibility of overdiagnosis, we compared the observed numbers with expected numbers based on the model.
Methods: We calculated the expected number of cancers on the basis of negative or positive history of screening tests within the previous year, based on assumed sensitivity and sojourn time. Observed numbers of screen-detected cases for stomach, colorectal, lung, prostate and breast cancer were compared with expected numbers.
Results: From February 2004 to January 2005, 3786 participants were enrolled in our study. The overall cancer detection rate was 5.8% (119/2061) for males and 4.1% (71/1725) for females. No statistically significant difference was found between observed and expected cases for colorectal cancer screening, gastric cancer screening for females and lung cancer screening for males. Observed numbers of breast, prostate and lung cancer for females exceeded those expected ($P < 0.05$).
Conclusions: Although cancer screening programs in the present study increased the detection of potentially curable cancers, these modalities, particularly lung, breast and prostate screening, might detect cancers which would not necessarily be clinically significant. We should therefore weigh up benefit and harm for such cancer screening programs.

Key words: cancer screening – detection rate – sensitivity – sojourn time – overdiagnosis

INTRODUCTION

In an attempt to prevent premature death, the Health Service Law for the Aged introduced cancer screening programs in Japan for all residents over the age of 40 in 1983. Screening for gastric and cervical cancer was introduced initially, and colorectal, lung and breast cancer screening programs followed. At present, five cancer screening programs are conducted nationwide, and over 25 million people are screened annually (1). Although the research group for cancer screening in Japan recommended six cancer screening programs (2) in 2001, new modalities for cancer screening have been introduced in several local municipalities without evaluation by reliable studies. To reduce mortality from a specific cancer, effective, evidence-based screening should be conducted and appropriate management of quality assurance is required.

In 2004, the Japanese Government initiated the Third-Term Comprehensive 10-Year Strategy for Cancer Control, aimed at reducing the incidence and mortality of cancer in Japan. The Research Center for Cancer Prevention and Screening (RCCPS) was established at the campus of the National Cancer Center, Tokyo, in the same year. Although development of the new modalities is worthwhile, a systematic approach for the evaluation of cancer screening programs is required. In order to investigate the efficacy of cancer screening, programs using new modalities have been conducted. Variable cancers were detected in the past year, but might consist of overdiagnosis

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cases. To investigate its possibility, we compared the observed numbers with expected numbers based on the model.

SUBJECTS AND METHODS

CANCER SCREENING PROGRAMS

The RCCPS Cancer Screening Program is a one-arm prospective study designed to evaluate the effect of multiple cancer screening modalities. This is a hospital-based program and participants are enrolled on a voluntary basis. Age for the target group was 50 years and over for males and 40 years and over for females. Exclusion criteria were previous diagnosis of cancer and followed-up for pre-cancerous disease based on self-reporting. The research and screening methods were explained to all participants using written materials and face-to-face presentations by health-care professionals. In addition, participants signed informed consent documents approved by the National Cancer Center. All participants responded to a questionnaire concerning life style, smoking, alcohol intake, nutrition, past history of disease including cancer, family history and previous investigations within a year. These participants will be followed using a questionnaire survey after the baseline screening year. Follow-up studies include a hospital survey to investigate medical records of cancer patients detected by cancer screening and interval cancer rates based on the participant's response. In addition, these participants are asked to attend repeat screening 5 years after the baseline.

Basic programs consisted of screenings for esophageal, gastric, colon, rectal, lung, hepatic, gall bladder, pancreatic and renal cancer. Cancer screening modalities were as follows: gastrofiberscopy (GFS) for the esophagus and stomach; total colonofiberscopy (TCF) or barium enema (BE) for the colon and rectum; computed tomography (CT) and sputum cytology for the lung; and abdominal ultrasonography (US) for the liver, gall bladder, pancreas and kidneys. The participants could choose TCF or BE based on their preferences. For males, prostate cancer screening was performed using an assay of prostate specific antigen (PSA) serum levels with a cut-off value of 2.7 ng/ml. For females, a combination of modalities was performed: two-view mammography (MMG), US and physical examination (PE) for the breasts, Pap smear for the cervix, and magnetic resonance imaging (MRI) for the endometrium and ovaries. Moreover, whole body scanning using positron emission tomography (PET) with injection of 2.78 MBq/kg fluorine-18-FDG was provided as an optional investigation. This study was approved by the Institutional Review Board of the National Cancer Center.

COMPARISON OF OBSERVED AND EXPECTED DETECTION NUMBERS

Numbers of subjects recruited into the program from February 2004 to January 2005 and observed numbers of detected cancers were classified by 5-year age group and by gender. In the questionnaire survey, we collected information on the following investigations performed within the previous year as follows: photofluorography, GFS, fecal occult blood test (FOBT), TCF, BE, chest radiography and MMG. We could not obtain information regarding previous investigation of CT for lung and PSA because these indicators were lack of the questionnaire.

Since screening detects cancer in a large prevalence pool, detection rate is influenced by previous investigations. Sojourn time (ST) is the duration of the detectable, preclinical phase of cancer (Fig. 1). The ST depends both on the natural history of the cancer and performance of screening modalities. Maximum lead time would therefore be achieved if screening was performed at the beginning of the ST. Although ST and sensitivity (SE) vary with age on individual cases, we used estimated mean values obtained from literatures. For simplicity of the present study, we assumed the following conditions: (i) ST and SE were constant in all age groups and (ii) SE was constant throughout ST.

We calculated the expected numbers of gastric, colorectal, lung, prostate and breast cancers in patients. The subjects are divided into three groups based on the previous history as follows: (i) subjects with no history of screening, (ii) subjects with history by the same test and (iii) subjects with history by the different test. In the first group, given that I represents underlying incidence and P target population numbers, expected numbers (E) at prevalence screening, which corresponds screening without previous investigation, can be derived from the following formula: $E = I \times (P/100\,000) \times ST \times SE(3)$. PSA screening is applicable to this case because previous history cannot be obtained from the questionnaire. In the second group, the expected numbers (Ex) is the sum of incidence and false-negative cases of previous investigation (Fig. 2). The sensitivity of modality1 assumed SE1 and ST1 for its sojourn time. Ex is calculated as follows: $Ex = I \times (P/100\,000) \times (ST1\text{-}(ST1\text{-}1) \times SE1) \times SE1$. The modality2 was previous investigation, which is different from the modality of RCCPS screening program. Similarly, the sensitivity of modality2 assumed SE2 and ST2 for its sojourn time. These cases are the participants who have a screening history using other modalities in colorectal, gastric and lung cancer screening. When participants had history of previous investigation

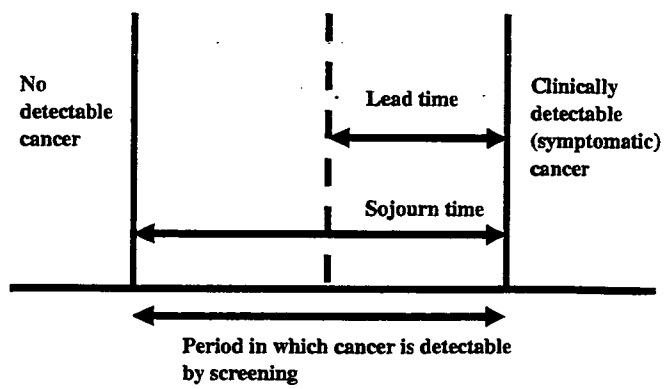

Figure 1. A graphical representation of the prognosis of clinical cancer and role of screening.

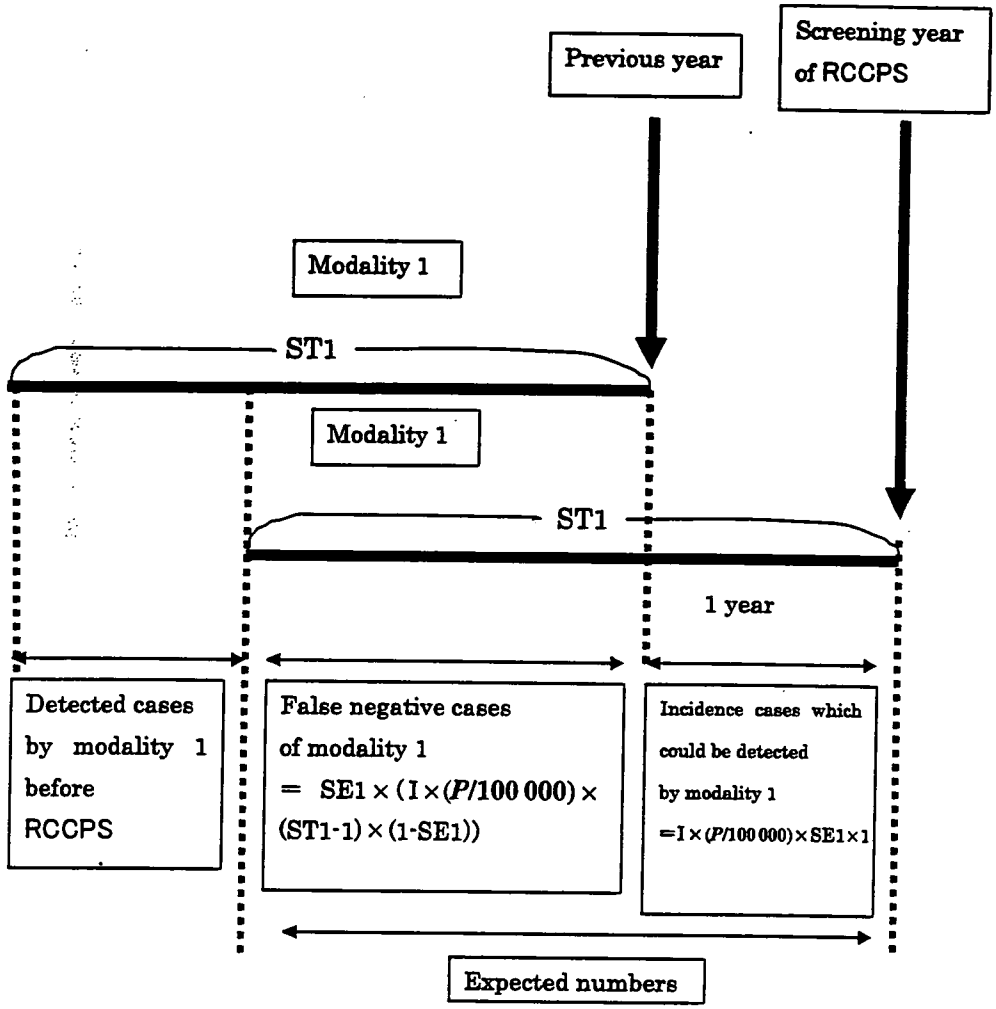

Figure 2. Calculation of expected numbers with previous examination using same modality. RCCPS: Research Center for Cancer Prevention and Screening; I: Incidence; P: Target population numbers; SE: Sensitivity; ST: Sojourn time.

using modality2, the expected number (Ey) including false-negative cases of previous screening is as follows: $Ey = I \times (P/100\,000) \times (ST1-(ST2 \times SE2)) \times SE1$ (Fig. 3).

The incidences of gastric, colorectal, lung, prostate and breast cancer were obtained from estimations calculated by cancer registries (4), while the ST and SE of breast cancer screening were assumed based on published reports (3,5–9). The ST or lead time of prostate cancer screening was determined from published articles and it ranged from 5 to 15 years (10–17). In other modalities, SE has been reported without adjustment for ST (18–20). In the baseline analysis, SE was assumed as follows: 70% for GFS; 70% for BE; 70% for TCF; 80% for CT; 80% for the combination of MMG, US and PE; 70% for MMG; 70% for PSA; 50% for chest radiography; 50% for FOBT; and 60% for photofluorography. ST was assumed as follows: 5 years for GFS; 5 years for BE; 10 years for TCF; 5 years for CT; 5 years for a combination of MMG, US and PE; 4 years for MMG only; and 10 years for PSA screening. In colorectal cancer screening, ST of immunological FOBT was assumed to be 2 years [published reports which reported the range from 2 to 4.70 years using various estimation models (21–23)]. The ST of chest radiography is 1 year based on previous reports (24,25). No references to ST of photofluorography could be found; this was assumed to be 3 years in the present study. We estimated E of detected cancers and compared these with observed numbers (O) to calculate the ratio O/E. The observed and expected numbers of detected cancer were compared using the chi-squared test. A sensitivity analysis was used to assess the effect of varying individual model parameters during the construction and testing of the models; this was performed to assess the effects of changes in our assumptions regarding ST and SE. We conducted a sensitivity analysis in the cases in which difference of the ratio O/E was significant.

RESULTS

Table 1 presents the distribution of all participants by 5-year age group and by gender. From establishment of the study in February 2003 to January 2004, 3786 participants were enrolled: 2061 males and 1725 females. In both genders, most participants (over 25%) were in the 60- to 64-year age

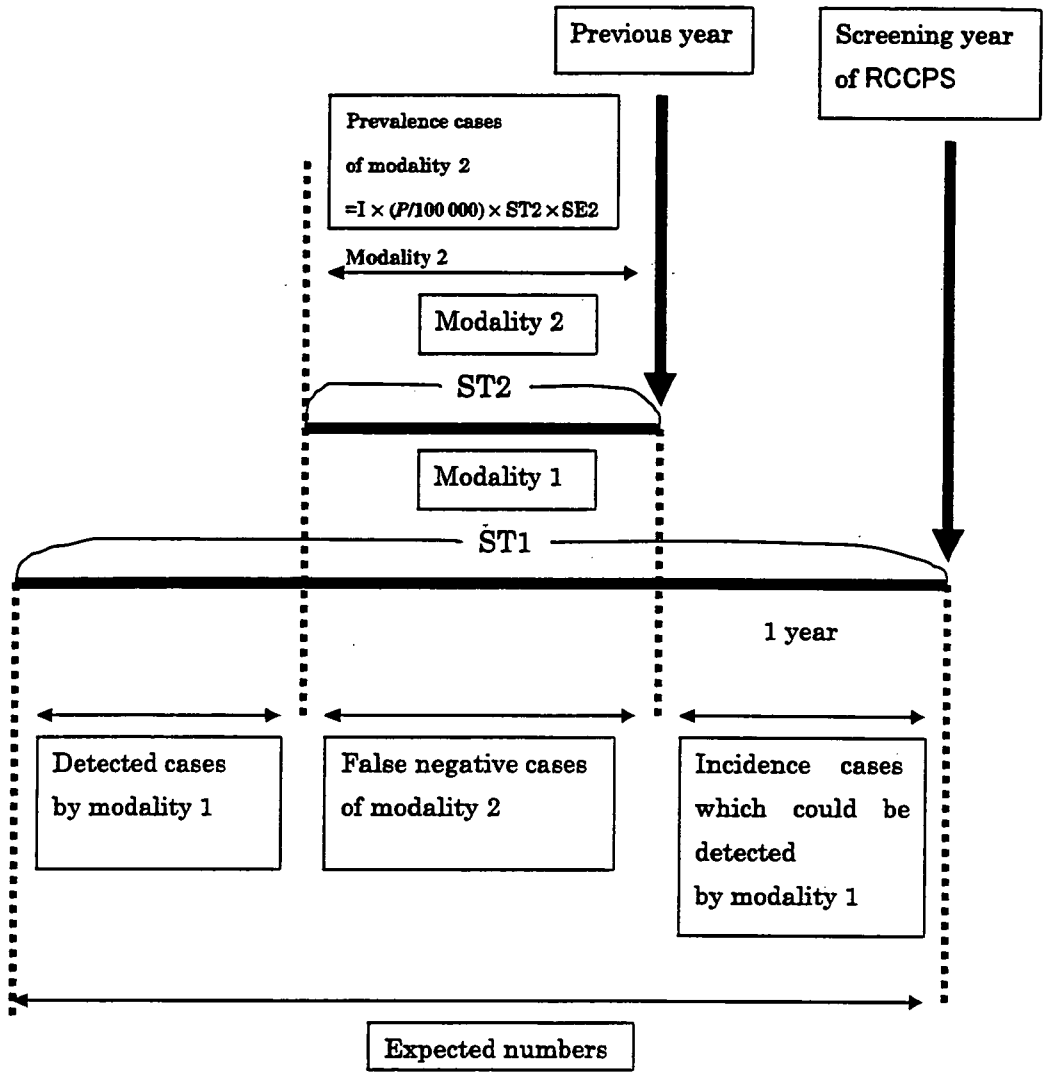

Figure 3. Calculation of expected numbers with previous examination using different modalities. RCCPS: Research Center for Cancer Prevention and Screening; I: Incidence; P: Target population numbers; SE: Sensitivity; ST: Sojourn time.

groups. Of participants over 70 years of age, 5.5% (114/2061) were males and 3.9% (67/1725) were females. Almost 90% of participants came from the Tokyo metropolitan area and the seven surrounding prefectures. Regarding colorectal cancer screening, TCF was performed in 83.6% (1723/2061) of male participants and 77.8% (1342/1725) of female participants, and the remaining 15.4% (317/2061) of male and 19.9% (343/1725) of female participants had BE. PET scans were performed for 79.0% (1629/2061) of males and 74.3% (1282/1725) of females. In the first year of the RCCPS programs, 190 cancers were detected (Table 2). The detection rate for all cancers was 5.8% (119/2061) for males and 4.1% (71/1725) for females. Approximately twice as many males as females had undergone TCF within the previous year (Table 3). In contrast, GFS had been performed in similar numbers of males and females. The frequency of MMG within the previous year was 18.5% (317/1712).

Expected numbers of detected cancers were calculated by classifying participants into groups by screening modalities for gastric, colorectal, lung, prostate and breast cancer (Table 4). In males, expected numbers of cancers were as follows: gastric cancer, 15.3 cases; colorectal cancer, 2.3 cases for BE and 21.9 cases for TCF; lung cancer, 10.9 cases; and prostate cancer, 7.0 cases. In females, expected numbers were as follows: gastric cancer, 3.7 cases; colorectal cancer, 1.1 cases for BE and 7.6 cases for TCF; lung cancer, 2.4 cases; and breast cancer, 6.2 cases. For TCF screening, observed numbers were almost equal. The observed numbers for gastric cancer were almost two times than expected numbers. But, in females, it was not significantly different. On the other hand, lung cancer was observed seven times more often in females but nearly equal in males. Prostate cancer and breast cancer were both detected over two times more frequently than expected. On the sensitivity analysis of prostate, breast and lung cancer screening for females, expected numbers of prostate and lung cancer increased in accordance with ST and SE. For prostate cancer screening, *O/E* ratio ranged between 5.36 and 16.07 according to SE values from 30 to 90% when ST was set at 5 years;

Table 1. Distribution of participants in RCCPS (February 2004–January 2005)

All participants	Sex	Age									
		40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80 years over	All
	Male	0	0	311	500	552	554	89	23	2	2061
	(%)	0.0	0.0	15.1	24.2	26.8	26.9	4.3	1.1	0.1	100.00
	Female	126	156	260	375	429	312	51	14	2	1725
	(%)	7.3	9.0	15.1	21.7	24.9	18.1	3.0	0.8	0.1	100.00
Examinees within participants											
BE	Male	0	0	48	69	91	92	13	3	1	317
	Female	25	31	46	66	86	77	7	4	1	343
TCF	Male	0	0	257	427	488	457	73	20	1	1723
	Female	97	121	208	298	337	230	40	10	1	1342
PET	Male	0	0	250	405	450	423	78	21	2	1629
	Female	78	114	196	276	334	228	41	13	2	1282

BE: barium enema; TCF: total colonoscopy; PET: positron emission tomography.

Table 2. Age distribution of screen-detected cancer and detection rate by screening modality among the participants in the RCCPS (February 2004–January 2005)

Cancer	Modality	Sex	Examinees	Detected numbers (years)										Detection rate (%)
				40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	Above 80	All	
Esophagus	GFS	Male	2040	0	0	0	0	2	5	1	0	0	8	0.39
		Female	1684	0	0	0	0	0	0	0	0	0	0	0.00
Stomach	GFS	Male	2042	0	0	0	5	11	10	2	0	0	28	1.37
		Female	1684	0	1	2	0	1	3	0	0	0	7	0.42
Colon and rectum	BE	Male	317	0	0	0	1	1	1	1	0	0	4	1.26
		Female	342	0	0	1	1	0	2	0	0	0	4	1.17
Colon and rectum	TCF	Male	1723	0	0	3	1	9	10	3	0	0	26	1.51
		Female	1342	0	0	4	1	3	6	0	1	0	15	1.12
Lung	CT	Male	2061	0	0	1	2	3	7	0	1	0	14	0.68
		Female	1697	2	1	5	5	1	3	1	0	0	18	1.06
Prostate	PSA	Male	2042	0	0	1	3	5	12	2	1	0	24	1.18
Breast	MMG + US + PE	Female	1712	2	3	2	3	2	0	2	0	1	15	0.88
Others		Male	2061	0	0	4	0	4	7	0	0	0	15	0.73
		Female	1725	1	2	2	2	1	2	1	1	0	12	0.70
All cancer		Male	2061	0	0	9	12	35	52	9	2	0	119	5.77
		Female	1725	5	7	16	12	8	16	4	2	1	71	4.12

GFS: gastrofiberscopy; BE: barium enema; TCF: total colonoscopy; CT: computed tomography;PSA: prostate specific antigen; MMG: mammography; US: ultrasonography; PE: physical examination.
Detected cancers included these cases: multiple cancers at the same organ (5 persons, 11 cancers) and multiple cancers at multiple organs (6 persons, 13 cancers).

observed numbers of prostate cancer always exceeded expected numbers at any cases if ST was changed from 5 to 15 years. For lung cancer screening for females, *O/E* ratio ranged between 6.72 and 12.10 according to SE values from 50 to 90% when ST was set at 5 years; observed numbers of breast cancer were three times more than expected at any cases if ST was changed from 5 to 10 years.

DISCUSSION

The efficacy of reducing mortality rates from cancer has been established for several cancer screening programs. Based on these studies, the research group for cancer screening in Japan recommended the following six cancer screening programs (2): photofluorography for gastric cancer, fecal occult blood

Table 3. Proportion of having previous investigations within a year by screening modalities

Examination	Modality	Previous examination within a year	
		Male (%)	Female (%)
Stomach	XP	43.5 (887/2040)	30.0 (505/1684)
	GFS	28.7 (586/2040)	23.3 (393/1684)
Colon and rectum	FOBT	52.7 (1074/2040)	40.7 (685/1684)
	BE	4.9 (99/2040)	3.0 (50/1684)
	TCF	15.4 (315/2040)	8.3 (139/1684)
Lung	Chest X-ray	73.9 (1524/2061)	62.0 (1052/1697)
Breast	MMG	–	18.5 (317/1712)

The percentage of previous examination compared males and females using the chi-squared test.
XP: gastrophotofluorography; FOBT: fecal occult blood test; GFS: gastrofiberscopy; BE: barium enema; TCF: total colonoscopy.
PSA: prostate specific antigen; MMG: mammography; US: ultrasonography; PE: physical examination.

test for colorectal cancer, chest radiography and sputum cytology for lung cancer, Pap smear for cervical cancer, a combination of physical examination and mammography for breast cancer, and hepatitis virus markers for hepatocellular carcinoma. Recently, the guideline for colorectal cancer screening has been revised, and chemical and immunological fecal occult blood tests have been recommended as population-based screening (20). Both TCF and BE could be introduced in opportunistic screening as long as well-controlled risk management is performed. Although these guidelines follow evidence-based cancer screening programs, new modalities which show no evidence of mortality reduction have rapidly been disseminated. These new modalities, such PET, CT and GFS, possess high sensitivity and are therefore anticipated to detect early cancer; however, while they are useful for cancer detection, their effectiveness in cancer screening is unclear.

The detection rates in our study were higher than those of population-based screening (20). There are two possibilities for this difference. First, for over 70% of participants, it was the first experience that they were examined by GFS, TCF, BE, CT and MMG. When screening is initiated, an apparent excess of diagnosed cancers is inevitable, because in the first round of screening a large number of cancers that would have occurred in future are diagnosed earlier. Second, the sensitivity of the modalities in our study was superior to those of population-based screening (18–20). Population-based screening programs have been conducted using chest radiography and sputum cytology for individuals at high risk of lung cancer, while similar programs using photofluorography for gastric cancer and immunological fecal occult blood testing for colorectal cancer have also been performed. Considered these conditions, we calculated the expected numbers of detected cancers in our cohort based on assumptions of sensitivity and sojourn time in several modalities. The difference of observed and expected numbers could be changed according to use of the data. We conducted a sensitivity analysis to investigate the robustness because it was possible that our conclusion would be changed according to the data used for the analysis. For example, we used incidence rates obtained from population-based cancer registries. The incidence rate from cancer registries is the weighed average of incidence among the population with and without previous history of screening. These assumptions might introduce under- or overestimation.

In the cases of prostate, breast and gastric cancer for males and lung cancer for females, the observed numbers exceeded expectation and were similar to those expected in the other cases. High detection rate is a consequence of the screening itself, i.e. overdiagnosis, especially in prostate and lung cancer for females. Overdiagnosis has been pointed out and was a major harm in both screening programs (26). Although the test was conducted using the same modality for lung cancer screening, the results were different between males and females in our study. The difference of two groups might be explained by the difference of the history of chest radiography. Strauss et al. (27) state that the overdiagnosis hypothesis is counter to virtually all known data on the natural history and biological behavior of lung cancer. In recent screening studies, both detection rate and stage I cancer by CT exceeded that of chest radiography (28,29). For the very reason, overdiagnosis could be a more serious problem for CT screening. On the other hand, the cut-off point for prostate cancer screening is controversial. PSA value of 4.0 ng/ml is a popular cut-off point for prostate cancer screening; 2.7 ng/ml was used in the present study. However, only two cases (8.3%) of the detected prostate cancers exhibited PSA levels below 4.0 ng/ml. In the European Randomized Study of Screening for Prostate Cancer, the cut-off PSA level was changed from 4.0 to 3.0 ng/ml (30). Krumholtz and colleagues (31) found a prostate cancer incidence rate of 22% in patients with 2.6–4.0 ng/ml PSA based on biopsies of 94 patients with clinical stage T1c. Recently, the prevalence of prostate cancer was reported to be 14.9% for those with PSA values below 4.0 ng/ml (32). Of these tumors, 15% contained Gleason pattern 4, indicating that high-grade cancer occasionally occurs in the presence of low PSA. Disagreement exists as to the best cut-off value for PSA. Greater detection of prostate cancer increases the risk of overdiagnosis and overtreatment, which can cause erectile dysfunction and urinary incontinence. The risk of overdiagnosis has been reported as more than 48% within a screening population with a 4-year screening interval (13). Etzioni and colleagues calculated the overdiagnosis rates of prostate cancer screening as 29% for whites and 44% for blacks, based on SEER-Medicare database (14). Men with low-grade prostate cancer (Gleason score of 2–4) have minimal risk of dying from prostate cancer during 20 years of follow-up compared with men with high-grade prostate cancer (Gleason score of 8–10) (33). On the other hand, Bill-Axelson et al. (34) reported that radical prostatectomy reduces disease-specific mortality and overall mortality compared with watchful waiting. Including selection of therapy, the efficacy of prostate

Table 4. Comparison of the observed and expected numbers of cancer by screening modality

Cancer screening	Modality	Baseline analysis		Male				Female			
		Sensitivity (%)	Sojourn time (years)	Observed numbers	Expected numbers	*O/E*	*P*-value	Observed numbers	Expected numbers	*O/E*	*P*-value
Stomach	GFS	70	5	28	15.31	1.83	0.0463	7	3.69	1.90	0.3649
Colon and rectum	BE	70	5	4	2.25	1.78	0.4120	4	1.08	3.70	0.1781
	TCF	70	10	26	21.90	1.19	0.5610	15	7.64	1.96	0.1427
Lung	CT	80	5	14	10.86	1.29	0.5473	18	2.38	7.56	0.0021
Prostate	PSA	70	10	24	7.00	3.43	0.0022	–	–	–	–
Breast	MMG+US+PE	80	5	–	–	–	–	15	6.22	2.41	0.0488

The observed and predicted numbers of detected cancer were compared using the paired *t*-test. XP: gastrophotofluorography; FOBT: fecal occult blood test; GFS: gastrofiberscopy; BE: barium enema; TCF: total colonoscopy; PSA: prostate specific antigen; MMG: mammography; US: ultrasonography; PE: physical examination. *O/E* = observed numbers/expected numbers.

cancer screening programs is still unclear. Although the cancer screening programs in the present study increased the detection of potentially curable cancers, these modalities might detect tumors that would not be clinically significant. We should accordingly weigh up the benefits and harms of cancer screening using these modalities, and such information should be given to the participants of our study.

The present study is the first report from the RCCPS and has several limitations. First, our cohort of around 4000 volunteers is insufficient to observe reduction of mortality rates from specific cancer and no comparable group was included. Second, participants were volunteers who were receptive to screening by the new modalities. Hence, a self-selection bias could not be excluded. In the present study, we estimated expected numbers using a simple model based on approximate assumptions. However, to estimate correct sojourn time accurately and to modify our model accordingly, lengthy follow-up is needed. We have started follow-up studies, which include an annual questionnaire survey of participants and a hospital survey to acquire information on cancer patients. Information concerning interval cancer can be obtained through this survey, and sensitivity and sojourn time of several cancers can be reinvestigated based on the new model. In addition, we aim to investigate all participants using the same modalities after 5 years and are planning further programs to evaluate the accuracy of the screening modalities.

Acknowledgments

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A Multicenter Randomized Controlled Trial to Evaluate the Effect of Adjuvant Cisplatin and 5-Fluorouracil Therapy after Curative Resection in Cases of Pancreatic Cancer

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Background: There have been few randomized controlled clinical trials until now to determine the effectiveness of adjuvant treatments for pancreatic cancer, and the results reported so far are inconsistent.

Methods: Patients with invasive ductal pancreatic cancer who underwent radical surgery with clear histological margins at 11 Japanese institutions were enrolled and randomly assigned to one of two groups: surgery-alone group (no further treatment after surgery) and the surgery + chemotherapy group [two courses of postoperative adjuvant systemic chemotherapy with cisplatin (80 mg/m^2, Day 1) and 5-fluorouracil (500 mg/m^2/day, Days 1–5)]. Patients with a positive resectional margin or with resected distant metastases were excluded from the trial in order to minimize the influence of residual cancer.

Results: Between 1992 and 2000, 89 patients were randomized into the two arms of the trial (45 patients to the surgery + chemotherapy arm and 44 patients to the surgery-alone arm). Four patients in total were found to be ineligible (three in the surgery + chemotherapy group and one in the surgery-alone group). The baseline characteristics were comparable between the two groups. In the surgery + chemotherapy group, four patients did not receive the adjuvant treatment because of patient refusal. Toxicity was minor and acceptable among the eligible patients in the surgery + chemotherapy group. The estimated 5-year survival rates were 26.4% in the surgery + chemotherapy group and 14.9% in the surgery-alone group, and the median duration of survival was 12.5 months and 15.8 months, respectively. The recurrence rates at 5 years were 73.6 and 80.8%, respectively, in the surgery + chemotherapy and the surgery-alone groups. The differences in the survival and recurrence rates between the two groups were not statistically significant.

Conclusions: Postoperative adjuvant chemotherapy using cisplatin and 5-fluorouracil was safe and well tolerated; however, no clear survival benefit could be demonstrated.

Key words: adjuvant – chemotherapy – clinical trials – pancreatic neoplasms

INTRODUCTION

Pancreatic cancer is the fifth most common cause of death from cancer in Japan (1) and the United States (2), and its incidence is rising. Although radical resection appears to be the only means to obtain a cure, the 5-year survival rate after potentially curative resection remains extremely low, in the range of 5–30% (3–5). Therefore, effective adjuvant therapy is currently being sought. The Gastrointestinal Tumor Study Group (GITSG) performed the first multicenter randomized controlled trial to evaluate the efficacy of adjuvant treatment (6), and they concluded that adjuvant chemoradiotherapy prolonged the postoperative survival of patients with pancreatic cancer. However, the results of a few subsequent randomized controlled trials (7–10) have been inconsistent, and further evidence concerning the effectiveness of adjuvant treatments for pancreatic cancer is awaited. Combination chemotherapy with 5-fluorouracil (5-FU) and cisplatin was considered to be a promising regimen for pancreatic cancer in the early 1990s (11,12). Based on our experience of using

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this regimen in patients with unresectable pancreatic cancer, we expected that it might prove to be suitable for postoperative adjuvant treatment (13). In 1992, we initiated a multicenter randomized controlled trial to evaluate the efficacy of adjuvant chemotherapy with cisplatin and 5-FU after margin-negative resection in patients with pancreatic cancer.

METHODS

PATIENTS AND DESIGN

Patients with ductal pancreatic cancer who underwent resectional surgery with histologically clear margins between April 1992 and March 2000 in 11 Japanese institutions were enrolled for the present study. Patients with other pancreatic and periampullary neoplasms, such as intraductal papillary mucinous neoplasm, cystadenocarcinoma and endocrine tumor, were excluded. Presence of distant metastases, even if they were resected, and presence of peritoneal seeding were regarded as criteria for exclusion from the study. After we obtained their written informed consent, the patients were registered with the randomization center by fax within 10 weeks of surgery and were then randomly assigned to one of two groups: the surgery-alone group and the surgery + chemotherapy group. They were stratified according to the institution and tumor stage using the minimization technique. The tumor stage was determined according to either the fourth or fifth edition of the UICC TNM classification, depending on the time of patient registration, and the patients were divided into two categories for stratification as follows: those with tumor in stage I or stage II according to the fifth edition (14) [equivalent to stage I of the fourth edition (15)] were assigned to one group and the remaining patients were included in the other group. Resection procedures and the range of dissection were determined according to institutional policy. Handling and histological examination of the resected specimens were carried out according to the recommendations of the Japan Pancreatic Society (16). Patients in the surgery-alone arm and those in the surgery + chemotherapy arm were followed up at 3 month intervals. Blood tests and imaging by computed tomography or ultrasound were carried out. Diagnosis of recurrence was made based on the imaging findings. Treatment after recurrence was not defined. All data were collected at a central registration office. Three pathologists performed the pathology reviews for the first 18 cases; thereafter, institutional histological diagnoses were relied upon. No external beam radiation was given to any of the patients. Intraoperative irradiation was administered on an institution-by-institution basis, and this was given to all candidates of any institution who opted to use it. The trial was conducted with the approval of the local ethics committee at each institution.

ADJUVANT CHEMOTHERAPY

Chemotherapy was started within 1 week of randomization. Two courses of treatment with a combination regimen of 5-FU and cisplatin were administered. Cisplatin was administered at a dose of 80 mg/m^2 on the first day of the treatment course; 5-FU was given at a daily dose of 500 mg/m^2 as a continuous infusion for the first 5 days of the treatment course. The second course was repeated 4–8 weeks after the start of the first course. Toxicity was assessed according to the World Health Organization (WHO) guidelines (17). The second course was withheld if toxicity of grade 3 or above severity was observed or if the patient's condition did not improve sufficiently to fit the eligibility criteria for registration within 8 weeks of the start of the initial course.

STATISTICS

The primary endpoint of the study was the duration of survival. Duration of survival was calculated from the date of registration to the date of death due to any cause or was censored at the latest follow-up. The two treatment arms were also compared for recurrence rate. Safety analyses were performed based on data obtained from all the eligible patients who had started chemotherapy. Efficacy analyses were performed according to the intention-to-treat principle. Survival curves were drawn using the Kaplan–Meier technique. Differences in the duration of survival were compared using a two-sided log-rank test, with the significance level set at 5%. The prognostic value of the variables was tested by multivariate analysis using the Cox proportional hazards model. Assuming an overall 2-year survival rate of 15% in the surgery-alone arm, the present study was designed to enroll more than 86 patients in order to detect an absolute increase by 25% (i.e. 40% survival rate for 2 years) in the surgery + chemotherapy arm, at a significance level of 5% with 80% power.

RESULTS

PATIENT CHARACTERISTICS

Between April 1992 and March 2000, 89 patients were randomized: 45 patients to the surgery + chemotherapy arm and 44 patients to the surgery-alone arm. Three patients in the surgery + chemotherapy group and one in the surgery-alone group were rated ineligible, resulting in 95.5% compliance. The reasons for ineligibility included resected distant metastases (two cases), histologically positive resection margin (one case) and severe postoperative complication (one case). The baseline characteristics of the patients in the two groups were comparable (Table 1).

TREATMENT DATA

Four patients assigned to the surgery + chemotherapy arm refused treatment after randomization, and the detailed data for three ineligible patients were not available. As a result, a total of 38 patients were evaluated for treatment toxicity. Of these, 31 patients (81.6% of the patients who received chemotherapy) received two courses of chemotherapy, and 7 patients received only one course of chemotherapy. The reasons for treatment discontinuation were patients' withdrawal from the

Table 1. Demographic and clinical data for the patients

	Surgery + chemotherapy	Surgery alone
Gender (M:F)	29:16	21:23
Age (mean ± SD)	60.8 ± 8.1	60.1 ± 8.9
Operative procedure (pancreaticoduodenectomy:others)	37:8	34:10
Intraoperative irradiation (30:0 Gy)	30:15	27:17
Location of the tumor (head:body/tail)	35:9	34:8
Size of the tumor (<4:≥4 cm)	35:10	36:8
Histological type (papillary and well-differentiated:others)	24:21	21:23
Nodal involvement (present:absent)	12:23	9:35
pT (pT1–3:pT4)	36:9	33:11

trial (four cases), development of recurrent disease (two cases) and unresolving leucopenia (one case).

Toxicity

One ineligible patient who was suffering from a severe post-operative complication that was not documented at the time of registration died of sepsis after one course of chemotherapy. Minor toxicity was commonly observed, especially nausea and vomiting, among the 38 eligible patients who actually received the adjuvant chemotherapy. In a few patients, toxicities of grade 3 or higher severity were encountered (Table 2). However, the toxicities were reversible and resolved with conservative treatment alone in all patients.

Table 2. Summary of toxicities according to WHO criteria (n = 38)

	Grade 1	Grade 2	Grade 3	Grade 4
Nausea/vomiting	15	12	5	0
Leukopenia	14	6	2	0
Granulocytopenia	6	5	3	1
Thrombocytopenia	7	2	0	0
Mucositis	1	1	2	0
Cardiac	0	0	0	0
Hepatic	17	9	3	0
Renal	3	1	0	0

Table 3. Sites of recurrence

	Surgery + chemotherapy	Surgery alone
Liver	20	22
Peritoneum	10	9
Pleura	1	1
Local recurrence	6	7
Lymph node	3	1
Lung	1	1
Bone	1	1
Skin	0	2
Brain	1	0
Number of patients with recurrence	32	34

Recurrence

Seventy-one patients died and 18 patients were alive at the end of the follow-up period. The median follow-up duration for the survivors was 44.8 months. The recurrence status remained unknown in one ineligible patient. Among the remaining 88 randomized patients, 34 (77.3%) in the surgery-alone group and 32 (71.1%) in the surgery + chemotherapy group developed recurrence. The recorded sites of recurrence are shown in Table 3. The liver was the most frequent site of recurrence for metastasis, followed by peritoneal seeding and local recurrence, in both groups. There was no significant advantage of adjuvant chemotherapy in terms of the recurrence rate (Figure 1). The median time to recurrence was 10.2 months in the 44 patients in the surgery-alone group and 8.6 months in the 44 patients in the surgery + chemotherapy group. The 5-year recurrence rates were 80.8 and 73.6%, respectively, in the two groups (P = 0.80).

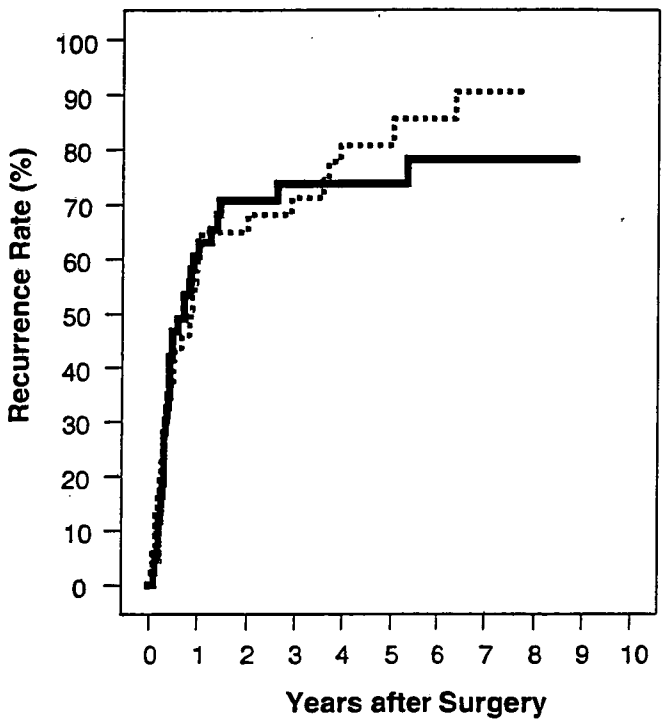
Duration of Survival

In the randomized patients, the cause of death was recurrent disease in 63 patients (32 from the surgery-alone group and 31 from the surgery + chemotherapy group), in-hospital death in 1 patient (from the surgery + chemotherapy group), non-malignant/non-toxicity death in 5 patients (3 from the surgery-alone group and 2 from the surgery + chemotherapy group) and unknown in 2 patients (1 from each group). The duration of survival was not influenced by adjuvant chemotherapy in either the randomized or the eligible patients. The survival curves of all the randomized patients are shown in Figure 2. The median survival was 15.8 months in the surgery-alone group and 12.5 months in the surgery + chemotherapy group, and the 5-year survival rate was 14.9% in the surgery-alone group and 26.4% in the surgery + chemotherapy group (P = 0.94).

Prognostic Factors

In order to assess the influence of prognostic factors, the relationship of the outcomes to the following variables were investigated: gender, age, histological type, size of tumor, tumor location, pT factor, nodal involvement, type of operative procedure and administration of intraoperative radiotherapy. Calculation of the correlation coefficients (r) of pairs of variables revealed a close correlation for the tumor location and the type of

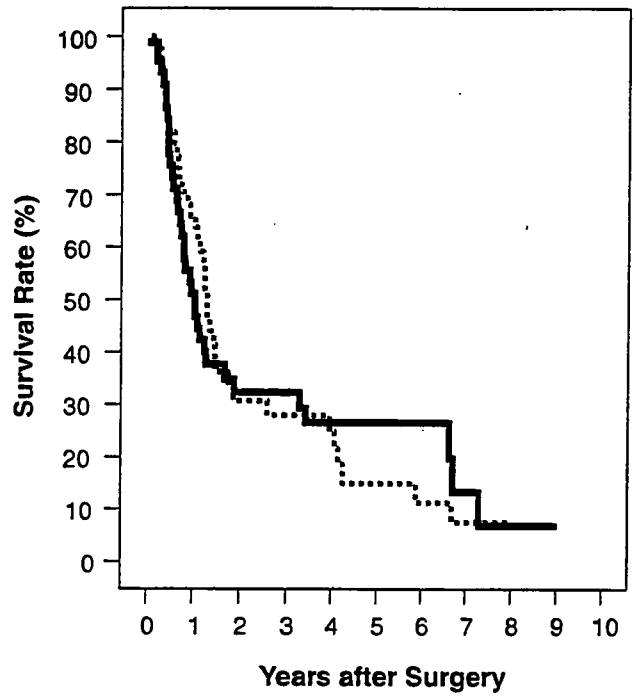
operative procedure ($r = 0.96$), whereas the coefficients for all the other pairs were less than 0.5. Consequently, 'operative procedure' was excluded from the subsequent multivariate analysis. The prognostic value of the remaining variables together with the assigned treatment arm as an additional variable was tested using multivariate analysis. The significant factors determined from this analysis were nodal involvement and the histological type of the tumor (Table 4); the effect of the pT factor was marginal. Consequently, the stage of the disease, the major determinants of which were the nodal status and the pT factor, was determined to be a good prognostic indicator. Patients with tumor in stage I or in stage II according to fifth edition of the UICC TNM classification survived significantly longer than those with more advanced disease (Figure 3). The median survival time in the two groups was 79.7 and 12.6 months, respectively ($P = 0.004$).



No. at risk

Observation	44	18	11	9	6	4	3	2
Chemotherapy	44	16	10	9	6	6	3	2

Figure 1. Cumulative recurrence rate. Solid line: surgery + chemotherapy group; dotted line: surgery-alone group.



No. at risk

Observation	44	29	11	10	8	4	3	2
Chemotherapy	45	23	12	11	7	7	5	2

Figure 2. Cumulative survival rate. Solid line: surgery + chemotherapy group; dotted line: surgery-alone group.

Table 4. Multivariate analysis

Variable	β	SE	*P*	HR	95% CI
Nodal involvement (absent versus present)	1.167	0.348	0.001	3.213	(1.626–6.350)
Histological type (papillary or well-differentiated tubular versus moderately or poorly differentiated tubular)	0.791	0.273	0.004	2.206	(1.291–3.769)
pT factor (pT1–3 versus pT4)	0.528	0.300	0.078	1.695	(0.942–3.050)
Gender (female versus male)	0.393	0.272	0.148	1.482	(0.869–2.526)
Size of tumor (<4 cm versus ≥4 cm)	0.166	0.172	0.334	1.181	(0.843–1.654)
Age	0.017	0.016	0.282	1.017	(0.986–1.049)
Chemotherapy	−0.053	0.254	0.835	0.948	(0.576–1.561)
Intraoperative radiotherapy	−0.280	0.299	0.349	0.756	(0.421–1.357)
Location of the lesion (head versus body or tail of the pancreas)	−0.354	0.291	0.224	0.702	(0.397–1.241)

SE, standard error; *P*, significance; HR, hazard ratio; CI, confidence interval.

DISCUSSION

Resectional surgery provides the only chance of cure for patients with pancreatic cancer. However, in most cases the operation is non-curative, and an extremely high recurrence rate is observed. Consequently, a number of adjuvant treatments have been tried in the hope of prolonging survival. GITSG performed the first randomized controlled trial to evaluate the effect of adjuvant treatment in a group of 43 patients with pancreatic cancer. They concluded that adjuvant chemoradiotherapy after curative resection prolonged patient survival (6). However, subsequent larger studies carried out in Europe failed to show any evident benefit of adjuvant chemoradiotherapy (8–10). Similarly, the value of systemic chemotherapy in an adjuvant setting also remains controversial owing to the scarcity of convincing evidence. Only three randomized controlled trials have been reported to assess adjuvant chemotherapy for pancreatic cancer in the literature (Table 5). Bakkevold et al. (7) claimed that adjuvant combination chemotherapy using 5-FU, doxorubicin and mitomycin C (AMF) prolonged the median survival time in a cohort of postoperative patients with pancreatic or ampullary cancer. However, their results were not definitive, because there was no detailed documentation of the data. Takada et al. found no advantage of adjuvant treatment using mitomycin C and 5-FU in a larger number of patients (18). Neoptolemos et al. (9,10) conducted a prospective randomized trial (ESPAC-1) to assess the effects of two types of adjuvant treatments, namely, chemotherapy and chemoradiotherapy. They concluded that chemotherapy alone improved the survival rate and that chemoradiotherapy may even have had an adverse effect on survival. However, their conclusion remains a subject of debate because of the unorthodox and complex design of the study.

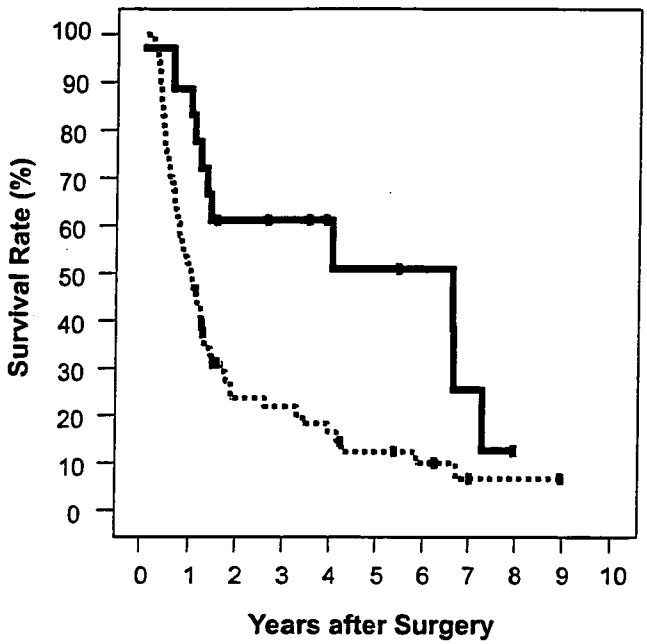


Figure 3. Cumulative survival rate categorized by the disease stage according to the fifth edition of the UICC TNM classification. Solid line: stages I and II; dotted line: stages III, IVa and IVb.

In contrast to the ESPAC-1 trial, our study was simple in design, allowing the comparison of survival between two patient groups: one group with adjuvant chemotherapy and the other group without adjuvant chemotherapy. Patients were stratified according to the institution and stage of the disease in order to minimize the influence of possible prognostic factors. Furthermore, patients with a positive histological margin were excluded from the study with the objective of excluding possible bias introduced by one of the strongest prognostic factors, the status of the resectional margin (19). However, this last criterion did interfere with the rapid recruitment of patients. It took almost 8 years to carry out the registration and randomization of 89 patients. Fortunately, there have been no remarkable changes in the diagnosis or treatment of pancreatic cancer during this period, and the trial could be continued without any major revisions of the protocol. Only two previous trials have evaluated adjuvant treatment for patients with R0 resection (6,7). Both encountered similar difficulties and a smaller number of patients were enrolled

Table 5. Randomized controlled trials of adjuvant chemotherapy for pancreatic cancer

Author	Year of publication	Disorder	Chemotherapy	Number of cases	MST (months)	5-year SR (%)	Significance
Bakkevold et al.	1993	PC and AMP (R0)	AMF	31	23	4	NS with generalized Wilcoxon's test
			Observation	30	11	8	
Takada et al.	2002	PC (R1)	MF	81	NA	11.5	NS with the log-rank test
			Observation	77	NA	18.0	
ESPAC	2004	PC (R1)	5-FU + LV	147	20.1	21	$P = 0.009$ the with log-rank test
			No chemotherapy	142	15.5	8	
Present study		PC (R0)	FP	45	12.5	26.4	NS with the log-rank test
			Observation	44	15.8	14.9	

AMF, doxorubicin + mitomycin C + 5-FU; AMP, ampullary carcinoma; LV, folinic acid; MF, mitomycin C + 5-FU; MST, median survival time; NA, not available; NS, not significant; PC, pancreatic cancer; SR, survival rate.

than in the present study. The patient characteristics, especially the stage distribution and proportion of patients with nodal involvement, were comparable among these trials.

The present study showed that adjuvant combination chemotherapy using 5-FU and cisplatin could be carried out with acceptable safety, as long as the patients met the eligibility criteria, although one patient died of sepsis after a single course of chemotherapy. The monitoring committee, after analysis of the case data, judged that this particular patient was unsuitable for enrollment into the trial. According to the recommendation of the committee, part of the study protocol was modified to clarify some requirements regarding the postoperative condition of the patients. No serious complications were encountered after the modification was carried out.

On the other hand, this trial failed to show any significant benefit of adjuvant chemotherapy in terms of either survival or recurrence, even though the absolute values of the survival rate and recurrence rate at 5 years were slightly better in the patients to whom adjuvant chemotherapy was administered. It is possible that a larger number of patients must be examined to appreciate the statistical significance of the treatment effect. However, a significant influence of the typical prognostic factors on survival was confirmed in the present trial. It is possible that the influence of adjuvant chemotherapy on survival is much weaker than that of these prognostic factors. Another possibility is that further courses of chemotherapy might reinforce the effectiveness of the treatment and allow it to become evident. However, it must also be considered that the life expectancy of patients with pancreatic cancer is extremely short. Adjuvant treatment for pancreatic cancer would be practical only when its beneficial effect can compensate for the compromised quality of life of the patient resulting from the treatment. Therefore, a distinct effect with a short treatment period, besides minimum toxicity, would seem to be the essential prerequisite of effective adjuvant chemotherapy. Otherwise, the lifetime spent with low quality of life can cancel out or even reverse the potentially beneficial effects of adjuvant treatment.

To conclude, the present trial did not prove that the regimen can be recommended as adjuvant treatment for pancreatic cancer.

Contributors

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(The affiliation of each member is the affiliation at the time of the patient recruitment.)

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特別講演

これからの日本のがん対策のあり方

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〔要　旨〕
これからの日本のがん対策のあり方について論じた。
がんという病期の本態の理解にもとづき，がん一次予防，がん二次予防（検診），がん診療を，研究に根ざして進めることが大切である。あわせて，がん登録にもとづくわが国のがんの実態を正確に把握し，その予測にもとづき，戦略を展開する必要がある。そのために，2006年6月に成立した，がん対策基本法は画期的な意味をもつ。この法律に沿う形で，厚生労働省内のがん対策推進室と国立がんセンターが緊密な連携をとり，国立がんセンター内のがん対策情報センターと地域がん診療連携拠点病院のネットワーク化により，がん医療の均てん化を実現する。さらに，たばこ対策や検診事業を強力に展開すれば，わが国でも，がん罹患，がん死の激減が必ず図れるはずである。

キーワード　日本，対がん戦略，がん対策基本法

はじめに

これからの日本のがん対策のあり方について，1. がんとはどういう病気か？　2. がんの一次予防，3. がんの二次予防，4. がん診療の現状と課題，5. わが国の対がん戦略，の5つのパートに分けて考えたい。これは，がんという病気の本質にもとづき，一次，二次予防を組み立て，がん診療の現状を把握し，これらにもとづき，今後のわが国の対がん戦略を組み立てることが合理的と考えるからである。

1. がんとはどういう病気か？

わが国では，年間に約32万人ががんで死亡している[1]。これは亡くなる人の約3人に1人にあたる。遠からず男性の2人に1人，女性の3人に1人ががんになると予想されており，がんは誰にとっても無縁な病気とはいえない状況にある。

全世界的に見ると，年間に約1,000万人の人ががんと診断され，毎年600万人が死亡し，2,200万人ががん経験者あるいはがん闘病者と言われている[2]。がんは先進国はもちろん，発展途上国も感染症が制御されてくると，がんが浮上してくる。この意味で，がんは全世界的な問題であり，World Health Organization（WHO），International Union against Cancer（UICC），International Agency for Research on Cancer（IARC）などの国際機関にとっても，全世界的な連帯で対処すべき大きな課題とされている。

人間の身体は約60兆個の細胞で構成され，1つひとつの細胞の中には核がある。この核の中には折りたたまれたDNAが収納されており，伸ばすと約1メートルとなる。このDANは，約2～3万個の遺伝子が載っており，そのうち，がん遺伝子，がん抑制遺伝子といった，がんに関連する遺伝子が100個以上知られている。がん遺伝子の活性化，がん抑制遺伝子の不活化，その組合せ，さらに遺伝子の発現の調節異常などが組み合わさって，正常細胞ががん細胞に変わり，がん細胞が増殖と分化を続ける。がんは遺伝子異常により惹起

された細胞の病気である。

1981年，Doll[3]らはそれまでの科学的知見をもとにアメリカにおける各がんリスク要因の寄与の割合を推計した。それによると，タバコが31%（25～40%），食事が35%（10～70%），感染が10%（1～?%），飲酒が3%（2～4%）などとなっている。1996年にHarvard Center for Cancer Preventionが再集計したものでも[3]，Dollらの推計と大きくは異ならず，たばこ30%，成人期の食事/肥満30%，運動不足5%，飲酒3%とされ，個人の生活習慣に関連する要因だけで70%を占める。

わが国では，各がんリスク要因の寄与割合を示すデータは必ずしも十分ではないが，Tominaga[5]の推測によれば，全がん罹患数を，禁煙率を半減することにより8.8%，食生活を改善することにより10.3%，感染症を予防根絶することにより7.0%，予防できるとしている。

こうした食品，栄養素，喫煙も含めたがん予防の関係をまとめたものが表1である。これは世界中の4,500にも及ぶ研究成果を一つの表にまとめたもので，具体的でわかりやすい。表では「確定的である」，「ほぼ確実である」，「可能性あり」，と正に働くものを+3，+2，+1，負に働くものを−3，−2，−1で整理した（W&A報告書）[6]。

がんは，[1]遺伝子の異常の蓄積により発生し進展する細胞の病気であり，[2]遺伝子の異常を引き起こす原因としては私たちの生活習慣があり，[3]がんの進展には長い時間を要する慢性の疾患である，とまとめることができる。この理解にもとづき，がんの発生／進展と医療の関わりをみると，図1のようになる。がんの約90パーセントは時間の経過とともに悪化するので，その発生／進展の状況に応じて予防，検診，診療が関わることとなる。一方，前立腺がんや甲状腺がんの一部に見られるような発育速度の極度に遅いがん，膵がんに代表されるような非常に発生／進展スピードの速いがんは，残念ながら予防や検診にはなじまない。こうした，がんの特性の理解にもとづき，がん対策を構築することが大切と思う。

表1　がん予防におけるリスク要因，予防要因の相関図[6]

	リスク⇩					リスク⇧					
がん	野菜	カロテノイド	果物	ビタミンC	身体活動	食塩	肉	卵	肥満	アルコール	喫煙
口腔・咽頭	−3	−3		−1						+3	+3
喉頭	−2	−2								+3	+3
食道	−3	−3	−1	−1						+3	+3
肺	−3	−3	−2	−1						+1	+3
胃	−3	−3	−1	−2		+2					
膵	−2	−2		−1							+3
結腸・直腸	−3		−1		−3		+2	+1		+2	+1
乳房	−2	−2	−1				+1		+2	+2	
子宮頸部	−1	−1	−1	−1							+3
前立腺	−1						+1				
膀胱	−2	−2									+3

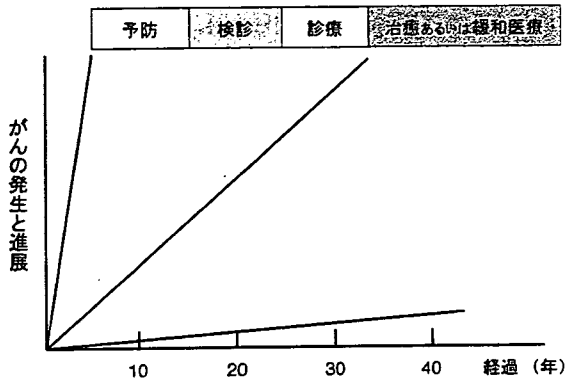

図1　がんの発生／進展と医療

2. がんの一次予防

わが国の喫煙対策上の重要課題としては，全国に散在する63万台の自販機の削減と，青少年に対するアクセス制限。それと，現在一箱300円程度のたばこの価格を少なくとも500円に上げることが，当面の目標として重要と思われる。そうすれば税収は代わらないで，喫煙率は半減すると試算されている。

アルコールは，口腔・咽頭，喉頭，食道，肝臓で確実，大腸，乳房でほぼ確実なリスク要因と考えられている。エタノールは発がん物質の粘膜透過性を高める作用があり，またその代謝物であるアセトアルデヒドがDNA障害性を有することも関連するのであろう。

塩は，W&A報告書では，上咽頭がんにたいして確実，胃がんに対してほぼ確実なリスク要因と評価されている。食塩にはそれ自体には発がん性はないものの，胃壁の粘膜層を破壊し，炎症を引き起こすことにより，用量相関性をもったプロモーター作用があるとする多数の動物実験データがある。これにヘリコバクターピロリ感染が加わると相加的な発がん促進作用があるとされ，日本人の生活習慣と胃がんの関連を考える上で重要である[7]。

運動不足や肥満についてもW&A報告書にある。運動は大腸がんの確実な予防要因とされ，肥満は子宮体がん，乳がん，腎がんに対して確実〜ほぼ確実なリスク要因とされている。これら喫煙と食事のがん予防との関わりについては祖父江[9]の良いレビューがある。

21世紀における国民健康づくり運動，いわゆる「健康日本21」のがん分科会も，生活習慣の改善によるがん予防の重要性を指摘し，喫煙対策，食生活の改善，飲酒対策が数値目標とともにあげられている（表2）[9]。

感染症の中で，日本人のがんにとって重要なのはヘリコバクター・ピロリ菌感染と胃がん，B型肝炎ウイルス，C型肝炎ウイルス感染と肝がん，HTLV-1ウイルス感染と成人T細胞白血病などがあるが，ここでは項目の指摘だけにとどめる。感染症とがんの関連は古くて新しい問題であり，がん細胞をとりまく周囲の微小環境と炎症の関連，浸潤，転移の関係は現在がん研究の中でも大変注目されている分野の一つといえる。

3. がんの二次予防

がんの二次予防は，「がんになっても死なない」ことを目指すものであり，がんの早期発見と早期治療，すなわち検診が重要である。がんの二次予防は，一次予防と同等に大切である。これは，がんは早期には無症状なので，その時に介入して発見し，治療してしまおうとする戦略である。わが国は検診に当初は国をあげて取り組み，現在，胃がん，子宮がん，肺がん，乳がん，大腸がんの5つのがんについて実施されている。胃がんは胃部X線検査によって，子宮頸がんは子宮頸部の細胞診により，肺がんは胸部X線検査と喀痰細胞診により，乳がんは触診とマンモグラフィーにより，大腸がんは便潜血反応によっている。がんの発見率は大よそ受診者の0.1%，検診受診者は対象人口の訳10〜15%とされている。近年は，がん検診に関わる国の関与が弱まっている点がわが国の対がん戦略上，大きな問題である。

がんが一般に高齢者の疾患で，わが国は急速に高齢社会に移行しつつあり，高齢者の母数が大きくなるため，がんになる人も増加する，という事態がまだ続くと予想されている。ところが，図2に示したように，米国を筆頭として，先進国では