Preventive Medicine 57 (2013) 220–226

Contents lists available at SciVerse ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Screening patterns within organized programs and survival of Italian women with invasive cervical cancer

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ARTICLE INFO

Available online 1 June 2013

Keywords:
Cervical cancer
Organized screening program
Screening history
Cytology

ABSTRACT

Objectives. To evaluate screening patterns within organized cervical screening programs (OCSPs) and survival of women with invasive cervical cancer (ICC).

Methods. A population-based study was conducted in Italian areas covered by cancer registries and OCSPs. The study included all women aged 25–65 years diagnosed with ICC between 1995 and 2008, and their screening histories within OCSPs were retrieved. Hazard ratios (HR) of death and 95% confidence intervals (CI) were computed according to screening pattern, using Cox models adjusted for age, ICC stage, and major confounders.

Results. Among 3268 women with ICC, 20% were never-invited to OCSP, 36% were never-compliant with OCSP's invitation, 33% were compliant and had a screen-detected ICC within OCSP (i.e., after a positive cytology), and 11% were compliant but had a non-screen-detected ICC. Screen-detected ICCs were more frequently micro-invasive (42%) compared to non-screen-detected ones (14%). Compared to women with screen-detected ICC, the adjusted HRs of death were 1.9 (95% CI 1.5–2.4) for those never-invited, 2.0 (95% CI 1.6–2.5) for never-compliant, and 1.7 (95% CI 1.3–2.4) for compliant women having non-screen-detected ICC.

Conclusion. Prolonged survival, beyond down-staging, of women with ICC detected within OCSPs in Italy, further calls for improvements of OCSPs' invitational coverage and participation.

Abbreviations: ICC, invasive cervical cancer; OCSP, organized cervical screening program; CR, Cancer Registry; ICD, International Classification of Diseases; NOS, not otherwise specified; OR, odds ratio; HR, hazard ratio; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; WHO, World Health Organization.

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0091-7435/$ – see front matter
http://dx.doi.org/10.1016/j.ypmed.2013.05.018

Introduction

It is well established that cervical cancer screening can strongly reduce invasive cervical cancer (ICC) incidence and mortality (IARC, 2005). ICC incidence decreased in Italy in the last 30 years, suggesting that screening was effective in Italy too (Bray et al., 2005). Organized cervical screening programs (OCSPs) may achieve high participation at regular intervals, equity of access, and high quality standards for diagnosis and treatment, thus being potentially more effective and cost-effective than opportunistic screening (i.e., left to a woman's initiative) (Arbyn et al., 2008, 2009; IARC, 2005; Nieminen et al., 1999; Quinn et al., 1999).

Italian OCSPs, following European guidelines (Arbyn et al., 2008), invite the target population (i.e., women aged 25–64 years) to perform a free-of-charge cytological test every three years. Started mostly in the mid '90s, OCSP's implementation was local with regional co-ordination. Data on invitations, cytologies, colposcopies, and histologies performed within OCSPs and process indicators are routinely produced (Ronco et al., 2012), showing wide geographical differences with regard to the ability of OCSPs to reach the target population. In 2010, 80% of the Italian target population lived in areas covered by OCSPs (67%, 97%, and 88% in North, Centre, and South, respectively). The proportion of target population regularly invited was 61% (58%, 76%, and 55% in North, Centre, and South, respectively) and the percentage of invited women who complied was 40% (49%, 38%, and 28% in North, Centre, and South, respectively). Opportunistic activity is also present in Italy. A national survey (PASSI, 2011) estimated that, in 2008–2011, 75.4% of Italian women aged 25–64 years had had a cytology within or outside OCSPs in the previous three years (83%, 81%, and 61% in North, Centre, and South, respectively).

The extent of screening coverage and population attendance are essential components of OCSPs' success, along with diagnostic, treatment, and follow-up paths. Monitoring these steps, therefore, allows for the identification of potential shortcomings in OCSPs (IARC, 2005; Ronco et al., 2005). In Italy, epidemiological studies to identify potential limitations of OCSPs have not been conducted at a national level yet. Audits based on linkage between screening and cancer registry data were available only for few Italian areas (Ronco et al., 2005; Zucchetto et al., 2010).

In order to identify strengths and limitations of OCSPs at a population level, and to evaluate screening patterns associated with survival, we retrieved screening histories within OCSPs of women with ICC identified by cancer registries (CRs).

Methods

This study was conducted in 17 Italian areas concurrently covered by population-based CRs and by OCSPs for at least three years (i.e., one screening round) (Appendix A). These areas included about 31%, 23%, and 10% of the resident population in northern, central, and southern Italy, respectively. This study included 3268 women aged 25–65 years (i.e., 1 year over OCSP target), out of 5308 women with a histologically confirmed diagnosis of ICC identified by CRs (International Classification of Diseases 10th revision: C53.3 – death certificates only excluded) in the period 1995–2008. Excluded women were those aged above 65 years (1924), younger than 25 years (17), or without screening information (99).

Tumor histological type (according to the International Classification of Diseases for Oncology 3rd edition and WHO classification) and stage at diagnosis (according to the International Federation of Gynecology and Obstetrics, FIGO) were retrieved from clinical charts. ICCs diagnosed at stage IA or IA1 were considered as micro-invasive.

CRs carried out a record-linkage with the local OCSPs to retrieve individual data on date of first invitation (or reason for non invitation), date of first cytological test within OCSP, presence of at least a positive or unsatisfactory cytology (according to the 2001 Bethesda System; Solomon et al., 2002), and date of the last negative cytology – if any. Women with ICC were classified according to the following screening patterns (Fig. 1):

- Never-invited (i.e., not yet having received an invitation to OCSP)
- Ever-invited (i.e., having received an invitation to OCSP)
  - Never-compliants (i.e., invited with no cytology within OCSP)
  - Ever-compliants (i.e., invited with at least one cytology within OCSP)
    - Compliants with OCSP invitation who had a screen-detected ICC (i.e., with atleast a positive/unsatisfactory cytology). Within this group, women were classified according to time elapsed from the date of the last negative cytology, if any, and ICC diagnosis (<3.5 or ≥3.5 years).
    - Compliants with OCSP invitation who had a non-screen-detected ICC (i.e., with only negative cytologies). Within this group, women were classified according to the time elapsed from the date of the last negative cytology to ICC diagnosis (<3.5 or ≥3.5 years)

The time elapsed from OCSP's start to ICC diagnosis was approximated by the difference between the calendar year of ICC diagnosis and the year of OCSP start in the relative area (Appendix A).

Statistical analyses

Associations between screening patterns and characteristics of women and ICCs were evaluated by odds ratios (ORs), and corresponding 95% confidence intervals (CIs), estimated using bi- or multi-nomial logistic regression models adjusted for quinquennia of age, and further adjusted for time between OCSP start and ICC diagnosis when appropriate (Hosmer and Lemeshow, 2000). Survival analysis was conducted on 2911 (89.1%) women with information on vital status. Each woman accumulated person-time from ICC diagnosis to death or last available follow-up (i.e., 31st December 2008–2010, depending upon areas), whichever came first. The Kaplan–Meier method was used to generate crude survival curves and the log-rank test to assess differences between sub-groups (Kaplan and Meier, 1958). Hazard ratios (HRs) of death for any cause were computed using Cox proportional hazard models, adjusted for age at diagnosis (quinquennia), area of residence, country of birth, screening patterns, histological type, and with or without adjustment for tumor stage (Cox, 1972).

Results

Of the 3268 studied women with ICC, 657 (20.1%) had never been invited by OCSPs, 1181 (36.1%) had never complied with invitation, and 1430 (43.8%) complied (Fig. 1). The ICC was screen-detected in 1075 women (32.9% of the studied women), including 809 women who had only positive/unsatisfactory cytologies within OCSPs. Among the 355 (10.9% overall) compliant women who had a non-screen-detected ICC, 200 had the last negative cytology <3.5 years before ICC diagnosis and 155 ≥3.5 years before ICC diagnosis. Overall, 366 women (11.2% of all those with ICC), including 200 with screen-detected and 166 with non-screen-detected ICC, had had a normal cytology less than 3.5 years before diagnosis (Fig. 1).

Table 1 shows the distribution of women with ICC by OCSP invitation according to selected variables at ICC diagnosis and the corresponding ORs of never having been invited. Non-invitation was significantly higher at the beginning of OCSPs' activity (never-invited women were 32% among those with ICC diagnosed 0–2 years since OCSP's start vs. 9% among those diagnosed ≥6 years later, OR = 4.6). Non-invitation was also significantly associated with age (lower among women aged 55–65 vs. 25–54 years, OR = 0.7), area of residence (higher in southern, OR = 2.7, and lower in central, OR = 0.6, vs. northern Italy), and country of birth (higher for women born abroad vs. Italian natives, OR = 2.2).

Among 2611 women with ICC previously invited to OCSP (Table 2), non-compliance was significantly lower at the beginning of OCSPs' activity (40% of women with ICC diagnosed 0–2 years since OCSP's start never complied vs. 47% of those diagnosed ≥6 years later, OR = 0.8). Non-compliance increased with age (48% of those aged 45–65 years vs. 37% of those <35 years never-complied) and was significantly associated with area of residence (higher in southern, OR = 4.9, and lower in central, OR = 0.8, vs. northern Italy).

Table 3 shows the distribution of the 1430 women who were compliant with OCSP's invitation, according to whether or not the ICC was detected at screening. Women living in northern Italy had the highest