Acta Med. Nagasaki 42 : 30−36

Adenocarcinoma of the Uterine Cervix Detected Over Long-Term Mass Screening in Japan

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We retrospectively reviewed the history, records of detailed examination and/or treatment, and cytologic/histologic specimens of 32 adenocarcinoma cases (0.006%) detected among 482,451 examinees in a mass screening for cervical cancer conducted over a 20-year period (1975-1994).

The detection rate of adenocarcinoma had increased gradually until 1989 with the increase of total examinees but became markedly lower in the last five-year period ($p = 0.0227$), probably because of the significant decrease in the number of initial examinees ($p<0.0001$). The frequency of early-stage adenocarcinoma (stage 0 or Ia) was 37.5% (12/32), markedly higher than the 8.4% (7/83) of the adenocarcinoma cases treated at our institution during the same period ($p = 0.0004$). Glandular epithelial neoplasms were suggested by cervical smears at detection in only 5/12 (41.7%) of the early-stage adenocarcinoma cases and in 17/20 (85.0%) of the frankly invasive adenocarcinoma cases ($p= 0.0184$). Atypical glandular epithelial cells could not be found in the smears at detection from the remaining 10 cases. Atypical cells from coexisting squamous cell neoplasms were found. The rate of the histologic coexistence of squamous cell neoplasms was 9/12 (75.0%) in the early-stage group and 6/20 (30.0%) in the frankly invasive group ($p = 0.0269$). This rate tended to decrease with the progress of the stage.

Mass screening can detect early-stage adenocarcinoma in cervical smears, but half or more of the cases are discovered in smears with atypical cells from coexisting squamous cell neoplasms and incidentally found later in histologic specimens. To improve the accuracy of detecting cervical adenocarcinomas, we should investigate the cytologic features of atypical glandular epithelial cells obtained from early-stage adenocarcinomas. The its epidemiologic profile of this cancer should be furthur delineated for efficient mass screening programs.

Key words ; Mass screening, Cervical smear, Adenocarcinoma, Uterine cervix, Early-stage adenocarcinoma, Frankly invasive adenocarcinoma

Introduction

A mass screening for uterine cancer has been performed in Japan since 1983 by local governments under the Health and Medical Services Law in women 30 or more years old. The number of examinees is slowly but steadily increasing. Most of the uterine cervical cancer patients detected by this mass screening have a squamous cell carcinoma. In the 1980s, an absolute increase of the incidence of adenocarcinoma in uterine cervical cancer was reported in Europe and the United States[1-8], and in Japan, a two- to three-fold increase of the incidence was reported in certain areas or at certain institutions[9,10]. In a mass screening for uterine cancer, however, the assessment of adenocarcinoma by cytologic diagnosis is more difficult than that of squamous cell carcinoma. Thus, adenocarcinoma may often be overlooked, and this may decrease the overall accuracy of cytologic diagnosis in mass screening[11].

Therefore, in the present study, the authors investigated the detection of adenocarcinoma of the uterine cervix in the mass screening for uterine cancer in Nagasaki Prefecture and then retrospectively reviewed the main cytodiagnostic and clinicopathological factors which would be involved in the improvement of the accuracy of cytologic diagnosis in mass screening.

Subjects and Methods

Subjects

For the 20-year period from April 1975 to March 1994, the mass screening conducted once a year using mass screening cars under the direction of the Nagasaki Prefecture Medical Center had 482,451 examinees (initial+repeated) 30 or more years old who resided in the nine health care regions (79 cities/towns/villages) of Nagasaki Prefecture. We retrospectively reviewed the all of the examinees' records. The records of all of the cases who were assessed as suspicious or positive by the screening smears in the mass screening and presented to the institutions for detailed examination or treatment were reviewed to investigate the smear results and histologic results at these institutions after the mass screening and

to identify the adenocarcinomas of the uterine cervix (including the mixed type of adenocarcinoma and squamous cell carcinoma) detected by the mass screening.

Pure adenocarcinoma and the mixed type of adenocarcinoma and squamous carcinoma were both regarded as "adenocarcinoma" in the present study for the following reasons. 1) In the mixed type of adenocarcinoma and squamous cell carcinoma, cells thought to be transitional from adenocarcinoma and squamous cell carcinoma are found, and the components of these two types of carcinoma may originate in the same stem cells (reserve cells)[12]; during the subsequent progress of the carcinoma, the adenocarcinoma may obliterate the squamous cell carcinoma and present the morphology of pure adenocarcinoma. 2) The efficiency of a mass screening for uterine cervical cancer is recognized for squamous cell carcinoma of the cervix, but not for adenocarcinoma or the mixed type of adenocarcinoma and squamous cell carcinoma[14,15].

The mass screening history (initial and repeated screenings) and clinicopathological factors in the adenocarcinoma cases detected by the mass screening were investigated with reference to the records at the institutions which conducted the detailed examination and/or treatment, and compared with those in the squamous cell carcinoma cases detected by the same mass screening at the same period or the uterine cervical cancer cases treated at our institution during the same period. The specimens of cytologic and histologic diagnosis from all of the adenocarcinoma cases were collected and reviewed at our laboratory.

The mass screening program for uterine cervical cancer

Ectocervical and endocervical scraping smears were collected using a spatula and swab, respectively, from all of the examinees of the mass screening after the investigation of their anamneses. These smears were immediately fixed in 95% alcohol fixative, transferred to the Nagasaki Prefecture Medical Health Center and stained for the Papanicolaou test.

All of the smears were screened by 1 to 3 cytotechnologists and those which were assessed to be suspicious or positive were further rescreened by 2 to 4 other cytotechnologists. Then, these abnormal smears were sent to our institution and 1 to 2 specialists in cytopathology reviewed them for the presence of histologic lesions. The examinees with abnormal smears were contacted by the institutions in their health care region for detailed examination.

Criteria of clinical staging, cytologic diagnosis and histologic diagnosis

Squamous cells in the cervical scraping smears were assessed by "Nichibo" cytologic classification and columnar epithelial cells by Papanicolaou classification. Based on these two classifications, the smears were divided into three groups : negative (class I and class II), suspicious (class III), and positive (class IV and class V).

The clinical stage and histologic type of the uterine cervical cancers were classified following the criteria specified in the "General Rules for Clinical and Pathological Management of Uterine Cervical Cancer"[16].

Statistical analysis

Comparisons between groups were made by the Fisher exact method, and $p<0.05$ was defined as significantly different.

Results

Incidence of cervical carcinoma detected in the mass screening

The results of the mass screening for uterine cancer over the 20-year period from April 1975 to March 1994, divided into five-year periods, are shown in Table 1. The number of the mass screening examinees steadily increased, from 86,578 in the first five-year period to 150,856 in the last five-year period. The largest increase was for the five-year period from 1985 to 1989, during which the mass screening system introduced in 1983 in accordance with the Health and Medical Law had been spreading and stabilized. The number of examinees during this period was about 31,000 more than at during the preceding five-year period, and the number of examinees who needed detailed examination was significantly higher than those during the other five-year periods ($p<0.0001$).

The detection rate of squamous cell carcinoma of the uterine cervix in the mass screening for uterine cancer tended to decrease slightly every five-year periods. The detection rate for the whole twenty-year period was 0.10%. The detection rate for adenocarcinoma and the mixed type of adenocarcinoma and squamous cell carcinoma of the uterine cervix for the whole twenty-year period was low, 0.0066%. However, it gradually increased until 1989 in every five-year period, reaching 0.0109% for the five-year period from 1985 to 1989. It significantly decreased (to 0.0033%) in the last five-year period compared with the preceding five-year period ($p = 0.0227$) (Table 1).

Clinical stage distribution of uterine cervical carcinomas

The clinical stage distribution of cervical carcinomas detected in the mass screening and that of the cases treated in our institution are shown in Tables 2 and 3, respectively. In total, 32 cases of adenocarcinoma of the cervix

Table 1. Numbers of examinees and cervical carcinomas detected in the mass screening for uterine cancer in Nagasaki Prefecture, Japan.

Time period	Total No. of examinees	No. of examinees needing detailed examinations	No. of cases of SCC detected	No. of cases of AC detected	No. of cases of MAS detected	No. of cases of AC & MAS detected
1975-79	86,578	407 (0.47)	131 (0.15)	4 (0.0046)	0	4 (0.0046)
1980-84	106,857	507 (0.47)	121 (0.11)	4 (0.0037)	4 (0.0037)	8 (0.0075)
1985-89	138,160	1,040 (0.75)	134 (0.10)	11 (0.0080)	4 (0.0029)	15 (0.0109)
1990-94	150,856	651 (0.43)	90 (0.06)	4 (0.0027)	1 (0.0007)	5 (0.0033)
Total	482,451	2,605 (0.54)	476 (0.10)	23 (0.0048)	9 (0.0019)	32 (0.0066)

Numbers in parentheses indicate the ratio to total examinees (%).
SCC, squamous cell carcinoma ; AC, adenocarcinoma ; MAS, mixed type of adenocarcinoma and squamous cell carcinoma.

Table 2. Clinical stage distribution of cervical carcinomas detected in the mass screening, by histologic type.

Clinical stage	No. of cases of SCC	No. of cases of AC	No. of cases of MAS	No. of cases of AC & MAS
Stage 0	307 (64.5%)	3 (13.0%)	4 (44.4%)	7 (21.9%)
Stage Ia	100 (21.0%)	3 (13.0%)	2 (22.2%)	5 (15.6%)
Stage Ib	52 (10.9%)	13 (56.5%)	3 (33.3%)	16 (50.0%)
Stage II-III	17 (3.6%)	4 (17.4%)	0	4 (12.5%)
Total	476 (100%)	23 (100%)	9 (100%)	32 (100%)

SCC, squamous cell carcinoma ; AC, adenocarcinoma ; MAS, mixed type of adenocarcinoma and squamous cell carcinoma.

Table 3. Clinical stage distribution of cervical carcinomas treated at the Nagasaki University School of Medicine (1975-1994), by histologic type.

Clinical stage	No. of cases of SCC	No. of cases of AC & MAS
Stage 0	346 (35.3%)	3 (3.6%)
Stage Ia	137 (14.0%)	4 (4.8%)
Stage Ib	209 (21.3%)	49 (59.0%)
Stage IIa-b	212 (21.6%)	21 (25.3%)
Stage IIIa-b	57 (5.8%)	5 (6.0%)
Stage IVa-b	19 (1.9%)	1 (1.2%)
Total	980 (100%)	83 (100%)

SCC, squamous cell carcinoma; AC, adenocarcinoma; MAS, mixed type of adenocarcinoma and squamous cell carcinoma.

Table 4. Clinical stage distribution of cervical adenocarcinomas* detected at initial and repeated mass screenings.

Clinical stage	No. of cases detected at initial screening	No. of cases detected at repeated screening	Total
Stage 0	2	5	7
Stage Ia	1	4	5
Stage Ib	9	7	16
Stage IIb	3	1	4
Total	15	17	32

* Including the mixed type of adenocarcinoma and squamous cell carcinoma.

(including the mixed type of adenocarcinoma and squamous cell carcinoma) were detected. The number of cases with adenocarcinoma at an early stage (stage 0 or stage Ia) was 12 (37.5%), significantly lower than the detection rate of squamous cell carcinoma at the early stage (407/476 cases, 85.5%) ($p<0.0001$) (Table 2). However, it was markedly higher than the detection rate of adenocarcinoma of the cervix at the early stage treated at our institution in the 20-year period from 1975 to 1994 (7/83 cases, 8.4%) ($p = 0.0004$) (Table 3).

The clinical stage distribution of the 32 adenocarcinoma cases detected by the intial and repeated mass screenings is shown in Table 4. The cases with adenocarcinoma of the cervix detected at an initial mass screening and at a repeated mass screening were 15 (46.9%) and 17 (53.1%), respectively, without a large difference between two groups. The rates of adenocarcinoma at an early stage (stage 0 or stage Ia) and frankly invasive adenocarcinoma (stage Ib or stage IIb) were 3/15 cases (20.0%) and 12/15 cases (80.0%) in the initial screening group, and 9/17 cases (52.9%) and 8/17 cases (47.1%) in the repeated screening group, respectively (Table 4). The adenocarcinomas in the early stage tended to be detected in the repeated screening, and the frankly invasive adenocarcinomas tended to be detected in the initial screening, but there was no significant difference between these two groups in their detection distribution ($p = 0.0759$).

Smear results at detection of cervical adenocarcinomas by clinical stage

The results of the review of the smears at the detection

Table 5. Smear results at detection of cervical adenocarcinomas* detected in the mass screening, by clinical stage.

Clinical stage	No. of cases presumed SN	No. of cases presumed GD or AC	Total
Stage 0	4	3	7
Stage Ia	3	2	5
Stage Ib	3	13	16
Stage IIb	0	4	4
Total	10	22	32

* Including the mixed type of adenocarcinoma and squamous cell carcinoma.
SN, squamous cell neoplasms (including dysplasia, carcinoma in situ, and microinvasive and invasive carcinoma); GD, glandular dysplasia; AC, adenocarcinoma.

Table 6. Number of cases with coexistence of squamous cell neoplasms in cervical adenocarcinomas* detected in the mass screening, by clinical stage.

Clinical stage	No. of cases with coexistence of				Total
	none	dysplasia	carcinoma in situ	invasive carcinoma	
Stage 0	1	2	4	0	7
Stage I	2	1	2	0	5
Stage Ib	10	3	1	2	16
Stage IIb	4	0	0	0	4
Total	17	6	7	2	32

* Including the mixed type of adenocarcinoma and squamous cell carcinoma.

of adenocarcinomas of the cervix (including the mixed type of adenocarcinoma and squamous cell carcinoma) are shown in Table 5.

It was possible to diagnose glandular epithelial neoplasms such as glandular dysplasia and adenocarcinoma from the smears at detection in 22/32 adenocarcinoma cases (68.8%). They could be diagnosed in only 5/12 of the cases (41.7%) of early-stage adenocarcinoma. Of the frankly invasive adenocarcinomas (stage Ib+stage IIb), it was possible to diagnose the neoplasms in 17/20 cases (85.0%); this rate was significantly higher than that of the early-stage adenocarcinoma ($p = 0.0184$). The diagnosable rate was 3/7 cases (42.9%) at stage 0 and 2/5 cases (40.0%) at stage Ia of the early-stage adenocarcinomas, with no significant difference. This rate was 13/16 cases (81.3%) at stage Ib and 4/4 cases (100%) at stage IIb and tended to increase with the progress of the adenocarcinoma (Table 5).

The remaining 10 cases (31.3%) were comprised of 7 cases (58.3%) of early-stage adenocarcinoma and 3 cases (15.0%) of frankly invasive adenocarcinoma; their smears at detection revealed only atypical cells originating in the coexisting squamous cell neoplasms. Thus, the adenocarcinoma of the cervix in these cases was detected incidentally by biopsy and/or conization specimens or hysterectomy specimens.

Frequency of coexisting squamous cell neoplasms in detected adenocarcinoma cases by clinical stage

As shown in Table 6, early-stage adenocarcinomas and frankly invasive adenocarcinomas histologically coexisted with squamous cell neoplasms in 9/12 cases (75.0%) and 6/20 cases (30.0%), respectively, indicating a high frequency of coexistence for early-stage adenocarcinomas ($p = 0.0269$). The frequencies of coexistence were 6/7 cases (85.7%) at stage 0, 3/5 cases at stage Ia (60.0%), 6/16 cases (37.5%) at stage Ib and 0/4 cases (0%) at stage IIb, showing a tendency to decrease with the progress of stage (Table 6). Of the 9 cases of early-stage adenocarcinoma coexisting with squamous cell neoplasms, more than half (6 cases) coexisted with squamous cell carcinoma in situ.

Clinical features of adenocarcinomas detected in the mass screening

The median age was 46 (33-62) years old in the 7 stage 0 cases, 36 (33-65) in the 5 stage Ia cases, 57.5 (32-72) in the 16 stage Ib cases and 49.5 (39-67) in the 4 stage IIb cases. It was 51 (32-72) in the total 32 cases. When divided into two groups of adenocarcinoma at an early stage (stage 0+stage Ia) and frankly invasive adenocarcinoma (stage Ib+stage IIb), the median ages were 35.5 (33-65) and 57.5 (32-72) years old, respectively. The postmenopausal women in these two groups were 4/12 cases (33.3%) and 12/20 cases (60.0%), respectively.

The median numbers of gravidity and parity were 3 (0-7) and 2.5 (0-5) in the early-stage adenocarcinoma group and 4 (1-10) and 3 (1-9) in the frankly invasive adenocarcinoma group. In total, the frequencies of nulligravidity and nulliparity were both 1/32 cases (3.1%).

Atypical genital bleeding occurred in 3/12 cases (25.0%) in the early-stage adenocarcinoma group and 8/20 cases (40.0%) in the frankly invasive adenocarcinoma group; i.e., in 11/32 cases of adenocarcinoma (34.4%).

Discussion

The frequency of adenocarcinoma in carcinoma of the uterine cervix has been shown to be increasing not only relatively with the decrease of squamous cell carcinoma but also absolutely[2,4,5]. Some registries recorded a 2% or more annual increase of the frequency in the 1972-1982 period, with the most marked increase in young women in middle to upper income levels who are likely to use oral

contraceptives[6,7]. Parazzini *et al*[8]. also reported a doubled frequency in the age group of less than 35 years old during a recent 10-year period. In Japan, Kimura *et al*[9]. and Hasumi *et al*[10]. reported approximately tripled and doubled frequencies in certain regions and institutions, respectively.In the present study, the detection rate for cervical carcinoma (squamous cell carcinoma, adenocarcinoma, and the mixed type of adenocarcinoma and squamous cell carcinoma) in the last five-year period of the mass screening for uterine cancer was 95/150,856 (0.063%), significantly lower than the 149/138,160 (0.108%) in the preceding five-year period ($p<0.0001$, chi-square test). The detection rate in each year of the last five-year period was reviewed; these rates were 24/30,139 (0.080%) in 1990, 12/31,497 (0.038%) in 1991, 13/28,437 (0.046%) in 1992, 30/31,122 (0.096%) in 1993 and 16/29,661 (0.054%) in 1994. We did not find a gradually decreasing tendency year after year, but the detection rate in each single year was lower than that during the preceding five-year period, 0.108%. However, the detection rates in each year during the last five-year period (1989-1993) in the nationwide statistics obtained by mass screenings for uterine cancer were 2,881/3,710,182 (0.078%), 2,722/3,843,501 (0.071%), 3,045/4,182,270 (0.073%), 2,749/3,992,439 (0.069%) and 2,680/4,133,959 (0.065%)[17]. The national detection rate tended to decrease gradually year after year.

The number and frequency of adenocarcinomas (including the mixed type of adenocarcinoma and squamous cell carcinoma) of the uterine cervix detected in the mass screening in this study tended to increase until 1989, but the increasing tendency was not found at all in the subsequent five-year period. However, this may be partly attributed to the slowing of the spread of the mass screening programs for uterine cancer, and to the increase of the rate of repeated examinees. In the mass screening for cancer, if the rate of initial examinees among total examinees is higher, the detection rate of cancer usually becomes higher. The rates of initial examinees among the total examinees in each of the three 5-year periods in the present study (1980-1984, 1985-1989 and 1990-1994) were 20,996/106,857 (19.6%), 19,010/138,160 (13.8%) and 12,718/150,856 (8.4%), respectively. The rate in the last five-year period proved to be significantly lower than that of the others($p<0.001$, chi-square test). This may explain the low detection rate of adenocarcinoma of the cervix during this period. The same phenomenon was noted in the detection rate of squamous cell carcinoma of the cervix. The results of the mass screening program in the present study thus do not preclude an increasing tendency of adenocarcinoma of the cervix.

The greatest significance of the mass screening for cancer lies in the contribution of the screening results toward the decrease of both the cancer incidence and mortality rate in the target region or population. Mass screening has been demonstrated to be effective in detecting squamous cell carcinoma of the cervix, but its efficacy in the detection of adenocarcinomas is not established[14,15,18-20]. We should consider this as a problem to be solved in present and future mass screening programs for cervical cancer. The present detected number (32 cases) and rate (0.0066%) for adenocarcinoma and the mixed type of adenocarcinoma and squamous cell carcinoma of the cervix in the mass screening program for cervical cancer for the past 20 years in Nagasaki Prefecture were markedly lower than the number (476 cases) and rate (0.01%) for squamous cell carcinoma of the cervix in the same population. However, these 32 adenocarcinoma cases correspond to 6.3% of the total 508 cases of cervical carcinoma detected in the mass screening, and this figure is not significantly different from the 83/1,063 cases (7.8%) for carcinoma of the cervix treated at our institution during the same period ($p = 0.3020$). Considering the general belief that adenocarcinoma accounts for 8 to 26% of primary carcinomas of the cervix[20], the detection rate of adenocarcinoma of the cervix is not particularly low, as Sugimori *et al*[11]. reported. Therefore, the detection accuracy for adenocarcinoma of the cervix in the present mass screening is no lower than it appears to be. We do not know the detection rate of adenocarcinoma of the cervix in relation to the examinees' history of undergoing the mass screening; some reports describe a rate similar to that for frankly invasive carcinoma of the cervix (about 50%) and others describe a much lower rate[11]. In the present study, 46.9% of the adenocarcinoma cases detected in the mass screening were detected in the initial screening, and 80% of them had frankly invasive adenocarcinoma at clinical stage Ib orIIb.

In the present study, the rate of carcinoma at an early stage (stage 0 or stage Ia) in the adenocarcinomas of the cervix detected in the mass screening was significantly lower than that of squamous cell carcinoma detected in the same mass screening. As one of its histopathological factors, the results of our previous study[13] indicate that the lesions of adenocarcinoma at the early stage are generally small and buried deeply in the endocervical gland, which may make the lesions difficult to detect in cervical scraping smears. Besides this factor, adenocarcinoma at an early stage may progress into frankly invasive carcinoma more quickly than dose squamous cell carcinoma at an early stage and, as a result, the latent period as carcinoma in the early stage may be short and the chance to be detected could be decreased. From the aspect of cytodiagnosis, information regarding the cytologic findings of early-stage adenocarcinomas is insufficient in comparison with that on early-stage squamous cell carcinomas, and this may result in false negative cases. As measures to overcome this problem, the need to improve cytodiagnostic skill at recognizing different glandular lesions of the cervix has been pointed out[21], and the use of better endocervical sampling devices was reported to

enhance the detection of adenoarcinoma[22].

The rate of early-stage adenocarcinomas among the adenocarcinomas detected in the present mass screening was significantly higher than that of adenocarcinomas of the cervix treated at our institution during the same period. This result indicates a possibility of early detection of not only squamous cell carcinoma of the cervix but also adenocarcinoma of the cervix through mass screening. The results of the review of the smears at detection in the present study indicate that the existence of glandular epithelial neoplasms could be diagnosed in a relatively small number of cases (41.7%) by atypical glandular epithelial cells appearing in the smears of adenocarcinoma cases in early stage. The majority of the cases (58.3%) were identified by atypical squamous cells in the screening smears from the coexisting squamous cell neoplasms described below, and were indicated to require detailed examinations, where as the adenocarcinomas at an early stage were often found later in biopsy and/or conization specimens or hysterectomy specimens. This appears to be a limit of the detection of pure adenocarcinoma at an early stage without squamous cell neoplasms in smears from mass screening. Among the cases of adenocarcinoma in situ of the cervix, the rate of the cases with abnormal cervical smears (smears with atypical glandular epithelial cells and/or atypical squamous cells) has been reported to be 50-70%[23-25], much lower than the frequency in squamous cell carcinoma in situ. This rate is estimated to be further lower when limited to the smears with only atypical glandular epithelial cells. Retrospective studies of the cases diagnosed as having adenocarcinoma in situ of the cervix by conization have revealed that the rate of the cases suspected to have adenocarcinoma in situ by cervical smears, colposcopy or office cervical biopsy before conization was 16/26 cases (61.5%)[25] or 20/40 cases (50.0%)[26]. Neither of these rates is high, indicating that many cases are found incidentally.

It is well known that early-stage adenocarcinomas often coexist histologically with squamous cell neoplasms of the cervix. The rate of coexistence is reported to be in a range of 50-90% in adenocarcinoma in situ (stage 0)[13,25-31] and 31-67% in microinvasive adenocarcinoma (stage Ia)[29-31]. These figures are high (85.7% and 60.0%) in the cases detected by the mass screening of the present study. The majority of coexisting squamous cell neoplasms are considered to be squamous cell carcinomas in situ, as found in the results of the present study. As mentioned in the above, these coexisting squamous cell neoplasms particularly help the identification of adenocarcinoma at an early stage. The rate of coexistence is relatively low in frankly invasive adenocarcinoma[13,20,29,30] This rate was 30.0% in the present study, and significantly lower than the 75.0% of the early-stage adenocarcinomas ; the reason for this is not known. We can consider as one of the possible reasons that, when adenocarcinoma in situ and squamous cell carcinoma in situ coexist, the former is higher in biological malignancy and possibly obliterates the latter in the process of further development.

The median age (35.5 years old) of the patients with early-stage adenocarcinoma detected in the mass screening of the present study coincided well with the reports in Europe and the United States[24-26,28,31,32] and supports the findings that these patients are 10-20 years younger than those with frankly invasive adenocarcinoma[31,33]. However, most of the Japanese studies have reported the mean age of patients with adenocarcinoma in situ to be 44-45 years old[13,29,30]. The reports in Europe and the United States indicate that the patients with adenocarcinoma of the cervix have a slight tendency toward nulligravidity, nulliparity and obesity[24-26] and share a few of the epidemiologic factors associated with endometrial carcinoma of the uterine body[20]. The frequencies of nulligravidity and nulliparity in the 32 cases of our study were both 3.1%. They were aiso low (2.7% and 10.8%) in our previous study of 37 cases of early-stage adenocarcinoma[13]. A possible difference in the etiology of adenocarcinoma of the cervix between Europe/the United States and Japan should also be considered. The frequency of the patients with atypical genital bleeding is not definite, particularly in adenocarcinoma at an early stage, and has been reported to be in the range of 14-16%[13,24-26]. However, the majority of patients with early-stage adenocarcinoma are women at an reproductive age. Thus, we should consider that atypical bleeding is not a feature specific to the lesions but that it is caused by coexisting cervical erosion. In order to improve the efficiency of mass screenings for adenocarcinoma of the cervix, the epidemiologic and clinical profiles of adenocarcinoma of the cervix should be further clarified, and a mass screening program should be designed based on these profiles.

Acknowledgments

The authors would like to thank Dr. Takeshi Matsuo, Director, and the cytotechnologists of the Pathological Laboratory, Nagasaki Prefecture Medical Health Center, for their cooperation in the collection of the mass screening data for uterine cancer in Nagasaki Prefecture. We thank also the physicians in the obstetric and gynecological departments of each health care region for their cooperation in the collection of detailed examination and/or treatment data.

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