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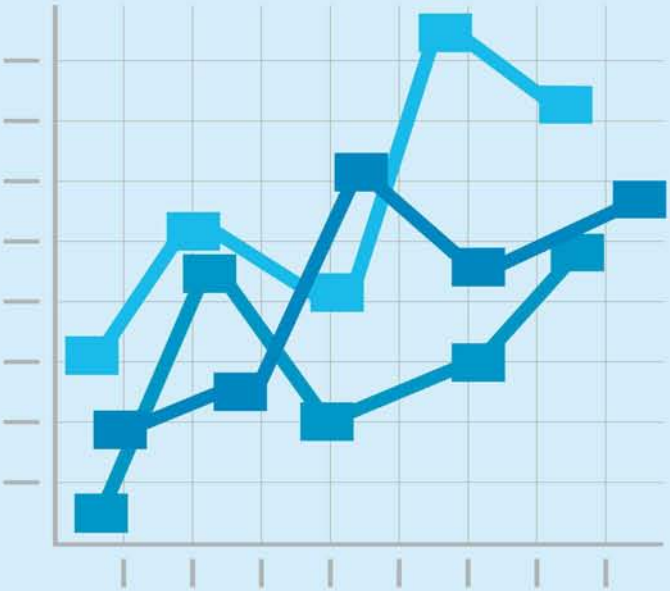
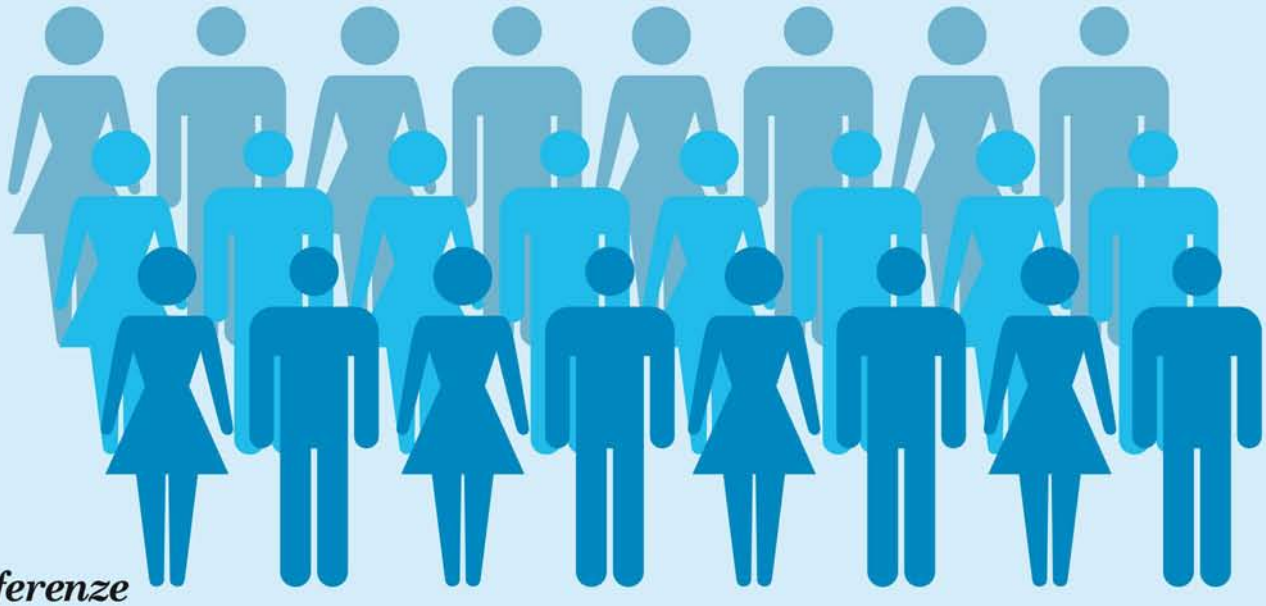


The National Centre for Screening Monitoring
Eleventh Report

Osservatorio Nazionale Screening
Undicesimo Rapporto



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THE NATIONAL CENTRE FOR SCREENING MONITORING
Eleventh Report

OSSERVATORIO NAZIONALE SCREENING
Undicesimo Rapporto

Editors / A cura di: Marco Zappa, National centre for screening monitoring (ONS)
Francesca Carozzi, Italian group for cervical screening (GISCi)
Livia Giordano, Italian group for mammographic screening (GISMa)
Romano Sassatelli, Italian group for colorectal screening (GISCoR)
Antonio Federici, Ministry of Health, Prevention Department

OSSERVATORIO NAZIONALE SCREENING

GISCi
Gruppo Italiano Screening Cervicocarcinoma

GISCoR
Gruppo Italiano Screening Colorettale

GISMa
Gruppo Italiano Screening Mammografico

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Tabella. Popolazione italiana nell'anno 2012, suddivisa per sesso e per Regione (www.demo.istat.it).

Region	Males	Females	Total
Abruzzo	633,941	672,475	1,306,416
Alto Adige (PA Bolzano)	248,407	256,301	504,708
Basilicata	282,546	295,016	577,562
Calabria	953,767	1,004,651	1,958,418
Campania	2,794,720	2,969,704	5,764,424
Emilia-Romagna	2,094,766	2,246,474	4,341,240
Friuli-Venezia Giulia	587,449	630,331	1,217,780
Lazio	2,635,689	2,864,333	5,500,022
Liguria	740,458	826,881	1,567,339
Lombardia	4,711,292	4,989,589	9,700,881
Marche	745,469	795,219	1,540,688
Molise	152,547	160,598	313,145
Piemonte	2,101,852	2,255,811	4,357,663
Puglia	1,962,375	2,087,697	4,050,072
Sardegna	800,451	837,395	1,637,846
Sicilia	2,417,426	2,582,428	4,999,854
Toscana	1,759,289	1,908,491	3,667,780
Trentino (PA Trento)	255,832	269,045	524,877
Umbria	423,559	459,656	883,215
Valle d'Aosta	61,775	64,845	126,620
Veneto	2,362,989	2,490,668	4,853,657
Total	**28,726,599**	**30,667,608**	**59,394,207**

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Introduction

The diffusion of screening programmes in Italy, years 2011-2012

La diffusione dei programmi di screening in Italia, anni 2011-2012

Marco Zappa,[1] Francesca Maria Carozzi,[2] Livia Giordano,[3] Romano Sassatelli,[4] Antonio Federici[5]

[1]National centre for screening monitoring (ONS) – Istituto per lo studio e la prevenzione oncologica (ISPO), Firenze

[2]Italian group for cervical screening (GISCi) – Istituto per lo studio e la prevenzione oncologica (ISPO), Firenze

[3]Italian group for mammographic screening (GISMa) – Centro per la prevenzione oncologica (CPO), Piemonte, Torino

[4]Italian group for colorectal screening (GISCor) – Azienda ospedaliera di Reggio Emilia, Emilia-Romagna

[5]Ministry of Health, Prevention Department, Dipartimento prevenzione, Ministero della salute, Roma

Corresponding author
Marco Zappa
m.zappa@ispo.toscana.it

In this report, we present the results of cancer screening programmes in Italy for the years 2011-2012. This report is produced by the National centre for screening monitoring (ONS), together with the Italian professional multidisciplinary screening groups: GISMa (Italian group for mammographic screening), GISCor (Italian group for colorectal screening), and GISCi (Italian group for cervical screening). Since 2004, ONS has been monitoring and supporting Italian screening programmes, in accordance with a decree issued by the Ministry of Health. Multidisciplinary groups work with ONS and provide the know-how required to promote the quality of public health programmes.
The following is a brief outline of the Italian screening programme setting:

- screening programmes (cervical, mammographic, colorectal) have been a Basic Healthcare Parameter (livello essenziale di assistenza, LEA) since 2001;
- guidelines are provided by the Ministry of Health's Department of Prevention in agreement with regional governments;
- regional governments are responsible for the organization, management, and quality assurance of screening programmes;
- since 2004, ONS has been responsible for monitoring and promoting screening programmes nationwide;
- the results of the screening programmes of each region are evaluated annually by the Ministry of Health in terms of coverage and impact.

The main characteristics of protocols of of mammographic, cervical and colorectal screening programmes are summarized in **table 1** (p. 7).
Overall, in 2011-2012 almost 20 million people were invited to undergo a screening examination (7,419,295; 5,271,248 and 7,744,295 for cervical, breast, and colorectal cancer, respectively). As compared to the previous years, an increase was observed for all the screening programmes. Almost 10 million actually complied to the invitation (3,051,852; 2,959,329 and 3,556,486 for cervical, breast, and colorectal cancer, respectively). Unfortunately, in the observed increase in invitation and participation inequality persisted and grew between Centre, North, and South of Italy.
The screening activity has already produced a remarkable impact on the epidemiology of these three cancers in Italy. Changes have been documented in several papers.[1-5]

CERVICAL CANCER SCREENING

Taking a closer look at the data (and adopting the same criteria for each year), we can observe that the actual extension of cervical cancer screening (i.e., how many 25-64 year-old women regularly received an invitation letter to perform a Pap smear every three years) in 2011-2012 was close to 70% (69.5%). This does not mean that 30% of the target population did not receive an invitation to screening. In some cases, it is possible that invitations were issued but the interval was longer than 3 years.

Extension in 2010-2012 was greater than in 2004-2006 (51.8%) and 2007-2009 (63%) (figure 1). This increase concerns all three Italian macro-areas (North, Centre, South), with a low heterogeneity among them, unlike what was observed in the other two types of screening. Unfortunately, this is partly due to the fact that the largest Italian regions in northern Italy did not implement a cervical screening programme throughout the entire region.

A crucial innovation for cervical screening policy is currently taking place. Italy is one of the first countries in Europe to move towards the use of DNA HPV test as a primary test. As reported by Ronco et al. in this issue,[6] in 2012, 19 Italian programmes from 10 regions invited women for HPV-based screening. During 2012, more than 300,000 (8% of the target population) women were invited to HPV testing and more than 130,000 accepted. As far as we know, this is one of the first reports in Europe on the performances of HPV-based screening programmes.

BREAST CANCER SCREENING

Regarding mammography screening, actual extension from 2005 to 2012 (percentage of 50-69 years old women regularly receiving a letter of invitation every two years) is reported in figure 2. In the biennium 2011-2012, almost 3 out of 4 women were invited (73.2%). Unfortunately, screening diffusion is still heterogeneous, with a higher distribution in northern/central Italy (nearing or over 90%), compared with southern/insular Italy (only 40%). Even though we observed a stable increase from 2005-2006 in all three areas (on average, each area showed twenty percentage points less in 2005-2006), this trend does not allow us to be fully optimistic. Due to the difficulties in spreading organized screening activity in southern Italy, the goal of assuring complete breast screening coverage in Italy remains uncertain.

It is worth mentioning that in 2011-2012, 227,00 women older than 69 (13.6% of the target population) were invited to continue screening till 74 years of age. Furthermore, two re-

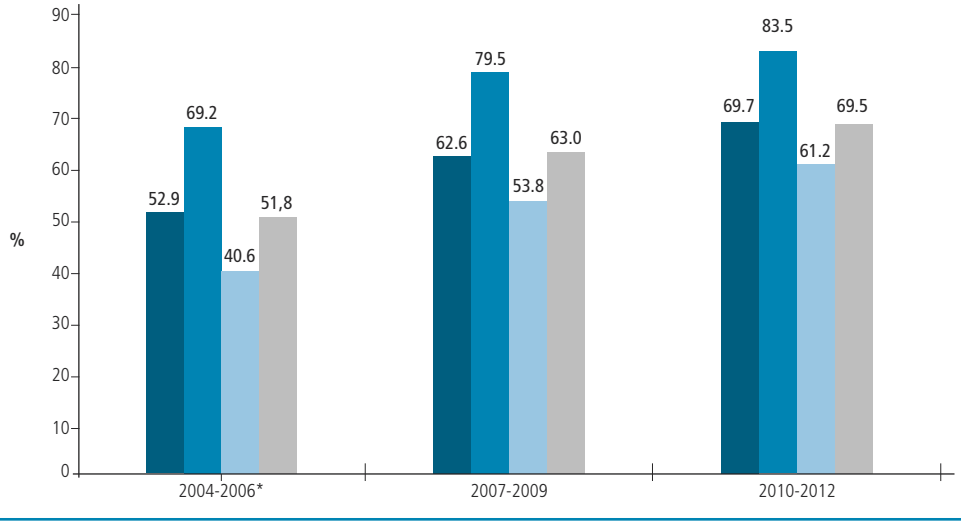

Figure 1. Actual extension of cervical screening programmes by geographical area. Years 2004-2012.
Figura 1. Estensione effettiva dei programmi di screening cervicale per area geografica. Anni 2004-2012.

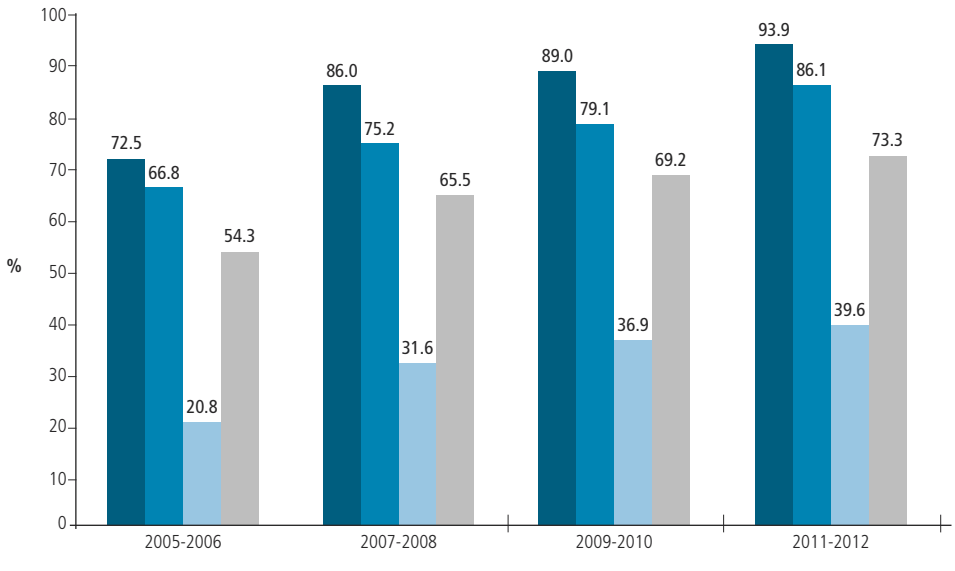

Figure 2. Actual extension of mammographic screening programmes by geographical area. Years 2005-2012.
Figura 2. Estensione effettiva dei programmi di screening mammografici per area geografica. Anni 2005-2012.

Mammographic screening	
Target population	women aged 50-69 (some regions have extended the age target from 45 to 74)
Primary test	2 views, doubling reading mammographic test
Screening interval	2 years
Cervical screening	
Target population	women aged 25-64
Primary test	Pap smear
Screening interval	3 years
Some programs have moved towards HPV testing as primary test:	
Target population	HPV: women aged 30/35-64 Pap smear: women aged 25-30/35
Primary test	HPV
Screening interval	5 years
Colorectal screening	
Primary test	fecal immunochemical test (FIT)
Target population	subjects aged 50-69 (some regions have extended the age target to 74 or 75 years)
Screening interval	2 years
Primary test	flexible sigmoidoscopy (FS) + FIT
Target population	subjects aged 58 or 60 (FS); subjects aged 59-69 (FIT)
Screening interval	flexible sigmoidoscopy once in a lifetime and FIT every 2 years for non-responders to FS

Table 1. Main characteristics of protocols of mammographic, cervical and colorectal screening programmes.
Tabella 1. Caratteristiche principali dei programmi di screening mammografico, cervicale e colorettale.

gions (Emilia-Romagna and Piemonte) also included younger women (ages 45-49) among those to be invited. In 2011-2012, almost 380,000 women in this age class were invited annually (7.9% of the Italian target population of 45-49 year-old women). The latter figure shows a small increase in comparison with the previous two years.

COLORECTAL CANCER SCREENING

Concerning colorectal cancer screening, in the period 2011-2012 we continued to observe an increase in the actual extension for the whole country (extension was 53% of the target population: men and women aged 50-69). Actual extension was almost double compared to the biennium 2005-2006 (29.7%). This is very encouraging, since colorectal cancer screening was only introduced recently (2005) in Italy. Unfortunately, once again, differences between North and South are evident and become increasingly greater, with 82%, 59%, and 12% actual extension in the North, Centre, and South, respectively. Even more worrisome is the fact that in the South we did not observe any relevant increase till 2012.

DISCUSSION

In conclusion, we observed an increase in the actual extension of all three screening programmes, although the differences between Centre, North, and South remained relevant, especially for breast and colorectal cancer screening.
Our data are consistent with the PASSI survey reported on in this issue by Carrozzi et al.[7] PASSI is a national telephone sur-

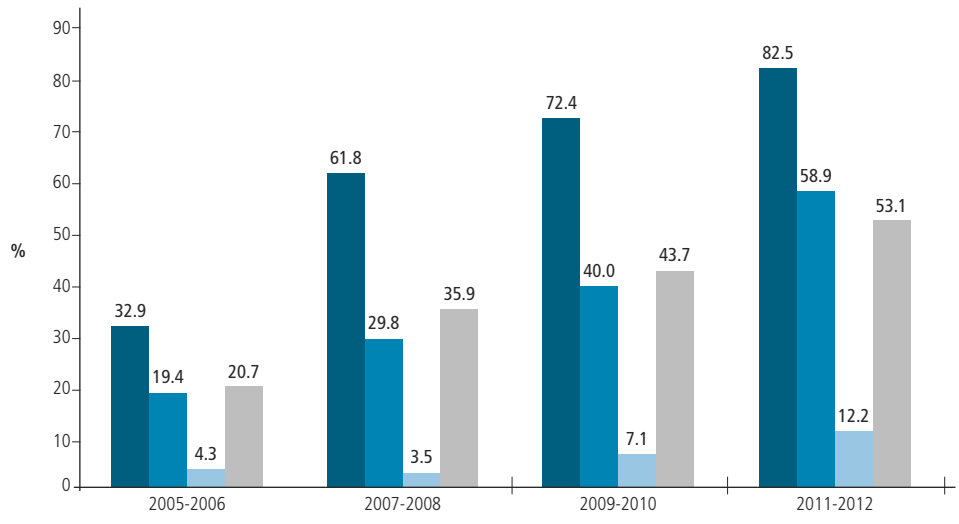

Figure 3. Actual extension of colorectal screening programmes by geographical area. Years 2005-2012.
Figura 3. Estensione effettiva dei programmi di screening colorettali per area geografica. Anni 2005-2012.

veillance system that continuously collects information about behavioural health risk factors and the diffusion of preventive health interventions. PASSI collects information both on organized screening programmes and spontaneous public and private screening. The PASSI survey reports that from 2010 to 2013 coverage increased for all types of screening and the increase was mostly due to the tests performed within organized programmes. All three screening types show a decreasing North-South trend in coverage. The gap between Centre-North and South is mainly due to organized screening.

A screening programme is not limited to the administration of a test. It is the construction of a process which takes care of the invited person from the primary test to (if necessary) the assessment phase, treatment, and follow-up of the detected lesions. Each of these phases requires a standardized protocol and a monitoring system in order to maintain high quality assurance. In the present issue, we present examples of the effort we are making in that direction.

Ponti et al.[8] reports on the audit system on Quality of breast cancer diagnosis and treatment (QT). QT is a voluntary quality assurance programme concerning screen-detected breast cancer care and it has been running in Italy since 1997. During the period 2000-2012, about 40,000 lesions in thirteen Italian regions were documented in QT.

Castagno et al.[9] deal with the quality and completeness of the information provided to women by Italian breast screening programmes. It reports the results of a survey promoted by the Italian group for mammography screening (GISMa) in the spring of 2014. Aim of the study was to compare information provided by invitation letters and leaflets of Italian breast screening programmes in 2001 and nowadays, and to verify whether there has been an evolution in the type of information provided, and, if so, of what type.

Bucchi et al.[10] report the position paper on interval cancers by the Italian group for mammography screening. In particular, the paper outlines problems and solutions with respect to appropriate assessment of the frequency of interval cancers in relation to expected incidence (proportional incidence).

Carozzi et al.[11] describe the HPV-based follow-up protocol for cervical lesions proposed by the Italian group for cervical screening (GISCi). Aim of the protocol is to improve follow-up appropriateness (eliminating too frequent check-ups) by using HPV testing. To date, screening programmes in Italy lack any clearly defined follow-up protocol after an abnormal Pap smear and negative colposcopy, or any uniform indications.

In the two papers by Zorzi et al.[4,5] the early impact of implementation of screening programmes on stage distribution at diagnosis and incidence of colorectal cancer is reported. Despite the brief time since programme implementation, clear changes have nevertheless been evident in the epidemiology of colorectal screening.

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Cancer screening uptake: association with individual characteristics, geographic distribution, and time trends in Italy

La copertura dei test di screening: caratteristiche, distribuzione geografica e trend temporali

Giuliano Carrozzi,[1] Letizia Sampaolo,[2] Lara Bolognesi,[1] Laura Sardonini,[3] Nicoletta Bertozzi,[3] Paolo Giorgi Rossi,[4,5] Marco Zappa,[6] Sandro Baldissera,[7] Stefano Campostrini,[8] Gianluigi Ferrante,[7] Maria Masocco,[7] Valentina Minardi,[7] Angelo D'Argenzio,[9] Pirous Fateh Moghadam,[10] Elisa Quarchioni,[7] Mauro Ramigni,[11] Massimo Oddone Trinito,[12] Stefania Salmaso[7] for the regional and local PASSI coordinators

[1]Dipartimento di sanità pubblica, AUSL Modena
[2]Dipartimento di sanità pubblica, AUSL Modena e Università Ca' Foscari, Venezia
[3]Dipartimento di sanità pubblica, AUSL della Romagna
[4]Servizio interaziendale di epidemiologia, AUSL Reggio Emilia
[5]IRCCS-Arcispedale S. Maria Nuova, Reggio Emilia
[6]Istituto per lo studio e la prevenzione oncologica, Osservatorio nazionale screening
[7]Centro nazionale di epidemiologia, sorveglianza e promozione della salute, Istituto superiore di sanità
[8]Dipartimento di economia, Università Ca' Foscari, Venezia
[9]Servizio epidemiologia e prevenzione, ASL Caserta
[10]Dipartimento salute e solidarietà sociale, Provincia autonoma di Trento
[11]Dipartimento di prevenzione, Azienda ULSS 9 Treviso
[12]Dipartimento di prevenzione, ASL Roma C

Corresponding author
Giuliano Carrozzi
g.carrozzi@ausl.mo.it

Abstract

Background. In Italy, organized screening programmes invite the vast majority of the population for cervical and breast cancer, and about one half of the population for colorectal cancer. Programme activity and quality are closely monitored. Nevertheless, there is a vast spontaneous activity, both public and private, for which information on service and coverage is missing. To estimate actual population coverage for the three types of screening the extent of spontaneous screening needs to be known.

Methods. PASSI is a national telephone-interview surveillance system that continuously collects information about behavioural health risk factors and the diffusion of preventive health interventions. From 2010 to 2013, more than 151,000 18- to 69-year-olds were interviewed. During 2013, 136 out of 147 Italian local health authorities participated in the survey. Information about screening includes: test uptake (Pap smear, HPV, mammography, faecal occult blood test, colonoscopy), date of the last test, provider of the last test (whether paid or for free, proxy of the organized screening programme), reason for not participating in screening, and screening promotion/recommendation received. Individual information on socio-economic characteristics is available.

Results. Seventy-seven percent of the 25-64 year-old women interviewed said they had undergone a Pap smear or HPV test in the three years before the interview, 40% within the screening programme, 37% spontaneously and paying. Seventy percent of the 50-69 year-old women interviewed reported having had a mammography in the two years before the interview, 51% within the screening programme, 19% spontaneously and paying. Thirty-eight percent of the 50-69 year olds interviewed reported having undergone colorectal screening in the two years before the interview, 31% within the screening programme, 7% spontaneously and paying.

All three screening programmes showed a decreasing North-South trend in coverage. From 2010 to 2013, coverage increased for all types of screening; the trend was stronger in the South; the increase was mostly due to the tests performed within the organized programmes. People with low education, economic problems, and immigrants from high migration pressure countries had lower coverage levels. In regions with well-implemented organized screening programmes, test coverage was higher and differences for socio-economic factors were smaller than in regions with incomplete programme activation.

Epidemiol Prev 2015; 39(3) Suppl 1: 9-18)
Keywords: breast cancer, cervical cancer, colorectal cancer, mass screening, opportunistic/spontaneous screening, Italy

Riassunto

Introduzione. In Italia sono attivi programmi di screening organizzati per il carcinoma della cervice uterina, della mammella e del colon-retto, la cui attività è dettagliatamente monitorata. Ciononostante esiste una intensa attività di screening spontanea, sia nel privato sia nel pubblico, di cui non si conosce il dettaglio delle prestazioni e della popolazione target. Per stimare la reale copertura della popolazione per i tre screening è dunque necessario conoscere il ricorso da parte della popolazione allo screening spontaneo.
Metodi. PASSI è un sistema di sorveglianza nazionale che raccoglie in continuo, tramite interviste telefoniche, informazioni sui fattori comportamentali di rischio per la salute e sulla diffusione degli interventi di prevenzione messi in campo dalle aziende sanitarie nei confronti delle persone tra i 18 e i 69 anni. Dal 2010 al 2013 sono state intervistate oltre 151.000 persone. Nel 2013 hanno partecipato al sistema 136 su 147 ASL italiane. Tra i vari temi indagati ci sono: l'effettuazione dei test di screening (Pap-test e test HPV, mammografia, sangue occulto e colonscopia), la data dell'ultimo test, il setting in cui è stato fatto (a pagamento o meno, proxy del programma di screening organizzato), i motivi di non adesione al programma di screening e gli interventi di promozione (lettera ASL, consiglio sanitario, campagna informativa). Sono raccolte, inoltre, informazioni sociodemografiche individuali.
Risultati. Il 77% delle donne di 25-64 anni intervistate ha eseguito un test di screening cervicale (Pap-test o test Hpv) nei tre anni precedenti l'intervista, il 40% all'interno di programmi organizzati dalle ASL e il 37% su iniziativa personale. Il 70% delle donne intervistate di 50-69 anni ha eseguito una mammografia a scopo preventivo nel corso dei due anni precedenti l'intervista, il 51% all'interno dei programmi organizzati e il 19% su iniziativa personale. Il 38% delle persone intervistate di 50-69 anni ha eseguito esami per la diagnosi precoce dei tumori colon-rettali, il 31% all'interno dei programmi di screening, il 7% su iniziativa personale.
La copertura di tutti i tre test mostra un gradiente Nord-Sud. Nel periodo 2008-2013 le coperture risultano complessivamente in crescita, andamento più evidente nelle regioni meridionali; aumentano soprattutto gli esami eseguiti all'interno dei programmi organizzati. La copertura mostra differenziali per livello di istruzione e difficoltà economiche; è inoltre più alta tra le persone con cittadinanza italiana o provenienti da altri Paesi a sviluppo avanzato (PSA) rispetto agli stranieri provenienti da Paesi a forte pressione migratoria (PFPM).
Nelle Regioni con programmi di screening organizzati con buona estensione e adeguatamente funzionanti l'esecuzione dei test di screening è significativamente più alta e le disuguaglianze socioeconomiche nella copertura sono minori.

(*Epidemiol Prev* 2015; 39(3) Suppl 1: 9-18)
Parole chiave: cancro del seno, cancro della cervice uterina, cancro del colon-retto, programmi di screening, screening opportunistico/spontaneo, Italia

INTRODUZIONE

In Italy, in accordance with the European Commission's 2003 Recommendation,[1] the Italian Ministry of Health guidelines recommend the implementation of organized screening programmes for cervical, colorectal, and breast cancer.[2] These programmes involve active invitation of the entire target population, free testing and treatment, quality assurance in all stages of the process, and process and early outcome monitoring system.
Activation of screening programmes is not complete and uniform throughout Italy.[3-5] Furthermore, cervical and breast cancer screening programmes started when Pap smears and mammography were already in widespread use in the population. For these reasons, in Italy, there is a strong opportunistic/spontaneous uptake of both mammography and, in particular, Pap smears, both in the public and private sector. The spontaneous activity is not precisely measurable, it is not monitored, and its target population is not defined. Any attempt to measure the spontaneous activity through routine or administrative data failed due to strong under-reporting of preventive tests in these databases.[6,7]
In order to estimate the actual population coverage for the three types of screening it is necessary to know the spontaneous uptake of preventive tests. To date, the most reliable source of information for spontaneous screening are population interviews.[8] Until 2007, the only national survey estimating mammography and Pap smear coverage was the National Health interview, which is repeated every five years.[9] Starting from 2007, the PASSI surveillance has monitored cervical, colorectal, and breast cancer screening coverage with a continuous survey.[10]
Aim of this paper is to present the coverage estimates for the three types of screening, their geographical differences, their association with individual socio-economic factors, and their time trends.

METHODS

PASSI is a National surveillance system that continuously collects information via phone calls about behavioural health risk factors and the diffusion of preventive health care services. From 2010 to 2013, more than 151,000 18-69 year-old people were interviewed. During 2013, 136 out of 147 Italian local health units participated in the survey.
The sampling and survey methodologies are described in detail elsewhere.[11] Briefly, the surveillance system is based on a random sample of people resident in the area and registered in the list of each Local Health Authority. Samples are stratified by gender and age to respect the proportion of the population (18-34, 35-49, 50-69). Eligibility criteria are: age 18-69, residence, ability to understand and answer the questions in Italian, and not being in a residential institution (hospital, nursing home, military barracks, prison).[12] The Local

Health Authority (LHA) alerts all sampled people with a letter informing them about the interviews, the privacy conditions, and the way to opt out and deny consent to being contacted by phone. The LHA also contacts GPs, asking them to help contact sampled people and explain the scope and aim of the interview. Interviews are conducted mostly by health personnel specifically trained with classroom and online courses. The interview takes about twenty minutes and is either a CATI (Computer Assisted Telephone Interview) or registered on paper with back office data entry. Interviews are stored anonymously in a national database. The questionnaire has closed questions on perceived health status, symptoms, depression, prevalence of chronic diseases and conditions, prevalence of behavioural risk factors, received preventive and health promotion screening interventions, vaccines, and safety on the road and at home.[13,14]

Information about screening includes: test uptake (Pap smear, HPV, mammography, faecal occult blood test, colonoscopy), date of the last test, provider of the last test (paying or for free, proxy of the organized screening programme), reason for not participating in screening, and screening promotion/recommendation received. Individual information on socio-economic characteristics is available.

Analysis

Coverage was defined as the proportion of people in the target population who had a test within the recommended time: women aged 25-64 who had a Pap smear or HPV test within three years before the interview for cervical cancer; women aged 50-69 who had a bilateral mammography within two years before the interview for breast cancer; women and men aged 50-69 who had a faecal occult blood test within two years before the interview or a colonoscopy/sigmoidoscopy within five years before the interview for colorectal cancer. For the region of Piemonte, where the screening programme adopts a strategy of a once-in-a-lifetime sigmoidoscopy at the age of 58, the target population was restricted to ages 58-69, and subjects were considered covered if they had had a colonoscopy/sigmoidoscopy in their life.

Regions were classified as having a well-implemented screening programme if more than 75% of the interviewed target population declared they had received the invitation letter.

Associations between coverage and individual characteristics were tested with logistic regression models; time trends were evaluated through Cochrane-Orcutt linear regression models. Time trends for colorectal cancer screening test coverage are limited to the period 2010-2013 because the questions in the questionnaire were changed at the end of 2009.

RESULTS

Cervical cancer screening test coverage

Overall, 77% of the 25-64 year-old women had a Pap smear or HPV test in the three years before the interview. There was a decreasing North-South trend (85% in the North, 84% in the Centre, and 65% in the South and Islands).

Forty percent of the women performed the test within a screening programme for free and 37% performed the test spontaneously paying it entirely or in part.

In northern regions, the proportion of women who performed the test within a screening programme was higher than in southern regions, where spontaneous testing was predominant (figure 1), with the exception of the province of Bolzano

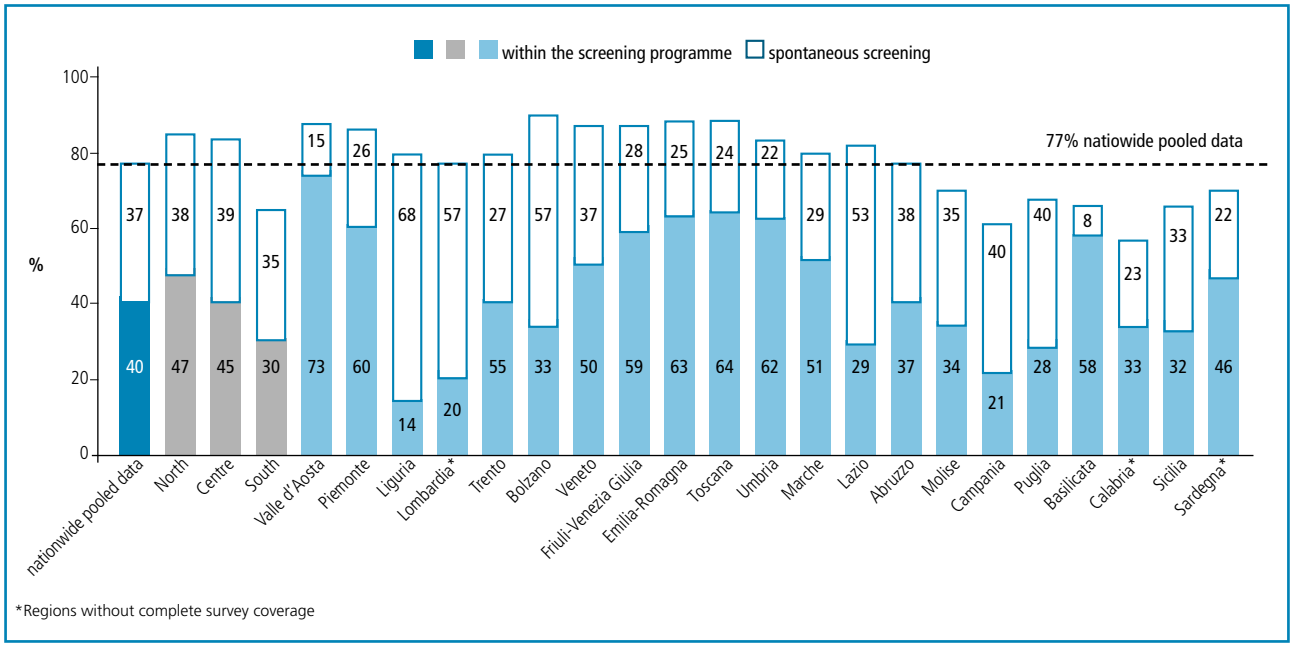

Figure 1. Cervical cancer screening test coverage. Proportion of 25-64 year-old women who had a Pap smear or HPV test in the three years before the interview, within screening programmes or spontaneously, by region. Nationwide pooled data, PASSI 2010-2013.

Figura 1. Copertura di un test per la prevenzione dei tumori del collo dell'utero. Proporzione di donne di età 25-64 anni che hanno avuto un Pap test o un test HPV negli ultimi tre anni, all'interno dei programmi di screening o spontaneamente. Pool, PASSI 2010-2013.

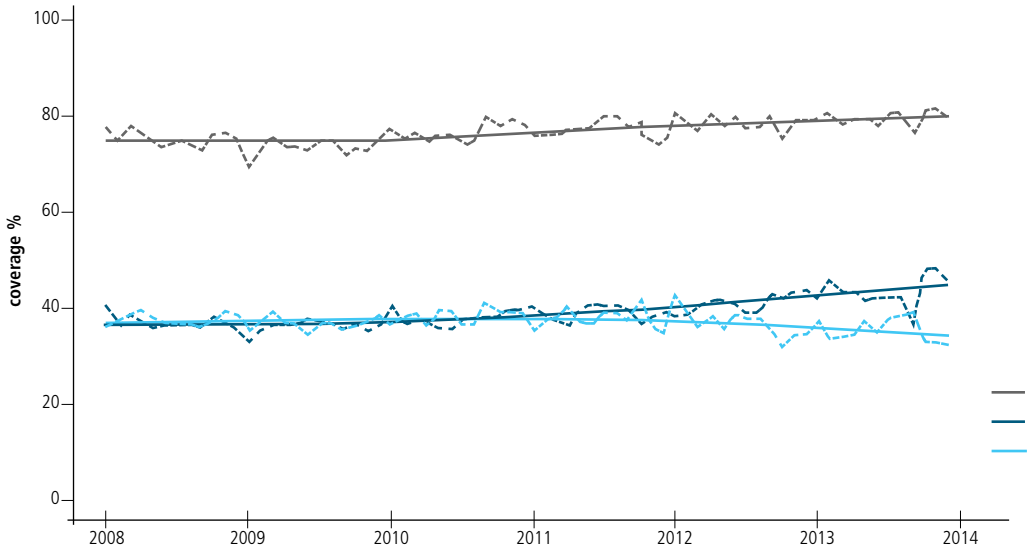

Figure 2. Time series of cervical cancer screening coverage in 25-64 year-old women within screening programmes or spontaneous screening. Nationwide pooled data, PASSI 2010-2013.
Figura 2. Andamento temporale della copertura dello screening cervicale (organizzato o spontaneo), tra le donne di 25-64 anni. Pool, PASSI 2010-2013.

(Alto Adige), , Lombardia and Liguria, northern regions with a low proportion of tests performed within the programmes, and Basilicata, which among southern regions has a low proportion of spontaneous screening.
From 2008 to 2013 coverage increased (p <0.001). The trend was appreciable in all three geographic areas, but was stronger in the South. The trend was entirely due to the increase in women who had a test within screening programmes (p <0.001), while the coverage due to spontaneous screening showed a slight decrease (p=0.052) (figure 2).
Coverage was higher in 35-49 year-old women, married or with a stable partner, with a medium or high educational level, without economic problems, and who are Italian or come from industrialized countries (compared to immigrants from high migration pressure countries).
Women 50-64 years old, married or with a stable partner, with low education, and who are immigrants from high migration pressure countries more frequently performed the test within the screening programmes. On the contrary, women aged 25-34, highly educated, without economic problems, with Italian nationality or coming from industrialized countries, more frequently performed the test spontaneously (figure 3, table 1). Multivariate analysis confirmed all the associations found (table 1).

	Within a screening programme				Spontaneous screening			
	OR	95%CI		p-value	OR	95%CI		p-value
Age								
25-34	1.00				1.00			
35-49	1.25	1.18	1.32	0.000	1.24	1.17	1.32	0.000
50-64	1.65	1.55	1.75	0.000	0.77	0.72	0.82	0.000
Married/with stable partner								
yes	1.00				1.00			
no	0.77	0.73	0.80	0.000	0.80	0.76	0.84	0.000
Education level								
none/elementary	1.00				1.00			
middle school	1.21	1.11	1.32	0.000	1.49	1.34	1.65	0.000
secondary school	1.17	1.07	1.27	0.000	2.04	1.84	2.26	0.000
academic degree	1.03	0.94	1.14	0.478	2.41	2.16	2.70	0.000
Economic difficulties								
major	1.00				1.00			
minor	1.10	1.03	1.18	0.004	1.19	1.10	1.28	0.000
none	1.12	1.05	1.20	0.001	1.35	1.26	1.46	0.000
Nationality								
Italian	1.00				1.00			
foreign	1.47	1.35	1.60	0.000	0.52	0.47	0.57	0.000

Table 1. Logistic regression model to analyze the characteristics associated with cervical cancer screening coverage. Nationwide pooled data, PASSI 2010-2013.
Tabella 1. Copertura di un test per la prevenzione dei tumori del collo dell'utero negli ultimi tre anni. Pool, PASSI 2010-2013.

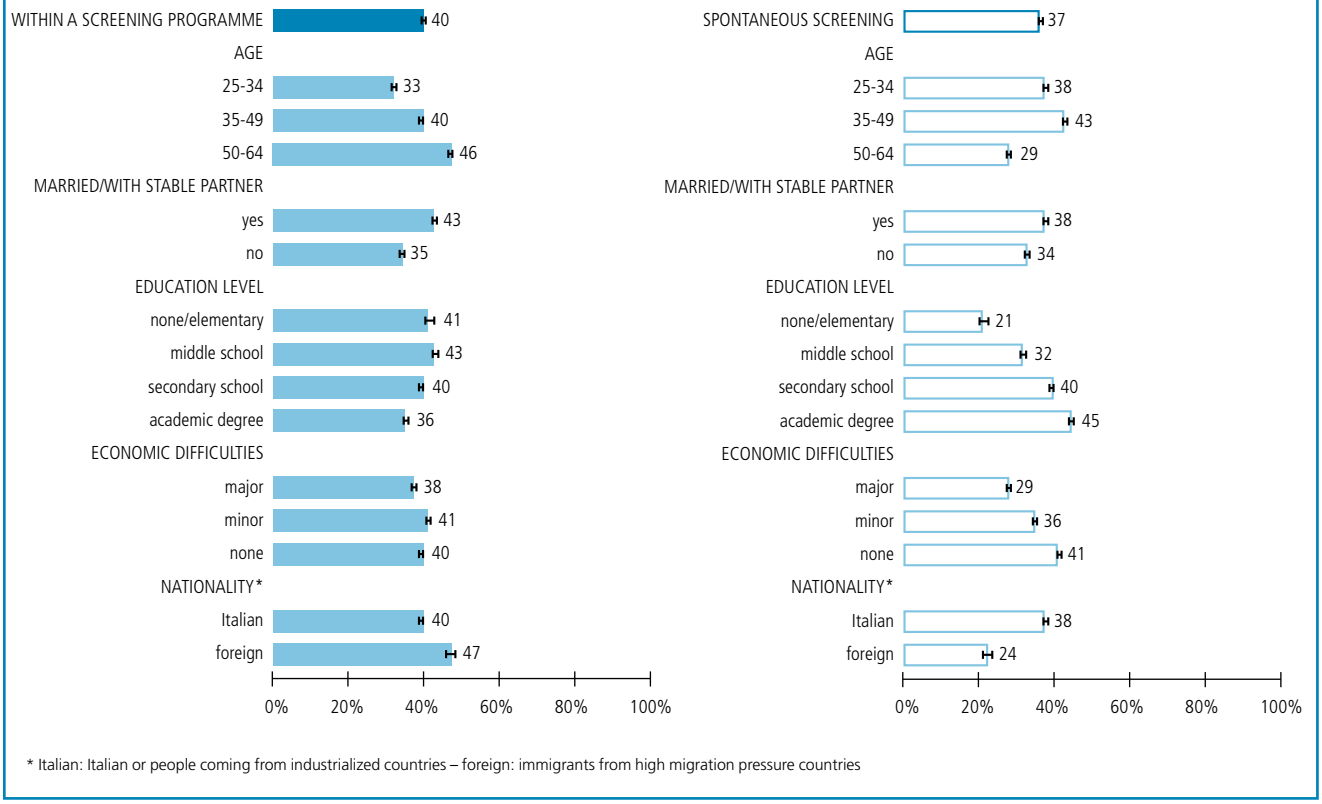

Figure 3. Proportion of 25-64 year-old women who had a Pap smear or HPV test in the three years before the interview, within screening programmes or spontaneously, according to socio-economic characteristics. Nationwide pooled data, PASSI 2010-2013.
Figura 3. Proporzione di donne di età 25-64 anni che hanno effettuato un Pap test o un test HPV negli ultimi tre anni, all'interno dei programmi di screening o spontaneamente, secondo lo stato socioeconomico. Pool, PASSI 2010-2013.

In those regions with well-implemented screening programmes, i.e., in which at least 75% of the target population declared they had received the invitation letter, coverage was higher than in those with incomplete programme activation, i.e., 87% *vs* 72% (p <0.001). Furthermore, in regions with well-implemented programmes the difference in coverage between women with a degree and women with lower education was 16% and the difference between women with major economic difficulties and with no economic problems was 11%; in regions with incomplete programme activation these differences were 38% and 20%, respectively.

Breast cancer screening test coverage

Overall, 70% of the 50-69 year-old women had a mammography in the two years before the interview. There was a decreasing North-South trend (81% in the North, 77% in the Centre, and 54% in the South and Islands).
Fifty-one percent of the women performed the test within a screening programme for free and 19% performed the test spontaneously paying it entirely or in part. The coverage due to spontaneous testing was similar in the three geographic areas, while the part due to organized screening varied (figure 4, p. 14). From 2008 to 2013 mammography coverage slightly increased (p=0.060). The increase was present in all three geographic areas and both in organized programmes and spontaneous screening, but was stronger in the South and in spontaneous activity (figure 5, p. 14).
Coverage was higher in 50-59 year-old women, married or with a stable partner, with high education, without economic problems, and who are Italian or come from industrialized countries (compared to immigrants from high migration pressure countries). Women 60-69 years old, with poor education, without economic problems, and who are immigrants from high migration pressure countries more frequently performed the test within the screening programmes. On the contrary, women 50-59 years old, with a degree, and who are Italian or come from industrialized countries, more frequently performed the test spontaneously (figure 6, table 2, p. 15). Multivariate analysis confirmed all the associations found (table 2).
In regions with well-implemented breast cancer screening programmes, i.e., in which at least 75% of the target population declared they had received the invitation letter, coverage was higher than in regions with incomplete programme activation, i.e., 81% *vs* 60% (p <0.001). Furthermore, in regions with well-implemented programmes the difference in coverage between women with a degree and women with lower education was 8% and the difference between women with major economic difficulties and those with no economic problems was 13%; in regions with incomplete programme activation the difference was 37% in both cases.

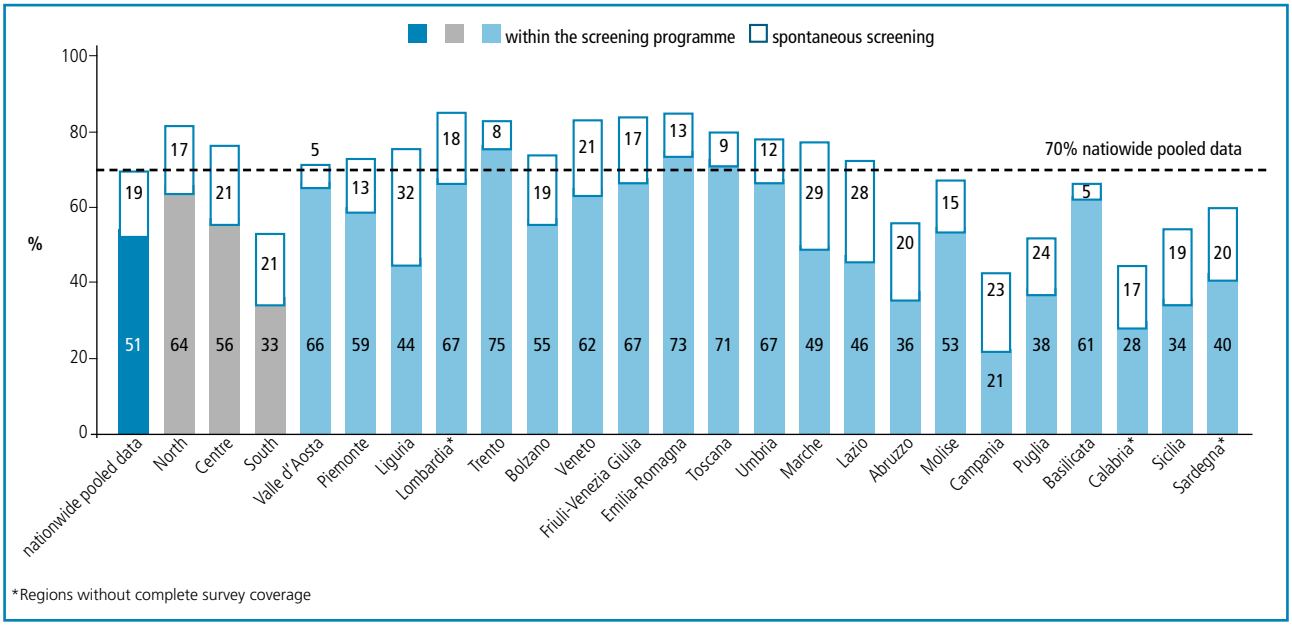

Figure 4. Breast cancer screening test coverage. Proportion of 50-69 year-old women who had a mammography in the two years before the interview, within screening programmes or spontaneously, by region. Nationwide pooled data, PASSI 2010-2013.
Figura 4. Copertura dello screening mammografico. Proporzione di donne di età 50-69 anni che hanno eseguito una mammografia negli ultimi due anni, all'interno dei programmi di screening o spontaneamente. Pool, PASSI 2010-2013.

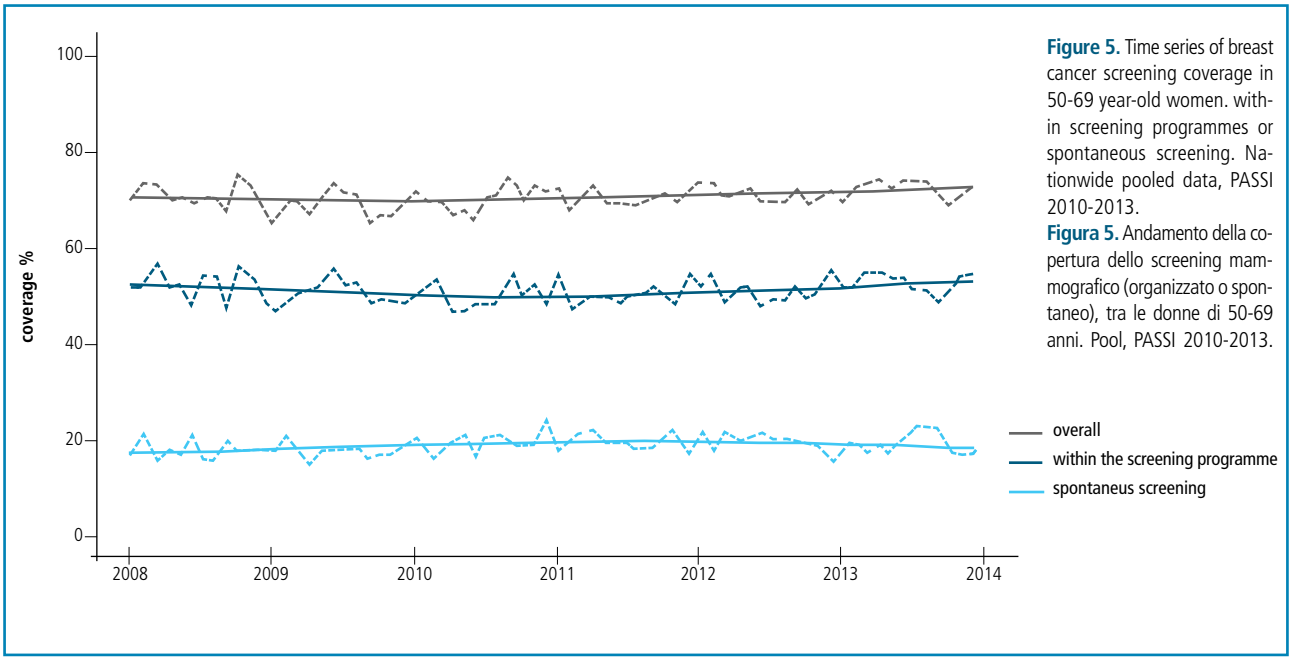

Figure 5. Time series of breast cancer screening coverage in 50-69 year-old women. within screening programmes or spontaneous screening. Nationwide pooled data, PASSI 2010-2013.
Figura 5. Andamento della copertura dello screening mammografico (organizzato o spontaneo), tra le donne di 50-69 anni. Pool, PASSI 2010-2013.

Colorectal cancer screening test coverage

Overall, 38% of people aged 50-69 years were covered for colorectal cancer screening; 33% had a faecal occult blood test in the two years before and 13% a colonoscopy five years before the interview (these data do not include the region of Piemonte). There was a decreasing North-South trend (59% in the North, 41% in the Centre, and 17% in the South and Islands).

Thirty-one percent performed the test within a screening programme for free and 7% performed the test, mainly a colonoscopy, spontaneously, paying it entirely or in part. The vast majority of occult blood tests was performed within screening programmes, while about half of the colonoscopies or sigmoidoscopies were preformed in spontaneous testing settings. The coverage due to spontaneous testing was similar in the three geographic areas, while the part due to organized screening varied (figure 7, p. 16).

From 2010 to 2013, colorectal cancer screening test coverage rapidly increased ($p < 0.001$). The increase was present in all three geographic areas and both in organized programmes and

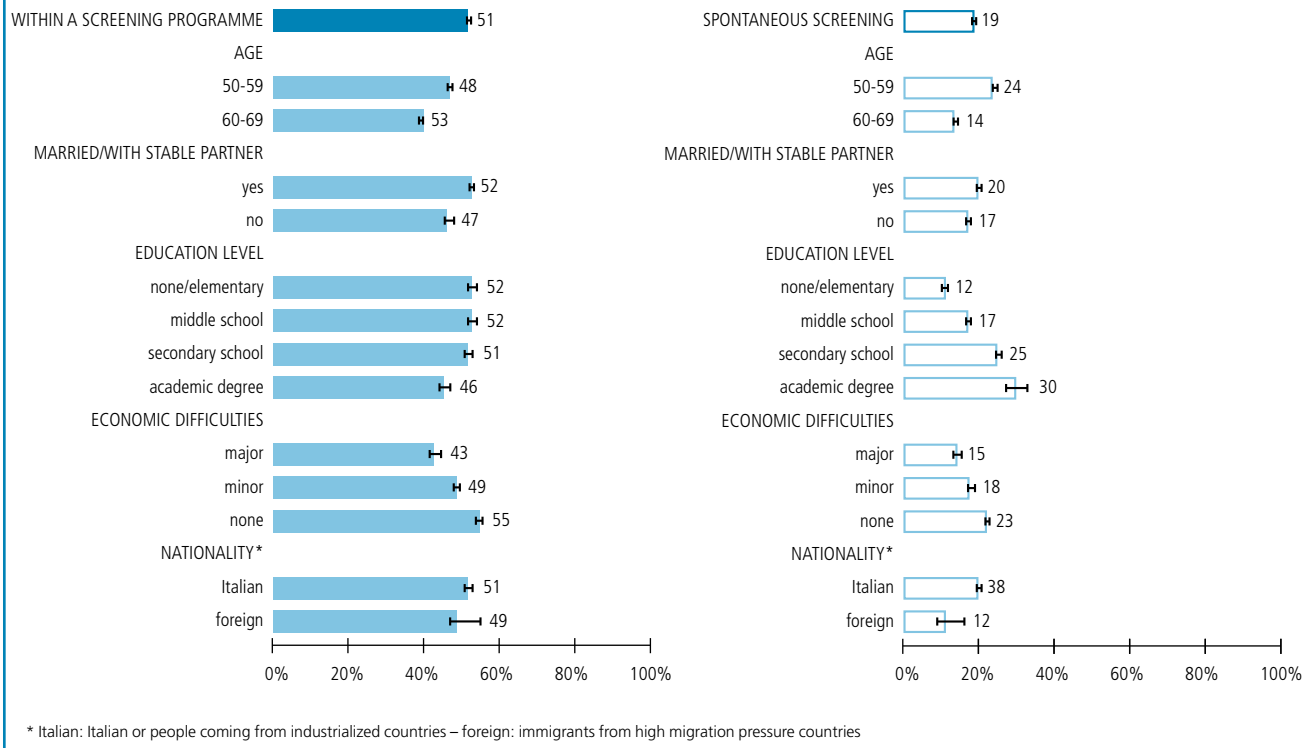

Figure 6. Proportion of 50-69 year-old women who had a mammography in the two years before the interview, within screening programs or spontaneously, according to socio-economic characteristics. Nationwide pooled data, PASSI 2010-2013.
Figura 6. Proporzione di donne di età 50-69 anni che hanno eseguito una mammografia negli ultimi sue anni, all'interno dei programmi di screening o spontaneamente, secondo lo stato socioeconomico. Pool, PASSI 2010-2013.

	Within a screening programme				Spontaneous screening			
	OR	95%CI		p-value	OR	95%CI		p-value
Age								
50-59	1.00				1.00			
60-69	1.18	1.11	1.26	0.000	0.61	0.56	0.66	0.000
Married/with stable partner								
yes	1.00				1.00			
no	0.84	0.78	0.90	0.000	0.83	0.76	0.92	0.000
Education level								
none/elementary	1.00				1.00			
middle school	0.99	0.91	1.08	0.851	1.28	1.13	1.45	0.000
secondary school	0.90	0.82	0.98	0.018	1.93	1.70	2.19	0.000
academic degree	0.72	0.63	0.81	0.000	2.55	2.18	2.98	0.000
Economic difficulties								
major	1.00				1.00			
minor	1.31	1.19	1.44	0.000	1.18	1.03	1.35	0.016
none	1.74	1.58	1.92	0.000	1.30	1.14	1.49	0.000
Nationality								
Italian	1.00				1.00			
foreign	1.14	0.94	1.38	0.171	0.47	0.35	0.64	0.000

Table 2. Logistic regression model to analyze the characteristics associated with breast cancer screening coverage. Nationwide pooled data, PASSI 2010-2013.
Tabella 2. Modello di regressione logistica per la copertura di una mammografia preventiva entro gli ultimi due anni. Pool, PASSI 2010-2013.

spontaneous screening, but was stronger in the northern and central regions. The increase was totally due to tests performed within the organized screening programmes (figure 8, p. 16). Coverage was higher in 60-69 year-olds men, without economic problems, and Italian or coming from industrialized countries (compared to immigrants from high migration pressure countries).

People aged 60-69, with poor education and without economic problems more frequently performed the test within the screening programmes. On the contrary, those with higher education,

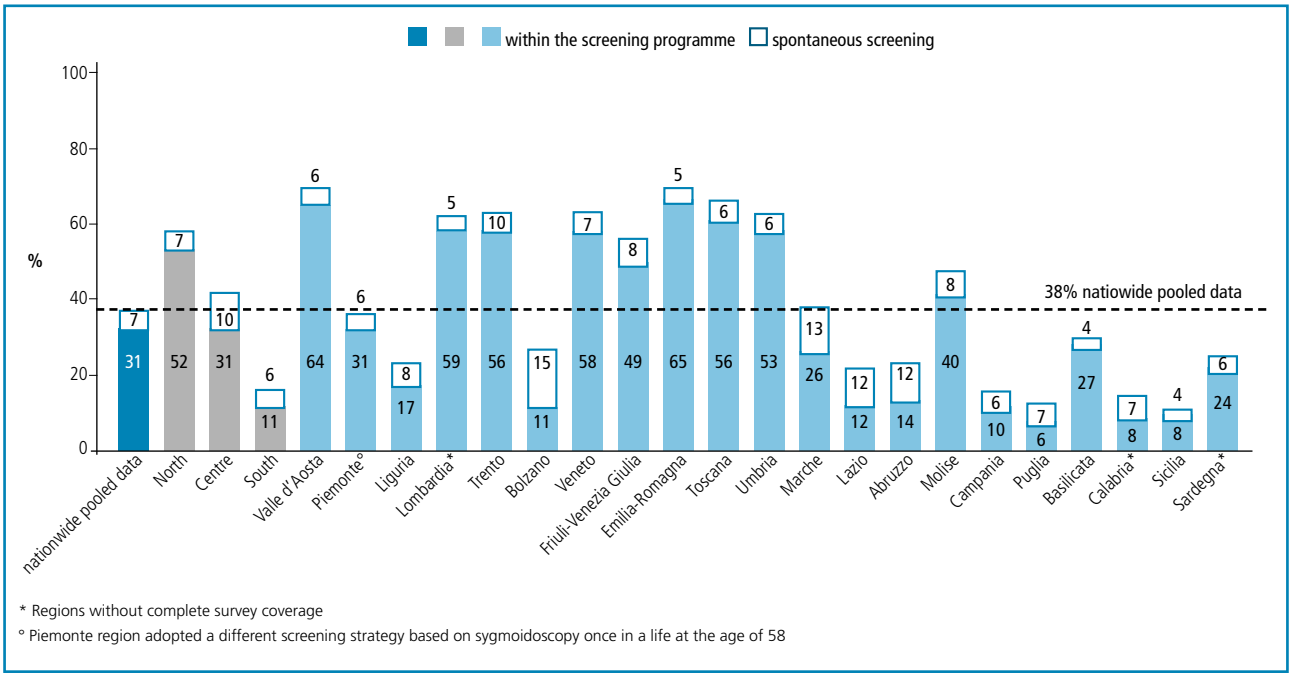

Figure 7. Colorectal cancer screening test coverage. Proportion of 50-69 year-old people who had a faecal occult blood test in the two years before the interview or colonoscopy/sigmoidoscopy in the five years before the interview, within screening programmes or spontaneously, by region. Nationwide pooled data, PASSI 2010-2013.
Figura 7. Copertura dello screening colorettale. Proporzione di persone di età 50-69 anni che hanno eseguito un test SOF (sangue occulto fecale) negli ultimi due anni o una colonscopia negli ultimi cinque anni, all'interno dei programmi di screening o spontaneamente. Pool, PASSI 2010-2013.

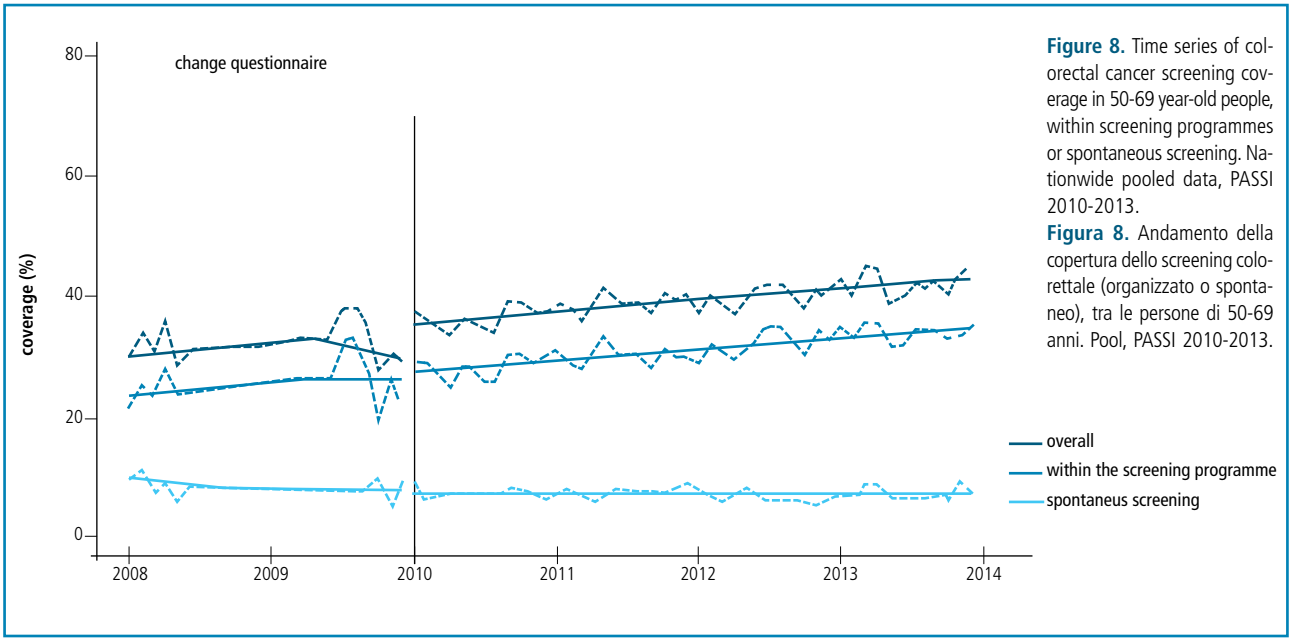

Figure 8. Time series of colorectal cancer screening coverage in 50-69 year-old people, within screening programmes or spontaneous screening. Nationwide pooled data, PASSI 2010-2013.
Figura 8. Andamento della copertura dello screening colorettale (organizzato o spontaneo), tra le persone di 50-69 anni. Pool, PASSI 2010-2013.

Italian nationality or coming from industrialized countries, and without economic problems more frequently performed the test spontaneously (figure 9, table 3). Multivariate analysis confirmed all the associations found (table 3).
In regions with well-implemented colorectal cancer screening programs, i.e., in which at least 75% of the target population declared they had received the invitation letter, coverage is higher than in regions with incomplete programme activation: 59% *vs* 14% (p <0.001). Furthermore, whereas in regions with well-implemented programmes those with a low level of education have higher coverage than people who hold a degree (+8%), the situation is exactly the opposite in regions where programmes are not well-implemented, where people with an academic degree have higher coverage (+24%) than those with a lower level of education. There is also a reduction in the difference in coverage for the economically disadvantaged: 29% *vs* 41%.

CONCLUSIONS

About three fourths of the female target populations are cov-

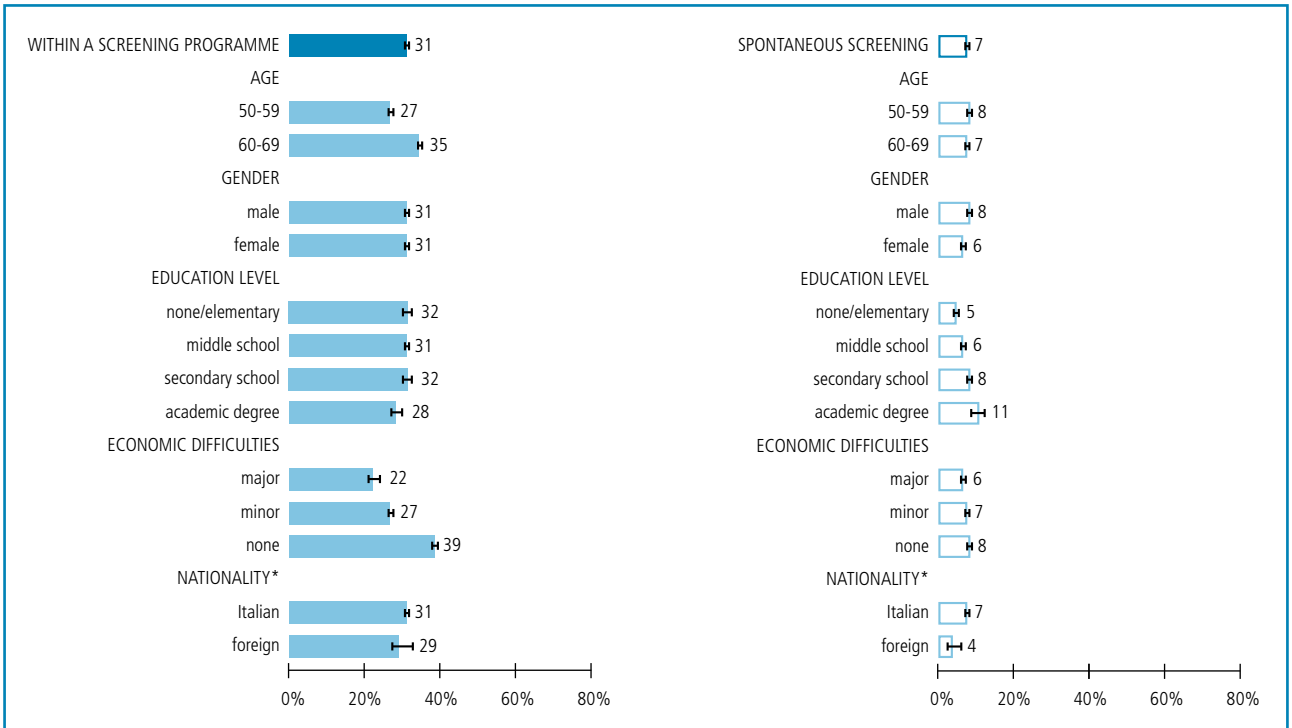

Figure 9. Proportion of 50-69 year-old people who had a foecal occult test in the two years before the interview or a colonoscopy in the five years before the interview, within screening programs or spontaneously, according to socio-economic characteristics. Nationwide pooled data, PASSI 2010-2013.
Figura 9. Proporzione di persone di età 50-60 anni che hanno eseguito un test SOF (sangue occulto fecale) negli ultimi due anni o una colonscopia negli ultimi cinque anni, all'interno dei programmi di screening o spontaneamente, secondo lo stato socioeconomico. Pool, PASSI 2010-2013.

	Within a screening programme				Spontaneous screening			
	OR	95%CI		p-value	OR	95%CI		p-value
Age								
50-59	1.00				1.00			
60-69	1.36	1.30	1.43	0.000	1.00	0.92	1.09	0.996
Gender								
male	1.00				1.00			
female	1.01	0.97	1.05	0.634	0.79	0.73	0.86	0.000
Education level								
none/elementary	1.00				1.00			
middle school	0.98	0.92	1.04	0.527	1.20	1.06	1.36	0.004
secondary school	0.88	0.82	0.94	0.000	1.59	1.40	1.80	0.000
academic degree	0.63	0.58	0.70	0.000	2.17	1.86	2.52	0.000
Economic difficulties								
major	1.00				1.00			
minor	1.37	1.27	1.48	0.000	1.05	0.91	1.20	0.498
none	2.58	2.39	2.78	0.000	1.13	0.99	1.29	0.071
Nationality								
Italian	1.00				1.00			
foreign	1.12	0.94	1.33	0.192	0.48	0.32	0.71	0.000

Table 3. Logistic regression model to analyze the characteristics associated with colorectal cancer screening coverage. Nationwide pooled data, PASSI 2010-2013.
Tabella 3. Modello di regressione logistica per la copertura di un esame preventivo per la diagnosi precoce dei tumori colorettali entro i tempi raccomandati. Pool, PASSI 2010-2013.

ered by cervical and breast cancer screening, although there are significant differences between northern-central and southern Italy. Colorectal cancer screening coverage is still below 40%. The role of spontaneous screening is relevant for female cancer screening, in particular cervical cancer screening, but the presence of well-implemented organized programmes makes it possible to reach high coverage levels and reduce inequalities in the access to evidence-based screening.

Conflicts of interests: none declared

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Breast cancer screening

Glossary/Glossario

Theoretical or potential or nominal extension: percentage of women involved in a screening programme out of the total female population in the 50-69 age range resident in the area covered by an organized screening programme.

Actual extension or Extension of invitations: percentage of women involved in a screening programme out of the total female population in the 50-69 age range who actually received an invitation to screening during the analyzed period.

Compliance with invitation or Crude attendance: number of respondents out of the total number of invited women excluding undelivered invitations.

Adjusted attendance (compliance): number of respondents out of the total number of invited women excluding undelivered invitations and women with a recent mammography (undergone during the last 12 months).

Recall rate: percentage of women recalled for further assessments out of the total number of women attending.

Total detection rate: number of women with screen-detected cancer out of 1,000 screened women.

Benign-malignant ratio: ratio between benign and malignant histological diagnosis, independently of the procedure of diagnosis.

Detection rate for cancers ≤10mm: number of women with screen-detected cancers smaller or equal to 10 mm out of 1,000 screened women.

Percentage of ductal carcinoma in situ: percentage of ductal carcinoma in situ out of the total number of screen-detected cancers.

Italian breast cancer screening survey group:
Gruppo di studio sullo screening mammografico:

Abruzzo: Tamara Agostini, Direzione politiche della salute, Regione Abruzzo, Pescara
Basilicata: Vincenzo Barile, Angelo Sigillito, Sergio Schettini, AO San Carlo, Potenza
Calabria: Liliana Rizzo, Dipartimento Tutela della salute e politiche sanitarie, Regione Calabria, Catanzaro
Campania: Renato Pizzuti, Osservatorio epidemiologico regionale, Assessorato alla sanità, Regione Campania, Napoli
Emilia-Romagna: Carlo Naldoni, Assessorato alle politiche per la salute, Regione Emilia-Romagna, Bologna
Friuli-Venezia Giulia: Nora Coppola, Direzione centrale salute, integrazione socio sanitaria, politiche sociali e famiglia, Regione Friuli-Venezia Giulia, Trieste
Lazio: Alessandra Barca, Lazio sanità, Agenzia di sanità pubblica, Roma
Liguria: Luigina Bonelli, Gabriella Paoli, Istituto nazionale per la ricerca sul cancro, Genova
Lombardia: Direzione generale salute, Regione Lombardia, Milano
Marche: Lucia Di Furia, Servizio salute, Regione Marche, Ancona
Molise: Ospedale Cardarelli, Regione Molise, Campobasso
Piemonte: Nereo Segnan, Centro prevenzione oncologia – CPO Piemonte, Torino
Provincia Autonoma di Bolzano (Alto Adige): Antonio Fanolla, Assessorato alla sanità, Osservatorio epidemiologico, Provincia autonoma di Bolzano, Bolzano
Provincia Autonoma di Trento (Trentino): Sivano Piffer, Giovanni De Pretis, Osservatorio epidemiologico, Azienda provinciale per i servizi sanitari, Trento
Puglia: Vincenzo Pomo, Cinzia Annatea Germinario, Agenzia regionale sanità, Regione Puglia, Bari
Sardegna: Pierina Thanchis, Assessorato dell'igiene e sanità e dell'assistenza sociale, Regione Sardegna, Cagliari
Toscana: Paola Mantellini, Istituto per lo studio e la prevenzione oncologica, Regione Toscana, Firenze
Umbria: Mariadonata Giaimo, Direzione regionale salute, coesione sociale e società della conoscenza, Regione Umbria, Perugia
Valle D'Aosta: Gabriella Furfaro, Servizio dipendenze patologiche, salute mentale e promozione della salute, Aosta
Veneto: Chiara Fedato, Registro tumori del Veneto, Padova

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Mammographic breast cancer screening in Italy: 2011-2012 survey

Lo screening mammografico in Italia: survey 2011-2012

Leonardo Ventura,[1] Daniela Giorgi,[2] Livia Giordano,[3] Alfonso Frigerio,[4] Paola Mantellini,[1] Marco Zappa[1] and the Italian breast cancer screening survey group

[1]Istituto per lo studio e la prevenzione oncologica (ISPO), Firenze
[2]SC Epidemiologia e screening, ASL 2, Lucca
[3]Unità di epidemiologia dei tumori, CPO Piemonte, AOU Città della salute e della scienza, Torino
[4]SSCVD Senologia di screening, AOU Città della salute e della scienza, Torino

Corresponding author
Marco Zappa
m.zappa@ispo.toscana.it

Abstract

This report is an update of a number of papers that have been published by the ONS (Osservatorio nazionale screening, National centre for screening monitoring) since 2002. Data for the survey come from several programmes that may have changed over time, and may have different settings of organization and management.

During 2011-2012, a slight increase in actual extension was recorded compared to the previous years. Currently, all Italian regions have implemented screening programmes. In 2011-2012, almost 5,300,000 women aged 50-69 years were invited to have a screening mammogram, and almost 3,000,000 were screened. While potential extension was 94.4%, actual extension was 73.3%. An imbalance in extension is still present when comparing northern and central Italy, that have an actual screening extension of 94% and 86% respectively, to southern Italy, that has less than 40%.

During the last few years, participation rates have been substantially stable, at around 56% for crude rate, and 60% for adjusted rate, respectively. Women actually screened during 2011-2012 were 38.9% of the national target population. Referral rates of 9.2% at first screening and 4.7% at repeat screening were recorded, showing an increasing trend in recent years. Detection rate was 4.8x1,000 at first screening and 4.4x1,000 at repeat screening, while benign to malignant surgical biopsy ratio for first and repeat screening was 0.2 and 0.1, respectively. Detection rate of small (≤10 mm) invasive cancers was 1.3x1,000 at first screening and 1.4x1,000 at repeat screening; the proportion of in situ carcinomas was 13.3% and 12.0% for first and repeat screening, respectively. Indicators by 5-year age group confirm greater diagnostic problems at younger ages (50-54 years), with higher referral rates and a substantially lower detection rate as compared to older age groups.

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Riassunto

Questo rapporto rappresenta un aggiornamento di precedenti pubblicazioni dell'ONS (Osservatorio nazionale screening) a partire dal 2002. I dati della survey derivano da programmi anche molto diversi tra loro, che possono rispecchiare situazioni differenziate, sia per il livello di esperienza sia per i modelli organizzativi e gestionali.

Nel periodo 2011-2012 si registra un lieve incremento dell'estensione teorica rispetto agli anni precedenti. Allo stato attuale tutte le Regioni italiane hanno implementato programmi di screening.

Nel 2011-2012 quasi 5.300.000 donne di età 50-69 anni sono state invitate a sottoporsi alla mammografia di screening, e circa 3.000.000 sono state esaminate. L'estensione teorica è risultata pari a 94,4%, mentre quella effettiva è stata del 73,3%. Il confronto tra le Regioni del Nord e del Centro con quelle del Sud Italia rivela ancora uno squilibrio nell'estensione dello screening: mentre al

Nord e al Centro l'estensione effettiva è rispettivamente del 94% e dell'86%, nel Sud il valore registrato è inferiore al 40%. Negli ultimi anni i tassi di partecipazione sono rimasti sostanzialmente stabili, intorno al 56% per l'adesione grezza e al 60% per l'adesione corretta. Le donne esaminate nel 2011-2012 sono state il 38,9% della popolazione obiettivo.
Ai primi esami si è registrato un tasso di richiami del 9,2%, del 4,7% agli esami successivi, rivelando un trend in aumento negli ultimi anni. Il tasso di identificazione è risultato pari a 4,8x1.000 ai primi esami e 4,4x1.000 agli esami successivi, mentre il rapporto benigni/maligni (B/M) registrato è stato 0,2 e 0,1 rispettivamente per i primi e per gli esami successivi. Il tasso di identificazione dei tumori invasivi ≤10 mm è risultato pari a 1,3x1.000 ai primi esami e 1,4x1.000 ai successivi; la percentuale di carcinomi duttali in situ è stata del 13,3% e del 12% rispettivamente per i primi esami e per i successivi.
Gli indicatori per fasce di età quinquennali confermano la presenza di maggiori problemi diagnostici nelle donne più giovani (50-54 annni), con tassi di richiamo più elevati e un tasso di identificazione sostanzialmente più basso rispetto ai gruppi di età più anziani.

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INTRODUCTION

In this paper the performances of Italian mammographic screening programmes for the biennium 2011-2012 are reported. Since the early 1990s, GISMa (Gruppo italiano per lo screening mammografico, Italian group for mammography screening) has carried out yearly surveys on the implementation of screening programmes in Italy. Starting from 2002, the results of these surveys have been published in the annual reports of the Osservatorio nazionale screening (ONS, National centre for screening monitoring). Moreover, monitoring, comparisons and evaluation activities have led to the publication of updated operating reports of process indicators for mammography screening.[1] In Italy, activation of mammography screening programmes is regulated by the Ministry of Health's new guidelines.[2] These guidelines recommend that women in the 50-69 year age range be personally invited to undergo mammography every two years, and require a monitoring system and quality evaluation activity for each phase of the programme. Recently, two regions (Emilia-Romagna and Piedmont) expanded the lower age of invitation to 45 (with an annual invitation). Several programmes continue the invitation up to age 74-75 with a two year interval.
This report is an update of previous papers published by the ONS; it is available on the ONS website (www.osservatorionazionalescreening.it).[3-12]

GUIDELINES FOR DATA INTERPRETATION

Data referring to the 2011-2012 activity are reported, stratified by region, 5-year age groups, and, where applicable, by first and repeat screening.
It should be considered that these are summarized data, that may reflect different situations, both as to varying levels of experience and dissimilar settings of organization and management. Therefore, when interpreting these results, it is important to bear in mind some critical aspects inherent to the data:
- not all programmes were able to separate first and repeat screening tests, so for these programmes results were assigned to the round that includes the majority of the screened women;
- a few programmes are not yet able to provide data stratified by five-year age group, so the age-stratified results provided relate to a subset of programmes;
- an important aspect to consider is the uneven completeness of the information provided by different programmes. The result of this is that the denominator of different indicators can vary within each programme.

EXTENSION

With the term "extension" we define the percentage of women involved in a screening programme out of the total female population in the 50-69 age range resident in the area.
For a deeper understanding of screening activity we considered two types of extension:
- potential extension (or programme extension), referring to eligible women residing in areas covered by an organized screening programme;
- actual extension (or invitation extension), related to women who were actually sent an invitation to screening during the analyzed period. Actual extension is calculated according to new rules introduced in 2008, in order to consider undelivered invitations and women excluded before invitation: the former are subtracted from the numerator (115,812 women, in 2011-2012, all Italy) and the latter from the denominator (420,830 women, in 2011-2012, all Italy).

In 2011-2012, the total target population was in excess of 7.5 million, and potential and actual extension were 94.4% and 73.3%, respectively.
For some regions (see **table 1** and **figure1**) a discrepancy is evident between the two figures, indicating a substantial difficulty in inviting all the target population within the protocol interval of two years. In 2011-2012, about three out of four women (73.3%) were actively invited to screening: actual extension showed a slight increase as compared to the previous year (69.1% in 2010). A strong imbalance in the screening offer still persists between northern-central and southern Italy. In the northern and central Italian regions, actual extension is rather good (93.9% in the North and 86.1% in the Centre). In the South the value is much lower (39.6%) although slightly higher compared to 2010 (37.8%). Within the southern area, two small regions (Basilicata and Molise) showed good results, comparable to the Centre-North. On the other hand, a very difficult situation still persists in Abruzzo.
Although some regions show good mean results, a large inter-

Regions	Target population	Theoretical extension (%)	N. of invited women	Actual extension (%)	10th-90th percentile
Valle d'Aosta	16,205	100.0	14,456	89.2	
Piemonte	585,794	100.0	436,849	74.6	49.8-98.0
Liguria	208,177	100.0	127,519	61.3	35.2-119.7
Lombardia	1,121,416	100.0	1,085,618	96.8	83.0-104.6
Trento	64,183	100.0	68,380	106.5	
Bolzano	52,898	100.0	53,866	101.8	
Veneto	525,161	100.0	525,775	100.1	91.7-120.2
Friuli-Venezia Giulia	158,663	100.0	163,341	102.9	
Emilia-Romagna	480,227	100.0	541,826	112.8	99,9-121,7
North	**3,212,721**	**100.0**	**3,017,630**	**93.9**	**69.2-119.7**
Toscana	474,441	100.0	462,567	97.5	93.1-104.8
Umbria	101,751	100.0	104,266	102.5	
Marche	171,086	100.0	152,910	89.4	49.6-114.1
Lazio	712,105	94.9	536,607	75.4	35.,3-115.6
Centre	**1,459,382**	**100.0**	**1,256,350**	**86.1**	**41.6-111.9**
Abruzzo	167,315	47.6	10,622	6.3	8.0-19.1
Molise	38,503	100.0	32,347	84.0	
Campania	674,303	75.8	208,824	31.0	19.4-75.6
Puglia	507,678	100.0	246,351	48.5	
Basilicata	71,226	100.0	63,735	89.5	
Calabria	234,761	94.0	68,585	29.2	17.5-58.5
Sicilia	609,254	75.2	262,131	43.0	21.2-95.3
Sardegna	217,081	100.0	104,673	48.2	31.1-161.9
South	**2,520,119**	**83.2**	**997,268**	**39.6**	**18.0-92.2**
Italy	**7,192,221**	**94.4**	**5,271,248**	**73.3**	**33.2-114.1**

Table 1. Potential and actual extension of Italian mammographic screening programmes. For regions with more than 3 local programmes, the tenth (p10) and the ninetieth (p90) percentiles of actual extension are reported.
Tabella 1. Estensione, teorica e reale, dei programmi di screening mammografico. Per le Regioni che hanno più di tre programmi locali sono forniti il 10° e il 90° percentile dell'estensione reale.

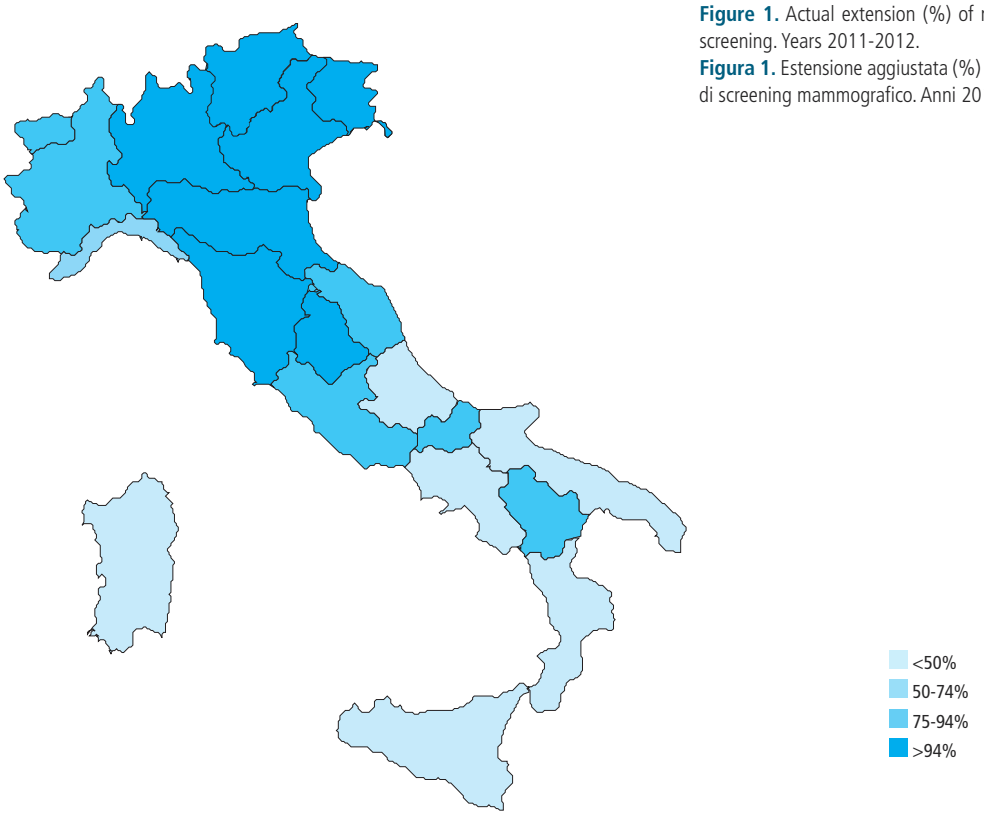

Figure 1. Actual extension (%) of mammography screening. Years 2011-2012.
Figura 1. Estensione aggiustata (%) dei programmi di screening mammografico. Anni 2011-2012.

nal variation is evident (among local programmes within each region). This is the case of Piemonte, Marche, and Lazio, where the gap between the 10th and 90th percentile varies from two to four times. The total gap between the 10th and 90th percentile remained unchanged compared to 2010.
During the last few years, screening invitation for women belonging to the age groups 45-49 and 70-74 has increased. In 2011-2012, out of a total target population of about 4,800,000 in the 45-49 year age group, 7.9% were invited, corresponding to 379,701 women. In women over 70 years of age, considering a target population of 1,671,000 women in the 70-74 year age range, 13.6% were invited to screening, corresponding to 227,387 women.

ATTENDANCE

The number of women invited and responding to the invitation is reported in table 2. Overall, more than 5 million women were invited in the biennium 2011-2012. This was an increase in comparison with the previous biennium when fewer than 5,000,000 were invited. Of all women invited in 2011-2012, almost 3 million attended. In the same table, the mean volumes of activity of each programme for 2011-2012 are also reported. Generally speaking, the volume of activity could be considered as an indirect indicator of the level of experience of the medical and technical personnel involved.

Most Italian regions (with the exception of the province of Trento and Lombardia) did not attain, on a regional mean basis, the desirable level of at least 20,000 examinations per local programme (although several local programmes actually did). In a few cases (Friuli-Venezia Giulia, Umbria, Basilicata, Puglia) data were collected at a regional level, from local programmes of limited sizes, as several programmes work at volumes of activity that are too low (below 10,000 or even 5,000 examinations per year) to assure an appropriate level of experience of the personnel involved. In evaluating these figures, two (opposite) considerations should be taken into account:
- in each programme more than one radiological centre can be present so that the actual number of mammograms is lower;
- in many cases the radiological screening centre also performs mammograms on "spontaneous" patients (i.e., non-invited, self-referred, or clinical patients). In such cases the actual number of mammograms performed could be much higher than it appears from the screening files. In some settings, a low volume of mammograms is justified by the small regional target population (Valle d'Aosta, Molise), but in some regions it is probably due to management choices that should be re-evaluated.

Table 3 shows the crude and adjusted attendance rates for Italy, for Italian macro-areas, and for each region. Screening programme attendance is one of the main indicators for the impact of mammography screening and it is also an indirect indicator

Table 2. Mean volume of activity by region. Years 2011-2012.
Tabella 2. Volume medio di attività per Regione. Anni 2011-2012.

Region	Total active programmes	Invited women	Attendees	Mean number of tests by local unit
Valle d'Aosta	1	14,456	10,124	5,062
Piemonte	9	436,849	274,463	15,248
Liguria	5	127,519	68,309	6,831
Lombardia	15	1,085,618	647,254	21,575
Trento	1	68,380	50,358	25,179
Bolzano	1	53,866	30,698	15,349
Veneto	21	525,775	346,562	8,251
Friuli-Venezia Giulia	1	163,341	95,035	47,518
Emilia-Romagna	11	541,826	352,344	16,016
North	**65**	**3,017,630**	**1,875,147**	**14,424**
Toscana	12	462,567	315,781	13,158
Umbria	1	104,266	69,026	34,513
Marche	5	152,910	76,358	7,636
Lazio	12	536,607	213,936	8,914
Centre	**30**	**1,256,350**	**675,101**	**11,252**
Abruzzo	2	10,622	5,086	1,272
Molise	1	32,347	15,593	7,797
Campania	12	208,824	59,654	2,486
Puglia	1	246,351	131,000	65,500
Basilicata	1	63,735	34,087	17,044
Calabria	7	68,585	27,303	1,950
Sicilia	9	262,131	91,002	5,056
Sardegna	8	104,673	45,356	2,835
South	**41**	**997,268**	**409,081**	**4,989**
Italy	**136**	**5,271,248**	**2,959,329**	**10,880**

Region	Crude attendance (%)	10th-90th percentile	Adjusted attendance (%)	10th-90th percentile
Valle d'Aosta	70.0		70.7	
Piemonte	62.8	53.3-75.3	64.8	56.5-76.4
Liguria	53.6	46.1-63.8	63.7	58.7-75.4
Lombardia	59.6	50.3-68.1	68.6	57.8-77.0
Trento	73.6		77.1	
Bolzano	57.0		57.9	
Veneto	65.9	53.3-78.4	75.2	63.7-83.1
Friuli-Venezia Giulia	58.2		58.2	
Emilia-Romagna	65.0	56.6-77.9	71.0	62.2-78.9
North	**62.1**	**53.0-77.1**	**68.7**	**58.7-82.2**
Toscana	68.3	58.4-75.4	72.6	64.2-80.1
Umbria	66.2		69.6	
Marche	49.9	44.9-57.7	50.7	46.2-57.8
Lazio	39.9	30.3-56.4	43.8	33.6-61.4
Centre	**53.7**	**35.9-74.3**	**57.5**	**39.6-78.3**
Abruzzo	47.9	37.6-53.0	48.2	37.6-53.8
Molise	48.2		48.5	
Campania	28.6	19.1-72.5	31.0	19.2-72.5
Puglia	53.2		55.9	
Basilicata	53.5		53.7	
Calabria	39.8	23.2-77.0	40.7	23.4-79.5
Sicilia	34.7	19.6-49.7	35.1	20.2-49.7
Sardegna	43.3	35.1-54.6	46.4	37.2-58.9
South	**41.0**	**20.7-54.6**	**42.7**	**21.0-58.9**
Italy	**56.1**	**30.3-74.2**	**60.9**	**33.5-80.1**

Table 3. Crude and adjusted attendance rates, with tenth and ninetieth percentiles (%). Years 2011-2012.
Tabella 3. Adesione, grezza e aggiustata, con il 10° e 90° percentile. Anni 2011-2012.

of perceived quality of the programme by the invited women. Adjusted attendance rate (where women reporting a recent mammogram outside the programme are excluded from the denominator) is more representative of the real response to invitation of the target population. Currently, GISMa recommended standards are: ≥50% (acceptable) and ≥70% (desirable) for crude attendance; ≥60% and ≥75% for adjusted attendance.

In the years 2011-2012, crude and adjusted attendance rates were 56.1% and 60.9%, respectively, showing a slight improvement compared to 2010. As already noted in the previous years, in 2011-2012 participation rates were substantially stable, placing the 10th and 90th percentiles close to the values recorded during the year 2010 both for crude rate (32.1%-74.0%) and adjusted rate (33.3%-80.0%). Furthermore, it is encouraging that with an increased extension of invitations, the attendance rate remained stable.

A large variance of participation exists both among regions and within each region. It is worth noting that in the large and well performing regions of the Centre-North (namely Veneto, Emilia-Romagna, Lombardia, Piemonte, and Toscana) we can observe a difference ranging from 15 to 25 percentage points between the tenth and the ninetieth percentiles in the distribution of the programmes' compliance rate. This means there is large room for improvement.

Women screened during 2011-2012 were 38.9% of the national target population. A strong imbalance still persists between the North, Centre, and South of Italy, with 53.1%, 44.1%, and 16%, respectively.

A decreasing trend towards the South of Italy is evident for these parameters. All regions showing attendance rates below the minimal standards are concentrated in the South and Islands areas. In 2011-2012, 8 out of 21 regions (more than one third of the total) were still below the minimum standards for crude attendance. Only the province of Trento and Valle d'Aosta were above the desirable level for these parameters.

Adjusted attendance rates reveal problems of completeness of data registration. It is important to consider that this parameter is often underestimated, as previously mentioned, since many programmes are unable to provide information about

Age	Crude attendance (%)	Adjusted attendance (%)
50-54	52.9	59.1
55-59	57.8	62.7
60-64	60.2	64.5
65-69	57.9	61.9
Total 50-69	**56.1**	**60.9**

Table 4. Crude and adjusted attendance rates (%) by 5-year age groups. Years 2011-2012.
Tabella 4. Adesione, grezza e aggiustata, per fasce d'età quinquennali. Anni 2011-2012.

women excluded due to recent mammograms. Table 4 reports attendance rates by 5-year age group. It is interesting to note that the highest attendance is recorded among women over age 54, i.e., in women invited to screening for several years; consequently they are more likely to participate, as they are aware of the efficiency and quality of the diagnostic procedures within an organized screening programme.

DIAGNOSTIC INDICATORS

Referral/recall rates

Referral/recall rate for further assessment is the main indicator of first level screening specificity. It indicates the proportion of screened women referred/recalled for diagnostic assessments. This value needs to be reasonably low, in order to limit negative psychological impact (anxiety), invasive procedures (cytology, core- or surgical biopsies), as well as costs. Recommended GISMa standards are: <7% (acceptable) and <5% (desirable) at first screening; <5% (acceptable) and <3% (desirable) at repeat screening. Table 5 shows crude referral rate, for first and repeat screening tests.

Considering first tests, rates beyond the maximum acceptable standard for this indicator persisted in 2011-2012; moreover, as already observed in previous surveys, an increasing trend was evident: 7.5% in 2008, 8.0% in 2009, 8.8% in 2010, and 9.2% in 2011-2012. Excessively high rates were recorded both nationally and (often) regionally: only three regions reported a value within the acceptable standard of 7% and five regions exceeded 10%.

A more detailed analysis shows that even at the individual, local programme level, minimum standards were often exceeded: only 10% of local programmes were within the desirable standard, while 10% of the programmes had unacceptably high referral rates (>17%). Again, a large variability exists within each region.

Repeat tests show better results: the national indicator was still within the acceptable standard and was rather stable in comparison with the previous year (4.7 % in 2011-2012 *vs* 4.6% in 2009-2010). Even variability within each region (at least in absolute numbers) seemed to become more limited, although in some cases intra-regional variability was still very high.

It is worth noting that the recall rate at repeat screening tends to be higher in the South as compared to Centre and North, even though the detection rates (see below) go in the opposite direction (higher in the North as compared to the South): as a consequence, positive predictive values are much lower in the South as compared to the North of Italy.

Detection rates

Table 6 reports the crude detection rates (DR) of carcinomas (per 1,000 screened women), the crude detection rates of cancers ≤10 mm, the benign to malignant surgery ratio (B/M), and the proportion of ductal carcinomas in situ at first and at

Table 5. Total crude recall rates (%) by region, first and repeat screening. Years 2011-2012.
Tabella 5. Tasso di richiami totale grezzo per Regione, primi esami e successivi. Anni 2011-2012.

Region	First exams		Repeat exams	
	recall rate (%)	10th-90th percentile	recall rate (%)	10th-90th percentile
Valle d'Aosta	8.9		4.9	
Piemonte	6.6	3.3-8.8	3.3	1.8-5.0
Liguria	10.3	5.3-15.0	6.0	1.5-8.7
Lombardia	8.9	6.5-13.7	4.6	3.3-7.2
Trento	8.3		3.2	
Bolzano	7.8		3.6	
Veneto	9.4	5.5-13.1	4.0	3.0-5.2
Friuli-Venezia Giulia	15.1		5.1	
Emilia-Romagna	9.1	5.5-13.1	3.9	2.2-5.2
North	**9.1**	**5.5-13.7**	**4.1**	**2.6-6.4**
Toscana	12.7	8.3-19.5	6.1	3.6-11.8
Umbria	8.4		3.2	
Marche	17.4	4.9-22.5	8.6	2.0-20.3
Lazio	7.6	5.8-15.7	5.1	2.6-12.3
Centre	**9.9**	**6.3-22.4**	**5.8**	**2.8-12.6**
Abruzzo	13.8	10.2-37.3	5.7	
Molise	3.4		2.8	
Campania	7.1	1.4-27.4	8.6	2.5-13.3
Puglia	NA		5.6	
Basilicata	0.0		7.1	
Calabria	9.9	2.8-22.3	8.6	3.2-25.0
Sicilia	6.9	1.6-16.4	4.8	3.4-4.8
Sardegna	9.0	4.0-21.5	5.2	0.0-11.1
South	**8.2**	**2.2-21.9**	**6.0**	**2.5-12.5**
Italy	**9.2**	**4.9-17.3**	**4.7**	**2.6-11.1**

Region	First exams				Repeat exams			
	total detection rate (x 1,000 screened)	B/M ratio	cancer ≤10 mm detection rate (x 1,000 screened)	ductal carcinoma in situ (% of all malignancies)	total detection rate (x 1,000 screened)	B/M ratio	cancer ≤10 mm detection rate (x 1,000 screened)	ductal carcinoma in situ (% of all malignancies)
Valle d'Aosta	3.7	0.0	1.2	33.3	5.5	0.1	1.8	11.8
Piemonte	7.3	0.2	1.3	17.1	5.0	0.1	1.4	14.2
Liguria	3.0	0.2	1.0	7.8	3.6	0.1	1.6	9.6
Lombardia	4.3	0.2	1.4	12.8	4.1	0.1	1.4	10.0
Trento	5.7	0.2	1.3	10.0	4.9	0.1	1.6	16.9
Bolzano	5.6	0.0	1.1	25.0	3.8	0.0	1.2	8.5
Veneto	5.3	0.3	1.4	14.2	4.9	0.1	1.5	10.8
Friuli-Venezia Giulia	8.2	0.1	2.2	15.7	5.1	0.1	1.6	13.6
Emilia-Romagna	7.6	0.2	1.9	24.3	5.6	0.1	1.9	16.8
North	**5.3**	**0.2**	**1.4**	**15.9**	**4.8**	**0.1**	**1.5**	**12.9**
Toscana	5.4	0.3	1.6	14.8	5.0	0.1	1.8	13.1
Umbria	4.2	0.1	0.7	19.6	4.0	0.0	1.4	15.7
Marche	5.0	0.1	1.3	12.2	3.3	0.2	0.9	12.4
Lazio	3.3	0.1	0.6	3.9	3.5	0.1	0.9	3.0
Centre	**4.2**	**0.2**	**1.0**	**10.3**	**4.3**	**0.1**	**1.4**	**11.0**
Abruzzo	6.9	0.0	3.0	28.0	0.0		0.0	
Molise	2.7	0.0	1.3	25.0	2.5	0.2	0.8	23.1
Campania	5.2	0.5	2.5	4.4	2.7	0.2	0.7	1.6
Puglia					3.0	0.1	0.2	6.9
Basilicata	7.2	0.3	2.1	0.0	3.7	0.2	1.0	0.0
Calabria	1.5	0.2	0.2	0.0	1.8	0.2	0.3	21.4
Sicilia	4.5	0.2	0.9	6.4	2.6	0.1	0.4	3.0
Sardegna	3.9	0.1	0.7	4.2	1.5	0.0	0.1	8.7
South	**4.1**	**0.2**	**1.1**	**6.4**	**2.7**	**0.1**	**0.3**	**6.3**
Italy	**4.8**	**0.2**	**1.3**	**13.3**	**4.4**	**0.1**	**1.4**	**12.0**

Table 6. Diagnostic indicators, first and repeat screening. Years 2011-2012.
Tabella 6. Indicatori diagnostici, primi esami e successivi. Anni 2011-2012.

subsequent tests. The first two indicators are the most commonly referred to indicators of a programme's diagnostic sensitivity (i.e., the capability of a programme to detect cancers and to detect cancer at an early stage). These indicators should be evaluated compared to expected incidence rate in the screened population, in order to take into consideration the variability of the baseline risk for breast cancer.

In the years 2011-2012, cancer DRs were 4.8/1,000 and 4.4/1,000 at first and repeat test, respectively, both slightly lower than in 2010 (5.3 and 4.6 for first and repeat tests, respectively). This decrease is mostly accounted for by the lower DRs observed in the South of Italy as compared to 2010. Table 7 (p. 28) reports DRs subdivided by 5-year age groups. As expected, DRs tended to increase in older age either at first or at repeat tests.

DRs of small invasive (≤10 mm) carcinomas were substantially stable as compared to 2010 (1.4/1,000 and 1.5/1,000 for first and repeat tests, respectively). At repeat tests, DRs of carcinomas ≤10 mm in southern Italy were very low. The possibility of incomplete registration of data in the programmes from the South might be considered. Again (see **table 7**) we observed an increase in DRs in older age groups.

Benign/malignant (B/M) surgical biopsy ratio

The B/M ratio is determined on women referred to surgery; it indicates the ratio of benign to malignant (B/M) pathology outcomes. It is an optimal indicator of the diagnostic specificity of the programme assessment phase. It should be as low as possible.

Recommended GISMa standards are: ≤1(acceptable) and ≤0.5 (desirable) at first screening; ≤0.5 (acceptable) and ≤0.25 (desirable) at repeat screening.

Results for this indicator are very satisfactory, well within the desirable standards both at first and subsequent tests (0.2 and 0.1, respectively); the results are quite homogeneous throughout Italy (see **table 6**).

Proportion of carcinomas in situ

It indicates the proportion of ductal carcinomas in situ every 100 total detected cancers, with histological diagnosis.

Recommended GISMa standards are 10% (acceptable) and 10%-20% (desirable) at any screening round.

Overall the results of 2011-2012 are in the desirable range both at first and repeat tests (13.3% and 12.0%, respectively). However, five regions reported values higher than 20% at first

Age	First exams					Repeat exams				
	recall rate (%)	total detection rate (x 1,000 screened)	B/M ratio	cancers ≤10 mm detection rate	ductal carcinoma in situ (% of all malignancies)	recall rate (%)	total detection rate (x 1,000 screened)	B/M ratio	cancers ≤10 mm detection rate	ductal carcinoma in situ (% of all malignancies)
50-54	9.6	4.1	0.3	1.0	15.6	5.6	3.0	0.2	0.8	16.0
55-59	8.6	4.8	0.2	1.2	14.6	4.6	3.6	0.1	1.1	13.4
60-64	8.3	6.2	0.1	1.9	7.6	4.3	4.9	0.1	1.5	11.2
65-69	8.4	8.0	0.1	2.2	10.3	4.3	6.0	0.1	2.0	10.5
Total 50-69	**9.2**	**4.8**	**0.2**	**1.3**	**13.3**	**4.7**	**4.4**	**0.1**	**1.4**	**12.0**

Table 7. Diagnostic indicators by age group, first and repeat screening. Years 2011-2012.
Tabella 7. Indicatori diagnostici per classe d'età, primi esami e successivi. Anni 2011-2012.

screening and two at subsequent screening, but this data may also reflect the relatively small number of cases involved. The proportion of carcinomas in situ tends to be inversely correlated to age (see table 7).

CONCLUSIONS

This paper presents the performance results of Italian organized mammographic screening programmes in the biennium 2011-2012. During that period, almost 75% of the national target population was actively invited by organized screening programmes, with a slight but constant increase compared to previous years. Unfortunately, a strong imbalance in mammography screening offer still persists in Italy between the North-Centre and the South of the country: while almost 90% of the target population was invited in the northern and central areas, only 40% of 50-69 year-old women resident in the South were invited. In the biennium 2011-2012, there were only small improvements in this critical issue.

The mean national value of attendance is satisfactory (at least comparing mammographic screening to cervical and colorectal cancer screening), although a decreasing trend from North to South is clearly evident. The combination of these two parameters paints an alarming picture for the South of Italy, for which we recorded only a small number of implemented programmes and low participation. A low number of invitations and low participation rates result in too few women screened and poor performance, as reflected by the indicator adopted by the Health Ministry to judge screening programme performance. To some extent, these data may reflect a different attitude towards prevention in the North and South, as shown by other national studies, such as Istat's Multiscopo and the PASSI survey.

In the biennium 2011-2012, our results confirm that screening coverage of the target population in Italy was steady, at a low 38.9%, suggesting the need for further investments and efforts. However, this rate is likely to underestimate the real situation, as our survey does not include women undergoing spontaneous screening, which in some programmes may account for a substantial proportion of the target population.

Though considering limitations included in the data (as previously indicated), overall the indicators recorded by Italian programmes in 2011-2012 appear rather good and comply at a satisfactory level with recommended national standards. The only critical diagnostic indicator is the recall rate, which has shown an increase over the past few years, with a consequent problem of testing overload for health facilities and stress for patients undergoing further assessments. To some extent, data on recall rates can suggest potential critical aspects for specificity in many programmes. They likely reflect an attitude that might be described as "defensive medicine", where diagnosticians tend to protect themselves from potential litigation. The diffusion of digital mammography may also have played a role, and it is worth noting that the increase in referral rate concerns in particular the first round tests, where previous mammograms are not available. This high recall rate apparently does not produce a high rate of unnecessary surgery, as demonstrated by the good performance of the B/M ratio.

A number of values exceeding acceptable standards may be explained by the scantiness of cases or by partial data registration. In any case, further opportunities for discussing observed difficulties and systematic interventions for quality assurance of the diagnostic procedures are required in the near future, especially in the South of Italy, where sensitivity indicators (such as total detection rate and detection of cancers ≤10mm) did not attain satisfactory values.

One of the main controversies in cancer screening is related to overdiagnosis. Usually overdiagnosis refers to detection of in situ lesions, part of which would never become clinically apparent without screening. The good results recorded for the percentage of in situ cancers during the years 2011-2012 suggest that the problem of overdiagnosis is contained.

Conflicts of interests: none declared

Data for the ONS/GISMa surveys for the year 2011-2012 was provided by:
Hanno fornito i dati per la survey ONS/GISMa 2011-2012:

Valle D'Aosta: L. Giordano
Piemonte: L. Giordano, L. Orione
Lombardia: F. Sambo, S. G. Domenighini, L. Cecconami, G. Magenes, M. Ignone, R. Lucchini, D. Cereda, E. Anghinoni, G. Marazza, A. Ilardo, M. Dal Soldà, S. Gotti, L. Tessandri, M. Crisetig, R. Cecchetti, A. Silvestri, M. Montanelli, G. Gola
Alto Adige: A. Fanolla
Trentino: M. Pellegrini, D. Bernardi, M. Gentilini
Veneto: C. Fedato
Friuli-Venezia Giulia: A. Franzo
Liguria: A. Franco, B. Scanu, L. Garibotto, I. Valle, M. Orlando, F. Maddalo
Emilia-Romagna: P. Baldazzi, C. Imolesi, D. Canuti, G. Benea, F. Falcini, L. Caprara, R. Negri, M. Zatelli, G. Gatti, M. Serafini, B. Vitali, A. Cattani, G. Monticelli, C. Debora
Toscana: E. Paci, P. Mantellini, F. D'Elia, F. Mirri, R, Capecchi, P. Piccini, R. Rosati, C. Maffei, D. Giorgi, P. Vivani, L. Del Chicca, M. Rapanà, L. Adbelghani, R. Turillazzi, A.A. Scarfantoni
Umbria: S. Prandini
Marche: A. Vaccaro, D. Cimini, B. Finocchi, M.G. Volpini, C. Ragaglia, A. Santone
Lazio: P. Bellardini, G. Baldi, L. Martufi, D. Baiocchi, R. Fulgenzi, F. Odoardi, S. Marzani, E. Rossi, G. Nicodemo, F. Puddu, M.G. Acampora, S. Sgricia, M. Arcara, M. Mammola, S. Brezzi, D. Boninsegna
Abruzzo: M. Muzi, M. Brucchi
Molise: F. Carrozza
Campania: C. Casullo, A. Frieri, M.P. Aversano, G. Capone, R. Papa, E. Barretta, A. Esposito, C. Maione, U. Scala
Puglia: C. Germinario
Basilicata: V. Barile
Calabria: E. Bova, A. Giorno, T. Landro, A. Bisbano, M.P. Montesi, M. Viola, M.B. Grasso
Sicilia: S. Malignaggi, R. Candura, P.M. Santino, R. Scillieri, L. Costa, G. La Perna
Sardegna: S. Tilocca, U. Stochino, A. Onnis, M.A. Atzori, M. Piga, O. Frongia, F.S. Congiu, L. Paoni

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[1]Unità di epidemiologia dei tumori, CPO Piemonte, AOU Città della salute e della scienza, Torino
[2]SC Epidemiologia e screening, ASL 2, Lucca
[3]Istituto per lo studio e la prevenzione oncologica (ISPO), Firenze

Corresponding author
Livia Giordano
livia.giordano@cpo.it

Breast cancer screening in Italy: evaluating key performance indicators for time trends and activity volumes

Lo screening mammografico in Italia: valutazione degli indicatori di performance per trend temporali e volumi di attività

Livia Giordano,[1] Roberta Castagno,[1] Daniela Giorgi,[2] Cristiano Piccinelli,[1] Leonardo Ventura,[3] Nereo Segnan,[1] Marco Zappa[3]

Abstract

Together with the National centre for screening monitoring (ONS), GISMa supports annual collection of data on national breast screening activities. Aggregated data on implementation and performance are gathered through a standardized form to calculate process and impact indicators. Analyzed data belong to 153 local programmes in the period 2006-2011 (2006-2012 for participation rate only).

During the whole period, Italian crude participation rate exceeded GISMa's acceptable standard (50%), even though a higher participation in northern and central Italy compared to southern Italy and Islands was observed. Time trend analysis of diagnostic indicators confirmed in 2011 an adequate quality of breast screening performance, especially at subsequent screening. Recall rate at initial screening did not reach the acceptable standard (<7%) and rose slightly over the period. On the contrary, a good performance was achieved at subsequent screening. The same trend was followed by the overall detection rate and positive predictive value. They both showed a progressive reduction (from 6.2‰ in 2006 to 4.5‰ in 2011 for DR and from 8.0% in 2006 to 5.2% in 2011 for PPV, respectively) at initial screening and a good, stable trend at subsequent screening.

Activity volume analysis shows that in programmes with greater activity (test/year ≥10,000) RR at both initial and subsequent screening has a better performance. This is also true for DR and PPV where programmes with high volumes of activity do better, especially when compared with those that interpret fewer than 5,000 mammograms per year.

In spite of a few limits, these results are reassuring, and they reward the efforts made by screening professionals. It is therefore important to continue to monitor screening indicators and suggest, test, and evaluate new strategies for continuous improvement.

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Keywords: breast cancer screening, time trends, activity volumes, process indicators, Italy

Riassunto

Il GISMa (Gruppo italiano screening mammografico) insieme con l'Osservatorio nazionale screening (OMNS) promuove ogni anno la raccolta sistematica dei dati sull'attività dei programmi organizzati di screening mammografico in Italia. I dati aggregati relativi all'implementazione e alla performance dei programmi vengono raccolti e registrati su un apposito questionario standard e utilizzati per calcolare indicatori di processo e precoci di impatto. I dati analizzati si riferiscono a 153 programmi locali attivi nel periodo 2006-2011 (2006-2012 solo per la parte relativa alla partecipazione).

L'indagine mostra che il tasso di partecipazione grezza raggiunge e mantiene nel tempo lo standard

accettabile GISMa del 50%, anche se si osservano livelli più alti di partecipazione al Nord e al Centro Italia rispetto al Sud/Isole. L'analisi temporale degli indicatori considerati (tasso totale di identificazione dei tumori, tasso di richiami in secondo livello e valore predittivo positivo) mostra una buona qualità. Il tasso di richiami si mantiene adeguato nel tempo soprattutto nei passaggi successivi (anche se sta avvicinandosi sempre di più alla soglia minima raccomandata) mentre, per i primi esami, non raggiunge lo standard accettabile (<7%).
Buoni andamenti si osservano anche per il tasso totale di identificazione dei tumori e dal valore predittivo positivo. Entrambi mostrano una riduzione progressiva nel tempo ai primi esami (passando dal 6.2‰ nel 2006 al 4.5‰ nel 2011 e dall'8.0% nel 2006 al 5.2% nel 2011, rispettivamente) e un andamento buono e stabile agli esami successivi.
L'analisi per volumi di attività indica che programmi con volumi più ampi (>10.000 test/anno) presentano indicatori migliori rispetto a programmi in cui l'attività è più bassa.
Nonostante alcuni limiti dell'analisi, i risultati raggiunti sono rassicuranti e ricompensano gli sforzi intrapresi da tutti gli operatori dello screening in questi anni. Resta comunque importante continuare il monitoraggio degli indicatori dello screening mammografico e valutare nuove strategie per un continuo miglioramento delle prestazioni dei programmi organizzati di screening in Italia.

Epidemiol Prev 2015; 39(3) Suppl 1: 30-39)
Parole chiave: screening mammografico, trend temporali, volumi di attività, indicatori di processo, Italia

INTRODUCTION

To obtain projected benefits and minimize negative outcomes, breast cancer screening programmes should be implemented with an organized, population-based approach, with quality assurance at all appropriate levels, and in accordance with *European guidelines for quality assurance in breast cancer screening and diagnosis*.[1] According to the IARC *Handbook of cancer prevention*[2] an organized screening programme requires the following six characteristics: a policy specifying target population, screening methods and interval; a defined target population; a team responsible for overseeing screening centres; a clear decision structure and responsibility for healthcare management; a quality assurance system utilizing relevant data; and monitoring of cancer occurrence in the target population.
The highest level of programme organization of population-based screening requires that all persons eligible for screening be identified and personally invited to attend a screening examination in each round of screening[3] and followed for the entire screening pathway.
Since its establishment in 1990, the Italian group for mammography screening (GISMa) has represented a cornerstone in monitoring and performance evaluation of organized breast screening programmes in Italy. Together with the National centre for screening monitoring (ONS), created in 2002 by the Italian Ministry of Health with the aim to monitor and promote screening programmes nationwide, GISMa supports the annual collection of data on national breast screening activities. Aggregated data on implementation and performance are gathered through a standardized form to calculate process and impact indicators which have been agreed on a national level.[4] Results are also compared with European standards.[1]
Despite some initial difficulties, annual surveys have improved over the years, thanks to the collaborative efforts of all screening professionals, who work together to reduce and overcoming heterogeneity in screening implementation, organization, and management among Italian areas, trying to ensure higher levels of standardization and data completeness.
The main aim of this work is to assess the time trend for selected process and impact indicators – participation rate, recall rate, overall detection rate and positive predictive value – in the period 2006-2011 (2006-2012 for participation only).
The same parameters are also analyzed and cross-checked by programme activity volumes.
This paper is an update of a previous report, published in the 2012 edition of the annual ONS Report.[5]

METHODS

In Italy there is no national breast cancer screening programme, but rather a number of regionally-coordinated local initiatives. All 20 regions work under the umbrella of ONS, which is responsible, with the GISMa group, for data collection and monitoring. Data are collected annually by means of a structured questionnaire, in a computerized form, which allows indicators to be calculated with automatic formulas. The questionnaire refers to the previous year's activity and is stratified by age group. It is sent out yearly by the ONS to the referent for data collection in every region. The regional referent then delivers the questionnaire to the referents of every programme in the region.
The filled-in questionnaires are returned from the local programmes to the Regional Centre and, subsequently, if approved by regional referents, to the National Centre. Logical and epidemiological checks are performed either at the regional or at the national level. In particular, if data are logically impossible or epidemiologically improbable (in comparison to historical trends, to the performances of other programmes in the area, etc.), a specific check on that information is carried out.
Questionnaires from 168 organized programmes (running for the entire 2006-2012 period or only a part of it) were collected. After a further check for completeness and consistency, 15 programmes with <100 tests per year and those providing incomplete/inconsistent information were excluded. A total of 153 questionnaires were analyzed: 68 for the North (44.4%), 49 for the Centre (32.0%), and 36 for the South (23.5%).

Table 1 illustrates the number of tests, recalled women, and screen-detected malignant cancers by the three Italian macro-areas and time period. Analysis was performed for the following indicators:

- Participation rate, PR (%):
- **overall crude PR**: the number of women who have a screening test as a proportion of all women who are invited to attend for screening;
- **adjusted PR**: the number of women who have a screening test as a proportion of all women who are invited to attend for screening, excluding from the denominator women with a recent (<12 months) mammogram outside the programme;
- Recall rate, RR (%): the number of women recalled for further assessments as a proportion of all women who had a screening examination;
- Detection rate, DR (‰): the number of all malignant cancers detected every 1,000 screened women;
- Positive predictive value, PPV (%): the ratio of lesions that are truly positive to those that test positive.

These parameters were examined and cross-checked by time trends for Italy and for the standard target population (50-69) as a whole, by 5 year age-classes (50-54; 55-59; 60-64; 65-69) and by geographical macro-areas (North, Centre, South-Islands). For RR, DR, and PPV only, data were also disaggregated by screening step: initial screening, referring to women undergoing screening for the first time, and subsequent screening, referring to women who previously underwent screening tests (for programmes implemented during the last two years this category is not yet available).

These last indicators were also associated with the volume of activity of the programmes, calculated as the number of tests (both at initial and subsequent rounds) performed by the programmes yearly. Four classes of volume were considered: <5,000; 5,000-9,999; 10,000-14,999, ≥15,000.

RESULTS

Time trends analysis

Participation rate (PR)

For cancer screening programmes to bring about reductions in mortality, a substantial proportion of the population must participate. Programmes with low uptake can be ineffective and can promote inequalities in health service. For these reasons, PR is a key parameter to assess both the impact of the screening programme and its acceptability among the target population.

However, evaluation and interpretation of results may be affected by contextual aspects (e.g., opportunistic screening activities, level of breast cancer awareness, socio-demographic characteristics of the target population) and other organizational factors (e.g., availability and accessibility of the services for diagnosis and treatment, invitation system and communication strategies used by the programme to increase informed participation). European guidelines consider 50% an acceptable level of PR and indicate 70% as a desirable standard. In the considered period, the overall Italian crude PR always exceeded the minimum benchmark (figure 1) although it never reached the optimal one.

Nevertheless, attendance rates by geographical macro-areas confirmed, in 2012, a higher participation in northern and central Italy compared to the South-Islands, where rates were still inadequate and did not reach the recommended minimum. Figure 2 shows the adjusted participation rate by 5-year age classes during the same 2006-2012 period. For the whole period, women of the intermediate classes had higher attendance rates compared to younger and older women and by far the highest participation was recorded for women who belong to the 60-64 age group.

Recall rate (RR), detection rate (DR), positive predictive value (PPV)

Although randomized controlled trials have shown that screen-

			2006	2007	2008	2009	2010	2011
North	number of performed tests	initial screening	174,640	175,280	176,375	161,885	164,838	156,173
		subsequent screening	546,044	608,385	624,087	649,449	712,159	765,994
	number of women recalled for further assessments	initial screening	13,719	13,628	13,662	12,598	14,209	13,954
		subsequent screening	21,648	24,423	25,558	25,799	29,263	31,524
	number of screen-detected malignant cancers	initial screening	1,262	1,072	967	801	879	809
		subsequent screening	2,601	2,772	2,900	3,025	3,236	3,542
Centre	number of performed tests	initial screening	68,903	50,575	61,151	53,425	52,043	78,972
		subsequent screening	189,298	191,649	228,545	210,381	227,910	232,433
	number of women recalled for further assessments	initial screening	4,796	3,831	4,944	4,962	4,862	6,420
		subsequent screening	10,502	9,977	11,109	12,610	11,686	12,648
	number of screen-detected malignant cancers	initial screening	295	330	262	240	201	250
		subsequent screening	820	937	878	877	950	1,003
South/ Islands	number of performed tests	initial screening	32,982	53,105	74,144	86,669	23,271	25,171
		subsequent screening	46,326	76,323	44,304	28,789	128,056	128,943
	number of women recalled for further assessments	initial screening	2,638	4,392	5,170	6,265	1,720	1,970
		subsequent screening	1,602	1,946	3,433	2,286	6,544	6,581
	number of screen-detected malignant cancers	initial screening	145	292	214	276	105	113
		subsequent screening	71	74	108	105	402	417

Table 1. Number of performed tests, recalled women and screen-detected malignant cancers by Italian macro-areas. Years 2006-2011.
Tabella 1. Numero di test eseguiti, di donne richiamate per approfondimenti e di tumori maligni rivelati allo screening per macroaree. Anni 2006-2011.

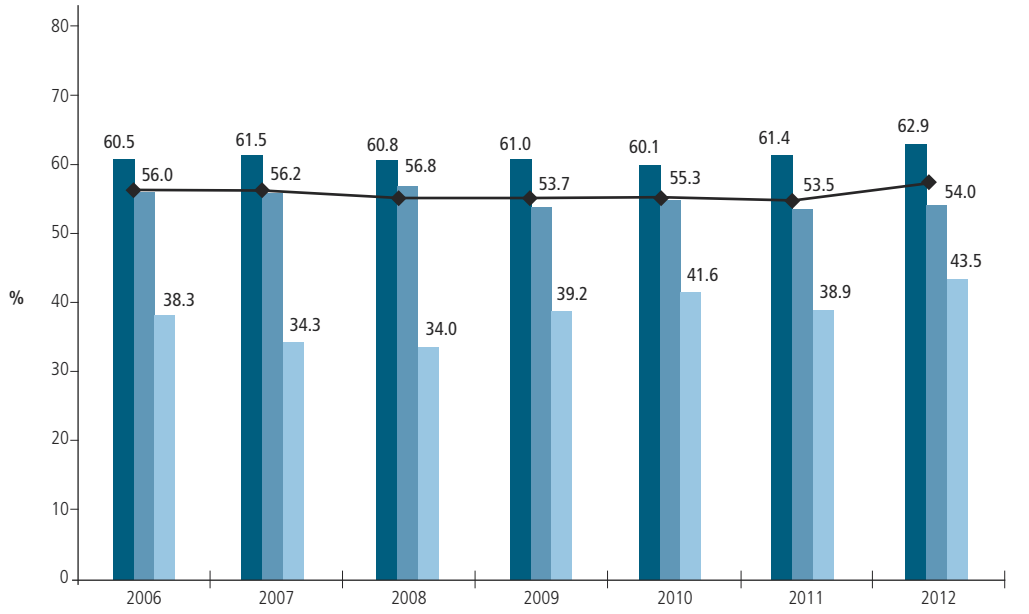


Figure 1. Overall crude participation rate in Italy and by macro-areas. Years 2006-2012.
Figura 1. Partecipazione complessiva grezza in Italia e per macroaree. Anni 2006-2012.

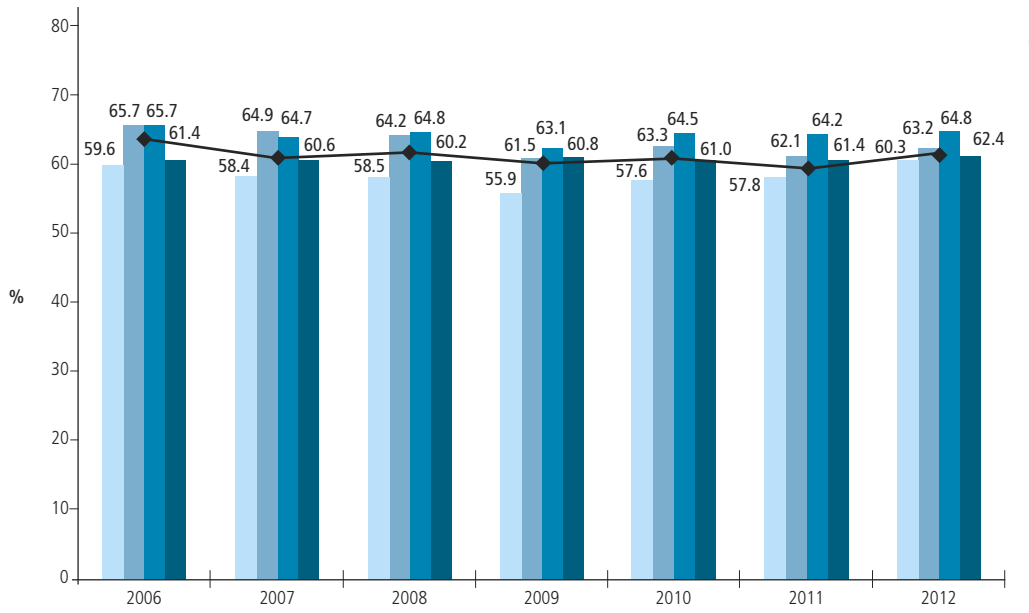


Figure 2. Adjusted participation rate by 5-year age classes. Years 2006-2012.
Figura 2. Partecipazione corretta, per fasce d'età quinquennali. Anni 2006-2012.

ing mammography reduces the mortality for breast cancer, the efficacy of mammography depends on the performance of the interpreting radiologist, technical quality of the mammograms, and proper implementation of a screening programme. The purpose of mammography is detection of cancer (high sensitivity), but this goal is ideally accomplished with reasonable recall and biopsy rates (high specificity).
Good RR, DR, and PPV levels indicate that the programmes are working in the right direction of getting a positive impact on breast cancer mortality.

Recall rate

Recall rate represents a good indicator of screening specificity (first level). In Italy in the whole period the percentage of screened women referred for further assessments at initial screening did not reach either the desirable (<5%) nor the acceptable standard (<7%), and the rate rose slightly over the years. On the contrary, a good performance for this indicator was achieved at subsequent screening, where the standard is <5% and <3% for the acceptable and desirable level, respectively. In subsequent screening tests, RR maintained a constant performance throughout the period (average value: 4.4%), although moving toward the warning threshold (**figure 3**, p. 34).
At initial screening, RR trend analysis by North, Centre, and South-Islands presents the same increasing trends within the three areas, while comparison between them does not reveal substantial differences, with the exception of central Italy, which had higher RRs in certain years.

Figure 3. Time trends of recall rate (%) for women 50-69 years. Years 2006-2011.
Figura 3. Andamento temporale dei richiami per approfondimento, età 50-69 anni. Anni 2006-2011.

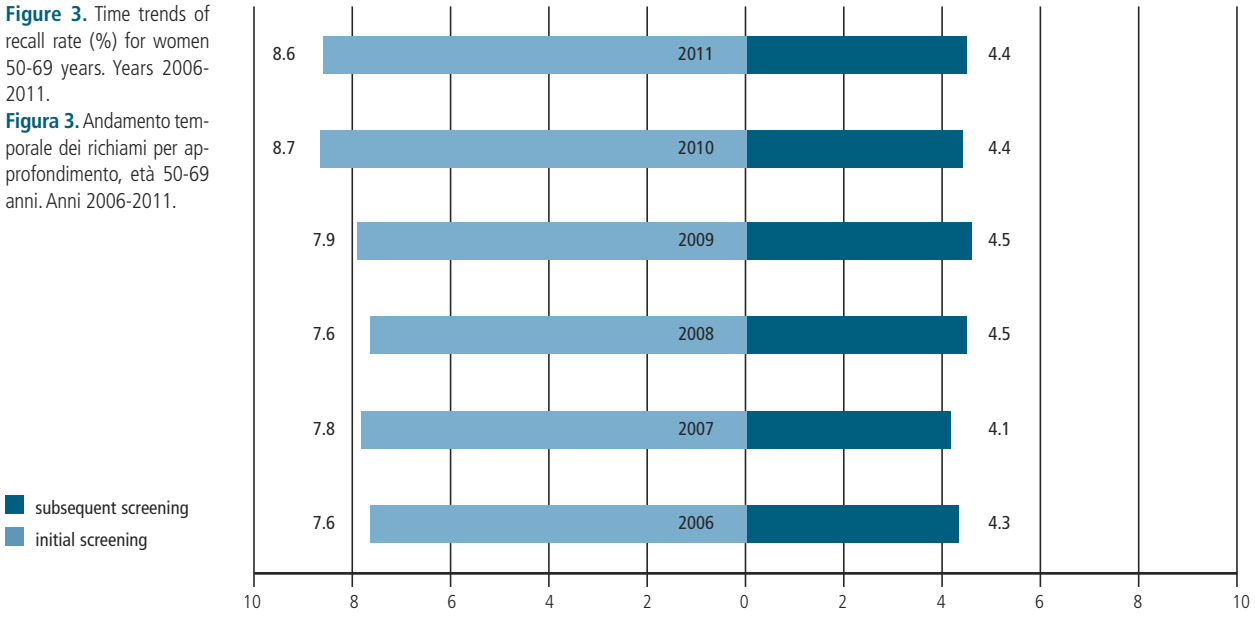


Table 2. Recall rate, detection rate and positive predictive value by North, Centre and South-Islands. Years 2006-2011.
Tabella 2. Tasso di richiamo, tasso di identificazione e valore predittivo positivo, per macroaree. Anni 2006-2011.

	2006	2007	2008	2009	2010	2011
RECALL RATE (%)						
initial screening						
North	7.9	7.8	7.7	7.8	8.6	8.9
Centre	7.0	7.6	8.1	9.3	9.3	8.1
South-Islands	8.0	8.3	7.0	7.2	7.4	7.8
Italy	7.6	7.8	7.6	7.9	8.7	8.6
subsequent screening						
North	4.0	4.0	4.1	4.0	4.4	4.1
Centre	5.5	5.2	4.9	6.0	5.1	5.4
South-Islands	3.5	2.5	7.7	7.9	5.1	5.1
Italy	4.3	4.1	4.5	4.6	4.4	4.5
DETECTION RATE FOR MALIGNANT CANCERS (‰)						
initial screening						
North	7.2	6.1	5.5	4.9	5.3	5.2
Centre	4.3	6.5	4.3	4.5	3.9	3.2
South-Islands	4.4	5.5	2.9	3.2	4.5	4.5
Italy	6.2	6.1	4.6	4.4	4.9	4.5
subsequent screening						
North	4.8	4.6	4.6	4.7	4.5	4.6
Centre	4.3	4.9	3.8	4.2	4.2	4.3
South-Islands	1.5	1.0	2.4	3.6	3.1	3.2
Italy	4.5	4.3	4.3	4.5	4.3	4.4
POSITIVE PREDICTIVE VALUE (%)						
initial screening						
North	9.2	7.9	7.1	6.4	6.2	5.8
Centre	6.2	8.6	5.3	4.8	4.1	3.9
South-Islands	5.5	6.6	4.1	4.4	6.1	5.7
Italy	8.0	7.8	6.1	5.5	5.7	5.2
subsequent screening						
North	12.0	11.3	11.3	11.7	11.1	11.2
Centre	7.8	9.4	7.9	7,0	8.1	7.9
South-Islands	4.4	3.8	3.1	4.6	6.1	6.3
Italy	10.3	10.4	9.7	9.8	9.7	9.8

At subsequent screening, RR trends appeared to be very stable in the North, less stable in the Centre, and in the South-Islands where a high variation among periods was present (table 2).

Analysis by 5-year age classes shows a fairly stable indicator within each age group over time, both at first and subsequent screening. Younger women have higher RRs whether they undergo mammography for the first time or not (table 3).

	2006	2007	2008	2009	2010	2011
RECALL RATE (%)						
initial screening						
50-54	8.7	8.7	8.6	8.7	9.1	9.1
55-59	6.8	7.2	7.0	7.1	7.9	8.4
60-64	6.7	6.8	6.8	6.4	7.7	7.6
65-69	7.0	7.0	6.0	7.2	8.0	6.9
Italy 50-69	7.6	7.8	7.6	7.9	8.7	8.6
subsequent screening						
50-54	5.3	5.2	5.4	5.8	5.6	5.4
55-59	4.4	4.2	4.4	4.6	4.4	4.5
60-64	4.1	3.8	4.3	4.2	4.1	4.2
65-69	3.8	3.7	4.1	4.3	4.1	4.1
Italy 50-69	4.3	4.1	4.5	4.6	4.4	4.5
DETECTION RATE FOR MALIGNANT CANCERS (‰)						
initial screening						
50-54	4.4	4.6	3.9	3.6	4.3	4.0
55-59	5.6	6.1	4.1	3.9	4.7	4.8
60-64	7.5	7.3	6.0	5.2	6.8	5.9
65-69	10.0	9.3	6.3	7.3	8.2	5.9
Italy 50-69	6.2	6.1	4.6	4.4	4.9	4.5
subsequent screening						
N50-54	2.9	2.7	2.7	3.0	2.8	3.0
55-59	3.8	3.6	3.4	3.6	3.3	3.6
60-64	5.0	4.9	4.8	4.7	4.8	4.8
65-69	5.7	5.6	5.8	6.1	5.7	5.8
Italy 50-69	4.5	4.3	4.3	4.5	4.3	4.4
POSITIVE PREDICTIVE VALUE (%)						
initial screening						
50-54	5.0	5.2	4.5	4.2	4.7	4.4
55-59	8.3	8.5	5.8	5.5	5.9	5.7
60-64	11.3	10.6	8.8	8.0	8.9	7.8
65-69	14.3	13.2	10.5	10.2	10.3	8.6
Italy 50-69	8.0	7.8	6.1	5.5	5.7	5.2
subsequent screening						
50-54	5.6	5.2	5.1	5.2	5.0	5.5
55-59	8.6	8.5	7.7	7.8	7.6	8.1
60-64	12.1	12.9	11.0	11.2	11.7	11.3
65-69	14.9	14.8	13.9	14.3	14.0	14.0
Italy 50-69	10.3	10.4	9.7	9.8	9.7	9.8

Table 3. Recall rate, detection rate and positive predictive value by 5-year age-classes. Years 2006-2011.
Tabella 3. Tasso di richiamo, tasso di identificazione e valore predittivo positivo, per fasce d'età quinquennali. Anni 2006-2011.

Overall detection rate

It is one of the main indicators of the diagnostic sensitivity of the programme. It should be referred to the expected cancer incidence rate in the screening population in order to take into account the baseline risk for breast cancer. Detection of invasive breast cancers is disaggregated into first and subsequent screening rounds because a woman is more likely to have a breast cancer detected the first time she visits the breast screening service than in subsequent visits. This is because a woman's first visit detects prevalent cancers that may have been present for some time rather than incident cancers that have grown between screens.
Concerning initial screening, despite a small increase in 2010 compared to 2009, the DR shows a progressive reduction over time (from 6.2‰ in 2006 to 4.5‰ in 2011). This might be associated with the percentage of women referred to in-depth diagnosis at initial screening, which is higher than expected.
The trend is quite good and stable at subsequent screening (average 4.4‰) (**figure 4**, p. 36).
Higher detection rates were found in northern Italy at initial screening in 2006 and 2007 (7.2‰ and 6.1‰, respectively), with a continuous reduction till 2011, while for central and southern Italy DRs were lower but more stable (**table 2**). At subsequent screening, DR values were lower in the South/Islands in 2006-2007 (1.5‰ and 1.0‰, respectively), with a constant increase in the following years till 2011, when the value doubled (3.2‰ in 2011 *vs* 1.5‰ in 2006).
Analysis by 5-year age classes shows higher detection rates for 65-69 year-old women (both at initial and subsequent screening) and lower DRs in women aged 50-59 years. Within each age group, DR had no substantial change over time (**table 3**).

Positive predictive value

Recall rate and detection rate are brought together by the positive predictive value (defined as the number of cancers detected as a percentage of all women recalled for further assessments). PPV is used as a central indicator of the quality of screening mammography programmes. A better performance of screening programmes is achieved when low rates of women re-

Figure 4. Time trends of overall detection rate (‰) for women 50-69 years. Years 2006-2011.
Figura 4. Andamento temporale del tasso di identificazione (‰), età 50-69 anni. Anni 2006-2011.

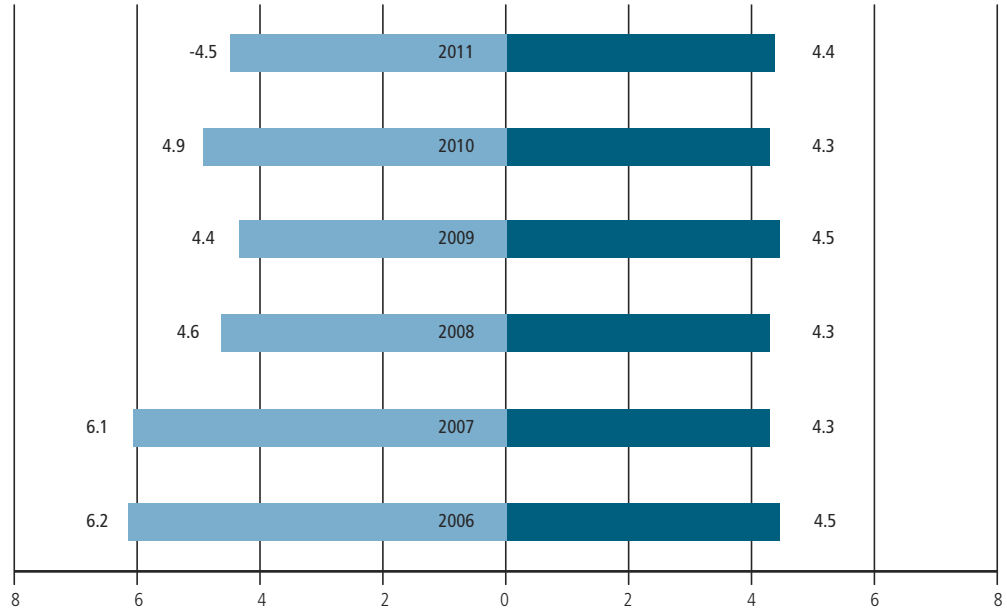
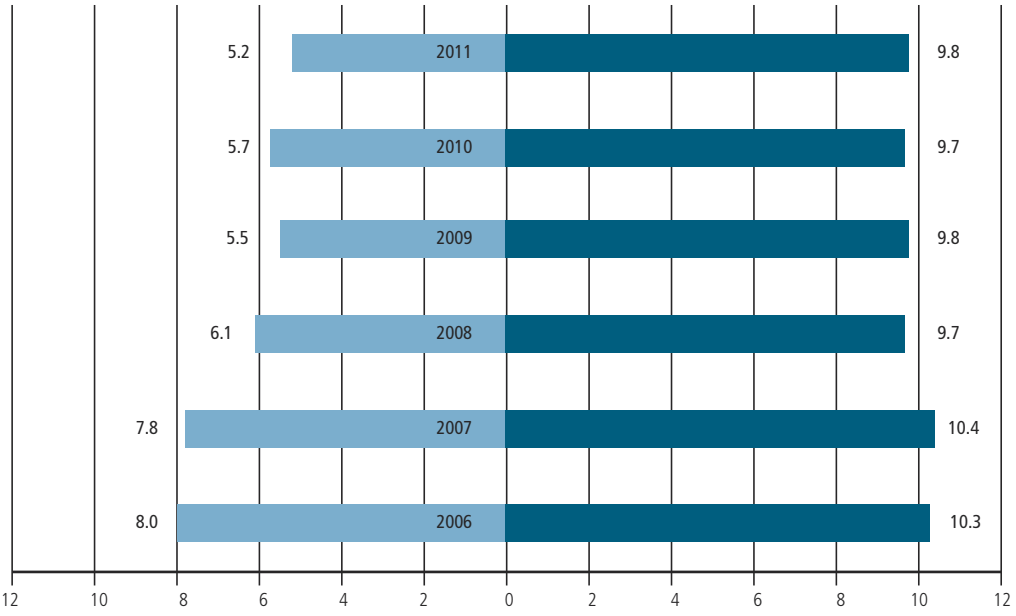


Figure 5. Time trends of positive predictive value (%) for women 50-69 years. Years 2006-2011.
Figura 5. Andamento temporale del valore predittivo positivo (%), età 50-69 anni. Anni 2006-2011.



called for further assessments are associated with high rates of screen-detected cancers and positive predictive value. In a programme with a low PPV and high RR, compared with one with the same cancer DR but high PPV and low RR, the workload on the screening staff and the anxiety experienced by women will be considerably greater.[6]

In the period under study, Italian programmes presented good, stable PPV at subsequent screening, while a progressive reduction in PPV at initial screening (from 8.0% in 2006 to 5.2% in 2011) was observed (figure 5).

In the analysis by macro-areas, PPV rates at first screening decreased over time in all areas, with the exception of the South-Islands where there was a slight increase in the last period. PPV in the latter area was generally lower compared to northern and central Italy. The trend for PPV at subsequent screening was quite stable in northern and central Italy compared to southern Italy, where the trend was more unstable and the values were significantly lower (table 2).

Analysis by age classes shows higher PPV rates for women aged 60-69 both at initial and subsequent screening compared to the other groups (table 3). All these parameters were stable over time.

Activity volumes analysis

Current European guidelines recommend that radiologists who report screening mammograms should read at least 5,000 cases per year. Data gathered through the questionnaire were also an-

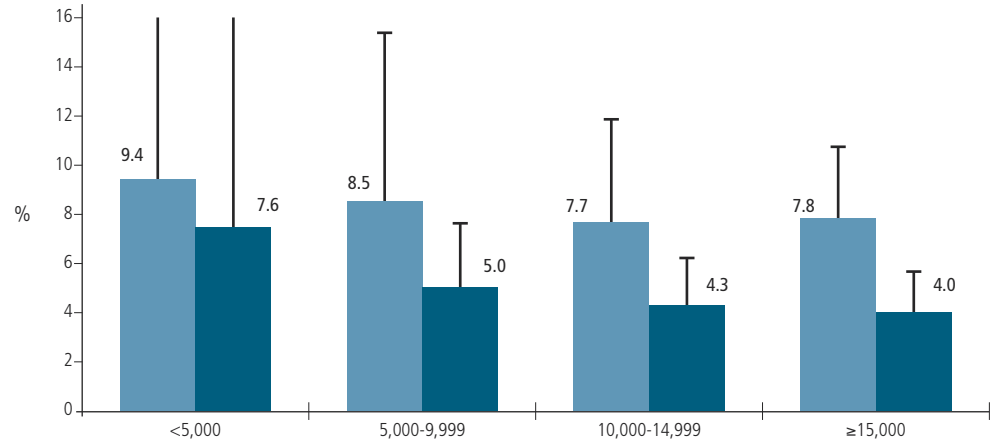


Figure 6. Recall rate for activity volumes of screening programmes.
Figura 6. Tasso di richiami per volumi di attività dei programmi di screening.

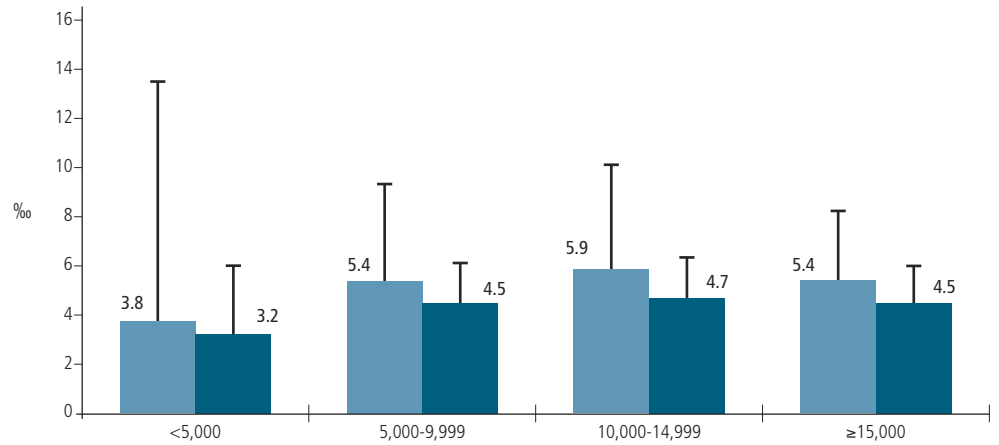


Figure 7. Detection rate for activity volumes of screening programmes.
Figura 7. Tasso di identificazione per volumi di attività dei programmi di screening.

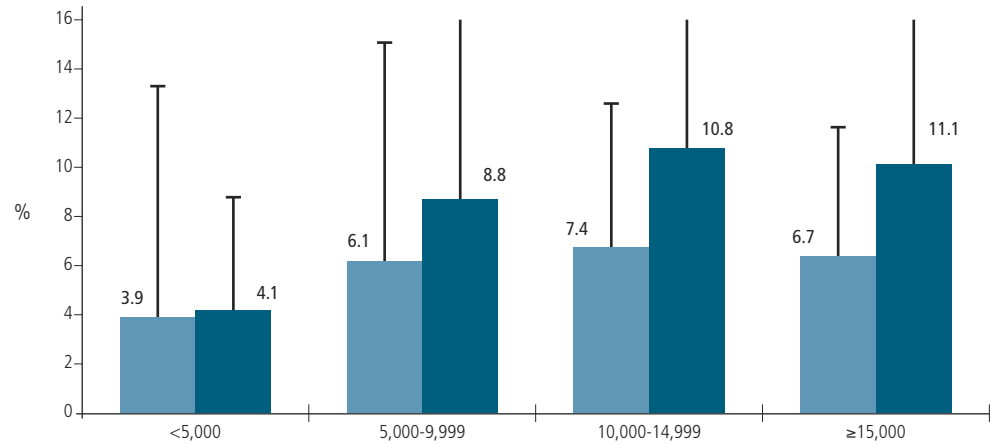


Figure 8. Positive predictive value for activity volumes of screening programmes.
Figura 8. Valore predittivo positivo per volumi di attività dei programmi di screening.

alyzed to compare the trend of RR, DR, and PPV according to the annual activity volume of each programme. Thus, four activity volume classes were defined, with a number of tests ranging from <5,000/year to >15,000/year. This preliminary analysis gives rise to some considerations about the impact of activity volume on performance indicators (figures 6-8).
In programmes with greater activity (test/year ≥10,000) the RR at both initial and subsequent screening was lower and, only at repeat screening, within acceptable standards (4.3%, 4.0%). This was also true for DR and PPV, for which programmes with high volumes of activity show better performance, especially when compared with those who read fewer than 5,000 mammograms per year; the latter had a critical level for all analyzed indicators, both at initial and subsequent screening.

CONCLUSIONS

GISMa surveys have progressively changed and have become increasingly complete and systematic. Thanks to the work of several operators, data collection makes it possible to evaluate the quality of programmes, produce local and national statistics, and compare different screening areas through standardized indicators. These investigations and comparisons are important in helping screening staff to properly manage their activity and improve programme effectiveness and quality.

However, GISMa surveys still have some limitations: data collected are aggregated, and not all programmes, particularly those covering large areas and with several territorial screening units, are able to provide a complete data set every year.

In general, analysis of the four parameters discussed above (PR, DR, RR, and PPV), though with due caution, shows a good average quality of screening performance, which was maintained over time. Conversely, a number of failures in screening offer or functioning, rather than in the diagnostic process, need to be highlighted.

The discrepancy between northern and southern Italy persisted. The absence of an organized screening activity, as well the chronic lack of dedicated professionals, invested resources, and clear-cut, well-planned political actions for prevention in southern Italy affect the overall quality of the programmes.

More in-depth investigations are needed to evaluate this discrepancy in order to suggest and discuss corrective strategies.

Participation rate is a key indicator for measuring and comparing the quality of screening, essential for stakeholders to evaluate the effectiveness of their choices. Low levels of attendance can make the organizational and economic efforts that go into screening ineffective.

In Italy, despite a good, constant time trend in activity, which reaches and exceeds the acceptable standard, a great variability still persists among central-northern and southern/Islands programmes and within individual regions.

For a better understanding of this trend, the portion of women undergoing spontaneous screening (quite relevant in some settings in southern Italy) should be assessed.

The presence of a massive opportunistic screening activity can explain both the difficulty for the programmes to invite all the target population and the wide heterogeneity in participation rates between and within Italian regions.

Furthermore, besides the presence of an opportunistic screening activity, participation rate can be influenced by many other factors, such as individual and socio-cultural conditions, and organizational aspects of the screening invitation design.

A centralized organization, as present in many northern Italian regions, can stimulate useful synergies among the various screening phases, resulting in a wider and more successful involvement of the target population. Resources and efforts should move in this direction, together with a strong monitoring and regulation of the opportunistic activity that can interfere with the efforts made by organized screening. In some Italian contexts, many efforts have been made to channel opportunistic screening activities within the organized system (e.g., in Piedmont a recent regional law banned the prescription of preventive mammograms outside the organized programme); for these efforts to be successful, the involvement of health care professionals, family doctors in particular, is crucial.

The assessment of diagnostic indicators confirms the trend observed in previous years.[5] Among these, RR is one of the more carefully monitored indicators of a programme's specificity. Having too many women referred for additional examinations (FNA, core or surgical biopsy) is a recognized problem both for operational reasons and financial costs. In addition, increased levels of anxiety and other adverse psychological consequences in women who are recalled are well-documented.[7,8]

In our surveys RRs exceeded or were very close to the recommended standards and call for further reflection. These values, referred to programmes that have already been running for several years, cannot be ascribed to the learning curve effect, typical of newly implemented programmes, even though the recent, gradual replacement of analogue equipment with digital devices could partly be responsible for this. High RRs, especially at initial screening, can also be due to an increasing number of screened women aged 50-54 years.

To better assess this trend, it would be useful to evaluate the RR by screening units and by radiologists. Multidisciplinary sessions on screen-detected lesions, collective revision of atypical outcomes and reinforcement of the training procedures can represent some practical approaches to improve the performance of the programmes.

As concerns overall DR and PPV, despite the presence of small annual fluctuations, Italian mammography screening programmes show good quality activity in general and over time. No large variations, other than the expected ones, were observed for age group analysis.

The results by geographical areas prompt distinct considerations. A delay in the implementation of organized screening programmes and the absence of structured coordination systems persisted in southern Italy. This has a strong impact both on data completeness and on the intermediate outcomes that are struggling to reach the recommended quality standard. Southern Italian regions continue to present critical outcomes which would require additional analysis involving health policies and health system organization.

Our results highlighting that activity volume can affect cancer detection accuracy are not very surprising and are consistent with those observed in other European programmes.[9] The volume of procedures or patients has been repeatedly demonstrated to be a strong determinant of quality in medical procedures.[10]

Indeed, the data from the Swedish population-based screening studies, in which mammography is performed by experts in high-volume centres, provide the foundation from which evidence-based recommendations for mammography screening are derived.[11] It is essential to discourage the activation of screening programmes with inadequate volumes of activity and to facilitate screening centralization as much as possible.

Our results underline a direct correlation between higher volume activity and good performances, especially for DR and

PPV. Programmes with higher volumes of activity are located mainly in central and northern Italy, where the incidence rates for breast cancer are higher. Since DR and PPV are greatly influenced by breast cancer incidence, this should be taken into consideration when analyzing these outcomes.
Although this analysis has many limitations, as it considers programmes and not operators, it encourages to implement new investigation strategies which combine sensitivity and specificity indicators with programme organizational characteristics. Overall, the results here described, despite the specified weaknesses, continue to be reassuring and reward the great effort undertaken by screening professionals over the years. It is therefore important to maintain the same level of co-operation and participation within screening experiences and support and reinforce indicator monitoring. In addition, further opportunities for discussing observed difficulties must be offered to the Italian screening community, in order to suggest, test, and evaluate strategies for continuous improvement.

Conflicts of interests: none declared

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Audit system on Quality of breast cancer diagnosis and Treatment (QT): results of quality indicators on screen-detected lesions in Italy, 2011-2012

Il "progetto SQTM" sulla qualità della diagnosi e della terapia entro i programmi di screening in Italia: risultati 2011-2012

Antonio Ponti,[1] Maria Piera Mano,[1] Mariano Tomatis,[1] Diego Baiocchi,[2] Alessandra Barca,[2] Rosa Berti,[3] Denise Casella,[1] Enrico D'Ambrosio,[4] Erika Delos,[5] Giovanni Donati,[3] Fabio Falcini,[6] Brunella Frammartino,[7] Alfonso Frigerio,[8] Fabiola Giudici,[9] Paola Mantellini,[10] Carlo Naldoni,[11] Carlo Olla Atzeni,[4] Lorenzo Orzalesi,[12] Giovanni Pagano,[13] Francesca Pietribiasi,[14] Sabina Pitarella,[1] Alessandra Ravaioli,[6] Anna Silvestri,[7] Mario Taffurelli,[15] Enrica Tidone,[7] Fabrizio Zanconati,[16] Nereo Segnan[1]

[1]CPO Piemonte, AOU Città della salute e della scienza, Torino
[2]ASP Lazio, Roma
[3]Servizio di chirurgia toracica, Aosta
[4]Anatomia patologica Ospedale Vito Fazzi, Lecce
[5]Chirurgia plastica Ospedale Vito Fazzi, Lecce
[6]IRCCS, Istituto scientifico romagnolo per lo studio e la cura dei tumori (IRST), Forlì
[7]ASL di Milano, Prevenzione oncologica, MPC
[8]SSCVD Senologia di screening, AOU Città della salute e della scienza, Torino
[9]Dipartimento di scienze mediche, chirurgiche e della salute, Università degli studi di Trieste
[10]Istituto per lo studio e la prevenzione oncologica (ISPO), Firenze
[11]Assessorato alle politiche per la salute, Regione Emilia-Romagna, Bologna
[12]Breast Unit Chirurgia, AOU Careggi, Firenze
[13]AUSL Roma H, Albano Laziale
[14]Anatomia patologica, ASL TO5 Moncalieri
[15]Dipartimento di chirurgia generale e dei trapianti d'organo, Chirurgia generale, Università di Bologna
[16]AOU Ospedali riuniti di Trieste, Dipartimento di scienze mediche, chirurgiche e della salute

Corresponding author
Antonio Ponti
antonio.ponti@cpo.it

Abstract

This annual survey, conducted by the Italian group for mammography screening (GISMa), collects individual data on diagnosis and treatment of about 50% of screen-detected, operated lesions in Italy. The 2011-2012 results show good overall quality and an improving trend over time. A number of critical issues have been identified, including waiting times (which have had a worsening trend over the years) and compliance with the recommendation of not performing frozen section examination on small lesions. Pre-operative diagnosis improved constantly over time, but there is still a large variation between Regions and programmes. For almost 90% of screen-detected invasive cancers a sentinel lymph node (SLN) biopsy was performed on the axilla, avoiding a large number of potentially harmful dissections. On the other hand, potential overuse of SLN dissection for ductal carcinoma in situ, although apparently starting to decline, deserves further investigation.

The detailed results have been distributed, among other ways by means of a web-based data-warehouse, to regional and local screening programmes, in order to allow multidisciplinary discussion and identification of the appropriate solutions to any issues documented by the data. The problem of waiting times should be assigned priority. Specialist Breast Units with adequate case volume and enough resources would provide the best setting for making monitoring effective in producing quality improvements with shorter waiting times.

Epidemiol Prev 2015; 39(3) Suppl 1: 40-47)
Keywords: breast cancer screening quality treatment survey, Italy

Riassunto

Questa survey annuale, condotta dal Gruppo italiano per lo screening mammografico (GISMa), raccoglie dati individuali su diagnosi e terapia di circa il 50% dei casi screen-detected operati in Italia.

I risultati 2011-2012 mostrano nel complesso una buona qualità e un trend in miglioramento nel tempo. Sono stati identificati alcuni aspetti critici, tra cui i tempi di attesa (che continuano a peggiorare anno dopo anno) e il rispetto della raccomandazione di non eseguire l'esame estemporaneo al

congelatore nelle lesioni piccole. L'indicatore sulla diagnosi preoperatoria è migliorato progressivamente negli anni ma esiste ancora un'elevata variazione tra Regioni e tra programmi. In quasi il 90% dei casi di cancro invasivo identificati allo screening è stato eseguito linfonodo sentinella (LNS) per la stadiazione, evitando un gran numero di dissezioni ascellari potenzialmente dannose. D'altra parte, il possibile eccessivo utilizzo del LNS nei carcinomi duttali in situ, che peraltro negli ultimi anni accenna a ridursi, merita indagini ulteriori.
I risultati dettagliati di questa survey sono stati distribuiti, anche attraverso una data-warehouse accessibile sul web, ai responsabili dei programmi di screening regionali e locali, allo scopo di permettere la discussione multidisciplinare, la verifica dei dati e l'identificazione delle soluzioni appropriate ai problemi che venissero così documentati. Al problema dei tempi di attesa dovrebbe essere assegnato carattere di priorità e urgenza. Unità diagnostico-terapeutiche di senologia con adeguati volumi di attività e sufficienti risorse fornirebbero il contesto adeguato per far sì che il monitoraggio sia efficace nel produrre miglioramenti nella qualità e tempi di attesa accettabili.

Epidemiol Prev 2015; 39(3) Suppl 1: 40-47)
Parole chiave: screening per il cancro della mammella, qualità, diagnosi, terapia, Italia

INTRODUCTION

Mammography screening rests upon a delicate balance of human benefits and costs which is highly sensitive to the quality, not only of the screening itself, but of the entire process of care for screen-detected lesions. Therefore, screening programmes should perform audits of further assessments, histopathology, diagnosis, and treatment, as well as the screening test itself.[1,2]
The mammography screening movement in Europe has been on the front line in introducing quality assurance and monitoring in all stages of breast cancer management and care. The European breast cancer screening network created an individual records database and audit system called QT (audit system on Quality of breast cancer Treatment) which can be downloaded at www.qtweb.it. At the same site, extensive documentation is available. QT can be used in six languages (English, French, German, Italian, Spanish, and Hungarian) and has been adopted by Breast units in several European countries. Within the Italian group for mammography screening (GISMa), a voluntary quality assurance programme for screen-detected breast cancer care has been ongoing since 1997,[3] and results of this activity have been published yearly in the reports of the National centre for screening monitoring since their first edition in 2003. The aim of this report is to publish results of the monitoring of diagnosis and treatment indicators in screen-detected lesions operated with open surgery in Italy during 2011-2012.

METHODS

Individual data on diagnosis and treatment of screen-detected operated lesions (benign or malignant) are recorded on QT either by clinical staff in charge of the patients or by local screening organization and evaluation units. Regional programmes report anonymous data yearly to the national co-ordination office, which performs data quality control and analysis.
Sources of outcome measures are Italian[4,5] and European[2,6-8] guidelines. This report includes indicators defined recently by a Senonetwork-GISMa consensus group.[9] Regions were excluded from the analysis of a given indicator if missing values for that indicator exceeded 30%.
Even though most programmes in Italy have designated surgical units where the majority of the cases are referred, the study protocol required that participating programmes record all screen-detected cases, regardless of where treatment had taken place. Piemonte, Valle d'Aosta, and Toscana use as index date the date of the screening test that originated surgical referral, while the remaining regions use date of surgery. To avoid selection bias, the study protocol requires that participating programmes record all screen-detected operated lesions. Known interval cases, operated in the index year, could also be included, but this was not required.
The results reported here were presented, in their preliminary version, at the National centre for screening monitoring's annual meeting in January 2014 in Bologna. Preliminary results were checked locally and updated. In several of the regions, data were discussed at specific multidisciplinary meetings prior to publication. Data have been made available to regional and screening coordinators on a web-based data-warehouse which allows for analysis and benchmarking.
In 2011-2012, data were reported for a portion only of the following regions: Lombardia (Milano), Friuli-Venezia Giulia (Trieste), Puglia (Lecce) and Toscana (Firenze). For the remaining four regions, data were reported region-wide. For the first time, results in this report are shown for ages 45-74, as some regions have extended the screening target population beyond the traditional 50-69 age group.
All indicators are proportions; 95% confidence intervals are given. Data analysis was performed with the tools included in SQTM and statistical programme R.

RESULTS

During 2000-2012, about 40,000 lesions in thirteen Italian regions were documented in QT. In 2011-2012, thirty-seven screening programmes belonging to GISMa participated in the QT project and individual data on 8,809 cases (including 7,284 malignant lesions) in eight regions were recorded in women between 45 and 74 years of age (**table 1**, p. 42).
Ductal carcinoma in situ (DCIS) accounted for 16.0% of all malignant lesions. Of invasive tumours, 35.1% had pathological size ≤10 mm. Operated benign or intraepithelial lesions (atypical hyperplasia, lobular "carcinoma" in situ grade 1 or 2,

Number of programmes	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Piemonte and Valle d'Aosta	8	9	10	10	10	10	10	10	10	10	10	10	10
Lombardia	1	-	-	-	1	1	1	-	-	1	1	1	1
Veneto	2	1	12	12	12	12	10	9	1	-	-	-	-
Friuli-Venezia Giulia	-	-	-	-	-	-	-	-	-	-	-	-	1
Emilia-Romagna	6	8	9	9	8	10	11	11	11	11	11	11	11
Toscana	1	1	1	1	1	9	9	11	11	1	1	1	1
Umbria	-	-	1	-	-	-	-	-	-	-	-	-	-
Lazio	2	5	3	7	7	6	6	8	8	10	11	11	12
Campania	1	-	-	-	-	-	-	-	-	-	-	-	-
Puglia	-	-	-	-	-	-	-	-	-	-	-	1	1
Sardegna	-	-	-	-	-	-	-	1	1	1	1	-	-
Sicilia	2	1	2	-	1	-	-	-	-	-	-	-	-
Total	**23**	**25**	**38**	**39**	**40**	**48**	**47**	**50**	**42**	**34**	**35**	**35**	**37**
Number of cases													
Piemonte and Valle d'Aosta	589	709	812	852	1,170	1,175	1,212	1,098	1,216	1,229	1,196	1,563	1,538
Lombardia	69	-	-	-	51	138	139	-	-	439	374	418	434
Veneto	158	76	270	426	369	432	392	191	176	-	-	-	-
Friuli-Venezia Giulia	-	-	-	-	-	-	-	-	-	-	-	-	57
Emilia-Romagna	394	796	663	742	856	920	992	984	1,107	1,129	1,103	1,536	2,016
Toscana	144	138	151	195	213	522	526	710	551	192	88	75	71
Umbria	-	-	33	-	-	-	-	-	-	-	-	-	-
Lazio	137	142	128	245	339	239	286	375	325	567	467	502	443
Campania	9	-	-	-	-	-	-	-	-	-	-	-	-
Puglia	-	-	-	-	-	-	-	-	-	-	-	61	95
Sardegna	-	-	-	-	-	-	-	74	72	17	62	-	-
Sicilia	135	23	36	-	10	-	-	-	-	-	-	-	-
Total	**1,635**	**1,890**	**2,093**	**2,460**	**3,008**	**3,426**	**3,547**	**3,432**	**3,447**	**3,573**	**3,290**	**4,155**	**4,654**

Table 1. Italian survey on diagnosis and treatment of screen-detected breast lesions, 2000-2012, age 49-70 (up to 2010) age 45-74 (from 2011). Number of screening programmes and cases, by region.

Tabella 1. Survey sulla diagnosi e la terapia delle lesioni mammarie screen-detected, 2000-2012, età 49-70 (fino al 2010), età 45-74 (dal 2011). Numero di programmi e di casi, per Regione.

atypia with columnar cells, atypical papillary lesions) represented 13% of cases with known diagnosis. However, benign and intraepithelial lesions were systematically recorded only by 5 out of 8 regions: Piemonte, Valle d'Aosta, Emilia-Romagna, Lazio, and Puglia. Within these regions, benign or intraepithelial lesions accounted for 15% of cases (benign/malignant ratio= 0.18, a value very similar to the one found in the GISMa aggregated data survey). The proportion of benign and intraepithelial lesions, as well as of DCIS, was greater in younger women (**table 2**).

The proportion of N+ invasive cases was 27.4% (missing: 9.1%). Grade of invasive carcinoma was distributed as follows: 20.5% I, 54.6% II, and 24.9% III (missing: 9.5%). Nuclear grade of DCIS was 25.4% I, 40.2% II, and 34.4% III (missing: 10.5%).

Results of outcome measures are shown in tables 3 and 5.

Eighty-two per cent of cancers had pre-operative cytological or micro-histological diagnosis (**table 3**). This figure is higher compared to previous years and is over the new[9] acceptable target of 80%. However, considerable variation exists between regions (range 45%-91%) and especially between programmes. Cases for which pre-operative diagnosis was not available are distributed by reason in **table 4**. Failure in performing any non-operative diagnosis was responsible for 14% of these cases (16% in 2010). A non-operative diagnosis involving "suspicion" of malignancy – C4 or B4, according to the classification proposed by the EC Working group on breast screening pathology[7] – rather than a higher degree of certainty was responsible for 50% of the cases (48% in 2010). The proportion of inadequate cytology and absolute sensitivity[7] of C5 were above the target (**table 3**).

Waiting times were still far from the target and had even worsened compared to previous years (**tables 5**, p. 44 and **7**, p. 46). Forty-three per cent of cancers received surgery within one month of referral (range between regions: 34%-79%), and 30% within two months of the screening date (22%-62%) (**table 5**). Just slightly more than 65% of cases received surgery within three months after screening (59%-92%).

Histopathological diagnosis	Age 45-49		Age 50-59		Age 60-69		Age 70-75		Missing		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
benign	231	18.0	293	11.6	199	6.2	34	3.6	21	2.4	778	8.8
intraepithelial	118	9.2	115	4.6	80	2.5	14	1.5	3	0.3	330	3.7
lobular carcinoma in situ (LIN 3)	2	0.2	1	0.0	4	0.1	0	0.0	1	0.1	8	0.1
ductal carcinoma in situ	208	16.3	351	14.0	375	11.7	123	13.0	91	10.5	1,148	13.0
micro-invasive	15	1.2	40	1.6	43	1.3	14	1.5	2	0.2	114	1.3
invasive (1A/1B)	40	3.1	136	5.4	178	5.6	31	3.3	49	5.6	434	4.9
invasive (other)	172	13.4	461	18.3	760	23.8	264	27.8	145	16.7	1,802	20.5
invasive (unknown size)	443	34.6	949	37.7	1,414	44.3	439	46.3	292	33.6	3,537	40.2
malignant not specified	10	0.8	48	1.9	67	2.1	13	1.4	103	11.8	241	2.7
unknown	41	3.2	122	4.8	75	2.3	16	1.7	163	18.7	417	4.7
Total	**1,280**	**100**	**2,516**	**100**	**3,195**	**100**	**948**	**100**	**870**	**100**	**8,809**	**100**

Table 2. It. Italian survey on diagnosis and treatment of screen-detected breast lesions, 2011-2012. Distribution by final histopathology diagnosis and age.
Tabella 2. Survey sulla diagnosi e la terapia delle lesioni mammarie screen-detected, 2011-2012. Distribuzione per diagnosi istopatologica definitiva ed età.

Outcome measure	Eligible cases	Missing %	Result %	95%CI	Minimum % required	Target %
pre-operative diagnosis in cancers (C5,B5)	6,878	2.6	82.2	81.3 - 83.1	≥80	≥90
non-inadequate cytology if final diagnosis is cancer	4,381	0.6	91.9	91.1 - 92.7		≥90
absolute sensitivity C5	4,381	0.6	67.6	66.2 - 69.0		≥60

Table 3. Summary on diagnostic indicators, 2011-2012, age 45-74. Results are calculated on eligible cases minus cases with missing information.
Tabella 3. Indicatori diagnostici, 2011-2012, età 45-74. I casi con informazione mancante sono esclusi dal denominatore.

Guidelines recommend avoiding intra-operative frozen section examination (even on margins) in lesions under or equal to 10 mm because of limited accuracy and the risk of deteriorating the specimen and impairing subsequent examination.[1,4-7] The result of this indicator (**table 5**) was still below the target, but had improved compared to the previous period, as in 2007 frozen section examination was performed in about one fourth, in 2008-2009 in about one fifth, and in 2010 and 2011-2012 in one eighth of cases only (the range between regions is wide: 9%-80%). Recent Italian guidelines[9] recommend the performance of two-view specimen X-rays on all lesions showing micro-calcifications only and set the numerical target at 90%. The indicator (**table 5**) gives a result of 66.0%. The number of missing data however is high (21%).
Breast conservation, both for invasive cancer (up to 3 cm)[9] and DCIS (up to 2 cm), was at high levels, 85% the former and 90% the latter. The proportion of axillary dissections with an adequate number of lymph nodes excised (92%) exceeded the target (**table 5**). The indicator on performing no more than one operation on the breast for clearing margins met the 90% target both for invasive cancer and DCIS. Margins were left wider than 1 mm in 93% of cases (**table 5**).
This survey investigated the gradual introduction over the years of the sentinel lymph node (SLN) biopsy, which makes staging possible with considerably fewer complications than axillary clearance.[4,8] An increasing proportion of invasive cancers and DCIS were studied with SLN biopsy over time until 2007-2008, then the use of SLN biopsy in invasive cancers reached a plateau around 87% while in DCIS it seemed to start decreasing from a maximum of 62% in 2010 to 53% in 2012 (**figure 1**, p. 44). The proportion of node-negative invasive cases staged by SLN biopsy only (**table 5** and **table 7**) was 91% in 2011-2012, with an increasing trend over the years and moderate variability by region (range 73%-100%). In 92% of cases no more than 3 sentinel lymph nodes were excised, as prescribed by the target (**table 5**).
In 2011-2012, 3.3% of DCIS (range between regions: 0%-7%) received clearance of the axilla (**table 5**), a procedure not recommended in these cases. The result of this indicator has improved over the years (**table 7**).
Overtreatment may also result from unnecessary open surgery in the breast on benign lesions. This issue is illustrated in **table 6** (p. 45) where operated benign or intraepithelial lesions are distributed by histopathology type. Benign lesions at no increased risk (all except intraepithelial lesions, papilloma, sclerosing adenosis, radial scar, and phylloid tumours) were 524 in 2011-2012 (49% of all operated benign or intraepithelial

	N	%
pre-operative diagnosis not performed	171	14.3
unsatisfactory	136	11.4
false negative (C2 or B2)	43	3.6
dubious (C3 o B3)	252	21.1
suspicious (C4 o B4)	592	49.6
Total	**1,194**	**100.0**

Table 4. Distribution of malignant cases without pre-operative diagnosis C5 or B5 by reason, 2011-2012, age 45-74.
Tabella 4. Distribuzione delle lesioni maligne senza diagnosi preoperatoria C5 o B5, per motivo della mancata diagnosi preoperatoria, 2011-2012, età 45-74.

Outcome measure	Eligible cases	Missing %	Result %	CI95%	Minimum % required	Target %	Excluded
waiting time for surgery from referral ≤30 days	7,263	16.7	43.5	42.3-44.8	≥75	≥90	Lombardia, Puglia
waiting time for surgery from first diagnostic test ≤42 days	7,263	8.3	28.8	27.8-30.0	≥75	≥90	Lombardia, Puglia
waiting time for surgery from screening test ≤60 days	7,123	10.2	29.9	28.8-31.0	≥75	≥90	Lombardia, Puglia, Toscana
waiting time for surgery from screening test ≤90 days	7,123	10.2	65.4	64.2-66.5			Lombardia, Puglia, Toscana
frozen section not performed in cancers ≤10 mm	1,423	12.0	87.5	85.6-89.3		≥95	Lazio, Lombardia, Toscana
specimen X-ray in cases with microcalcifications only	768	21.2	66.3	62.3-70.0	≥90	≥98	Puglia
only one operation after pre-operative diagnosis (invasive)	5,728	0.7	92.9	92.2-93.6	≥80	≥90	
only one operation after pre-operative diagnosis (in situ)	1,112	0.4	89.9	87.9-91.6	≥80	≥90	
conservative surgery in invasive cancers ≤30 mm	5,367	10.5	84.7	83.6-85.7	≥70	≥90	
conservative surgery in DCIS (ductal carcinoma in situ) ≤20 mm	511	1.2	90.1	87.1-92.5	≥80	≥90	
margins >1 mm after last surgery	4,547	18.5	92.8	91.9-93.6			Lazio, Lombardia
number of lymph nodes >9 in axillary dissection (sampling excluded)	1,057	2.3	92.3	90.4-93.8	≥80	≥90	
axillary staging by SLN only in pN0	3,407	0	91.1	90.1-92.0	≥80	≥90	
no axillary dissection (sampling included) in DCIS	1,106	6.1	96.7	95.4-97.7	≥90	≥95	
no more than 3 LNs at SLN biopsy	5,726	29.5	92.4	91.5-93.2	≥80	≥90	Lombardia, Puglia

Table 5. Summary on surgical indicators, 2011-2012, age 45-74. Results are calculated on eligible cases minus cases with missing information. Due to missing values exceeding 30%, some regions were excluded from the calculation of specific indicators.
Tabella 5. Indicatori chirurgici, 2011-2012, età 45-74. I casi con informazione mancante sono esclusi dal denominatore. Sono state escluse dal calcolo di specifici indicatori le Regioni con una proporzione di valori mancanti >30%.

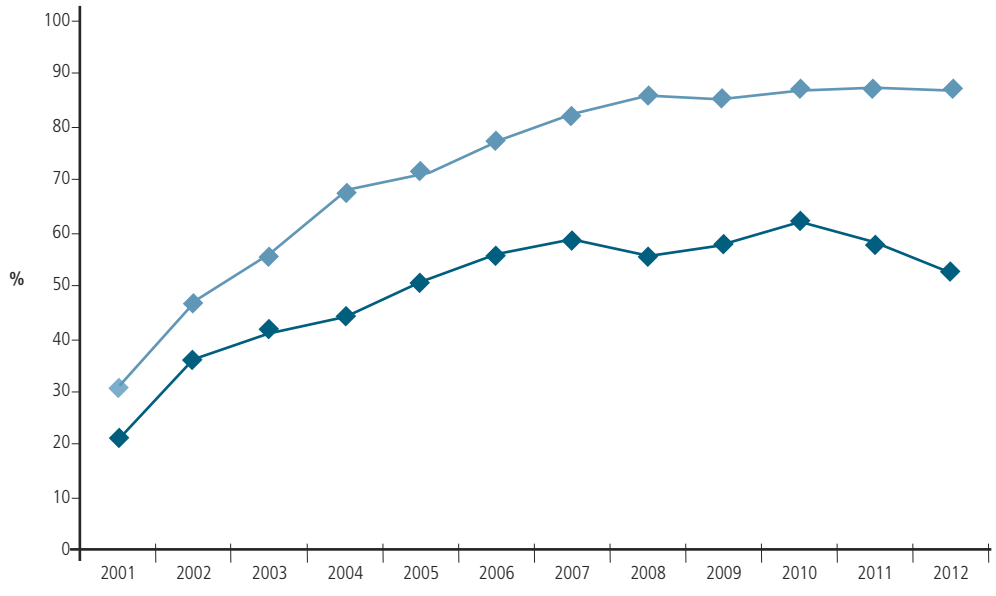

Figure 1. Italian survey on diagnosis and treatment of screen-detected breast cancers. Trend (%) in the use of SLN technique (age 49-74). Years 2001-2012.
Figura 1. Survey sulla diagnosi e la terapia dei carcinoma della mammella screen-detected. Trend (%) nell'uso della tecnica del linfonodo sentinella (età 49-70). Anni 2001-2012.

		N	%
benign	normal tissue	15	1.4
	fibroadenoma	161	15.1
	cysts	17	1.6
	columnar cell change without atypia	8	0.7
	fibrocystic breast diseae	102	9.5
	benign phylloid tumour	20	1.9
	sclerosing adenosis	80	7.5
	radial scar	21	2.0
	papilloma/papillomatosis	110	10.3
	other	149	13.9
	unknown	72	6.7
	total benign	**755**	**70.6**
intraepithelial	atypical lobular hyperplasia (LIN1)	16	1.5
	lobular carcinoma in situ (LIN2)	65	6.1
	atypical columnar cell change (DIN1a)	66	6.2
	atypical ductal hyperplasia (DIN1b)	165	15.4
	atypical papillary lesion	2	0.2
	total intraepithelial	**314**	**29.4**
Total		**1,069**	**100.0**

Table 6. Distribution by histological type of benign and intraepithelial lesions operated by open surgery (excluding synchronous lesions), age 45-74. Years 2011-2012
Tabella 6. Distribuzione per tipo istologico delle lesioni benigne e intraepiteliali operate (lesioni sincrone escluse), età 45-74. Anni 2011-2012.

lesions, excluding double lesions and lesions with missing histological type: a result similar to previous years).
Table 7 shows time trends from 2000 to 2012 for selected performance parameters. The frequency of pre-operative diagnosis and avoidance of frozen section examination in small lesions showed improvement over time. Waiting times had a consistent and important negative trend over the years.

DISCUSSION

In 2011-2012, most outcome measures were near or met the target set by GISMa.[5,9] Major exceptions, similarly to 2010, were waiting times for surgery, compliance with the recommendation on avoiding frozen section examination on small lesions and performing specimen X-rays.
The proportion of cancers with pre-operative diagnosis has clearly increased over the years, due to increasing use of microhistology techniques, and reached the acceptable target for the first time in 2005. However, the result only slightly increased compared to 2007, despite the fact that a wide margin for improvement still exists in order to reach the European desirable target of 90%.[7] This is also supported by the finding of a considerable variation between programmes: about 25% did not reach the acceptable target, while more than 20% did. Pathologists and radiologists should be involved with surgeons in analyzing the reasons for underperformance in programmes scoring in the lower part of the range. It may be worthy of notice that fine needle aspiration cytology (FNA) was still used for pre-operative diagnosis in the majority of cases: out of 7,449 lesions receiving needle biopsies, 3,560 (48%) received FNA only, 2,620 (35%) core or vacuum assisted biopsy only, and 1,269 (17%) both.
Waiting time from screening to surgery embraces much of the entire process of care (time from screening to first assessment, time from first assessment to result, time from result of assessment to first surgery). Results have been worsening over the years, and in 2011-2012 the decreasing trend continued, with as few as 30% of patients being operated within 60 days of the screening examination. Regional authorities should inspect the reasons for this considerable delay, especially in regions in the lower part of the range. Even though two or three months of treatment delay are not expected to affect clinical outcomes,[10] they can cause anxiety and impair quality of life, in addition to contradicting the idea itself of early detection. Furthermore, many cases experience a delay greater than three months.
Avoiding the use of frozen section examination entails a difficult change in attitude by the surgeon, when it is not due to lack of pre-operative diagnosis. This procedure, even when aimed at the evaluation of margins in impalpable lesions, should be substituted by two-view specimen X-ray.[4,9]
Use of axillary dissection in DCIS was in compliance with the target (less than 5%) but could further decrease, since this procedure is useless in DCIS and is a potential cause of complications. Pre-operative multidisciplinary discussion is the way to minimize this problem, as only through discussion with the pathologist and radiologist can the surgeon learn about the non-invasiveness of the lesion.[8] This should also help in decreasing the use in benign lesions, LIN, and low- and intermediate-grade DCIS, of SLN dissection, which is not free of complications. Importantly, for the first time, this survey shows a decline in the use of SLN biopsy in DCIS.
The proportion of missing values is still relatively large for waiting time, frozen section examination, and performance of specimen X-ray.
Although this survey includes a large share of screen-detected

Indicator	Eligible	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Min. % req.	Target
pre-operative diagnosis in cancers (C5,B5)	33,397	52.4	58.1	61.4	66.5	69.9	73.2	73.7	75.8	78.2	76.9	80.3	81.5	84.3	≥80	≥90
waiting time for surgery from referral ≤30 days	24,362	63.1	54.8	59.0	59.0	56.4	60.6	58.2	53.8	52.2	45.3	43.6	44.7	42.5	≥75	≥90
waiting time for surgery from first diagnostic test ≤42 days	29,560	69.2	49.6	47.4	46.6	41.3	42.7	42.3	36.8	32.9	35.3	31.3	30.2	27.9	≥75	≥90
waiting time for surgery from screening test ≤60 days	27,918	60.4	54.2	58.5	55.4	55.2	52.3	48.7	44.2	39.6	41.2	38.0	32.9	26.9	≥75	≥90
waiting time for surgery from screening test ≤90 days	27,918	87.0	79.6	82.7	80.1	80.4	79.2	78.9	75.7	70.0	73.6	71.1	68.9	61.9		
frozen section not performed in cancers ≤10 mm	6,200	44.4	51.8	59.6	68.3	79.5	73.0	69.3	75.8	81.0	86.1	87.2	90.8	89.4	≥95	≥95
specimen X-ray in cases with microcalcifications only	1,960	77.7	58.2	61.2	34.2	45.1	45.3	57.1	32.9	44.2	64.8	68.8	64.2	68.4	≥90	≥98
only one operation after pre-operative diagnosis (invasive)	23,523	84.9	85.4	87.1	87.8	87.9	88.7	90.0	90.4	91.3	91.8	92.8	92.4	92.4	≥80	≥90
only one operation after pre-operative diagnosis (non-invasive)	4,443	74.8	81.6	82.9	86.0	86.0	86.6	86.1	87.3	86.4	88.5	90.5	90.3	89.0	≥80	≥90
conservative surgery in invasive cancers ≤30 mm	20,680	85.2	84.3	83.1	86.6	86.9	88.4	87.9	88.0	88.9	88.6	86.6	87.1	84.7	≥70	≥90
conservative surgery in DCIS (ductal carcinoma in situ) ≤20 mm	2,956	89.8	89.4	89.0	88.5	93.5	93.0	89.1	92.3	91.0	95.5	93.9	92.8	88.2	≥80	≥90
margins >1 mm after last surgery	20,579	85.5	85.1	83.2	87.3	89.0	90.1	89.4	89.2	89.4	93.6	90.9	93.5	93.4		
number of lymph nodes >9 in axillary dissection (sampling excluded)	7,048	92.9	95.0	95.1	92.1	90.4	93.3	92.4	92.6	91.0	90.2	91.5	93.8	90.8	≥80	≥90
axillary staging by SLN only in pN0	14,741	0	14.7	47.9	60.2	69.1	75.6	82.9	86.3	89.4	91.7	90.1	90.3	92.2	≥80	≥90
no axillary dissection in DCIS	4,103	79.7	85.9	93.2	89.2	96.0	94.5	93.6	93.8	97.4	97.3	97.8	95.0	98.3	≥90	≥95
no more than 3 LNs at SLN biopsy	20,276	-	94.0	95.5	93.2	94	94.5	92.8	92.9	92.3	93.6	94.0	92.7	94.2	≥80	≥90

Table 7. Time trends for selected indicators (%), 2000-2012, age 49-70. Only regions having contributed data for the whole period (Piemonte, Valle d'Aosta, Emilia-Romagna, Toscana, Lazio) were included. Due to missing values exceeding 30%, Lazio was excluded from the indicators for waiting time for surgery from referral, specimen X-ray, and no more than 3 LNs at SLN biopsy.

Tabella 7. Andamento temporale (%) per alcuni indicatori, 2000-2012, età 49-70. Sono incluse solo le Regioni che hanno contribuito per l'intero periodo (Piemonte, Valle d'Aosta, Emilia-Romagna, Toscana e Lazio). Avendo una proporzione di valori mancanti >30%, il Lazio è escluso dal calcolo degli indicatori sui tempi di attesa dalla prescrizione, l'esecuzione della Rx sul pezzo e il numero di linfonodi sentinella escissi.

malignant cases in Italy (about 50% of cases documented in the GISMa aggregated data survey), a selection towards inclusion of cases from better-organized Regions cannot be excluded. Benign operations, furthermore, are under-recorded in some of the Regions. A larger participation in the survey by Italian regions and programmes would be appropriate, perhaps coupled with simplified data collection methods. On the other hand, it is important to maintain the connection between screening and clinical Breast units[11,12] that has been established by this project over the years: a strong point of this project is the production of timely and detailed information of interest to both clinicians and public health professionals.

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Conflicts of interests: none declared

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[1]Unità di epidemiologia dei tumori, CPO Piemonte, AOU Città della salute e della scienza, Torino
[2]Azienda sanitaria locale della Romagna, Emilia-Romagna
[3]ASL 2 Umbria - last affiliation
[4]Registro tumori della Romagna, Istituto scientifico romagnolo per lo studio e la cura dei tumori (IRST) IRCCS, Meldola, Forlì
[5]Settore promozione e sviluppo igiene e sanità pubblica, Regione Veneto, Venezia

Corresponding author
Roberta Castagno
roberta.castagno@cpo.it

Information provided by Italian breast cancer screening programmes: a comparison between 2001 and 2014

Informazioni fornite dai programmi di screening mammografico in Italia: un confronto tra il 2001 e il 2014

Roberta Castagno,[1] Debora Canuti ,[2] Marco Petrella,[3] Lauro Bucchi,[4] Chiara Fedato,[5] Francesca Garena,[1] Livia Giordano[1]

Abstract

Debate on efficacy, benefits, and risks of breast cancer screening continues to rage, and scientific controversy surrounding overdiagnosis, false positives/false negatives, raises questions about communication to women attending screening programmes.

The study compares information provided by invitation letters and leaflets of Italian breast screening programmes in 2001 (N=47) and 2014 (N=80). At both times, nearly all programmes provided adequate practical information and details about screening objectives and test procedures. Information regarding epidemiology/figures was scarce or absent in 2001, while in 2014 a number of programmes began to inform women about screening risks (false negative and positive results and overdiagnosis, 65%, 16%, and 21% respectively) although actual figures were rarely supplied.

Despite this small improvement, Italian programmes are still far from giving balanced information. Further efforts should be addressed to providing accurate and transparent information, enabling women to make an informed choice.

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Keywords: breast cancer screening, invitation letter, leaflets, overdiagnosis, Italy

Riassunto

Il dibattito sull'efficacia, i benefici ed i rischi dello screening mammografico, in termini di sovradiagnosi e sovratrattamento, falsi positivi/negativi, hanno portato a riflettere su quale tipo di comunicazione occorre dare alle donne. Lo studio confronta le informazioni fornite dalle lettere di invito e gli opuscoli dei programmi di screening mammografico italiani nel 2001 (N=47) e nel 2014 (N=80). Quasi tutti i programmi, sia nel 2001 che attualmente, forniscono adeguate informazioni logistico-organizzative e dettagli sugli obiettivi dello screening e la procedura del test. Le informazioni epidemiologiche/numeriche, nel 2001, sono per lo più assenti o solo raramente presenti, mentre nel 2014 alcuni programmi cominciano a dare informazioni anche sui rischi dello screening (falsi negativi, falsi positivi e sovradiagnosi, rispettivamente 65%, 16% e 21%), anche se solo raramente quantificano tali concetti. Nonostante qualche miglioramento, i programmi italiani non forniscono ancora informazioni complete e bilanciate. Saranno quindi necessari ulteriori sforzi per migliorare la capacità dei programmi nel produrre e trasmettere un'efficace comunicazione sullo screening mammografico al fine di permettere alle donne di fare una scelta informata.

(*Epidemiol Prev* 2015; 39(3) Suppl 1: 48-51)

Parole chiave: screening mammografico, lettere di invito, opuscoli, sovradiagnosi, Italia

INTRODUCTION

The former approach to breast cancer screening information emphasized screening benefits for the population, following the imperative of achieving adequate uptake to have an impact on mortality.[1]

Over the last few years, there has been growing European concern about risks and benefits of mammography screening[2-3] and how to communicate this to women.[4] Whether breast screening causes more harm than good has been widely debated. The main issues are how great the benefits of screening are in terms of reduced breast cancer mortality[2,5] and how significant the harms are, especially in terms of overdiagnosis (defined as cancers detected at screening that would not have otherwise become clinically apparent in a woman's lifetime[2]) and false positive and false negative outcomes.[7-9] Therefore, the entire scientific community now supports the need for balanced information that explains both the harms and benefits for women attending screening. Invitation letters and written information material are the most common means of communication used by organized screening programmes.

In spring 2014, the Italian group for mammography screening (GISMa) promoted a survey to investigate what information Italian organized breast cancer screening programmes provide to women. The same investigation had been carried out in 2001. The aim of the current study is to compare the two surveys to verify how mammography screening information has evolved over time.

METHODS

In 2001 and 2014, invitation letters and leaflets in use by Italian organized mammography screening programmes were collected and evaluated through a score sheet designed for this purpose. The score sheet assesses the presence of logistic and organizational information, screening objectives, mammography and screening information, and epidemiological/quantitative data, including the presence of epidemiological figures and estimates. All issues are detailed in **table 1** (p. 50).

All materials were assessed by two readers with the support of a supervisor. There was no evaluation concerning layout quality and wording of these tools in this phase of the study.

RESULTS

Nearly 90% of active programmes in Italy responded both years (53/60 programmes in 2001 and 110/124 in 2014). Among these, 47 and 80 information sets (invitation letter plus leaflet) were included in the 2001 and 2014 analysis, respectively.

The main results of the two surveys are presented in **table 1** and summarized below.

Logistic and organizational information

Compared to 2001, in 2014 a greater number of programmes notified women about how and when to obtain their mammography results (88.8% *vs* 61.6% and 33.8% *vs* 17.0%, respectively).

In 2001, no programme conveyed messages of informed consent and only 6.4% informed on data confidentiality. In 2014, 25% of programmes mentioned informed consent and, after the Data Protection Code came into effect in 2003, many more of the information tools in use referred to data confidentiality (45.1%). In addition, in 2014 nearly 75% of programmes provided explanations about quality control activities and the involvement of properly trained professionals (compared to only 17.0% in 2001).

This type of practical information was present and carefully described in both surveys and was essentially conveyed by the invitation letter.

Screening objectives

The percentage of tools describing «what a screening programme is» more than doubled over time (44.6% in 2001 *vs* 92.5% in 2014).

The entirety of programmes fully described the target population and benefits of mammography screening (in terms of the importance of early detection to reduce breast cancer mortality and increase the chances of recovery), both in 2001 and 2014.

Mammography and screening information

In both surveys almost all programmes described «what a mammography is» (93.6% in 2001 *vs* 98.9% in 2014) and the interval between the two tests (95.7% in 2001 *vs* 100% in 2014).

The percentage of tools specifying the double reading of the test was nearly twice in 2014 compared to 2001 (56.3% *vs* 27.7%).

In 2001, poor information about side effects (pain and discomfort caused by the test) and radiation-related risks were provided (34% and 6%, respectively) compared with today's material (86.4% on both topics).

In 2014, 97.5% of programmes informed women about the possibility to be recalled for further assessments (68% in 2001), 55.1% described what further assessments consist of (no programmes in 2001) and 25% also stated the rate (recall rate).

Detailed information related to test procedures was provided both in 2001 and 2014 almost exclusively by the information leaflet.

Epidemiological information/quantitative data

In 2001, epidemiological information and numerical data were very rare or missing. The data mentioned by programmes were breast cancer incidence (14.9%), lifetime risk of developing breast cancer (8.5%), and relative risk reduction mortality (23.4%). No information was given about overdiagnosis, false negative and false positive results.

In 2014, a greater number of tools illustrated information about breast cancer incidence (16.3%), lifetime risk of developing breast cancer (20%), and relative risk reduction mortality (25.1%). Furthermore, some programmes also began to

	Invitation letter only (%)		Leaflet only (%)		Both (%)		Total (%)	
	2001 (N=47)	2014 (N=80)	2001 (N=47)	2014 (N=80)	2001 (N=47)	2014 (N=80)	2001 (N=47)	2014 (N=80)
Logistic and organizational information								
How to fix and/or how to change the appointment	51.1	41.3	2.1	1.3	40.4	52.5	93.6	95.1
Documents women should bring	38.3	61.3	6.4	0.0	40.4	38.8	85.1	100.0
Free test or not	17.0	15.0	0.0	0.0	83.0	83.8	100.0	98.8
How to get the results	10.6	18.8	25.5	25.0	25.5	45.0	61.6	88.8
When to get the results	2.1	10.0	14.9	23.8	0.0	0.0	17.0	33.8
Informed consent	0.0	12.5	0.0	10.0	0.0	2.5	0.0	25.0
Data confidentiality	2.1	38.8	4.3	3.8	0.0	2.5	6.4	45.1
Quality control/operator training	0.0	1.3	17.0	63.8	0.0	8.8	17.0	73.9
Screening objectives								
What a screening programme is	2.1	20.0	40.4	7.5	2.1	65.0	44.6	92.5
Mammography benefits	0.0	3.8	66.0	63.8	34.0	32.5	100.0	100.0
Who the test is for	0.0	6.3	36.2	36.3	63.8	57.5	100.0	100.0
Mammography and screening information								
What a mammography is	0.0	3.8	63.8	73.8	29.8	21.3	93.6	98.9
Screening interval	4.2	6.3	51.1	47.5	40.4	46.3	95.7	100.0
How it is performed	0.0	0.0	29.8	47.5	0.0	3.8	29.8	51.3
How long it takes	0.0	0.0	59.6	48.8	26.7	3.8	86.3	52.6
Who reads the test	0.0	1.3	27.7	50.0	0.0	5.0	27.7	56.3
Side effects	2.1	1.3	29.8	78.8	2.1	6.3	34.0	86.4
Radiation risk	0.0	1.3	6.4	83.8	0.0	1.3	6.4	86.4
Breast awareness	0.0	0.0	0.0	77.5	0.0	1.3	0.0	78.8
Further assessments (mentioned)	23.4	2.5	36.2	45.0	8.5	50.0	68.1	97.5
Further assessments (described)	0.0	1.3	0.0	53.8	0.0	0.0	0.0	55.1
Epidemiological and quantitative data								
Breast cancer incidence	0.0	2.5	14.9	13.8	0.0	0.0	14.9	16.3
Lifetime risk of developing breast cancer	0.0	0.0	8.5	20.0	0.0	0.0	8.5	20.0
Lifetime risk of dying from breast cancer	0.0	0.0	0.0	6.3	0.0	0.0	0.0	6.3
Survival from breast cancer	0.0	0.0	2.1	2.5	0.0	0.0	2.1	2.5
Relative risk reduction mortality	0.0	0.0	23.4	21.3	0.0	3.8	23.4	25.1
Absolute risk reduction mortality	0.0	0.0	0.0	11.3	0.0	0.0	0.0	11.3
Proportion of screened women who would be recalled	0.0	0.0	0.0	25.0	0.0	0.0	0.0	25.0
Proportion of breast cancers detected by mammography (sensitivity)	0.0	1.3	2.1	18.8	0.0	0.0	2.1	20.1
Proportion of women without breast cancer who would have a positive mammogram (specificity)	0.0	1.3	0.0	0.0	0.0	0.0	0.0	1.3
Proportion of women with positive mammogram who would have a breast cancer (PPV)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
False negative results	0.0	0.0	0.0	61.3	0.0	3.8	0.0	65.1
False positive results	0.0	0.0	0.0	16.3	0.0	0.0	0.0	16.3
Overdiagnosis	0.0	0.0	0.0	21.3	0.0	0.0	0.0	21.3

Table 1. Information provided in invitation letters and leaflets in 2001 and 2014.
Tabella 1. Informazioni fornite nelle lettere di invito e nelle brochure distribuite nel 2001 e nel 2014.

inform women about overdiagnosis (21.3%), false negative results (65.1%), and false positive results (16.3%). Nevertheless, numerical data were seldom provided. All this information, when present, was conveyed by the leaflets.

DISCUSSION

Comparison between the two surveys shows that completeness of information has increased over time. Nevertheless, there is still a great degree of variation in the information provided by mammography screening programmes, especially relating to epidemiological and numerical information.

Italian programmes have consistently provided adequate logistic and organizational information, which is conveyed mainly by the invitation letters.

Leaflets attached to invitation letters give more detailed information about screening programme organization, test procedures and benefits and harms of mammography screening. The latter, such as overdiagnosis, false negative and false pos-

itive results, were mentioned more often in 2014, although rarely quantified.

Despite this small improvement, Italian programmes are still far from providing balanced information. Adequate communication (including figures and estimates) about all negative effects of screening is still a challenge that requires the efforts and resources of the entire screening community.

This analysis may be taken as a starting point for defining the most appropriate tools and circumstances to facilitate an informed choice. It could also help to evaluate strategies to improve the quality of information.

In a screening context, information can be conveyed by various means, even though written materials (invitation letter plus leaflet) remain the main source of communication, especially in organized screening programmes. A crucial issue that needs to be discussed within the GISMa group is that of how to promote consistency of breast cancer screening information among Italian programmes. In particular, discussion should focus on the need for recommendations concerning the contents of invitation letters and leaflets, to standardize invitation tools nationwide.

Moreover, the quality of layout and wording of the material should also be studied in depth, to assess information accuracy, especially in terms of clarity of language and syntax.

Conflicts of interests: none declared

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Problems, solutions, and perspectives in the evaluation of interval cancers in Italian mammography screening programmes: a position paper from the Italian group for mammography screening (GISMa)

Problemi, soluzioni e prospettive nella valutazione dei cancri d'intervallo nei programmi italiani di screening mammografico: un position paper del Gruppo italiano screening mammografico (GISMa)

Lauro Bucchi,[1] Alfonso Frigerio,[2] Manuel Zorzi,[3] Chiara Fedato,[4] Giovanni Angiolucci,[5] Daniela Bernardi,[6] Cinzia Campari,[7] Emanuele Crocetti,[8] Stefano Ferretti,[9] Daniela Giorgi,[10] Francesca Marchisio,[11] Doralba Morrone,[12] Carlo Naldoni,[13] Marco Petrella,[14] Antonio Ponti,[15] Alessandra Ravaioli,[1] Gianni Saguatti,[16] Dolores Santini,[11] Priscilla Sassoli de Bianchi,[13] Monica Serafini,[17] Viviana Vergini,[15] Livia Giordano[15]

This article is dedicated to the memory of Stefano Ciatto

[1]Registro tumori della Romagna, Istituto scientifico romagnolo per lo studio e la cura dei tumori (IRST) IRCCS, Meldola, Forlì
[2]Centro di riferimento regionale per lo screening mammografico, Torino
[3]Registro tumori del Veneto, Regione Veneto, Padova
[4]Coordinamento regionale screening, Regione Veneto, Venezia
[5]Senologia diagnostica, Azienda unità sanitaria locale, Arezzo
[6]Unità operativa di senologia clinica e screening mammografico, Azienda provinciale servizi sanitari, Trento
[7]Centro screening, Azienda unità sanitaria locale, Reggio Emilia
[8]Unità di epidemiologia clinica e descrittiva, Istituto per lo studio e la prevenzione oncologica, Istituto tumori toscano, Firenze
[9]Registro tumori di Ferrara, Ferrara
[10]Unità di epidemiologia, Azienda sanitaria locale, Istituto tumori toscano, Lucca
[11]Centro screening mammografico, Azienda unità sanitaria locale, Modena
[12]Unità operativa di senologia, Istituto per lo studio e la prevenzione oncologica, Istituto tumori toscano, Firenze
[13]Assessorato alle politiche per la salute, Regione Emilia-Romagna, Bologna
[14]Unità operativa di epidemiologia, Azienda unità sanitaria locale 2 dell'Umbria, Perugia
[15]Unità di epidemiologia dei tumori, Centro di riferimento per l'epidemiologia e la prevenzione oncologica in Piemonte, AOU Città della salute e della scienza, Torino
[16]Unità operativa di senologia, Azienda unità sanitaria locale, Bologna
[17]Centro di prevenzione oncologica, Azienda unità sanitaria locale, Ravenna

Corresponding author: Lauro Bucchi, lauro.bucchi@irst.emr.it

Abstract

In this position paper, a self-convened team of experts from the Italian Group for Mammography Screening (Gruppo italiano screening mammografico, GISMa) pointed out the problems that increasingly hamper the feasibility and validity of the estimate of the proportional incidence of interval breast cancer (IBC) in Italy, suggested potential solutions and an agenda for research, and proposed that the question of the sensitivity of mammography be viewed in a larger perspective, with a greater attention to radiological review activities and breast radiology quality assurance programmes.

The main problems are as follows: the coverage of cancer registration is incomplete; the robustness of using the pre-screening incidence rates as underlying rates decreases with time since the start of screening; the intermediate mammograms performed for early detection purposes may cause an overrepresentation of IBCs; the classification of many borderline screening histories is prone to subjectivity; and, finally, the composition of cohorts of women with negative screening results is uncertain, because several mammography reports are neither clearly negative nor clearly positive, and because of the limitations and instability of the electronic mammography records.

Several possibilities can be considered to cope with these issues: standard methods for using the hospital discharge records in the identification of IBCs should be established; for the calculation of regional estimates of the underlying incidence, a suitable mathematical model should be identified; the definition of IBC according to the 2008 GISMa guidelines needs to be updated, especially with respect to in situ cancers and to invasive cancers with borderline screening histories; a closer adherence to standard screening protocols, with a simplified patient management, would make it easier to objectively identify IBCs; alternative methods for estimating the sensitivity of mammography should be taken into consideration; and, finally, analysis could be restricted to the absolute incidence rate of IBC, which would make comparison of the risk between neighbouring populations possible.

Epidemiologists must extend their attention to the prevention of the risk of IBC and the implementation of breast radiology quality assurance practices. Epidemiologists and radiologists can share common objectives: it is necessary to promote the idea that the availability of a registry-based series of IBCs is not a prerequisite for their radiological review; radiological review of breast cancers greater than 20mm in size detected at second and subsequent screens, that are potential substitutes for IBCs, needs radiological and epidemiological validation studies; the advent of digital mammography brings about the possibility to create libraries of mammograms accessible online, which enables the conduct of large studies of the diagnostic variability of radiologists; and, finally, epidemiologists and radiologists have the responsibility to monitor the effects that a loss of cumulative professional experience in screening centres, due to the imminent retirement of a substantial proportion of healthcare workforce, could cause on their performance.

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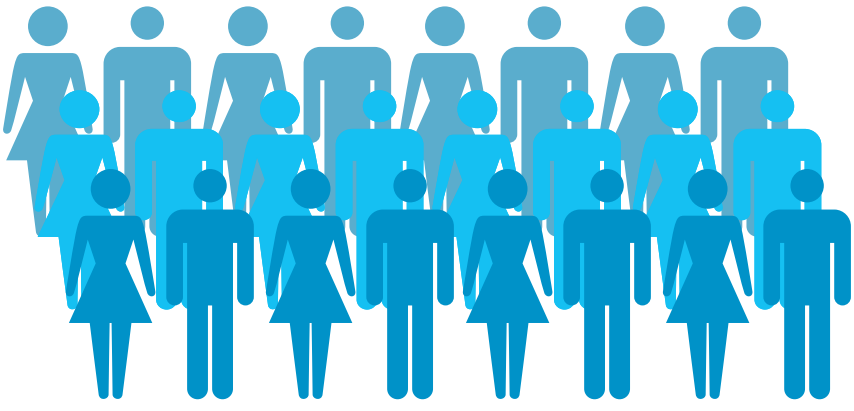
Keywords: screening, mammography, quality assurance, breast cancer, interval cancer

Riassunto

In questo position paper, un team spontaneo di esperti associati al Gruppo italiano screening mammografico: (1) puntualizza i limiti metodologici e i fattori distorsivi che compromettono la valutazione dell'incidenza dei cancri d'intervallo nei programmi di screening in Italia, (2) suggerisce le possibili soluzioni e un'agenda per la ricerca, e (3) propone che il problema dei cancri d'intervallo sia inserito in una prospettiva più ampia, con una maggiore attenzione per le attività di revisione radiologica e per i programmi di quality assurance in radiologia senologica.

(*Epidemiol Prev* 2015; 39(3) Suppl 1: 52-57)

Parole chiave: screening, mammografia, cancro della mammella, cancro d'intervallo



INTRODUCTION

The sensitivity of mammography is a major factor for the effectiveness of a breast screening programme. The reference method to evaluate the sensitivity of mammography is based on the estimate of the proportional incidence of interval breast cancer (IBC).

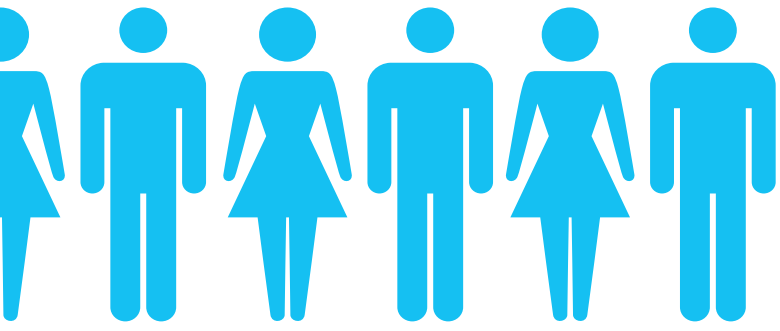
IBCs are cancers diagnosed after a negative mammography result and before next invitation to screening, or within two years if the woman has reached the age for screening cessation. The proportional incidence of IBC is the incidence observed during the screening interval as compared to the incidence that would be expected in the absence of screening, or underlying incidence. This proportion gives an approximation of the rate of mammography failures in abolishing the incidence of breast cancer during the screening interval. In other words, the proportional incidence of IBC is equal to 1 – the sensitivity of mammography.

According to the 2008 guidelines from the Italian group for mammography screening (Gruppo italiano screening mammografico, GISMa),[1] the scientific society that gathers all professionals involved in any aspect of mammography screening in the country, the performance indicators of every screening programme must include the absolute and proportional rates of IBC, as well as the rate of IBCs interpreted to be visible on retrospective radiological review. In the epidemiological guidelines chapter of the *European guidelines for quality assurance in breast cancer screening and diagnosis*,[2] the estimate of the proportional incidence of IBC is among the impact indicators, although it is stated that it suffers from «several limitations».

This position paper originated from an initiative of members of GISMa's Coordinating Committee, who drafted a working document and asked for amendments and proposals from epidemiologists and radiologists members of the society. The paper aims at:

- pointing out the problems that increasingly hamper the feasibility and validity of the estimate of the proportional incidence of IBC in Italy;
- suggesting potential solutions and an agenda for research;
- proposing that the question of IBC be viewed in a larger perspective, with a greater attention to radiological review activities and breast radiology quality assurance programmes.

The authors of this paper will submit a set of essential proposals to the incoming Coordinating Committee of the GISMa.



PROBLEMS

The problems that affect the estimate of the proportional incidence of IBC can be summarized as follows.

- With respect to the identification of IBCs, the main limitations are the incomplete coverage of cancer registration and the delay – of a few years – by which the annual case series are completed. The only available alternative is to create efficient special breast cancer registries, whether based on standard methods of cancer registration or hospital discharge records. This can also be done by the screening centres themselves. GISMa guidelines accepted the use of hospital discharge records, although they stated that developing standard methods was an urgent need.[1] To this end, they proposed the formation of a workgroup.
- The robustness of using the pre-screening incidence rates as underlying rates decreases with time since the start of the screening programme. It is unsafe both to assume that those rates, if not modified by screening, would have been stable over time, and to linearly extrapolate them to the present time. This limitation is mentioned in the epidemiological guidelines chapter of the European guidelines.[2] The 2008 GISMa guidelines suggested the calculation and use of regional incidence estimates.[1] These too were defined as an urgent need.
- Intermediate mammograms performed at clinical radiology facilities for early detection purposes may cause an overrepresentation of IBCs. They lead to the detection of asymptomatic cancers that cancer registries, if lacking information on their actual clinical status, inevitably classify as IBCs. The same may happen following intermediate mammograms actively offered within the screening programmes (early rescreen), if they are recorded as diagnostic examinations rather than true screening examinations. It is an epidemiological paradox that the practice of performing intermediate mammograms, while increasing the sensitivity of mammography for early breast cancer, causes apparently the opposite effect.
- GISMa guidelines took into consideration the question of whether the definition of interval cancer may include the cancers diagnosed during the third interval year or later, or after a negative or an inconclusive assessment, or after a woman's refusal to undergo assessment, or after discontinuation of participation in the programme, or after a previous diagnosis of breast cancer.[1] The definition of IBC was expanded to include some of these screening histories, but their interpretation in a real-world screening setting remains prone to subjectivity.
- Another source of variability is the eligibility of in situ breast cancers, which is interconnected with the problem of their registration. GISMa guidelines suggested excluding in situ breast cancers from the estimate of the proportional incidence of IBC, given that they are incompletely registered and given their benign and generally non-progressive behaviour. Nevertheless, the guidelines recommended that interval in situ breast cancers known to the screening centres be subject to radiological review.[1]
- Along with the diffusion of mammography screening into widespread use, the procedure has become increasingly het-

erogeneous and complex. This change is connected to the emerging idea of an individually tailored screening.[3] One of the most notable consequences of this is that the classic dichotomous classification of mammography results has been abandoned in certain screening programmes and in certain circumstances. More and more often there are borderline mammography reports that are neither clearly negative nor clearly positive. In the estimate of the proportional incidence of IBC, this introduces a degree of uncertainty both in the composition of cohorts of women with negative screening results and in the detection mode of incident breast cancers.

■ The composition of cohorts of women with negative screening results is also uncertain because of the limitations and instability of the electronic mammography records. Screening centres are equipped with a variety of computer systems and softwares. Many of these are designed solely for the delivery of the service, not for the evaluation of results.

SOLUTIONS

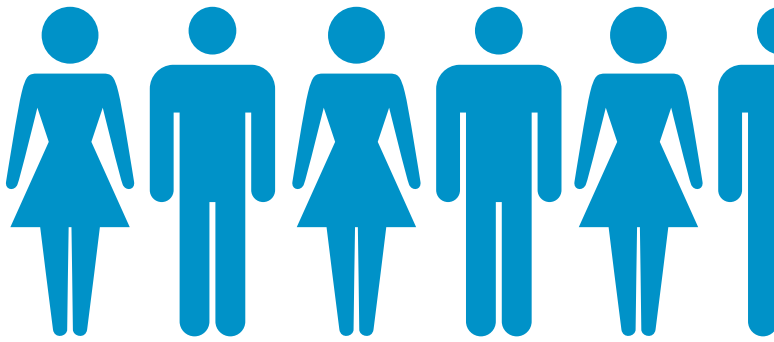
Several possibilities can be considered to resolve these issues, at least to a certain extent.

■ The GISMa guideline recommending that a workgroup be appointed to establish standard methods for using the hospital discharge records in the identification of IBCs[1] should be implemented. The workgroup can be comprised of those epidemiologists who are currently using the hospital discharge records as a basis for registration.

■ As far as the underlying incidence rates are concerned, the GISMa guideline recommending the calculation and use of regional estimates[1] remains valid. It can be suggested to GISMa's Coordinating committee to formally ask the National centre for screening monitoring (Osservatorio nazionale screening, ONS) to examine the mathematical models that are being used to estimate breast cancer incidence, and to select the most suited one.

■ Certain issues of the 2008 GISMa guidelines[1] need to be updated. In particular, it would be advisable to re-examine the eligibility of in situ cancers and of invasive cancers diagnosed during the third interval year or later, or after a negative or an inconclusive assessment, or after a woman's refusal to undergo assessment, or after discontinuation of participation in the programme, or after a previous diagnosis of breast cancer. Moreover, the chapter on the definition of IBC should include a definition of what a negative mammography result is, taking the problem of borderline screening histories into consideration. Epidemiologists with previous experience in the classification of IBC detection modes should compare their methods with each other and with the radiologists' point of view.

■ Theoretically, an option to objectively classify IBC detection mode is to draw the attention of screening units to the opportunity of adhering more closely to standard screening protocols. A simplified patient management would make it easier to identify IBCs and – no less important – limit the diffusion of unplanned forms of individually tailored screening. This could be coupled with an effort to standardize the nomenclature used in mammography reports as well as their format, at least on a regional scale.



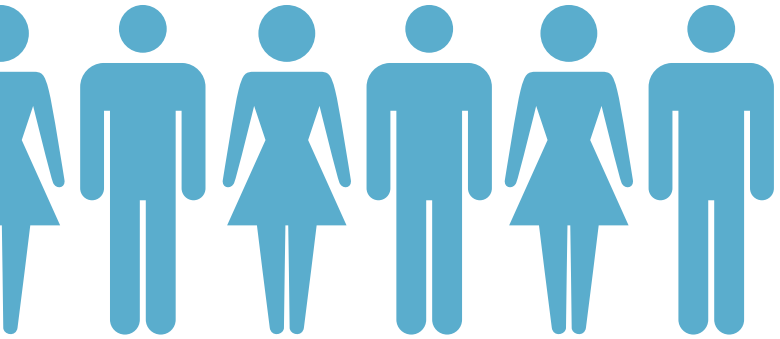
■ An innovative approach to the evaluation of the sensitivity of mammography, which is commonly referred to as the unbiased set method,[4] is not to use estimates of the underlying incidence nor pre-screening incidence rates. The method requires the availability of a general or a special cancer registry and of information on the detection mode of registered breast cancers. However, it uses only screen-detected cancers (except those detected in the prevalence screen) and IBCs. The method was explicitly proposed for screening programmes of long duration, which is the case for most programmes in Italy. It could be suggested to GISMa as well as ONS to consider adopting the unbiased set method as a reference method.

■ A minimalist approach to the evaluation of the incidence of IBC, which has already been advised by European guidelines,[2] would be to restrict analysis to the absolute incidence rate. On the one hand, this would mean neglecting the estimate of mammography sensitivity. On the other hand, however, it would allow the risk of IBC to be compared between neighbouring populations (for example, those living in different health care districts of an administrative region) who can be assumed to have the same underlying breast cancer incidence. This would also provide radiologists with a practical self-evaluation tool.

■ Until workable and effective solutions are found, the limitations in estimating the proportional incidence of IBC need to be well understood across the health system. The present paper aims at preventing the use of currently available estimates for legal and administrative purposes.

■ The same caution should be used in public communication concerning the harms of mammography screening, which is recommended by European guidelines.[5] In the presentation of screening programmes (public advertising campaigns and invitation letters), information on false-negative mammography results is insufficient. However, the information material should simply state that false-negative results are possible, and should describe the radiology facility characteristics that may influence the accuracy of diagnosis (for example, the range of annual screening mammogram reading volume of local radiologists). Numerical estimates of the sensitivity of mammography, which are poorly reliable and difficult to communicate, must be avoided.

■ Lastly, we suggest a change in the scientific paradigm that has



so far underlain IBC evaluation. GISMa guidelines recommend not only to estimate the proportional incidence of IBC, but also to retrospectively review the mammograms.[1] More attention and resources should be devoted to the reviewing process. The value of radiological review, both for quality assurance and continuing education purposes, is repeatedly emphasized by European guidelines.[2,6]

■ Approaching the problem of IBCs from the perspective of breast radiology quality assurance would give practical implementation to a 2008 document from the Ministry of Health (Direzione generale della prevenzione sanitaria del Ministero della salute) in which it was stated that the registration of IBCs should be accompanied by actions aimed at increasing the levels of quality of the screening process.[7] The document suggested that the review process be done in a semi-informed manner, which has a greater educational impact in that it focuses on criteria for women's recall and not on medico-legal evaluations. For medico-legal purposes, the reference method is a blinded review of mammograms performed by a group of non-informed expert consultants from a national certified register.

PERSPECTIVES

Epidemiologists must extend their attention to the prevention of the risk of IBC, and consider that the implementation of breast radiology quality assurance practices can be a common point of interest with radiologists. The proportional incidence of IBC, which is generally calculated at the screening programme level and not at the single radiologist level, does not provide clues to improve the sensitivity of mammography, because it has no specific feedback on the diagnostic performance. Conversely, radiological review of IBCs has a direct educational impact.[8] The estimate of the proportional incidence of IBC is a good example of how the descriptive epidemiology of cancer provides valuable information about the size of problems, but often without the capacity to make a real contribution to cope with them.[9] Unfortunately, in the long run, a descriptive work that fails to promote appropriate actions loses its rationale.

Following this line of reasoning, it must be noted that the annual GISMa surveys of results of mammography screening in Italy have shown for years a situation where the recall at second and subsequent screens is above the acceptable standard of 5% for one-third of local programmes, and where the practice of performing intermediate mammograms is widespread.[10] This would require regular training programmes that are currently insufficient.

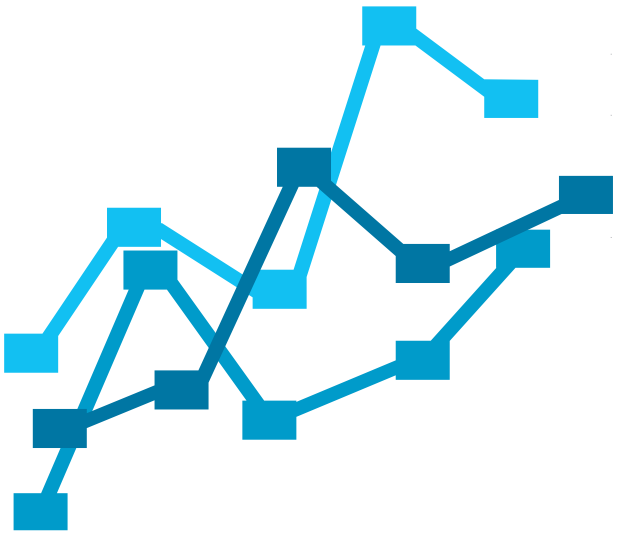
The following are some suggestions on how epidemiologists and radiologists can interact positively and fruitfully.

■ The absence of radiological review activities in those screening centres that are served by a general or a special cancer registry is an unacceptable situation, in addition to being an original type of underuse of cancer registration.[9] Where this occurs, epidemiologists and radiologists should work together to find a solution.

■ At the same time, both epidemiologists and radiologists should promote the idea that the availability of a complete, registry-based series of IBCs is a prerequisite only for estimating their proportional incidence, not for their radiological review. Besides, this should be done as soon as an IBC is detected or becomes known to the screening centre.

■ GISMa guidelines[1] and a study from the screening unit of Trento[11] have supported the radiological review of breast cancers greater than 20 mm in size detected at second and subsequent screens. GISMA's Workgroup on diagnosis (Gruppo di lavoro area diagnosi) has proposed, in particular, that these cancers be used as substitutes for IBCs in radiological review activities at those screening centres where reviewing IBCs is problematic.[12] The radiological review of screen-detected breast cancers greater than 20 mm in size is potentially feasible on a national scale and would make it possible to set up true national standards for all screening programmes in the country. This approach, however, requires radiological and epidemiological validation studies.

■ Screening units that have already estimated the proportional incidence of IBC should be encouraged to determine whether, in their data, there is a relationship between the sensitivity of mammography and the prevalence of breast cancers greater than 20 mm in size detected at second and subsequent screens.[13]



■ The advent of digital mammography has brought about the possibility to create, in conjunction with central radiological review activities, libraries of mammograms accessible online. Although there remains the problem of obtaining the informed consent of patients, radiologist access to reviewed mammograms would represent an important opportunity for research and training. Online libraries could be completed with images representing a larger spectrum of mammographic abnormalities. Epidemiologists could contribute to these developments by designing studies of the radiologist variability in interpretation of mammography findings.

■ Between mid-2013 and early 2014, GISMa's Coordinating committee carried out a national questionnaire survey of radiologist's experience-related characteristics (for example, annual screening mammogram reading volume, and the percentage of working time devoted to breast radiology). The survey is particularly topical given that the budget constraints that the Italian National Health Service is facing may lead to increasing flexibility of mammogram-reading teams, as has been reported from the United Kingdom.[14] The data from the survey will have to be evaluated both from a radiological and an epidemiological point of view, because they could support the hypothesis that radiologist's experience-related characteristics are associated with current results of local screening programmes.[10]

■ In the 1980s, the implementation of the new National Health Service, coupled with an aggressive policy of deficit spending, originated a dramatic increase in the number of medical and paramedical staff in the public sector. The imminent retirement of this workforce makes it urgent to assess the professional and training needs of screening centres. The basic role of high-level specific training would suggest that part of the resources currently devoted to mammography screening programmes be allocated to the creation and maintenance of a limited number of multidisciplinary national training centres, following the experience of other European countries. Epidemiologists are responsible, in collaboration with radiologists, for monitoring the effects that a loss of cumulative professional experience in screening centres could cause on their performance.

Conflicts of interests: none declared

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Cervical cancer screening

Glossary

Theoretical or potential or nominal extension: percentage of women involved in a screening programme out of the total female population in the 25-64 age range resident in the area covered by an organized screening programme.

Actual extension or Extension of invitations: percentage of women involved in a screening programme out of the total female population in the 25-64 age range who actually received an invitation to screening during the analyzed period.

Compliance with invitation or Attendance: percentage of women attending screening out of invited women.

Referral rate: percentage of women referred to colposcopy (for any reason) out of the total number of screened women.

Recommendation to repeat cytology: percentage of women recommended to repeat cytology out of the total number of screened women.

Compliance to recommendation to repeat cytology: percentage of women who actually repeated cytology among those who were recommended to do so.

Compliance to colposcopy for ASCUS+: percentage of women who underwent colposcopy out of women referred to colposcopy because of ASCUS or more severe cytology.

Compliance to colposcopy for HSIL+: percentage of women who underwent colposcopy out of women referred to colposcopy because of HSIL or more severe cytology.

Positive predictive value (PPV) of referral to colposcopy because of ASCUS+ cytology for histologically confirmed CIN2+: proportion of women with histologically confirmed CIN2+ out of women referred to colposcopy because of ASCUS or more severe cytology.

Detection rate (DR) CIN2+ unadjusted: number of women who had a CIN2+ detected out of 1,000 screened women.

Detection rate (DR) CIN2+ stand. Ita.: number of women who had a CIN2+ detected out of 1,000 screened women, adjusted for age in 5-year groups on the Italian population.

Italian cervical cancer screening survey group:
Gruppo di lavoro italiano per la survey sullo screening cervicale:

Abruzzo: Tamara Agostini, Direzione politiche della salute, Regione Abruzzo, Pescara
Basilicata: Vincenzo Barile, Angelo Sigillito, Sergio Schettini, AO San Carlo, Potenza
Calabria: Liliana Rizzo, Dipartimento Tutela della salute e politiche sanitarie, Regione Calabria, Catanzaro
Campania: Renato Pizzuti, Osservatorio epidemiologico regionale, Assessorato alla sanità, Regione Campania, Napoli
Emilia-Romagna: Carlo Naldoni, Assessorato alle politiche per la salute, Regione Emilia-Romagna, Bologna
Friuli-Venezia Giulia: Nora Coppola, Direzione centrale salute, integrazione socio sanitaria, politiche sociali e famiglia, Regione Friuli-Venezia Giulia, Trieste
Lazio: Alessandra Barca, Lazio sanità, Agenzia di sanità pubblica, Roma
Liguria: Luigina Bonelli, Gabriella Paoli, Istituto nazionale per la ricerca sul cancro, Genova
Lombardia: Direzione generale salute, Regione Lombardia, Milano
Marche: Lucia Di Furia, Servizio salute, Regione Marche, Ancona
Molise: Ospedale Cardarelli, Regione Molise, Campobasso
Piemonte: Nereo Segnan, Centro prevenzione oncologia – CPO Piemonte, Torino
Provincia Autonoma di Bolzano (Alto Adige): Antonio Fanolla, Assessorato alla sanità, Osservatorio epidemiologico, Provincia autonoma di Bolzano, Bolzano
Provincia Autonoma di Trento (Trentino): Sivano Piffer, Giovanni De Pretis, Osservatorio epidemiologico, Azienda provinciale per i servizi sanitari, Trento
Puglia: Vincenzo Pomo, Cinzia Annatea Germinario, Agenzia regionale sanità, Regione Puglia, Bari
Sardegna: Pierina Thanchis, Assessorato dell'igiene e sanità e dell'assistenza sociale, Regione Sardegna, Cagliari
Toscana: Paola Mantellini, Istituto per lo studio e la prevenzione oncologica, Regione Toscana, Firenze
Umbria: Mariadonata Giaimo, Direzione regionale salute, coesione sociale e società della conoscenza, Regione Umbria, Perugia
Valle D'Aosta: Gabriella Furfaro, Servizio dipendenze patologiche, salute mentale e promozione della salute, Aosta
Veneto: Chiara Fedato, Registro tumori del Veneto, Padova

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[1]AOU Città della salute e della scienza, CPO Piemonte, Torino
[2]Istituto per lo studio e la prevenzione oncologica (ISPO), Firenze
[3]AOU Città della salute e della scienza, Ospedale S. Anna, Torino
[4]Servizio interaziendale di epidemiologia, AUSL Reggio Emilia
[5]IRCCS-Arcispedale S. Maria Nuova, Reggio Emilia

Corresponding author:
Guglielmo Ronco
guglielmo.ronco@cpo.it

Extension of organized cervical cancer screening programmes in Italy and their process indicators, 2011-2012 activity

Estensione dei programmi organizzati di screening cervicale in Italia e loro indicatori di processo

Guglielmo Ronco,[1] Pamela Giubilato,[1] Francesca Carozzi,[2] Giovanni Maina,[3] Paolo-Giorgi-Rossi,[4,5] Marco Zappa[2] and the Italian cervical cancer screening survey group

Abstract

Italian national guidelines recommend regional implementation of organized screening programmes for cervical cancer. As we have been doing since 1998, we collected aggregated tables of data from Italian organized cervical screening programmes in order to centrally compute process indicators. Data on women invited during 2011 and 2012 and screened up to April of the subsequent year were considered.
In 2012, the target population of Italian organized screening programmes included 14,497,207 women, corresponding to 87.3% of Italian women aged 25-64 years.
Compliance to invitation was 41.2% in 2011 and 40.8% in 2012, with a strong decreasing North-South trend. However, it should be considered that many women are screened outside any organized programmes. In 2012, of the women screened, 3.5% were referred for repeat cytology and 71.1% of them complied; 2.4% of screened women were referred to colposcopy.
Compliance with colposcopy referral was 85.3% among women referred because of ASC-US or more severe cytology and 90.4% among those referred because of HSIL or more severe cytology. The positive predictive value (PPV) of referral because of ASC-US or more severe cytology for CIN2 or more severe histology was 16.9%. The unadjusted detection rate of CIN2 or more severe histology was 3.4 per 1,000 screened women (3.6 standardized on the Italian population, truncated 25-64). CIN2 or more severe histology was detected in 64.6% of colposcopies classified as grade 2 or higher. Of all colposcopies during which a CIN2 or more severe histology was obtained, 33.6% were classified as grade 2 or higher. Follow-up only was recommended to 81.7% of women with CIN1.
Excision by radio-frequency device was the most common treatment for women with CIN2 (52.8%) and CIN3 (57.0%). However 0.4% of all CIN2 and 2.3% of all CIN3 had hysterectomy.

(*Epidemiol Prev* 2015; 39(3) Suppl 1: 61-76)
Keywords: cervical cancer, Pap test, colposcopy, mass screening, Italy

Riassunto

Le linee guida nazionali italiane raccomandano alle Regioni di attivare programmi organizzati di screening per il cervicocarcinoma. Come negli anni precedenti, a partire dal 1998, dai programmi organizzati italiani di screening cervicale si sono raccolte tabelle aggregate di dati per calcolare centralmente indicatori di processo. Si sono considerati i dati delle donne invitate nel corso del 2009 e screenate fino ad aprile 2011.
Nel 2012 i programmi organizzati italiani includevano nella loro popolazione obiettivo 14.497.207 donne, corrispondenti all'87,3% delle donne italiane di età 25-64 anni. La compliance all'invito è stata

41,2% nel 2011 e 40,8% nel 2012, con un deciso trend a diminuire da Nord a Sud. Bisogna comunque ricordare che molte donne vengono screenate al di fuori dei programmi organizzati.
E' stato raccomandato di ripetere la citologia al 3,5% delle donne e il 71,1% di esse l'ha fatto. Il 2,4% delle donne screenate è stato inviato in colposcopia. La compliance alla colposcopia è stata 85,3% tra le donne inviate per citologia ASC-US o più grave e 90,4% tra quelle inviate per citologia HSIL o più grave. Il valore predittivo positivo (VPP) dell'invio in colposcopia per citologia ASC-US o più grave per istologia CIN2 o più grave è stato 16,9%. La detection rate (DR) grezza di istologia CIN2 o più grave è stata 3,4 ogni 1.000 donne screenate (3,6 quella standardizzata sulla popolazione italiana, troncata 25-64). Nel 64,6% delle colposcopie classificate come di grado 2 o più elevato l'esame istologico ha dato un responso CIN2 o più grave. Tra tutte le colposcopie con istologia CIN2 o più grave, il 33,6% è stato classificato come di grado 2 o più elevato. All'81,7% delle donne con esito CIN1 si è consigliato il follow-up. L'escissione con radiofrequenza è stato il trattamento più comune per donne con istologia CIN2 (52,8%) e CIN3 (57,0%). Lo 0,4% delle donne con istologia CIN2 e il 2,3% di quelle CIN3 ha avuto un'isterectomia.

(*Epidemiol Prev* 2015; 39(3) Suppl 1: 61-76)
Parole chiave: cancro cervicale, Pap test, coloscopia, screening di massa, Italia

INTRODUCTION

The Italian health system is managed by Italy's 20 regions. Since 1996, Italian national guidelines have recommended to regions to implement organized screening programmes for cervical cancer.[1-3] Recommendations, largely based on European guidelines,[4,5] include personal invitations to women aged 25 to 64 years for a Pap test every three years, a monitoring system, and quality assurance for each phase of the programme.
Surveys designed to assess the level of implementation of organized programmes in Italy and to collect process indicators have been conducted by GISCi (Italian group for cervical screening) since 1997. Their results have been evaluated and published by the ONS (Osservatorio nazionale screening, National centre for screening monitoring), on behalf of the Italian Ministry of Health, since 2002.[6-15] Diagnostic work-up and particularly treatment have also been monitored in order to reduce under- and over-treatment.
A number of programmes moved to HPV-based screening tests as pilot projects or as routine activity after the recommendation of the national Ministry of Health.[16] Detailed data on HPV-based screening are presented elsewhere.[17]
In the present report, data on coverage and compliance and data on second-level activities included all women, independently of the primary screening test. Conversely, process indicators for first-level tests include only women screened with Pap smears.

METHODS

Surveys of organized cervical screening programmes active in Italy in 2011 and 2012 were conducted by the ONS on behalf of the Italian Ministry of Health in 2012 and 2013. A programme was considered active each year if at least 1,000 women were invited during that year. For each year, women invited during that year and screened within the first 4 months of the subsequent year were considered.
Given the different approaches to integration of invitations and spontaneous activity, some programmes reported data only on women screened after invitation and others on all screened women, independently of invitation. In the latter case, data on spontaneous activity included women screened during the relevant year.
We collected tables of aggregated data, in general nested, so that each table was the denominator of the next. They were used to centrally compute process indicators (most of those recommended by Italian[2,3] and European[5] guidelines) and to study their distribution. Data were centrally checked for completeness and consistency. Each region appointed a person to provide data and finally verify them. We interacted, sometimes repeatedly, with providers, to obtain clarifications and integrations, if needed.
For each indicator we computed the national overall mean, i.e., the value obtained by pooling all the population for which data were available. In addition, we analyzed the distribution of indicators between regions and between local programmes within each region.
"Programme" is defined as each entity for which we obtained aggregated data. In general, according to national guidelines,[1-3] this corresponds to an organizational unit that manages and co-ordinates the different steps of screening, from invitation to diagnostic assessment and treatment. These units are generally well defined, but sometimes they underwent re-organization (typically, aggregation of smaller programmes). Furthermore, their size is highly variable. For example, in some regions there is a single programme (e.g., Basilicata and Friuli) while others have many local programmes with regional co-ordination and evaluation (e.g., Piemonte, Veneto, Emilia-Romagna, Toscana).
We report (**table 3**, p. 66) the mean national value, of some indicators and their 10th and 90th percentile. The values of the last three surveys are reported. The year denotes the period of screening activity considered (therefore the year before the conduction of the survey). In addition, we present graphs with the distribution between regions in 2011 and 2012. **Figures 2** (p. 67) and 5 (p. 68) report the mean for 2011 and 2012.
Data on second-level activities (about correlation between colposcopic findings and histology and about the management of women with screen-detected CIN or invasive cancer) are presented at an overall national level as tables including data from all programmes that provided them in 2010 and 2011. Colposcopic findings were classified according to the International classification (IFCPC). The Rome 1990 classification[18] was adopted in the first experimental surveys and kept in use

for comparability. In this section each colposcopy was considered as a statistical unit. In case of multiple biopsies during a same colposcopy, the most severe histology was considered. In the section on management of women with screen-detected CIN/cancer each woman was a unit. For this purpose we considered the worst histology before treatment and the first treatment. A "see and treat" approach – i.e., treatment in the absence of a histological diagnosis – is very limited in Italian organized programmes.

RESULTS

Extension of organized programmes and invitation of the target population

Concerning this section of the survey, we obtained questionnaires from 116 and 119 programmes for 2011 and 2012, respectively. The target population of active organized programmes in these and previous surveys is reported in **table 1** (p. 64). Target populations are also expressed as the percentage of women aged 25 to 64 years resident in a given area. It must be kept in mind that denominators are based on census for 2012 and estimated for previous years.

Active programmes in Italy had a target population of 14,301,979 women in 2011 and 14,497,209 women in 2012, representing 84.1% and 87.3%, respectively, of the Italian female population aged 25-64, compared to 80.1% in 2010. In 2012, active programmes included in their target population the entire female population aged 25 to 64 years in 15/21 regions, over 95% in 3 regions and close to 80% in 2 regions (Sardegna and Liguria). Incomplete nominal extension is mainly caused by the choice of not implementing a population-based screening in the region of Lombardia, where only local initiatives are active (**table 2**, p. 65).

The values above consider the entire target population regardless of the proportion actually invited. It is obviously relevant that active programmes invite women at a rate sufficient to reach the entire target population within the standard screening interval (3 years for cytology-based screening). **Table 1** reports the ratio between the number of women invited during each year and the number that should have been invited in case of full implementation (i.e., 1/3 of the resident population aged 25-64 years). In 2012, actual extension was 70.4% at national level. Because variations between years can result from local criteria of organization, the percentage of women in the target population invited in the last 3 years is reported in **table 2**. The completeness of invitation is also computed excluding from the denominator women not invited because of recent testing or for other specified reasons (adjusted %). Programmes adopt different criteria for exclusion and some programmes do not exclude any women at all. There is a clear North-South gradient in completeness of invitation. As the interval between HPV-based screens is now 5 years, actual coverage is now underestimated, but this effect is minimal for 2011 and 2012 activity.

During 2011 and 2012, 41.2% and 40.8%, respectively, of invited women were screened, compared to 39.8% in the previous year (**table 1**). A clear decreasing trend in compliance with invitation from northern to central and especially southern Italy (49.1%, 40.2%, and 29.5%, respectively, in 2012) was

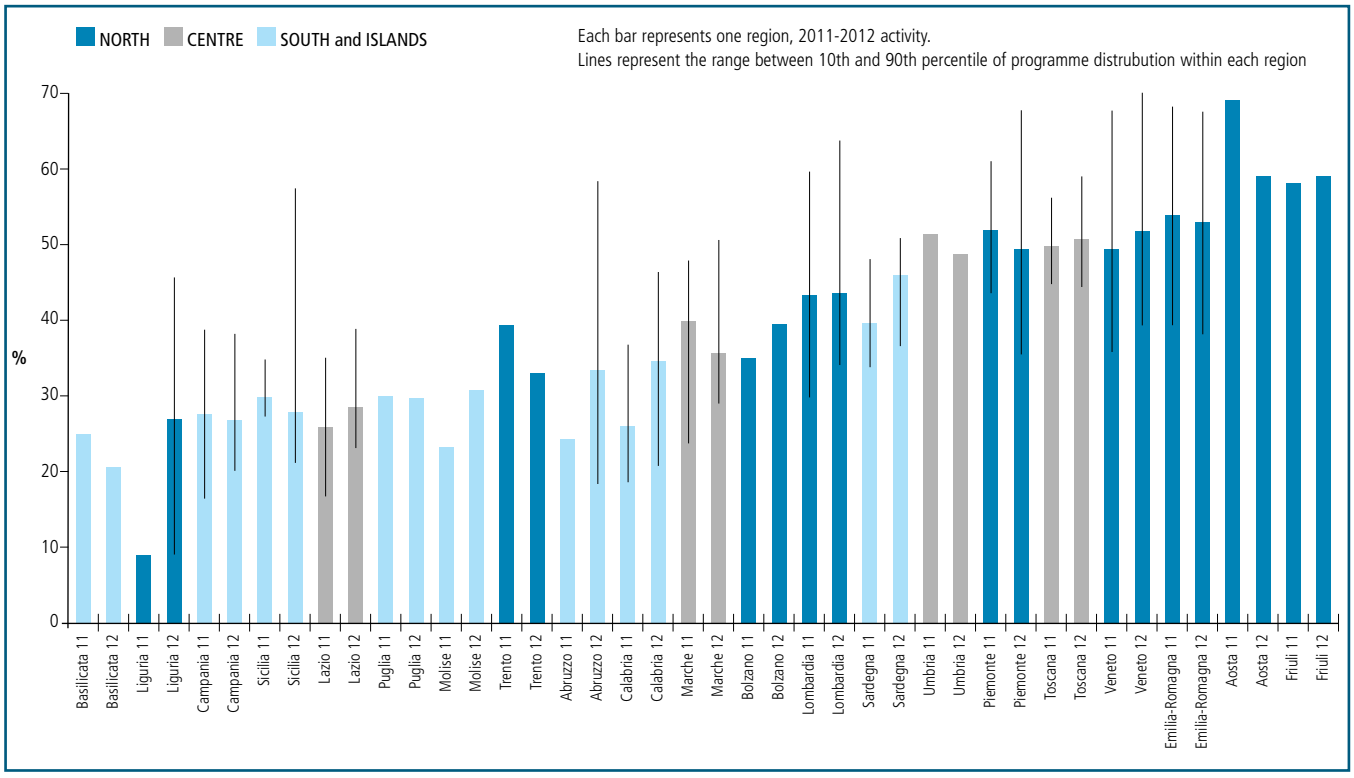

Figure 1. Uptake percentage by region. 2011-2012 activity. / **Figura 1.** Adesione percentuale all'invito, per Regione. Attività 2011-2012.

	2006	2007	2008	2009	2010	2011	2012
Number of women 25-64 yrs. included in the target population of organized programmes	11,362,580	11,872,810	13,094,025	13,133,604	13,538,080	14,301,979	14,497,209
Population 25-64 yrs	16,463,948*	16,543,059*	16,693,052*	16,812,052*	16,900,554*	17,006,946*	16,600,566**
Nominal extension[a]	69.01	71.77	78.44	78.12	80.10	84.10	87.33
Actual extension[b]	52.91 (2,873,202/ 5,487,982)	54.80 (3,021,734/ 5,514,353)	59.85 (3,330,289/ 5,564,350)	63.30 (3,547,457/ 5,604,016)	63.64 (3,584,955/ 5,633,511)	62.19 (3,525,522/ 5,668,982)	70.37 (3,893,773/ 5,533,522)
Compliance to invitation (%)[c]	38.49 (1,116,006/ 2,899,817)	39.83 (1,217,000/ 3,055,353)	39.69 (1,332,376/ 3,356,931)	39.27 (1,393,243/ 3,547,457)	39.84 (1,374,745/ 3,450,755)	41.17 (1,451,056/ 3,524,863)	40.76 (1,600,796/ 3,927,403)
Percentage of population screened[d]	20.34% (1,116,006/ 5,487,983)	22.07% (1,217,000/ 5,514,353)	23.94% (1,332,376/ 5,564,351)	24.86% (1,393,243/ 5,604,017)	24.40% (1,374,745/ 5,633,518)	25.60% (1,451,056/ 5,668,982)	28.93% (1,600,796/ 5,533,522)
Northern Italy							
Number of women 25-64 yrs. included in the target population of organized programmes	4,911,641	4,942,788	5,210,405	5,133,658	5,155,376	5,513,736	5,590,488
Population 25-64 yrs	7,545,425	7,555,407	7,615,828	7,674,160	7,712,312	7,771,110	7,564,052
Nominal extension[a]	65.09	65.42	68.42	66.90	66.85	70.95	73.91
Actual extension[b]	52.91 (1,330,768/ 2,515,141)	55.38 (1,394,613/ 2,518,469)	55.38 (1,525,113/ 2,538,609)	59.75 (1528455/ 2558053)	60.32 (1,550,770/ 2,570,768)	62.51 (1,619,150/ 2,590,370)	69.25 (1,745,942/ 2,521,348)
Compliance to invitation (%)[c]	45.62 (612,069/ 1,341,812)	46.93 (664,344/ 1,415,361)	47.67 (734,577/ 1,541,010)	49.15 (751,283/ 1,528,455)	49.39 (742,219/ 1,502,820)	49.87 (815,607/ 1,635,630)	49.12 (867,589/ 1,766,270)
Percentage of population screened[d]	24.34% (612,069/ 2,515,142)	26.38% (664,344/ 2,518,469)	28.94% (734,577/ 2,538,609)	29.37% (751,283/ 2,558,053)	28.87% (742,219/ 2,570,771)	31.49% (815,607/ 2,590,370)	34.41% (867,589/ 2,521,351)
Central Italy							
Number of women 25-64 yrs. included in the target population of organized programmes	3,029,340	3,008,931	3,252,167	3,113,448	3,277,736	3,308,299	3,246,268
Population 25-64 yrs	3,224,341	3,275,594	3,315,532	3,347,197	3,367,589	3,391,992	3,283,420
Nominal extension[a]	93.95	91.86	98.09	93.02	97.33	97.53	98.87
Actual extension[b]	75.05 (806,609/ 1,074,780)	74.54 (813,887/ 1,091,865)	80.51 (889,801/ 1,105,177)	80.26 (895,459/ 1,115,732)	80.62 (904,993/ 1,122,528)	79.42 (897,918/ 1,130,664)	81.48 (891,778/ 1,094,473)
Compliance to invitation (%)[c]	35.70 (290,632/ 814,208)	40.23 (330,925/ 822,548)	40.17 (357,846/ 890,868)	38.12 (341,325/ 895,459)	37.98 (327,029/ 860,981)	38.52 (346,654/ 899,824)	40.18 (358,958/ 893,437)
Percentage of population screened[d]	27.04% (290,632/ 1,074,780)	30.31% (330,925/ 1,091,865)	32.38% (357,846/ 1,105,177)	30.59% (341,325/ 1,115,732)	29.13% (327,029/ 1,122,530)	30.66% (346,654/ 1,130,664)	32.80% (358,958/ 1,094,473)
Southern Italy and Islands							
Number of women 25-64 yrs. included in the target population of organized programmes	3,421,599	3,921,091	4,631,453	4,886,498	5,104,968	5479944	5,660,453
Population 25-64 yrs	5,694,182	5,712,058	5,761,692	5,790,695	5,820,653	5,843,844	5,753,109
Nominal extension[a]	65.63	68.65	80.38	84.39	87.70	95.39	98.39
Actual extension[b]	38.77 (735,825/ 1,898,060)	42.71 (813,234/ 1,904,019)	47.66 (915,375/ 1,920,564)	58.21 (1,123,543 /1,930,231)	58.20 (1,129,192/ 1,940,215)	51.77 (1,008,454/ 1,947,948)	65.50 (1,256,053/ 191,7701)
Compliance to invitation (%)[c]	28.68 (213,305/ 743,797)	27.12 (221,731/ 817,444)	27.73 (239,953/ 925,053)	26.76 (300,635/ 1,123,543)	28.11 (305,497/ 1,086,954)	29.19 (288,795/ 989,409)	29.52 (374,249/ 1,267,696)
Percentage of population screened[d]	11.24% (213,305/ 1,898,061)	11.65% (221,731/ 1,904,019)	12.49% (239,953/ 1,920,564)	15.58% (300,635/ 1,930,232)	15.75% (305,497/ 1,940,218)	14.83% (288,795/ 1,947,948)	19.52% (374,249/ 1,917,703)

[a] percentage of the resident 25-64 year-old population that is included in the target population of active organized programmes.
[b] numerator: population invited in the relevant year; denominator: 1/3 of the resident population aged 25-64 (invited women include both those invited for cytology and those invited for HPV testing as primary screening test).
[c] denominator: number of women invited; numerator: number of women who underwent screening among them (by the first 4 months of the following year).
[d] numerator: number of women who underwent screening among invited women (by the first 4 months of the following year); denominator: 1/3 of the resident 25-64 year-old population.
* estimated by the National institute of statistics (Istat).
** obtained by census.

Table 1. Target population of active organized screening programmes in Italy, population invited and compliance to invitation.
Tabella 1. Popolazione obiettivo dei programmi organizzati di screening cervicale in Italia, quota di donne invitate e donne che hanno effettivamente risposto.

Region	Programmes active in 2012	Target polpulation 25-64 yrs (%) (2012)	Nominal extension (%) (2012)	Target population invited (%) (2011)	Target population invited* (%) (2012)	Target population invited* (%) (2010+ 2011+2012)	Adjusted target population invited** (%) (2010+ 2011+2012)
Valle d'Aosta	**Single regional programme**	35,777	100	29.6	30.4	96.59	96.59
Piemonte	**Regional programme. Fully active**[a] Città di Torino, Cuneo, Alessandria, Moncalieri, Rivoli, Ivrea, Biella-Vercelli, Novara, Asti	1,206,933	100	27.8	30.1	87.51	87.51
Liguria	**Regional programme.** Genova 3, Imperia, Savonese	336,105	79.1	6.9	11.0	28.34[$]	
Lombardia	**Regional programme.** The following are active: Brescia. Cremona, Lodi, Mantova, Pavia, Vallecamonica	778,096	28.7	28.1	31.6	87.31	100
Self-governing province of Trento	**Single regional programme**	145,719	100	46.2	63.9	100	100
Self-governing province of Bolzano	**Single regional programme**	137,647	100	24.3	23.6	71.78[$]	
Veneto	**Regional programme. Fully active**[a] Adria, Alta Padovana, Alto Vicentino, Asolo, Bassano Del Grappa, Belluno, Bussolengo, Chioggia, Este, Feltre, Legnago, Dolo Mirano, Padova, Vicenza Ovest Vicentino, Verona, Pieve Di Soligo, Rovigo, Treviso, Veneto Orientale, Veneziana	1,353,553	100	28.2	32.1	87.52	100
Friuli-Venezia Giulia	**Single regional programme**	343,353	100	28.4	30.3	83.70	100
Emilia-Romagna	**Regional programme. Fully active**[a] Bologna, Cesena, Ferrara, Forlì, Imola, Modena, Parma, Piacenza, Ravenna, Reggio Emilia, Rimini	1,255,986	100	35.6	34.2	100	100
Toscana	**Regional programme. Fully active**[a] Arezzo, Empoli, Firenze, Grosseto, Livorno, Lucca, Massa, Pisa, Pistoia, Prato, Siena, Viareggio	1,022,925	100	31.2	33.0	95.89	100
Umbria	**Single regional programme**	265,114	100	24.2	37.7	83.82	99.48
Marche	**Regional programme. Fully active**[a] Area vasta 1, Area vasta 2, Area vasta 3, Area vasta 4, Area vasta 5	422,224	100	31.7	31.7	93.98	100
Lazio	**Regional programme.** The following are active: Latina, Rieti, Roma A, Roma B, Roma C, Roma D, Roma E, Roma G, Roma H, Viterbo	1,536,005	96.4	23.6	20.8	66.48	68.41
Molise	**Single regional programme**	85,637	100	13.1	14.0	53.60	53.67
Abruzzo	**Single regional programme. Fully active**[a]	368,882	100	15.9	29.5	61.05	100
Campania	**Regional programme.** The following are active: Avellino, Benevento, Caserta, Napoli 1, Napoli 2, Napoli 3, Salerno	1,624,086	100	14.7	15.7	46.15	54.12
Basilicata	**Single regional programme**	167,348	100	-	-	100	100
Calabria	Catanzaro, Cosenza, Lamezia Terme, Locri, Palmi, Reggio Calabria, Vibo Valentia	530,517	97.7	19.6	14.8	57.44	60.25
Sicilia	**Regional programme.** The following are active: Agrigento, Catania, Caltanissetta, Enna, Messina, Palermo, Ragusa, Siracusa, Trapani	1,375,898	99.3	19.2	30.0	78.25	78.27
Sardegna	**Regional programme.** The following are active: Cagliari, Carbonia, Nuoro, Olbia, Oristano, Sanluri	377,031	79.4	30.5	24.9	78.76	80.79
Puglia	**Single regional programme**	1,131,054	100	14.0	18.3	50.43	34.5

[a] fully active means that the entire regional female population aged 25-64 is included in the target population of active cervical screening programmes.
* only women aged 25-64 years are considered both in the numerator and denominator.
** numerator: women aged 25-64 years invited in the last 3 years. Denominator: target population aged 25-64 years minus women excluded before invitation because already invited or due to other reason.
[$] active only for 2 years.

Table 2. Active organized cervical screening programmes and target population (age 25-64), by region. Years 2011-2012.
Tabella 2. Programmi organizzati di screening cervicale attivi e popolazione obiettivo (25-64 anni), per Regione. Anni 2011-2012.

Year of activity[a]	2010				2011				2012			
	N*	Mean (%) (num/den)	centile (%) 10th	centile (%) 90th	N*	Mean (%) (num/den)	centile (%) 10th	centile (%) 90th	N*	Mean (%) (num/den)	centile (%) 10th	centile (%) 90th
Population screened[b]	118	1,456,665			107	1,508,595			104	1,467,808		
Recommendation to repeat cytology[c]	111	4.7 (71,820 1,512,430	1.2	10.0	103	4.1 (59,934/ 1,449,562)	1.0	9.0	100	3.5 (51,674/ 1,467,808)	1.0	7.5
Compliance to recommendation to repeat cytology[d]	100	62.7 (33,410 53,288)	40.8	86.9	98	64.8 (34,591 53,405)	41.1	94.1	94	71.1 (32,507/ 45,691)	41.9	95.3
Referral rate[e]	114	2.5 (36,647/ 1,445,138)	1.0	4.2	105	2.4 (36,525/ 1,492,349)	1.1	4.2	102	2.4 (36,432/ 1,494,122)	1.0	4.2
Compliance to colposcopy for ASC-US+[f]	106	85.9 (29,725/ 34,600)	64.8	98,6	101	87.7 (30,115/ 34,346)	64.8	98.3	99	85,3 (25,510/ 34,605)	72.6	100
Compliance to colposcopy for HSIL+[g]	105	88.7 (2,834/ 3,194)	64,0	100	98	89.5 (2,749/ 3,072)	66,6	100	99	90.4 (2,868/ 3,172)	66.7	100
PPV of referral to colposcopy because of ASC-US+ cytology for histologically confirmed CIN2+[h]	102	16.0 (4,597/ 28,723)	6.4	28.3	95	15.3 (4,268 27,802	5.2	29.0	92	16,9 (4,724/ 27,988)	5.8	31.1
DR CIN2+ unadjusted[i]	102	3.2 (4,597/ 1,393,654)	1.1	5.2	95	3.2 (4,268/ 1,323,390	0.8	5.0	92	3.4 (4,741/ 1,393,544)	1.5	5.2
DR CIN2+ stand. Ita.[j]	98	3.5	0.9	5.6	88	3.2	1.2	5.5	89	3.5	1.2	5.8

* number of programmes that provided information

[a] year before the conduction of the survey; each survey includes women invited during the previous year and screening within the first 4 months of the current year (see text).

[b] in some programmes this includes only women screened after invitation, in others all screened women, independently of invitation (see text)

[c] denominator: number of screened women; numerator: number of women recommended to repeat cytology.

[d] denominator: total number of women recommended to repeat cytology; numerator: women who repeated within 15 April 2013.

[e] denominator: number of screened women; numerator: number of screened women referred to colposcopy (any reason).

[f] denominator: number of women referred to colposcopy because of ASC-US or more severe citology; numerator: number of the latter who underwent colposcopy.

[g] denominator: number of women referred to colposcopy because of H-SIL or more severe citology; numerator: number of the latter who underwent colposcopy.

[h] denominator: number of women who underwent colposcopy because of ASC-US or more severe citology; numerator: number of the latter who had CIN2 or more severe detected (histologically confirmed – most severe lesion within six months from cytology considered).

[i] denominator: number of screened women; numerator: number of the latter who had a CIN2+ detected (histologically confirmed – most severe lesion within six months from cytology considered). Cases per 1,000 screened women.

[j] see ([i]); adjusted for age in 5-year groups on the Italian population (census 1991, truncated 25-64); the national mean was directly computed for the pool of all programmes with valid needed data; percentiles were obtained after computing the standardized DR for each programme with valid required data.

Table 3. Value of some process indicators (national mean, 10th, and 90th percentile) in the last three surveys.
Tabella 3. Valore di alcuni indicatori di processo (media nazionale, 10° e 90° percentili) nelle ultime tre survey.

present, as previously observed. In 2012, compliance was over 50% in Umbria, Valle d'Aosta, Friuli-Venezia Giulia, Emilia-Romagna, and the province of Trento (figure 1).

Process indicators in organized programmes

Data in this section include only women screened by cytology. In 2011 and 2012, programmes that provided this type of data were 107 and 104, while screened women were 1,508,959 and 1,467,808, respectively. Some programmes reported data only on women screened after invitation. Decreases in number of programmes and screened women are due to the increase in HPV-based screening. Table 3 reports for each indicator the number of programmes for which that indicator could be computed.

In 2011 and 2012, 4.1% and 3.5% of screened women were recommended to repeat cytology, compared to 4.7% in 2010 and values between 5% and 7% in 2005-2009. In 2012, in two regions cytology repeat was recommended to more than 15% of screened women and in three others to more than 6% (figure 2). In three of these regions, many repeats were due to «other reasons», likely reactive changes, which represent a relevant source of variability. Repeats for unsatisfactory smears were very high in Molise. In some regions, a proportion of women was recommended to repeat the smear after ASC-US, AGC, and L-SIL cytology. However, these reasons represent a substantial proportion of repeats only in Sardegna and Veneto. Among women who had been recommended to repeat the smear, 65% actually had a new one in 2011 and 71% in 2012, following a monotonously increasing trend (60% in 2007). In 2012 two regions were below 50% and seven were above 80% (figure 3). These values do not take into account that some women should have repeated cytology after a time interval that had not ended when data were collected.

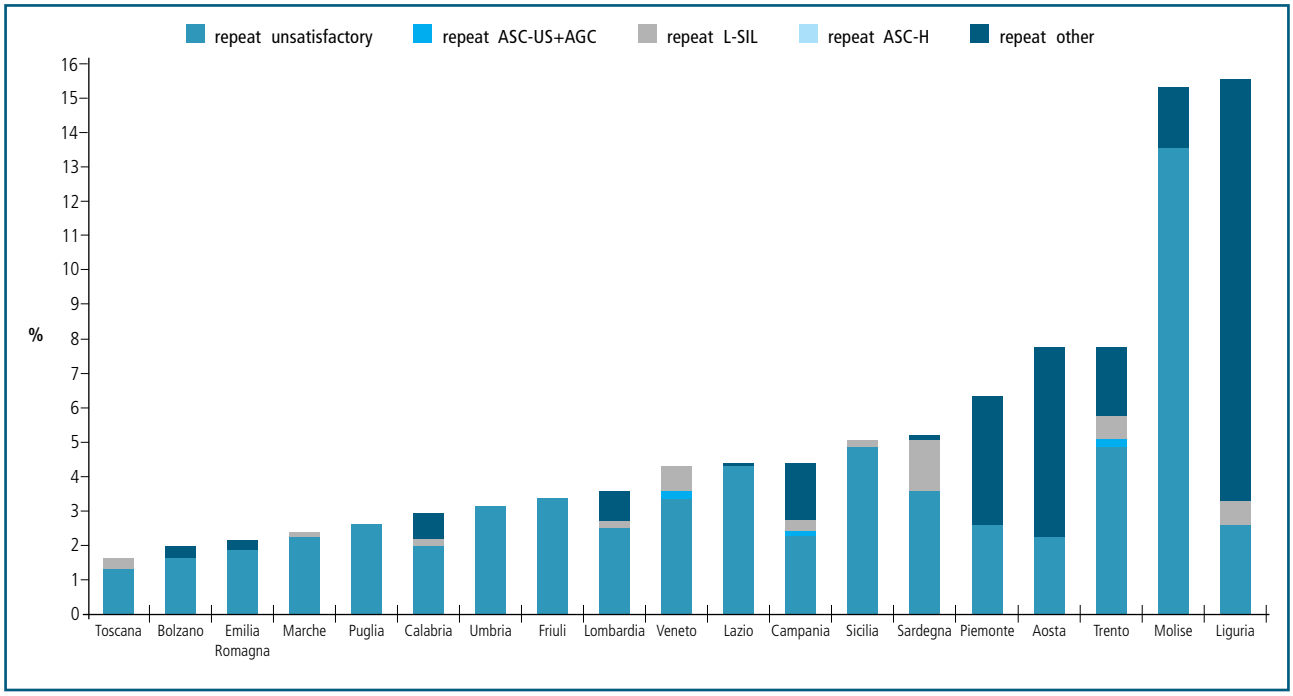

Figure 2. Percentage of screened women referred for repeat cytology, by region. 2011-2012 activity.
Figura 2. Percentuale della popolazione screenata che ha avuto indicazione a ripetere la citologia per qualsiasi causa, per Regione. Attività 2011-2012.

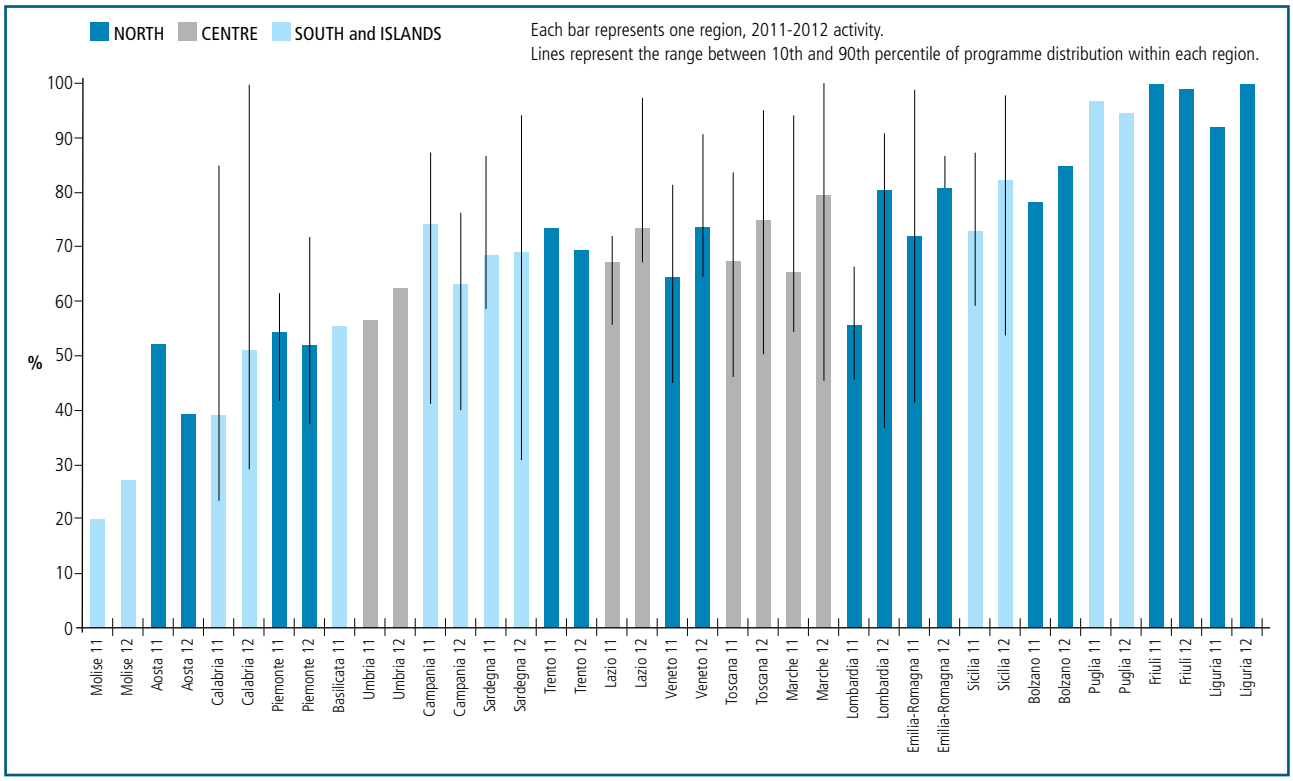

Figure 3. Compliance with repeat cytology. Women who repeated cytology by 15 April 2012 and by 15 April 2013 out of all those referred for repeat cytology. 2011-2012 activity.
Figura 3. Compliance alla ripetizione della citologia. Donne che hanno ripetuto entro il 15 aprile 2012 ed entro il 15 aprile 2013 su tutte le donne che hanno avuto indicazione a ripetere. Attività 2011-2012.

The referral rate to colposcopy was 2.4% both in 2011 and 2012 (table 3). Values between 2.3% and 2.5% had been registered in all years from 2005 to 2010.

The referral rate was above 4% in both 2011 and 2012 in Valle d'Aosta and in 2011 in Molise and Basilicata (figure 4, p. 68). There was a high variability within some regions. In 2012, out

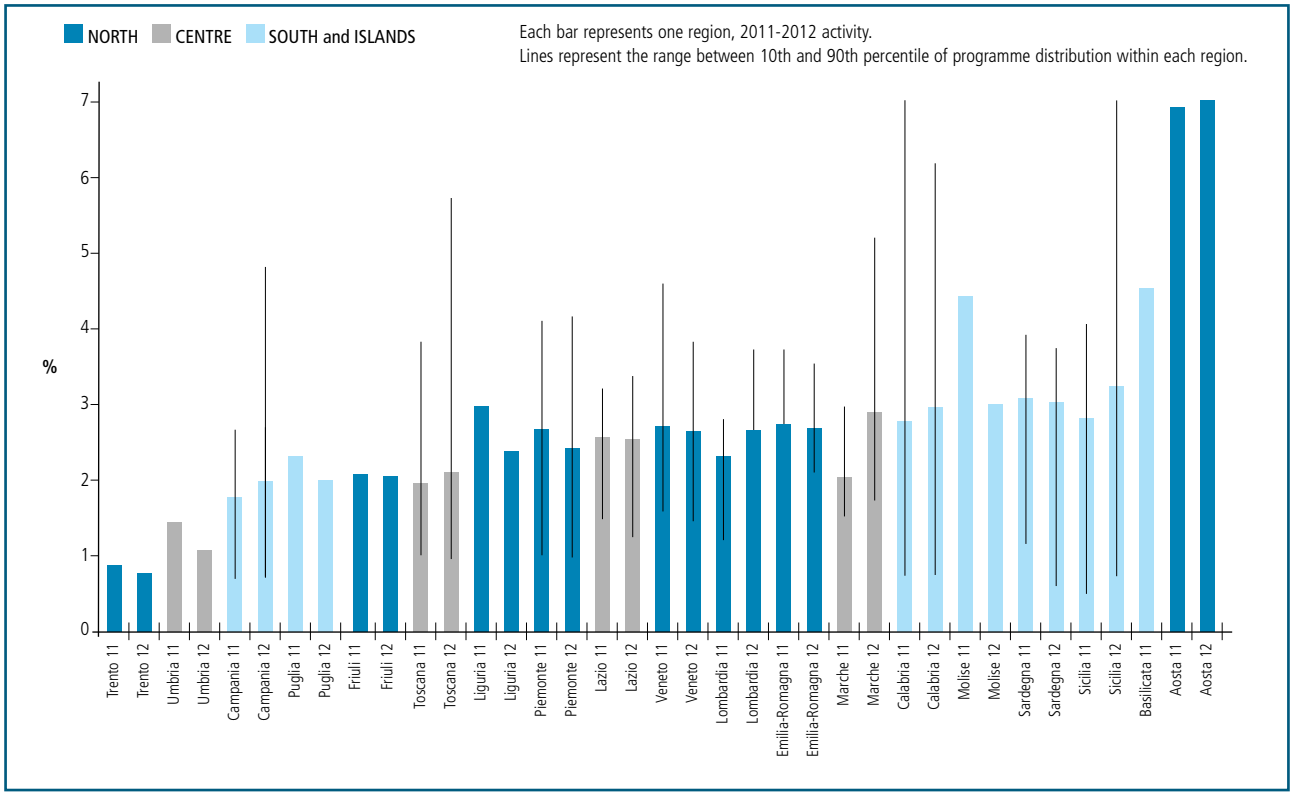

Figure 4. Proportion of women referred to colposcopy for any reason, by region. 2011-2012 activity.
Figura 4. Proporzione di donne invitate in colposcopia per qualsiasi motivo, per Regione. Attività 2011-2012.

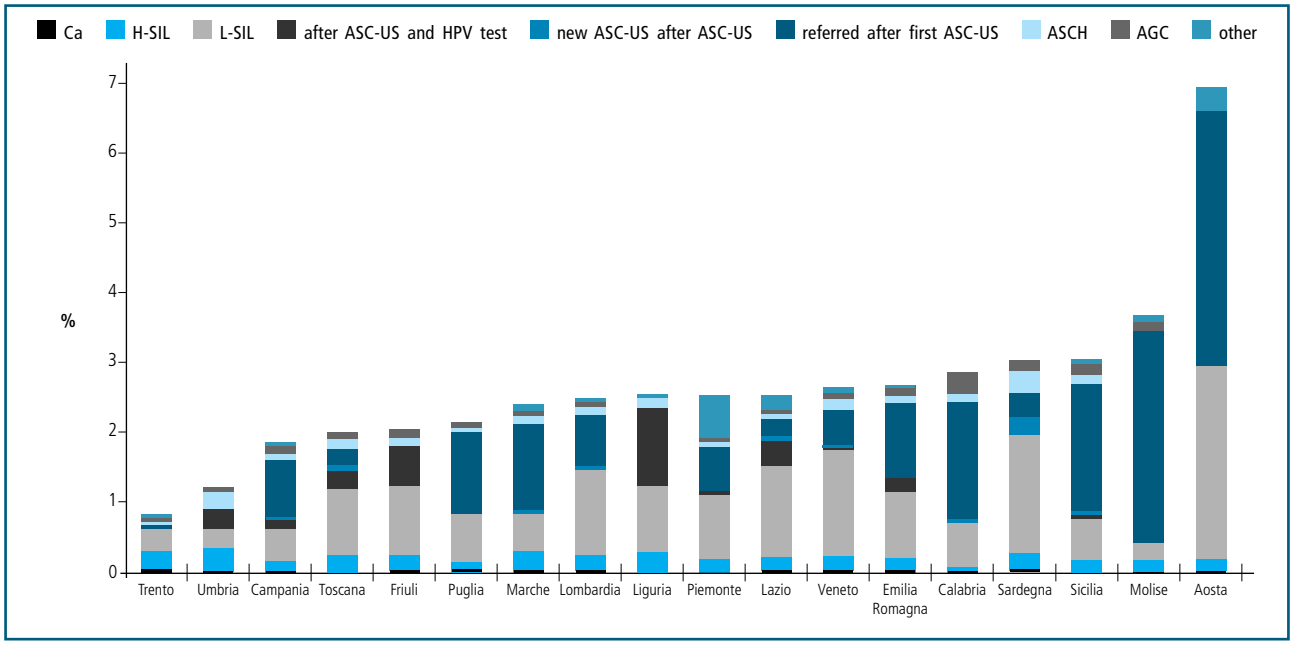

Figure 5. Proportion of women referred to colposcopy, by region and reason. 2011-2012 activity.
Figura 5. Proporzione di donne invitate in colposcopia, per Regione e motivo. Attività 2011-2012.

of 102 programmes with relevant data, 68 (66.7%) referred to colposcopy fewer than 3% of screened women, and 89 (87.3%) fewer than 4%. However, in 8 programmes the referral rate was >5% and in two of them >6%. With respect to the reason for referral (figure 5), ASC-US cytology was still a major source of variability and reached very high levels in Molise and Valle d'Aosta. Clearly, the regions with the lowest referral rate invited a very low number of women with ASC-US directly to colposcopy but did a previous repeat of cytology or a triage by HPV testing. However, L-SIL cytology has become now the most frequent reason in many regions and is a second major cause of variability.

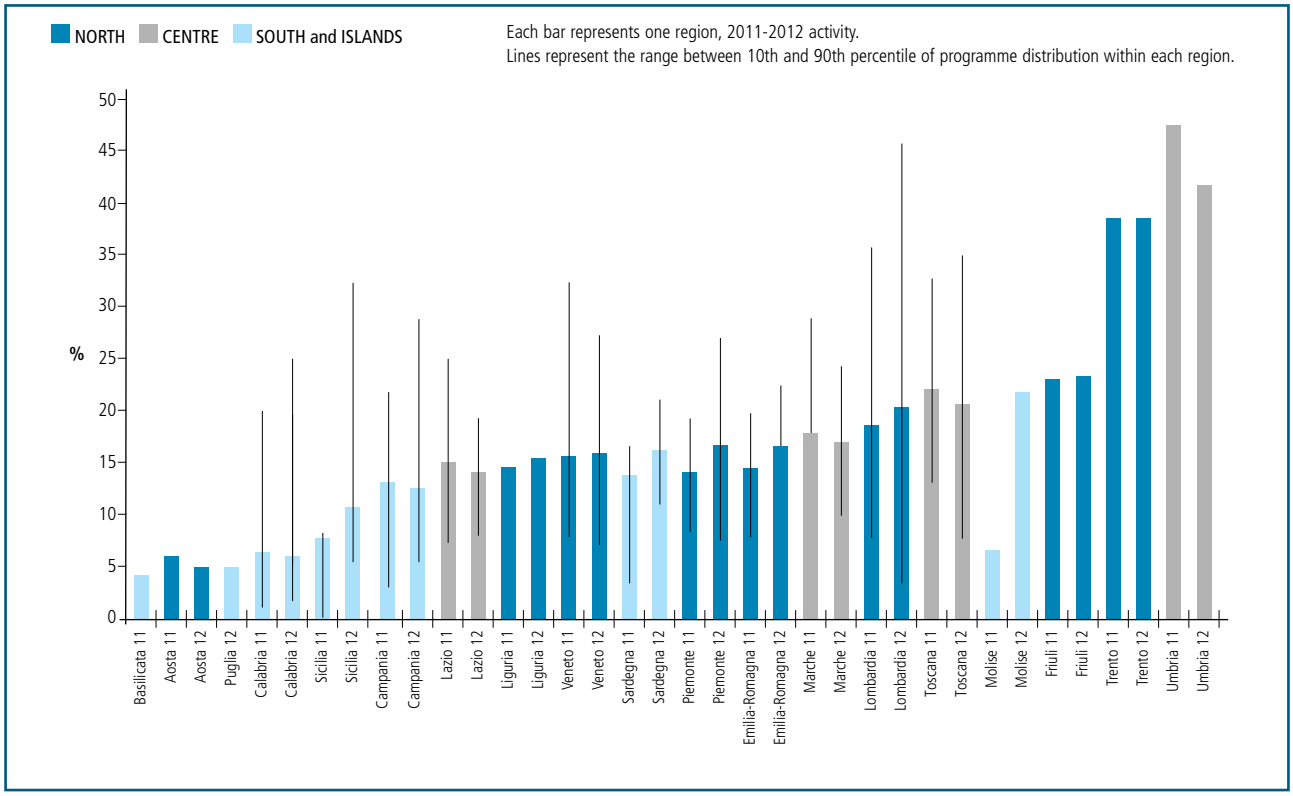

Figure 6. Positive predictive value, by region. 2011-2012 activity. / **Figura 6.** Valore predittivo positivo, per Regione. Attività 2011-2012.

At a national level, the positive predictive value (PPV) of ASC-US or more severe cytology for CIN2 or more severe histology was 15.3% in 2011 and 16.9% in 2012. Its value was just above 16% from 2006, after a rising trend which started in 2000 (when PPV was 11.4%).

Figure 6 shows the distribution of PPV in Italian regions during 2011 and 2012. Its value was inversely correlated to the referral rate (data not shown) and was <10% in Valle d'Aosta and Calabria both years and for one year in Basilicata, Puglia (only one available), Sicilia, and Molise. In 2012 Sicilia was just above 10%, but Molise registered a remarkable increase, reaching 22%. Values stably >20% were observed in four regions (Umbria, province of Trento, Friuli-Venezia Giulia, and Toscana).

Three of them refer to colposcopy no or very few women at the first diagnosis of ASC-US, as a result of the implementation of triage systems for this cytological category. However, PPV was not very high in some regions where no or few women with ASC-US were directly referred to colposcopy but referral because of L-SIL is relevant. Indeed, looking at specific reasons of referral (table 4) L-SIL cytology had a PPV for CIN2+ <10%. In addition, women referred to colposcopy because of persistent ASC-US cytology had a lower PPV for CIN2+ than that of women referred at the first ASC-US cytology.

Among women referred to colposcopy because of an ASC-US or more severe cytology during 2011 and 2012, 87.7% and 85.3% respectively actually had one colposcopy, compared to 85.9 in 2010 and 85.1% in the two previous years (figure 7, p. 70).

Among women referred to colposcopy because of a H-SIL or more severe cytology, compliance was 89.5% in 2011 and 90.4% in 2012 (figure 8, p. 71).

Figure 9 (p. 71) shows the detection rate (DR) of histologically confirmed CIN2 or more severe lesions. The standardized (on the Italian population truncated 25-64 yrs) DR was 3.2 lesions detected per 1,000 screened women in 2011 and 3.5 in 2012. Previously, DR increased from 3.0 in 2004 to 3.5 in 2010.

Overall, there was a decreasing trend from North to South. However, high DRs, despite being lower than in 2009 and 2010, were still observed in Sardegna, where a new programme was recently started, and there was a strong increase in Sicilia in 2012 following invitation extension. An increase from 3.2 in 2011 to 4.9 in 2013 was also observed in Marche (central Italy), again related to an increased proportion of women at their first cervical screen.

Second-level activity

Colposcopic findings and their correlation with histology

Data were reported from 81 programmes both in 2011 and 2012 (table 5, p. 72). Most of the 54,776 colposcopies included in the analysis were classified as normal (38.9%), G1 (34.8%) or unsatisfactory (11.9%).

At least one biopsy was performed in 49.5% of all colposcopies: 84.2% of those with abnormal findings, 33.4% of unsatisfactory colposcopies, and 16.8% of normal colposcopies. When considering only colposcopies with biopsy, CIN1 or more severe histology was detected in 69.0% of those classified as grade 1 and CIN2+ in 65.0% of those classified as grade 2 and 89.2% of those suggestive of cancer, but just in

Criterion of referral	Endpoint	2011			2012		
		Mean (%) (num/den)	P10 (%)	P90 (%)	Mean (%) (num/den)	P10 (%)	P90 (%)
H-SIL cytology	CIN2+	70.2 (1,844/2,626)	46.0%	100.0	71.7 (1,719/2,397)	50.0	100.0
H-SIL cytology	CIN3+	46.4 (1,218/2,626)	16.0	79.3	47.2 (1,132/2,397)	12.5	68.4
L-SIL cytology	CIN2+	9.7 (1,227/12,622)	3.3	20.0	9.1 (1,098/12,022)	3.0	20.0
L-SIL cytology	CIN3+	2.9 (362/12,622)	0.0	8.0	3.1 (367/12,022)	0.0	8.1
ASC-US cytology followed by TRIAGE HPV	CIN2	13.7 (247/1,808)	2.1	33.3	12.2 (172/1,416)	0.0	17.2
ASC-US cytology followed by TRIAGE HPV	CIN3	4.9 (89/1,808)	0.0	12.3	6.0 (85/1,416)	0.0	10.8
Repeat ASC-US cytology	CIN2	4.0 (13/324)	0.0	11.5	4.5 (17/380)	0.0	10.0
Repeat ASC-US cytology	CIN3	0.3 (1/324)	0.0	3.85	1.8 (7/380)	0.0	9.1
First ASC-US cytology	CIN2	5.6 (440/7,814)	0.0	15.6	4.8 (427/8,845)	0.0	13.64
First ASC-US cytology	CIN3	2.4 (188/7,814)	0.0	5.8	2.1 (187/8,845)	0.0	5.8

The table includes data from the 95 programmes that provided data in 2011 and the 92 that provided data in 2012.

Table 4. Positive predictive value for CIN2 or more severe histology and for CIN3 or more severe histology according to different criteria of referral.
Tabella 4. Valore predittivo positivo per istologia CIN2 o più grave e per istologia CIN3 o più grave, secondo diversi criteri di invio.

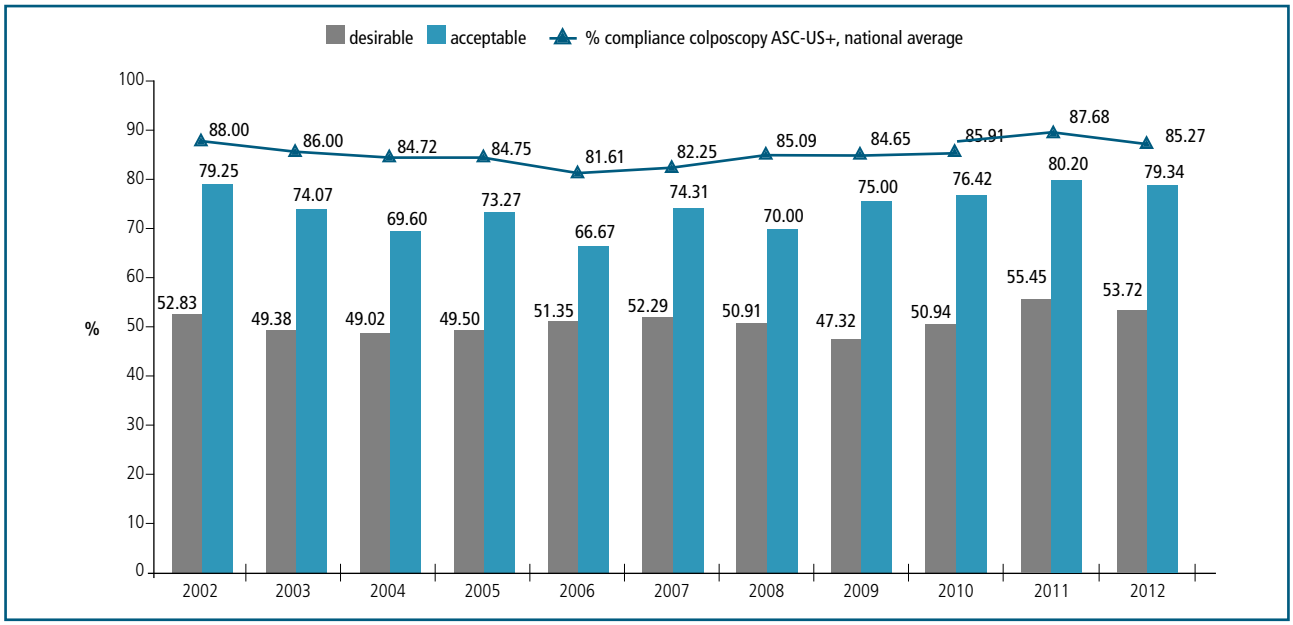

Figure 7. Compliance with colposcopy (referral because of ASC-US or more severe cytology). Percentage of programmes that reach "acceptable" and "desirable" values by year of activity.
Figura 7. Compliance alla colposcopia (invio per citologia ASC-US o più grave). Percentuale di programmi che raggiungono valori "accettabili" e "desiderabili", per anni di attività.

50.8% of those with atypical vessels. When excluding from computations the lesions diagnosed during unsatisfactory or unclassified colposcopies, 95.1% of CIN3+ and 93.7% of CIN2 were identified during colposcopies with abnormal findings (58.9% and 33.6% of CIN3+ and CIN2, respectively, during colposcopies classified as G2, atypical vessels, or suggestive of cancer).

Management and treatment of women with screen-detected biopsy-proven CIN

Data were reported by 86 programmes in 2011 and 93 in 2012 (table 6, p. 73). No information was available for 4.8% of women and the type of treatment was unknown for a further 1.8%.

Of all women with CIN1, 81.7% were recalled for follow-

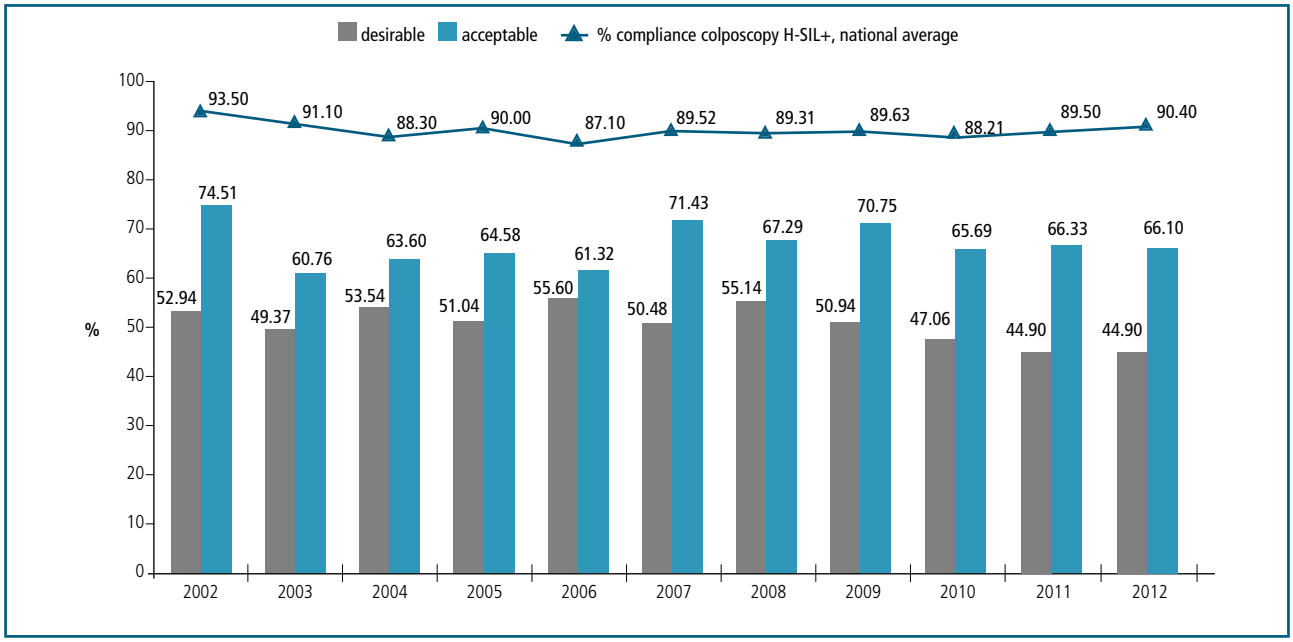

Figure 8. Compliance with colposcopy (referral because of H-SIL or more severe cytology). Percentage of programmes that reach "acceptable" and "desirable" values by year of activity.
Figura 8. Compliance alla colposcopia (invio per citologia H-SIL o più grave). Percentuale di programmi che raggiungono valori "accettabili" e "desiderabili", per anni di attività.

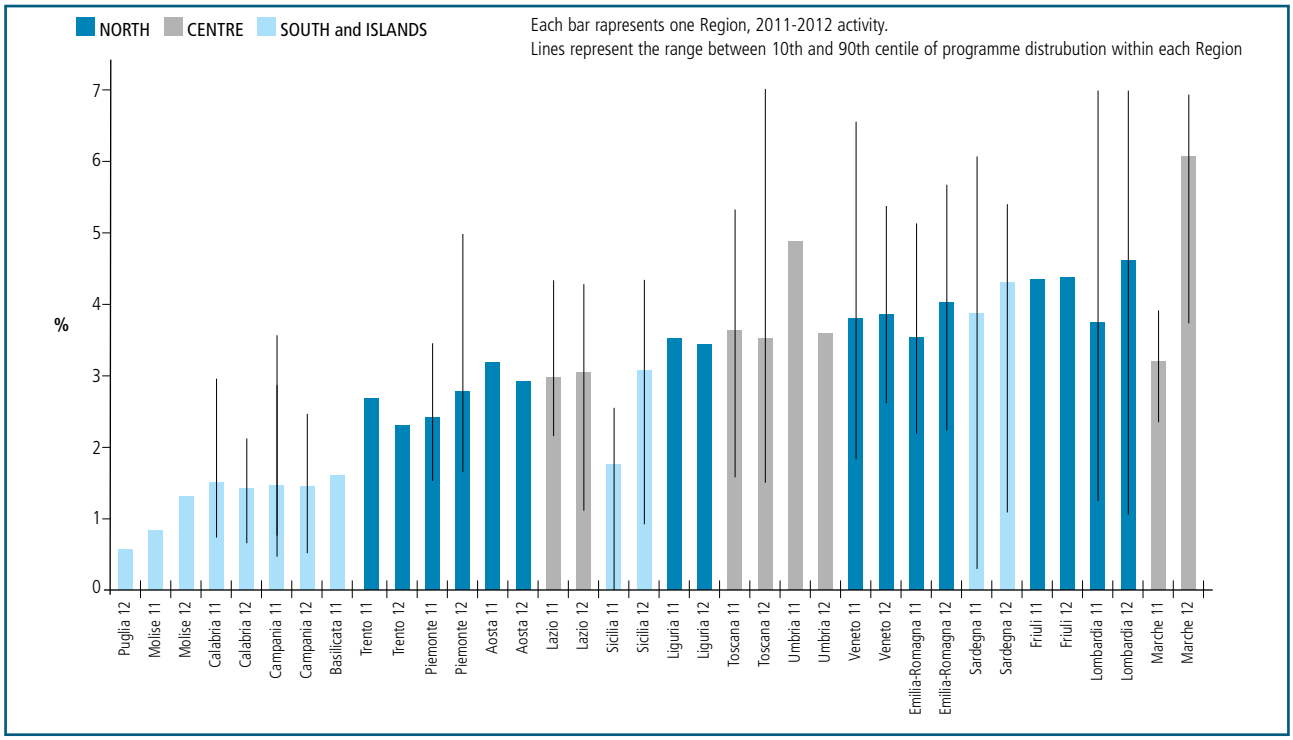

Figure 9. Unadjusted detection rate (per 1,000 women) of histologically confirmed CIN2+, by region. 2011-2012 activity.
Figura 9. Tasso di identificazione grezza di CIN2+ con conferma istologica, per Regione. Attività 2011-2012.

up only, in agreement with the recommendation not to treat these lesions except if persistent.[5-7] This proportion increased from previous years (78.8% in 2010 and 73.0% in 2009). Most of women with CIN2 (52.8%) and CIN3 (57.0%) were treated by stand-alone radio-frequency devices. Laser conisation was applied in 7.2% of women with CIN2 and 9.1% of those with CIN3. Destructive treatments were still used in association with radio-frequency devices (laser in 5.4% and 3.2% of women with CIN2 and CIN3 respectively), but very uncommonly alone, especially for CIN3. Cold knife conisation was limited to 8.8% of women with CIN2 and 14.5% of those with CIN3. Of the women with adenocarcinoma in situ, 35.8% had hys-

Colposcopic findings	Histology									
	no biopsy performed	no CIN	CIN1	CIN2	CIN3	adeno carcinoma in situ	invasive squamous carcinoma	invasive adeno carcinoma	total with biopsy	total
normal colposcopic findings - transformation zone fully visible (N)	17,701	2,217	992	215	137	8	4	7	3,580	21,281
% of total	83.2%	10.4%	4.7%	1.0%	0.6%	0.0%	0.0%	0.0%		
% of total with biopsy		61.9%	27.7%	6.0%	3.8%	0.2%	0.1%	0.2%		
grade 1 (N)	3,379	4,874	7,634	2,038	1103	25	25	7	15,706	19,085
% of total	17.7%	25.5%	40.0%	10.7%	5.8%	0.1%	0.1%	0.0%		
% of total with biopsy		31.0%	48.6%	13.0%	7.0%	0.2%	0.2%	0.0%		
grade 2 (N)	233	460	1,092	1125	1626	37	79	15	4,434	4,667
% of total	5.0%	9.9%	23.4%	24.1%	34.8%	0.8%	1.7%	0.3%		
% of total with biopsy		11.6%	23.6%	24.8%	36.8%	1.4%	1.5%	0.3%		
atypical vessels (N)	194	51	9	13	27	2	16	4	122	316
% of total	61.4%	16.1%	2.8%	4.1%	8.5%	0.6%	5.1%	1.3%		
% of total with biopsy		41.8%	7.4%	10.7%	22.1%	1.6%	13.1%	3.3%		
colposcopic features suggestive of invasive cancer (N)	11	5	5	4	14	10	39	16	93	104
% of total	10.6%	4.8%	4.8%	3.8%	13.5%	9.6%	37.5%	15.4%		
% of total with biopsy		5.4%	5.4%	4.3%	15.1%	10.8%	41.9%	17.2%		
other - unsatisfactory colposcopy (N)	4,343	1,262	613	144	141	6	6	6	2,178	6,521
% of total	66.6%	19.4%	9.4%	2.2%	2.2%	0.1%	0.1%	0.1%		
% of total with biopsy		57.9%	28.1%	6.6%	6.5%	0.3%	0.3%	0.3%		
Number of colposcopies where colposcopy result is not available (N)	1,783	514	284	95	100	3	6	7	1,009	2,792
% of total	63.9%	18.4%	10.2%	3.4%	3.6%	0.1%	0.2%	0.3%		54,766
% of total with biopsy		50.9%	28.1%	9.4%	9.9%	0.3%	0.6%	0.7%		

Table 5. Colposcopic findings and histology in the colposcopies performed by 81 Italian cervical screening programmes during 2011 and 2012.
Tabella 5. Grading colposcopico ed esito istologico delle colposcopie effettuate da 81 programmi italiani di screening negli anni 2011 e 2012.

terectomy, 15.6% cold knife conisation, and 32.1% other more conservative excisional treatment. As first treatment, some 59% of women with invasive cancer had hysterectomy, 7% cold knife conisation and 10% LLETZ. These plausibly include diagnostic assessment procedures. We do not know about subsequent treatments.

No recommendation of treatment was registered for 7.0% of CIN2 and 2.2% of CIN3. On the other hand, hysterectomy was reported in 0.1%, 0.4%, and 2.3% of women with CIN1, CIN2, and CIN3, respectively. Italian guidelines recommend no more than 2% hysterectomies on CIN2/3 and virtually none on CIN1.[1,2] Diathermocoagulation, which is not recommended by guidelines,[5,19] was still applied for 4.3% of CIN1 and 1.6% of CIN2.

No treatment was registered, despite referral, in 3-4% of women with CIN2/3 or adenoCa. In most of these cases, referrals were made >3 months in advance, suggesting refusal.

Correlation between colposcopy-guided biopsy and excised specimen histology

Excisional histology was CIN1 or lower in 13% of women with a CIN2-3 colposcopy-guided biopsy, similar to what was observed in 2010 (14%). Among women with CIN1 who had a colposcopy-guided biopsy, 23% had CIN2 or more severe histology on the excised specimen. Higher values had been observed in previous years: 30% in 2009 and 32% in 2010 (table 7).

DISCUSSION

Organized cervical screening programmes have now reached almost complete nominal extension. Italian women not included in organized programmes are substantially only those from most of Lombardia, which chose not to implement invitational programmes. However, the programmes active in northern and central Italy now frequently reach complete or almost complete invitational coverage, while in some regions of southern Italy the invitation rate is much lower than needed. Some decrease in invitational coverage, compared to previous years, was observed in regions of southern but also northern and central Italy.

It is important to avoid that funding restrictions due to the economic crisis result in an inversion of the growing trend observed up to now: this would mean losing the results of a great amount of efforts and resources allocated for many years. Recent national results[20,21] confirm the early local observation[22]

	Most severe histology before treatment										
	CIN1*	%	CIN2*	%	CIN3*	%	adeno carcinoma in situ	%	invasive carcinoma	%	total
First treatment											
laser vaporisation	231	2.3	103	2.5	24	0.7	0	0.0	0	0.0	358
cryotherapy	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1
radical diathermy	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
diathermocoagulation	436	4.3	65	1.6	6	0.2	0	0.0	0	0.0	507
excision by radio-frequency device	469	4.7	2,147	52.8	1,929	57.0	24	22.0	25	10.0	4,594
cold knife conisation	84	0.8	359	8.8	490	14.5	17	15.6	18	7.2	968
laser conisation	47	0.5	293	7.2	308	9.1	10	9.2	4	1.6	662
LLETZ + Laser	20	0.2	220	5.4	108	3.2	1	0.9	0	0.0	349
hysterectomy	13	0.1	15	0.4	79	2.3	39	35.8	147	59.0	293
Other treatments											
conisation NOS	0	0.0	2	0.0	2	0.1	0	0.0	0	0.0	4
radio/chemotherapy	0	0.0	0	0.0	0	0.0	0	0.0	3	1.2	3
photo-thermocoagulation	3	0.0	1	0.0	1	0.0	1	0.9	0	0.0	6
trachelectomy	0	0.0	1	0.0	1	0.0	0	0.0	0	0.0	2
polipectomy	2	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2
type of treatment unknown	66	0.7	122	3.0	112	3.3	4	3.7	19	7.6	323
not treated - no treatment recommended	8,233	81.7	285	7.0	73	2.2	3	2.8	0	0.0	8,594
not treated - treatment recommended <3 months before	36	0.4	29	0.7	24	0.7	0	0.0	2	0.8	91
not treated - treatment recommended ≥3 months before	74	0.7	92	2.3	85	2.5	4	3.7	5	2.0	260
unknown if treated	365	3.6	331	8.1	140	4.1	6	5.5	26	10.4	868
Total	**10,080**	**100.0**	**4,065**	**100.0**	**3,382**	**100.0**	**109**	**100.0**	**249**	**100.0**	**17,885**

Table 6. Treatment or management of the intraepithelial lesions, performed by 86 Italian screening programmes in 2011 and 93 in 2012.
Tabella 6. Trattamento o gestione delle lesioni intraepiteliali effetuati da 86 programmi italiani di screening nel 2012.

	Histology on excised specimen							
worse histology before treatment	negative (<CIN) (%)	CIN1 (%)	CIN2/3 (%)	adeno Ca in situ (%)	invasive cervical cancer (%)	total available	not available (%)	total
CIN1	188 (20.4)	**521 (56.6)**	205 (22.3)	5 (0.5)	2 (0.2)	921	51 (5.2)	972
CIN2/3	154 (2.9)	537 (10.2)	**4,428 (83.7)**	43 (0.8)	126 (2.4)	5,288	184 (3.4)	5,472
Adeno Ca in situ	4 (5.7)	2 (2.9)	8 (11.4)	**42 (60.0)**	14 (20.0)	70	1 (1.4)	71
Invasive cervical cancer	7 (3.7)	0 (0.0)	40 (21.2)	7 (3.7)	**135 (71.4)**	189	9 (4.5)	198.

The number of women is given, followed by percentages in brackets. "Not available" percentages are computed on row totals. The other percentages are computed based on the "total available" data.

Table 7. Correlation between colposcopy-guided biopsy and excised specimen histology.
Tabella 7. Correlazione tra biopsia guidata dalla colposcopia e istologia del campione prelevato.

that organized programmes can increase the overall proportion of women screened within the needed interval, thus showing their utility. A recent nationwide analysis of the screening histories of women who developed invasive cancer[23] also showed (in agreement with previous local analyses[24,25]) that the large majority of those women did not comply with invitation. Therefore, an effort to increase compliance and reduce its negative North-South trend is needed.

When interpreting time trends of performance indicators it must be taken into account that the population examined has partly changed over time, mainly because of the increased extension of organized programmes. Furthermore, the detection rate of high-grade CIN is expected to be higher in newly activated programmes than in screening programmes that are already at subsequent screening rounds. In some areas, this phenomenon was however compensated by an increase in immigrants from high migration pressure countries, who have a higher prevalence of high-grade CIN than Italian women.[26-29]

Performance indicators show little variation in the last years at a national level. There is surely a long-term trend to reduce recall for cytology repeat (which is plausibly attributable to the training activity in cytology interpretation, mainly performed by GISCi) and increasing compliance to recall for repeat. Referral to colposcopy was stable or slightly on the rise. However, PPV was also substantially stable, after a previous increase from 2000. Many indicators show increased homogeneity between regions for the past few years. A number of outliers, however, are still present: two regions recall over 10% of screened

women to repeat cytology and a group of regions has an extremely low PPV. A crucial factor in determining PPV is clearly the management of ASC-US, and its heterogeneity explains part of the heterogeneity in PPV. However, variability in criteria of interpretation of cytology still plays a relevant role. Although implementation of triage systems for ASC-US is needed in order to obtain high PPVs, it is not always sufficient. In fact, triaging ASC-US by repeat cytology did not reach high PPVs, possibly because criteria of interpretation were too loose in any case. In addition, high frequency of ASC-US was replaced by high frequency of LSIL reports, without reaching high PPVs.

Programmes with low PPV are mainly (but not only) from southern Italy, where organized programmes started their activity more recently. The very low CIN2+ detection rate observed in a few regions in southern Italy also requires attention. In southern Italy recent data showed a prevalence of HPV infection similar to that in central and northern Italy. This suggests a similar baseline risk at least in younger cohorts.[30] Therefore, the low detection rate could be the result of a selective uptake of invitation of women who had already been intensively screened, low sensitivity of cytology and/or histology, or low compliance to colposcopy. Part of the low compliance to colposcopy may depend upon incomplete registration (especially of colposcopies performed outside reference centres). Moreover, part of the low detection rate may depend upon incomplete registration or missing links with histology results. In any case, it is essential to strive for the implementation of good fail-safe systems. Lack of diagnostic work-up can make the efforts made for primary screening useless.

In conclusion, data suggest that most of the programmes that have been active for many years reached a good quality, likely thanks to the long-lasting monitoring and intensive activity of quality assurance. On the other hand, the newly started programmes in southern Italy need strong support to improve quality, particularly as for the specificity of first-level cytology and the completeness of follow-up and registration. There is a need for intervention, as, in some areas, the current situation does not guarantee effectiveness of screening and acceptable levels of undesired effects. A shift to HPV testing could solve problems concerning quality of cytology interpretation, but it would not be an effective solution to problems of loss to follow-up.

The application of appropriate treatments has largely improved during the last few years and has now reached levels that are acceptable – although still not optimal – in almost all geographical areas. In addition, these data are still missing from many programmes. High quality of diagnostic work-up and treatment and strict adherence to positive women management algorithms are needed in view of a shift to HPV-based screening.

Conflicts of interests: none declared

Data for the years 2011-2012 was provided by:
Hanno fornito i dati per gli anni 2011-2012:

Valle D'Aosta: G. Furfaro, T. Meloni, M. Cognein
Piemonte: N. Segnan, E. Mancini (Torino); G. Faragli (Alessandria); S. Polizzi (Moncalieri); L. Orione (Cuneo); M.P. Alibrandi (Ivrea); T. Miroglio (Asti); M. Sartori, M. Ciminale (Rivoli-Val di Susa); C. Magnani, P. Bestagini (Novara); F. Germinetti (Vercelli-Biella)
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Campania: R. Pizzuti, A. Pugliese, G. Albano (Avellino 1); M. Cozza (Avellino 2); G. Ragozzino (Benevento); G. Capone (Caserta 1); C. Vatiero, E. Frezza (Caserta 2); R. Papa (Napoli 1); M.T. Pini (Napoli 2); M. Panico (Napoli 3); A. Esposito, C. Maione, R.P. Esposito (Napoli 4); F.S. Manco (Napoli 5); U. Scala (Salerno 1); G. Auriemma (Salerno 2); G. Martuscelli (Salerno 3)
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Puglia: V. Pomo (Dir. Area politiche per la promozione della salute, delle persone e delle pari opportunità, Regione Puglia); G. Labate, C. Ladalardo (Servizio PATP, Assessorato alle politiche della salute, Regione Puglia); V. Piazzolla (ARES Puglia); N. Albano (Resp. RIP NSISR); C. Germinario, D. Martinelli, M.S. Gallone (OER Puglia); N. Morelli (ASL Bari); A. Belsanti (ASL Bt); G. Spagnolo (ASL Brindisi); R. Prato (ASF Foggia); M.R. Canitano (ASL Lecce); S. Sabato (ASL Taranto)
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Sardegna: R. Masala e P. Tanchis (dal 2012) (Ass. Reg. Sanità); S. Tilocca (Cagliari); F. Congiu (Sanluri); O. Frongia (Oristano); M.A. Atzori (Nuoro); U. Stochino (Lanusei); M. Piga (Olbia); A. Onnis (Carbonia)

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[1]AOU Città della salute e della scienza, CPO Piemonte, Torino
[2]Servizio interaziendale di epidemiologia, AUSL Reggio Emilia
[3]IRCCS-Arcispedale S. Maria Nuova, Reggio Emilia
[4]Istituto oncologico veneto IRCSS
[5]Istituto per lo studio e la prevenzione oncologica (ISPO), Firenze

Corresponding author:
Guglielmo Ronco
guglielmo.ronco@cpo.it

A first survey of HPV-based screening in routine cervical cancer screening in Italy

Prima survey sull'utilizzo routinario del test HPV nello screening cervicale in Italia

Guglielmo Ronco,[1] Paolo Giorgi-Rossi,[2,3] Pamela Giubilato,[1] Annarosa Del Mistro,[4] Marco Zappa,[5] Francesca Carozzi[5] and the HPV screening survey working group

Abstract

Pilot HPV-based cervical screening programmes have recently started in Italy, partly on the strength of a large randomized trial. The Ministry of Health recommended that regions shift toward HPV-based screening in early 2013 and provided guidelines for its application (stand-alone HPV testing by validated methods, cytological triage of HPV positives, beginning at age 30-35, 5-year intervals). A first survey on the 2012 activity was conducted in 2013.

In 2012, 19 Italian organized cervical screening programmes from 10 regional programmes invited 311,856 women (8.0% of all women invited for cervical screening in 2012 in Italy) for HPV-based screening; 41.5% complied, with a decreasing North-South trend. Among screened women, 7.9% (range 4.3%-13.9%) were HPV positive, decreasing to 6.6% (range 4.0%-12.4%) when considering women aged 35-64 years. Among HPV positive women, 34.8% (with high variability between programmes: range 11.1%-59.3%) were judged to have ASC-US or more severe cytology (5.3% ASC-US, 26.6% L-SIL, 5.2% H-SIL). Out of all screened women, those referred to colposcopy based on HPV and cytology results were 2.9% (range 0.6%-4.8%), whereas they were 2.0% when considering only women aged 35-64 years.

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Keywords: cervical cancer, mass screening, HPV test, Italy

Riassunto

Recentemente, in parte sull'onda dei risultati di un ampio trial randomizzato, in Italia sono stati attivati programmi pilota di screening cervicale basati sul test HPV. All'inizio del 2013 il Ministro della salute ha raccomandato alle Regioni di passare a screening basati sul test HPV e ha fornito linee guida per la sua applicazione (utilizzo del solo test HPV applicando metodi validati, triage citologico dei casi positivi al test, inizio all'età di 30-35 anni, intervalli di 5 anni). Una prima survey sull'attività del 2012 è stata condotta nel 2013.

Nel 2012, 19 programmi organizzati di screening cervicale afferenti a 10 regioni hanno invitato allo screening basato sul test HPV 311.856 donne (8,0% di tutte le donne invitate allo screening cervicale nel 2012 in Italia) . Di queste, il 41,5% ha aderito con un trend decrescente da Nord a Sud. Tra le donne sottoposte a screening, il 7,9% (range 4,3%-13,9%) era HPV positivo, percentuale che diminuisce al 6,6% (range: 4,0%-12,4%) se si considerano solo le donne di età fra 35 e 64 anni. Tra le donne positive all'HPV, il test citologico ha dato esito ASC-US o più grave (5,3% ASC-US; 26,6% L-SIL; 5,2% H-SIL) nel 34,8% dei casi (con un'alta variabilità fra programmi, range: 11,1%-59,3%).

Di tutte le donne sottoposte a screening, quelle inviate in colposcopia sulla base dei risultati del test HPV e degli esiti ctologici sono state il 2,9% (range: 0,6%-4,8%), percentuale che si abbassa al 2,0% se si considerano solo le donne di età fra 35 e 64 anni.

(*Epidemiol Prev* 2015; 39(3) Suppl 1: 77-83)
Parole chiave: cancro cervicale, scereening di massa, test HPV, Italia

INTRODUCTION

Testing for the DNA of oncogenic HPV types as a primary screening test for cervical cancer precursors has been intensively studied over the past few years.

Randomized controlled trials (RCTs) comparing HPV-based to cytology-based screening have been conducted in Sweden (Swedescreen[1]), the Netherlands (POBASCAM[2]), England (ARTISTIC[3]), Italy (NTCC[4]), India,[5] Finland,[6] and Canada (CCCast[7] and FOCAL[8]).

The first four studies[1-4] published data on two screening rounds showing increased detection of high-grade CIN at the first round and decreased detection in the second when comparing the HPV and cytology groups. This proves that HPV-based screening allows earlier detection of persistent high-grade CIN than cytology. In addition, the Indian study showed a reduced incidence of cervical cancer mortality and advanced cancers after a once-in-a-lifetime screen by HPV.[5] These findings were confirmed by a pooled analysis of the RCTs that published results on two screening rounds with respect to invasive cancer incidence, which provided direct evidence of increased protection with HPV-based screening.[9]

Over the past few years, partly on the strength of the NTCC experience, a number of pilot HPV-based screening projects have started up within Italian organized cervical screening programmes. They have mainly aimed at evaluating the feasibility of HPV-based screening in routine activity.

In the meanwhile, an Italian Health Technology Assessment report was published in 2012.[10] It concluded that HPV-based screening was more effective than cytology-based cervical screening and entailed little or no increase in negative effects if appropriate protocols were applied. This included using stand-alone HPV as a primary screening test, with only clinically validated DNA-HPV tests,[11] starting HPV-based screening at 30 to 35 years of age, adopting 5-year intervals and applying a «cytological triage» protocol. The latter entailed testing HPV-positive women for cytology (using material taken during the HPV sampling visit) and referring directly to colposcopy only women with ASC-US or more severe cytology, while re-testing HPV-positive women with normal cytology after one year for stand-alone HPV and referring them to colposcopy only if HPV was still positive (**figure 1**).

Among other recommendations, the HTA report recommended strict monitoring of HPV-based screening. In early 2013, the Italian Ministry of Health adopted these recommendations as a guide for screening planning by regional health authorities.[12]

In 2013, a first Italian national survey of HPV-based screening was conducted as part of the yearly survey of cervical cancer screening by organized programmes.

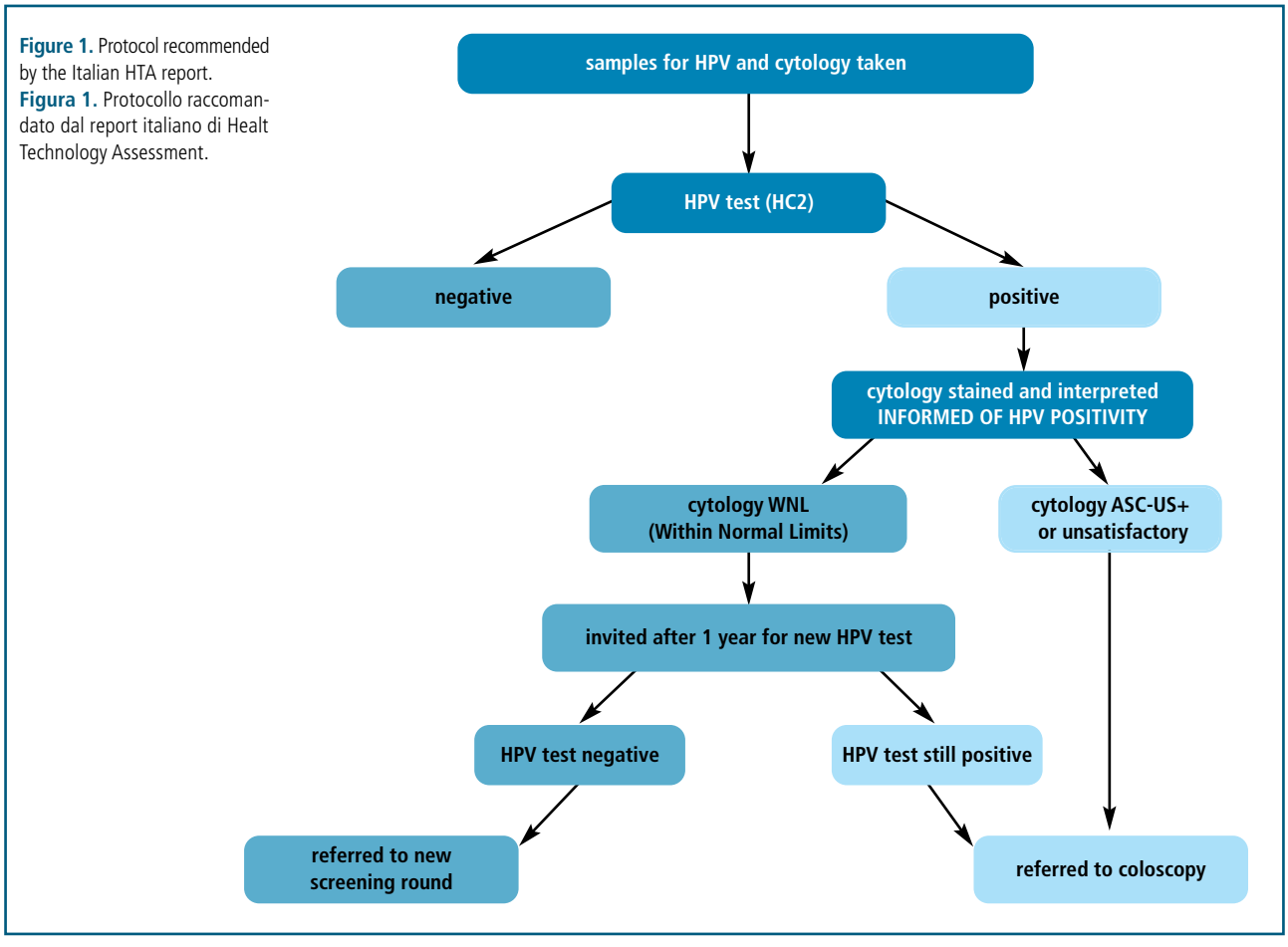

Figure 1. Protocol recommended by the Italian HTA report.
Figura 1. Protocollo raccomandato dal report italiano di Healt Technology Assessment.

METHODS

Surveys designed to assess the level of implementation of organized cervical screening programmes in Italy and collect process indicators are conducted every year by the ONS (Osservatorio nazionale screening, National centre for screening monitoring) on behalf of the Italian Ministry of Health. Data are collected through a questionnaire as aggregated tables of data. Details are provided elsewhere.[13]

A survey section dedicated to HPV-based screening was added to the general survey in 2013, related to the 2012 activity. It was designed assuming that the protocol suggested by the HTA and Ministry guidelines was applied. As the protocol entails 1-year repeats for HPV-positive women with normal cytology, it was decided to split the collection of data on women invited each year for primary screening into two sections. The first section, including data on invitation and participation to the HPV test, its result and results of triage cytology, is collected in the year after the invitations. In September 2013, therefore, data were collected on women invited for primary HPV testing during 2012 and tested by April 2013. The second section, including 1-year repeats and colposcopies resulting both from cytology and 1-year repeat HPV tests, were collected during 2014 for women invited for primary testing in 2012.

In addition to these data, information on the screening protocol applied was also collected.

RESULTS

Extension of HPV-based screening and participation

In 2012, 19 Italian programmes from 10 regions invited women for HPV-based screening (table 1). Eleven of them were from northern Italy, 3 from central Italy, and 5 from southern Italy. Five programmes (Torino, Trento, Reggio Emilia, Firenze, and Molise) invited both women to HPV-based and cytology-based screening (the first 3 within a randomized pilot project), while the remaining 14 invited women just to HPV-based screening. Overall, 311,856 women aged 25-64 years were invited to HPV screening, representing 8.0% of all women invited for cervical screening in Italy in 2012 (9.5%, 4.0%, and 8.8% of those invited in northern, central, and southern Italy, respectively). The regions with the largest number of women invited to HPV were Veneto, where 6 programmes converted completely to HPV, and Abruzzo, where the entire region moved to HPV testing. In addition, the region of Liguria, where only a small area was previously covered by organized programmes, chose to extend coverage inviting to HPV testing. In 2012, 61% of women invited for cervical screening in Liguria were invited to HPV testing.

As the national guideline came out in 2013, all programmes active in 2012 were pilot projects. Among them, 12 programmes started inviting women to HPV testing at 25 years and 7 at 35. However, after publication of the national guidelines, many programmes have planned to shift age of first testing to 30 or 35 years. All programmes used clinically-validated DNA-HPV tests (mostly Digene Hybrid Capture2, and in few cases Roche's Cobas or the Abbott real-time PCR test) except one which used an mRNA test. This programme was excluded from further analyses.

In 2012, 41.5% of all women invited to HPV DNA-based screening complied. There was a strong variability between centres. The lowest values, below 20%, were in southern Italy and the highest, above 65%, in northern Italy, reproducing outcomes observed with all invitations[13] (figure 2, p.80). Results were very similar when restricted to women aged 35-64 years (mean 42.1%, data by centre not shown).

Process indicators with HPV

All programmes used stand-alone HPV as primary test and adopted cytological triage as recommended by national

Region	Number of programmes	Target age	Women invited	Women screened
Abruzzo	4	25-64	108,739	34,094
Emilia-Romagna	1	35-64	5,192	3,280
Lazio	2	25-64 e 35-64	36,052	13,068
Liguria	1	35-64	14,164	6,453
Lombardia	1	25-64	8,317	5,294
Molise	1	35-64	2,000	251
Piemonte	1	35-64	24,289	12,419
Toscana	1	35-64	40	29
Trento	1	35-64	2,865	1,134
Veneto	6	25-64	110,198	55,147
Northern Italy	**11**		**165,025**	**83,727**
Central Italy	**3**		**36,076**	**13,083**
Southern Italy	**5**		**110,739**	**34,345**
Italy	**19**		**311,840**	**131,155**

Table 1. Organized programmes that invited women to HPV-based screening in Italy. 2012 activity.

Tabella 1. Programmi organizzati che hanno invitato a uno screening basato sul test HPV in Italia. Attività 2012.

guidelines and reported in figure 1. One programme (Firenze) was excluded from calculations given the very low number of women screened in 2012.
Since HPV infection prevalence is age-dependent and age of start was different between programmes, we computed the proportion of women positive to the primary HPV test both for any age and restricted to age 35-64 years (figure 2). Overall, 7.9% (range 4.3%-13.9%) of screened women of any age and 6.6% (range 4.0%-12.4%) of those aged 35-64 years (excluding Roma G because data by age were not available) were HPV positive. Within programmes that invited women aged 25-34 years, the overall prevalence was 1.5%-2.7% higher than the prevalence in the same programmes restricted to women aged 35-64 years. The lowest value was observed in Trento (as was already the case in the NTCC study[14]). High values were observed in Abruzzo and Molise (southern Italy).
Overall, when including all ages, 34.8% of HPV-positive women were judged to have ASC-US or more severe cytology, with a very large variation, ranging from 11.1% in Trento and 19.4% in Torino to 59.3% in a programme in Veneto (figure 3). The proportion of HPV-positive women classified as ASC-US or AGC was 5.3% (range 0.0%-23.1%), that of women classified as L-SIL was 24.6%

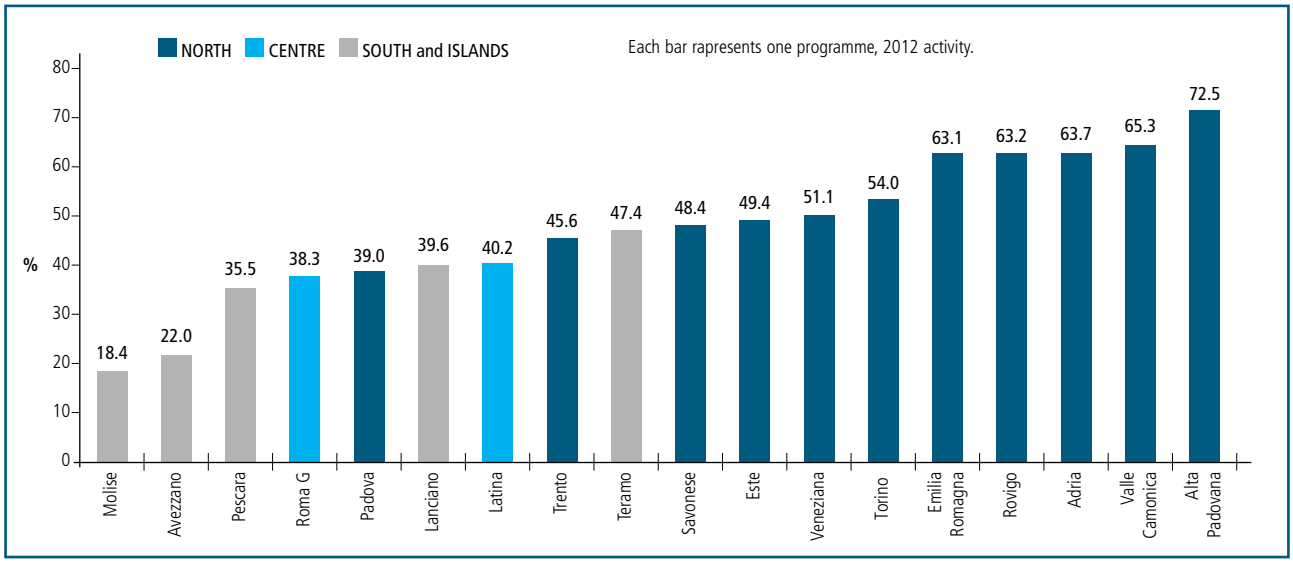

Figure 2. Compliance to invitation to HPV-based screening. All ages included. Italian organized programmes 2012 activity.
Figura 2. Compliance all'invito allo screening basato sul test HPV. Tutte le età incluse. Attività 2012 dei programmi organizzati.

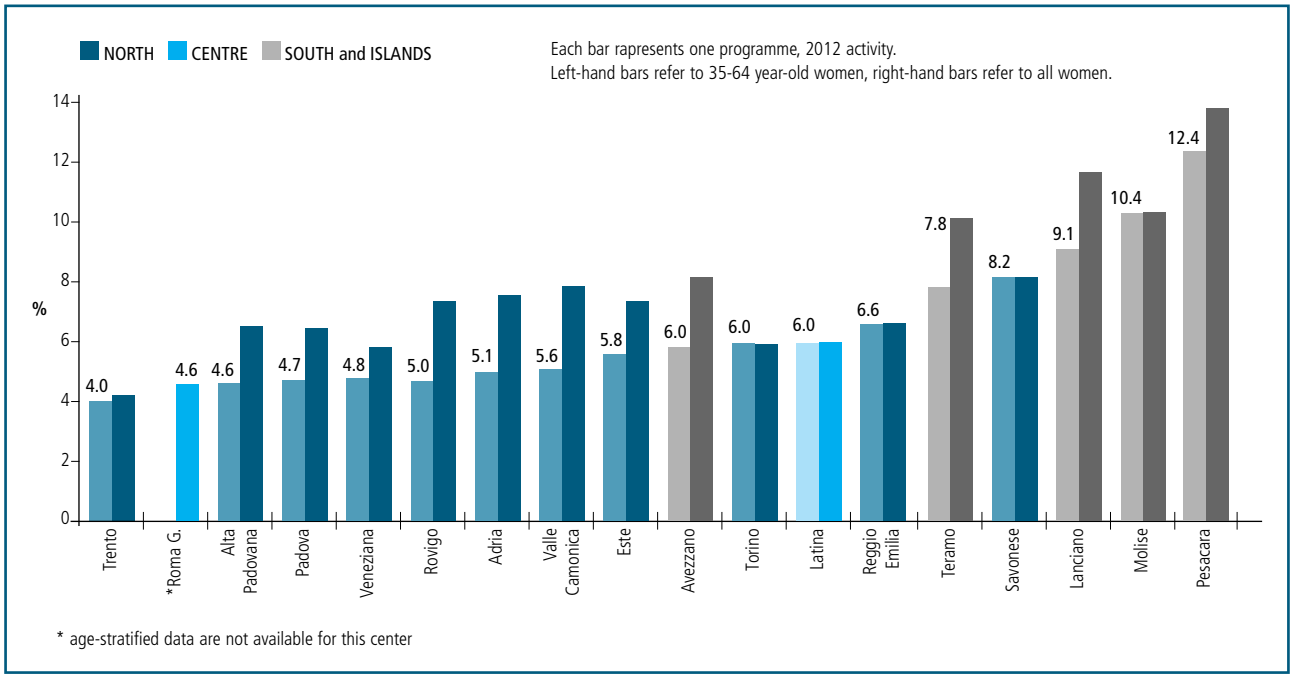

Figure 3. Proportion of HPV-positive women. Italian organized programmes 2012 activity.
Figura 3. Proporzione di donne HPV-positive. Attività 2012 dei programmi organizzati.

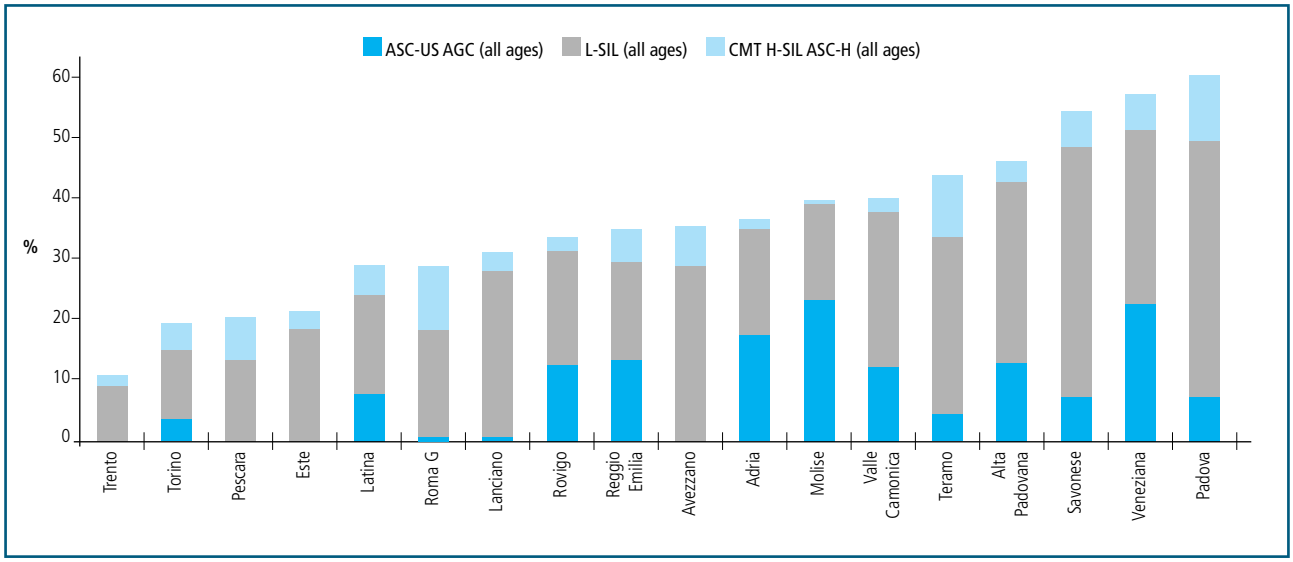

Figure 4. Proportion of HPV-positive women with abnormal cytology. Women of any age. Italian organized programmes 2012 activity.
Figura 4. Proporzione di donne HPV-positive con citologia anomala. Donne di ogni età. Attività 2012 dei programmi organizzati.

(range 9.8%-41.7%), and of women classified as H-SIL or ASC-H was 5.2% (range 1.7%-11.0%). Results were similar when restricted to women aged 35-64 years: 34.8% of HPV+ women were classified as ASC-US or higher.

When considering all ages, 2.9% of screened women were referred to colposcopy on the basis of the primary HPV test and simultaneous cytology. Variability was still very high, ranging from 0.6% in Trento to 4.8% in Savona. Values were below 2% in 5 programmes and below 3% in 11 (**figure 4**). When restricting data to women aged 35-64 years, 2.0% of women were referred. Trento (0.5%) and Savona (4.8%) were again the programmes with the lowest and highest values. Within the centres that invited women from age 25, the referral rate including all women was 1.09 to 1.60 times the referral restricted to women aged 35-64 years.

DISCUSSION

In this first survey of HPV-based screening, only an incomplete set of performance indicators can be presented. Data dealing with the entire screening process on women screened in 2012 will be presented next year. Nevertheless, these are, to our knowledge, the first nationwide data on routine HPV screening based on a large population.

The shift to HPV-based screening is becoming relevant in Italy. In 2012, about 10% of women invited for primary screening by Italian organized programmes were invited to HPV testing. This proportion is expected to rapidly increase after the publication of the guidelines of the Ministry of Health in January 2013. To our knowledge, in May 2014, 7/21 regions had decided to implement HPV-based screening as the routine screening method to the entire female population in the recommended age range, although this implementation will be progressive (3 to 5 years) in most cases.[15] For example, the region of Toscana started by inviting the 55-64 age group in December 2012 and expects to complete accrual in three years by progressively inviting younger women. Conversely, the region of Piemonte plans to invite for HPV an increasing proportion of randomly defined women over a span of three years, and the entire target population starting from the fourth year.

One of the crucial issues with HPV-based screening is the application of appropriate protocols, in order to avoid negative effects for women and increased costs. Indeed, recommendations on stand-alone HPV testing and cytological triage were adopted by all centres. On the other hand, guidelines were delivered by the Ministry after the period of activity considered here. This explains the inclusion of younger women in the target population. Due to the same reason, screening intervals were still, officially, 3 years, but are now being changed.

Compliance to invitation was slightly higher than nationwide when considering compliance to all invitations (to HPV or cytology), which was 40.8% in 2012. Given the high variability between centres and ages, a comparison of this sort is not reliable, but at least suggests that invitation to HPV testing is not a barrier to participation. Indeed, an increased compliance to invitation to HPV when compared to historical controls was observed in the pilot programmes in Veneto[16,17] and Lazio.[18]

Variability in the proportion of women positive to HPV testing was substantial even when restricting data to women of the same age. However, it could well reflect true differences in screened populations. Substantial variability was also observed in the NTCC study, where prevalence was lowest in Trento.[14] High prevalence was also previously observed in Abruzzo.[19]

There was also a striking variability between programmes in the proportion of HPV-positive women classified as having abnormal cytology, resulting in strong variability of referral to colposcopy on the basis of cytological abnormalities.

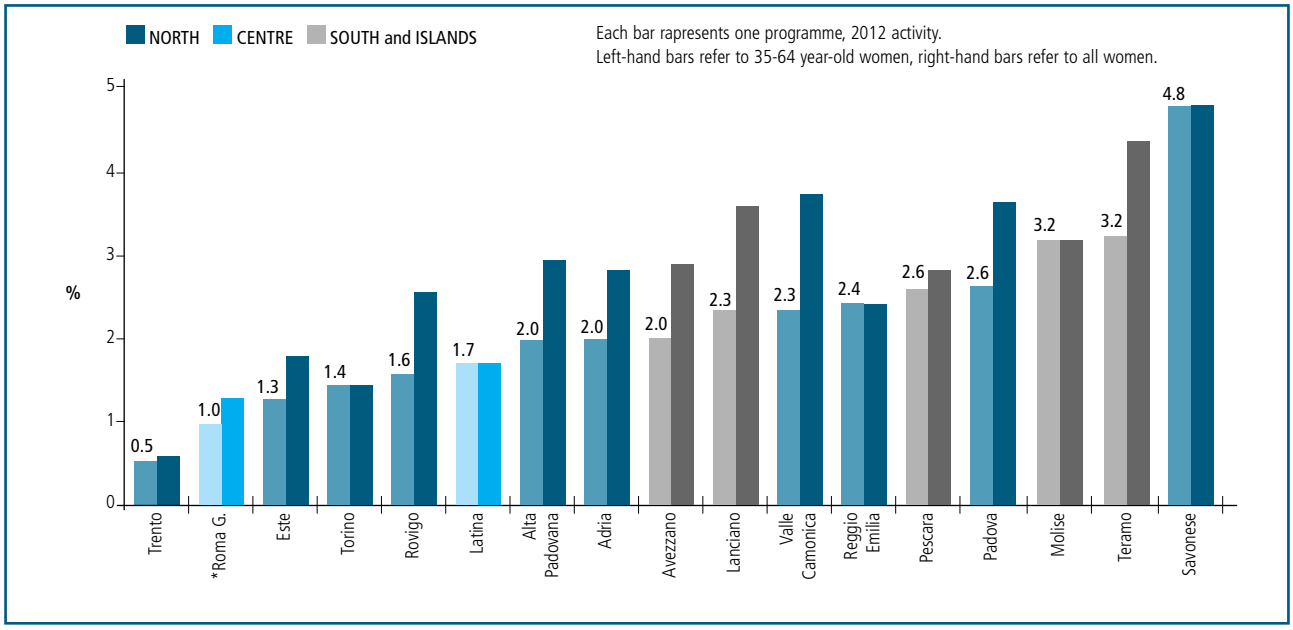

Figure 5. Proportion of women screened by HPV who are immediately referred to colposcopy because both HPV positive and judged to have abnormal cytology.
Figura 5. Proporzione di donne screenate per HPV che sono immediatamente inviate a colposcopia perché positive all'HPV e con citologia anomala.

The PPV of stand-alone HPV testing for high-grade CIN was actually quite stable (except for an inverse correlation to the previous screening activity) in different situations.[20] Therefore, variability between areas is expected to be lower than the variability in abnormal cytology in the entire population (which also reflects true variations in baseline risk). Thus, the observed variability in cytology triage plausibly reflects variability in the criteria of interpretation. Knowledge that slides came from HPV-positive women probably had a strong impact. Very high frequencies of cytological abnormalities were also observed in early reports of pilot projects.[16,18] These data clearly show the need to train cytologists and cytopathologists involved in the triage of HPV-positive women.

Conflicts of interests: One of the authors, Paolo Giorgi Rossi, as principal investigator in a study funded by the Italian Ministry of Health, is in charge of leading negotiations with Hologic, Roche Diagnostics, Qiagen, and Abbot in order to obtain reagents for free or at lower costs.

HPV screening survey working group:
Gruppo di lavoro per la survey sullo screening con HPV:

N. Segnan, A. Gillio Tos: CPO Piemonte
L. Bonelli: IRCCS AOU San Martino-IST, Genova
A. Franco, E. Venturino: ASL2 Savonese
L. Pasquale, G. Luciano: ASL Valle Camonica Sebino
E. Polla, P. Dalla Palma: Ospedale S. Chiara, Trento
M. Zorzi: Registro tumori Veneto
C. Fedato: Regione Veneto
F. Zago: ULSS 12 Venezia
A. Pupo: ULSS 15 Alta Padovana
I. Simoncello: ULSS 16 Padova
A. Ferro: ULSS 17 Este-Monselice
L. Gallo: ULSS 18 Rovigo
A. Del Sole: ULSS 19 Adria
L. Paterlini, C. Campari: AUSL Reggio Emilia
A. Iossa, M. Confortini: ISPO, Firenze
A. Barca: Regione Lazio
M.C. Tufi: ASL Roma G
P. Bellardini: ASL Latina
C. Fortunato: ASL Teramo
M. Minna: ASL Pescara
A. Macerola: ASL Av-Sulmona-L'Aquila
D. Caraceni: ASL Lanciano-Vasto-Chieti

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hr-HPV testing in the management of women with ASC-US+ and in the follow-up of women with cytological abnormalities and negative colposcopy. Recommendations of the Italian group for cervical cancer screening (GISCi)

Test hr-HPV nella gestione delle donne con citologia ASC-US+ e nel follow-up delle donne con citologia anormale e colposcopia negativa. Raccomandazioni del Gruppo italiano per lo screening del carcinoma della cervice uterina (GISCi)

Francesca Maria Carozzi,[1] Anna Iossa,[1] Aurora Scalisi,[2] Mario Sideri,[†] Karin Louise Andersson,[1] Massimo Confortini,[1] Annarosa Del Mistro,[3] Giovanni Maina,[4] Guglielmo Ronco,[5] Patrizio Raggi,[6] Maria Luisa Schiboni,[7] Marco Zappa,[1] Paolo Giorgi Rossi[8,9]

[1]Istituto per lo studio e la prevenzione oncologica, Firenze
[2]Azienda sanitaria provinciale, Catania
[3]Istituto oncologico veneto IOV - IRCCS, Padova
[4]Azienda ospedaliera Città della scienza e della salute di Torino - Presidio S.Anna
[5]Centro di riferimento per l'epidemiologia e la prevenzione oncologica in Piemonte, Torino
[6]Azienda sanitaria locale, Viterbo
[7]Azienda ospedaliera San Giovanni - Addolorata, Roma
[8]Servizio interaziendale di epidemiologia, AUSL Reggio Emilia, IRCCS
[9]Arcispedale S. Maria Nuova, Reggio Emilia

Corresponding author: Francesca Maria Carozzi, f.carozzi@ispo.toscana.it

Abstract

Compared to spontaneous screening, an organized screening programme is characterized by the presence of protocols and recommendations for all stages including follow-up. Despite the availability of well-functioning screening programmes throughout the country, the follow-up protocol after an abnormal Pap test and negative colposcopy is not clearly defined in Italy, and there is no uniformity of indications.

HPV testing for oncogenic human papillomavirus (hr-HPV) has a high negative predictive value (NPV) and high positive predictive value (PPV) for CIN2+ and its employment can reduce follow-up assessments.

In order to provide indications about the management of women with ASC-US+ and the follow-up of women with cytological abnormalities and negative colposcopy, a literature analysis was carried out, taking into consideration European and American guidelines and good practice recommendations from the most important scientific associations and regulatory agencies. GISCi (Italian Group for Cervical Screening) drafted recommendations for the management of women with ASC-US, L-SIL, ASC-H, AGC, and H-SIL until their return to the routine screening interval. This protocol can be applied not only in the management of abnormal Pap smears in cytology-based programmes, but also in the management of abnormal Pap test triage after HPV positive test when HPV is the primary screening test. The protocols approved within the screening programmes must have an extensive consensus among all involved professionals, including any that women might meet outside the programme.

(*Epidemiol Prev* 2015; 39(3) Suppl 1: 84-90)

Keywords: cervical cancer screening, colposcopy, human papillomavirus, follow-up, Italy

Riassunto

Rispetto allo screening spontaneo, un programma di screening organizzato è caratterizzato dalla presenza di protocolli e raccomandazioni per tutte le fasi, incluso il follow-up. Nonostante l'ampia diffusione dei programmi di screening su tutto il territorio, il protocollo di follow-up dopo Pap test anormale e colposcopia negativa in Italia non è chiaramente definito e non c'è uniformità nelle indicazioni date dai programmi. Il test HPV per la ricerca di papillomavirus oncogeni ha un elevato valore predittivo negativo (NPV) e un elevato valore predittivo positivo (PPV) per CIN2+ e il suo utilizzo può ridurre i controlli di follow-up. Al fine di fornire indicazioni sulla gestione delle donne con ASC-US+ e nel follow-up delle donne con citologia anormale e colposcopia negativa è stata effettuata una analisi della letteratura, delle linee guida europee e americane e delle raccomandazioni di buona pratica delle principali associazioni scientifiche. Il Gruppo italiano per lo screening del carcinoma della cervice uterina (GISCi) ha prodotto le raccomandazioni per la gestione delle donne con ASC-US, L-SIL, ASC-H, AGC e H-SIL fino al loro ritorno al normale intervallo di screening. Questo protocollo può essere applicato non solo nella gestione del Pap test anormale nello screening con Pap test primario, ma anche nella gestione del Pap test di triage anormale dopo hr-HPV test positivo, quando HPV è il test di screening primario. I protocolli approvati nell'ambito dei programmi di screening devono avere un ampio consenso tra tutti i professionisti coinvolti, compresi coloro che potrebbero entrare in contatto con le donne al di fuori del programma.

(*Epidemiol Prev* 2015; 39(3) Suppl 1: 84-90)

Parole chiave: screening carcinoma cervice uterina, colposcopia, papillomavirus umano, follow-up, Italia

INTRODUCTION

No clear guidelines concerning the follow-up protocol after an abnormal Pap test and negative colposcopy exist in Italy, and actual management of these cases is highly variable.

Purpose of this article is providing recommendations on the use of hr-HPV testing in the management of colposcopies after an abnormal cytology (either applied as primary screening test or as triage of HPV-positive women) and in follow-up after colposcopy. The rational of recommendations is the high negative predictive value for cervical intraepithelial neoplasia grade 2 or more severe (CIN2+) of HPV testing for oncogenic human papillomavirus (hr-HPV).[1,2] This makes it possible to reduce and standardize follow-up controls.

Persistent infection with one of 12 high-risk HPV types is a necessary cause of invasive cervical cancer.[3] Thus, hr-HPV testing can be used as a negative triage test to determine whether a woman can be safely returned to routine screening[4] in the follow-up of abnormal cytology and after a negative colposcopy.

MATERIALS AND METHODS

A literature review was carried out: European and American guidelines were considered, along with good practice recommendations from the most important scientific associations and regulatory agencies.

Recommendations are based on the risk of harbouring a CIN2+ (i.e., on PPV) by primary cytology result. The PPV of cytology is highly variable between Italian screening programmes (2.8% to 52.7% for ASC-US or higher). Nevertheless, the difference between cytological categories is very large: PPV for CIN2+ is <10% in women with ASC-US and L-SIL cytology and >40% in women with ASC-H, and H-SIL cytology (**figure 1**).

For cytology classification we refer to the 2001 Bethesda system.[4] «Second-level negative for CIN2+» means that no CIN2+ was detected, either because histology was negative or because no biopsy was taken as no colposcopic abnormality was observed.

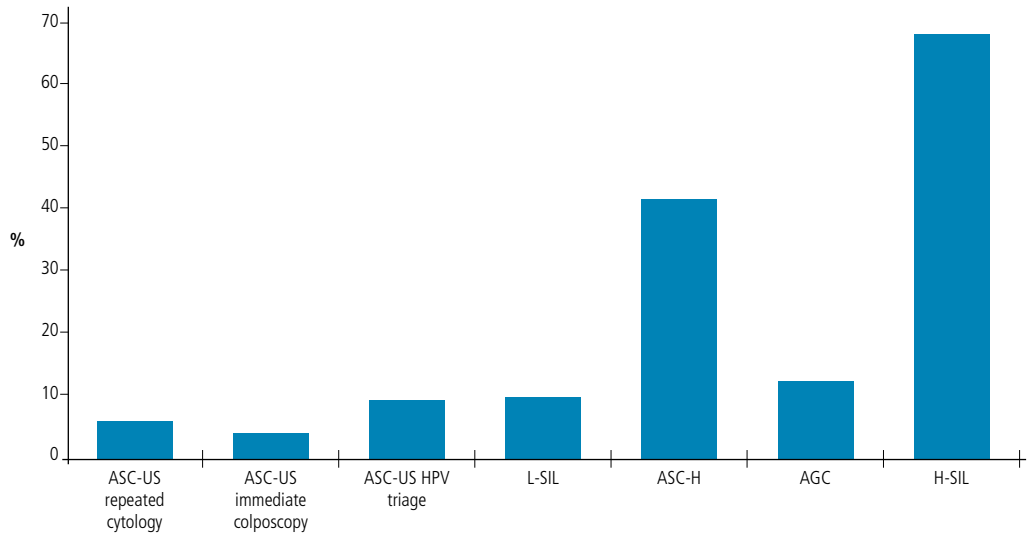


Figure 1. ASC-US+ positive predictive value for CIN2+. Survey ONS, 2009.
Figura 1. Valore predittivo positivo per CIN2+ delle ASC-US+. Survey ONS, 2009.

MANAGEMENT OF WOMEN WITH AN ABNORMAL SCREENING TEST

Atypical squamous cells of undetermined significance (ASC-US)

ASC-US is the most common cytologic abnormality and entails a low risk of CIN2+. In 2006, national guidelines and GISCi recommended three possible management strategies: immediate referral, repeat cytology at 1 year or hr-HPV triage.[5]

In 2011, a report of the English NHSCSP pilot study on hr-HPV triage of women with ASC-US and L-SIL,[6] pointed out that hr-HPV triage makes it possible to return about one third of women with ASC-US to routine screening, with a considerable reduction in colposcopies. The study also showed a good acceptability of triaging to women.

The 2012 American Cancer Society Guidelines[7] recommend to return women with ASC-US and negative hr-HPV to the normal screening interval, i.e., 3 years. For the management of ASC-US/hr-HPV positive women who have a negative second-level assessment for CIN2+, American[7] and European guidelines[8,9] provide two options: repeat an hr-HPV test after 12 months or repeat cytology after 6 and 12 months. American guidelines[7] also recommend not to repeat hr-HPV testing earlier than 12 months. Since 2005/2007, GISCi[5] has recommended hr-HPV testing as one of the three possible options for the management of ASC-US, and endorsed the use of hr-HPV tests validated for screening. Data from the 2010 GISCi survey showed that triage with hr-HPV has a PPV for CIN2+ greater than the other two options (figure 1), and reduces variability between centres.

Recommended management

If cytology is the primary test, triage by hr-HPV testing (HPV triage) is recommended (figure 2). Women with ASC-US cytology and negative hr-HPV should return to routine screening,[10] while women with ASC-US and positive hr-HPV should have colposcopy.

For women that are ASC-US/hr-HPV positive and second-level negative for CIN2+, re-testing for hr-HPV test after 1 year is strongly recommended. If the hr-HPV test is negative, return to normal screening is recommended. If it is positive, colposcopy should be repeated. In the latter case, if the new second-level analysis comes out negative for CIN2+, women are invited to repeat hr-HPV testing after 12 months. If the repeat hr-HPV test is negative, women return to routine screening. If the repeat hr-HPV test is positive, women are invited to repeat colposcopy and cytology.

Low-grade squamous intraepithelial lesions

hr-HPV triage is recommended for women with L-SIL cytology if age is ≥35 years, according to the GISCi 2005-2007 document.[5] Triage is not recommended in younger women. In the Italian programmes that have adopted this approach, the proportion of hr-HPV positive women is variable, and in many cases high.[11] This likely reflects different criteria for reporting cytology. Depending on the local situation, hr-HPV triage could be proposed for older (i.e., above the age of 45 years) women only.[1]

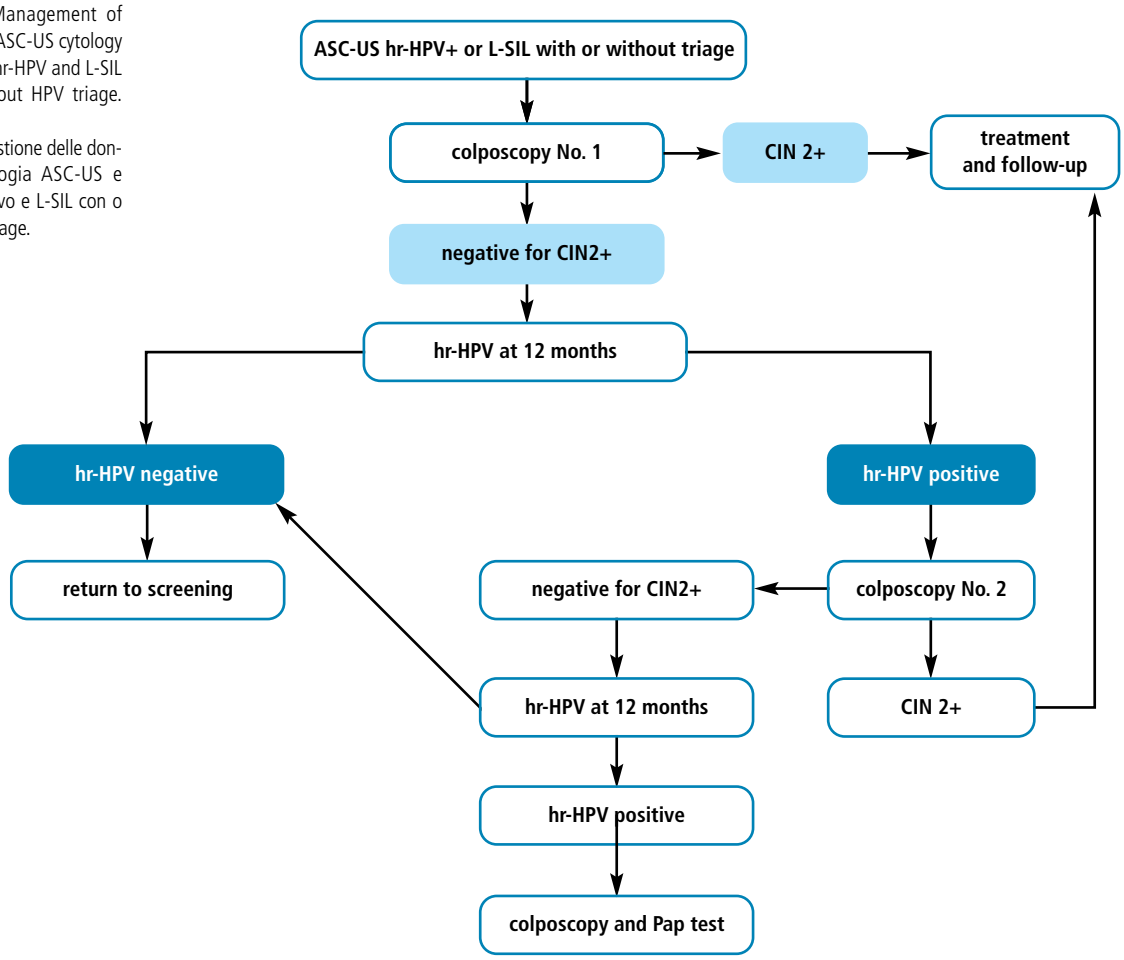
For women with L-SIL cytology and negative colposcopy, European and American guidelines[7-9] recommend repeating an hr-HPV test after 1 year. If the test is negative, the woman returns to routine screening; if it is positive the woman will be referred to colposcopy.[7] English guidelines[10] did not initially provide protocols, pending the results of a pilot study. The protocol proposed at study[6] publication (2011) recommended, in the case of negative 2nd level result for CIN, to return the woman to routine screening while, in the case of CIN 1 without treatment, repeating cytology in 12 months was recommended.

Recommended management

hr-HPV triage for L-SIL is recommended for programmes where L-SIL cytology has a low PPV (<5-10 %) and after an evaluation of the local proportion of hr-HPV-positive L-SIL

Figure 2. Management of women with ASC-US cytology and positive hr-HPV and L-SIL with or without HPV triage.

Figura 2. Gestione delle donne con citologia ASC-US e HPV-hr positivo e L-SIL con o senza HPV triage.



through a pilot study. For women ≥35 years of age and L-SIL-hr-HPV negative, return to routine screening is recommended (figure 2). For women ≥35 years and L-SIL-hr-HPV positive and for women with L-SIL cytology and no HPV result, colposcopy is recommended.

If colposcopy is negative for CIN2+, the woman is invited for an hr-HPV test after a year. If the test is negative, the woman returns to routine screening. If it is positive, the woman is referred for colposcopy. If the second colposcopy is also negative for CIN2+, the woman is invited to repeat an hr-HPV test at 12 months. In case this further hr-HPV test is positive, the woman is referred to a new colposcopy and Pap test. This follow-up protocol, which uses the hr-HPV test after an in-depth analysis of 2nd negative level for CIN2+, can be applied even where there is no initial triage with hr-HPV.

Atypical glandular cells (AGC)

AGC is an uncommon cytology[12] and is often associated with benign conditions, such as reactive cellular changes or polyps. In the literature, however, 9% to 38% of women with AGC are reported to have CIN2+, and 3% to 17% to have an invasive carcinoma.[12]

Atypia on glandular cells may affect endometrial as well as endocervical cells. European guidelines[8,9] make a distinction between «AGC, favour neoplasia or AIS» and «AGC not otherwise specified (NOS)». For women older than 35 years, in case of AGC favour neoplasia, a colposcopy with endocervical sampling is indicated. Even if this colposcopy is negative for CIN2+, a diagnostic conisation is recommended in this age group. In case of AGC NOS with negative colposcopical findings, European guidelines recommend a Pap test every 6 months for 2 years. American guidelines suggest for both categories of AGC a colposcopy with endocervical sampling. An endometrial sampling in all women over the age of 35 years or those with clinical elements suggestive for neoplastic pathology of the endometrium is also encouraged. A negative hr-HPV test can be useful in identifying women who have a greater risk of endometrial cancer rather than cervical disease.[7]

Recommended management: initial workup

For women with AGC cytology, colposcopy is recommended; at the time of colposcopy hr-HPV testing is also recommended: the hr-HPV test will assist in excluding an origin from cervical glandular lesions in case of initial negative colposcopy workup.

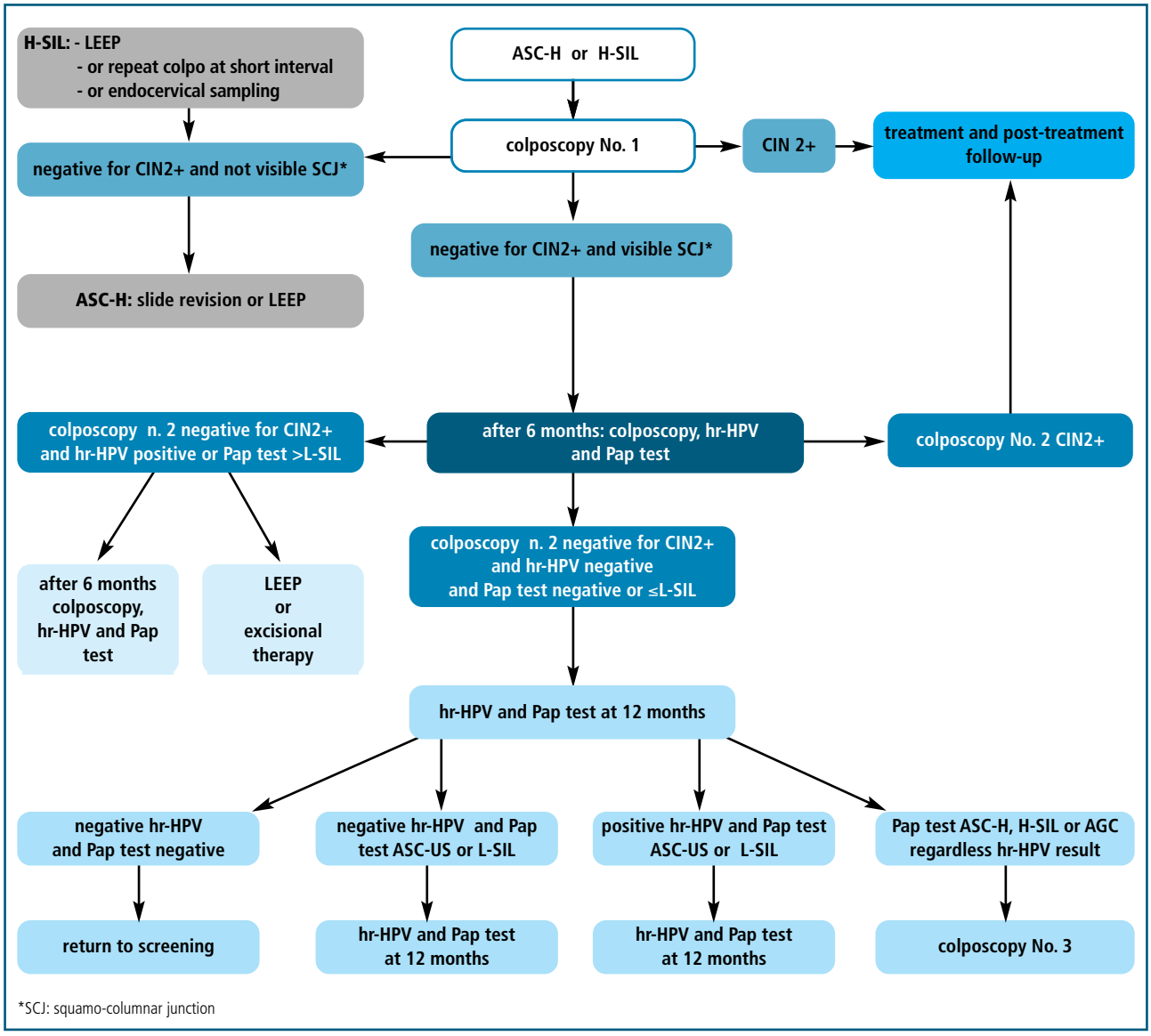


Figure 3. Management of women with cytology ASC-H and H-SIL. / **Figura 3.** Gestione delle donne con citologia ASC-H e H-SIL.

Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H) and high-grade squamous intraepithelial lesions (H-SIL)

Given their high positive predictive value (PPV), women with ASC-H and H-SIL cytology should be referred directly to colposcopy. While there is consensus for the management in case of CIN2+ (excisional therapy), there is no uniformity of indications in case of negative 2nd level workup for CIN2+. American guidelines[12] in case of H-SIL always recommend, in addition to colposcopy, an examination of the cervical canal. As for ASC-H with negative 2nd level for CIN2+, American and European guidelines[7-9] recommend a Pap test after 6 and 12 months or, alternatively, hr-HPV testing after 12 months. If both Pap tests or the hr-HPV test are negative, guidelines suggest a return to routine screening (1 or 2 years at the time of the 2006 guidelines expanded to 2/3 in 2010). In case of Pap test ≥ASC or positive hr-HPV a new colposcopy is recommended. For H-SIL with negative 2nd level for CIN2+, guidelines offer three options:

- combined cytology and colposcopy at 6 and 12 months with return to screening in case of negativity of both tests;
- excisional therapy;
- review of cytology and histology (recommended by European guidelines).

Recommended management for ASC-H and H-SIL

Women with ASC-H or H-SIL should be referred to colposcopy. If colposcopy is positive for CIN2+, excisional treatment must be provided. The management of women with ASC-H and H-SIL and negative 2nd level for CIN2+ differs according to squamo- columnar junction visibility. To exit follow-up and return to routine screening, in any case, two negative colposcopies, two negative hr-HPV tests, and a negative cytology are needed.

If, during the first colposcopy, the squamo-columnar junction is visible and no CIN2+ is identified histologically, the woman is invited after 6 months for a new colposcopy (**figure 3**, p. 88), an hr-HPV test and a Pap test, recommended especially in case of initial ASC-H cytology:

- if after 6 months the 2nd level in-depth analysis turns out to be positive for CIN2+, the woman should be referred to treatment;
- if after 6 months the 2nd level in-depth analysis remains negative, i.e., histology does not identify any CIN2+, colposcopy does not locate suspicious areas on which to perform a biopsy, and hr-HPV test and Pap test are negative or ≤L-SIL, the woman should be asked to repeat an hr-HPV test and a Pap test after 12 months. If after 12 months there is H-SIL, ASC-H or AGC cytology, the woman should be referred to colposcopy, regardless of the hr-HPV test result. If after 12 months the hr-HPV test remains negative and the Pap test is negative, the woman can return to routine screening. If after 12 months the hr-HPV test is confirmed negative but the Pap test shows ASC-US or L-SIL, hr-HPV test and Pap test repeat at 12 months are recommended. If after 12 months the hr-HPV test turns out positive and the Pap test is negative or ASC-US or L-SIL cytology, the woman is recommended to repeat an hr-HPV test and a Pap test after 12 months;
- if after six months the 2nd level in-depth analysis is negative for CIN2+ but the hr-HPV test is positive, the gynaecologist can either (**figure 3**):

a) schedule a diagnostic LEEP (loop electrosurgical excision procedure) or excisional therapy

or:

b) repeat colposcopy, hr-HPV, and PAP test at 6 months.

If, during the first colposcopy, the squamo-columnar junction is not visible and no CIN2+ is detected, different options can be considered (**figure 3**) on the basis of initial cytology. For H-SIL there are 3 options:

- repeat colposcopy after a short interval;
- perform endocervical sampling;
- perform a diagnostic LEEP.

For initial ASC-H it is suggested to perform diagnostic LEEP or to review the slide. If the review is negative, or ASC-US, or L-SIL, an hr-HPV test should be repeated after one year. If the review confirms ASC-H cytology, then endocervical sampling is carried out.

DISCUSSION AND FUTURE PERSPECTIVES

Organized screening programmes are more effective than opportunistic activity. The availability and quality of field and laboratory facilities for screening and diagnostic follow-up, as well as the available treatment facilities, are key elements of any screening programme. Monitoring the management of each patient with an abnormal screening result is of crucial importance.[13]

Pap smear testing is widely available and has shown high efficacy in reducing cervical cancer incidence. Nevertheless, every year in Italy many new cervical cancers are diagnosed (2,200 in 2012), and 5-year relative survival rates have only slightly increased, from 64% in 1990-1994 to 67% in 2000-2004.[14] Reasons for Pap-test-based screening failure include lack of Pap testing, failure of the Pap smear to detect an abnormality, and lack of adequate follow-up after an abnormal Pap test.

Compared to spontaneous activity, organized screening is characterized by protocols and guidelines for all its stages, including follow-up. Protocols to be applied within screening programmes must have an extensive consensus among all involved professionals, including those that women might meet outside the programme. It is of utmost importance to verify compliance to follow-up protocols. In 2014, GISCi conducted a specific survey to evaluate the workload induced by follow-up after a negative colposcopy. Evidence to set forth the optimal management of women with negative colposcopy after abnormal cytology or with CIN1 is poor. A recent paper[2] confirmed that hr-HPV testing is able to identify, among women with cytology ≥ASC-US and no evidence of high-grade disease, those at risk of developing CIN2+. Performing hr-HPV testing within 1 year could avoid 30% of follow-up colposcopies in women with ASC-US and 33% in selected women with the remaining cytological abnormalities (ASC-H, L-SIL, H-SIL, AGC).[15] We stress that only tests for the DNA of oncogenic HPV types, validated according to European guidelines as for sensitivity and specificity for high-grade lesions, should be applied, even when the test is used for follow-up.

Determining which hr-HPV-positive women are at future clinical risk and identifying robust markers of disease progression is the challenge for the future. Follow-up studies of women managed by HPV genotyping, p16 immunostaining, and methylation markers are needed to establish their role in the management of cervical abnormalities. New HPV DNA tests, including direct partial genotyping for types 16 and 18,[15] or $p16^{INK4a}$,[16] have also been shown to be promising triage test methods. Hence, with the introduction of new biomarkers for cervical cancer, more screening options will become available. As the number and sophistication of tools applied to cervical cancer prevention continue to increase, the complexity of management promises to grow.

Conflicts of interests: none declared

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Colorectal cancer screening

Glossary

Theoretical or potential or nominal extension: percentage of subjects involved in a screening programme out of the total female population in the 50-69 age range resident in the area covered by an organized screening programme.

Actual extension or Extension of invitations: percentage of subjects involved in a screening programme out of the total female population in the 50-69 age range who actually received an invitation to screening during the analyzed period.

Compliance with invitation or Crude attendance: number of respondents out of the total number of invited subjects minus undelivered invitations.

Adjusted attendance: number of respondents out of the total number of invited women excluding undelivered invitations and subjects with a recent test (FIT or total colonoscopy, according to the local protocols for exclusion).

Positivity rate: percentage of subjects with a positive FIT (FS) out of the total number of attendees.

Attendance to colonoscopy assessment: number of subjects attending colonoscopy out of the total number of subjects with a positive FIT (FS).

Complete colonoscopy rate: number of subjects with a complete colonoscopy (i.e., with caecal intubation), including repeat colonoscopies, out of the number of subjects who underwent a colonoscopy.

Proportion of complications after colonoscopy: number of subjects with a complication that caused admission to hospital within 30 days after colonoscopy out of the number of subjects who underwent a colonoscopy.

Detection rate: number of subjects with a screen-detected lesion out of 1,000 screened subjects. The detection rate is calculated separately for carcinoma, advanced adenoma (i.e., an adenoma with a diameter ≥1 cm, with villous/tubulo-villous type or with high-grade dysplasia) and non-advanced adenoma (an adenoma without the characteristics of advanced adenomas).

Positive predictive value (PPV) of FIT+ (FS+) at colonoscopy: number of subjects with a diagnosis of carcinoma or advanced adenoma, as a proportion of FIT+ (FS+) subjects that underwent colonoscopy.

Italian colorectal cancer screening survey group:
Gruppo italiano survey screening colorettale:

Abruzzo: Tamara Agostini, Direzione politiche della salute, Regione Abruzzo, Pescara
Basilicata: Vincenzo Barile, Angelo Sigillito, Sergio Schettini, AO San Carlo, Potenza
Calabria: Liliana Rizzo, Dipartimento Tutela della salute e politiche sanitarie, Regione Calabria, Catanzaro
Campania: Renato Pizzuti, Osservatorio epidemiologico regionale, Assessorato alla sanità, Regione Campania, Napoli
Emilia-Romagna: Carlo Naldoni, Assessorato alle politiche per la salute, Regione Emilia-Romagna, Bologna
Friuli-Venezia Giulia: Nora Coppola, Direzione centrale salute, integrazione socio sanitaria, politiche sociali e famiglia, Regione Friuli-Venezia Giulia, Trieste
Lazio: Alessandra Barca, Lazio sanità, Agenzia di sanità pubblica, Roma
Liguria: Luigina Bonelli, Gabriella Paoli, Istituto nazionale per la ricerca sul cancro, Genova
Lombardia: Direzione generale salute, Regione Lombardia, Milano
Marche: Lucia Di Furia, Servizio salute, Regione Marche, Ancona
Molise: Ospedale Cardarelli, Regione Molise, Campobasso
Piemonte: Nereo Segnan, Centro prevenzione oncologia – CPO Piemonte, Torino
Provincia Autonoma di Bolzano: Antonio Fanolla, Assessorato alla sanità, Osservatorio epidemiologico, Provincia autonoma di Bolzano, Bolzano
Provincia Autonoma di Trento: Sivano Piffer, Giovanni De Pretis, Osservatorio epidemiologico, Azienda provinciale per i servizi sanitari, Trento
Puglia: Vincenzo Pomo, Cinzia Annatea Germinario, Agenzia regionale sanità, Regione Puglia, Bari
Sardegna: Pierina Thanchis, Assessorato dell'igiene e sanità e dell'assistenza sociale, Regione Sardegna, Cagliari
Toscana: Paola Mantellini, Istituto per lo studio e la prevenzione oncologica, Regione Toscana, Firenze
Umbria: Mariadonata Giaimo, Direzione regionale salute, coesione sociale e società della conoscenza, Regione Umbria, Perugia
Valle D'Aosta: Gabriella Furfaro, Servizio dipendenze patologiche, salute mentale e promozione della salute, Aosta
Veneto: Chiara Fedato, Registro tumori del Veneto, Padova

WWW.EPIPREV.IT

[1]Registro tumori del Veneto, Padova
[2]Settore promozione e sviluppo igiene e sanità pubblica, Regione Veneto, Venezia
[3]Istituto per lo studio e la prevenzione oncologica (ISPO), Firenze
[4]Assessorato alle politiche per la salute, Regione Emilia-Romagna, Bologna
[5]Centro per la prevenzione oncologica, CPO Piemonte e Ospedale San Giovanni Battista, Torino
[6]Istituto oncologico veneto IRCCS, Padova

Corrispondenza
Manuel Zorzi
manuel.zorzi@regione.veneto.it

Screening for colorectal cancer in Italy: 2011-2012 survey

Screening del cancro colorettale in Italia: survey 2011-2012

Manuel Zorzi,[1] Filippo Da Re,[2] Paola Mantellini,[3] Carlo Naldoni,[4] Priscilla Sassoli de' Bianchi,[4] Carlo Senore,[5] Anna Turrin,[6] Carmen Beatriz Visioli,[3] Marco Zappa[3] and the Italian colorectal cancer screening survey group

Abstract

We present the main results of the 2011-2012 survey of the Italian screening programmes for colorectal cancer carried out by the National centre for screening monitoring (Osservatorio nazionale screening, ONS) on behalf of the Ministry of Health.

By the end of 2012, 112 programmes were active, of which 11 had been activated during 2012 and 4 during 2011. The national theoretical extension increased from 66% of Italians aged 50-69 years residing in areas covered by organized screening programmes in 2010 to 73.7% in 2012. The majority of programmes employ the fecal immunochemical test (FIT), while some have adopted flexible sigmoidoscopy (FS) once in a lifetime and FIT for non-responders to FS.

Overall, about 7,744,000 subjects were invited to undergo FIT, 53.1% of those to be invited within the two years. The adjusted attendance rate was 47.1% and 3,531,937 subjects were screened. Large differences in the attendance rate were observed among regions. Positivity rate of FIT programmes was 5.2% at first screening (range: 1.0-12.4%) and 4.0% at repeat screening (range: 3.4-6.4%). The average attendance rate to total colonoscopy (TC) was 81.2% and in two regions (Molise and Campania) it was lower than 70%. Completion rate for total colonoscopy (TC) was 91%. Among the 1,316,327 subjects attending screening for the first time, the detection rate (DR) per 1,000 screened subjects was 2.0 for invasive cancer and 9.1‰ for advanced adenomas (AA, adenomas with a diameter ≥1 cm, with villous/tubulo-villous type or high-grade dysplasia). As expected, the corresponding figures in the 2,215,610 subjects at repeat screening were lower (1.0‰ and 6.8‰ for invasive cancer and AA, respectively). Many programmes reported some difficulties in guaranteeing TC in the appropriate time frame to FIT+ subjects: in 15% of cases the waiting time was longer than two months.

Ten programmes in 2011 and eight in 2012 employed FS as the screening test: 24,549 subjects were screened in the two years, with an attendance rate of 24.5%. Overall, 85.9% of FSs were classified as complete. Overall, TC referral rate was 9.8% and the DR per 1,000 screened subjects was 3.0 and 48.2 for invasive cancer and AA, respectively.

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Keywords: screening, colorectal cancer, national survey, faecal immunochemical test, flexible sigmoidoscopy, Italy

Riassunto

Presentiamo i dati nazionali di attività dei programmi di screening del carcinoma colorettale relativi al biennio 2011-2012. A fine 2012 erano attivi in Italia 112 programmi, di cui undici attivati nel corso del 2012 e quattro attivati nel 2011. In particolare, sono stati attivati: un programma in Puglia e il programma della provincia autonoma di Bolzano, due nuovi programmi in Lazio, due in Abruzzo, uno in Campania, cinque in Sicilia e tre in Sardegna. L'estensione teorica nazionale del-

lo screening è passata dal 66% della popolazione eleggibile di età compresa tra i 50-69 anni nel 2010 al 72,3% a fine 2012. Complessivamente, nel 2011 e 2012 sono state invitate allo screening con la ricerca del sangue occulto fecale immunochimico (SOF) 7.744.295 persone, pari al 53,1% della popolazione target da invitare nel biennio. I soggetti che nel 2011-2012 hanno eseguito il SOF sono stati 3.531.937, con un'adesione corretta all'invito del 47,1%, con notevoli differenze tra Regioni.
La proporzione di positivi è stata del 5.2% nei soggetti al primo esame di screening (range: 1,0-12,4%) e del 4,0% agli esami successivi (range: 3,4-6,4%). L'adesione alla colonscopia delle persone con SOF+ è stata dell'81,2%, con valori inferiori al 70% in sole due Regioni (Molise e Campania). Più del 95% dei soggetti ha avuto una colonscopia completa e/o completata da un ulteriore esame di approfondimento.
Tra i 1.316.327 soggetti al primo esame di screening, il tasso di identificazione dei carcinomi è stato del 2,2 ogni 1.000 screenati e quello degli adenomi avanzati del 10,3‰. I tassi di identificazione sono maggiori nei maschi rispetto alle femmine e aumentano progressivamente con l'età in entrambi i sessi. Come atteso, tassi di identificazione più bassi (1,0‰ e 6,8‰ per carcinomi e adenomi avanzati, rispettivamente) sono stati registrati nei 2.215.610 soggetti presentatisi a episodi di screening successivi al primo. Molti programmi hanno riportato serie difficoltà a garantire in tempi brevi la colonscopia in caso di positività al SOF: circa un sesto delle persone ha dovuto attendere più di due mesi (15%).
Dieci programmi nel 2011 e otto nel 2012 hanno proposto come test di primo livello la rettosigmoidoscopia (RS) a singole coorti di età (58/60enni). Nel biennio hanno esaminato complessivamente 24.549 persone, con un'adesione corretta all'invito del 24,5%. E' stato classificato come completo l'85,9% delle RS. Sono stati inviati ad approfondimento colonscopico il 9,8% degli screenati e sono stati diagnosticati 3,0 carcinomi e 48,2 adenomi avanzati ogni 1.000 screenati.

(*Epidemiol Prev* 2015; 39(3) Suppl 1: 93-107)
Parole chiave: screening, carcinoma colorettali, survey nazionale, sangue occulto fecale, rettosigmoidoscopia, Italia

INTRODUCTION

This paper presents the data from the survey carried out by the National centre for screening monitoring (Osservatorio nazionale screening, ONS) on behalf of the Ministry of Health, regarding the activities performed by Italian screening programmes for colorectal cancer during 2011-2012. The previous surveys are available at the ONS website.[1]
Important differences prevail among colorectal cancer screening programmes in Italy. The main difference regards the type of screening test performed. While the majority of programmes employ the fecal immunochemical test (FIT), some (nearly restricted to one region, Piemonte) have adopted flexible sigmoidoscopy (FS) once in a lifetime and FIT for non-responders to FS (**figure 1**). Moreover, FIT programmes have different targets as far as age is concerned. Invitation to attend screening starts at the age of 50 years; whereas the maximum age is 69 or 70 years in most programmes, in a number of programmes it is as high as 74 or 75 years. FS programmes invite a single cohort of subjects aged 58-60.
All FIT programmes are set to invite their target population by mail every 2 years to undergo a 1-time immunochemical FIT, without any dietary restriction. Quantitative haemoglobin analysis is performed by automated instruments using the 100 ng Hb/ml threshold to determine positivity (80 ng Hb/ml in a few programmes). People with a negative FIT are notified of their results by mail and they are advised to repeat screening 2 years later. Non responders to the first invitation are mailed a reminder, usually within 6 months. Subjects with a positive screening test are contacted to undergo a total colonoscopy (TC) or, when a complete colonoscopy is not possible, a double-contrast barium enema X-ray or a colonography (virtual colonoscopy). Colonoscopies are usually performed at an endoscopic referral centre, during dedicated sessions. Patients with screen-detected neoplasms are referred to surgery or endoscopy, and then enrolled in a follow-up programme.
In 2007, the Italian group for colorectal cancer screening (Gruppo italiano screening mammografico, GISCoR) published an *Operative report of quality indicators* for the evaluation of colorectal cancer screening programmes. For each indicator the reference standards (acceptable, desirable) are provided. Table 1 (p. 96) shows the indicators and standards utilized in this paper. The operative report is available at the ONS website.[2]

DATA COMPLETENESS

Only 44% of the 215 questionnaires collected in 2011-2012 provided complete data (31% in 2011; 56% in 2012). The items with the lowest level of completeness were screen-detected lesions and surgery: time to surgical treatment, stage at diagnosis, kind of treatment (endoscopic *vs* surgical). However, some programmes (N=7) were unable to provide even baseline data.

EXTENSION AND COMPLIANCE

Programmes activated as of 31.12.2012

During 2011-2012, 15 new programmes were launched, 12 of which in the South of Italy and Islands (**figure 1**).
As of 31st December 2012, 112 programmes were active in all regions (**table 2**, p. 97). The vast majority of programmes (N=104) employ the fecal immunochemical test (FIT), while eight have adopted flexible sigmoidoscopy (FS) once in a lifetime, and FIT for non-responders to FS. In 2012, 7 programmes, mainly from the South of Italy and Islands, were suspended.
The results of FIT programmes are reported in the following sections; data of FS programmes are presented in a specific section. In order to describe the national situation, it is necessary to

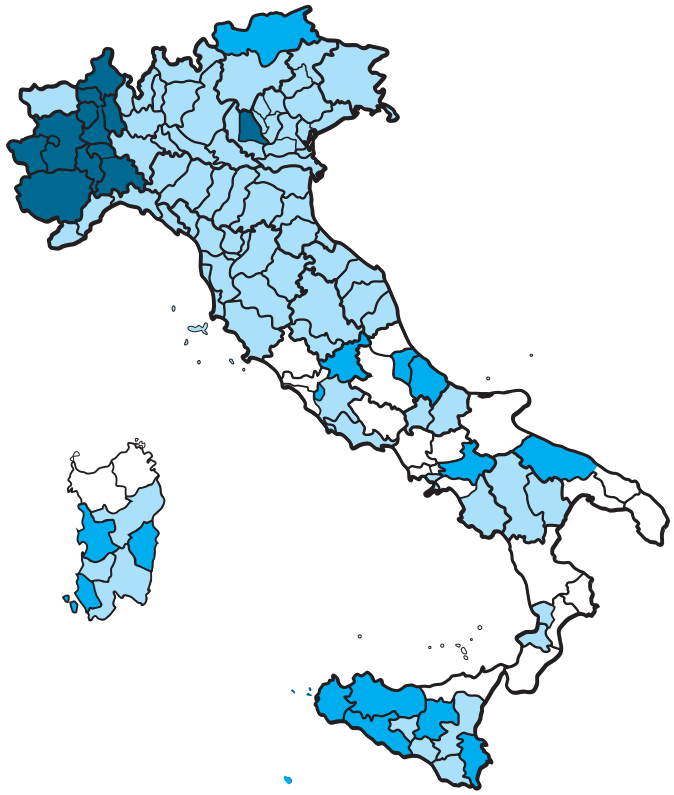

Figure 1. Colorectal cancer screening programmes: first-level test, target population, and programmes started in 2011-2012.
Figura 1. Programmi di screening colorettale: test di primo livello, popolazione target e programmi attivati nel 2011-2012.

simplify the variability of the target population among the programmes, by narrowing the analysis to a homogeneous age group. Therefore, we provide the data related only to subjects aged 50-69 years that are common to all FIT programmes and constitute the real target population of most of them.

Theoretical extension

Theoretical extension refers to eligible subjects residing in areas covered by organized screening programmes.
According to the National institute of statistics (Istat), at the beginning of 2012 approximately 14,718,125 people aged 50-69 years were living in Italy.[3] The number of subjects residing in areas where an organized screening programme was active was 10,272,496, with a national theoretical extension of 73.3% (table 2), more than eight points higher than that observed in 2011 (64.9%). Compared to the previous years, the northern and central regions were almost completely covered by screening programmes, while in the South of Italy and Islands theoretical extension increased to 45.2% (compared to 29% in 2010), notwithstanding the discontinuation of some programmes.
In particular, programmes on a regional-scale basis were activated in Emilia-Romagna, Friuli-Venezia Giulia, Liguria, Lombardia, Marche, Molise, Piemonte, Toscana, Umbria, Valle d'Aosta, Veneto, Trento, and Bolzano.

Extension of invitations

We define extension of invitations as the proportion of the resident population who was sent a screening invitation during the study period.
During 2011-2012, some 7,744,295 subjects were invited to attend a screening programme, accounting for 53.1% of the Italian resident population aged 50-69 years to be invited in the biennium (table 3, p. 98). Extension showed a clear trend across the country, with the highest value in the North (82.5%) and the lowest in the South of Italy and Islands (12.2%). While some regions confirmed the full capacity reached in the previous years, other regions reported low levels, due either to the recent activation of many programmes or to the chronic difficulty of many programmes in ensuring the necessary number of invitations.
If we restrict analysis to the areas with ongoing programmes, the extension of invitations was 77.7%, higher in the North (92.0%), intermediate in the Centre (73.7%), and lower in the South of Italy and Islands (35.2%). The most recent programmes reported a lower performance (46.4%; 10th percentile: 9.7%) than those that had been activated before 2007 (94.1%; 10th percentile: 72.5%) (table 4, p. 98).
Overall, 63.1% of programmes reached GISCoR's acceptable standard of >80% (85% of programmes that started by 2007, 42.6% of those that started by 2007-2009, and 27.3% of the others). Intra-regional variability, illustrated in table 3 through the percentiles for the regions with at least four programmes, was high in all but a few regions, where all programmes reached high levels.

Table 1. Indicators and reference standards.
Tabella 1. Indicatori e standard di riferimento.

Indicator	Standard	
	acceptable	desirable
actual extension	>80%	>90%
compliance to invitation	>45%	>65%
positivity rate	**FIT:** first test: <6%; repeat tests: <4.5% **FS:** <8%	**FIT:** first test: <5%; repeat tests: <3.5% **FS:** <6%
inadequate screening tests	**FIT:** <1% **FS:** <10%	**FS:** <5%
attendance to further assessment	**FIT:** >85% **FS:** >90%	**FIT:** >90% **FS:** >95%
complete FS rate	>85%	>90%
complete TC rate	>85%	>90%
detection rate	**FIT** carcinoma: first test: >2.0‰; repeat tests: >1.0‰ adv. adenoma: first test: >7.5‰; repeat tests: >5.0‰ **FS** carcinoma >3.0‰ adv. adenoma >35‰	**FIT** carcinoma: first test: >2.5‰; repeat tests: >1.5‰ adv. adenoma: first test: >10‰; repeat tests: >7.5‰ **FS** carcinoma >4.0‰ adv. adenoma >40‰
detection rate of adenomas at FS	males >10% females >5%	males >15% females >10%
PPV of FIT at colonoscopy for advanced adenoma or carcinoma	first test >25% repeat tests >15%	first test >30% repeat tests >20%
PPV of FS at colonoscopy for proximal advanced adenoma	>7%	>10%
delay between FIT screening and negative result	>90% within 21 calendar days	>90% within 15 calendar days
delay between the call for assessment and the assessment procedure	>90% within 30 calendar days	>95% within 30 calendar days
proportion of screen-detected cancers in stage III+	<30%	<20%

FIT: faecal immunochemical test; FS: flexible sigmoidoscopy; TC: total colonoscopy; PPV: positive predictive value.

Adapted from: Zorzi M et al. Indicatori di qualità per la valutazione dei programmi di screening dei tumori colorettali. *Epidemiol Prev* 2007;6 (Suppl 1):1-56.

Compliance with invitation

We report data on adjusted compliance, calculated as the proportion of subjects invited to attend screening (minus those with a wrong address and those excluded after invitation for a recent test) who underwent a screening test.

Overall, about 3,351,937 people were screened with FIT in 2011-2012. Adjusted compliance (47.1%) slightly decreased compared to the 48% rate observed in 2010 (table 3). Adjusted compliance was higher in the northern (52%) and central regions (40.6%), while in the South of Italy and Islands it was lower (28.6%).

The analysis of compliance by region shows a high inter-regional variability, with values ranging from 13.7% in Campania to 67.7% in Valle d'Aosta (table 3). Moreover, a high intra-regional variability in almost all regions must be highlighted.

The 10th percentile (24%) is clearly insufficient to guarantee suitable coverage of the population and, consequently, efficiency of a screening programme. Overall, 57.1% of programmes reached the acceptable GISCoR standard (>45%) (table 4).

As was the case for extension, attendance was likewise greater in programmes that started before 2007 (50.8%; 10th percentile: 40.3%) compared to those that started after 2009 (27.6%; 10th percentile: 11.8%), independently of geographical area.

This result in part depends on the higher proportion of subjects that have never been invited that characterizes recent programmes. The attendance rate of subjects invited for the first time was 34.3%, that of those who had already responded to previous invitations was 82.5%, while 17.8% of subjects who had never responded to previous invitations responded to a new invitation during 2011-2012.

DIAGNOSTIC INDICATORS

The most important diagnostic indicators (positivity rates, detection rates, positive predictive values) are strongly influenced by the underlying frequency of the disease in the screened population. Colorectal cancer and pre-cancerous lesions are more frequent in males than females, and progressively increase with age.[4] Moreover, the disease is more frequently detected in subjects at first screening test (prevalence round) than in those at repeat tests (incidence round).

Therefore, these indicators are presented separately for subjects at first and repeat screening tests, as well as by gender and five-year age group. Subjects screened in newly activated pro-

Region	Programmes[1]	Total resident subjects (N)[2]	Subjects residing in areas covered by a programme in 2012 (N)	Theoretical extension 2011 (%)[3]	Theoretical extension 2012 (%)[3]	Coverage 2011-2012 (%)[4]
Abruzzo	0 / 2	324.572	176.812	0.0	54.5	0.1
Alto Adige*	0 / 1	114.793	114.793	0.0	100	0.9
Basilicata	1 / 0	139.899	0	59.3	0.0	7.0
Calabria	2	470.890	129.729	14.7	27.5	1.8
Campania	3 / 2	1.333.753	299.315	26.8	22.4	1.6
Emilia-Romagna	11	1.083.295	1.083.295	100	100	60.4
Friuli-Venezia Giulia*	1	322.158	322.158	100	100	56.7
Lazio	6 / 7	1.366.176	783.637	55.0	57.4	5.4
Liguria	5	421.051	421.051	100	100	15.9
Lombardia	15	2.400.066	2.400.066	100	100	45.4
Marche	5	380.090	380.090	100	100	26.2
Molise*	1	78.110	78.110	100	100	29.7
Piemonte**	9	1.134.756	428.158	39.1	37.7	23.6#
Puglia	0 / 1	980.945	393.271	0.0	40.1	1.7
Sardegna	3 / 6	434.190	329.153	51.3	75.8	22.8
Sicilia	5 / 8	1.194.196	834.151	34.1	69.9	3.4
Toscana	12	944.371	944.371	100	100	45.0
Trentino*	1	129.509	129.509	100	100	57.6
Umbria*	1	222.785	222.785	100	100	48.2
Valle d'Aosta*	1	32.358	32.358	100	100	61.6
Veneto	21	1.210.162	1.132.237	93.7	93.6	59.5#
Italy	**103 / 112**	**14.718.125**	**10.635.049**	**64.9**	**72.3**	**25.1**
North	**64 / 65**	**6.848.148**	**6.063.625**	**87.0**	**88.5**	**41.8**
Centre	**24 / 25**	**2.913.422**	**2.330.883**	**78.6**	**80.0**	**23.7**
South/Islands	**15 / 22**	**4.956.555**	**2.240.541**	**25.2**	**45.2**	**4.4**

1 pairs of values refer to 2011 / 2012
2 residents 50-69 yrs old at 01.01.2012 (source: Istat)
3 proportion of eligible subjects residing in areas covered by a screening programme
4 proportion of eligible subjects that were screened in 2011-2012
* regional-based programmes
** programmes screen only subjects aged 58-69 years
\# subjects who underwent a flexible sigmoidoscopy included

Table 2. Main data of FIT programmes, 50-69 year-old subjects, by region. Years 2011-2012.
Tabella 2. Dati principali dei programmi di screening colorettale, soggetti 50-69enni, per Regione. Anni 2011-2012.

grammes all undergo first screening, while in the older programmes the proportion of subjects at repeat screening progressively increases. Moreover, while subjects at first screening test are younger (47.4% were 50-54 year old in 2012), those at repeat screening are mainly distributed in the older age classes (65-69 years old: 30%; 50-54 years old: 15.8%).
The mean values of these indicators by region are standardized by age and gender, using the national mean as standard population. The data refer to 3,531,937 subjects screened during 2011-2012 for which data are available; of these 1,316,327 (37%) underwent first screening and 2,215,610 (63%) subsequent examinations.

Positivity rates

In subjects at first screening, the proportion of positive FIT was 5.2%, with quite homogeneous values among the mean regional values of the regions with a significant number of screens (table 5, p. 99). The 10th and 90th percentile of positivity rates reported by the programmes were 3.7% and 6.6%, respectively. Outlier values were observed in programmes with a few number of screened subjects and in some of the recently-activated programmes.
In subjects at repeat screening, the proportion of FIT+ was 4.0%, with a higher homogeneity between programmes (10th-90th: 3.3%-5.1%). Seventy-six percent of programmes met the acceptable standard at the first (<6%) exam and sixty-six at repeat examination (<4.5%).
As shown in figure 2 (p. 99), the proportions of positive results were higher in males both at first and repeat examinations, and progressively increased with age, particularly at first screening test.

Inadequate tests

Inadequate tests are essentially due to an incorrect sampling by the subject.
During 2011-2012, 95% of programmes reported a proportion of inadequate FITs lower than the standard (<1%). Overall, the national mean value was 0.3%.

Region	Invited subjects (N)	Extension of invitations[1]		Screened (N)	Adjusted compliance[2]	
		%	10th - 90th percentile[3]		%	10th - 90th percentile[3]
Abruzzo	445	0.2		174	46.2	
Alto Adige	2.549	2.2		1.020	40.1	
Basilicata	26.868	19.2		9.524	36.8	
Calabria	18.384	3.8		8.293	47.2	
Campania	154.394	11.9		21.039	13.7	
Emilia-Romagna	1.084.128	116.6	89.7 - 118.9	557.021	52.1	44.4 - 61.7
Friuli-Venezia Giulia	309.016	108.3		156.208	52.3	
Lazio	321.952	22.5	6.3 - 66.8	73.757	24.0	11.7 - 41.9
Liguria	227.489	55.5	29.1 - 110.1	64.327	29.1	11.2 - 41.7
Lombardia	2.189.985	97.2	83.3 - 110.8	1.027.550	48.5	41.4 - 65.9
Marche	311.050	92.9	54.2 - 116.2	87.420	28.2	23.3 - 35.5
Molise	64.468	81.3		23.221	36.6	
Piemonte°	299.236	26.3	24.3 - 103.4	132.428	44.7	34.2 - 49.7
Puglia	64.605	4.6		16.305	36.5	
Sardegna	207.105	40.8		98.836	50.3	
Sicilia	277.331	19.2		40.312	15.6	
Toscana	842.794	90.7	68.1 - 104.7	409.649	50.1	38.6 - 59.4
Trentino	112.473	97.7		66.225	59.8	
Umbria	213.225	106.4		95.939	45.8	
Valle d'Aosta	29.632	89.8		19.869	67.7	
Veneto	987.166	91.9	78.5 - 117.2	622.820	65.5	46.1 - 76.7
Italy	**7.744.295**	**53.1**	**21.5 - 111.8**	**3.531.937**	**47.1**	**24.0 - 67.7**
North	**5.241.674**	**82.5**	**59.4 - 115.2**	**2.647.468**	**52.0**	**36.2 - 70.0**
Centre	**1.689.021**	**58.9**	**19.5 - 105.0**	**666.765**	**40.6**	**23.2 - 56.6**
South/Islands	**813.600**	**12.2**	**0.4 - 89.9**	**217.704**	**28.6**	**12.9 - 63.1**

[1] proportion of the target population that was actually invited in 2011-2012
[2] subjects attending out of those invited, excluding from the denominator those reporting a recent test and those who did not receive the invitation letter
[3] only Regions with at least four programmes
° programmes screen only subjects aged 59-69 years

Table 3. FIT programmes: extension of invitations and adjusted compliance in 2011-2012, by region.
Tabella 3. Estensione degli inviti ed adesione aggiustata dei programmi SOF nel biennio 2011-2012, per Regione.

	Start year			
	<2007	2007-2009	2010+	Total
Number of programmes				
Total	60	27	22	109
North	46	14	5	65
Centre	12	6	6	24
South/Islands	2	7	11	20
Extension of invitations (%)*	94.1	68.6	46.4	77.7
10th-90th percentile	72.5 - 112.9	15.9 - 116.1	9.7 - 99.0	24.2 - 112.9
proportion of programmes with extension >80%	85.0	42.6	27.3	63.1
Adjusted compliance (%)	50.8	44.7	27.6	47.1
10th-90th percentile	40.3 - 68.4	27.5 - 62.3	11.8 - 50.7	26.4 - 67.2
proportion of programmes with adjusted compliance >45%	79.2	37.0	20.5	57.1

* proportion of the target population of the areas with a screening programme that was actually invited in 2011-2012

Table 4. FIT programmes: extension of invitations and adjusted compliance in 2011-2012, by year of programme start.
Tabella 4. Estensione degli inviti e adesione corretta dei programmi SOF nel biennio 2011-2012, per anno di attivazione del programma.

Region	First screening episode		Repeat screening episode	
	Positivity rates (%)	10th - 90th percentile[1]	Positivity rates (%)	10th - 90th percentile[1]
Abruzzo	1.0			
Alto Adige°	7.1			
Basilicata	12.4			
Calabria	5.3		6.4	
Campania	6.1		4.7	
Emilia-Romagna	5.5	5.0 - 6.3	4.0	3.7 - 4.3
Friuli-Venezia Giulia	5.2		3.9	
Lazio	4.9	2.4 - 5.9	4.7	3.3 - 9.9
Liguria	5.3	2.6 - 18.8	4.3	
Lombardia	5.5	4.5 - 6.2	4.0	3.2 - 4.8
Marche	6.3	2.5 - 8.7	3.6	
Molise	4.6		4.2	
Piemonte°	6.6		4.6	
Puglia	4.6			
Sardegna	4.5		4.9	
Sicilia	5.5			
Toscana	5.1	4.3 - 7.5	3.9	3.7 - 4.5
Trentino	4.7		3.9	
Umbria	4.8		4.0	
Valle d'Aosta	4.3		3.4	
Veneto	5.1	3.4 - 6.4	3.9	3.1 - 4.8
Italy	5.2	3.7 - 6.6	4.0	3.3 - 5.1
North	5.3	4.0 - 6.6	4.0	3.3 - 4.8
Centre	5.4	3.3 - 6.6	3.9	3.5 - 5.7
South/Islands	5.0	3.1 - 6.2	4.6	4.3 - 10.6

[1] only Regions with at least four programmes

° not standardized (Piemonte screened only subjects aged 59-69 years, Alto Adige in 2012 screened only subjects aged 65-69 years)

Table 5. FIT programmes: positivity rates at first and repeat screening episodes in 2011-2012 standardized (by age and gender, utilising the overall screened population as standard population) by region.

Tabella 5. Programmi SOF: tassi di positività ai primi esami e agli esami successivi nel 2011-2012 standardizzati (per età e sesso utilizzando come riferimento l'intera popolazione screenata), per regione.

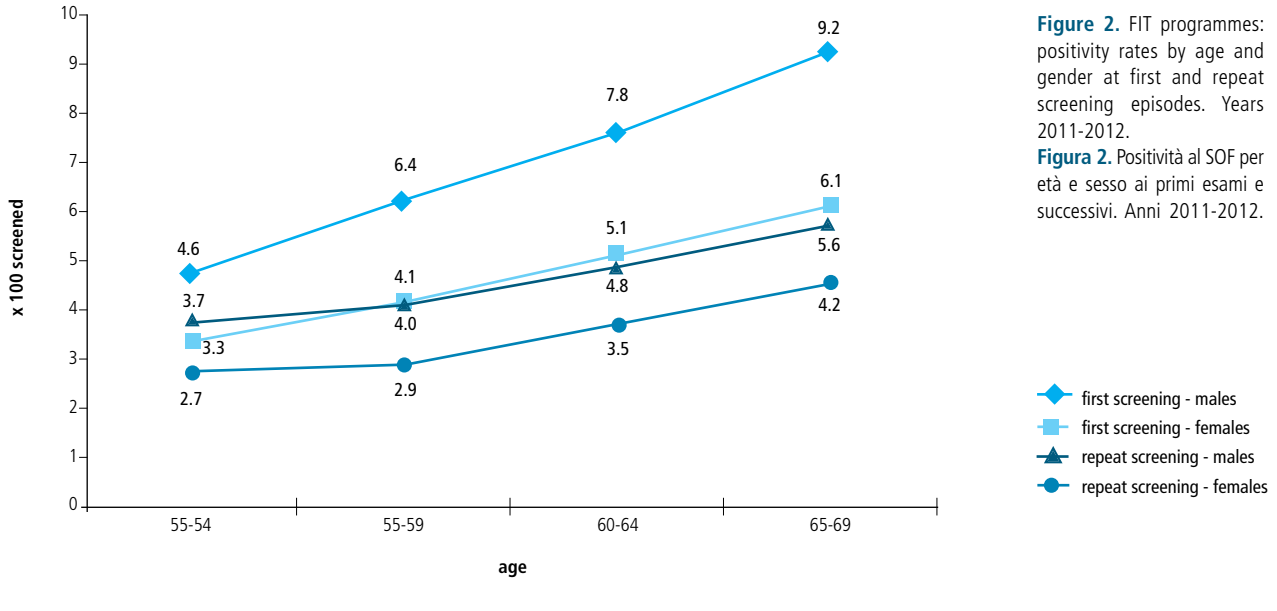

Figure 2. FIT programmes: positivity rates by age and gender at first and repeat screening episodes. Years 2011-2012.

Figura 2. Positività al SOF per età e sesso ai primi esami e successivi. Anni 2011-2012.

Region	Complete colonoscopy rate[1] (%)	Complete workup rate[2] (%)
Basilicata	80.6	81.0
Campania	96.5	96.7
Emilia-Romagna	91.5	96.5
Friuli-Venezia Giulia	93.7	97.0
Lazio	88.7	98.4
Liguria	80.2	85.4
Lombardia	91.7	95.7
Marche	92.1	95.5
Piemonte	91.1	91.1
Sardegna	96.6	99.7
Sicilia	83.2	87.5
Toscana	87.9	94.5
Trentio	97.0	98.9
Umbria	88.0	91.9
Valle d'Aosta	95.0	95.0
Veneto	93.0	97.5
Italy 2011-2012	91.5	95.5

[1] proportion of first total colonoscopies following a positive screening test that reached caecal intubation

[2] proportion of subjects who underwent a second-level workup who had a complete assessment (a complete total colonoscopy and/or other exams)

Table 6. Complete colonoscopy rate and complete workup rate in 2011-2012, by region.

Tabella 6. Tasso di colonscopie complete e tasso di approfondimenti completi, per Regione. Periodo 2011-2012.

Attendance to colonoscopy assessment

Attendance to colonoscopy assessment is essential for screening programmes to achieve colorectal cancer mortality reduction. Overall, 81.1% of FIT+ subjects attended colonoscopy in 2011-2012, a figure which is similar to those observed in 2010 (81.4%) and 2009 (82.5%). Attendance rate was higher in the North (83.0%) and progressively decreased in the Centre (79.6%) and South and Islands (67.0%).

Only 19.5% of programmes met the desired standard (>90%), while 7.8% was under the cut-off of 70%.

As already reported in the previous years, attendance was higher in males (80.6%) than in females (78.9%).

Complete colonoscopies

Besides compliance to colonoscopy, a cornerstone element in measuring the effectiveness of a screening programme is the completeness of the endoscopic examination. Overall, 91.5% of the colonoscopies carried out in 2011-2012 were classified as complete, a highly satisfactory result (table 6). Eighty-one percent of programmes met the acceptable (>85%) and 61.5% the desired standard (>90%).

Mean regional values ranged from 80.2% in Liguria to 97% in Trentino. The values of single programmes ranged from 53.8 and 100% and the lowest values were due to a small number of outliers (10th percentile: 82.6%). Programmes generally reported higher proportions of complete exams in males compared to females (overall 91.6% vs 89.3%, respectively), as reported in the literature.[5]

Since a proportion of subjects complete the second-level assessment by repeating colonoscopy or undergoing other exams, we also calculated the rate of completion of the diagnostic workup. Overall in 2011-2012, second-level assessment was completed by 95.5% of subjects with a positive first-level test.

Complications at colonoscopy

Two hundred and nine cases of bleeding were reported, 165 of which were during operative TCs, with a rate of 0.065% for non-operative and 0.29% for operative TCs; both values are in accordance with GISCoR standards (<0.5% and <2.5%, respectively). Sixty-five perforations were recorded (52 during operative TCs), with a rate of 0.02% for non-operative and 0.09% for operative TCs, in line with GISCoR standards (<0.5% and <2.5%, respectively).

Overall these results are good; however, a high variability in the collection and recording of criteria was observed. Most programmes do not provide a systematic data collection within a fixed interval of time after the examination (e.g., 30 days), possibly resulting in an underestimation of complications, including the most serious ones. On the other hand, the data about bleeding might refer to self-limiting episodes that did not require any intervention such as hospitalisation, blood transfusion, or endoscopic interventions. In that case, the indicator would be overestimated.

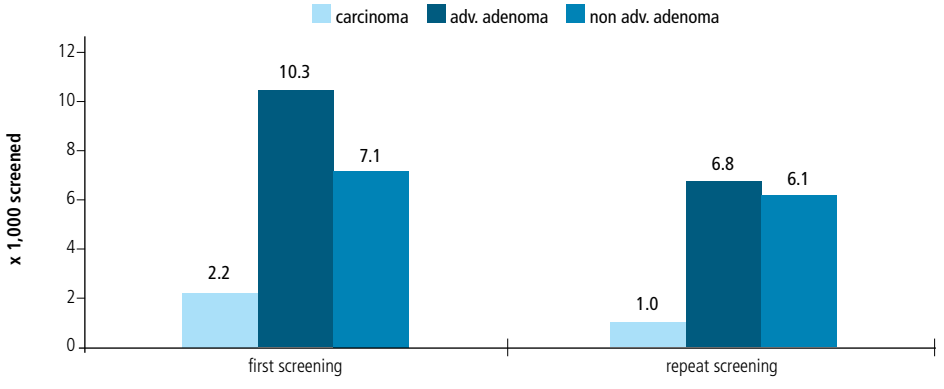

Figure 3. FIT programmes: detection rates of carcinoma, advanced adenoma, and non advanced adenoma at first and repeat screening episodes in 2011-2012.

Figura 3. Programmi SOF: tassi di identificazione di carcinoma, adenoma avanzato e adenoma iniziale ai primi esami e successivi. Anni 2011-2012.

Detection rates

We describe the detection rates (DR) of invasive carcinomas, advanced adenomas (i.e., adenomas with a diameter ≥1 cm, villous/tubulo-villous type, or high-grade dysplasia) and non-advanced adenomas (smaller in size, tubular type, and low-grade dysplasia). DRs are defined as the number of histologically-confirmed lesions detected per 1,000 screened subjects.

Overall, in subjects screened for the first time, 2,916 carcinomas, 13,578 advanced adenomas, and 9,320 non-advanced adenomas were detected. Therefore, the DR was 2.2‰ for carcinoma, 10.3‰ for advanced adenomas and 7.1‰ for non-advanced adenomas (**figure 3**). Sixty-three percent of programmes reached the acceptable standard for carcinoma (>2‰), and 75% for advanced adenoma (>7.5‰).

In subjects undergoing repeat testing, 2,306 carcinomas, 15,001 advanced adenomas, and 13,427 non-advanced adenomas were detected. As expected, the DRs were lower than the corresponding figure at first exams (**figure 3**). Sixty-nine percent of programmes reached the acceptable standard for carcinoma (>1‰), and 63% for advanced adenoma (>5‰).

The ratio between the DRs of advanced and non-advanced adenomas does not reflect the underlying prevalence of the two groups of lesions in the screened population, the frequency of non-advanced adenomas being higher than that of advanced adenomas. The DR of advanced adenomas is higher, since FIT appears to be highly selective for these lesions, which tend to bleed more easily than non-advanced adenomas, as described in the literature.[6] However, we observed a high variability among programmes in the ratio between advanced and non-advanced adenomas. This result suggests a low standardisation of the diagnostic criteria used by the different programmes to classify adenomas.

At first exams, we observed a high variability among the regional mean values of DRs of carcinoma (from 1.7‰ in Calabria to 7.8‰ in Bolzano, both non-standardized values), advanced adenomas (from 1.9‰ in Puglia to 13.7‰ in Marche and Emilia-Romagna; in Piemonte, with its 19.4‰, programmes screened only subjects aged 58-69 years) and non-advanced adenomas (from 3.3‰ in Puglia to 14.7‰ in Friuli-Venezia Giulia and Bolzano) (**figure 4**).

We did not observe any geographical North-South trend in the detection rates of carcinoma and advanced adenoma, as expected according to the underlying epidemiological figures (carcinoma: North 2.3‰, Centre 2.2‰, South-Islands 2.2‰; advanced adenoma: North 11.2‰, Centre 10.6‰, South/Islands 7.1‰; non-advanced adenoma: North 7.6‰, Centre 7.5‰, South/Islands 4.8‰). At repeat examinations, a higher homogeneity was reported among regions for the DR of carcinoma (from 0.6‰ in Marche to 2.3‰ in Calabria), but not for advanced adenoma (from 2.3‰ in Calabria to 10.3‰ in Sardegna) nor non-advanced adenoma (from 3.1‰ in Valle d'Aosta to 11.6‰ in Trentino) (**figure 5**, p. 102).

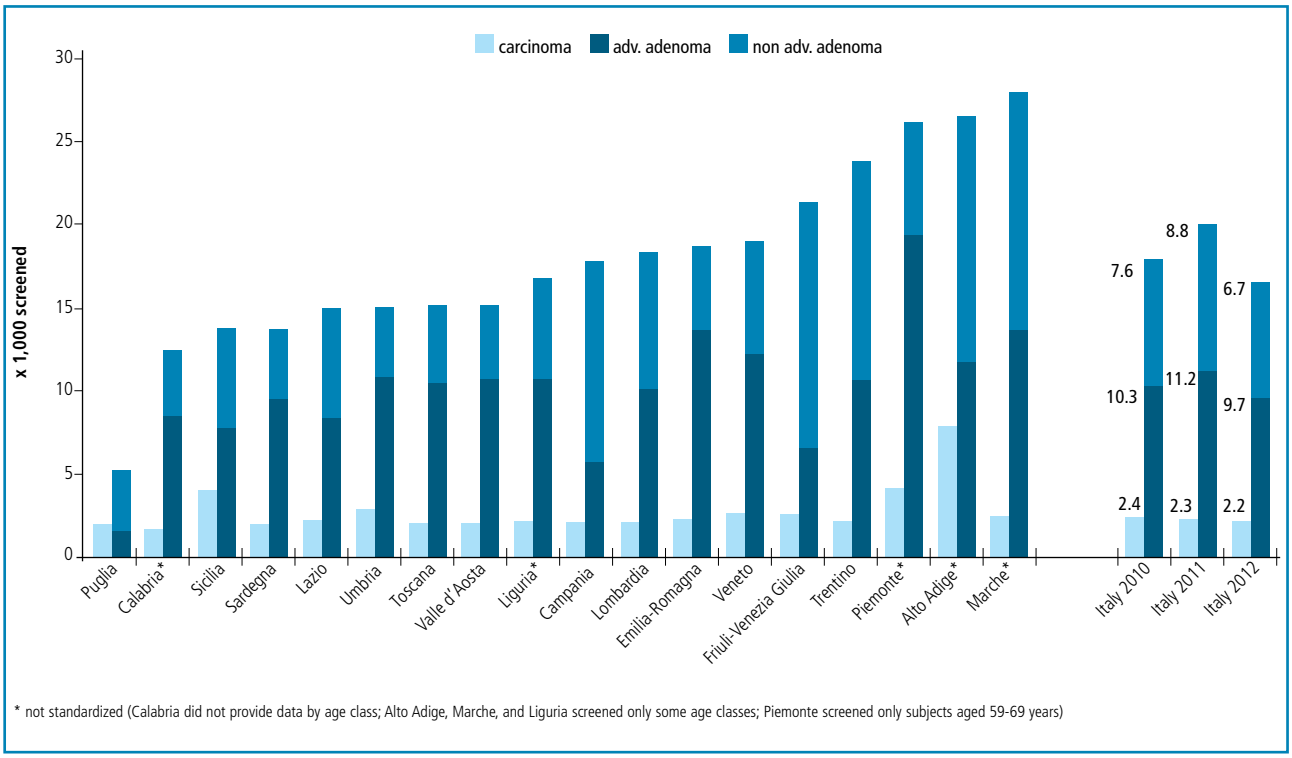

Figure 4. FIT programmes: standardized (by age and gender, utilising the overall screened population as standard population) detection rates for carcinoma, advanced adenoma and non-advanced adenoma at first screening, by region. Years 2011-2012.

Figura 4. Programmi SOF: tassi di identificazione di carcinoma, adenoma avanzato e adenoma iniziale ai primi esami, standardizzati (per età e sesso, utilizzando come riferimento l'intera popolazione screenata), per regione. Anni 2011-2012.

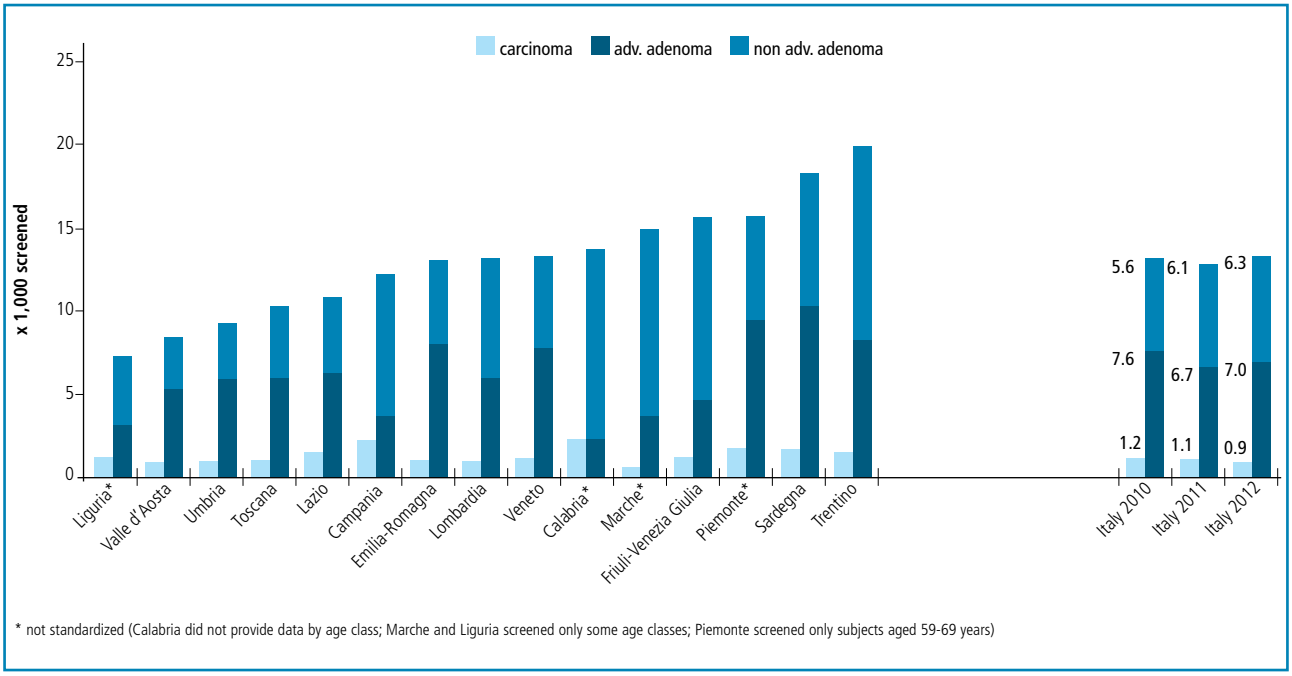

Figure 5. FIT programmes: standardized (by age and gender, utilising the overall screened population as standard population) detection rates for carcinoma, advanced adenoma and non-advanced adenoma at repeat screening episodes, by region. Years 2011-2012.

Figura 5. Programmi SOF: tassi di identificazione di carcinoma, adenoma avanzato e adenoma iniziale agli esami successivi, standardizzati (per età e sesso, utilizzando come riferimento l'intera popolazione screenata), per regione. Anni 2011-2012.

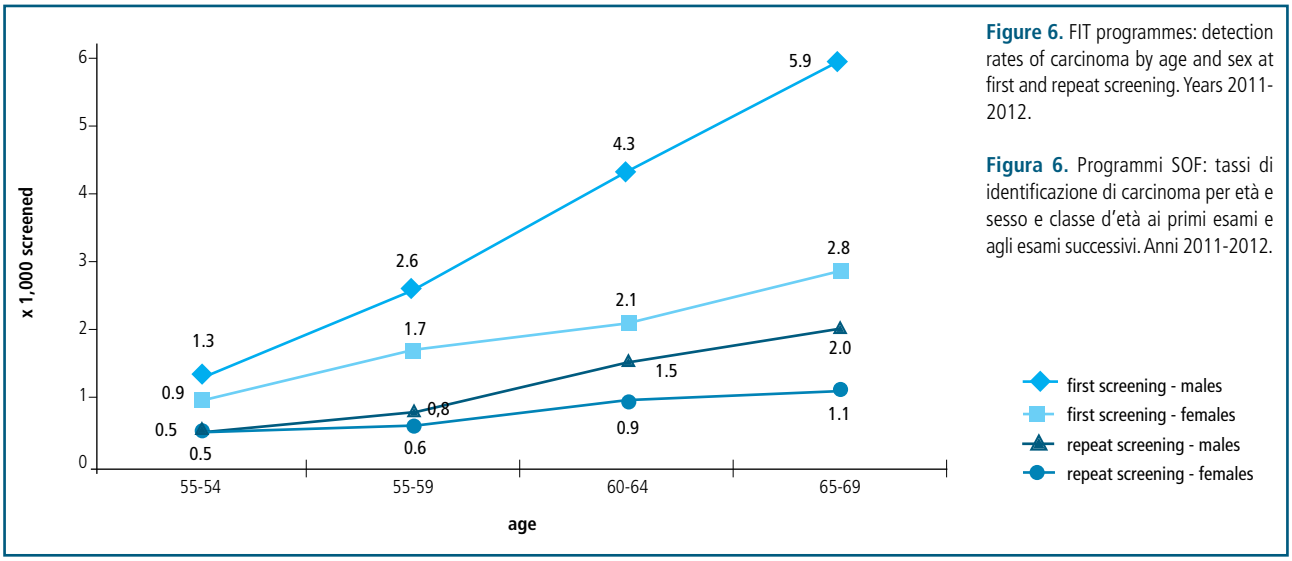

Figure 6. FIT programmes: detection rates of carcinoma by age and sex at first and repeat screening. Years 2011-2012.

Figura 6. Programmi SOF: tassi di identificazione di carcinoma per età e sesso e classe d'età ai primi esami e agli esami successivi. Anni 2011-2012.

As expected, on the basis of underlying epidemiological figures, the DRs of carcinoma were higher in males and progressively increased with age in both genders (figure 6). This trend may be observed both in subjects screened for the first time and in those at repeat screening.

The reduction in DRs between first and repeat exams was larger in males and in the older groups: this could be due to a proportionally higher impact in these subjects of the polyps' removal that takes place in the prevalence round, and it is in agreement with the data about positivity rates of FIT (figure 2).

Positive predictive value

Positive predictive value (PPV) of FIT+ at colonoscopy is defined as the number of subjects with a diagnosis of carcinoma or advanced adenoma, as a proportion of FIT+ subjects that underwent colonoscopy.

In 2011-2012, the FIT showed a noteworthy capability of selecting subjects with a high risk of invasive carcinoma or advanced adenoma, as already reported in the previous years. Among the 55,419 subjects at first screening round who underwent a colonoscopy after a FIT+, a diagnosis of carcinoma was formulated in 5.3% and advanced adenoma in a further 24.5%.

	Males	Females	Total
screened 2012 (N)	5,983	5,741	11,724
screened 2011 (N)	6,646	6,179	12,825
compliance with invitation to FS (%)	25.8	23.2	24.5
compliance with invitation to FS+FIT (%)	35.3	37.5	36.4
reason prompting colonoscopy (%)			
advanced adenoma*	7.4	3.6	5.6
other	4.6	3.8	4.2
detection rate (‰)			
carcinoma	4.4	1.5	3.0
advanced adenoma	63.9	31.1	48.2
non advanced adenoma	96.8	61.6	79.9
PPV (%) for proximal neoplasia**	12.0	9.0	11.0

* at least one advanced adenoma (with a diameter ≥10 mm, villous/tubulo-villous type, or high-grade dysplasia); 3 or more adenomas with diameter <10 mm, tubular type, and low grade dysplasia
** carcinoma or advanced adenoma

Table 7. Main results of FS programmes. Years 2011-2012.
Tabella 7. Risultati principali dei programmi RS. Anni 2011-2012.

Among the 74,810 subjects at repeat screening, the corresponding values were respectively 3.1% for carcinoma and 20.1% for advanced adenoma.
Seventy-five percent of programmes reached the acceptable standard for subjects at first screening (>25%) and 85% for those at repeat screening (>15%).
Once again, males showed constantly higher values than females (31.0% *vs* 22.6% for carcinoma and advanced adenoma altogether) and an increasing PPV trend was observed with age (from 24.2% in subjects 50-54 years old to 29.4% in those aged 65-69).

Waiting times

In order to reduce the anxiety of screened subjects, the delay between the test and mailing of a negative result or the carrying out of a further assessment for those positive must be kept as short as possible. Since FIT is a laboratory test, it can be carried out quite quickly (as compared to the reading of mammograms and Pap smears), therefore the delay between the test and the mailing of a negative result is generally short. In fact, about 94% of letters after a negative result were mailed within 15 days and a further 3% within 21 days.
On the contrary, all regions recorded serious difficulties in guaranteeing a colonoscopy to FIT+ subjects within a short period of time. Overall, colonoscopy was carried out within 30 days after FIT only in 53.3% of cases and only nine programmes met the acceptable standard (>90% within 30 days). Fifteen percent of subjects had to wait for more than two months.
Finally, surgery was performed within 30 days after diagnosis in 52% of cases, and in a further 33% within two months.

FS SCREENING PROGRAMMES

FS is proposed as a first level test by 9 programmes in Piemonte and 1 in Veneto (in 2012 two programmes were suspended). These programmes also offer FIT to subjects refusing FS screening and to those up to 69 years of age. The principal data are presented in table 7.

Overall, these programmes invited 53,668 subjects in 2011, corresponding to an 88.2% actual coverage of their target population (N= 61,973) and 47,499 subjects in 2012 (84% of 55,871 subjects in the target population).
Overall, 12,825 subjects were screened in 2011 and 11,724 in 2012. Uptake of invitation was 24.5% (range: 6.9-36.8%). In almost all programmes, uptake was higher for males in comparison to females (overall: 25.8% *vs* 23.2%), as reported in the literature. Compliance to FS screening was lower than for FIT. However, the comparison is related to different geographical areas.
The programmes offer FIT to subjects refusing FS screening. This strategy makes it possible to increase overall coverage and reduce gender differences, as reported where this strategy has been ongoing for a number of years. In fact, the proportion of subjects that underwent one of the two tests was 36.4% and was higher among females (37.5%) than males (35.3%) (table 7).
Since FS is performed on a once-in-a-lifetime basis, the proportion of complete exams should be as high as possible. On the other hand, caution must be taken to avoid perforations, bleeding, or other complications. Overall, 85.9% of FS were classified as complete, with higher levels in males (88.6%) than in females (82.5%). This result is in line with GISCoR's acceptable standard (>85%). A considerably high variability between programmes was recorded (range: 74.4-94%).
Generally, the programmes referred to colonoscopy assessment 9.8% of screened subjects (12.0% of males and 7.4% of females). Only in 57% of these cases was the reason prompting colonoscopy an advanced adenoma, which, according to the literature, is associated with an increased probability of neoplasia in the proximal colon.
The overall attendance rate of the assessment was 93.5% in 2011 and dropped to 81.9% in 2012, probably due to a loss of data. The colonoscopy completeness rate was 91.9%, with values of single programmes ranging from 86.2% to 100%.
Among the subjects referred to colonoscopy, the prevalence of

Stage	FIT programmes		FS programmes (N=62) (%)
	first screening (N=1,910) (%)	repeat screening (N=1,823) (%)	
I	41.9	42.9	37.1
I*	10.8	9.8	22.6
II	20.4	19.5	12.9
III-IV	26.8	27.9	27.4

Stage I: T1 or T2. N0. M0
Stage I*: T1. NX
Stage II: T3 or T4. N0. M0
Stage III-IV: lymph-node involvement or distant metastases

Table 8. Stage distribution of screen-detected cancers in 2011-2012. Cases with known stage (3,733 out of 5,222 carcinomas).
Tabella 8. Distribuzione per stadio alla diagnosi dei carcinomi diagnosticati allo screening nei programmi SOF e RS nel biennio 2011-2012 (%). Casi con stadio noto (3.733 su 5.222 carcinomi totali).

proximal advanced lesions (advanced adenomas plus cancers) ranged between 2.7% and 14.9%.
Overall, FS programmes detected 71 carcinomas, of which 67 in the distal tract of the colon, and 1,129 advanced adenomas, with a DR of 3.0 and 48.2‰, respectively.

Stage at diagnosis

Overall, 2,916 cancers were detected in subjects at first screening and 2,306 at repeat screening. Invasive malignant polyps represented 27.6% of cancers at first screening and 22.3% at repeat screening. FS programmes detected 71 cancers, 14 of which were invasive malignant polyps.
As already observed in the previous years, many programmes did not collect any data about stage at diagnosis, while information provided by others was incomplete. Therefore, stage is available only for 3,733 cases (71.5%) of the 5,222 carcinomas, similar to 2010 and 2009 (73.5% and 71.7% respectively). The incompleteness of this information was one of the most critical issues encountered by Italian programmes during 2010.
Table 8 shows the distribution by stage at diagnosis of cases screen-detected by FIT and FS programmes. The distribution of cases diagnosed at first *vs* repeat FIT are similar, with more than half of cases at stage I and a considerable proportion of cases treated only by endoscopic resection.
Overall, 27.3% of cases were in stage III+ at diagnosis, in accordance with the acceptable standard (<30%). As for the proportion of cases in stage III-IV, small differences were reported between cases at first and repeat screening.
Sixty percent of cases diagnosed by FS programmes were at stage I; of these, 22.6% were invasive (pT1) malignant polyps that underwent endoscopic resection alone.

Surgery

This survey collects data about the kind of therapy performed on carcinomas, invasive malignant polyps and advanced adenomas, and distinguishes between surgical intervention and endoscopic resection alone. Overall, data were provided for 81.4% of carcinomas and 91.8% of advanced adenomas.
Eighty-five percent of carcinomas underwent surgery, while in 15% of cases treatment was limited to endoscopic resection. This percentage increased to 40.8% considering only pT1 cases. As for advanced adenomas, treatment was exclusively endoscopic in 96.7% of cases.

Post-colonoscopy follow- up

The national survey collected information about recommendations given at the end of the diagnostic workup by type of diagnosis, and distribution of the colonoscopies carried out by the screening programmes, by type: second-level assessments, repetition, follow-up, etc.

■ Recommendations after a clean colon

Most subjects with a negative colonoscopy were invited to perform a FIT after 5 years (79.6%), in line with the European guidelines[7] (table 9). Thirteen percent of the cases were recommended to undergo a further colonoscopy, at different intervals, without any relevant difference between geographical areas. The European guidelines recommend to return subjects to screening even in case of a diagnosis of non-advanced adenoma. This recommendation was respected only by 10.7% cases, while the indication in the vast majority of cases was a further colonoscopy, at longer intervals in the North (53% after 5 years and 20% after 3) compared to the Centre (37% after 5 years, 34% after 3) and the South of Italy and Islands (23% and 25%, respectively).
Advanced adenomas should be recalled to colonoscopy after 1 or 3 years (depending on the number and dimension of the adenomas). This recommendation was given in 73% of cases,

Table 9. Distribution of recommendations after *clean colon*, by diagnosis at colonoscopy in 2011-2012.
Tabella 9. Distribuzione percentuale delle raccomandazioni dopo *clean colon* per diagnosi istologica nel biennio 2011-2012.

Recommendation	Negative (%)	Low-risk adenoma (%)	High-risk adenoma* (%)	Cancerized adenoma (%)
FIT after 5 years	79.6	8.1	1.4	1.9
FIT after 2 years	4.4	2.6	0.6	0.0
colonoscopy after 5 years	7.3	50.8	5.8	0.6
colonoscopy after 3 years	3.3	22.2	48.4	4.0
colonoscopy after 6 months/1 year	2.4	7.9	33.9	16.9
surgery	0.6	1.9	5.7	68.9
other	2.4	6.5	4.2	7.7

* high-risk adenoma: at least one advanced adenoma (with a diameter ≥10 mm, villous/tubulo-villous type, or high-grade dysplasia); 3 or more adenomas with diameter <10 mm, tubular type, and low-grade dysplasia

Type of colonoscopy	Total	Programmes with active follow-up (%)	
		start date 2000-2006	start date 2007-2010
second level assessment after a positive first-level exam	74.5	66.7	74.3
repetition, etc	4.8	5.0	5.6
follow-up (after *clean colon*)	20.3	27.9	19.3
other	0.4	0.4	0.8

Table 10. Distribution of colonoscopies performed in 2011-2012, by type (%).
Tabella 10. Distribuzione percentuale delle colonscopie per motivo di esecuzione nel biennio 2011-2012.

while in 9.6% of cases colonoscopy was anticipated after 6 months and 2% of cases were recalled to FIT.

Sixty-nine percent of the cases of invasive malignant polyps were sent to surgery, a further 8.3% to repeat colonoscopy after 6 months.

■ Distribution by reason prompting colonoscopy

Seventy-four percent of the colonoscopies performed in 2011-2012 were second-level assessments in subjects with a positive screening test (table 10), 20.3% were post-colonoscopy follow-up and 4.8% completion or repetitions of a previous colonoscopy.

The proportion of follow-up colonoscopies was very low (1.6%) in the programmes without an active invitation to follow-up, while it rose to 26.5% in those with an active follow-up. Among the latter, the proportion of follow-up colonoscopies was highest in programmes older than 6 years (27.9%).

DISCUSSION

During 2011 and 2012, colorectal cancer screening programmes continued to spread gradually, and by the end of the period they covered 74% of the national target population.

About 7.7 million subjects were invited to screening, half of whom underwent a screening test; 5,222 carcinomas and 28,579 advanced adenomas were diagnosed, making the Italian experience one of the most advanced in the world.

Fifteen new programmes were started, 12 of which were in the South of Italy and Islands, which maintained a delay in comparison with the North and Centre, in part because a number of programmes was suspended.

Overall, 78% of the annual target population residing in areas with a programme were invited.

The extension of invitations of the programmes that had been activated before 2007 was optimal, while the more recent programmes showed much lower performances (on average, 46%). It seems that the new programmes are meeting more problems in reaching adequate numbers of invitations. We recommend a careful monitoring of this indicator to all programmes.

Compliance with invitation is in line with the previous years. However, the very low values that affect many programmes, particularly when associated with a limited extension of invitations, are of particular concern, as in some cases the combined effect of these two elements makes the proportion of the target population that has been effectively screened marginal. Intra-regional attendance showed high levels of variability, which suggests the possibility of increasing the performance of many programmes.

Overall, 82% of the subjects that had attended a screening episode responded to the subsequent invitation. No differences according to age or gender were observed, suggesting that the experience of the previous screening episode becomes the main driver for subsequent attendance, as already described in the literature.[8] Thus, the effect of other factors, which influence response to the first invitation, decreases. It is therefore important for programmes to identify the limitations that may have determined a lack of satisfaction in the screened population, especially if the attendance rate is low, because attendance in subsequent rounds is necessary to obtain the expected protection.

Attendance among subjects that had already been invited but never attended was 18%. This reflects the possibility to enrol subjects at higher risk (because they have never been screened) and the importance of continuing to regularly invite this group of people that might seem reluctant to participate in screening.

These data suggest that the screened population changes over the years. This means that:

■ the test coverage of the target population is higher than the number of screened subjects;

■ for subjects who do not regularly undergo screening, the protective effect of screening will be lower than expected.

This aspect should be taken into consideration when comparing the impact of FIT *vs* FS programmes, because the latter provides a protection that lasts for at least 12 years to all screenees. On the other hand, the protection afforded by FIT will be extended to a greater number of subjects than those annually recorded in the survey.

The available data are not enough to estimate the length of the protection of FIT and hence the interval between two tests that still confers a consistent risk reduction.

The evaluation of diagnostic indicators is difficult because many programmes produced incomplete data and this may be misleading when interpreting the results on a regional basis: some indicators depend on many factors (e.g., DRs are influenced by the distribution of the screenee by age and sex, by FIT positivity, and by compliance to colonoscopy) and they should be interpreted according to their intra-regional composition. For each indicator we had to select the programmes that sent complete data, with a possible selection bias. Unfortunately, the less complete questionnaires came from the regions with the lower number of programmes, leading to an even greater bias.

FIT showed to be an excellent first-level test for colorectal screening in terms of homogeneity of positivity rates both at first and subsequent episodes, with high PPVs and short delay between the test and the mailing of a negative result. Other evidence is still sparse, such as evaluation of the sensitivity of FIT-based programmes through interval cancers. GISCoR produced an *Operative report* on the collection of interval cancers and the estimate of sensitivity, for the purpose of making

the monitoring of this fundamental aspect of screening programmes easier and more homogenous.

Particular attention should be given to attendance to colonoscopy (81.1%). This is a critical point of FIT programmes which has been observed in the last 5 years without any sign of improvement. The actual proportion of FIT+ subjects that did not undergo any further assessment was probably lower, since many programmes did not collect data about assessments performed in non-screening settings. According to a multicentric Italian study, about 3% of FIT+ subjects underwent TC outside the screening programme.[9]

However, it must be stressed that the duty of screening programmes is not only that of reaching high levels of attendance to colonoscopy, but also making sure that FIT+ subjects have undergone assessment, even if outside the programme. The data reported suggest that many programmes did not concern themselves with this aspect.

A further issue that needs to be analyzed locally is the relationship between attendance to colonoscopy and the use of sedation and waiting time for assessment. During 2011-2012, we observed a generalized difficulty for endoscopic services in dealing with the workload deriving from screening positives, as the burden of colonoscopies for the follow-up of adenomas progressively increases.

Italian data are similar to those reported in the literature.[10-12] Some Italian experiences, which recorded attendance rates higher than 90%, underlined the relationship between a high compliance to colonoscopy and the diagnostic yield of screening programmes.[13,14] A multicentric study recently showed that different modalities of invitation may be used to increase compliance with colonoscopy.[9]

The analysis of PPV of FIT+ at colonoscopy confirms the high values reported in the previous years. According to these findings, it is essential that screening programmes adopt strategies in order to maximise colonoscopy attendance, or to ensure that subjects with a positive FIT undergo further diagnostic assessment in non-screening structures.

Compared to the last years, the overall DRs of carcinoma and advanced adenoma were stable, even though many programmes showed a lower DRs at first screening. This is not worrisome, since for programmes at subsequent rounds, a high proportion of the population that undergoes the screening test for the first time is represented by fifty-year-old subjects, which are at lower risk of disease.

Since DRs are calculated dividing the diagnosed lesions by the screened population, they are inversely associated with loss of attendance to colonoscopy. In fact, when adjusting the DRs by attendance to colonoscopy, we observed a levelling off of the differences between regional means (data not shown).

The fluctuations of DRs between programmes and regions suggest, beyond different underlying prevalence rates, the presence of other factors responsible for this aspect influencing the diagnostic sensitivity of the screening programme, such as the quality of endoscopy and the different criteria locally used to classify adenomas as advanced or non-advanced. The high variability among programmes of the ratio between advanced and non-advanced adenomas seems to confirm the importance of the latter factor.

Adenoma detection rate is one of the most important indicators to monitor the quality of colonoscopy.[7] The data obtained from programmes show a good quality of colonoscopies in terms of completeness (91% of caecal intubation rates) and complication rates, both for surgical and non-surgical TCs.

The National centre for screening monitoring, together with GISCoR and with the major Italian scientific societies of endoscopy, carried out an assessment, the Equipe study, in order to evaluate the performance of colonoscopies at the level of individual endoscopists and endoscopy services. The results of the study are in line with those produced by the national survey. In particular, the analysis of 75,569 total colonoscopies carried out in 44 screening programmes showed that policies addressing organizational issues, such as sedation and the availability of screening sessions, may improve adenoma detection rate and overall quality of colonoscopy.[15]

As for treatment, we collected information about the use of surgical intervention versus endoscopic resection alone. Overall, 15% of carcinomas underwent endoscopic resection alone, resulting in improved patient quality of life and cost reduction. This percentage increased only to 41% in pT1 cases, which mostly involve invasive malignant polyps. A possible overtreatment of these subjects should be accounted for. Overall, 97% of advanced adenomas were treated through endoscopic resection alone.

An important step that requires evaluation is post-colonoscopy follow-up, which represents a relevant share of the total endoscopic workload of programmes that actively invite subjects to follow-up. Application of the European guidelines protocols would reduce the burden of these exams substantially, because the observed recommendations mainly result in an over-prescription of endoscopic follow-up. We encourage screening programmes to locally evaluate the indicators that are reported in this survey, in order to verify compliance with the European guidelines, both of endoscopists and endoscopy services, especially if the waiting time for colonoscopy is particularly long.

This survey could not evaluate the outcomes of follow-up: this would require an individual collection of information about the timing and diagnosis of the index colonoscopy. We recommend that programmes and regions that have adequate historical databases carry out these analyses, which are expected to confirm the evidence underlying the recommendations of the European guidelines and would be useful to support the spread of their application.

Finally, the results of this survey may be used by new programmes to estimate the burden of colonoscopic workload they may expect as time goes by.

Conflicts of interests: none declared

Data for the 2011-2012 survey was provided by:
Hanno fornito i dati per la survey 2011-2012:

Valle D'Aosta: S. Crotta
Piemonte: C. Senore (Torino), S. Polizzi (Moncalieri), M. Sartori (Rivoli-Collegno), M.P. Alibrandi (Ivrea), F. Germinetti (Biella-Vercelli), P. Bestagini (Novara), L. Orione (Cuneo), T. Miroglio (Asti), G. Faragli (Alessandria)
Lombardia: D. Cereda, L. Coppola, L. Zerbi, M. Gramegna (Regione); L. Tessandri, P. Imbrogno, G. Rocca, B. Pesenti (ASL Bergamo); M. Schivardi, M. Crisetig, E. Grassi, F. Speziani (ASL Brescia); G. Gola (ASL Como); S. Gotti, M. Dal Soldà, L. Boldori (ASL Cremona); G. Moretti, A. Ilardo (ASL Lecco); A. Belloni, E. Rossetti, G. Marazza (ASL Lodi); E. Anghinoni, (ASL Mantova); A. Silvestri, E. Tidone, B. Frammartino, N. Leonardo, S. Deandrea (ASL Milano); P. Ceresa, G. Beghi (ASL Milano 1); R. Lucchini, L. Acerbi (ASL Milano 2); F. Lo Buono, L. Cavalieri d'Oro (ASL MB); G. Magenes, L. Camana (ASL Pavia); A.M. Cioccarelli, A.C. Fanetti, L. Cecconami (ASL Sondrio); R. Bardelli, M. Violini, F. Sambo (ASL Varese); S. Domenighini, G. Pieracci (ASL Valle Camonica Sebino)
Trentino: R. Pertile, S.Piffer
Veneto: C. Fedato
Friuli-Venezia Giulia: A. Franzo, J. Fabro, M. Gobbato, L. Zanier
Liguria: L. Bonelli (IRCCS AOU San Martino-IST); M. Orlando, D. Vaccari (ASL 1 Imperiese); A. Franxo, M. Scotto (ASL 2 Savonese); I. Valle (ASL 3 Genovese); M. Ferrari Bravo, C. Sticchi (ASL 4 Chiavarese); F. Maddalo, F. Pensa (ASL 5 Spezzino)
Emilia-Romagna: C. Naldoni, P. Sassoli de' Bianchi, P. Landi (Regione Emilia-Romagna); E. Borciani, F. Fornari, G. Gatti (Piacenza); C. Zurlini, M. Zatelli (Parma); F. Maradini (AOSP Parma); L. Paterlini, C. Campari (Reggio Emilia); R. Sassatelli (AOSP Reggio Emilia); R. Corradini, C. Goldoni (Modena); A. Pasquini, M. Manfredi, P. Baldazzi (Bologna); R. Nannini, L. Caprara (Imola); M.C. Carpanelli, G. Zoli, (Ferrara); V. Matarese (AOSP Ferrara); O. Triossi, M. Serafini, B. Vitali (Ravenna); F. Falcini, A. Colamartini, O. Giuliani, R. Vattiato (Forlì); M. Palazzi, C. Imolesi, P. Pazzi (Cesena); D. Canuti, C. Casale, M. Giovanardi, G. Monticelli (Rimini)
Toscana: C. Nicolai, P. Vivani (Massa e Carrara); D. Giorgi, G. Finucci (Lucca); M. Rapanà (Pistoia); C. Epifani, L. Abdelghani (Prato); G. Allegrini (Pisa); C. Maffei (Livorno); R. Turillazzi (Siena); F. Mirri, P. Ceccatelli (Arezzo); R. Rosati, P. Piacentini (Grosseto); C.B. Visioli, P. Falini (Firenze); P. Amico (Empoli); C. Ciabattoni (Viareggio)
Umbria: M. Giaimo, S. Prandini (Regione Umbria); G. Vinti (Città di Castello); A. Di Marco (Foligno); M. Malaspina (Perugia); R. Corvetti (Terni)
Marche: L. Di Furia
Lazio: A. Barca, D. Baiocchi, F. Quadrino
Abruzzo: M. Di Giacomo (Regione Abruzzo); F.M. Lattanzio (ASL Lanciano-Vasto-Chieti); M. Minna (ASL Pescara)
Molise: A. Di Credico
Campania: R. Pizzuti
Basilicata: A. Sigillito
Calabria: M.P. Montesi (Lamezia Terme); T. Landro (Vibo Valentia); A. Giorno (Cosenza)
Sicilia: M. Santino (Caltanissetta); G. Magrì (Catania); G. Ferrara (Ragusa)
Sardegna: R. Masala

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Characteristics of the colorectal cancers diagnosed in the early 2000s in Italy.

Figures from the IMPATTO study on colorectal cancer screening

Caratteristiche dei tumori del colon retto diagnosticati in Italia nei primi anni Duemila.

Dati dello studio IMPATTO sdelo screening colorettale

Manuel Zorzi,[1] Lucia Mangone,[2,3] Emanuela Anghinoni,[4,5] Susanna Baracco,[1] Elisabetta Borciani,[6] Adele Caldarella,[7] Fabio Falcini,[8] Anna Clara Fanetti,[9] Stefano Ferretti,[10] Paolo Giorgi Rossi,[11,12] Maria Michiara,[13] Giorgia Randi,[14] Fabrizio Stracci,[15] Massimo Vicentini,[11] Antonella Zucchetto,[16] Marco Zappa[7,17] and IMPATTO COLONRETTO working group

[1]Registro tumori del Veneto, Padova

[2]Registro tumori di Reggio Emilia, Reggio Emilia

[3]Associazione italiana registri tumori (AIRTUM)

[4]Servizio medicina preventiva nelle comunità, ASL di Mantova

[5]Gruppo italiano screening colorettale (GISCoR)

[6]UO Epidemiologia e comunicazione del rischio AUSL Piacenza

[7]Istituto per lo studio e la prevenzione oncologica (ISPO), Firenze

[8]Registro tumori dell'Emilia-Romagna, Meldola, Forlì

[9]Osservatorio epidemiologico, Registro tumori della provincia di Sondrio, Sondrio

[10]Registro tumori di Ferrara, Ferrara

[11]Servizio interaziendale di epidemiologia, AUSL Reggio Emilia

[12]IRCCS-Arcispedale S. Maria Nuova, Reggio Emilia

[13]Registro tumori di Parma, Parma

[14]Registro tumori di Milano, Milano

[15]Registro tumori umbro di popolazione, Scuola di specializzazione in igiene e medicina preventiva Università di Perugia, Perugia

[16]Istituto nazionale tumori, CRO, Aviano (Pn)

[17]Osservatorio nazionale screening (ONS)

Corrispondenza
Manuel Zorzi
manuel.zorzi@regione.veneto.it

Abstract

The impact of organized screening programmes on colorectal cancer (CRC) can be observed at a population level only several years after the implementation of screening. We compared CRC characteristics by diagnostic modality (screen-detected, non-screen-detected) as an early outcome to monitor screening programme effectiveness.

Data on CRCs diagnosed in Italy from 2000 to 2008 were collected by several cancer registries. Linkage with screening datasets made it possible to divide the cases by geographic area, implementation of screening, and modality of diagnosis (screen-detected, non-screen-detected). We compared the main characteristics of the different subgroups of CRCs through multivariate logistic regression models.

The study included 23,668 CRCs diagnosed in subjects aged 50-69 years, of which 11.9% were screen-detected (N=2,806), all from the North-Centre of Italy. Among screen-detected CRCs, we observed a higher proportion of males, of cases in the distal colon, and a higher mean age of the patients. Compared with pre-screening cases, screen-detected CRCs showed a better distribution by stage at diagnosis (OR for stage III or IV: 0.40, 95%CI: 0.36-0.44) and grading (OR for poorly differentiated CRCs was 0.86, 95%CI: 0.75-1.00).

Screen-detected CRCs have more favourable prognostic characteristics than non-screen-detected cases. A renewed effort to implement screening programmes throughout the entire country is recommended.

(*Epidemiol Prev* 2015; 39(3) Suppl 1: 108-114)

Keywords: colorectal cancer screening, colorectal cancer, Italy

Riassunto

L'impatto dei programmi di screening del tumore del colon retto (CRC) può essere osservato a livello di popolazione solo alcuni anni dopo l'attivazione degli stessi. Abbiamo confrontato le caratteristiche dei CRC, suddivisi per modalità diagnostica (screen-detected, non-screen-detected), come indicatore precoce di efficacia dei programmi di screening.

Sono stati raccolti da diversi Registri tumori i dati sui CRC diagnosticati in Italia dal 2000 al 2008. Tramite linkage con gli archivi di screening è stata raccolta la modalità diagnostica dei casi, oltre al-

l'area geografica e alla presenza di un programma di screening organizzato. Abbiamo confrontato le principali caratteristiche dei diversi sottogruppi di CRC tramite modelli di regressione logistica multivariata.
Lo studio riguarda 23.668 CRC diagnosticati in soggetti di età 50-69 anni, l'11,9% dei quali screen-detected (N=2.806), tutti di aree del Nord o Centro Italia. Tra i casi screen-detected abbiamo osservato una maggiore proporzione di maschi, di casi a carico del colon distale e un'età media più alta. Rispetto ai casi diagnosticati prima dell'attivazione degli screening, i casi screen-detected avevano una migliore distribuzione per stadio alla diagnosi (odds ratio per stadio III o IV: 0,40; IC95%: 0,36-0,44) e grading (OR per grading scarsamente differenziato: 0,88; IC95%: 0,75-1,00).
I casi screen-detected avevano caratteristiche prognostiche migliori anche rispetto ai casi non-screen-detected. Si raccomanda uno sforzo rinnovato per attivare programmi di screening colorettale in tutto il territorio nazionale.

(*Epidemiol Prev* 2015; 39(3) Suppl 1: 108-114)
Keywords: screening colorettale, tumore del colon retto, Italia

INTRODUCTION

Colorectal cancer (CRC) survival is strictly related to the stage at diagnosis, with a better prognosis for stage I compared to stage III and IV.[1] CRC screening with a biennial faecal occult blood test (FOBT) has been shown to reduce mortality through the early detection and treatment of cancer in large population-based trials.[2] Routine, organized screening programmes (SPs) based on the faecal immunochemical test (FIT) have been shown to achieve even better outcomes on mortality.[3] Furthermore, there is some evidence that screening can also reduce invasive colorectal cancer through the identification and treatment of adenomas, preventing their transformation into cancer.[4-6]
The effects of screening can be observed at a population level only several years after the implementation of screening and only if SP participation is high. The stage at diagnosis of screen-detected cancers is an interesting early outcome to monitor screening programme effectiveness and predict the impact on mortality, since a necessary condition to achieving a reduction in mortality in the short term is to detect cancer at an earlier stage than clinically detected cancers.
With few exceptions, CRC SPs are aimed at Italian residents aged 50 to 69 or 74 years who receive a mailed invitation to undergo a single FIT every two years. Subjects with positive screening tests are contacted to undergo a total colonoscopy at an endoscopic referral centre. In only one region (Piemonte) has a different programme been established, with either a flexible sigmoidoscopy at the age of 58 or a FIT invitation every 2 years in the 59-69 years age range. The implementation of CRC SPs started gradually in 2005-2006, and has been more rapid in northern and central Italy than in the South. In 2008, theoretical extension, (i.e., the proportion of the resident population aged 50-69 years living in areas covered by an SP), was 73.7% in the North, 56.3% in the Centre, and 21.4% in the South and on the Islands (Sicilia and Sardegna).[7]
In order to describe the impact of implementing the CRC SPs in Italy, the Italian Ministry of Health financed the IMPATTO study, a research project that collected and linked information from both SP archives and cancer registries.
In this paper, we used the IMPATTO study's archives to compare the characteristics of CRCs diagnosed in Italy from 2000 to 2008 by diagnostic modality (screen-detected, non-screen-detected).

MATERIALS AND METHODS

Data

The data collected in the IMPATTO study database have been described in the associated paper of this article.[8] Briefly, for the purpose of this paper, CRCs diagnosed in patients aged 50-69 years were selected and characterized according to the following patterns of diagnosis:

- CRCs diagnosed in areas where an SP has been implemented:
  - pre-screening (i.e., diagnosed before the onset of the SP);
  - screen-detected;
  - not screen-detected, diagnosed after the onset of the SP;
- CRCs diagnosed in areas where no SP has been implemented.

Analysis

The Chi square test was used to compare the distribution of the main CRC characteristics included in the study by pattern of diagnosis: anatomic sub-site, stage at diagnosis, grading, number of lymph nodes examined and positive lymph nodes. The association between pattern of diagnosis and CRC characteristics was evaluated using logistic regression models which included the variables that resulted significantly associated at univariate analysis. In particular, we explored which factors were associated with stage and grading, including the pattern of diagnosis among the explanatory variables.

RESULTS

Overall, the study included 23,668 invasive cases of CRCs diagnosed in subjects aged 50-69 years between 2000 and 2008. The cancer registries took part in the study with cases from different periods. Moreover, the SPs were introduced in different years. In particular, the SPs were implemented in most areas during 2005-2006, as opposed to Veneto (2002) and Firenze-Prato, where SPs were already in place at the beginning of this study. Finally, there were no SPs in the South and on the Islands during the study period.
Table 2 (p. 110) shows the main characteristics by macro-area and period: the North-Centre in 2000-2005 (before the SPs became widespread), the North-Centre with SPs (2006-2008), and the South and the Islands. The cases from the latter macro-area represented about one-sixth of the overall study (15.8%). As expected, the largest proportion of cases was males (59%) from the older age group.

Macro-area	Cancer registry	Number of cases									
		2000	2001	2002	2003	2004	2005	2006	2007	2008	Total
Northwest	Genova				312	294	283				889
	Milano	449	456	415	427	399	**367**	**452**			2,965
	Sondrio	47	41	54	50	48	**54**	**73**	**77**	**67**	511
	Biella		64	54	64	57	**67**	**54**	**63**		423
Northeast	Trentino			120	129	117	138	140			644
	Veneto	138	155	**166**	**188**	**179**	**162**				988
	Friuli-Venezia Giulia						418	395	369		1,182
	Emilia-Romagna	137	240	629	954	**1,334**	**1,519**	**1,994**	**1,565**	**385**	8,757
Centre	Firenze-Prato	**341**	**343**	**319**	**322**	**323**	**319**				1,967
	Umbria					287	296	**266**	**383**	**372**	1,604
South-Islands	Latina					126	129	108	132		495
	Napoli				88	90	111	116	123		528
	Siracusa		78	80	89	88	82				417
	Palermo				268	261	258				787
	Catania-Messina				318	366	368				1,052
	Sassari				114	117	117	111			459

Figures in color represent the years when a screening programme was active

Table 1. Number of colorectal cancer cases by cancer registry and calendar year. Ages 50-69 years.
Tabella 1. Casi di tumore del colon retto per registro tumori e anno. Età 50-69 anni.

	North-Centre 2000-2005		North-Centre 2006-2008			South and the Islands 2000-2008		
	N	%	N	%	p-value[1]	N	%	p-value[1]
Total	13,275	100	6,655	100		3,738	100	
Gender								
male	7,817	58.9	4,075	61.2	0.002	2,151	57.5	0.14
female	5,458	41.1	2,580	38.8		1,587	42.5	
Age (years)								
50-59	4,291	32.3	2,115	31.8	0.44	1335	35.7	<0.001
60-69	8,984	67.7	4,540	68.2		2,403	64.3	
Pattern of diagnosis								
screen-detected	569	4.3	2,237	33.6	<0.001	0	0	-
not screen-detected*	12,706	95.7	4,418	66.4		3,738	100	
Anatomic site								
proximal colon	3,557	26.8	1,776	26.7	<0.001	1,001	26.8	<0.001
distal colon	4,820	36.3	2,631	39.5		1,152	30.8	
rectum	4,276	32.2	1,890	28.4		1,321	35.3	
colon NOS**	622	4.7	358	5.4			7.1	
Stage at diagnosis								
I	2,146	16.2	1,878	28.2	<0.001	471	12.6	<0.001
II	3,299	24.9	1,518	22.8		905	24.2	
III	3,817	28.8	1,598	24.0		852	22.8	
IV	2,461	18.5	1,087	16.3		841	22.5	
not available/missing	1,552	11.7	574	8.6		669	17.9	
Grading								
well-differentiated	1,165	8.8	935	14.0	<0.001	232	6.2	<0.001
moderately differentiated	7,792	58.7	3,740	56.2		2,290	61.3	
poorly differentiated	1,981	15.0	1,178	17.7		531	14.2	
not available/missing	2,337	17.6	802	12.1		685	18.3	

[1] p-value of Chi square test comparing the distribution by each variable in the table with the reference group = North-Centre, 2000-2005
* it includes pre-screening, not screen-detected in areas with screening, diagnosed in areas with no screening
** NOS: not otherwise specified

Table 2. Distribution of colorectal cancer cases according to main characteristics, by macro-area and period.
Tabella 2. Distribuzione dei casi di tumore del colon retto per varie caratteristiche, per macroarea e periodo.

There were 2,806 screen-detected cases, or 11.9% of the whole. This percentage rose to 33.6% in areas with an SP. One-third of the cases (31.6%) were localized in the rectum.

The proportion of stage I cases and of cases with grade I was highest in the North-Centre in 2006-2008 and lowest in the South and on the Islands. Overall, the proportion of cases with a stage missing at diagnosis was 11.8%. This was highest in the South and on the Islands, and lowest in the North-Centre in 2006-2008.

Table 3 shows the characteristics of cases by pattern of diagnosis. Compared to the CRCs diagnosed during the pre-screening period, screen-detected CRCs showed a different distribution for most variables. In particular, the proportion of subjects aged 65-69 years was greater than 40% (41.7%), as compared to 38.3%. Screen-detected cases were more frequently located in the distal colon than pre-screening cancers (50.6% *vs* 36.8%). Grading was more favourable, with 20.1% of screen-detected cases being well-differentiated and only 11% poorly differentiated, compared respectively to 9.6% and 15.6% in the pre-screening period. Also stage at diagnosis was less advanced: 42.8% of screen-detected cases were diagnosed at stage I (*vs* 16.2%) and only 6.2% at stage IV (*vs* 19.8%).

Finally, the number of lymph nodes examined in screen-detected CRCs was similar to pre-screening cases (15.6 in both groups), while the mean number of positive lymph nodes overall and for cases stages III/IV was significantly lower in the former (1.0 *vs* 2.1 and 3.4 *vs* 4.2, respectively).

Both not screen-detected CRCs and CRCs diagnosed in areas without screening showed similar distributions to those of CRC in the pre-screening period, according to major characteristics (except macro-area and number of lymph nodes). Compared with the CRCs diagnosed before implementation of the screening programmes, the probability of stage III or IV at

	Total		Areas with a screening programme			Areas without a screening programme
				period with screening		
	N	%	pre-screening period	screen-detected	not screen-detected	
Total (N)	23,668	100	6,710	2,806	6,759	7,393
Macro-area						
Northwest	4,788	20.2	39.1	6.7	16.1	12.0
Northeast	11,571	48.9	52.2	74.4	47.6	37.4
Centre	4,066	17.2	8.7	18.9	36.4	6.7
South-Islands	3,243	13.7	0.0	0.0	0.0	43.9
Gender						
male	4,043	59.3	58.8	61.7	60.0	158.3
female	9,625	40.7	41.2	38.4	40.0	41.7
Mean age (years) (SD)	61.8 (5.3)		61.8 (5.3)	62.3 (5.2)	61.7 (5.4)	61.7 (5.3)
Mean age (years)						
50-54	2,954	12.5	12.5	9.9	13.6	12.5
55-59	4,787	20.2	19.8	20.2	19.6	21.2
60-64	6,821	28.8	29.4	28.2	28.3	29.0
65-69	9,106	38.5	38.3	41.7	38.5	37.4
Anatomic site						
proximal colon	6,334	26.8	27.2	24.3	27.8	26.4
distal colon	8,603	36.4	37.8	50.6	35.7	30.2
rectum	7,487	31.6	31.2	23.2	32.5	34.5
colon NOS	1,244	5.3	3.9	2.0	4.0	8.9
Grading						
well-differentiated	2,332	9.9	9.6	20.1	9.4	6.5
moderately differentiated	13,822	58.4	57.2	56.9	56.5	61.8
poorly differentiated	3,690	15.6	15.6	11.0	16.7	16.3
not available/missing	3,824	16.2	17.5	12.0	17.4	15.4
Lymph nodes examined						
mean number (SD)	16.1 (9.9)		15.6 (9.3)	15.6 (9.7)	18.0 (11.0)	14.5 (8.7)
Positive lymph nodes						
mean number (SD)	2.0 (4.2)		2.1 (4.0)	1.0 (2.7)	2.4 (4.9)	2.1 (4.2)
Positive lymph nodes in stage III/IV cases						
mean number (SD)	4.3 (5.3)		4.2 (4.9)	3.4 (4.0)	4.6 (6.0)	4.3 (5.0)
Stage at diagnosis						
I	4,495	19.0	16.2	42.8	17.2	14.2
II	5,722	24.2	24.9	19.1	24.4	25.2
III	6,267	26.5	27.5	20.1	28.3	26.3
IV	4,389	18.5	19.8	6.2	20.3	20.5
not available/missing	2,795	11.8	11.6	11.9	9.8	13.8

Table 3. Distribution of colorectal cancer cases according to main characteristics, by pattern of diagnosis.

Tabella 3. Distribuzione dei casi di tumore del colon retto per varie caratteristiche, per modalità di diagnosi.

Table 4. Odds ratios of colorectal cancers diagnosed at stage III or IV (as compared to stage I-II), according to selected variables.
Tabella 4. Odds ratio di stadio avanzato (III o IV), per diverse variabli.

	N stage III-IV*	N stage I-II	Odds ratio**	95%CI
Gender				
male	6,249	6,104	1*	-
female	4,407	4,113	1.02	0.97-1.08
Age (5-year linear increase)			0.91	0.89-0.94
Anatomic site				
proximal colon	3,166	2,770	1*	-
distal colon	3,647	4,019	0.83	0.77-0.88
rectum	3,226	3,026	0.91	0.84-0.97
colon NOS	617	402	1.19	1.04-1.37
N examined lymph nodes			1.002	1.001-1.003
Pattern of diagnosis				
pre-screening	3,182	2,774	1*	-
screen-detected	737	1,734	0.40	0.36-0.44
not screen-detected	3,566	3,090	1.04	0.97-1.12
areas with no screening	3,171	2,619	1.05	0.97-1.13

* reference
** estimated using logistic regression model (response variable stage III-IV vs. stage I-II), adjusted by all the variables in the table

Table 5. Odds ratios of poorly differentiated grading colorectal cancers (as compared to well/moderately differentiated), according to selected variables.
Tabella 5. Odds ratio di grading scarsamente differenziato, per diverse variabli.

	N poorly differentiated*	N well mod. differentiated	Odds ratio**	95%CI
Gender				
male	2,120	9,627	1*	-
female	1,570	6,527	1.07	1.00-1.16
Age (5-year linear increase)			1.00	0.96-1.03
Anatomic site				
proximal colon	1,401	4,114	1*	-
distal colon	1,104	6,411	0.54	0.49-0.59
rectum	980	4,973	0.61	0.56-0.68
colon NOS	205	656	0.93	0.78-1.11
N examined lymph nodes			1.00	0.998-1.00
Pattern of diagnosis				
pre-screening	1,075	4,491	1*	-
screen-detected	308	2,160	0.86	0.75-1.00
not screen-detected	1,298	4,859	1.06	0.96-1.16
areas with no screening	1,009	4,644	0.96	0.87-1.06

* reference
** estimated using logistic regression model (response variable stage III-IV vs. stage I-II), adjusted by all the variables in the table

diagnosis was reduced by 60% among screen-detected cases (table 4, p. 112). Instead, there were no significant differences regarding cases that were not screen-detected and cases diagnosed in areas with no screening. The risk of an advanced stage decreased with age and was lower for cases of cancer located in the distal colon and the rectum.
The probability of a poorly differentiated grading was significantly lower (14%) among screen-detected cases (table 5) as compared to the period prior to screening, even when adjusting for stage at diagnosis (OR not adjusted for stage was 0.62, 95%CI 0.54-0.71), while non-screen-detected cases and cases diagnosed in areas with no screening did not show a different risk from pre-screening CRCs. The risk of poorly differentiated grading was higher in cases with an advanced stage at diagnosis and for cases located in the proximal colon.

DISCUSSION

Using data collected from the large number of CRCs diagnosed from 2000 to 2008, this study found that screen-detected CRCs significantly differ from non-screen-detected ones. In particular, the study confirms what is expected by the diagnostic anticipation of screenings, i.e., more favourable prognostic characteristics of screen-detected CRCs: a better distribution by stage at diagnosis and by grading, and a lower number of positive lymph nodes overall and for stage III/IV cases.
Compared to non-screen-detected cases, the proportion of screen-detected CRCs in males was higher, as was the mean age of the patients.
We also observed a higher proportion of CRCs in the distal colon. This figure could be due to the FIT's higher sensitivity to lesions of the left colon[9-11] and hence to a higher impact on the prevalence round of screening at this anatomic site. Most screen-detected cases included in this study were diagnosed in the first or second screening round, when many of the prevalent pre-clinical lesions are detected, thus producing a transient increase in incidence rates. Another reason why screen-detected CRCs are more frequent in the distal colon could de-

pend on the different biology of these lesions, that have been associated to a slow natural history with a long pre-clinical phase.[12] This would increase the difference in diagnostic yield of the distal versus the proximal colon.

Age was inversely correlated to the probability of stage III or IV at diagnosis. The prevalence round of screening (which occurs at a younger age) could play a role in this effect.

The number of lymph nodes examined was positively associated with a more advanced stage. The interpretation of this effect is controversial: on the one hand, the higher likelihood of a staging upgrade the more lymph nodes are examined; on the other hand, it could be hypothesized that more lymph nodes are examined in more advanced cancers.

In areas with an SP, the proportion of screen-detected cases was about one-third of the total. Besides the diagnostic sensitivity of the first-level test and second-level assessment, this figure depends on the extension of invitations and compliance with invitation to screening. Even though this study monitored the impact of screening in the first years after SP implementation (when the spread of screening over the target population is reasonably lower than expected in well-established programmes), we observed a relevant impact of screening even when evaluating all the CRCs diagnosed in the entire population.

Compared to the North-Centre, cases in the South and Islands showed a worse distribution by stage at diagnosis and by grading. These figures suggest a diagnostic delay in this macro-area that was worsened by the increase in the number of SPs in the North-Centre. This hypothesis is in line with the results from the latest report of the Italian association of cancer registries (AIRTUM) on cancer patient survival. CRCs diagnosed during 2001-2004 in the South and on the Islands showed a lower 5-year survival rate compared to cases diagnosed in other areas of Italy.[13]

Another important result of this study was that, after screening was implemented, the cases diagnosed before the onset of an SP and those not screen-detected in the same areas were very similar in terms of distribution by age and anatomic site, stage at diagnosis, and grading. The only exception was the number of examined and positive lymph nodes, which was higher in the latter group. However, this figure could be due to a period effect.

The cases that were diagnosed outside the SPs were not different from the cases detected before the onset of screening. Therefore, they do not seem to have been significantly affected by SP implementation. This fact has at least three consequences:

- the presence of an SP does not seem to generate a "halo" effect (i.e., an increase in the spontaneous, extra-screening, uptake of FIT and/or total colonoscopy) to produce a visible diagnostic anticipation; this hypothesis needs to be confirmed in areas where SPs have been active for more years;
- non-screen-detected cases are representative of the cases that were diagnosed in the absence of SPs, therefore they can be safely used as a comparison group for screen-detected CRCs;
- the differences that we observed in the screen-detected cases may be entirely attributed to the specific pattern of diagnosis.

The risk of selection bias (i.e., compliance with the screening invitation being higher among healthier subjects, who would have a more favourable pattern of disease even without an SP) seems unlikely. Otherwise, non-screen-detected cases would have shown worse characteristics than cases diagnosed before the onset of screening.

This is in line with data from a national survey on preventive behaviours and service utilization, which showed that in Italy spontaneous screening for CRC is very low and the coverage in regions with well-implemented population-based SPs is higher among subjects with a lower educational level.[14]

However, this picture could be modified as SPs age and following changes in compliance with invitation.

CONCLUSION

Screen-detected CRCs showed a favourable distribution by different prognostic factors, while cases diagnosed in the South and on the Islands reported the worst figures.

A renewed effort to implement screening programmes throughout the entire country, and particularly in the South and on the Islands, is therefore warranted, filling the prognostic gap among geographic areas, to increase the equity of access to a public health programme that is proving to be highly protective of the population.

Conflicts of interests: none declared

Members of the IMPATTO COLONRETTO working group:
Membri del gruppo di studio IMPATTO COLONRETTO:

Biella: A. Giacomin (Registro tumori del Piemonte, Provincia di Biella), A. Azzoni (S.S. Gastroenterologia, ASL Biella)
Bologna: P. Baldazzi, N. Collina, P. Pandolfi, P. Biavati, G. Gualandi (Registro tumori di Bologna)
Catania-Messina: S. Sciacca, P. Pesce, A. Torrisi, C. Sciacchitano, M. Fidelbo (Registro tumori integrato di Catania-Messina, Catania)
Emilia-Romagna: A.C. Finarelli, C. Naldoni, P. Sassoli de' Blanchi, P. Landi (Assessorato alle politiche per la salute, Regione Emilia-Romagna, Bologna)
Ferrara: V. Matarese (UO Gastroenterologia, AOU S. Anna, Cona-Ferrara), A. De Togni, C. Palmonari (Centro screening oncologici AUSL Ferrara)
Firenze: E. Crocetti, G. Grazzini, G. Manneschi, P. Mantellini (Istituto per lo studio e la prevenzione oncologica – ISPO, Firenze)
Friuli-Venezia Giulia: D. Serraino, E. Bidoli, M. Taborelli, A. Gini, S. Virdone (Istituto nazionale dei tumori – CRO, Aviano)
Genova: A. Puppo, C. Casella, M. Celesia, R. Cogno, E. Marani (Registro tumori Regione Liguria, UO Epidemiologia clinica, IRCCS AOU San Martino – IST, Genova)
Latina: E. Bugliarello, S. Fattoruso, L. Tamburo, S. Tamburrino (Registro tumori di Latina, Latina); P. Bellardini (Coordinamento screening ASL Latina)
Milano: M. Autelitano, B. Frammartino, L. Bisanti, S. Ghilardi, R. Leone (Registro tumori di Milano)
Modena: R. Corradini, F. De Girolamo (Centro screening oncologici AUSL di Modena, Italy); K Valla (Registro tumori di Modena)
Napoli: R. Palombino, L. Gigli, S. Russo Spena (Servizio epidemiologia e prevenzione, ASL Napoli 3 Sud); M.F. Vitale (Registro tumori di popolazione Regione Campania, Napoli)
Palermo: M.A. Cascio, R. Mannino, W. Mazzucco, A. Mistretta, B. Ravazzolo (Registro tumori di Palermo e Provincia, AOU Policlinico "Paolo Giaccone" di Palermo, UOC di epidemiologia clinica con Registro tumori, Palermo)
Parma: P. Sgarzi, F. Bozzani (Registro tumori di Parma); M. Zatelli, C. Zurlini (Centro screening oncologici AUSL Parma); P. Caruana (AOU Parma)
Piacenza: P. Seghini, G. Gatti, R. Prazzoli (UO Epidemiologia e comunicazione del rischio, AUSL Piacenza)
Reggio Emilia: C. Campari, L. Paterlini (Centro screening, AUSL Reggio Emilia); T. Cassetti (Registro tumori di Reggio Emilia); R. Sassatelli (UO Gastroenterologia ed endoscopia digestiva, Arcispedale Santa Maria Nuova – IRCCS, Reggio Emilia)
Romagna: C. Imolesi (Centro screening, OCM Bufalini, Cesena); C. Casale (Centro Screening, O. Infermi, Rimini); M. Serafini (Centro Screening, OC S.M. delle Croci); R. Vattiato, O. Giuliani (Registro tumori della Romagna, Istituto dei tumori della Romagna IRCCS, Meldola)
Sassari: R. Cesaraccio, O. Sechi, M. Budroni (Registro tumori di Sassari)
Siracusa: A. Madeddu, M.L. Contrino, A. Colanino Ziino, M. Russo, F. Tisano (Registro tumori di Siracusa)
Sondrio: A.C. Fanetti, S. Maspero, E. Moroni, I. Cometti (Osservatorio epidemiologico - Registro tumori della Provincia di Sondrio)
Trentino: M. Gentilini, S. Piffer (Registro tumori di Trento); G. De Pretis (UO Gastroenterologia, Ospedale S. Chiara, Trento); P. Caciagli (Dipartimento laboratorio e servizi, APSS, Trento); R. Pertile (Servizio epidemiologia clinica e valutativa, APSS, Trento)
Umbria: F. Bianconi (Registro tumori Umbro di Popolazione / Scuola di specializzazione in Igiene e medicina preventiva, Università di Perugia); D. Bucchi, M.E. Galeotti (Scuola di specializzazione in Igiene e medicina preventiva, Università di Perugia); M. Malaspina (Servizio di screening USL 1 Umbria)
Veneto: A. Greco, A.R. Fiore, C.F. Stocco (Registro tumori del Veneto, Padova); C. Fedato (Coordinamento regionale screening, Regione Veneto, Venezia)

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Incidence trends of colorectal cancer in the early 2000s in Italy.

Figures from the IMPATTO study on colorectal cancer screening

Trend di incidenza del tumore del colon retto nei primi anni Duemila in Italia.

Dati dello studio IMPATTO dello screening colorettale

Manuel Zorzi,[1] Lucia Mangone,[2,3] Romano Sassatelli,[4,5] Susanna Baracco,[1] Mario Budroni,[6] Marine Castaing,[7] Claudia Cirilli,[8] Rosanna Cusimano,[9] Mario Fusco,[10] Adriano Giacomin,[11] Paolo Giorgi Rossi,[12,13] Carlo Naldoni,[14] Fabio Pannozzo,[15] Silvano Piffer,[16] Antonella Puppo,[17] Francesco Tisano,[18] Marco Zappa[19,20] and IMPATTO COLONRETTO working group

[1]Registro tumori del Veneto, Padova
[2]Registro tumori di Reggio Emilia, Reggio Emilia
[3]Associazione italiana registri tumori (AIRTUM)
[4]UO Gastroenterologia ed endoscopia digestiva, IRCCS Arcispedale Santa Maria Nuova, Reggio Emilia
[5]Gruppo italiano screening colorettale (GISCoR)
[6]Registro tumori di Sassari, Sassari
[7]Registro tumori integrato di Catania-Messina, Catania
[8]Registro tumori di Modena, Modena
[9]Registro tumori di Palermo, Palermo
[10]Registro tumori di popolazione Regione Campania, Napoli
[11]Registro tumori del Piemonte, Provincia di Biella, Biella
[12]Servizio interaziendale di epidemiologia, AUSL Reggio Emilia
[13]IRCCS-Arcispedale S. Maria Nuova, Reggio Emilia
[14]Assessorato alle politiche per la salute, Regione Emilia-Romagna, Bologna
[15]Registro tumori di Latina, Latina
[16]Registro tumori di Trento, Trento
[17]Registro tumori Regione Liguria, Genova
[18]Registro tumori di Siracusa, Siracusa
[19]Istituto per lo studio e la prevenzione oncologica (ISPO), Firenze
[20]Osservatorio nazionale screening (ONS)

Corrispondenza
Manuel Zorzi
manuel.zorzi@regione.veneto.it

Abstract

We utilised the IMPATTO study's archives to describe the 2000-2008 colorectal cancer (CRC) incidence rate trends in Italy, once screening programmes based on the faecal immunochemical test were implemented in different areas.

Data on CRCs diagnosed in Italy from 2000 to 2008 in subjects aged 40-79 years were collected by 23 cancer registries. Incidence rate trends were evaluated as a whole and by macro-area (North-Centre and South-Islands), presence of a screening programme, sex, ten-year age class, anatomic site, stage at diagnosis, and pattern of diagnosis (screen-detected, non-screen-detected). The annual percent change (APC) of incidence rate trends, with 95% confidence intervals (95%CI), were computed.

The study included 46,857 CRCs diagnosed in subjects aged 40-79 years, of which 2,806 were screen-detected. The incidence rates in the North-Centre were higher than in the South and on the Islands. During the study period, screening programmes had been implemented only in the North-Centre and had a significant effect on incidence rates, with an initial sharp increase in incidence, followed by a decrease that started in the 3rd-4th years of screening. These incidence rate trends were exclusively due to modifications in the rates of stage I cases. After screening programmes started, incidence increased in all anatomic sites, particularly in the distal colon.

The differential figures introduced by the implementation of screening programmes warrant a continuous surveillance of CRC incidence and mortality trends to monitor the impact of screening at a national level.

(*Epidemiol Prev* 2015; 39(3) Suppl 1: 115-125)
Keywords: colorectal cancer, screening, incidence rates, fecal immunochemical test, Italy

Riassunto

E' stato utilizzato l'archivio dello studio IMPATTO per descrivere i trend di incidenza del tumore del colon retto (CCR) in Italia nel periodo 2000-2008, quando sono stati avviati programmi di screening colorettale basati sul test per la ricerca del sangue occulto fecale in diverse aree.

23 Registri tumori hanno fornito i dati relativi ai CCR diagnosticati nel periodo 2000-2008 in sog-

getti di età compresa fra 40 e 79 anni. Sono stati calcolati i trend di incidenza complessivi e per macroarea (Centro-Nord e Sud-Isole), presenza di un programma di screening, sesso, età, localizzazione anatomica, stadio alla diagnosi e modalità diagnostica (screen-detected, non-screen-detected). Sono riportati gli APC (annual percent change) con intervalli di confidenza al 95%. L'archivio riguarda 46,857 CRC, di cui 2,806 screen-detected. I tassi di incidenza nel Centro-Nord erano maggiori rispetto al Sud-Isole. Nel periodo di studio sono stati avviati programmi di screening solo in aree del Centro-Nord, con un effetto significativo sui tassi di incidenza, con un ripido incremento iniziale seguito da una riduzione a partire dal 3°-4° anno dall'avvio dei programmi. L'effetto degli screening era a carico esclusivamente dei CCR in stadio I alla diagnosi. Dopo l'avvio degli screening, l'incidenza è aumentata per tutte le sottosedi anatomiche del colon, in particolare per il colon distale.
L'avvio dei programmi di screening colorettale in Italia ha avuto un forte impatto portando a un aumento dell'incidenza e delle forme precoci. E' necessario un continuo monitoraggio delle aree italiane per capire gli effetti dello screening su tutta la popolazione.

(*Epidemiol Prev* 2015; 39(3) Suppl 1: 115-125)
Parole chiave: tumore del colon retto, screening colorettale, tassi di incidenza, test per la ricerca del sangue occult fecale, Italia

INTRODUCTION

Colorectal cancer (CRC) is a major public health problem. In Italy it represents the most frequent tumour in terms of incidence with more than 50,000 new cases and is the second cause of death among cancers, with about 19,000 deaths per year.[1]
According to estimates by the Italian Association of Cancer Registries (AIRTUM), mortality rates showed a reduction in both genders starting in the early 1990s, while incidence rates increased, particularly in males.[2]
A number of case series from cancer registries in the North of Italy showed that at the end of the 1990s the proportion of cases that were TNM stage III or IV at diagnosis still ranged between 39% and 51% of the total.[3-5] Stage at diagnosis is well known to be closely related to prognosis: a case series from the SEER study showed a 5-year survival of 93% for cases at AJCC stage I, 80% for those at stage II, 58% at stage III, and only 7% at stage IV.[6] The SEER study compared series of cases diagnosed in different periods (from 1973 to 1997) and showed that the increase in stage-specific survival had been very limited.[7]
Therefore, the reported increase in survival, from 51% in 1990-1992 to 64% in 2005-2007,[8] is plausibly associated with a more favourable distribution of stage at diagnosis, which derived from the spread of the uptake of exams for early diagnosis, first spontaneously and then within organized screening programmes (SP). The distribution by stage at diagnosis of screen-detected CRCs is better than that of clinically diagnosed CRCs, with more than 50% of cases at stage I, while those at stage III or IV are about one-fourth of the total.[9-11]
In Italy, CRC SPs were progressively implemented in most regions starting in the early 2000s. By the end of 2010, 66% of the Italian population lived in areas with active CRC screening programmes, but strong geographical differences were present: the corresponding figures were 87% in the North, 79% in the Centre and only 29% in the South and Islands.[9]
Four randomized controlled trials showed that SPs based on the guaiac faecal occult blood test (gFOBT) reduce mortality by 16%,[12,15-19] which rises to 23% in the per-protocol analysis.[12]
Results from a gFOBT population-based SP showed similar figures,[13] while early evidence from faecal immunochemical test (FIT)-based programmes reported a greater reduction in mortality that began earlier compared to the trials, i.e., in the 5th year after screening started.[14]
A population-based SP is expected to initially increase incidence rates, thanks to the diagnostic anticipation of cancers that would otherwise be diagnosed later. In the medium and long term, a progressive reduction of incidence rates is expected, deriving from the prevention of new CRCs as a result of the detection and removal of a large number of precancerous lesions (i.e., advanced adenomas). As a matter of fact, the four trials showed contrasting effects on the incidence rates, with a 17-20% reduction in one of them[15-16] but no effect in the other three.[17-19] The latter reported low compliance with the study by the enrolled subjects (respectively 67%, 60%, and 63%).
A recent paper showed a reduction of incidence rates in the medium term (22% 11 years after screening started).[20] Many studies have shown that FIT sensitivity for advanced adenoma and cancer is higher than that of gFOBT.[21-26] Thus the effect on incidence observed in screening programmes and not in trials could be due to FIT having a higher sensitivity for adenomas than gFOBT.
In Italy, CRC SPs are aimed at residents aged 50-69 or 74 years, who are invited via mail every 2 years to perform a single FIT. Subjects with a positive screening test are contacted to undergo a total colonoscopy performed at an endoscopic referral centre. In only one region (Piemonte) has a different programme been established, with either one sigmoidoscopy at the age of 58, or a FIT invitation every 2 years in the age interval of 59-69 years. The average detection rate of advanced adenomas in organized programmes in Italy is high, compared to that of guaiac trials,[18,27] reaching 13 x 1,000 at the prevalence round and 8 x 1,000 at the incidence round, respectively.[11] Consequently, the impact of screening programmes on incidence is an open question.
To describe the impact that implementing CRC screening programmes has had in Italy, a research project, the IMPATTO study, was financed by the Italian Ministry of Health; the study collects and links information from both screening programme archives and cancer registries.
This paper utilizes the IMPATTO study's archives to describe the CRC incidence rate trends in Italy during 2000-2008, when several SPs were implemented in different areas.

MATERIALS AND METHODS

Data

The IMPATTO study collected data from CRC cases (International Classification of Diseases, 10th revision: C18–C20) in subjects aged 40-79 years that were diagnosed between 2000 and 2008 in the populations covered by 23 population-based cancer registries (CR) in 13 Italian regions (Piemonte, Liguria, Lombardia, Veneto, Trentino, Friuli-Venezia Giulia, Emilia-Romagna, Toscana, Umbria, Lazio, Campania, Sicilia, Sardegna). These areas included about 36%, 17%, and 24% of the resident population in northern, central, and southern Italy, respectively.

Cases based on death certificates only, autopsies without histology, or autopsies with histology and incidence data equal to date of death were excluded. All multiple metachronous cases were included.

Collected data included incidence date, morphology and topography, stage at diagnosis (according to Dukes' classification as modified by Astler and Coller[39]) and grading, surgical intervention, lymph nodes examined and positive lymph nodes. Multiple synchronous cases (incidence date within six months from the index case) were recorded if located in different anatomic sub-sites (fourth digit of the ICD-10 topography code) and only the most advanced were staged. If more cancers were located in the same sub-site, only the most advanced was recorded, maintaining the recording rules of different morphologies.

Vital status was recorded for all cases up to either 31.12.2008 or 31.12.2010, according to the CR. Information about the cause of death was collected for deceased subjects, according to the International Classification of Diseases, 9th revision.

Tumour histological type was recorded according to the International Classification of Diseases for Oncology, 3rd edition.

CRs carried out a record-linkage with the local SPs to retrieve individual data on the screening history of patients before the incidence date by collecting the date of the first invitation and the dates of screening tests. Patients were then classified according to the following screening patterns:

- screen-detected at the first screening episode;
- screen-detected at a repeat screening episode;
- screen-detected at follow-up;
- not compliant with diagnostic work-up after a positive screening test;
- subjects with at least one negative screening test before incidence;
- never compliant (i.e., invited, but not tested within the SP);
- never invited to screening.

Two categories were then created according to the diagnostic modality: screen-detected cases, including the first three classes, and non-screen-detected cases, including the last four.

Finally, age- and sex-specific data on the resident population in the study period for each CR were collected.

Analysis

Cases were classified by geographic macro-area according to the Istat (Italian National Statistics Agency) classification: Northwest, Northeast, Centre, and South and Islands. They were then grouped into two epidemiologically homogeneous areas, North-Centre and South-Islands, apart from Latina, in the southern part of the Lazio region (the centre of Italy), which was included in the South-Islands according to its epidemiological pattern.

During the study period, the CR included in the study only SPs active in the North-Centre. The number of SPs increased particularly in 2006, when the actual extension of invitations rose to 51% of the target population (subjects aged 50-69 years) compared to 16% in 2005.[11] In the IMPATTO study, the proportion of screen-detected cases in subjects aged 50-69 years in the North-Centre rose from 9.1% in 2005 to 30.3% in 2006 and reached 45.9% in 2008. Therefore, two periods were identified, pre-2005 and from 2006 onward. Period-specific indicators were reported for areas where SPs were present.

Incidence rate trends (standardized on the 2001 European population) were evaluated as a whole and by macro-area (North-Centre and South-Islands), sex, ten-year age class, anatomic site (proximal colon: C18.0-C18.4; distal colon: C18.5-C18.8; colon NOS: C18.9; and rectum: C19-C20), stage at diagnosis (according to Dukes' classification), and pattern of diagnosis (screen-detected, non-screen-detected). The annual percent change (APC) of incidence rate trends, with 95% confidence intervals (95%CI), were computed.

RESULTS

We collected data on 47,830 CRCs, of which 973 were excluded (775 anus and anal canal, 129 lymphomas, sarcoma, or melanoma, and 69 for other reasons). The study archives used in this paper are therefore the 46,857 CRCs diagnosed between 2000 and 2008 in subjects aged 40-79 years.

About one-sixth of the cases (15.7%) were from the South and the Islands (**table 1**, p. 118). Most cases were male (58%) and in the upper age class (70-79 years, 44.8%).

There were 3,164 screen-detected cases (6.8% of the total; the proportion increased to 16.6% when considering only cases of 50- to 69-year-olds from areas with an SP).

One third of the cases were in the rectum. The stage was available for 87.6% of the cases.

Overall, the incidence rate was 133.7 and 83 per 100,000 in males and females, respectively.

The incidence in the North-Centre was higher than in the South-Islands: 141 *vs* 103.9 x 100,000 in men and 86.4 *vs* 69.4 x 100,000 in women.

As shown in **table 2** (p. 118), the CRs took part in the study with cases from different periods. Moreover, the SPs were introduced in different years.

Standardized incidence rates of single CRs over the entire study period were between 153.4 in Genova and 99.1 in Sassari in men and between 94.8 in Genova and 65.6 in Sassari in women.

In the North-Centre, incidence rose more steeply from 2006 in both genders, the year that many SPs were implemented in this macro-area (**figure 1**, p. 119). In the South and on the Islands, the figure was stable for both genders.

Table 1. Main characteristics of the study subjects.
Tabella 1. Principali caratteristiche dei soggetti studiati.

	N	%
Total	46,857	100
Macro-area		
North-Centre	39,487	84.3
South-Islands	7,370	15.7
Gender		
male	27,195	58.0
female	19,662	42.0
Age (years)		
40-49	2,180	4.7
50-59	7,741	16.5
60-69	15,927	34.0
70-79	21,009	44.8
Pattern of diagnosis (all areas, age 40-79 years)		
screen-detected at the first screening episode	2,897	6.2
screen-detected at a repeat screening episode	220	0.5
screen-detected at follow-up	47	0.1
not compliant with work-up after a positive screening test	116	0.2
subjects with a negative screening test before incidence	862	1.8
never compliant (i.e., invited but without a screening test)	2,102	4.5
never invited to screening	40,613	86.7
Pattern of diagnosis (areas with a screening programme, age 50-69 years)		
screen-detected	2,805	16.6
non-screen-detected	14,061	83.4
Anatomic site		
proximal colon	13,772	29.4
distal colon	16,278	34.7
rectum	14,278	30.5
colon NOS	2,529	5.4
Stage at diagnosis (Dukes)		
I	8,218	17.5
II	12,051	25.7
III	12,206	26.0
IV	8,577	18.3
unknown	5,805	12.4

Geographic area	Cancer registry	Cases (N)	Incidence rate (x 100,000)								
			2000	2001	2002	2003	2004	2005	2006	2007	2008
Northwest	Genova	2,014				112.1	105.7	102.1			
	Milano	6,019	104.8	108.1	102.0	101.9	102.5	**90.0**	**107.4**		
	Sondrio	875	91.7	88.8	101.1	95.1	89.7	**90.6**	**130.4**	**120.7**	**110.2**
	Biella	893		104.3	88.4	111.6	99.9	**115.3**	**100.5**	**107.3**	
Northeast	Trentino	1,215			91.5	92.2	88.1	90.0	95.8		
	Veneto	1,894	97.9	109.5	**107.7**	**119.5**	**118.8**	**110.8**			
	Friuli-Venezia Giulia	2,336						105.6	104.8	98.9	
	Emilia-Romagna	17,017	120.2	104.1	112.4	108.0	109.5	**117.4**	**139.5**	**117.3**	**113.4**
Centre	Firenze-Prato	3,935	**111.9**	**113.0**	**112.5**	**106.4**	**106.3**	**107.2**			
	Umbria	3,289					111.7	115.6	**111.6**	**142.3**	**128.2**
South/Islands	Latina	932					89.7	86.4	85.3	87.3	
	Napoli	945				83.3	77.2	98.2	84.8	90.5	
	Siracusa	821		81.1	79.7	83.9	83.6	79.1			
	Palermo	1,628				86.3	87.6	86.9			
	Catania-Messina	2,236				78.6	87.3	84.4			
	Sassari	808				87.9	86.8	82.6	79.1		

Numbers in color represent the years when a screening programme was active

Table 2. Number of colorectal cancer cases and incidence rates (standardized Eu 2001) by cancer registry and year. Males and females aged 40-79 years.
Tabella 2. Casi di tumore del colon retto e tassi standardizzati di incidenza (popolazione europea 2001) per Registro tumori e anno. Uomini e donne, età 40-79 anni.

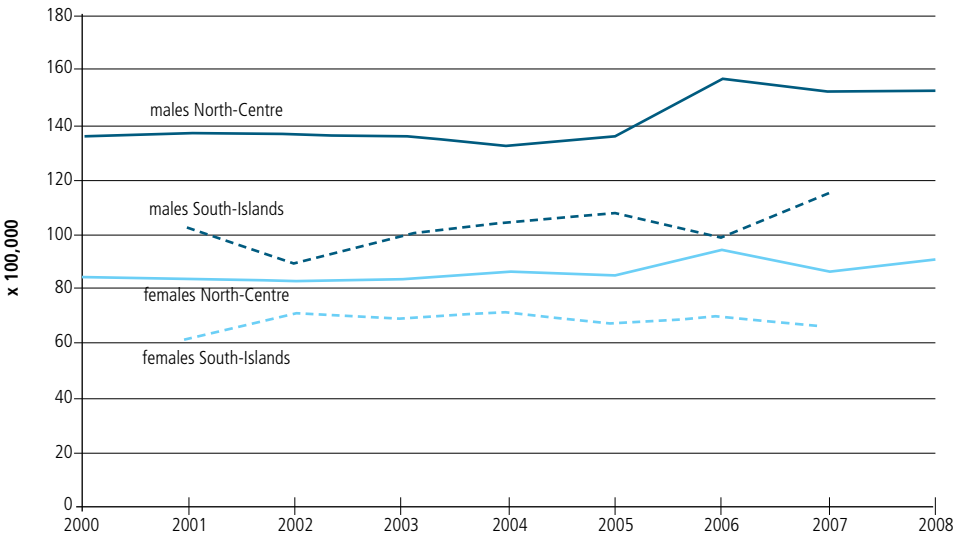

Figure 1. Trends of incidence rates (standardized Eu 2001) by macro-area and gender. Ages 40-79 years.
Figura 1. Andamento temporale dei tassi standardizzati di incidenza (popolazione europea 2001) per macroarea e genere. Età 40-79 anni.

APC (95%CI)
NORTH-CENTRE
males (2000-2008) 2.1 (0.1 ; 4.1)
females (2000-2008) 1.3 (-0.2 ; 2.7)

SOUTH-ISLANDS
males (2001-2007) 2.5 (-0.6 ; 5.7)
females (2001-2007) -0.4 (-3.0 ; 2.2)

The increase observed in the North-Centre regarded only those areas where SPs were implemented, with the APC in areas without SP being -0.7 (95%CI -4.3 to 3.1) for males and -2.5 (95%CI -5.6 to 0.7) for females (table 3).
The trends in the South and on the Islands showed a non-significant increase in males (APC 2.5; 95%CI -0.6 to 5.7) and a decrease in females (APC -0.4; 95%CI -3.0 to 2.2).
In the North-Centre with an SP present, we recorded a non-significant increase in males 50-69 years old (APC 3.6; 95%CI -0.1 to 7.4) and in females 50-69 years old (APC 2.3; 95%CI -0.8 to 5.4), while the 40-49 and 70-79 year age classes showed small, non-significant decreases.
In the North-Centre without SPs no significant trends were observed in the age class of 50-69 years, while in the South and on the Islands incidence increased in males (APC 4.4; 95%CI 0.4 to 8.5) and overall (APC 3.3; 95%CI 1.3 to 5.3).
Figure 2 (p. 120) shows incidence rates by age in areas with an SP, on a time scale centred on the year of implementation of screening. The pre-screening incidence rates of the four 10-year age classes were stable. During the first two years after screening started, incidence rates increased in all age groups, apart from the youngest, and then decreased. The increase was higher in subjects aged 60-69 years, whose incidence rates shifted from 169 to 249 cases per 100,000 (+47.3%) as opposed to subjects 50-59 years old (+21.7%). The decrease in incidence after year 2 was evident both in subjects aged 60-69 years (APC -5.7; 95%CI -28.3 to 24.2) and in those older than 70 years (APC -7.4; 95%CI -22.7 to 11.0).
In subjects aged 50-69 years, the pre-screening incidence rates were similar to those of areas without SPs in the North-Centre, and became significantly higher after the implementation of SPs (table 4, p. 120). Incidence rates in the South and on the Islands were lower. In particular, pre-screening incidence rates in the North-Centre were generally comparable to North-Centre

	Males		Females		Total	
	APC	95%CI	APC	95%CI	APC	95%CI
North-Centre with SP						
40-79 years	2.5	-0.3 ; 5.4	1.3	-0.8 ; 3.5	2.2	-0.1 ; 4.5
50-69 years	3.6	-0.1 ; 7.4	2.3	-0.8 ; 5.4	3.1	-0.1 ; 6.5
North-Centre with SP pre-screening						
40-79 years	0.2	-1.7 ; 2.2	1.7	-1.9 ; 5.4	1.1	-0.1 ; 2.4
50-69 years	0.4	-2.3 ; 3.1	1.8	-1.9 ; 5.7	1.2	-0.7 ; 3.1
North-Centre with SP post-screening						
40-79 years	2.5	-0.3 ; 5.4	1.3	-0.8 ; 3.5	1.8	-0.8 ; 4.4
50-69 years	3.6	-0.1 ; 7.4	2.3	-0.8 ; 5.4	2.5	-1.1 ; 6.2
North-Centre without SP						
40-79 years	-0.7	-4.3 ; 3.1	-2.5	-5.6 ; 0.7	-1.3	-3.6 ; 1.1
50-69 years	-2.0	-6.4 ; 2.6	-2.7	-9.1 ; 4.2	-2.0	-5.1 ; 1.2
South and the Islands						
40-79 years	2.5	-0.6 ; 5.7	-0.4	-3.0 ; 2.2	1.3	-0.4 ; 3.0
50-69 years	4.4	0.4 ; 8.5	1.5	-2.2 ; 5.3	3.3	1.3 ; 5.3

Table 3. Annual percent change (APC), with 95% confidence intervals, of incidence rates by macro-area, implementation of screening programme (SP), age class, and gender. Years 2000-2008.
Tabella 3. Annual percent change (APC) dei tassi di incidenza (con intervalli di confidenza al 95%) per macroarea, presenza di programmi di screening (SP), classe d'età e genere. Anni 2000-2008.

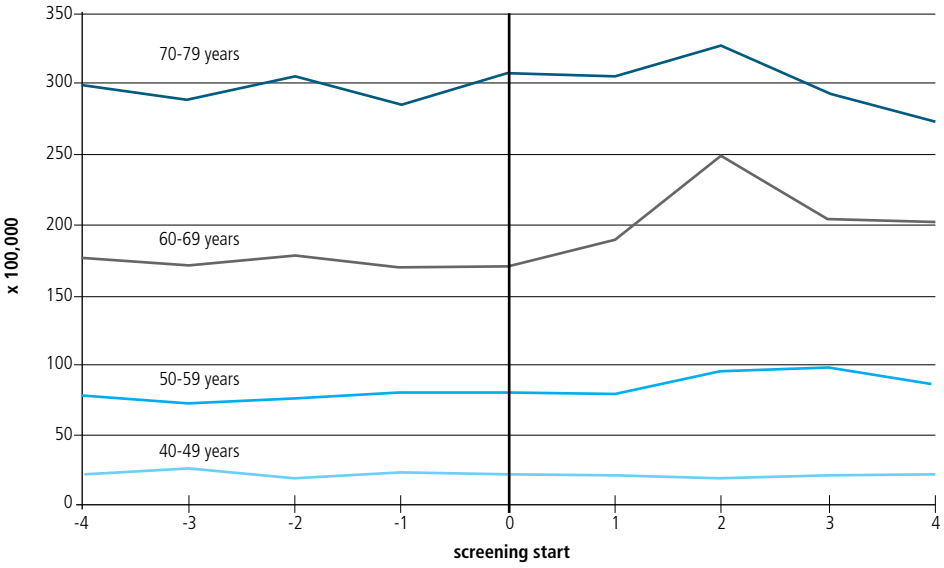

Figure 2. Trends in incidence rates by age class. Cancer registries of areas with screening programme only. The time scale is centred on the year the programme was implemented.
Figura 2. Andamento temporale dei tassi di incidenza per classe d'età. Solo registri tumori di aree dove è attivo un programma di screening. La scala temporale è centrata sull'anno in cui il programma è stato attivato.

Table 4. Incidence rates (standardized Eu 2001) by macro-area, implementation of screening programme and period with respect to different characteristics, x 100,000. Ages 50-69 years.
Tabella 4. Tassi standardizzati di incidenza (popolazione europea 2001) per macroarea, con e senza screening, per periodo, x 100.000. Età 50-69 anni.

	North-Centre without screening programme	North-Centre with screening programme				South-Islands	
		pre-screening		post-screening			
	incidence rates	incidence rates	p-value*	incidence rates	p-value* rates	incidence rates	p-value*
Overall	112.1	116.3	0.10	137.1	<0.001	93.7	<0.001
Gender							
male	142.2	144.0	0.66	170.5	<0.001	112.3	<0.001
female	84.2	91.7	0.02	106.8	<0.001	76.9	<0.001
Age (years)							
50-59	72.9	78.1	0.07	89.7	<0.001	62.2	<0.001
60-69	168.9	171.4	0.59	205.5	<0.001	139.1	<0.001
Pattern of diagnosis							
screen-detected	-	-	-	37.4	-	-	-
non-screen-detected	112.1	116.3	0.10	99.7	<0.001	93.7	<0.001
Stage at diagnosis (Dukes)							
I	18.0	18.6	0.57	32.8	<0.001	11.7	<0.001
II	26.9	29.2	0.08	31.7	<0.001	22.5	<0.001
III	31.4	32.4	0.45	36.6	<0.001	21.4	<0.001
IV	23.2	23.1	0.89	22.0	0.28	21.1	0.18
unknown	12.6	13.1	0.64	13.9	0.14	16.9	<0.001

* compared to reference = North-Centre without screening programme

without screening for all categories of the variables studied, apart from females (+7.5%) and those younger in age (+5.2%). Instead, the respective incidence rates were higher in the North-Centre post-screening and lower in the South and on the Islands for all variables, except for stage IV at diagnosis.
We could not compare the incidence rates by anatomic site of the different areas, because the proportion of colon NOS in the North-Centre without active SPs was too high and unevenly distributed during the years of the study.

Analysis by stage at diagnosis

In the North-Centre without active SPs, and in the South and on the Islands, incidence rates by stage were stable (apart from some fluctuations in the North-Centre during the early years (figures 3 and 4). The APCs for both macro-areas were not significant.
Instead, stage-specific incidence rates in the North-Centre with active SPs showed two different phases (figure 5). Before screening, the incidence rates of stage II, III, and IV cases were stable while those of stage I increased. In fact, during the years before screening the proportion of cases for which the stage was not available decreased. We therefore carried out a sensitivity analysis attributing to such cases the distribution by stage observed among the cases whose stage was known. The pre-screening incidence rates obtained in this way showed a smaller but still significant increase for stage I cases (+5.7 x 100,000 over the entire period).
During the screening period, the incidence rates of stage I cases in-

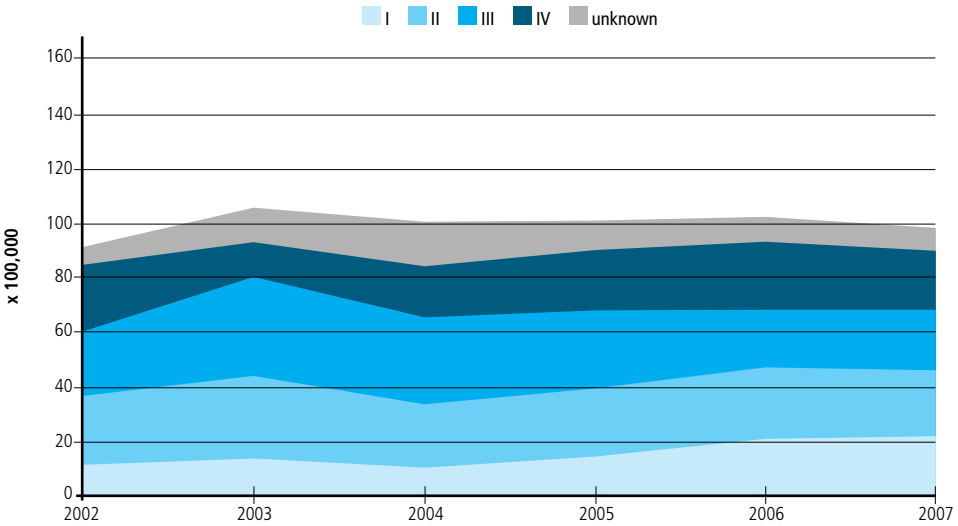

Figure 3. Trends in incidence rates (standardized Eu 2001) by stage at diagnosis. North-Centre with no screening programme. Ages 40-79 years.

Figura 3. Andamento temporale dei tassi standardizzati di incidenza (popolazione europea 2001) per stadio alla diagnosi. Centro-Nord senza programmi di screening. Età 40-79 anni.

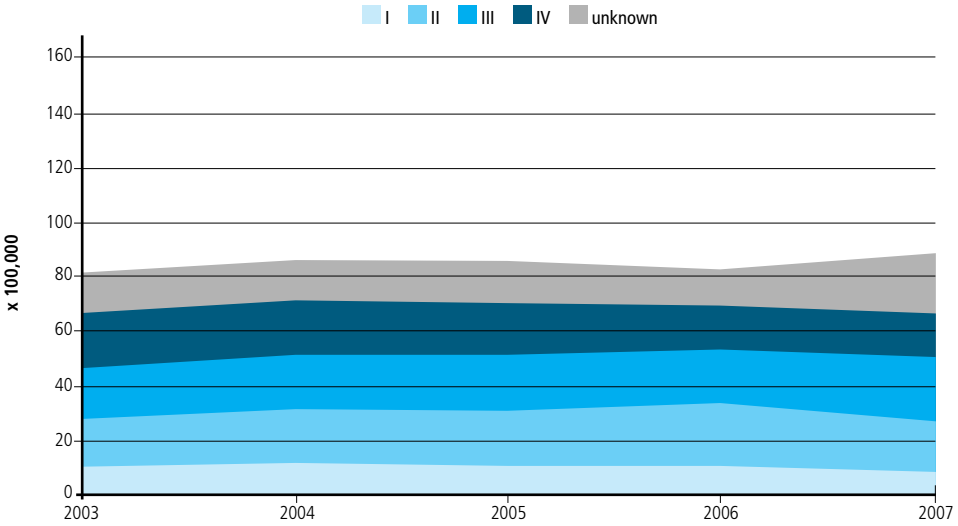

Figure 4. Trends in incidence rates (standardized Eu 2001) by stage at diagnosis. South-Islands. Ages 40-79 years.

Figura 4. Andamento temporale dei tassi standardizzati di incidenza (popolazione europea 2001) per stadio alla diagnosi. Sud-Isole. Età 40-79 anni.

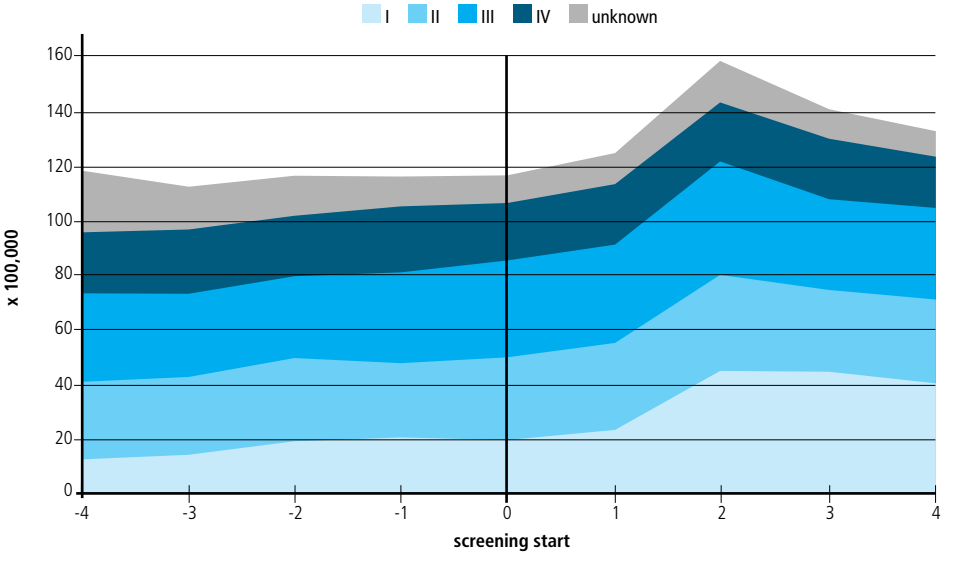

Figure 5. Trends in incidence rates (standardized Eu 2001) by stage at diagnosis. Only areas with a screening programme. Ages 50-69 years. The time scale is centred on the year of implementation of the screening programme.

Figura 5. Andamento temporale dei tassi standardizzati di incidenza (popolazione europea 2001) per stadio alla diagnosi. Solo aree con programmi di screening attivi. Età 50-69 anni. La scala temporale è centrata sull'anno in cui il programma è stato attivato.

Table 5. Distribution by stage at diagnosis, by macro-area with and without a screening programme, and by period (%).
Tabella 5. Distribuzione per stadio alla diagnosi, per macroarea, con e senza un programma di screnning, per periodo (%).

	North-Centre without screening programme 40-79 years		South/Islands 40-79 years	North-Centre with screening programme 40-69 years	
Stage	**2000-2006 (N=4,488)**	**2006-2008 (N=1,805)**	**2001-2007 (N=7,370)**	**pre-screening (N=6,713)**	**post-screening (N=8,186)**
I	13.7	21.2	12.8	16.0	26.7
II	25.6	25.5	23.9	25.3	23.2
III	29.1	21.7	23.1	27.8	25.8
IV	18.1	22.7	21.3	19.6	15.4
unknown	13.4	8.9	18.8	11.3	8.8

creased from 19.5 to 44.7 x 100,000 in the 2nd year, those of stage II from 30.3 to 35.8 x 100,000, while stage III and IV cases were quite stable, their sum ranging between 68 and 73 cases x 100,000.
In the North-Centre with no active SP during the final years of the study, stage I cases increased by 7.5 percent points and stage IV cases by 4.6 points, while stage III cases decreased by 7.4 points and the proportion of cases with unavailable stage also declined (table 5).
In the South and on the Islands, no variation occurred during the study period. A relevant proportion of cases were stage IV (21.3%), while stage I cases were 12.8%, lower than in the North-Centre. The proportion of cases with an unknown stage was around 20%.
In areas with an SP, the proportion of stage I cases in subjects aged 50-69 years increased from 16% before SP implementation to 26.7% after, while stage III and stage IV cases decreased respectively by 2.0 and 4.2 percent points.

Analysis by anatomic site

The proportion of colon NOS in the North-Centre with no active SP was too high to produce the incidence rates without SP by site for the North-Centre.
In the South-Islands macro-area, incidence rates in the proximal colon decreased, while those in the distal colon were stable and those in the rectum increased (figure 6). Only the latter trend was statistically significant (APC 3.0; 95%CI 0.3 to 5.7).
In areas where SPs were implemented, the pre-screening trend for all sites was stable (figure 7). When the SPs started, we recorded a steep increase of incidence rates in the distal colon (from 43.9 to 69.3 x 100,000 in the 2nd year) and, to a lesser extent, in the proximal colon (from 32.3 to 40.9 x 100,000) and the rectum (from 36.7 to 45.5 x 100,000). This increase ended two years after the implementation of screening and was followed by a reduction in the rates for all three sites.

DISCUSSION

We evaluated CRC incidence rates in Italy from the early 2000s, with particular regard to the effects of the implementation of the SPs introduced during that period in several areas of the country.
Overall, we observed a remarkable difference between the North-Centre and the South and Islands, with the incidence rates in the former macro-area being much higher than in the latter. A different risk of CRC throughout the country, mainly attributed to different exposure to risk factors (e.g., diet), had already been reported.[28]
Of the areas included in the study, SPs had been implemented only in the North-Centre and showed a significant effect on incidence rates. As expected, a sharp increase in incidence was observed in the first years of screening, the prevalence round,[29] followed by a decrease that started quite soon, i.e., within 3-4 years of screening start. For subjects aged 70-79 years, the in-

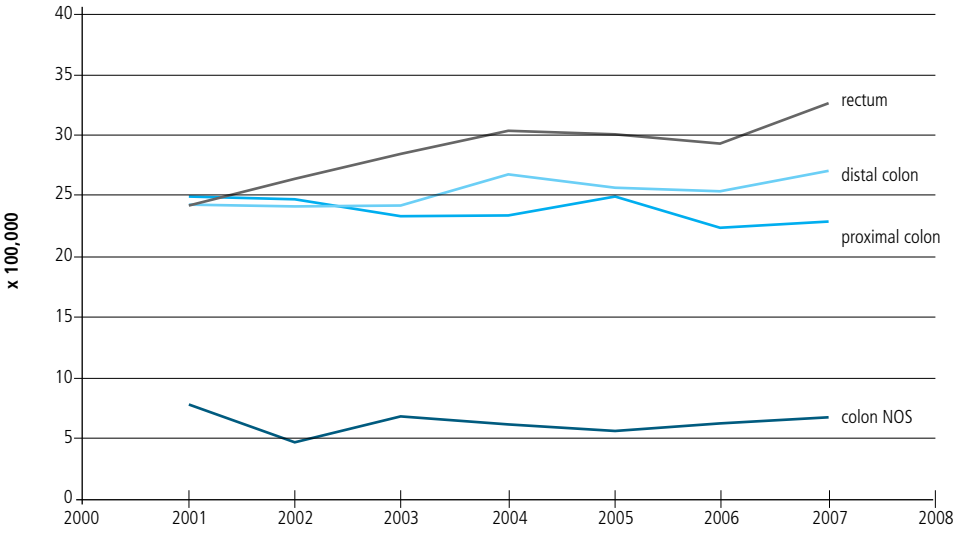

Figure 6. Trends in incidence rates (standardized Eu 2001) by anatomic site. South-Islands. Ages 40-79 years.
Figura 6. Andamento temporale dei tassi standardizzati di incidenza (popolazione europea 2001) per sede anatomica. Sud-Isole. Età 40-79 anni.

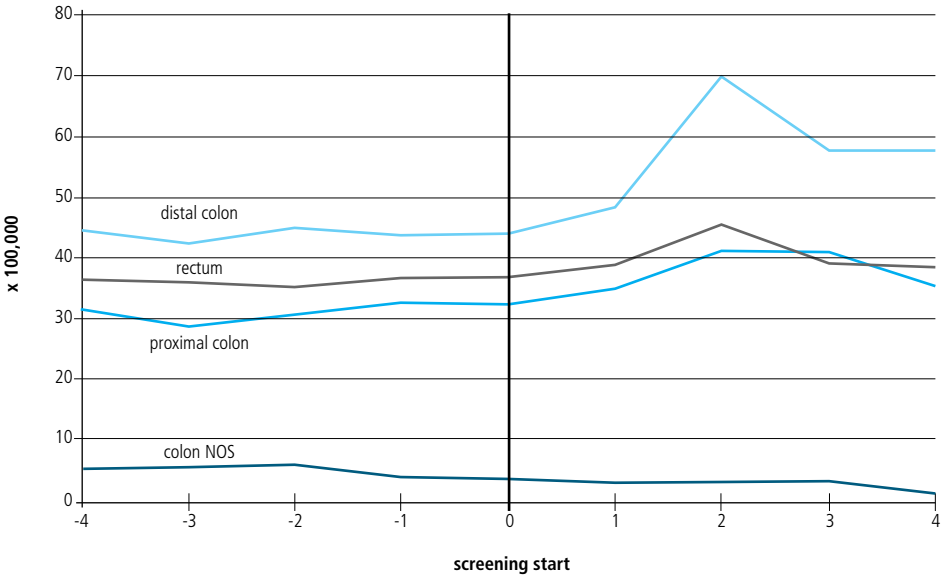

Figure 7. Trends in incidence rates (standardized Eu 2001) by anatomic site. Cancer registries only of areas with a screening programme. Ages 50-69 years. The time scale is centred on the year of implementation of the screening programme.
Figura 7. Andamento temporale dei tassi standardizzati di incidenza (popolazione europea 2001) per sede anatomica. Solo registri tumori di aree dove è attivo un programma di screening. Età 50-69 anni. La scala temporale è centrata sull'anno in cui il programma è stato attivato.

cidence trend after the prevalence round is suggestive of a decrease to values lower than the pre-screening level.

The overall increase is evident even when considering the whole age range included in the study (40-79 years), which exceeds the specific target population of screening, as well as in the national statistics regarding all ages (0-85+ years).[2] It is of utmost importance that such trends be correctly interpreted in terms of any transient effect related to the implementation of screening and not as an increased risk of CRC in the population.

SPs increased the incidence gap between macro-areas: in the South and on the Islands, no significant trend was observed, in either gender, nor in the pre-screening in those areas where screening was implemented. After the introduction of SPs, the increase in incidence was more evident in the 60-69 year age class than in the 50-59 year one. A differential effect of FIT with age has been described.[30] We also observed a small, non-significant but consistent increase in both genders and across centres, in the age classes above 70 years (probably related to a significant proportion of screen-detected cases in that age group: 15.1% in the 70-74 year class – the SP of Umbria is aimed at residents aged from 50 to 74 years). We do not have enough power to observe even considerably strong trends in the youngest age class because incidence is quite low. Nonetheless, our data suggest a decreasing trend.

These figures are highly suggestive of the expected increase in incidence rates that the introduction of SPs produces through the anticipated diagnosis of cases that otherwise would emerge later and, in part, through a (hard to quantify) number of over-diagnoses.

One relevant aspect analyzed regards the impact of screening on incidence trends by stage at diagnosis. In the areas where an SP was implemented, we recorded a pre-screening trend only for stage I cases. This could be related to a spontaneous (i.e., in the absence of a population-based SP) increased spread of colonoscopies in the population. The implementation of SPs modified exclusively the rates of stage I cases, with the "classic" pattern of initial increase and subsequent reduction in incidence. None of the other stages were affected by screening. This suggests that diagnostic anticipation takes place mainly for cases at an initial stage.

Our data do not allow us to assess the issue of over-diagnosis, mainly because the follow-up period for SPs is too short to determine whether the decrease in incidence observed beginning in the 3rd year will reach the level of pre-screening incidence or drop even lower. However, it has been argued that over-diagnosis of invasive CRC is not a worrisome phenomenon in CRC screening, because the removal of precancerous lesions (i.e., advanced adenomas) determines a relevant incidence reduction.[31-34]

Screening is expected to reduce the incidence rates of advanced stages. We did not notice such an effect, probably because the slow implementation of SPs is still delaying the end of the prevalence round. In fact, only a few programmes have invited the entire target population within the first two years, and all Italian programmes have seen quite low participation rates. Consequently, the proportion of first screening tests is very high even 3 or 4 years after programme start, due to people being invited for the first time or those who did not respond to the first invitation and decided to respond to a second one. Only a longer follow-up period and a more detailed analysis of the cohorts actually invited or participating will make it possible to confirm any effect of screening on the incidence of advanced cancers and incidence as a whole. It is worth underlining that none of the studies evaluating the impact of colorectal screening on incidence rates have found a cumulative reduction of incidence within 5 years of starting to screen,[16,20] including those based on flexible sigmoidoscopy.[35-36]

Differently from areas with SPs, both the North-Centre without SPs and the South and Islands did not record any signifi-

cant trend at any stage of diagnosis. However, notwithstanding the lower overall incidence rates, the specific rates of stage IV in the South and on the Islands were comparable to the other areas of the country. This figure may be attributed to a delay of diagnosis in this macro-area. The lack of any decrease during the study period suggests that no improvements took place to enhance the anticipation of CRC diagnosis. Thus, the widespread implementation of SPs in this macro-area seems particularly relevant.

Unfortunately, we could not evaluate incidence trends by anatomic site in the northern-central areas without SPs, due to a high percentage of missing data. In the South and on the Islands, incidence trends by site showed a significant increase for the rectum.

In areas with SPs, the pre-screening rates in the proximal colon, distal colon, and rectum were stable. After SP started, incidence increased in all anatomic sites, particularly in the distal colon. This figure is in line with the results of many studies that have shown a higher sensitivity for advanced neoplasia in the left versus right colon with faecal occult blood testing[37] and colonoscopy.[38]

The major strength of this study is the large number of cases included in the analysis and the quality of the data collected. The study is based on almost 47,000 CRCs collected by a large number of cancer registries throughout the entire country, and thus offers the best available representation of CRC epidemiology in Italy in relation to SP implementation. On the other hand, the areas included in this study represent a relevant proportion (27% overall) of the national population, but the various macro-areas are unevenly represented. Therefore, projecting our results to the whole country should be done with caution.

This study also has several limits. First, the results of this study do not exclusively reflect the performance of the screening protocols utilised by SPs (first level test and further assessment), but were very much influenced by the spread of screening in the target population, a result associated with the effective extension of invitations and compliance with the invitation to a first-level test, as well as diagnostic workup for subjects with a positive test, etc. These figures are quite different among programmes and make generalizations difficult. This implies that our results should be regarded as purely indicative of what can be expected when implementing an SP, but the figures obtained in a different setting may be very different.

Second, the study only included the few years since screening started. Therefore it could not show how long the decrease in incidence rates, following the initial peak, might last and the size of the reduction that could be achieved.

CONCLUSION

We described the trends of CRC incidence rates in Italy from 2000 to 2008, when several SPs were implemented in different areas. The differential figures introduced by the implementation of SPs warrant a continuous surveillance of CRC incidence and mortality trends to monitor the impact of screening at a national level.

Conflicts of interests: none declared

Members of the IMPATTO COLONRETTO working group:
Membri del gruppo di studio IMPATTO COLONRETTO:

Biella: A. Azzoni (S.S. Gastroenterologia, ASL Biella)
Bologna: P. Baldazzi, N. Collina, P. Pandolfi, C. Petrucci, G. Gualandi (Registro tumori di Bologna)
Catania-Messina: S. Sciacchitano, A. Ieni, F. Bella, A. Torrisi, M. Varvarà (Registro tumori integrato di Catania-Messina, Catania)
Emilia-Romagna: A.C. Finarelli, P. Sassoli de' BIanchi, P. Landi (Assessorato alle politiche per la salute, Regione Emilia-Romagna, Bologna)
Ferrara: S.Ferretti (Rewgistro tumori di Ferrara); V. Matarese (UO Gastroenterologia, AOU S. Anna, Cona-Ferrara, Italy); A. De Togni, C. Palmonari (Centro screening oncologici AUSL Ferrara)
Firenze: A. Caldarella, E. Crocetti, G. Grazzini, G. Manneschi, P. Mantellini (Istituto per lo studio e la prevenzione oncologica – ISPO, Firenze)
Friuli-Venezia Giulia: D. Serraino, E. Bidoli, M. Taborelli, A. Gini, S. Virdone (Istituto nazionale dei tumori – CRO, Aviano, PN)
Genova: C. Casella, M. Celesia, R. Cogno, E. Marani (Registro tumori Regione Liguria, UO Epidemiologia clinica, IRCCS AOU San Martino–IST, Genova)
Latina: S. Busco, E. Bernazza, S. Curatella, L. Macci, M. Rossi (Registro tumori di Latina, Latina)
Milano: G. Randi, B. Frammartino, A. Bonini, L. Filippazzi, C. Giubelli (Registro tumori di Milano, Milano)
Modena: R. Corradini, F. De Girolamo (Centro screening oncologici AUSL di Modena, Italy); K. Valla (Registro tumori di Modena, Modena)
Napoli: R. Palombino, M. D'Orsi, M. Isernia (Servizio epidemiologia e prevenzione, ASL Napoli 3 Sud); M. Fusco, M.F. Vitale (Registro tumori di popolazione Regione Campania, Napoli)
Palermo: M.S. Adamo, R. Amodio, A. Brucculeri, A. Guttadauro, W. Mazzucco (Registro tumori di Palermo e Provincia, AOU Policlinico "Paolo Giaccone" di Palermo, Epidemiologia clinica con Registro tumori, Palermo)
Parma: P. Sgarzi, F. Bozzani (Registro tumori di Parma); M. Zatelli, C. Zurlini (Centro screening oncologici AUSL Parma); P. Caruana (AOU Parma)
Piacenza: E. Borciani, G. Gatti, R. Prazzoli, P. Seghini (UO Epidemiologia e comunicazione del rischio, AUSL Piacenza)
Reggio Emilia: C. Campari (Centro screening, AUSL Reggio Emilia); E. Di Felice, C. Sacchettini, T. Cassetti (Registro tumori di Reggio Emilia)
Romagna: F. Falcini, S. Mancini, R. Vattiato, O. Giuliani (Registro tumori della Romagna, Istituto dei tumori della Romagna IRCCS, Meldola); L. Caprara (Anatomia patoligica OC S.M. della Scaletta, Imola)
Sassari: R. Cesaraccio, O. Sechi (Registro tumori di Sassari)
Siracusa: A. Madeddu, M.L. Contrino, A. Colanino Ziino, M. Russo (Registro tumori di Siracusa)
Sondrio: A.C. Fanetti, S. Maspero, E. Moroni, I. Cometti (Osservatorio epidemiologico - Registro tumori della Provincia di Sondrio)
Trentino: M. Gentilini (Registro tumori di Trento); G. De Pretis (UO Gastroenterologia, Ospedale S. Chiara, Trento); P. Caciagli (Dipartimento laboratorio e servizi, APSS, Trento); R. Pertile (Servizio epidemiologia clinica e valutativa, APSS, Trento)
Umbria: F. Bianconi, G.M. Masanotti (Registro tumori umbro di popolazione / Scuola di specializzazione in Igiene e medicina preventiva, Università di Perugia); M.C. De Lio (Scuola di specializzazione in Igiene e medicina preventiva, Università di Perugia); S. Leite (Registro tumori umbro di popolazione); B.U. Passamonti (Servizio di screening USL 1 Umbria)
Veneto: A.P. Dei Tos, A. Rosano, D. Monetti, S.Guzzinati, S. Tognazzo (Registro tumori del Veneto, Padova)

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