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A Phase III study of combination therapy of the oral fluorinated pyrimidine compound tegafur-uracil (UFT) with low dose cisplatin compared with UFT alone in patients with locally advanced gastric cancer as postoperative adjuvant chemotherapy

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Abstract

Background: While surgery remains the sole mainstay of any curative treatment for gastric cancer, the relapse rate is high and survival remains low even after surgical resection with curative intent.

Methods: Based on biochemical modulation theory, this trial was assigned for gastric cancer patients as post operative adjuvant setting with at least 4 cycles of either UFT (UF group) or 5-FU plus low dose cisplatin (CF) and UFT (CD group). The planned 4 cycles of CF treatment was received by 95% of patients in the CD group. One year of UFT was received by 93 (99%) and 91 (97%) of the patients in the groups administered UFT and cisplatin/5FU+UFT, respectively.

Results: The result suggests better 5 year survival rate in the combination treatment group, with a reduction in risk of 13%. 5 year DFS was also showed benefit of combination therapy over UFT alone, with a reduction in risk of 15%.

Conclusion: These findings from our phase III randomized trial suggest that low dose cisplatin+5-FU followed by UFT may hold promise as a treatment for curatively resected locally advanced gastric cancer patients.

Key Words: gastric cancer, adjuvant chemotherapy, low dose cisplatin, combination therapy

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Introduction

Numbers of clinical trials have been conducted on combination and administration schedule of anticancer agents in attempts to increase the clinical response rate and prolong prognosis. For gastrointestinal cancers, 5-fluorouracil (5-FU) and related fluorinated pyrimidine compounds has widely been used and tested in various clinical trials. Combination of protracted infusion of 5-FU combined with low dose cisplatin attracted attention of clinical investigators in terms of their reciprocal and synergistic actions. Briefly, cisplatin inhibits the transport of neutral amino acids, increasing L-methionine and also induced an elevation of the intracellular levels of reduced folates such as 5, 10-methylenetetrahydrofolate (CH_2FH_4) and tetrahydrofolate, whereby the increase of CH_2FH_4 resulted in a 2.5 fold increase in the binding of FdUMP to TS, thereby enhancing cytotoxic effect of fluorinated pyrimidines[1]. This mechanism is basically different from the previous combination of 5-FU plus high dose cisplatin[2] in terms of the biochemical point of view and was considered to exert comparable antitumor effect with milder toxicity to the patients.

A phase I/II study was conducted to evaluate a combination of continuous 5-FU infusion and consecutive low-dose cisplatin for advanced gastric cancer[3]. In this study, enrolling 31 patients demonstrated over 80% of response rate with less toxicity compared to widely used 5-FU+high dose cisplatin regimen, with a MST of 11 months[3].

In this regard, the present phase III randomized clinical trial involves in the comparisons of the effect of low dose cisplatin combined with one of the oral fluorinated

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pyrimidines, tegafur-Uracil (UFT) over the UFT alone for locally advanced gastric cancer in an adjuvant setting.

Patients and Methods

Patients and Treatment

Eligible patients were 20 to 80 years of age and had undergone macroscopically complete resection of histologically proven Stage IIIa, IIIb and IVa gastric cancer. Prior chemotherapy, immunotherapy or radiotherapy was not permitted. All patients provided written informed consent, and the study was approved by the ethics committee of the participating centers.

In this open labeled study, patients were randomly assigned to receive at least 4 cycles of either UFT (UF group) or 5-FU plus low dose cisplatin (CF) and UFT (CD group).

UFT was purchased from Taiho Pharmaceutical Co. Ltd (Tokyo, Japan), cisplatin was obtained from Bristol-Myers Co. (Wallingford Conn USA). In the UF group, UFT, which is a combined form of 1 M tegafur and 4 M uracil, was administered orally at dose of 200 mg/m^2 twice daily. In the CD group low dose cisplatin 5 mg/body was infused on days 1 to 5 together with 5-FU 350 mg/body/day. This treatment was continued for 6 cycles in repeated administration followed by the same dose and schedule of UFT as in the UF group.

Follow-up

Patients were evaluated before random assignment, every two weeks during treatment, and then every 6 months up to 5 years after completion of study. Assessments were made for relapse, second cancers, late toxicity, and death. The cutoff dates for final analysis was May 31, 2005. Adverse events were graded according to National Institute Common Toxicity Criteria, version 1.

Statistical Analysis

Random assignment was performed centrally; the minimization method was used to balance treatment allocation according to the TNM stage (IIIa, IIIb, IVa), curability (R1 or R-2) and the medical center. The original planned sample size was 378 patients which provided a power of more than 80% to detect a difference in survival with a two sided $\alpha=0.05$ derived with the use of the log-rank test. The primary efficacy variable was OS, which was defined as the time from the date of curative resection to death from any cause.

The secondary endpoint was DFS, defined as the time from the date of curative resection to relapse or death, whichever occurred first. The duration of follow-up was defined as the number of months from the operation until the last follow-up visit or data cutoff. Second gastric cancers were considered relapses, whereas non-gastric tumors were disregarded in the analysis.

Comparisons of OS and DFS between groups according to the intent-to -treat (ITT) principle were performed using a two-sided stratified log-rank test. Analysis adjusted by disease stage, were performed using Cox regression modeling. Hazard ratios (HR) with 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model. Survival curves were presented according to Kaplan-Meier methods. Subgroups used to identify prognostic factors for survival included age, sex, stage, lymphatic duct invasion, venous invasion, and macroscopic type of gastric cancer.

The final OS and DFS analysis was performed as per the initial protocol when the last patient included had 5 years of follow up. Safety was analyzed in all patients who received at least one dose of protocol-specified treatment (safety population).

Results

Patient and Treatment

Between May 1, 1996 and March 31, 2000, 190 patients were enrolled, 95 in each treatment arm. One patient in UF group was excluded from the analysis because of far advanced stage IVb disease. One patient in the CD group was also excluded because of synchronous multiple cancer, detected within one year after operation. Patient characteristics were well matched between the two treatment groups (Table 1). In these groups, approximately 50%, 40%, and 10% of patients had stage IIIa, IIIb, and IVa disease, respectively. At least one cycle of study treatment was received by 93 patients in the UF group and 92 patients in the CD group. The planned 4 cycles of CF treatment was received by 95% of patients

Table. 1 Patient Characterisitics

Characteristic	CD (N=94) No. of Patients	%	UF (N=94) No. of Patients	%	Overall (N=188) No. of Patients	%	P Value*
Sex							
Male	60	63.8	60	63.8	120	63.8	1.000
Female	34	36.2	34	36.2	68	36.2	
Age, years							
20-49	12	12.8	8	8.5	20	10.6	0.950
50-59	31	33.0	32	34.0	63	33.5	
60-69	29	30.9	38	40.4	67	35.6	
70-	22	23.4	16	17.0	38	20.2	
Clinical Staging							
IIIa	38	40.4	47	50.0	85	45.2	0.223
IIIb	42	44.7	35	37.2	77	41.0	
IVa	14	14.9	12	12.8	26	13.8	
Histlogic Nodal Status							
n0	1	1.1	2	2.1	3	1.6	0.614
n1	35	37.2	35	37.2	70	37.2	
n2	43	45.7	46	48.9	89	47.3	
n3	15	16.0	11	11.7	26	13.8	
Histology							
differenciated	37	39.4	34	36.2	71	37.8	0.972
undifferenciated	55	58.5	50	53.2	105	55.9	
other	2	2.1	10	10.6	12	6.4	
Curability							
B	90	95.7	90	95.7	180	95.7	1.000
C	4	4.3	4	4.3	8	4.3	

Abbrebiations: CD, low dose CDDP+5-FU followed by UFT; UF, UFT alone.

*P values are for the differences from the two groups.Those of sex and histology were calculated using the two-sided chi-square test. The others were calculated using the two-sided Wilcoxon rank-sum test.

in the CD group. One year of UFT was received by 93 (99%) and 91 (97%) of the patients in the groups administered UFT and cisplatin/5FU+UFT, respectively. The median cisplatin dose received per patient in the CD group was 125 mg. The median UFT dose received per patient was 171 g in the UF group and 134 g in the CD group.

OS in eligible patients

While a follow-up time of 8.5 years, the probabilities of surviving at 5 years were 48.4% and 40.7% in the CD and UF groups, respectively (HR=0.87; 95%CI, 0.60 to 1.26 ; p=0.46; Fig. 1) corresponding to a 13% reduction in the risk of death in favor of CD combination chemotherapy. Because the disease stage was the main prognostic factors for OS (for stage IIIb; HR=1.95; 95% CI, 1.29-2.95; p=0.0015, for stage IV; HR=3.39; 95%CI, 2.01-5.71; p<0.0001) additional independent OS analyses were performed for patients with stage IIIa, IIIb, and IVa tumors. However, the interaction between stage of the disease and treatment was not statistically significant. Overall, there were 54 deaths in the CD group and 58 deaths in the UF group. The vast majority of deaths were a result of relapse or recurrence with 46 and 54 of deaths in CD and UF group being a result of adverse events. The median time from relapse to death was 6 months for the CD group and 7 months for the UF group.

OS in stage IIIa, IIIb, and stage IVa

Among the patients with stage IIIa disease (n=48 and n=51 in the CD and UF groups, respectively), the probabilities of surviving at 5 years were 66.1% and 53.9%, respectively, corresponding to a 25% risk reduction in favor of CD treatment (HR=0.75; 95%CI, 0.42 to 1.35; p=0.36) (Fig. 2A). Among the patients with stage IIIb disease (n=33 and n=32 in the CD and UF groups, respectively), the probabilities of surviving at 5 years were 36.4% and 31.3%, respectively, corresponding to a 4.0% risk reduction in favor of UF treatment (HR=1.04; 95%CI, 0.58 to 1.86; p=0.91) (Fig. 2B). Also, among the patients with stage IVa disease (n=13 and n=11 in the CD and UF groups, respectively), the probabilities of surviving at 5 years were 15.4% and 9.1%, respectively, corresponding to a 51% risk reduction in favor of CD treatment (HR=0.49; 95%CI, 0.21 to 1.17; p=0.11) (Fig. 2C).

DFS in all Patients

During a follow-up time of 8.5 years for both groups, the number of patients who had an event was 56 (59.6%) in the CD group and 61 (64.9%) in the UF group. The HR for DFS was 0.85 (95%CI. 0.59 to 1.22; p=0.37), corresponding to a 15% risk reduction of DFS in favor of CD treatment (Fig. 3).

Five Year DFS in Stage IIIa, IIIb, and Stage IVa

Among patients with stage IIIa disease, the probabilities of DFS events at 5 years were 62.0% and 48.0% in the CD and UF groups, respectively (HR=0.79; 95%CI, 0.45 to 1.37; p=0.40) (Fig. 4A). Among stage IIIb patients, the probabilities of DFS events at 5 years were 36.4% and 28.1% in the CD and UF groups, respectively (HR=0.94; 95%CI, 0.53 to 1.68; p=0.83) (Fig. 4B). Also, among IVa patients, the probabilities of DFS events at 5 years were 11.2% and 9.1% in the CD and UF groups, respectively (HR=0.54; 95%CI, 0.22 to 1.32; p=0.18) (Fig. 4C).

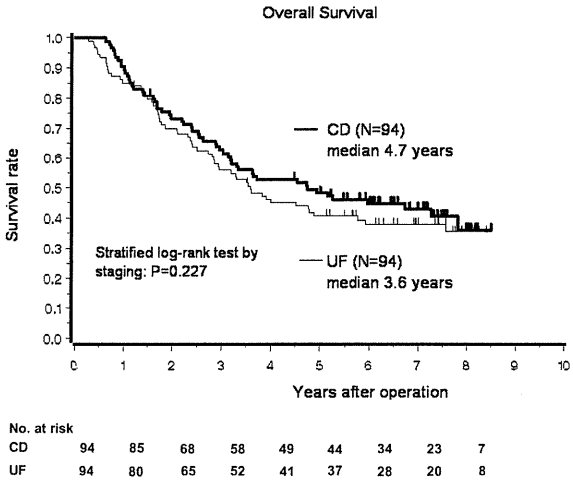

Fig. 1 Kaplan-Meier estimates of Overall Survival

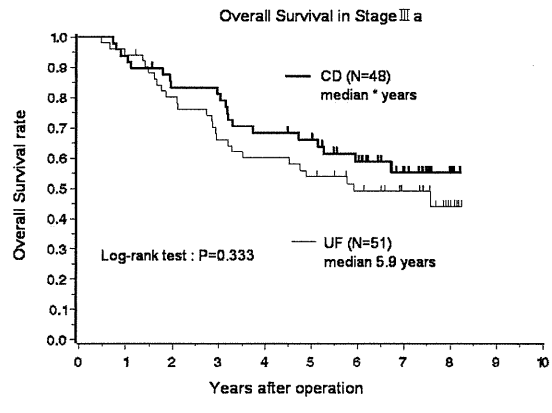

Fig. 2A Kaplan-Meier estimates of Overall Survival in Stage IIIa

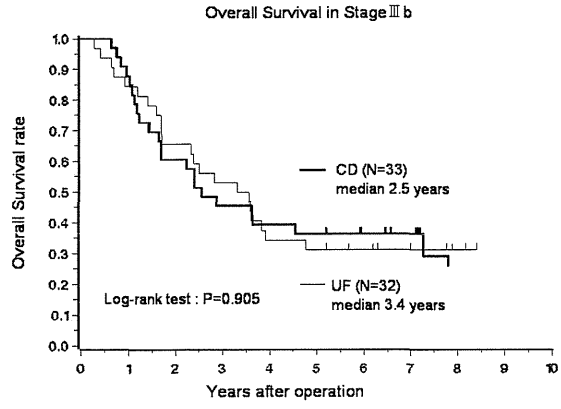

Fig. 2B Kaplan-Meier estimates of Overall Survival in Stage IIIb

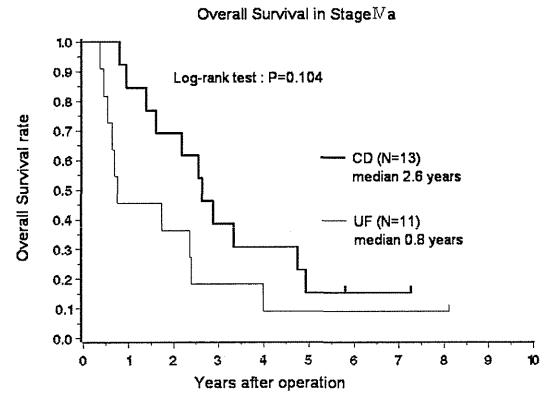

Fig. 2C Kaplan-Meier estimates of Overall Survival in Stage IVa

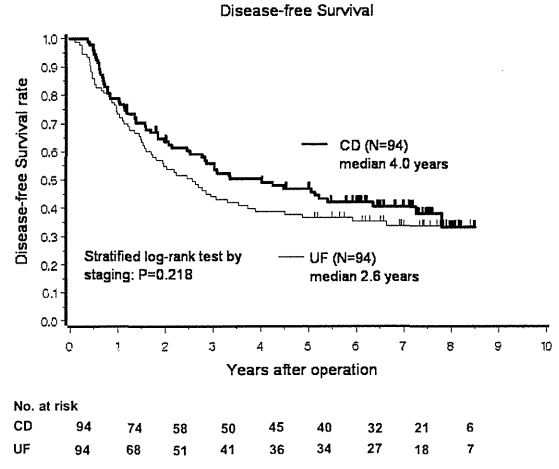

Fig. 3 Kaplan-Meier estimates of Disease-free Survial

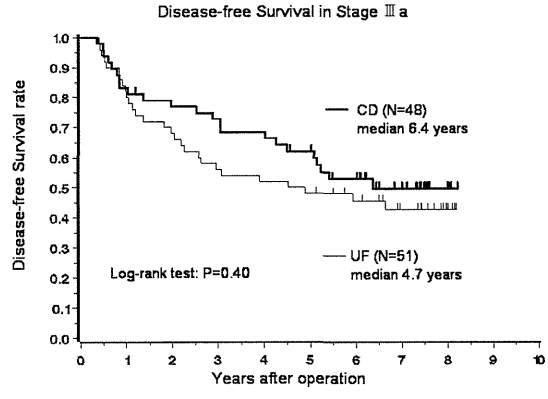

Fig. 4A Kaplan-Meier estimates of Disease-free Survival in Stage IIIa

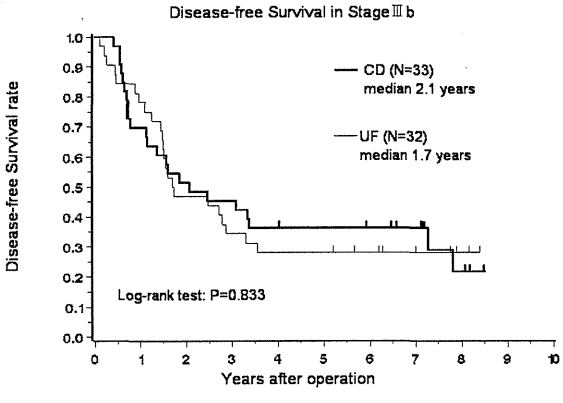

Fig. 4B Kaplan-Meier estimates of Disease-free Survival in Stage IIIb

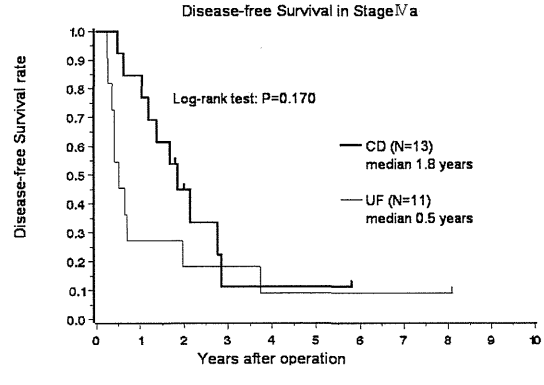

Fig. 4C Kaplan-Meier estimates of Disease-free Survival in Stage IVa

Safety

The safety analysis included all patients who received at least one cycle of treatment. Over grade III leucopenia during treatment was observed in 6 cases (6.4%) in the CD group and none in UF group (p=0.014). Diarrhea was observed in 5 patients in each arm (5.3%). Another over grade III toxicities like thrombocytopenia, neutropenia, elevation of hepatic function related enzymes, were reported in a few patients, although their incidences were low and not considered to be serious side effects (Table 2).

Table. 2 Grade3 or 4 Toxicities Related to Treatment

Toxicity	CD (N=94) No. of Patients	%	UF (N=94) No. of Patients	%	P Value*
Leukopenia	6	6.4	0		0.014
Thrombocytopenia	3	3.2	2	2.1	0.681
Elevated Bilirubin	0		0		1.00
Elevated GOT (GPT)	1	1.1	1	1.1	1.00
Oral Mucositis	0		1	1.1	1.00
Anorexia	5	5.3	9	9.6	0.405
Diarrhea	5	5.3	5	5.3	1.00

Abbrebiations: CD, low dose CDDP+5-FU followed by UFT; UF, UFT alone; GOT,Glutamic oxaloacetic Transaminase; GPT, Glutamic Pyruvate Transaminase.

Values are proportions of each group or overall sample size.

Grades were according to Common Toxicity Criteria of the National Cancer Institute (ver.1.0).

*P values are for the differences from the two groups. They were calculated using the two-sided Fisher's exact test combining grades 3and 4. Not available data is excluded from the Fisher's exact test.

Compliance

In the CD group patients, over 90% of the cases were safely treated with the projected cisplatin and 5-FU regimen for 4 to 6 cycles. With regard to UFT compliance, the mean percentage of the total doses to the expected ones per year which was calculated by multiplying one year dosage time by 400 mg of UFT were 82.9% and 89.4% during first year of therapy in the CD group and UF groups, respectively. Compliances for longer administration of UFT were also favorable and over 80% of the patients safely received UFT for 2 and 3 years after the beginning of the therapy in the two groups.

Discussion

While surgery remains the sole mainstay of any curative treatment for gastric cancer, the relapse rate is high and survival remains low even after surgical resection with curative intent. Several types of postoperative adjuvant chemotherapies have therefore been administered in the hope of preventing relapse and increasing the cure rate.

Macdonald et al. reported a large randomized controlled trial (RCT) comparing surgery versus surgery + postoperative 5-fluorouracil (5-FU) + leucovorin + radiation, with median survivals of 27 months and 36 months, respectively ($P<0.001$) and this modality, radiation chemotherapy, is considered as a standard therapy in the United States[4, 5]. On the other hand, in Japan, adjuvant chemotherapy using oral fluorinated pyrimidines has been investigated for decades as postoperative adjuvant chemotherapy, without robust evidence for its efficacy[6]. This difference between United States and Japanese perspectives regarding adjuvant chemotherapy for gastric cancer may result from a difference in surgical backgrounds. In the United States, the standard "curative operation" refers to gastrectomy plus D0 or D1 lymphadenectomy, and chemoradiotherapy appears to be effective for local control after curative resection[7]. In Japan, however, the standard operation for gastric cancer has been established as gastrectomy plus D2 lymphadenectomy, and it was not favorable to conduct chemoradiotherapy after D2 lymphadenectomy because of the renal toxicity, making it difficult to adopt the Western results for Japanese conditions[8]. Complying with this background, the efficacy of adjuvant chemotherapy using oral fluorinated pyrimidines was systematically evaluated in publication-based meta-analyses in Japan[9, 10]. Although those oral agents were proved to have positive effect by those meta-analyses, it still remains unclear which specific treatment is really effective. Among several oral fluorinated pyrimidines, UFT, a combination of uracil and tegafur at the molecular ratio of four to one has been most widely used in both clinical trials and general clinical practice[11]. A new meta-analysis of adjuvant chemotherapy with UFT suggested benefit for curatively resected gastric cancer[12]. The test for heterogeneity of the data yielded P=0.235; thus accepting the hypothesis of heterogeneity. Combining the data for the four relevant trials demonstrated HR=0.75 (95%CI, 0.58-0.98; p=0.037) and significant effect of the UFT was confirmed[13].

With regard to the advanced gastric cancer, on the other hand, combination regimens using multiple chemotherapeutic agents have been prevalent. Among those regimens, combination of 5-FU and cisplatin has long been considered as a standard treatment of care for metastatic and/or recurrent gastric cancers[2, 14-16]. Obviously, the most recent successful clinical trial by Ajani et al. has utilized combination of 5-FU plus cisplatin as the control arm[17]. Although combination therapy with 5FU, cisplatin plus docetaxel has shown significant benefit in survival of the patient, quality of life of those patients was impaired by the strong combination chemotherapy[18].

In an adjuvant setting where the target of the therapy is possibly remaining minimal residual disease, however, renal dysfunction which is a problematic side effect with high dose administration of cisplatin and requires administration of large volume of fluid and diuretics for the washout of the drugs during treatment precluded wider adoption and employment of this regimen. In this regard, search for less toxic combination regimen with similar effectiveness was considered to be indispensable. Kondo et al. investigated feasibility of protracted infu-

sional 5-FU and low-dose cisplatin for gastric cancer[3]. In their study they used 24-hours infusion of 5-FU plus low dose cisplatin 6 mg/m^2/day on days 1-5 were utilized. Surprisingly enough, the overall response rate was 45% which is comparable to the combination regimen of 5FU+cisplatin with no renal dysfunction without the aid of hydration.

Based upon the fact that UFT was proved to be effective as protracted infusion of 5-FU, Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC) was encouraged to start the JFMC23 randomized trial for resected locally advanced gastric cancer using the combination therapy of UFT plus low dose cisplatin.

The result of the present study, could not have demonstrated a statistically significant benefit of UFT+cisplatin over UFT alone therapy. However, the data suggests better 5 year survival rate in the combination treatment group, with a reduction in risk of 13%. 5 year DFS was also showed benefit of combination therapy over UFT alone, with a reduction in risk of 15%. Looking at the effect on different stage of disease, combination regimen was consistently better than monotherapy with UFT, although the difference was not statistically significant both in terms of survival and DFS.

These findings from our phase III randomized trial suggest that low dose cisplatin+5-FU followed by UFT may hold promise as a treatment for curatively resected locally advanced gastric cancer patients.

Recently, an elaborated version of new oral fluorinated pyrimidine S-1 was developed, and was proved to be significantly effective for curatively resected gastric cancer in a large randomized trial involving over 1000 patients and is now considered to be the standard treatment in Japan[19]. In order to further improve the prognosis of the patient, phase I study of combination therapy with S-1 plus low-dose cisplatin proved excellent safety[20, 21], and a phase II study for advanced gastric cancer is on going to examine the efficacy of the S-1+low-dose cisplatin treatment[22].

Combination therapy of S-1 plus low-dose cisplatin could next be examined in a future randomized trial comparing to S-1 alone referring to our UFT/low-dose cisplatin study results.

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Evaluation of the national breast cancer screening program in Poland in 1999-2009. National Cancer Registry overview.

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Abstract

Background: The Polish breast cancer screening program was initiated as part of National Cancer Control Program in July 2005 by establishing a network of accredited regional centers and the central coordination point. The changes in reproduction behaviors and lifestyle in Poland have contributed to rapid increase of breast cancer incidence and mortality. The aim of this article is to describe the results of the program after 7 years from its implementation and to advocate for its continuance.

Methods: Data on incidence and mortality due to breast cancer among women aged 50-69 were extracted from the National Cancer Registry. Annual reports of the National Cancer Control Program and other data provided by the Ministry of Health in Poland were analyzed.

Results: Between January 1999 and December 2009 there were 142,307 new cases of breast cancer and 54,927 deaths because of it reported in Polish females. Poland is a country with relatively low and dynamically increasing incidence of breast cancer compared to Western European countries. The coverage of the nationwide screening program was around 40%.

Conclusion: The late introduction of the screening program with a high recall rate resulted in dynamic increase of incidence. This leads to stabilization of the breast cancer mortality since more cases could be detected at early stage and treated more effectively. The Polish National Cancer Control Program which includes the breast cancer screening met the interim measures recommended in the European Guidelines and should be continued in the future with higher coverage on the target population.

Key Words: breast cancer, screening program, mortality, Poland.

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Introduction

Breast Cancer (BC) is the major cause of cancer mortality among females in developed countries[1]. According to the World Health Organization (WHO) in Europe cancer represents the second most important cause of death and morbidity. The population of Europe is 731 million which accounts for 10.7% of the total world population of 6,840 million, however with 3.2 million of new cancer patients and 1.7 million deaths due to cancer each year, Europe accounts for approximately 25% of all cancer worldwide[2, 14]. In the European Union (EU) cancer is responsible for 20% of all deaths and is the biggest killer of people aged 45-64 where it causes 41% of all deaths. Cancers of lungs and throat are the most common among men, while BC is the leading cause of female cancer death, causing 17% of all deaths from cancers in women in the EU[3].

Many researches were conducted in order to determine the risk factors of BC. It was found that maternal behaviors such as childlessness, abortions, late first pregnancies, early age at menarche, no breastfeeding and hormonal therapies were recognized as an important risk factor of BC[4, 10]. Other risk factors included fat diet, obesity and insufficient exercise[5, 10]. These risk factors are the characteristics of developed countries where females shift from family housewife to career-oriented lifestyles.

In order to control and prevent the continuous increase in mortality due to BC, from the late 1980s many countries started introducing early BC screening programs which were necessary for more accurate diagnosis and treatment of BC. Due to innovations such as mammography screening, chemotherapy, hormzone treatments, innovations in radiotherapy and surgery, big improvements were observed in BC survival in Europe[1, 8]. In Central and East-European countries the small decreases or continued increase in BC mortality were correlated with low, usually non-organized, screening activities[7], low number of mammography machines[8], slow uptake of anticancer

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drugs[6], and health expenditure below the European average[2]. These patterns can also be linked to rapid changes in BC risk factors that took place in the countries after the collapse of the Soviet Union and the communist regime in 1990s, such as decreasing fertility and increasing age at first birth, no breastfeeding, hormonal therapies or abortions[9]. We can observe that these behaviors are more frequent in West-European capitalist countries with open markets where women are more likely to sacrifice their family life for career.

In 2000-2004 the rate of BC mortality in Poland was 17% lower compared to the average of all European Union (EU) countries, 11% lower in 2007 and was predicted to be only 4% lower than in 2011, reflecting a long-term tendency toward leveling of BC rates in Europe, starting from rates 25% to 30% lower in Eastern than in Western Europe[4]. Compared with other European countries, Poland has a relatively young population[19]. Any currently observed epidemiological parameters, such as a relatively low incidence rate of cancer, should be considered in this context. However, the coming years will see rapidly rising numbers of the elderly along with the incidence of health events characteristic for this type of population. The BC incidence and mortality rates in Poland have been dynamically increasing compared to other European countries[10]. According to the National Cancer Registry the prognosis for the years 2010-2025 indicates further increase of BC incidence. For women before menopause the increase of incidence will be probably slight (from 16 per 100,000 in 2006 to 19 per 100,000 in 2025). The highest increase in incidence is expected for the group of women aged 50 to 69 years old[12].

To resolve the problem in 2005 the Polish government introduced the National Cancer Control Program (NCCP), which included the first nationwide BC screening program. In previous studies it was found that the BC mortality rates in Poland will remain about double than those of five other countries from the Soviet Bloc, reflecting the delay observed in the adoption of effective preventive strategies and screening programs[11].Since the total budget spent on the Polish public healthcare is reviewed and reshaped on annual basis in order to meet the priorities of patients, preventive activities such as the BC screening program and its effectiveness have been questioned. The purpose of this study is to analyze the changes in temporal trends in BC incidence and mortality rates in women living in Poland based on the data extracted from the National Cancer Registry. This kind of analysis can be used to track the epidemics of BC, to focus attention on the quality of BC treatment and diagnosis as well as to emphasize the importance of BC screening program.

Materials and Methods

The BC mortality and incidence data for Poland was extracted from the National Cancer Registry's website (http://85.128.14.124/krn/) accessed on 29 January 2012, whereas the BC incidence and mortality data for other European countries were extracted from the verified World Health Organization (WHO) database in December 2009.

This study includes data on new breast cancer cases and deaths caused by breast cancer among females in all 16 regions of Poland in 1999-2009. Incidence and mortality rates are calculated as mean annual numbers per 10,000 females of all age groups. The structure of the Polish population by sex and by 5-years age groups was presented on the basis of data received from the Central Statistical Office on the 30th June 2008.

Data collection

The new cases of cancer and cancer deaths in Poland are collected on the basis of the cancer registration forms (MZ/N-1a). The 16 regional (voivodeship) cancer registries receive the data in the registration forms from approximately 350 hospitals spread across Poland, validate them and reports to the National Cancer Registry in the Maria Skłodowska-Curie Memorial Cancer Centre - Institute of Oncology in Warsaw, where these data is verified in terms of logical and essential correctness and are joined into the national annual dataset and cancer report. The annual reports are created from the data submitted by the voivodship registries, which are supposed to send in the regional data no later than by 31st December of each next year[13].

Breast cancer screening program

The nationwide BC screening program has been officially introduced by the Polish government on 1st July 2005 with a legislation act as part of the National Cancer Control Program (NCCP). According to law the state budget designated to NCCP per annum cannot be less than 250 million PLN (approx. $72.14 million) and the amount designated to early cancer detection has to be the equivalent of at least 10% of the above sum. In order to maximize coverage, encourage women to breast checkups and to spread awareness every year the Ministry of Health posts invitations to all women from the target group in Poland. Some endorsement techniques for breast checkups such as product placement in the Polish national television have been introduced. The NCCP recommends doing mammography and cytology screening tests every two years for all women aged 50-69. The mammography tests are done in line with the *European Guidelines for Quality Assurances in Breast Cancer Screening and Diagnosis.*

The BC screening program has been divided into two parts: basic mammography and advanced diagnosis. In the first stage – the basic mammography – all women who are screened are registered in the database and interviewed face-to-face with a predesigned survey. After the interview two mammography X-rays of each breast are taken and described. Based on the mammography results, doctors have to choose one of the following options:

a. In case of negative results with no risk factors, the complete results ought to be given directly to the patient or be posted to the patient's address along with recommendation of another checkup after 24 months.
b. In case of negative results with minor risk factors defined by the program, the complete results ought to be given directly to the patient or be posted to the patient's address along with recommendation of another checkup after 12 months.
c. In case of positive results of mammography done in the hospital, the complete results ought to be given to the patient directly while collecting results. If the patient does not turn up for the results in three months, a reminder letter to collect the results is sent to patient's address and the patient is directed to the advanced analysis.
d. In case of positive results of mammography done in the mobile mammography unit (bus), the results ought to be informed to the patient via telephone or in writing. The complete medical documentation should be handed over to the patient or to the advanced diagnosis center which is chosen by the patient and noted in the complete medical documentation.
e. In case of positive results and inability to contact the patient, the copy of medical documentation is sent to the patient's primary health-care doctor along with a request to visit the patient at their home address.

The guidelines for the advanced diagnosis have been established as part of the program. At the medical consultation doctor does a physical checkup and runs the necessary tests which end up with diagnosis. Based on the first mammography, the palpation results, the mammary gland structure, the applied hormone replacement therapy, the diagnosis as solid tumor or as a cyst of mastoid, the doctor decides whether the patient needs further the breast ultrasonography check. Thereafter additional mammography image is taken and either a fine needle aspiration or core biopsy is done. When the results arrive the patient is referred to treatment in a designated hospital which offers appropriate treatment financed by the National Health Fund. The exact procedure of patient's treatment is illustrated in Fig. 1.

As breast cancer is often a hereditary disease the Ministry of Health decided to include in the risk group those women whose relatives had BC history or those who were identified as the carriers of the mutated cancer genes such as BRCA1 or BRCA2. Those included in the risk group are advised to do a self-checkup every month after menstruation as well as do a clinical checkup twice per year. Also those qualified to the risk group should do

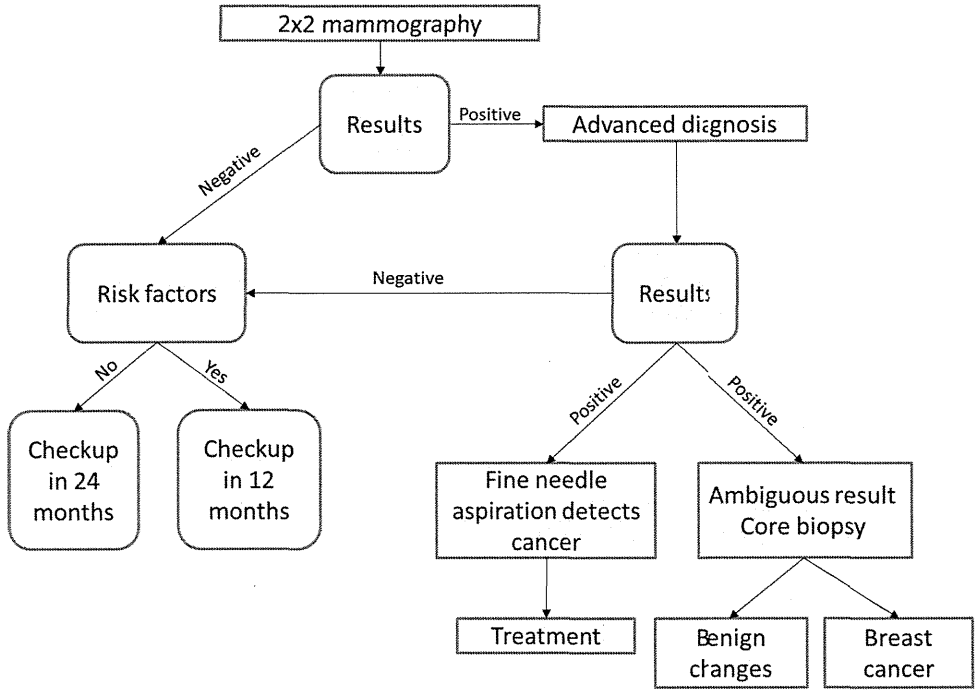

Fig. 1. Flow chart of breast screening activities

Table 1. Breast cancer incidence and mortality in Poland in 1999-2009

Year	Total population	Total incidence	Incidence per 10,000	Age-standardized cancer incidence (per 100,000)	Total mortality	Mortality per 10,000	Age-standardized cancer mortality (per 100,000)
1999	19,864,929	10,903	5.49	38.8	4,553	2.29	14.8
2000	19,868,732	11,853	5.97	41.8	4,712	2.37	15.0
2001	19,872,476	12,118	6.10	42.4	4,825	2.43	15.0
2002	19,715,122	12,132	6.15	42.0	4,825	2.45	15.0
2003	19,702,235	11,733	5.96	40.2	4,942	2.51	15.0
2004	19,701,881	12,049	6.12	40.6	4,887	2.48	14.5
2005	19,700,583	13,385	6.79	44.5	5,112	2.59	14.9
2006	19,696,176	13,322	6.76	44.2	5,212	2.65	14.8
2007	19,698,893	14,484	7.35	47.7	5,255	2.67	14.5
2008	19,707,504	14,576	7.40	47.2	5,362	2.72	14.8
2009	19,730,046	15,752	7.98	50.4	5,242	2.66	14.1

a mammography or ultrasonography check every year. This is also recommended to all women with adipose breast structure aged 30 plus.

Doctors are obliged to report all newly detected cases of breast cancer as well as the benign changes on a designated cancer registration forms (Mz/N-1a) with annotation "S" which stands for screening.

All patients should also sign the consent for personal data processing. Information such as home phone, mobile phone and email address are gathered along with patients' personal information so that the negative results can be emailed or sent via text along with the reminder to redo the checkup after 24 months.

Quality Assurance

In order to guarantee the quality of the BC screening program, all participating hospitals need to meet the requirements for hospital staff (doctors with specialty in radiology and image diagnostics, who analyzed at least 500 mammography images and X-ray technicians who attended the official training of the Polish Medical Imaging Association and did at least 1000 mammography images) and for the diagnostic equipment which passed the quality tests.

All digital mammography imaging should be done in line with the European guidelines for quality assurance in breast cancer and diagnosis. The mammography imaging devices should be tested at least once per year. Should the device go under maintenance, additional tests are required.

Results

In the analyzed period between January 1999 and December 2009 there were 142,307 new cases of BC reported in Polish females of all ages. Throughout the analyzed period the incidence has been increasing every year. The number of those who died because of BC in that period was 54,927. The annual BC incidence, mortality as well as their age-standardized rates are presented in Table 1.

Total number of incidents shifted from 10,903 in the year 1999 to 15,752 in 2009 which is an increase by 44.5%. In the same time the BC mortality increased by 15% from 4,553 in 1999 to 5,242 in 2009.

The total population of women in Poland in the analyzed period was used as the reference to calculate the BC incidence and mortality per 10,000. In 1999 there were 19,864,929 females in Poland compared to 19,730,046 in the year 2009 which is a decrease of 0.7%. The trend of the BC incidence and mortality per 10,000 females of all ages in Poland is presented in Fig. 2.

In Poland each year the Minister of Health presents in the Parliament the summary of the annual activities included in the NCCP. According to these summaries the number of breast screenings among Polish women aged 50-69 has been gradually increasing from 934,777 in the year 2007 (which is 38.15% of the target population), up to 1,008,942 in 2011 (which is 41.51% of the target population). Coverage data for the first year of the nationwide BC screening in 2005-2006 was 23.37%[15]. The number of mammography checks per annum is shown in Fig. 3.

The annual reports on NCCP show the numbers of detected breast cancers, benign lesions in breast as well as the number of BC suspicions which in the year 2010 were 4,341, 245,059 and 38,116 respectively compared to 1,762, 228,353 and 10,564 in the year 2007. The data on incidence and mortality trends per 10,000 women from the target population were extracted from the National Cancer Registry and are showed in Fig. 4.

The mortality trend in the studied period among the target group is stable, whereas the incidence is increasing. The increasing trend in incidence can be noticed after 2005 when the nationwide breast screening program was introduced.

Discussion

The intensity of the debates regarding BC screening programs has exceeded any other medical controversy in the past three decades. The debate has addressed the

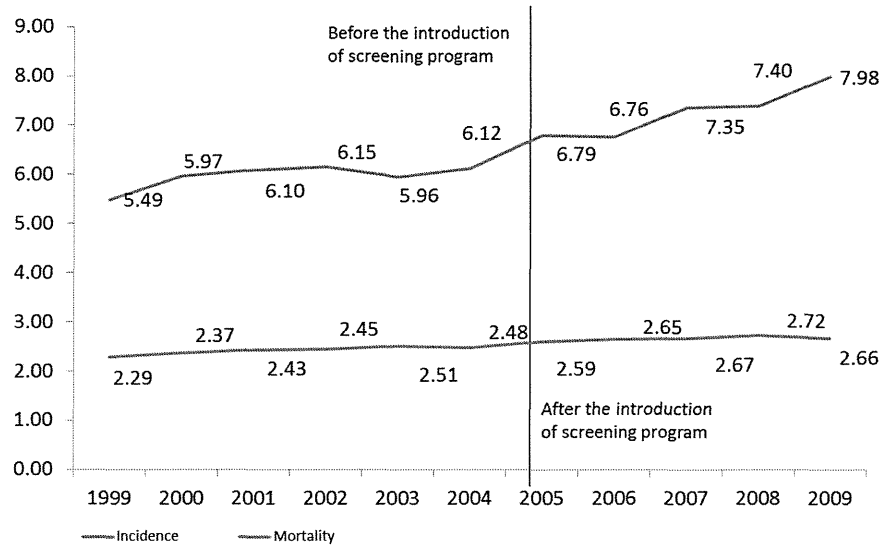

Fig. 2. Breast cancer incidence and mortality per 10,000 women in Poland

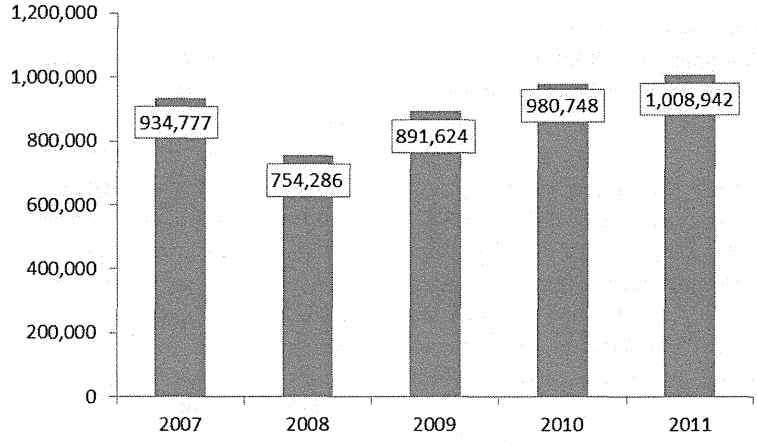

Fig. 3. The number of mammography checks per annum.

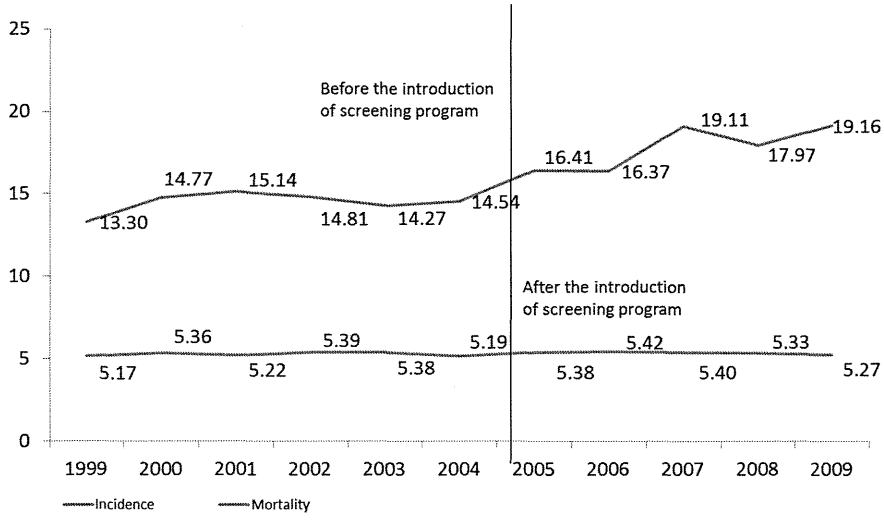

Fig. 4. Breast cancer incidence and mortality per 10,000 women aged 50-69.

benefits, cost-effectiveness and adverse consequences such as false positive findings leading to unnecessary excision biopsies. To assure the optimal level of quality of the screening program a continuous quality control is necessary[27]. Population-based BC screening has been proposed as an effective control method for certain types of cancer and in this respect it has been recommended by numerous scientific organizations and societies. Europe is a model for implementation of organized population-based programs and the European quality guidelines for cancer screening programs have been instrumental in the development of BC screening program in most European countries, including Poland. This fact has been extremely relevant in discussions held at the screening program network and has enabled consensus to be reached on indicators, quality criteria and assessment of regional programs. The adherence to European guidelines and standards as well as the other European countries' experiences with BC screening programs have been very helpful in justifying the budget for this preventive program in Poland.

In many developed countries which introduced organized early screening programs in the 1980s and 90s, the number of deaths caused by BC is decreasing, however, this is happening at a lower rate in Central and Southern Europe[1, 3, 6]. In Poland the number of deaths due to BC has been rising since the beginning of the analyzed period in 1999. Standardized death rates (SDR) for BC indicate a slightly lower mortality due to BC screening programs in Western European countries in comparison with those in Central and Eastern Europe[1]. A drop in SDR has been observed also in Poland, however, it has been significantly slower in comparison with other countries[18].

In this study we compared the reported rates of BC incidence and mortality before and after introduction of the nationwide breast cancer screening program. The BC incidence among women aged 50-69 increased by 31%, from 14.54 new cases per 10,000 women in 2005, when the program was started, up to 19.16 in the year 2009. In the same period the mortality due to BC in this age group decreased by 2% from 5.38 to 5.27 per 10,000.

The results of this study demonstrate an increase in impact of mammography screening on the prevention of BC attributed death over time. There have been significant improvements in mammographic screening and treatment over the last 30 years thanks to which early detected BC can be cured or treated effectively as never before[16]. Incidence of malignancies in Poland has been rising as in almost all post-Soviet countries. Poland presently has an aging society and the elderly population is generally more likely to develop cancer[17].

However, the differences in standardized incidence rates (SIR) indicate the existence of factors, besides age, that strongly affect the incidence of cancer. The main factors identified in Poland are reproduction-related such as late first pregnancy, childlessness, hormone therapies, lack of breast feeding; lifestyle-related such as fatty diet, obesity, low physical activity, alcohol intake, smoking, red meat consumption; and the family history of BC[4]. According to the recent evidence more than 50% of cancer incidence could be prevented if a knowledge of risk factors would be applied to behavior changes[26]. Even though the incidence of developing neoplasms measured with the SIR in Poland is among the lowest in the European Union, it has very fast dynamics and therefore should not be ignored[19]. The number of new cases of breast cancer in women has been growing every year throughout the analyzed period from 10,903 new cases in 1999 to an estimate of 19,000 by the year 2020[18]. This could mean an increase by 75% in barely two decades.

Therefore the early BC detection in Poland should be continued and intensified in order to minimize the social damage caused by cancer. The challenge that is to be faced is how to maximize the coverage of breast checkups among the target population. The current Polish system of recruitment through written invitations, reinforced by independent non-governmental organizations' media campaigns and recall for subsequent screenings by screening centers was able to achieve a modest coverage of approximately 40%[15]. This is still rather low compared with the participation rates in other successful European population-based programs such as those in Spain[20], Denmark[21] or United Kingdom[22], where the coverage approaches the European Guidelines target of 70% or even exceeds it, i.e. Finland[23]. However, the invitation may also fail to achieve the stated target i.e. due to decentralized invitation in Hungary[24] or invitation without appointment in Luxembourg[25]. It is therefore necessary to properly plan, implement and monitor the invitation process. The weak point of the Polish setup is the insufficient involvement of primary health care physicians in the promotion of BC screenings. They get to see the full knowledge of the patient's medical history and preferences, which enables the proper tailoring of an individual preventive strategy.

Given that the official implementation of the program was in 2005, it is still hard to accurately estimate the expected annual incidence in Poland for the future years. However, judging by the results of the last seven years, the detection rate can be estimated to lie below the expected European range. With almost 20 new BC cases per 10,000 women participating in the program, the incidence looks much more optimistic compared to other European countries i.e. Spain with 34 or UK with over 67 new cases per 10,000 women[1, 22].

From the data provided by the Polish Ministry of Health we can see that between 2007 and 2010 the number of newly detected thanks to the national BC screening program, the incidence of malignant BCs increased

by 146.4% from 1,762 up to 4,341, whereas the incidence of benign lesions in breast in that time increased only by 7.3% from 228,353 up to 245,059[15]. Such discrepancies between the dynamics of malignant tumors and benign lesions suggest that the screening program should be continued and monitored in order to provide more reliable results and reveal more accurate expected incidence rate for the future years. The types of tumor detected in the reported years ought to be consistent in order to enable the Ministry of Health to plan their policies and estimate budget for fighting cancer in subsequent years. All indicators extracted from the National Cancer Registry follow the European guidelines and suggest that the incidence of BC in Poland will continue to increase, however it will remain below the average European level in the next decades.

The weak point of this study comes from the analysis of differences between the numbers detected malignant BCs, benign lesions and BC suspicions between years 2007 and 2010. The discrepancies in the above data (especially the malignant BCs) can result from the fact that the NCCP was started in the middle of 2005 and the reporting system was not fully established by 2007 when first reports were submitted. Another limitation of this study is that no data on the amount of false positive cases of BC have been found.

Conclusions

The nationwide mammography screening program has been introduced relatively late in Poland compared to the other European countries. The incidence of BC in Poland is still below the European average but increases every year. The screening program leads to stabilization of the breast cancer mortality since more cases could be detected at early stage and treated more effectively. The Polish National Cancer Control Program should be continued in the future with higher coverage on the target population.

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Trends and distributions of common types of cancer in Bangladesh: Results from the cancer registry data of 2008-10

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Abstract

Inadequate knowledge about health, illiteracy, cultural and religious issues, poverty, chronic infection, and malnutrition are continuously adding additional threat on the huge burden of cancers in Bangladesh. The aim of this study was to determine the trends and distributions of cancers in Bangladesh. Retrospective analysis was done on the cancer patients registered in the National Institute of Cancer Research and Hospital (NICRH) in Dhaka, Bangladesh during January, 2008 to December, 2010. Of total 27,281 cancer patients, 56.2% were male and majority were from 45-54 years age group. There was an increasing trend of cancers during the study period (P <0.05). According to International Classification of Diseases for Oncology (ICD-O, 3rd edition), most frequent cancers were respiratory system and intrathoracic organs (23.1%) followed by digestive organs (18.5%), female genital organs (11.9%), breast (11.7%), and lip, oral cavity and pharynx (11.6%). Overall, lung cancer was the leading cancer followed by breast, cervical, lymph node and lymphatics, and esophageal cancer. Lung cancer was the leading cancer among male followed by lymph node and lymphatics, and esophagus. However, top of the list was occupied by the breast cancer among females followed by cervical cancer, and lung cancer. In conclusion, an increasing trend of cancer was observed in Bangladesh. Lung and breast cancer was the leading cancer in male and female, respectively; and most frequent cancer was observed among illiterate and middle aged population. We recommend exerting proper emphasis on anti-tobacco campaign and breast self-examination for the females in addition to increasing overall awareness against cancers in Bangladesh.

Key Words: Common cancers, distributions, cancer registry, Bangladesh

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Introduction

According to the report of World Health Organization (WHO) in 2003, worldwide, around 22 million people were living with cancer and approximately 10 million are added every year, and more than 6 million annual deaths[1)]. Total burden of cancer is highest in affluent society mainly due to high incidence of tumors associated with western lifestyle. In the United States, there were an estimated 1.3 million invasive cancer cases, of which 556,000 were death, during 2003[2)]. It is the leading cause of death among women aged 40 to 79 years and among men aged 60 to 79 years[3)]. Lung (17.8%), stomach (10.4%), and liver (8.8%) were the top three cancers contributing to the highest proportions of 12% to 13% annual cancer deaths[4-7)].

In developing countries, problems of cancers is a substantial issue. Diet- and lifestyle-related issues contribute more for the socially disadvantaged population in developing cancers like, lung, stomach, breast, cervix etc.[8)], several infectious agents are abundant to develop cancer in the uterine cervix, stomach, Burkitt's lymphoma, liver, urinary bladder and biliary tract among these population[1)]. During 2008, 56% of the estimated 12.7 million new cancer cases, and 63% out of 7.6 million cancer deaths occur in the less developed countries. The proportion of cancer deaths attributable to infectious agents is about 20%-25% in developing countries and 7%-10% in developed countries[9)]. Among women cervical cancer is the third most common cancer overall, accounting for 13% of all female cancers; however, 85% of these new cases occur in developing countries[10)].

According to WHO (2008), in the South East Asia Region (SEAR), an estimated 1.1million people died of cancers in 2008[11)]. A large proportion of cancer deaths occur in the economically productive age group. Fifty-two per cent of cancer deaths among women and 45% of cancer deaths among men were of those below the age of 60 years. Each year, an estimated 1.7 million new cancer

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cases occur in the SEAR. The most common sites of cancers among males are the lung (17%), followed by mouth and oropharynx (15%), and liver (7.5%). Among women, cervical and breast cancers are the most common, accounting for 35% of all cancer deaths[11]. The majority of cancer cases present at an advanced stage of the disease and with complications, which imposes a heavy burden on the family and the health-care system.

Cancer is one of the major causes of morbidity and mortality, and it is sixth leading causes of mortality in Bangladesh. It is estimated that projected figure of cancer load, incidence, prevalence and mortality can be estimated approximately as 1,200,000; 200,000; 800,000 and 150,000 respectively for the 130 million people of Bangladesh. Cancer is expected to be double in Bangladesh like other developing countries in the next 20 to 25 years[12, 13]. According to WHO, at least 30% of these cancers are preventable[14]. Despite these alarming speculations and availability of abundant predisposing factors like, higher rate of tobacco use, environmental pollution, and irrational use of chemicals, increased illiteracy, malnutrition, and poverty, there is no reliable statistical data about trends of cancer and its distributions in Bangladesh.

This study was aimed to determine the trends of cancers in Bangladesh and to explore distributions of common types of cancer based on the data available in the 'Cancer Registry' at National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh.

Materials and methods

Retrospective study was done on 27,281 cancer patients registered in the 'Cancer Registry' of NICRH, Dhaka during January 2008 to 2010. This is the ever first cancer registry established in Dhaka, Bangladesh. A checklist was developed and used to extract relevant information from the cancer registry.

Flow of patients at NICRH

After initial registration, patient identification, socio-demographic characteristics and history of tobacco uses were noted at cancer register interview room. Method of diagnosis, clinical stages and details of treatment were obtained from the diagnosed and referred cases. After completing this session each patient was directed to the medical officers of respective departments. The medical officer then took a brief clinical history and conducted appropriate physical examination. Attending doctors reviewed all the relevant documents of the concern disease and used to give new investigations if needed. Patients along with all investigation reports were then sent to chief medical officer, who placed the patients before the Tumor Board. Tumor Board was consisted of experienced professors, associate and assistant professors of various sub-specialties. They then decided on the final diagnosis and treatment modalities.

ICD-O coding

In the next step, an experienced coder coded the cancer on the basis of International Classification of Disease and Related Health Problems, 10th Revision, ICD-O (3rd edition)[15]. Data for this were extracted for all relevant records of the hospital like inpatient registry, Tumor Board Record, etc. In the registry form the most valid basis of diagnosis was recorded. Data management and other operational works were done by cancer epidemiology department of NICRH.

During data analysis and reporting, a strict procedure was applied to maintain confidentiality of the information of the patients. A prior permission was obtained from the all patients during registration consenting for use of their information for subsequent analysis and use without recognizing their identity.

Statistical analysis

Statistical analyses were performed with the Statistical Package for the Social Science, version 19.0 (SPSS, Chicago, IL, USA). Descriptive statistics were applied. Chi-square test for trend was used to see the trend of cancers over years. Student's t test for continuous variables and the chi square test for categorical variables were used in the assessment of differences between the two groups when appropriate. All the statistical tests were two-tailed and P values <0.05 were considered as statistically significant.

Results

There were an estimated 27,281 cancer patients attending at NICRH during the year 2008 to 2010. Out of these total, 15,333 (56.2%) were male and majority were married. Illiterate patients were suffering from cancer more than literate for both sexes (20.5% for male and 19.0% for female). Two-fifth of them were housewives and one-fifth of the respondents were agriculturist by profession (Table 1). Fig. 1 describes age wise distribution of different types of cancers. Majority (25.4%) were at the age group 45-54 years followed by 21.8% and 16.6% at the age group 55-64 years and 35-44 years, respectively.

Table 2 showed different types of cancer based on ICD-O-3rd. We found majority, 6304 (23.1%) of the cancer involving respiratory system and intra thoracic organs followed by digestive organs, 5048 (18.5%) and female genital organs, 3255 (11.9%). Breast cancer was steadily increasing during the past three years. The figure on 2008, 2009 and 2010 was 759 (10.2%), 1196 (12.3%) and 1242 (12.3%), respectively. We found a significant upward trend of over cancer rate during 2008-2010 (P for

Table 1. Gender-and yearwise socio-demographic characteristics of the cancer patients attending at National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh during the period of 2008 to 2010.

Variables	2008		2009		2010		2008-2010	
	Male	Female	Male	Female	Male	Female	Male	Female
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Religion								
Islam	3987 (53.4)	2984 (40.0)	5026 (51.5)	4099 (42.0)	5339 (53.0)	4056 (40.2)	14352 (52.6)	11139 (40.8)
Hinduism	262 (3.5)	209 (2.8)	324 (3.3)	277 (2.8)	376 (3.7)	268 (2.7)	962 (3.5)	754 (2.8)
Christianity	7 (0.1)	6 (0.1)	8 (0.1)	19 (0.2)	3 (0.0)	23 (0.2)	18 (0.1)	48 (0.2)
Buddhism	1 (0.0)	2 (0.0)	0 (0.0)	3 (0.0)	0 (0.0)	2 (0.0)	1 (0.0)	7 (0.0)
Marital status								
Never married	368 (94.9)	167 (2.2)	376 (3.9)	225 (2.3)	463 (4.6)	265 (2.6)	1207 (4.4)	657 (2.4)
Married	3883 (52.0)	2839 (38.1)	4972 (51.0)	4086 (41.9)	5231 (52.0)	4036 (40.1)	14086 (51.6)	10961 (40.1)
Widow/Widower	4 (0.1)	192 (2.6)	7 (0.1)	78 (0.8)	16 (0.2)	48 (0.5)	27 (0.1)	318 (1.2)
Divorced	2 (0.0)	3 (0.0)	3 (0.0)	9 (0.1)	8 (0.1)	0 (0.0)	13 (0.0)	12 (0.0)
Education								
Not applicable (up to 5 years)	87 (1.2)	36 (0.5)	74 (0.8)	47 (0.5)	78 (0.8)	57 (0.6)	239 (0.9)	140 (0.5)
Illiterate	1760 (23.6)	1568 (21.0)	1484 (15.2)	1566 (16.1)	2356 (23.4)	2049 (20.4)	5600 (20.5)	5183 (19.0)
Primary	1452 (19.5)	1144 (15.3)	1982 (20.3)	1702 (17.4)	1628 (16.2)	1294 (12.9)	5062 (18.6)	4140 (15.2)
Secondary	630 (8.4)	328 (4.4)	1163 (11.9)	745 (7.6)	1038 (10.3)	702 (7.0)	2831 (10.4)	1775 (6.5)
Higher secondary	167 (2.2)	72 (1.0)	394 (4.0)	206 (2.1)	334 (3.3)	106 (1.1)	895 (3.3)	384 (1.4)
Graduate and above	158 (2.1)	56 (0.8)	263 (2.7)	130 (1.3)	285 (2.8)	140 (1.4)	706 (2.6)	326 (1.2)
Occupation								
Not applicable (up to 5 years)	87 (1.2)	36 (0.5)	74 (0.8)	47 (0.5)	78 (0.8)	57 (0.6)	239 (0.9)	140 (0.5)
Service	424 (5.7)	58 (0.8)	648 (6.6)	170 (1.7)	629 (6.2)	128 (1.3)	1701 (6.2)	356 (1.3)
Business	512 (6.9)	19 (0.3)	603 (6.2)	16 (0.2)	692 (6.9)	16 (0.2)	1807 (6.6)	51 (0.2)
Agriculture	1124 (15.1)	29 (0.4)	1621 (16.6)	28 (0.3)	2248 (22.3)	20 (0.2)	4993 (18.3)	77 (0.3)
Day labourer	266 (3.6)	4 (0.1)	514 (5.3)	21 (0.2)	384 (3.8)	18 (0.2)	1164 (4.3)	43 (0.2)
House wife	N/A	2755 (36.9)	N/A	3571 (36.6)	N/A	3590 (35.7)	N/A	9916 (36.3)
Retired/aged	1486 (19.9)	191 (2.6)	1447 (14.8)	391 (4.0)	1476 (14.7)	222 (2.2)	4409 (16.2)	804 (2.9)
Industrial worker	68 (0.9)	17 (0.2)	116 (1.2)	65 (0.7)	103 (1.0)	17 (0.2)	287 (1.1)	99 (0.4)
Student	271 (3.6)	111 (1.5)	245 (2.5)	179 (1.8)	217 (2.2)	172 (1.7)	733 (2.7)	462 (1.7)

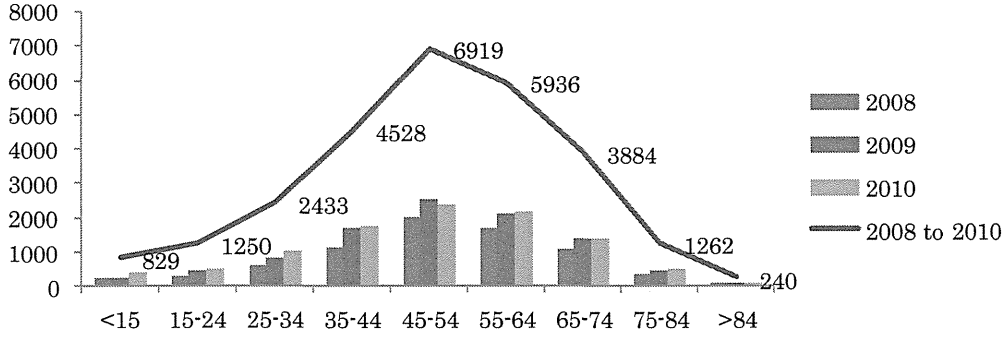

Fig. 1. Age-groupwise (years) distributions of cancer patients during 2008 to 2010.

trend <0.001).

Lung cancer 4915 (17.9%), breast cancer 3185 (11.5%), cervix cancer 2532 (9.2%), lymphnode and lymphatics cancer 1948 (7.0%), oesophagus cancer 1437 (5.5%), and stomach cancer 1193 (4.6%) were the top six cancer throughout the three years. Top 10 cancers in Bangladesh were shown in Table 3.

Based on gender, we found the leading cancer among male were lung cancer 3641 (23.8%), followed by lymphatics 1254 (8.2%), oesophagus 903 (5.9%), larynx 811 (5.3%) and stomach 765 (5.0%). The top five cancer among female were breast cancer 3160 (26.4%), followed by cervical cancer 2532 (21.1%), lung cancer 587 (4.9%), lymphnode and lymphatics cancer 515 (4.3%), and oral cavity cancer 455 (3.8%). Top 10 cancers based on gender depicted in Fig. 2.

Fig. 3 showed the distribution of cancers in different districts. Highest number of cancer patients were in Dhaka district 2691 (9.9%) followed by Comilla 1777 (6.5%), Gazipur 1225 (4.5%), Tangail 1150 (4.2%), and Chandpur 1067 (3.9%).

Table 2. Year-wise distribution of different cancers according to ICD-O classification.

ICD-O	Topography	2008	2009	2010	2008-2010
		N(%)	N(%)	N(%)	N(%)
00-14	Lip, oral cavity and pharynx	905 (12.1)	1114 (11.4)	1149 (11.4)	3168 (11.6)
15-26	Digestive organ	1344 (18.0)	1832 (18.8)	1868 (18.6)	5048 (18.5)
30-39	Respiratory system and intrathoracic organs	1765 (23.7)	2266 (23.2)	2273 (22.6)	6304 (23.1)
40-41	Bones, joints and articular cartilage	147 (1.9)	55 (0.6)	82 (0.8)	284 (1.1)
42	Haemopoietic and reticuloendothelial systems	62 (0.8)	40 (0.4)	46 (0.4)	148 (0.5)
44	Skin	94 (1.3)	89 (0.9)	95 (0.9)	278 (1.0)
47	Peripheral nerve and autonomic nervous system	1 (0.0)	4 (0.1)	6 (0.1)	11 (0.1)
48	Retroperitoneum and peritoneum	18 (0.2)	30 (0.3)	40 (0.4)	88 (0.3)
49	Connective, subcutaneous and other soft tissues	150 (2.0)	319 (3.3)	347 (3.5)	816 (2.9)
50	Breast	759 (10.2)	1196 (12.3)	1242 (12.3)	3197 (11.7)
51-58	Female genital organs	942 (12.6)	1112 (11.4)	1201 (11.9)	3255 (11.9)
60-63	Male genital organs	129 (1.7)	147 (1.5)	177 (1.8)	449 (1.7)
64-68	Urinary tract	199 (2.7)	249 (2.6)	163 (1.6)	611 (2.2)
69-72	Eye, brain and other parts of CNS	194 (2.6)	178 (1.8)	185 (1.8)	557 (2.1)
73-75	Thyroid and other endocrine glands	77 (1.1)	104 (1.1)	129 (1.3)	310 (1.1)
76	Other ill defined sites	56 (0.8)	72 (0.7)	76 (0.8)	204 (0.8)
77	Lymph nodes	520 (7.0)	773 (7.9)	801 (7.9)	2094 (7.7)
80	Unknown primary site	96 (1.3)	176 (1.7)	187 (1.9)	459 (1.7)
Total		7458 (100.0)	9756 (100.0)	10067 (100.0)	27281 (100.0)

ICD-O: International Classification of Diseases for Oncology

Table 3. Top-10 Leading cancer prevalence during 2008 to 2010.

Position	2008		2009		2010		2008-2010	
	Cancer site	N(%)	Cancer site	N(%)	Cancer site	N(%)	Cancer site	N(%)
1	Lung	1299 (17.4)	Lung	1708 (17.5)	Lung	1908 (18.9)	Lung	4915 (17.9)
2	Breast	754 (10.1)	Breast	1189 (12.2)	Breast	1242 (12.3)	Breast	3185 (11.5)
3	Cervix	694 (9.3)	Cervix	849 (8.7)	Cervix	989 (9.8)	Cervix	2532 (9.2)
4	Lymph node and lymphatics	467 (6.3)	Lymph node and lymphatics	680 (6.9)	Lymph node and lymphatics	801 (7.9)	Lymph node and lymphatics	1948 (7.0)
5	Oesophagus	367 (4.9)	Oesophagus	500 (5.9)	Oesophagus	570 (5.7)	Oesophagus	1437 (5.5)
6	Stomach	286 (3.8)	Stomach	420 (5.1)	Stomach	487 (4.8)	Stomach	1193 (4.6)
7	Oral Cavity	248 (3.3)	Liver	298 (4.3)	Oral Cavity	354 (3.5)	Oral Cavity	880 (3.3)
8	Larynx	228 (3.1)	Oral Cavity	278 (3.1)	Liver	342 (3.4)	Liver	855 (3.5)
9	Liver	215 (2.9)	Larynx	253 (2.6)	Larynx	298 (2.9)	Larynx	779 (2.9)
10	Gall bladder	152 (2.0)	Gall bladder	192 (1.9)	Gall bladder	192 (1.9)	Gall bladder	536 (1.9)

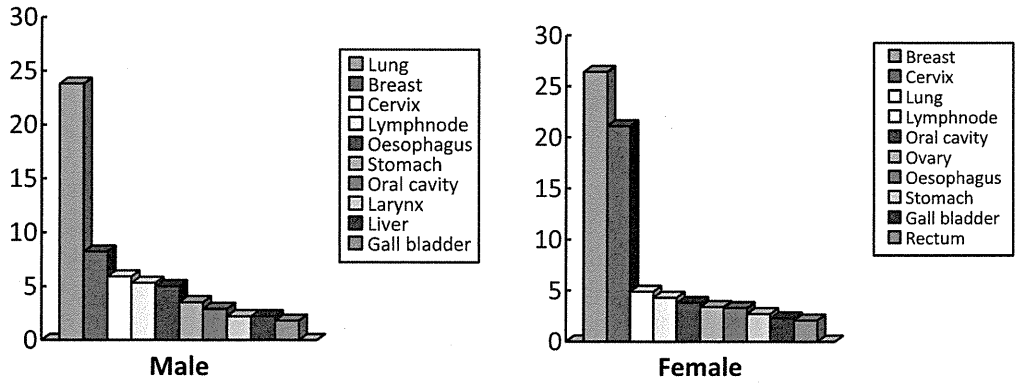

Fig. 2. Gender-wise ranking of top 10 leading cancers (%) during 2008 to 2010 (n=27281; Male=15,333 & Female=11,948).