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Full Length Research Paper

Impact of Opportunistic Screening on Squamous Cell Carcinoma Diagnosis in Women Over 70: A Study from Trentino, Italy

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The objective of this paper is to assess the value of opportunistic screening in diagnosis of invasive squamous carcinoma found in >70 years old women in Trentino (Italy). From 2007 to 2010, the Cytopathology Section of Institute of Anatomic Pathology of Rovereto Hospital have been examined; 28589 opportunistic pap-smears was performed in all histological specimens with diagnosis of low, high grade intraepithelial lesions and invasive cervical carcinoma. 111 cases (0.38%) of cervical intraepithelial neoplasia-3-squamous cell carcinoma have been identified in 28589 opportunistic pap smears. The cytological diagnosis of cervical intraepithelial neoplasia-3 was performed in three cases, confirmed by cone biopsy in two patients with presence of HPV-16 and HPV-58. The diagnosis of squamous cell carcinoma was performed with pap-smear in three patients; non-keratinizing squamous cell carcinoma was diagnosed with pap-smear in two cases. An estimated 2,927 new cases of cervical cancer occurred in Italy in 2005. 34.64% of cases has been diagnosed in >65 years old women. Consequently, early diagnosis is necessary to the decrease mortality, morbidity and direct management costs of disease. The present study should be support the screening policy to perform Pap test every 3 years until aged 69 years, independently to sexual activity.

Key words: Invasive cervical carcinoma, opportunistic screening, cancer in elderly women.

INTRODUCTION

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 (Ronco et al., 2007). 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) exists for women aged 25 to 65. The target population comprises of 146737 women. In the period 1993 to 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 has examined only pap-tests of Opportunistic Screening (OpS), that is, 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, independent of personal letter invitation of OrS. An estimated 2,927 new cases of cervical cancer occurred in Italy in 2005 (crude incidence 9.7/100,000; world age-standardized incidence 6.0/100,000). 1014 (34.64%) has been diagnosed in >65

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

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

years old women (AIRTum: I Tumori in Italia – Rapporto, 2006; ISTAT, 2005). Early diagnosis is necessary to decrease the direct management costs of disease. In the present study, we have examined the screening histories, treatment, human papillomavirus (HPV) detection of cervical intraepithelial neoplasia(CIN)3- invasive squamous cell carcinoma in >65 years-old women, diagnosed in the period 2007 to 2010 with opportunistic pap-tests in the Cytopathology Section of Institute of Anatomic Pathology of Rovereto Hospital.

MATERIALS AND METHODS

The pap-smear was performed by gynaecologist to the woman's initiative. An experienced cytopathologist (TP) whose diagnostic experience exceeds 20 years have examined all abnormal smears and 10% of the normal smears were previously observed by 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.

Consensus polymerase chain reaction (PCR) and direct sequencing of PCR products (DNA HPV typing) were used to determinate the type or types of human papillomavirus (HPV) in histological specimens.

RESULTS

The distribution of women for decades is reported in Table 1. Between the women >64 years-old with CIN3-squamous carcinoma, the 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.

DISCUSSION

There are approximately 493,000 new cases of invasive cervical cancer worldwide and 274,000 women die of the disease annually (Waterhouse et al., 1982). 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 (Carmichael et al., 1986). From an epidemiological point of view, an HPV infection meets the criteria as a causal agent for cervical cancer (Schiffman et al., 1993; Bosch et al., 2002). Having sexual contact is the main source of HPV infection. HPVs are a group of host specific DNA virus with remarkable epithelial cell specificity. More than 120 different HPV genotypes have been identified and almost 45 subtypes, isolated from the low genital tract, have been grouped into high- and low- risk HPV types, con-sidering their risk potential to induce an invasive cervical cancer. In a recent study, Muñoz et al. (2003) classified HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 as high risk viruses, detectable in high grade squamous intraepithelial lesions or in invasive cancer; HPV 26, 53 and 66 as potential high risk with a not well known oncogenic potential; while types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and 89 can be considered as viruses with low oncogenic risk and they can be isolated from low grade epithelial lesions. Functionally, high risk HPV-types infection contributes to carcinogenesis and tumour progression predominantly through the action of two viral oncogenes, E6 and E7. The E6 protein exerts rapid degradation of p53, in corporation with E6-associated protein (E6-AP), via ubiquitin-mediated proteolysis pathway (Scheffner et al., 1993; Huibregtse et al., 1993). The E7 protein mediates the release of the E2F transcription factor from pRb-E2F complex (Nevins, 1992). 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 (Nakagawa et al., 1992). The p53 mutations are the most frequent genetic abnormalities found in a wide variety of human malignant tumours (Harris, 1993). Once DNA damage occurs, p53 protein is induced and arrests cells in the G1 phase to enhance DNA repair (Kuerbitz et al., 1992), or triggers apoptosis following DNA damage (Lowe et al., 1993). 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 (Cho et al., 1994). In this way, once p53 is mutated, DNA damage is fixed and subsequent genetic rearrangement progress may be putative mechanisms to initiate cancer. Thus far, exceptionally low prevalence (0 to 6%) of the p53 mutations had been documented in cervical carcinomas (Fujita et al., 1992; Choo and Chong, 1993; Helland et al., 1993; Paquette et al., 1993; Miwa et al., 1995). The p53 protein in cervical carcinoma is thought to be inactivated presumably due to complex formation with HPV E6 oncoprotein. 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

Table 2. Age, treatment, histological diagnosis, HPV detection in women over 70 years-old with CIN3-squamous cell carcinoma.

S/no. of patient	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

NOS = not other specified.

cancer. One of the main differences between high- and low-risk types is the possibility of integration in the genome. Approximately 1% of the high-risk HPV types and only 0.1% of the low-risk HPV types will lead to the development of cervical cancer (Ferlay et al., 2001). In our case, HPV 16 and HPV 58 were detected in two cases of CIN3 and HPV 58 and 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. The other hypothesis takes into account that HPV 16 is only integrated in 72% of all invasive cervical cancers (Walboomers et al., 1999). 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% integration.

In light of recent studies demonstrating that mutation of p53 gene was found in over 20% of the patients with vulvar carcinoma (Lee et al., 1994; Milde-Langosch et al., 1995), a disease of elderly women and a known HPV- related malignancy, Nakagawa et al. (1999) analysed mu-tation of the p53 gene in 46 women with cervical carcinomas at the age of 60 or more (mean; 71 years, range; 60 to 96 years). Of the 46 patients, 41 had squamous cell carcinoma and five had adenocarcinoma. 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. Although falling short of statistical significance reduces the strength of the conclusion, data presented by Nakagawa et al. imply that p53 gene mutations 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. (2000) have analyzed for HPV typing via polymerase chain reaction, the expression of p53, the 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.

EGFR and Cox-2 overexpression have been reported in many neoplasms (Tsujii et al., 1995; Tsujii et al., 1997). To find information on invasive squamous cervical carcinoma in the elderly,

Giordano et al. (Giordano et al., 2011) have analyzed 110 invasive squamous cervical carcinomas obtained from 2 groups of patients for HPV status

Table 3. Organised cervical cancer screening programmes in Italy: value of some process indicators in Trentino region between 2006 to 2009(National Centre for Screening Monitoring).

Process indicator	Trentino			
	2006	2007	2008	2009
Nominal extension (%)	30	30.1	29.8	29.6
Number of invited woman	43.455	45.104	44.852	42.249
Adhesion rate of invited women (%)	36.2	37	53.2	48.0
Inadequate citology (%)	5.7	5.5	5	4.4
Colposcopy recommendation (%)	1.3	1.3	1.2	1.3
Compliance colposcopy with referral for ASCUS+	78.5	79	76	82.8
Standardised DR° for cytologyc lesions CIN2+	2.4	3.2	2.4	3.3
PPV for CIN2+ of ASCUS+ referred to colposcopy	23.9	31.5	28.3	35.3

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, lymph nodal status and overall survival.

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 (Baay et al., 2001; Garcia-Pineres et al., 2006; Subbaramaiah and Dannenberg, 2007). 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 (Mubiayi et al., 2002).

Inadequate immunologic control of HPV infection resulting in viral persistence is likely an important determinant of risk of progression to cervical neoplastic disease. Immunologic competence has been reported to decrease with aging (81 to 93). Garcia Piňeres et al. (2006) 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

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 than for the control. The decreases were most profound in women with long-term persistence and were only ob-served for the oldest age group (≥65 years). The results of this study indicate that impairment in host immunologic responses is associated with persistent HPV infection.

Since 1993, at least 7 studies have described the screening histories of women with invasive cervical cancer (Ciatto et al, 1993; Kenter et al., 1996; Stuart et al., 1997). In 2007, the almost 30% of the Italian popu-lation 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 2007, 121 active programmes had a target population of 11,872,810 women, correspon-ding to 71.8% of Italian women aged 25 to 64 years compared to 69% in 2006. During 2007, 39.8% of invites women were screened compared to 38.5% in the previous year. The last report of National Centre for Screening Monitoring as been published in 2008 and various process indicators of all regions have been described with exclusion of Liguria. Only 39.7% of invited women were screened, compared to 39.8% in the previous year. The data of Trentino Region has been reported in Table 3. The data of other Italian regions has been described in Table 4. The nominal extension varied from 8% (Puglia 2007) to 65.9% (Basilicata 2009), the inadequate cytology from 0.8% (Valle D'Aosta 2008) to 12.1% (Molise 2008). The main examined process indicators have been not reported in all the regions. In conclusion, the data of National Centre for Screening Monitoring provides information regarding the deluded performance of the organized screening programmes

Table 4. Organised cervical cancer screening programmes in Italy: Value of some process indicators in single regions between 2006-2009 (National Center for Screening Monitoring)

Process indicator	Abruzzo				Basilicata			
	2006	2007	2008	2009	2006	2007	2008	2009
Nominal extension (%)	33.5	20.2	23.8	20.88	64.6	54.9	54.4	65.9
Number of invited woman	118.054	73.981	88.974	74.607	111.808	96.613	95.476	112.961
Adhesion rate of invited women (%)	32.9	18	31.5	21.5	36.1	36.9	33.4	33.2
Inadequate citology (%)	2.4	3.2	3.9	4.2	2.2	3	1.8	1.5
Colposcopy recommendation (%)	3.7	4.3	4.5	5.2	2.1	4.3	2.4	2.5
Compliance colposcopy with referral for ASCUS+	60.4	68.7	77.2	85.3	95.8	68.7	97.1	96.9
Standardised DR° for cytologyc lesions CIN2+	2.5	3	4.2	4.8	1.1	1.1	0.9	1.0
PPV for CIN2+ of ASCUS+ referred to colposcopy	16.2	10.8	12.1	10.7	5.5	3.5	4.3	4.3
	Campania				**Emilia Romagna**			
	2006	**2007**	**2008**	**2009**	**2006**	**2007**	**2008**	**2009**
Nominal extension (%)	14.9	17	18.5	22.0	31.4	30.8	33.4	32.0
Number of invited woman	241.649	283.007	285.593	335.561	377.409	379.162	409.376	394.285
Adhesion rate of invited women (%)	26.1	27	27.2	25.2	50.8	56	56.5	57.6
Inadequate citology (%)	2.6	2.6	2.7	1.8	1.7	2	2	1.7
Colposcopy recommendation (%)	1.8	2.3	1.6	1.9	2.9	2.7	3.1	2.9
Compliance colposcopy with referral for ASCUS+	63.9	40	63.4	55.3	83.2	85.9	88.8	88.8
Standardised DR° for cytologyc lesions CIN2+ PPV for	1.3	1. 4	1.5	0.9	3.8	4	4.4	4.3
CIN2+ of ASCUS+ referred to colposcopy	11.7	12.8	17.2	11.0	15.7	17.9	16.4	16.4
	Lazio				**Lombardia**			
	2006	**2007**	**2008**	**2009**	**2006**	**2007**	**2008**	**2009**
Nominal extension (%)	22.1	24.2	23.3	27.0	27.1	29.7	25.7	30.7
Number of invited woman	303.896	299.466	360.688	375.511	154.165	164.979	198.728	235.119
Adhesion rate of invited women (%)	21.8	31.3	30.3	25.5	41.5	41	39.7	42.0
Inadequate citology (%)	1.9	2.6	3.9	4.3	2.4	2.5	2.4	2.3
Colposcopy recommendation (%)	2.4	2.7	2.7	2.3	1.4	2	1.9	1.9
Compliance colposcopy with referral for ASCUS+	86.6	91.3	87.6	92.9	83.9	93	86	87.8
Standardised DR° for cytologyc lesions CIN2+ PPV for	1.8	2. 4	2.7	3.2	3	4	4	3.5
CIN2+ of ASCUS+ referred to colposcopy	10.2	12.3	12	15.4	27.0	21.5	22.3	18.0

Table 4. Contd.

Process indicator	Molise				Piemonte			
	2006	2007	2008	2009	2006	2007	2008	2009
Nominal extension (%)	18.6	-	21.5	29.1	27	30	31.8	30.9
Number of invited woman	15.908	-	23.459	24.850	330.188	371.226	396.661	383.010
Adhesion rate of invited women (%)	14.4	-	19.3	21.5	42.9	43	44.7	44.9
Inadequate citology (%)	6.3	-	12.1	6.7	2.6	3	3.2	3.0
Colposcopy recommendation (%)	2.2	-	2.5	2.7	1.9	2	2	2.4
Compliance colposcopy with referral for ASCUS+	37.1	-	63.1	48.2	91.6	92.2	90.5	91.8
Standardised DR° for cytologyc lesions CIN2+	0.62	-	1	0.35	2	2.2	2.3	2.5
PPV for CIN2+ of ASCUS+ referred to colposcopy	7.7	-	5.9	2.9	15.1	17.2	17.2	15.8

	Sardegna				Sicilia			
Nominal extension (%)	2006	2007	2008	2009	2006	2007	2008	2009
Number of invited woman	24.6	20.4	26.4	23.1	24.6	21.1	21.2	16.8
Adhesion rate of invited women (%)	35.368	29.329	74.765	86.556	126.905	131.256	133.590	121.224
Inadequate citology (%)	23.7	31.4	33.7	42.3	29.1	25.4	19.7	19.8
Colposcopy recommendation (%)	5.8	6	6.1	7.2	3.5	0.3	1.9	3.4
Compliance colposcopy with referral for ASCUS+	5.6	5.7	3	3.2	3.2	3.8	4	4.3
Standardised DR° for cytologyc lesions CIN2+ PPV for	93.1	8 8.2	91.1	86.3	73.4	81	83.9	80.5
CIN2+ of ASCUS+ referred to colposcopy	4.5	5.7	4.2	4.5	2.6	3.1	3	3.7

	Toscana				Umbria			
	2006	2007	2008	2009	2006	2007	2008	2009
Nominal extension (%)	29.8	31.3	29.9	28.5	29.3	23.5	31.5	32.7
Number of invited woman	303.307	319.444	309.365	296.965	73.206	58.556	78.215	81.980
Adhesion rate of invited women (%)	46.6	48	49.6	49.7	47.1	58.2	47.5	48.1
Inadequate citology (%)	2.1	1.8	1.5	1.5	3.4	1.3	2.3	2.9
Colposcopy recommendation (%)	1.6	1.5	1.5	1.5	2	1.6	1.6	1.0
Compliance colposcopy with referral for ASCUS+	77.6	81.3	82.7	83.3	70.7	66.1	78	70.1
Standardised DR° for cytologyc lesions CIN2+ PPV for	2.9	2. 8	3	3.2	4.2	2.4	4.2	3.6
CIN2+ of ASCUS+ referred to colposcopy	25.1	24.2	23.9	23.8	29.1	22.6	34.2	52.7

Table 4. Contd.

Process indicator	Valle d'Aosta				Veneto			
	2006	2007	2008	2009	2006	2007	2008	2009
Nominal extension (%)	32.6	28	26.7	32.0	24.1	24.4	25.7	25.8
Number of invited woman	11.486	9.728	9.478	11.378	315.619	321.378	346.496	353.688
Adhesion rate of invited women (%)	63.8	59.4	73.8	59.5	43.8	44.8	41.8	46.9
Inadequate citology (%)	4.5	1	0.8	1.5	4.7	5.4	5.4	5.4
Colposcopy recommendation (%)	4.5	2.4	1.6	2.9	2.8	3	3.1	2.7
Compliance colposcopy with referral for ASCUS+	94.1	93.9	95.2	95.6	91.6	92.3	91.6	91.0
Standardised DR° for cytologyc lesions CIN2+	2.5	3. 8	1.6	2.7	2.9	2.8	3.3	3.4
PPV for CIN2+ of ASCUS+ referred to colposcopy	12.9	20.8	13.9	11.2	13.3	13.1	14.0	15.0

	Friuli Veneziagiulia				Marche			
	2006	2007	2008	2009	2006	2007	2008	2009
Nominal extension (%)	-	25.2	29.4	27.1	31.8	32.7	33.4	32.3
Number of invited woman	-	86.085	100.548	93.166	134.799	140.035	142.600	139.135
Adhesion rate of invited women (%)	-	56.2	59.2	56.7	36.2	35.2	40.6	41.6
Inadequate citology (%)	-	6.0	4.1	5.3	1.1	2.0	1.7	1.4
Colposcopy recommendation (%)	-	2.1	3.0	2.1	1.8	2.0	2.0	1.9
Compliance colposcopy with referral for ASCUS+	-	88.0	85.8	99.9	79.7	84.7	82.5	86.6
Standardised DR° for cytologyc lesions CIN2+ PPV for	-	4.6	4.4	4.3	1.05	2.1	1.7	2.7
CIN2+ of ASCUS+ referred to colposcopy	-	24.7	17.3	20.0	12.1	17.1	17.7	20.6

	Alto Adige (Sudtirol)				Calabria			
	2006	2007	2008	2009	2006	2007	2008	2009
Nominal extension (%)	13.4	26.1	24.3	-	24.2	35.6	23.8	25.6
Number of invited woman	18.542	37.699	34.871	-	94.105	162.164	117.597	145.294
Adhesion rate of invited women (%)	34.0	32.2	33.5	-	25.0	24.4	23.9	23.5
Inadequate citology (%)	0.75	0.85	1.8	-	2.3	3.6	2.8	3.9
Colposcopy recommendation (%)	-	-	-	-	2.2	2.7	2.7	3.0
Compliance colposcopy with referral for ASCUS+	-	-	-	-	75.5	81.7	64.4	69.6
Standardised DR° for cytologyc lesions CIN2+ PPV for	-	-	-	-	2.24	1.3	1.7	0.8
CIN2+ of ASCUS+ referred to colposcopy	-	-	-	-	9.5	6.3	11.2	4.0

Table 4. Contd.

Process indicator	Puglia			
	2006	2007	2008	2009
Nominal extension (%)	-	8.0	9.9	19.3
Number of invited woman	-	41.094	105.599	205.443
Adhesion rate of invited women (%)	-	36.2	17.2	28.3
Inadequate citology (%)	-	3	4	4.4
Colposcopy recommendation (%)	-	4.4	1.2	1.2
Compliance colposcopy with referral for ASCUS+	-	45.9	59.2	40.7
Standardised DR° for cytologyc lesions CIN2+ PPV for	-	0.3	0.7	-
CIN2+ of ASCUS+ referred to colposcopy	-	1.6	9.2	-

The data of Liguria region have not been reported.

programmes for cervical cancer. The distinction between OpS and OS screening has not been done. Ricciardi et al. (2009) examined the direct cost of managing invasive cervical cancer in Italy. An estimated 2,927 new cases of cervical cancer occurred in Italy in 2005. The estimated numbers of new cases by FIGO stage were: FIGO I, 1,927; FIGO II, 556; FIGO III, 259; and FIGO IV, 185. Costs for the most frequent procedures were estimated as: €6,041 for radical hysterectomy or other surgery; € 4,901 for radio-chemotherapy; € 1,588 for brachytherapy; and €3,795 for palliative chemotherapy. Mean management costs for incident cases (including 10 years follow-up) were estimated at: FIGO I, € 6,024; FIGO II, € 10,572; FIGO III, € 11,367; FIGO IV, € 8707; and € 5,854 for the terminal phase (1 month). The total direct management cost was estimated at € 28.3 million per year. For the reason that the 34.64% of invasive cervical carcinoma has been diagnosed, in >65years old women it is necessary to consider the extension of screening programs after 65 years. With regard to screening histories of invasive cervical carcinoma, in Italy there are no published studies, of our knowledge, with exception of OrS programme of Friuli Venezia Giulia. 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 regions, an OrS was initiated in 1999, targeting women aged 25 to 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 to 64 years.

Zucchetto et al. (2010) 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 >65 years old. Histological type and HPV detection of invasive cervical cancers has been reported. The study of Zucchetto et al. (2010) 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. are in agreement with research conducted in northern Europe. Bos et al. (2006) analysed the screening history of 3.175 women with invasive cervical cancer diagnosed in the years 1994 to 1997 in the Netherland. 57% of 3175 women with invasive cervical cancer had no previous smears. Given to 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 re-gional 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. 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 National Cervical Screening Program of Australian Government believes that at age 70 women should con-sult with their doctor about whether they need to continue to have a regular Pap smear.

In conclusion, the present study support the screening policy to perform Pap test every 3 years until aged 69 years, independently to sexual activity because 34.64% of invasive cervical carcinoma has been diagnosed in > 65 years old women. Consequently, it is necessary to early diagnose to the decrease to mortality, morbidity and direct management costs of disease.

REFERENCES

AIRTum: I Tumori in Italia – Rapporto (2006). I dati di incidenza e mortalità dei Registri Tumori generali, 1998-2002. Epidemiol. Prev., Suppl 2: 1-148.

Baay MF, Tjalma WA, Weyler J, Pattyn GG, Lambrechts HA, Goovaerts G, Baekelandt M, Buytaert P, Van Marck EA, Lardon F, Vermorken JB (2001). Prevalence of human papillomavirus in elderly women with cervical cancer. Gynecol. Obstet. Invest., 52: 248-251.

Bos AB, Rebolj M, Habbema JD (2006). Nonattendance is still the main limitation for the effectiveness of screening for cervical cancer in the Netherlands. Int. J. Cancer, 119: 2372-2375.

Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV (2002). The causal relation between human papillomavirus and cervical cancer. J. Clin. Pathol., 55: 244–265.

Carmichael JA, Clarke DH, Moher D, Ohkle ID, Karchmar EJ (1986). Cervical carcinoma in women aged 34 and younger. Am. J. Obset. Gynecol., 66: 82-85.

Cho Y, Gorina S, Jeffrey PD, Pavletich NP (1994). Crystal structure of a p53 tumor suppressor-DNA complex: understanding tumorigenic mutations. Science, 265: 346-355.

Choo KB, Chong KY (1993). Absence of mutation in the p53 and retinoblastoma susceptibility genes in primary cervical carcinomas. Virology, 193: 1042-1046.

Ciatto S, Grazzini G, Cecchini S, Iossa A (1993). Screening history of incident cases of invasive carcinoma of the cervix. Tumori, 79: 311–313.

Ferlay J, Bray F, Parkin DM (2001). Globocan 2000. Cancer Incidence, Mortality and Prevalence Worldwide. IARCPress: Lyon.

Fujita M, Inoue M, Tanizawa O, Iwamoto S, Enomoto T (1992). Alterations of the p53 gene in human primary cervical carcinoma with and without human papillomavirus infection. Cancer Res., 52: 5323-5328.

Garcia-Pineres AJ, Hildesheim A, Herrero R, Trivett M, Williams M, Atmetlla I, Ramírez M, Villegas M, Schiffman M, Rodríguez AC, Burk RD, Hildesheim M, Freer E, Bonilla J, Bratti C, Berzofsky JA, Pinto LA (2006). Persistent human papillomavirus infection is associated with a generalized decrease in immune responsiveness in older women. Cancer Res., 66: 11070-11076.

Giordano G, D'Adda T, Dal Bello B, Brigati F, Bersiga A, Campanini N, Berretta R, Rocco A, Merisio C (2011). Clinicopathologic implications of the epidermal growth factor receptor, cyclooxygenase 2 expression, and human papillomavirus status in squamous cell carcinoma of the uterine cervix in the elderly. Int. J. Gynecol. Cancer, 21: 337-348.

Harris CC (1993). p53: At the crossroads of molecular carcinogenesis and risk assessment. Science, 262: 1980-1981.

Helland A, Holm R, Kristensen G, Kaern J, Karlsen F, Trope C, Nesland JM, Børresen AL (1993). Genetic alterations of the p53 gene, p53 protein expression and HPV infection in primary cervical carcinomas. J. Pathol., 171: 105-114.

Huibregtse JM, Scheffner M, Howley PM (1993). Cloning and expression of the cDNA for E6-AP, a protein that mediates the interaction of the human papillomavirus E6 oncoprotein with p53. Mol. Cell Biol., 13: 775-784.

National Institute of Statistics, ISTAT: "Multipurpose Household 2005" on the health status and use of health services 2005.

Kenter GG, Schoonderwald EM, Koelma IA, Arentz N, Hermans J, Fleuren GJ (1996). The cytological screening history of 469 patients with squamous cell carcinoma of the cervix uteri; does interval carcinoma exist? Acta Obstet. Gynecol. Scand., 75: 400–403.

Kuerbitz SJ, Plunkett BS, Walsh WV, Kastan MB (1992). Wild-type p53 is a cell cycle checkpoint determinant following irradiation. Proc. Natl. Acad. Sci., USA, 89: 7491-7495.

Lee YY, Wilczynski P, Chumakov A, Chih D, Loeffler HP (1994). Carcinoma of the vulva: HPV and p53 mutations. Oncogene, 9: 1655-1659.

Lowe SW, Schmitt EM, Smith SW, Osborne BA Jacks T (1993). p53 is required for radiation-induced apoptosis in mouse thymocytes. Nature, 362: 847-849.

Milde-Langosch KM, Albrecht K, Joram S, Schlechte H, Giessing M, Loning T (1995). Presence and persistence of HPV infection and p53 mutation in cancer of the cervix uteri and the vulva. Int. J. Cancer, 63: 639-645.

Miwa K, Miyamoto S, Imamura T, Nishida M, Yoshikawa Y, Nagata Y, Wake N (1995). The role of p53 inactivation in human cervical cell carcinoma development. Br. J. Cancer, 71: 219-226.

Mubiayi N, Bogaert E, Boman F, Leblanc E, Vinatier D, Leroy JL, Querleu D (2002). Cytological history of 148 women presenting with invasive cervical cancer. Gynaecol. Obstet. Fertil., 30: 210–217.

Muñoz N, Bosch FX, de Sanjosé S, Herrero R, Castellsagué X, Shah KV. (2003). International Agency for Research on Cancer Multicenter Cervical Cancer Study Group, et al: Epidemiologic classification of human papillomavirus types associated with cervical cancer. N. Engl. J. Med., 348(6): 518-527.)

Nakagawa S, Watanabe S, Yoshikawa H, Taketani Y, Yoshiike, K Kanda T (1992). Mutational analysis of human papillomavirus type 16 E6 protein: transforming function for human cells and degradation of p53 *in vitro*. Virology, 212: 535-542.

Nakagawa S, Yoshikawa H, Jimbo H, Karmakar A, Kizaki M, Miller CW, Koeffler HP (1999). Elderly Japanese women with cervical carcinoma show higher proportions of both intermediate-risk human papillomavirus types and p53 mutations. Elderly Japanese women with cervical carcinoma show higher proportions of both intermediate-risk human papillomavirus types and p53 mutations. Br. J. Cancer Mar., 79: 1139-1144.

Nevins JR (1992). E2F: A link between the Rb tumor suppressor protein and viral oncoproteins. Science, 258: 424-429.

Paquette RL, Lee YY, Wilczynski SP, Raffaele M, Cohet C, Federici A, Palazzo F (1993). Mutation of p53 and human papillomavirus infection in cervical carcinoma. Cancer, 72: 1272-1280.

Ricciardi A, Largeron N, Giorgi Rossi P, Raffaele M, Cohet C, Federici A, Palazzo F (2009). Incidence of invasive cervical cancer and direct costs associated with its management in Italy. Incidence of invasive cervical cancer and direct costs associated with its management in Italy. Tumori, 95: 146-152.

Ronco G, Giubilato P, Naldoni C, Zorzi M, Anghinoni E, Scalisi A, Dalla Palma P, Zanier L, Federici A, Angeloni C, Prandini S, Maglietta R, Mancini E, Pizzuti R, Iossa A, Segnan N, Zappa M (2007). Extension of organised cervical screening programmes in Italy and their process indicators. Epidemiol. Prev., 31 Suppl(2): 33-47.

Saito J, Hoshiai H, Noda K (2000). Type of human papillomavirus and expression of p53 in elderly women with cervical cancer. Gynecol Obstet InvestGynecol. Obstet. Invest., 49: 190-193.

Scheffner M, Werness BA, Huibregtse JM, Levine AJ, Howley PM (1993). The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. Cell, 63: 1129-1136.

Schiffman MH, Bauer HM, Hoover RN, Glass AG, Cadell DM, Rush BB, Scott DR, Sherman ME, Kurman RJ, Wacholder S (1993). Epidemiologic evidence showing that human papillomavirus infection causes most cervical intraepithelial neoplasia, J. Natl. Cancer Inst., 85: 958–964.

Stuart GC, Mc Gregor SE, Duggan MA, Nation JG (1997). Review of the screening history of Alberta women with invasive cervical cancer.

CMAJ, 157: 513–519.
Subbaramaiah K, Dannenberg AJ (2007). Cyclooxygenase-2 transcription is regulated by human papillomavirus 16 E6 and E7 oncoproteins: evidence of a corepressor/coactivator exchange. Cancer Res., 67: 3976-3985.
Tsujii M, DuBois RN (1995). Alterations in cellular adhesion and apoptosis in epithelial cells overexpressing prostaglandin endoperoxide synthase-2. Cell, 83: 493-550.
Tsujii M, Kawano S, DuBois RN (1997). Cyclooxygenase-2 expression in human colon cancer cells increases metastatic potential. Proc. Natl. Acad. Sci. U S A, 94: 3336-3340.
Walboomers M, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders PJ, Peto J, Meijer CJ, Munoz N (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide, J. Pathol., 189: 12-19.
Waterhouse J, Muir C, Stranmugaratnam K, Powell J (1982). Cancer incidence in five continent; Vol IV. IARC scientific publication series, Lyon: IARC Press. p. 42.
Zucchetto A, Franceschi S, Clagnan E, Serraino D, Zanier L, Franzo A (2010). Screening history of women with invasive cervical cancer in north-east Italy.Screening history of women with invasive cervical cancer in North-East Italy. Eur. J. Obstet. Gynecol. Reprod. Biol., 152: 200-204.