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Incidence of Invasive Squamous Cell Carcinoma Diagnosed with Opportunistic Screening in >70 Years-Old Women: Italy as a Case Study

Teresa Pusiol
Section of Cytopathology, Institute of Anatomic Pathology, Rovereto Hospital
Italy

1. Introduction

Cervical cancer is still one of the leading cancers worldwide (1), although there is a discrepancy between developed and developing countries. In developed countries, there is a continuous decline in incidence and mortality, whereas in developing countries, there is a more stable or even increasing pattern. The latter is more likely to be due to the lack of screening and infectious cofactors than to ethnic differences. Cervical cancer remains the only human malignancy that has been successfully reduced by medical intervention. Organised screening (OrS) for cervical cancer by the conventional Pap smear is the only means with proven efficacy of reducing the incidence and mortality of this disease in countries where it has been successfully implemented. According to the official statistics, the age standardized incidence rate of cervical cancer in Italy currently (2002) levels of at 8.1/100.000 with a mortality rate of 2.2/100.000 (2). Italy is another European country with no unified national screening programme, but each region has adopted a screening policy of its own. (3)Cervical cancer screening in Italy started as a spontaneous activity, with no national organization, which, not unexpectedly, led to incomplete population coverage. The Italian health system is managed by Italy's 20 Regions (Figure 1).

Since 1996, Italian national guidelines have recommended to Regions the implementation of organised screening programmes for cervical cancer. These recommendations, largely based on European guidelines, include personal invitations to women aged 25 to 64 years for a Pap smear every three years, a monitoring system, and quality assurance for each phase of the programme. Surveys designed to assess the level of implementation of organised programmes in Italy and to collect process indicators have been conducted by Italian Group for Cervical Screening since 1997 (4,5,6,7,8,9,10,11,12,13). Their results have been published by the Osservatorio Nazionale Screening (ONS),(National Centre for Screening Monitoring) since 2002. Since 1993 in Trentino province (North Italy) an Organized Screening (OrS) exist for women 25-65 aged. The target population comprises 146737 women. In the period 1993 – 2006 the pap-smears of OrS were examined in the Institutes of Anatomic Pathology and Cytopathology of S.Chiara Hospital Trento and Rovereto Hospital. Since 2007 the Cytopathology Section of Institute of Anatomic Pathology of Rovereto Hospital have examined only pap-tests of Opportunistic Screening (OpS), i.e. left to the woman's initiative.

OpS may be considered as all Pap-test performed outside an OrS program. For example, some women have Pap-test at their doctor's office during their physical examination independently of personal letter invitation of OrS. In Italy the complete screening history of women diagnosed with invasive cervical cancer has been performed only in Friuli Venezia Giulia – North eastern Italy -. In these region an OrS was initiated in 1999, targeting women aged 25 – 64 years, who are invited to have a Pap-test every 3 years. The screening histories of Cervical Intraepithelial Neoplasia (CIN)3 - squamous cell carcinoma in >65 years-old women may be made with study of OpS, because the OrS offers a free-of-charge Pap-test every 3 years to all women aged 25-64 years. In the present study we have examined the screening histories, treatment, human papillomavirus (HPV) detection of CIN3- invasive squamous cell carcinoma in >65 years-old women, diagnosed in the period 2007-2010 with opportunistic Pap-tests in the Cytopathology Section of Institute of Anatomic Pathology of Rovereto Hospital.

Fig. 1. Italy's regions

2. Materials and methods

In the period 2007-2010 the Cytopathology Section of Institute of Anatomic Pathology of Rovereto Hospital have been examined 28589 opportunistic Pap smears. The standard technique of conventional opportunistic Pap smears involves taking two samples (one from the endocervix with cytobrush and one from ectocervix with Ayre spatule) and smearing the cytological materials on two slides. The cytological diagnosis was performed using the 2001 Bethesda System (14). An experienced cytopathologist whose diagnostic experience exceeds 20 years have examined all abnormal smears and 10% of the normal smears

previously observed a senior cytotechnologist. Colposcopic and cervical biopsies were taken by an experienced colposcopist (in practice for more than 10 years) and review by a senior colposcopist as part of the routine. HPV genotyping by PCR was performed in all histological specimens (biopsy, cone, hysterectomy) with diagnosis of low grade and high grade intraepithelial lesions and invasive cervical carcinoma.

3. Results

111 cases (0,38%) of CIN3-squamous cell carcinoma has been identified in 28589 opportunistic Pap smears. The distribution of women for decades is reported in Table 1. Between the women >64 years-old with CIN3-squamous carcinoma cytological diagnosis all were > 70 years-old and were not invited to OrS because of age > 64 years. We have reported in Table 2 the age, histological diagnosis, treatment and HPV detection of 8 patients over 70 years with CIN 3 squamous cell carcinoma cytological diagnosis.

Total number opportunistic Pap-tests	≤ 20 Years (percentage).	21 – 40 Years (percentage).	41 – 70 Years (percentage).	> 70 Years (percentage).
28.589	892 (3.2%)	11240 (39.3%)	14848 (51.9%)	1620 (5.6%)

Table 1. Opportunistic screening: decades of age of 28.589 women in the period 2007-2001

Number patients	Age	Treatment	Histological diagnosis (pT)	HPV finding
1	81	Hysterectomy with bilateral salpingo-oophorectomy	CIN3	HPV16
2	82	Cone biopsy	CIN3	Negative
3	71	Cone biopsy	CIN3	HPV58
4	79	Cone biopsy + radiotherapy	Keratinizing squamous cell carcinoma NOS	Negative
5	75	Hysterectomy with bilateral salpingo-oophorectomy	Non keratinizing squamous cell carcinoma (pT1b1)	Negative
6	82	Biopsy	Keratinizing squamous cell carcinoma NOS	Negative
7	72	biopsy + radiotherapy	Keratinizing squamous cell carcinoma NOS	HPV58
8	75	Hysterectomy with bilateral salpingo-oophorectomy + radiotherapy	Non keratinizing squamous cell carcinoma (pT1b1)	Negative

Table 2. Age, treatment, histological diagnosis, HPV detection in women over 70 years-old with CIN3-squamous cell carcinoma. NOS= not other specified

The Pap smear was performed by gynecologist to the woman's initiative. In the Pap smear of keratinizing squamous cell carcinoma the cells showed significant nuclear and cytoplasmic abnormalities, the later usually showing a marked deviation from normal cells of the same origin. The malignant keratinized cells had a characteristic bright orange or occasionally yellow cytoplasm that was dense and lack the transparent qualities of normal squamous cells. The size of keratinized cancer cells may vary from very large, comparable with normal superficial cells, to small, about the size of small parabasal cells. Their shape varies from round or polyhedral to quite irregular and bizarre (Figure 2).

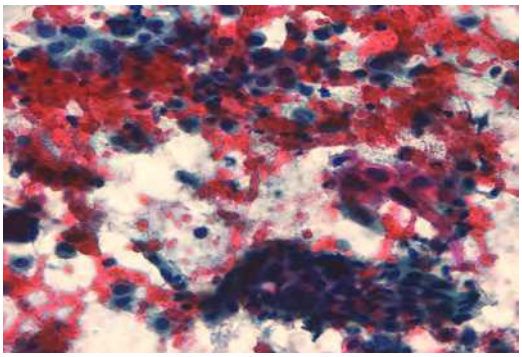

Fig. 2. Cancer cells with elongated keratinized eosinophilic cytoplasm and hyperchromatic nuclei in necrotic and hemorrhagic background. (Papanicolaou 40X).

The nuclei were usually large for the size of the cells. As is often the case in the presence of cytoplasmic keratinization, nuclear pyknosis and karyorrhexis may occur, conferring on the nucleus a dark appearance. "Tadpole" cells were present. They were elongated, club-shaped cells, with one board and one narrow end. The round or irregular hyperchromatic nucleus was eccentrically located within the larger area of the cytoplasm . The degree of cytoplasmic keratinization was variable. The spindly squamoid cells were an unusual finding in the Pap smear. These cells were narrow, elongated, and needle-shaped. Keratinization was not necessarily seen, the cytoplasm may be either eosinophilic or basophilic. The nuclei were nearly always elongated and hypercromatic (Figure 3).

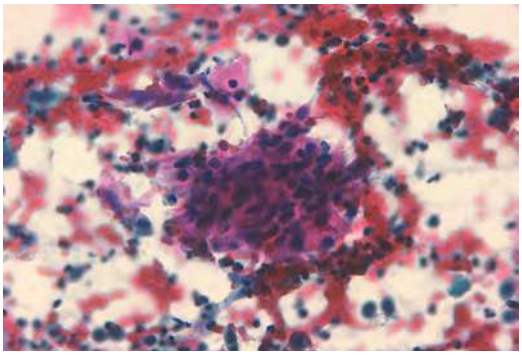

Fig. 3. Spindly squamous cancer cells. Note the markedly hyperchromatic nuclei and the cytoplasmic keratinization. (Papanicolaou 40X).

The squamous "pearls" was a very rare finding in Pap smear of squamous cell carcinoma. These were concentrically arranged clusters of being squamous cells. The difference between the benign and malignant "pearls" was in the configuration of the nuclei which, in the cancerous pearl, are enlarged and hypercromatic. In the Pap smears of non-keratinizing squamous cell carcinoma the malignant cells were solitary or arranged in syncytia (Figure 4) and show anisokaryosis. The nuclei were relatively large with unevenly distributed, coarsely granular chromatin and may have irregular nucleoli. The Pap smear of CIN-3 were characterised by cells with nuclear-to-cytoplasmatic ratio significantly increased. The cytoplasm remained well-defined resembling that of very immature metaplastic cells. Nuclei tended to be considerably hyperchromatic, and marked irregularities of nuclear envelope might be present. The cytological characteristics of menopause were found in the Pap smear with malignant cells (Figures 5-6) and CIN-3.

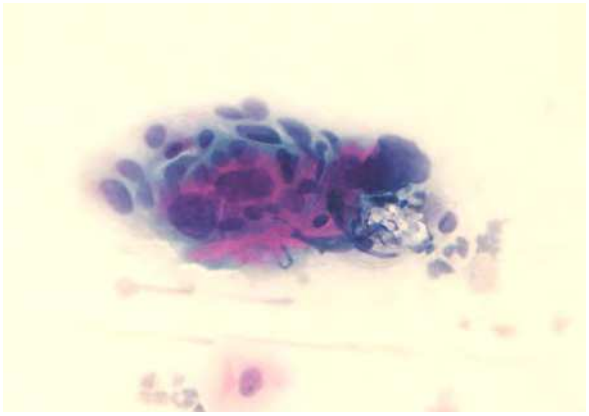

Fig. 4. A cluster concentrically arranged of undifferentiated cancer cells (Papanicolaou 40X).

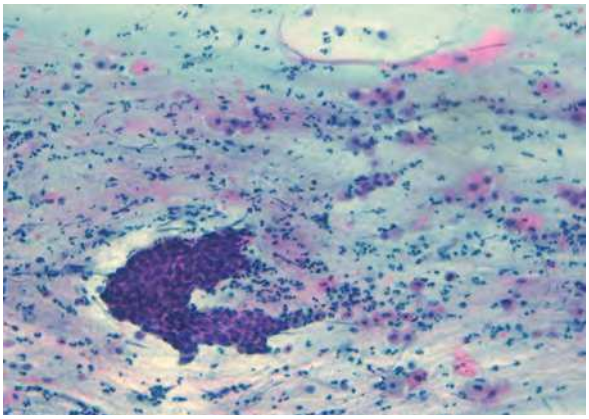

Fig. 5. Cellular pattern of advanced menopause: the cells are parabasal with filaments of nuclear material resulting from breakdown of nuclei. A cluster of undifferentiated cancer cells of invasive squamous carcinoma with dark hyperchromatic nuclei is found. (Papanicolaou 10X).

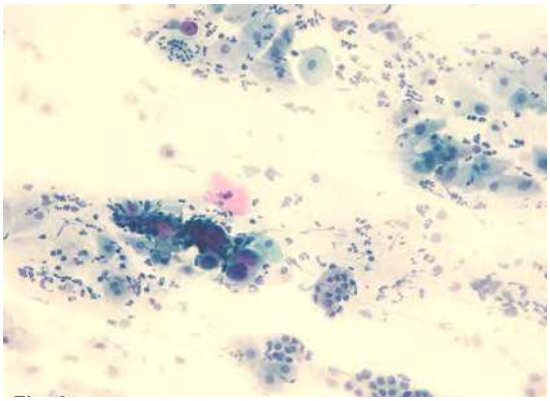

Fig. 6. Cellular pattern of intermediate menopause with cluster of neoplastic squamous cells containing hyperchromatic and irregular nuclei. (Papanicolaou 10X).

The cytologic patterns of the advanced atrophic menopause were influenced by dryness of the genital tract and scarsity of recoverable cellular material. The predominant cell was of the size and the degree of maturity corresponding to the parabasal cells. Two main effects of dryness might be observed: one was the uniform enlargement of the cell accompanied by a characteristic uniform gray discoloration of the degenerated nucleus; the second was by nuclear pyknosis and karyorrhexis. In the smear material of the eosinophilic pyknotic type there might be a striking variation in cell size and shape. Some cells might be relatively large, approaching the size of superficial cells, whereas others were the size of small parabasal cells. Sheets of spindly cells with elongated cytoplasm and large, pale nuclei may make their appearance in cervical smears and sometimes might be difficult to interpret. Nuclear pyknosis may be quite striking and often simulates the hyperchromasia of cancer cells; one must search for evidence of karyorrhexis in the form of granules of nuclear material within the cytoplasm. In some instances of extreme dryness, the cells break up during the process of smearing and will appear as standards and filaments of blue- staining nuclear material. The endocervical columnar cells in smear of the cervics were usually scarse or absent. When observed , the endocervical cells were smaller than during the childbearing age, although their columnar configuration was still preserved. The nuclei, although of normal size, may appear somewhat hypercromatic, and the cytoplasm was scanty, opaque, and shows no evidence of secretory activity except for an occasional vacuole. One Pap smear CIN-3 and one Pap smear of keratinizing squamous cell carcinoma cointained cells with koilocytotic changes (Figure 7). In the biopsies of CIN-3 maturation (including surface keratinization) was absent or confined to the superficial third of the epithelium. Nuclear abnormalities were marked throughout most or all of the thickness of the epithelium. Mitotic figures were numerous and were found at all levels if the epithelium. Abnormal mitoses were frequent. Focal koilocytosis was present in one case. Keratinizing squamous cell carcinoma were histologically characterized by mature squamous cells arranged in irregularly shaped nests or cords that varied considerably in size. The most striking feature was the present of keratine pearl within the nests of neoplastic squamous epithelium (Figures 8 and 9).

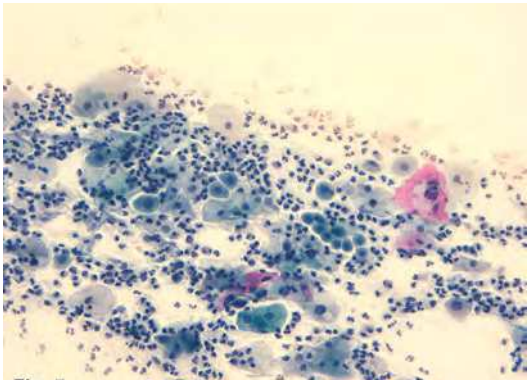

Fig. 7. Cellular pattern of intermediate menopause with nuclear enlargement of parabasal cells. Superficial squamous cell with koilocytotic atypia is present. (Papanicolaou 10X).

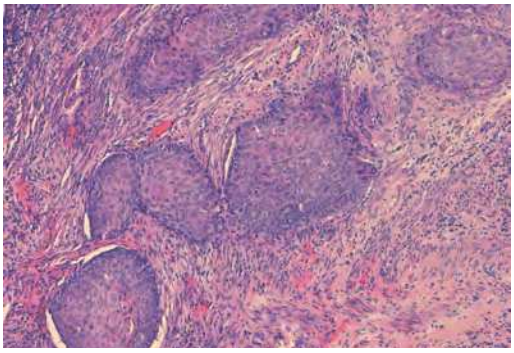

Fig. 8. Cone biopsy of keratinizing squamous invasive carcinoma of the cervix. Nests of keratinizing, markedly atypical squamous neoplastic cells are evident. (H&E 10X).

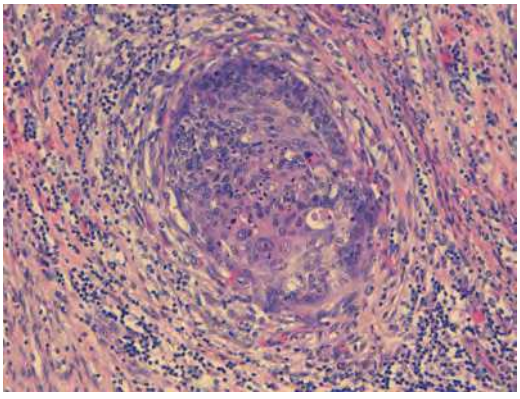

Fig. 9. Cone biopsy of keratinizing squamous invasive carcinoma of the cervix. Nest of keratinizing, markedly atypical squamous neoplastic cells is surrounded by dense inflammatory infiltrate . (H&E 10X).

Individual squamous cells were large ,with abundant eosinophilic cytoplasm, and many showed individual cell keratinization. The cells were closely apposed and often had prominent intercellular bridges. The nuclei may be enlarged or pyknotic. Mitotic activity was relatively low compared with the other tumor types.

The non-keratinizing tumors were composed of generally recognized polygonal squamous cells that might have individual cell keratinization and intercellular bridge but keratin pearls were absent (Figure 10). Cellular and nuclear pleomorphism was more obvious than in the well differentiated tumours, and mitotic figures were usually numerous.

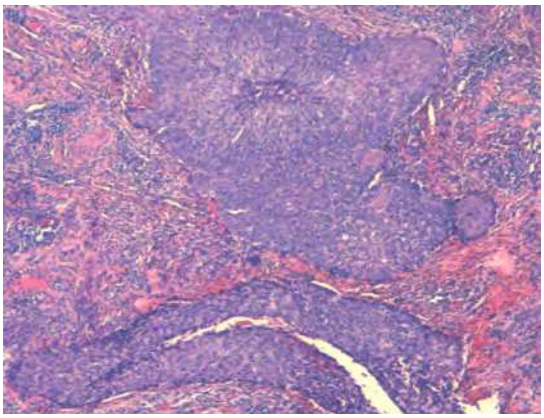

Fig. 10. Cone biopsy of non-keratinizing squamous invasive carcinoma of the cervix. The neoplasm is composed of nests of tumor cells with basaloid differentiation.(H&E 10X).

4. Discussion

In 1990 cervical cancer comprised 10% of cancers in women for a total of approximately 470,000 cancer cases world-wide (15), representing the third most common cancer in females and the most common cancer in Sub-Saharan Africa., Central America and South Central Asia. Approximately 230,000 women die annually from cervical cancer and over 190,000 of these are from developing countries. Zimbawe and India stand out not only for their high incidence, but also for an unfavourable incidence to mortality ratio. Some relatively high-incidence countries can also be found in Eastern and Central Europe (16).The incidence and mortality of invasive squamous cell cervical carcinoma have decreased dramatically in the United States over the last three decades. The incidence in the United States was 34/100,000 in 1947, 15/100,000 in1970, and 12/100,000 in 1986 (17). Although the incidence was decreased in the United States before the implementation of mass cervical cancer screening programs, screening has had an additional major impact on both the incidence and mortality (65,111). The significance of cytologic screening in reducing the incidence of cervical cancer is further underscored by comparing the 4.5/100,000 incidence per year in a screened population to the 29/100,000 incidence in an unscreened population(18). Both cohorts exhibited similar epidemiologic characteristics. In the United States, approximately half of the women who develop cervical cancer have not had a cervical smear in the preceding 3 years(19). According to the most recent global estimates, invasive squamous cell

carcinoma is the second most common cancer in women world-wide, with the exception of skin cancer. There are approximately 493,000 new cases of invasive cervical cancer worldwide and 274,000 women die of the disease annually (20). The highest rates are reported in Latin America, where cervical cancer accounts for half of all female cancers. The annual incidence of invasive cervical cancer in women between 30 and 50 years of age in high-risk areas is 1/1,000. In developing countries throughout the world, cervical cancer is a major public health problem and is one of the leading causes of death (21). Recent increases in incidence and mortality rates have been observed in some Western countries including Canada, Great Britain, Sweden, and Norway (22,23,24,25). In the United States, there were 12,800 new cases and 4,600 cervical cancer deaths in 2000 (26). The incidence among blacks and Hispanics is two times higher than among whites in the United States. Moreover, in a recent study, after adjusting for a number of demographic factors, age, Federation of Gynecology and Obstetrics (FIGO) stage, other tumor characteristics, and treatment, black women had a higher mortality rate than white women, indicating that race is an independent predictor of cervical cancer survival (27). Socioeconomic, religious, sexual, obstetric, dietary factors, immunosuppression, smoking, and oral contraceptive intake have been studied in relation to cervical cancer. Studies suggest that dietary carotenoids and vitamin C have a protective effect against cervical cancer (28,29). The risk of cervical cancer is increased by the number of sexual partners, the age at which sexual intercourse is initiated, and the sexual promiscuity of the male partner. Husbands of women with cervical cancer have more sexual partners than husbands of controls (30). In a recent study, smokers had a two-fold excess risk of cancer, with the risk linked to smoking intensity and duration (31). The effect was most striking among women who had smoked continuously up to the time of cancer diagnosis and women who began smoking late in life, suggesting that smoking played a promotional role in cervical cancer rather than an initiating role. Long-duration use of hormonal contraceptives is associated with an increased risk of cervical cancer, but the public health implications depend largely on the extent to which the association remains long after the use of the contraceptives has ceased (31). Invasive squamous cell carcinoma is uncommon before the age of 30 years. Half of the patients, however, are less than 50 years old (32). In the United States, 22 percent of all women with cervical cancer are under the age of 35 years (33), but most are between 45 and 55 years of age al the time of diagnosis. Cervical cancer, however, can occur at almost any age between 17 and 90 years. The majority of the patients present with intermittent painless vagina, bleeding, often first noted after sexual intercourse or douching. With advancing disease, bleeding may become continuous, and be accompanied by a malodorous discharge and pain. Pain is frequently referred in the flank or leg as a result of tumor invasion of the pelvic wall or sciatic nerve. A cervical biopsy is mandatory for diagnosis. Although sampling problems and incorrect interpretation are partly responsible for false negative smears, necrosis and inflammation on the surface of the tumor may result in only an "atypical smear" that lacks obvious tumor cells. Consequently, the cervix that is abnormal by inspection or palpation is biopsied, even if the cytology smear is normal. In addition to biopsy of the ectocervix, an endocervical curettage Is performed as an integral part of the evaluation because invasive carcinoma, particularly adenocarcinoma, frequently involves the endocervical canal and may not be visible on the ectocervix. Cervical cancer is the most common gynecologic cancer to occur during pregnancy: about 3 lo 10 percent of cervical

cancers occur in pregnant women. In these women, 83 percent present with stage I disease (34). Invasive cervical cancer can be divided in two major histological types: squamous cell carcinoma and adenocarcinoma. In terms of percentages, 80–85% of cases are squamous cell carcinoma, 10% are adenocarcinoma, and 3% are adenosquamous carcinoma and other rare tumours (35). HPV infection is the most common sexually transmitted disease, with more than 80% of the population infected at some time in their life. The main risk factor is undoubtedly genital infection with HPV. HPV infections are found in almost all pre-invasive lesions, so-called CIN and invasive squamous cell cancers (36). Based on the still-rising figures of HPV infections, one could consider it to be one of the most prevalent sexually transmitted pathogen diseases worldwide (1). From an epidemiological point of view, an HPV infection meets the criteria as a causal agent for cervical cancer (37,38). Current epidemiological and fundamental data have confirmed infection with HPV to be the basic cause of the disease (37,38). Having sexual contact is the main source of HPV infection. It is estimated that for every three people who have sex with a HPV-positive person, two will develop an infection within the next few months (1-19). In the majority of cases (75%), the infection will be asymptomatic. The peak prevalence of genital HPV infections is soon after the onset of sexual activity in women. HPV deoxyribonucleic acid (DNA) persists for about 6–12 months in the genital tract and spontaneously disappears in the majority of patients until an infection with a new type occurs. A persistent infection is the most important risk factor for initiating malignant transformation in the cervical epithelium. The time from initial infection to pre-invasive and, ultimately, invasive disease appears to be at least 10–15 years (1). Based on their association with cervical cancer, genotypes of HPV are divided into low-risk and high-risk groups, according to their presence in malignant lesions of the cervix. Functionally high risk HPV types infection contributes to carcinogenesis and tumour progression predominantly through the action of two viral oncogenes, E6 and E7. The coordinated expression of E6 and E7 has been town to transform rodent cells and immortalize primary human keratinocytes (39,49). The E6 and E7 proteins of high-risk HPVs have been demonstrated to be able to associate with the products of p53 and retinoblastoma susceptibility (Rb) genes, respectively, and inactivate the functions of these tumour suppressor proteins (40,41). The E6 protein exerts rapid degradation of p53, in corporation with E6-associated protein (E6-AP), via ubiquitin-mediated proteolysis pathway (42, 43). The E7 protein mediates the release of the E2F transcription factor from pRb-E2F complex (44). Mutational analysis of HPV 16 E6 protein revealed that a certain level of the activity to degrade p53 is required for E6 to manifest its transforming function (45). The p53 mutations are the most frequent genetic abnormalities found in a wide variety of human malignant tumours (46). Once DNA damage occurs, p53 protein is induced and arrests cells in the G1 phase to enhance DNA repair (47), or triggers apoptosis following DNA damage (48). These functions of p53 protein are important to maintain the genomic integrity. Mutant p53 proteins are devoid of these functions, because they lose the ability of DNA contact or destabilize the structure of the core domain (49). In this way, once p53 is mutated, DNA damage is fixed and subsequent genetic rearrangement progress which may be putative mechanisms to initiate cancer. Thus far, exceptionally low prevalence (0-6%) of the p53 mutations had been documented in cervical carcinomas (50, 51, 52, 53, 54). The p53 protein in cervical carcinoma is thought to be inactivated presumably due to complex formation with HPV E6 oncoprotein. Although Crook et al initially

postulated that p53 mutations were confined to the HPVnegative cervical carcinomas (55,56), several recent studies implicated that p53 mutation was a very rare event and the occurrence was not strictly correlated with HPV status in primary cervical carcinomas (50,51,52,53,54). It has been also shown that p53 mutants identified in the HPV-positive anogenital cancers exhibit increased resistance to HPV E6-directed degradation, suggesting that mutation of p53 may play a role in the progression of the HPV-positive cervical cancer (56). The p53 mutation has been found only in 0–6% of cervical carcinomas. In light of recent studies demonstrating that mutation of p53 gene was found in over 20% of the patients with vulvar carcinoma (57, 58), a disease of elderly women and a known HPV- related malignancy, Nakagawa et al (59) analysed mutation of the p53 gene in 46 women with cervical carcinomas at the age of 60 or more (mean; 71 years, range; 60–96 years). Of the 46 patients, 41 had squamous cell carcinoma (keratinizing type, ten; large cell non-keratinizing type, 31) and five had adenocarcinoma (endocervical type, four; endometrioid type, one). On the basis of the FIGO criteria, 12 women had Stage I, 18 Stage II, 15 Stage III and 1 Stage IV. The presence of HPV and its type were analysed by polymerase chain reaction (PCR)-based assay using the consensus primers for L1 region. Mutation of the p53 gene was analysed by PCR-based single-strand conformation polymorphism and DNA sequencing technique. Point mutation of the p53 gene was detected in 5 out of 46 (11%) cervical carcinomas: 1 of 17 (6%) samples associated with high-risk HPVs (HPV 16 and HPV 18) and 4 of 27 samples (15%) with intermediate-risk HPVs, whereas no mutation was found in 2 HPV negative cases. The mutated residues resided in the selective sequence known as a DNA-binding domain. The immunohistochemistry revealed the overexpression in cancer tissues positive for p53 mutation. All of the observed mutations of the p53 gene were transition type, suggesting that the mutation may be caused by endogenous mutagenesis. Although falling short of statistical significance reduces the strength of the conclusion, data presented by Nakagawa et al imply that p53 gene mutation, particularly along with intermediate risk HPV types, may constitute one pathogenetic factor in cervical carcinoma affecting elderly women. To clarify the age-related genetic events in cervical cancer in elderly (>65 years) women, Saito et al (60) have analyzed for HPV typing via polymerase chain reaction, the expression of p53 via immunohistochemical study, and clinical behaviour 66 tissue specimens obtained from patients with stage Ib-IIb cervical carcinoma. Of this group, 50 women aged 64 years and younger were designated as the younger group (mean age 46.7), and 16 women aged 65 years and older were designated as the older group (mean age 67.6) The prevalence of HPV DNA was higher in the younger group than in the older group (84.0 vs. 50.0%) as was the detection rate of HPV 16 (44.0 vs. 6.3%). In contrast, HPV 18, 33, 52, 58, were frequently detected in older patients. The positive rate of p53 overexpression in the older group was similar to that in the younger group (46.7 vs. 48.8%). There was no significant difference in the incidence of lymph node metastasis, histology, and the distribution of clinical stage between the two groups. In elderly Japanese women with stage Ib-IIb, the association of HPV of types other than HPV 16 is suggested to influence the progression of cervical cancer. The most common member of the high-risk group is HPV 16, which accounts for more than 60% of all cervical cancers. The high-risk types account for more than 95% of all cases of cervical cancer. One of the main differences between high- and low-risk types is the possibility of integration in the genome. Approximately 1percent of the high-risk HPV types and only 0.1% of the low-risk HPV

types will lead to the development of cervical cancer (61). In our case HPV 16 and HPV 58 were detected in two cases of CIN3 and HPV 58 in one case of squamous cell carcinoma. In one case of CIN3 and in 4 cases of squamous cell carcinoma the HPV type has been not detected. Two hypotheses may be made. There is a subset of squamous cell carcinomas that is unrelated to HPV. Other hypothesis takes into account that HPV 16 is only integrated in 72 percent of all invasive cervical cancers(62). The finding of the absence of HPV 16 DNA integration in some carcinomas implies that integration is not always required for malignant progression, but does not exclude the importance of HPV integration in the initiation of cervical cancer. Hypothetically, after the development of a carcinoma, the abnormal clone could lose the viral DNA. HPV 18, on the other hand, shows 100 percent integration. The epidermal growth factor receptor (EGFR) represents a cell membrane receptor characterized by an extracellular ligand-binding domain and an intracellular domain with tyrosine activity involved in signal transduction. EGFR receptor ligands such as epidermal growth factor (EGF) and tumor growth factor > binding to EGFR lead to a cascade of cellular events that are responsible for DNA synthesis, cell proliferation, mutation, survival maturation, and apoptosis (63). Aberrant EGFR expression results in abnormal growth, inhibition of apoptosis, angiogenesis,and the promotion of invasion/metastasis (64). EGFR overexpression has been observed in several malignancies (65). Cyclooxygenase (Cox) is the enzyme involved in the conversion of arachidonic acid to prostaglandins in the critical steps of tumor onset and progression. Two Cox isoforms have been characterized. Cox-1 is expressed constitutively in almost all tissues and serves homeostatic functions. Cox-2, which is highly inducible by growth factors, prostaglandins, and tumor promoters, plays a key role in inflammatory response (66). Cox-2 overexpression has been reported in many neoplasms; its overexpression is associated with carcinogenesis and is linked to proliferation, neoangiogenesis, high microvessel density, and inhibition of apoptosis (67). Some authors have also clarified that the aggressiveness of Cox-2 expression in different malignant neoplasms is due to the ability of this substance to modulate adhesion molecule and protease expression (68,69). To find information on invasive squamous cervical carcinoma in the elderly, Giordano et al (70) have analyzed 110 invasive squamous cervical carcinomas obtained from 2 groups of patients for HPV status by polymerase chain reaction study, for immunohistochemical EGFR, Cox-2 expression, and clinicopathologic features. In this study 64 women 60 years or younger were designated as the younger group and 46 who were 61 years or older were designated as the older group. The HPV status and the expression of Cox-2 and EGFR in the younger and older women were compared and correlated with the grading, staging neoplasm, and lymph nodal status. Overall survival curves were drawn using Kaplan-Meier estimates and were compared using log-rank tests in the whole series of 110 patients. The number of neoplasms with higher staging was significantly greater than those in the younger women. The mortality was higher in the older group than in the younger patients. In the elderly, the presence of HPV DNA in 65% of cases, and in the absence of sexual activity, could be due to reactivation of latent HPV infection. In accordance with data provided by the literature, this finding demonstrated that HPV DNA can be detected in elderly women and can be associated with cervical carcinoma (59,71,72). Thus, it is possible that, in elderly women, HPV presence, in the absence of sexual activity, could be due to reactivation of latent HPV infection because of impairment of host immunologic response (73). The overexpression of Cox-2 in a number of cases was

significantly higher in the older group than in the younger group, but this immunoreactivity is not related to the staging, grading, EGFR expression, or to the presence of HPV. The simultaneous expression of Cox-2 and EGFR had a poor prognostic significance, showing lower survival rates than cases without this immunoreactivity. On multivariate analysis, Cox-2 and EGFR immunopositivity did not reveal any correlation between these markers and prognosis probably because the number of cases considered was not particularly high. Inadequate immunologic control of HPV infection resulting in viral persistence is likely an important determinant of risk of progression to cervical neoplastic disease. Previous studies have provided evidence supporting this view. Higher prevalence of HPV infection is observed in HIV-infected individuals (74, 75). Studies have also reported associations between deregulation of cytokine production and impairment of CD4+ T cell–mediated immunity and cervical precancers (76,77,78,79). Finally, the consistent association observed between HLA alleles and cervical neoplasia argue for a role of the host immune response to HPV in cervical cancer pathogenesis (80). Immunologic competence has been reported to decrease with aging (81-93). Garcia Piňeres et al (72) examined the association between lymphoproliferative responses to antigens/mitogens and persistent HPV infection in women older than 45 years. Women included in this study were participants in a 10,000-woman population-based cohort study of cervical neoplasia in Costa Rica. Women older than 45 years and HPV DNA positive at a screening visit were selected as cases (n = 283). Garcia Piňeres et al selected a comparably sized control group of HPV DNA–negative women, matched to cases on age and time since enrollment (n = 261). At an additional clinical visit, women were cytologically and virologically rescreened, and cervical and blood specimens were collected. Proliferative responses to phytohemagglutinin (PHA), influenza virus (Flu), and HPV16 virus-like particle (VLP) were lower among women with persistent HPV infection [median counts per minute (cpm): 72,849 for PHA, 1,241 for Flu, and 727 for VLP] than for the control group (median cpm: 107,049 for PHA, 2,111 for Flu, and 2,068 for VLP). The decreases were most profound in women with long-term persistence and were only observed for the oldest age group (≥65 years). The results of this study indicate that an impairment in host immunologic responses is associated to persistent HPV infection. The fact that effects were evident for all studied stimuli is suggestive of a generalized effect. Since 1993, at least 7 studies have described the screening histories of women with invasive cervical cancer (95,96,97,98). The number of cases in these studies was between 469 and 481All studies concluded that the lack of a cervical smear history is the major reason why the disease still occurs. The percentage of women with invasive cervical cancer that had no screening history varied between 28% in Connecticut, USA (99) and 54% for Maori women in New Zealand (100). This percentage strongly depends on the population coverage of screening. With a 100% coverage, the percentage will only include young women diagnosed before the starting age of the programme. In 2007 the almost 30%of the Italian population not included in organised programmes is partly the result of an implementation process still in progress in some Regions in Southern Italy, but mainly of a very limited or completely absent implementation in a few Regions in Northern Italy. In 2008 the extension of organised cervical cancer screening programmes in Italy had had a target population 13.8095.025 women, corresponding to 78,44% of Italian women aged 25-64 years vs 69% in 2006. During 2008, 39.69% of invites women were screened, vs 39.83% in the previous year. The results of single regions are not homogeneous(Table 3-13).

	2008	2007	2006
Women 25-64 yrs included in the target population of organised programmes	13.094.025	11.872.810	11.362.580
Population 25-64 yrs	78,44	71,77	69,01
Nominal extension	25,34(3.356.931/13.247.487)	25,58(3.055.353/11.943.507)	25,32(1.116.006/2.899.817)
Compliance with invitation (%)	39,69(1.332.376/3.356.931)	39,83(1.217.000/3.055.353)	38,49(1.116.006/2.899.817)
NORTHERN ITALY			
Women 25-64 yrs included in the target population of organised programmes	5.210.405	4.942.788	4.911.641
Population 25-64 yrs	68,42	65,42	65,09
Nominal extension	29,5(1.541.010/5.222.404)	28,46(1.415.361/4.972.858)	27,17(1.341.812/4.938.269)
Compliance with invitation (%)	47,67(734.577/1.541.010)	46,93(664.344/1.415.361)	45,62(612.069/1.341.812)
CENTRAL ITALY			
Women 25-64 yrs included in the target population of organised programmes	3.252.167	3.008.931	3.029340
Population 25-64 yrs	98,09	91,86	93,95
Nominal extension	26,52(890.868/3.359.359)	27,16(822.548/3.028.432)	26,84(814.208/3.033.546)
Compliance with invitation (%)	40,17(357.846/890.868)	40,23(330.925/822.548)	35,70(290.632/814.208)
SOUTHERN ITALY AND ISLANDS			
Women 25-64 yrs included in the target population of organised programmes	4.631.453	3.921.091	3.421.599
Population 25-64 yrs	80,38	68,65	60,09
Nominal extension	19,83(925.053/4.665.724)	21,38(817.444/3.942.217)	21,38(743.797/3.479.433)
Compliance with invitation (%)	27,73(239.953/925.053)	27,12(221.731/817.444)	28,68(213.305/743.797)

The data of Liguria region have not been reported.

Legend:

Nominal extension: percentage of the resident population aged 24-64 that is included in the target population of active organised programmes.
PPV = Positive predictive value.
DR = Detection rate.
ASCUS = Atypical squamous cells of undetermined significance.
CIN = Cervical Intraepithelial Neoplasia.

Table 3. Extension of organised cervical cancer screening programmes in Italy. (http://www.osservatorionazionalescreening.it)

	ABRUZZO				BASILICATA			
	2005	2006	2007	2008	2005	2006	2007	2008
Nominal extension (%)	24,9	33,5	20,2	23,8	52	64,6	54,9	54,4
Number of invitated women	87.398	118.054	73.981	88.974	90.013	111.808	96.613	95.476
Compliance to invitation (%)	24,9	33,5	20,2	23,8	52,0	64,6	54,9	54,4
Compliance with recommendation to repeat cytology%	26,9	32,9	18	31,5	32,9	36,1	36,9	33,4
Inadequate (%)	2,4	3,2	3,9		2,6	2,2	3	1,8
Recommendation to repeat cytology(%)	2,8	3,7	4,3	4,5	2,1	2,1	4,3	2,4
Compliance colposcopy with referral for ASCUS+	62,3	60,4	68,7	77,2	96,3	95,8	68,7	97,1
DR° for lesions CIN2+ unadjusted	2,7	2,5	3	4,2	1,2	1,1	1,1	0,9
PPV for CIN2+ of ASCUS+ referred to colposcopy	16,2	16,2	10,8	12,1	5,1	5,5	3,5	4,3

Table 4. Organised cervical cancer screening programmes in Italy: value of some process indicators in Abruzzo and Basilicata regions between 2005-2008(National Centre for Screening Monitoring). (http://www.osservatorionazionalescreening.it)

	CAMPANIA				**EMILIA ROMAGNA**			
	2005	2006	2007	2008	2005	2006	2007	2008
Nominal extension (%)	24	14,9	17	18,5	27,8	31,4	30,8	33,4
Number of invitated women	357.06	241.64	283.00	285.59	332.65	377.40	379.162	409.376
Compliance to invitation (%)	24,0	14,9	17,0	18,5	27,8	31,4	30,8	33,4
Compliance with recommendation to repeat cytology%	16,8	26,1	27	27,2	57,1	50,8	56	56,5
Inadequate citology (%)	2,1	2,6	2,6	2,7	1,5	1,7	2	2
Recommendation to repeat cytology(%)	2,1	1,8	2,3	1,6	2,8	2,9	2,7	3,1
Compliance colposcopy with referral for ASCUS+	75,3	63,9	40	63,4	89,1	83,2	85,9	88,8
DR° for cytologyc lesions CIN2+ unadjusted	1,6	1,3	1,4	1,5	3,6	3,8	4	4,4
PPV for CIN2+ of ASCUS+ referred to colposcopy	17,4	11,7	12,8	17,2	14,6	15,7	17,9	16,4

Table 5. Organised cervical cancer screening programmes in Italy: value of some process indicators in Campania and Emilia Romagna regions between 2005-2008(National Centre for Screening Monitoring). (http://www.osservatorionazionalescreening.it)

	LAZIO				LOMBARDIA			
	2005	2006	2007	2008	2005	2006	2007	2008
Nominal extension (%)	13,7	22,1	24,2	23,3	24,9	27,1	29,7	25,7
Number of invitated women	227.356	303.896	299.466	360.688	136.919	154.165	164.979	198.728
Compliance to invitation (%)	13,7	22,1	24,2	23,3	24,9	27,1	29,7	25,7
Compliance with recommendation to repeat cytology%	24,1	21,8	31,3	30,3	37,8	41,5	41	39,7
Inadequate citology (%)	3,5	1,9	2,6	3,9	2,2	2,4	2,5	2,4
Recommendation to repeat cytology(%)	2,9	2,4	2,7	2,7	1,5	1,4	2	1,9
Compliance colposcopy with referral for ASCUS+	92	86,6	91,3	87,6	86,3	83,9	93	86
DR° for cytologyc lesions CIN2+ unadjusted	3,2	1,8	2,4	2,7	3,3	3	4	4
PPV for CIN2+ of ASCUS+ referred to colposcopy	14,9	10,2	12,3	12	27	21,5	22,3	

Table 6. Organised cervical cancer screening programmes in Italy: value of some process indicators in Lazio and Lombardia regions between 2005-2008(National Centre for Screening Monitoring). (http://www.osservatorionazionalescreening.it)

	MOLISE				PIEMONTE			
	2005	2006	2007	2008	2005	2006	2007	2008
Nominal extension (%)	59,6	18,6	Activated only for 4 months	21,5	29,7	27	30	31,8
Number of invitated women	50	16		23	365.893	330.188	371.226	396.661
Compliance to invitation (%)	59,6	18,6		21,5	29,7	27,0	30,0	31,8
Compliance with recommendation to repeat cytology%	21,7	14,4		19,3	42,4	42,9	43	44,7
Inadequate citology (%)	6,3	6,3		12,1	2,8	2,6	3	3,2
Recommendation to repeat cytology(%)	1,4	2,2		2,5	1,8	1,9	2	2
Compliance colposcopy with referral for ASCUS+	61,5	37,1		63,1	90,7	91,6	92,2	90,5
DR° for cytologyc lesions CIN2+ unadjusted	1,5	0,62		1	2,1	2	2,2	2,3
PPV for CIN2+ of ASCUS+ referred to colposcopy	17,3	7,7		5,9	17,7	15,1	17,2	17,2

Table 7. Organised cervical cancer screening programmes in Italy: value of some process indicators in Molise and Piemonte regions between 2005-2008(National Centre for Screening Monitoring). (http://www.osservatorionazionalescreening.it)

	TRENTINO				PUGLIA			
	2005	2006	2007	2008	2005	2006	2007	2008
Nominal extension (%)	37	30	30,1	29,8			8	9,9
Number of invitated women	52.305	43.455	45.104	44.852			41.094	105.599
Compliance to invitation (%)	37,0	30,0	30,1	29,8			8,0	9,9
Compliance with recommendation to repeat cytology%	35,7	36,2	37	53,2			36,2	17,2
Inadequate citology (%)	4,8	5,7	5,5	5			3	4
Recommendation to repeat cytology(%)	1,5	1,3	1,3	1,2			4,4	1,2
Compliance colposcopy with referral for ASCUS+	75,5	78,5	79	76			45,9	59,2
DR° for cytologyc lesions CIN2+ unadjusted	3,4	2,4	3,2	2,4			0,3	0,7
PPV for CIN2+ of ASCUS+ referred to colposcopy	29,6	23,9	31,5	28,3			1,6	9,2

Table 8. Organised cervical cancer screening programmes in Italy: value of some process indicators in Trentino and Puglia regions between 2005-2008(National Centre for Screening Monitoring). (http://www.osservatorionazionalescreening.it)

	SARDEGNA				SICILIA			
	2005	2006	2007	2008	2005	2006	2007	2008
Nominal extension (%)	27	24,6	20,4	26,4	26,1	24,6	21,1	21,2
Number of invitated women	38.813	35.368	29.329	74.765	153.31	126.90	131.256	133.590
Compliance to invitation (%)	27,0	24,6	20,4	26,4	26,1	24,6	21,1	21,2
Compliance with recommendation to repeat cytology%	24	23,7	31,4	33,7	19,03	29,1	25,4	19,7
Inadequate citology (%)	6,3	5,8	6	6,1	3,4	3,5	0,3	1,9
Recommendation to repeat cytology(%)	5,2	5,6	5,7	3	2,8	3,2	3,8	4
Compliance colposcopy with referral for ASCUS+	82,6	93,1	88,2	91,1	70,5	73,4	81	83,9
DR° for cytologyc lesions CIN2+ unadjusted	3,7	4,5	5,7	4,2	1,9	2,6	3,1	3
PPV for CIN2+ of ASCUS+ referred to colposcopy	29,2	8,6	11,5	15,2	9,7	16,3	12,9	9,6

Table 9. Organised cervical cancer screening programmes in Italy: value of some process indicators in Sardegna and Sicilia regions between 2005-2008(National Centre for Screening Monitoring). (http://www.osservatorionazionalescreening.it)

	TOSCANA				UMBRIA			
	2005	2006	2007	2008	2005	2006	2007	2008
Nominal extension (%)	28,7	29,8	31,3	29,9	27,3	29,3	23,5	31,5
Number of invitated women	291.516	303.307	319.444	309.365	67.635	73.206	58.556	78.215
Compliance to invitation (%)	28,7	29,8	31,3	29,9	27,3	29,3	23,5	31,5
Compliance with recommendation to repeat cytology%	44,1	46,6	48	49,6	44,4	47,1	58,2	47,5
Inadequate citology (%)	2	2,1	1,8	1,5	1,7	3,4	1,3	2,3
Recommendation to repeat cytology(%)	1,6	1,6	1,5	1,5	2	2	1,6	1,6
Compliance colposcopy with referral for ASCUS+	78,5	77,6	81,3	82,7	68,3	70,7	66,1	78
DR° for cytologyc lesions CIN2+ unadjusted	2,6	2,9	2,8	3	3,3	4,2	2,4	4,2
PPV for CIN2+ of ASCUS+ referred to colposcopy	21,8	25,1	24,2	23,9	57,3	29,1	22,6	34,2

Table 10. Organised cervical cancer screening programmes in Italy: value of some process indicators in Toscana and Umbria regions between 2005-2008(National Centre for Screening Monitoring). (http://www.osservatorionazionalescreening.it)

	VALLE D'AOSTA				VENETO			
	2005	2006	2007	2008	2005	2006	2007	2008
Nominal extension (%)	31,8	32,6	28	26,7	22,8	24,1	24,4	25,7
Number of invitated women	11.490	11.486	9.728	9.478	305.925	315.619	321.37	346.4
Compliance to invitation (%)	31,8	32,6	28,0	26,7	22,8	24,1	24,4	25,7
Compliance with recommendation to repeat cytology%	62	63,8	59,4	73,8	44,47	43,8	44,8	41,8
Inadequate citology (%)	5,5	4,5	1	0,8	5,7	4,7	5,4	5,4
Recommendation to repeat cytology(%)	3,4	4,5	2,4	1,6	2,8	2,8	3	3,1
Compliance colposcopy with referral for ASCUS+	85	94,1	93,9	95,2	90,5	91,6	92,3	91,6
DR° for cytologyc lesions CIN2+ unadjusted	2,5	2,5	3,8	1,6	2,7	2,9	2,8	3,3
PPV for CIN2+ of ASCUS+ referred to colposcopy	12,2	12,9	20,8	13,9	12,8	13,3	13,1	14

Table 11. Organised cervical cancer screening programmes in Italy: value of some process indicators in Valle D'Aosta and Veneto regions between 2005-2008(National Centre for Screening Monitoring). (http://www.osservatorionazionalescreening.it)

	FRIULI VENEZIA GIULIA				MARCHE			
	2005	2006	2007	2008	2005	2006	2007	2008
Nominal extension (%)	30	27,8	25,2		32,4	31,8	32,7	
Number of invitated women	98,619	90,948	86,085		145,35	134,79	140,03	
Compliance to invitation (%)	30,0	27,8	25,2		32,4	31,8	32,7	
Compliance with recommendation to repeat cytology%	54,9	51,9	56,2		33	36,2	35,2	
Inadequate citology (%)		6,5	6			1,1	2	
Recommendation to repeat cytology(%)	2,3	2,2	2,1		1,9	1,8	2	
Compliance colposcopy with referral for ASCUS+	88,8	90,7	88		90,4	80	84,7	
DR° for cytologyc lesions CIN2+ unadjusted					2,1	1.05	2,1	
PPV for CIN2+ of ASCUS+ referred to colposcopy					26,4	12,1	17,1	

Table 12. Organised cervical cancer screening programmes in Italy: value of some process indicators in Friuli Venezia Giulia and Marche regions between 2005-2008(National Centre for Screening Monitoring). (http://www.osservatorionazionalescreening.it)

	ALTO ADIGE (SUDTIROL)				CALABRIA			
	2005	2006	2007	2008	2005	2006	2007	2008
Nominal extension (%)	22,4	13,4	26,1		41,4	24,2	35,6	
Number of invitated women	32,194	18,542	37,699		21,619	94,105	162,16	
Compliance to invitation (%)	22,4	13,4	26,1		41,4	24,2	35,6	
Compliance with recommendation to repeat cytology%	32,2	34	32,2		25	25	24,4	
Inadequate citology (%)	1,1	0,75	0,85			2,3	3,6	
Recommendation to repeat cytology(%)					0,6	2,2	2,7	
Compliance colposcopy with referral for ASCUS+					71,4	75,5	81,7	
DR° for cytologyc lesions CIN2+ unadjusted					0,9	2.24	1,3	
PPV for CIN2+ of ASCUS+ referred to colposcopy					25	9,5	6,3	

Table 13. Organised cervical cancer screening programmes in Italy: value of some process indicators in Alto Adige and Calabria regions between 2005-2008(National Centre for Screening Monitoring). (http://www.osservatorionazionalescreening.it)

The main examined process indicators has been not reported in all the regions. The distinction between OpS and OS screening has not been done. In the literature numerous studies has been reported the recommendations and the results of cervical cancer screening(100-101-102-103-104). With regard to screening histories of invasive cervical carcinoma, in Italy has been not published studies with exception of OrS programme of Friuli Venezia Giulia. Zucchetto et al (105) have examined the screening histories of 438 women with invasive cervical cancer diagnosed in Friuli Venezia-Giulia between 1999 and 2005. 82 cases (49.7%) were found in >65 years-old women. 165 (37.7%) women were not screening. 69 (15.8%) women were not invited to OrS because of age >64 years old. Histological type and HPV detection of invasive cervical cancers has been reported. The study of Zucchetto et al (105) shows that the lack of screening among older women and of compliance with organized programs among women in the target population are the main limitation in cervical cancer secondary prevention. The results of Zucchetto et al (105) are in agreement with research conducted in northen Europe. Bos et al (106) have analized the screening history of 3.175 women with invasive cervical cancer diagnosed in the years 1994-1997 in the Netherland. 57% of 3175 women with invasive cervical cancer had no previous smears. Given the high proportion of women with invasive cervical cancer older than 64 years at diagnosis, the possibility of inviting them to have at least one Pap smear in life after 64 years should be taken in consideration. In according to American Cancer Society Guidelines for the early detection of cancer and the guidelines of other national regional screening programme, women 70 years of age or older who have had 3 or more normal Pap-test in a know and no abnormal Pap-test results in the last 10 years may choose to stop having Pap-test. But according to National Cervical Screening program the current policy of screening women of New Zealand is to continue organized regular screening until aged 69 years with pap test every three years if the women have ever been sexually active remain in place. The present study should be support the screening policy to perform Pap test every 3 years until aged 75 years, independently to sexual activity. In older post-menopausal women the transformation zone may be difficult to see. The cervix is often much smaller and the amount of cervical cells found in the smears may be not optimal. We believe that two samples (one from the endocervix with cytobrush and one from ectocervix with Ayre spatule) and smearing the cytological materials on two slides is the procedure of choice in order to obtain adequate material.

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6. References

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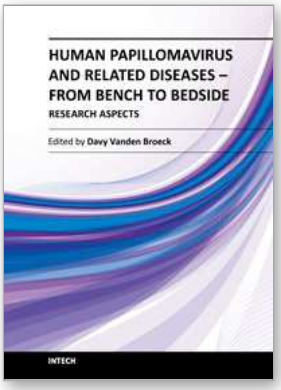

Human Papillomavirus and Related Diseases - From Bench to Bedside - Research aspects

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Cervical cancer is the second most prevalent cancer among women worldwide, and infection with Human Papilloma Virus (HPV) has been identified as the causal agent for this condition. The natural history of cervical cancer is characterized by slow disease progression, rendering the condition, in essence, preventable and even treatable when diagnosed in early stages. Pap smear and the recently introduced prophylactic vaccines are the most prominent prevention options, but despite the availability of these primary and secondary screening tools, the global burden of disease is unfortunately still very high. This book will focus on epidemiological and fundamental research aspects in the area of HPV, and it will update those working in this fast-progressing field with the latest information.

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Phone: +86-21-62489820
Fax: +86-21-62489821