



Review

The Role of Vaccination and Screening in Limiting the Worldwide Disease Burden of Preventable Female Cancers: A Review

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Abstract: Cancer represents one of the most common causes of death worldwide. Among women, breast cancer is the most diagnosed cancer and the principal cause of death due to malignant disease, while cervical cancer ranks fourth for both incidence and mortality. The present review aims to analyze the epidemiology of cervical and breast cancer (incidence, mortality, survival rates, and trends). Moreover, the most important primary and secondary preventive strategies (reduction of risk factors, exposure, vaccination, cancer screening) intended to reduce the future burden of cervical and breast cancer, that should be adopted actively and free of charge, were discussed in accordance to more recent and evidence-based findings.

Keywords: women; female cancer; cervical cancer; breast cancer; cancer screening; vaccination; prevention

1. Background

Worldwide, cancer represents one of the most common causes of death among women, both in high-income and middle-income countries [1].

Over the last decade, the cancer burden is expanding in countries with low income levels, whereas an increasing average of life expectancy, due to public health measures such as prevention of infectious diseases and reductions in maternal, infant, and childhood mortality, contribute to the growth and aging of the general population [1,2].

Risk factors for female cancer can be classified in two main classes: cancer associated to exposures like men and those exposures and forms of cancer unique to women [1].

The economic transition with an exposure to new risk factors, such as smoking and sexual habits, excess body weight and physical inactivity, has been playing a major role in this increasing trend [3,4]. Due to these transitions, cancers that were previously common in high-income areas are becoming more prevalent also in low- and middle-income areas [5].

Moreover, changes in reproductive patterns, such as a later age at first childbirth and lower parity, have contributed to the higher female cancer burden worldwide [6]. In addition to the morbidity and mortality burdens, cancer diagnoses worldwide carry a considerable economic impact on health systems, including direct costs, mostly the ones related to treatment; and indirect costs, such as the ones charged to the families or the society according to loss of income or productivity [7].

Other quantifiable costs, such as time spent by caregivers, transportation, and assistance at home, could be associated with cancer diagnosis and treatment [8].

Furthermore, cancer burden and the associated incremental costs can also be related to the improvement in cancer survival both in high- and low-income countries [8,9]. In particular, patient survival rates vary across the different types of female cancers and are largely dependent on the stage at which a particular cancer is diagnosed [9].

For all these reasons, cancer prevention and early detection are necessary in high and low resource settings in order to limit the impact of this disease [10].

Primary prevention could prevent about one-third to half of cancer cases limiting the exposure to well-known risk factors [10]. Vaccinations, such as the ones against human papillomavirus (HPV) and hepatitis B, health education, prevention of smoking or drinking habits, positive lifestyles (such as healthy nutrition and/or physical activity) represent the basic preventive strategies in order to prevent cancers in both sexes [11].

Moreover, secondary prevention, such as cervical, breast, and colorectal cancer screening, can detect precancerous lesions or cancer at early stages [12,13].

We review here the scientific literature to summarize the epidemiology and to highlight the most recent findings in primary and secondary prevention of cervical and breast cancers, two of the major public health issues related to cancers occurring among women.

2. Epidemiology of Cervical Cancer

Cervical cancer (CC) represents the fourth most common female cancer in the world, with more than 500,000 new cases and 300,000 deaths estimated yearly [14,15].

Incidence rates of CC are highest in women 35 to 44 years old, whereas the highest rates of ovarian or uterine cancer are documented in women aged 55 to 64 years (median age at diagnosis: 63 years) [16,17]. Of note, the median age at diagnosis of CC is 49 years [18]. While the highest incidence for CC was registered among Hispanics with approximately 10.9 new cases per 100,000 persons, 13.3 incidents per 100,000 ovarian cancer cases resulted more frequently in white women [19].

Over the past three decades, incidence of CC has halved, prominently due to HPV vaccination and progressive extension of Pap-test screening [19,20].

Since 2006, the availability of three vaccines against the human papillomavirus (HPV) has allowed a reduction of HPV infections and will likely influence the burden of HPV-associated diseases, including CC [21,22].

While incidence rates of uterine, vaginal, and vulvar cancers have remained relatively stable over the last decade, cervical cancer diagnoses have tended to occur earlier in the disease process due to adoption of secondary (cervical cancer screening) preventive strategies [19,23].

The median age of deaths due to CC is 57 years, with specific mortality rates that are twice those among black women than white women [24].

Factors associated with an increased risk for CC include HPV infection, smoking, immunosuppression (either from human immunodeficiency virus infection or from immunosuppressive drugs), chlamydia infection, long-term use of oral contraceptives, reproductive history (number of pregnancies), younger age at first full-term pregnancy, high deprivation index and family history of CC [25,26].

HPV infection is recognized as the main risk factor for cervical cancer, accounting for more than 90% of all CC [19,22,27]. By contrast, use of intrauterine devices was associated with a decreased risk for CC [28].

3. Epidemiology of Breast Cancer

With over 2 million cases annually, breast cancer (BC) is the most common cancer diagnosed and one of the most significant causes of death among women [29,30]. Although this neoplasia occurs all over the world, incidence, mortality, and survival rates change considerably among different countries, relative to population structure, genetic factors, lifestyle, and environment [31].

BC incidence rates range from 27 per 100,000 in Central Africa and Eastern Asia to 92 per 100,000 in North America and around 100 per 100,000 in European countries, representing the fifth most common cause of death from cancer in women, with 522,000 deaths estimated every year [29].

The risk of BC doubles each decade until menopause (after which it slows) and diagnosis is generally more common after menopause.

Previous research conducted among women who migrated from areas of low risk (less developed countries) to areas of high risk (more developed countries) showed that they assume the host country incidence rate of BC, within one or two generations, confirming the fundamental role of environment.

As a matter of fact, BC is a multifactorial disease and various factors contribute to its occurrence (such as a familial history of breast cancer, dietary effects combined with later first childbirth, lower parity, and shorter breastfeeding) [32].

Despite BC having been the subject of several epidemiological studies, the understanding of its aetiology remains under investigation and there are still some preventable factors missing and yet to be identified [30].

Hormones (both exogenous and endogenous) have a recognized role in BC risk among women and, specifically, oral contraceptives are associated with increased risk of BC in women up to 38 years old, even if they have a role in the prevention of ovarian and endometrial cancer [33].

Oestrogen therapy as hormonal replacement increased the risk of endometrial cancer and the association with BC could not be excluded [34,35].

In order to design targeted breast cancer screening programs and to improve risk-free methods, a classification of women with BC diagnosis in accordance with risk factors could be considered [36]. Nowadays, overall survival rates for BC vary among different countries and generally it depends on adherence to breast cancer screening programs of the general population [1].

Although breast cancer screening can substantially reduce the burden of BC, some side effects, such as over-diagnosis and the related increased costs, represent possible disadvantages and could lead the general population to limited access to this fundamental preventive strategy, applied in order to reduce mortality and increase survival rates [36,37].

4. Strategies for Prevention of Cervical Cancer

4.1. Primary Prevention: HPV Vaccination

Vaccination against HPV represents the best strategy for primary prevention of cervical cancer [38]. HPV vaccines could effectively prevent pre-cancerous cervical lesions when administered before the start of sexual activity (and virus exposure) and, therefore, the World Health Organization (WHO) recommends offering HPV vaccination to all pre-adolescent girls and boys [38].

Since 2006, the HPV vaccination has been introduced through national immunization programs for girls in 71 countries, and for boys in 11 countries [22].

In 2006–2007, the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) approved two HPV vaccines containing respectively four (6, 11, 16, and 18—quadrivalent) and two antigens (16 and 18—bivalent) against HPV-serotypes [23].

Finally, in 2015, a vaccine extending antigens to five more HPV-serotypes (31, 33, 45, 52, and 58—nonavalent) in addition to the ones contained in the quadrivalent vaccine, was licensed, extending the protection against oncogenic circulating HPV-serotypes to more than 90% [22,23] (Table 1).

The current HPV vaccination programs are mainly dedicated to preadolescents (age range 9–14 years) as primary targets, either through organized school-based vaccination plans or delivered through primary care services (including general practitioners, paediatricians, nurses, obstetrics, and gynaecologists). Moreover, according to the information provided by the Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP), HPV vaccination is also recommended for everyone by the age of 26 [38,39].

Vaccine	Number of Doses and Timing of Human Papillomavirus (HPV) Vaccination	HPV-Serotypes Included in the Vaccine	Coverage of Circulating Oncogenic HPV-Serotypes
Bivalent Quadrivalent Nonavalent	2: 0, 6 months if ≤14 years old 3: 0, 2, 6 months if ≥5 years old	16, 18 * 6, 11, 16, 18 * 6, 11, 16, 18, 31, 33, 45, 52, 58 *	Around 75% Around 75% Around 90%

Table 1. Human papillomavirus (HPV) vaccines licensed and approved by international health authorities.

After ten years since the introduction of the vaccine and sixteen years of cervical cancer screening availability, a decrease in hospital admissions for CC and other HPV-related diseases was observed in several contexts [20,21]. Decreasing hospitalization rates could be attributable to several factors, including HPV vaccination, which reduces HPV infection and carcinogenesis [20]. Adherence to cervical cancer screening programs and a level of compliance over time to these preventive practices had a key role in hospitalization rates and mortality reduction as well [23].

Instead, the documented decrease in cervical cancer incidence was mainly due to HPV vaccination. In 2014, HPV vaccination coverage reported in EU countries reached about 50% in the primary target, while in African countries a mean of 88% HPV vaccination coverage rates (VCRs) was reported [40].

A study on HPV VCRs over 31 European countries reported data largely unsatisfactory, with adherence to HPV vaccination ranging \geq 71% (high) in ten countries, 51–70% in seven, 31–50% in four, and \leq 30% (very low) in four [41].

Several factors were recognized as associated with HPV vaccine refusal, such as the education level of parents, which was discussed in several studies evidencing a discordant trend [42–44]. In England, Jean et al. showed that Local Health Units (LHUs) with higher deprivation levels had higher VCR of HPV vaccination for all doses [45]. In this and similar studies, young adults with a lower educational level had better literacy on HPV disease and vaccination and, consequently, higher rates of HPV VCRs [46,47]. Furthermore, a survey conducted in Sicily documented that only a very small proportion of medical students believed that genital warts can be the most frequent clinical presentation of sexually transmitted infections [48]. Of interest, a very high reduction of CC as a consequence of HPV vaccination introduction into vaccination schedule was observed in the Sicilian region (–64% in ten years), where vaccination has been offered for free to female adolescents since 2006, as compared to data reported in Italy or in other European countries as a whole (25–40%) [20,21,23].

Moreover, a decreasing trend in the incidence of vulvar cancers was observed among older women in Western countries, particularly in Italy, resulting in a decrease in total rate [49].

4.2. Secondary Prevention: Cervical Cancer Screening

The main tests available for cervical cancer screening are Papanicolau (Pap) test, offered every three years to women between the ages of 25 and 30 (and until 64 years old in other countries that had not introduced other screening tests), and the human papillomavirus DNA testing (HPV-DNA test) offered every five years to women between 30 and 64 years old [50,51] (Table 2).

Cervical Cancer
Screening TestTimingAge RangeConfirmation Test for
PositivePapanicolau (Pap) testEvery three years25-64 years or 25-31 years
(if associated with HPV-DNA test)ColposcopyHPV-DNA testEvery five years31-64 yearsPap test and colposcopy

Table 2. Cervical cancer screening tests authorized by international health authorities.

Even though the test used so far has been the Pap test, recent scientific evidence has found that over 30 years of age the most cost-effective is the HPV-DNA test [52,53].

^{*} In boldface oncogenic serotypes.

The mortality reduction for CC that can be achieved by a universal screening program depends on several factors [54].

These include the epidemiology of HPV infection in the population and the characteristics of the screening program, including type of offer, starting and stopping ages, performance of screening activities (calculated as sensitivity and specificity) screening interval, adherence and quality of follow-up [55].

These parameters can vary among different countries and regions and the observed reductions in CC mortality could also vary [56,57].

Several studies reported a reduction in CC mortality in women attending screening compared with non-attendees, although not all studies reported whether there was a significant reduction [58]. In cohort studies conducted among women that attended organized screening programs, the CC mortality reduction ranged between 17% and 79% in Northern Europe [59].

Moreover, a reduction ranging between 51% and 86% of CC mortality was observed in women participating in an organized screening program, corrected for self-selection bias [60].

Additionally, a systematic review showed that data on efficacy of the HPV screening in CC mortality reduction were consistent in randomized intervention trials and observational studies conducted in many countries [61].

Many countries are planning to modify their screening program, and among them Italy has stated the intention to implement the new screening test based on the search for high risk HPV infection at the end of 2020 [51]. If the HPV test is positive, the woman must undergo a Pap test which could appropriately select women who have cellular changes and should proceed with the colposcopy.

If the cytology does not show important alterations, the HPV test will be repeated after one year [51].

Instead, from age 25 to 30 the reference remains the Pap test to be performed every three years. HPV-DNA tests demonstrated higher sensitivity and specificity than cytology in identifying cervical intraepithelial neoplasia or cancer in women aged \geq 31 years old [62,63].

These results should be used as a benchmark for using similar screening tests in other countries [64]. In Europe, 63.6% of the target populations of any age and 59.2% of aged 30–59 years were invited for cervical screening [65].

Only 26.1% of the target population (any age) had cervical screening after invitation (29.8% restricted to the age range 30–59 years) [65]. However, the previous coverages did not include opportunistic activity [66].

Exploring reasons associated with CC screening adherence is essential. Several factors could reduce cervical cancer screening rates including low educational level, poor self-reported health status, country of origin, and having a comorbidity [67,68].

Lastly, it was discovered that counselling from obstetrician-gynaecologists has higher CC screening adherence rates among patients than counselling from a general practitioner (GP) or other physician which were, in any case, positively associated with Pap testing adherence [69].

5. Strategies for Prevention of Breast Cancer

5.1. Primary Prevention: Removing Risk Factors

Several risk factors for BC have been documented and some of these could be prevented through correct lifestyles [70,71].

Immutable factors include how a familial history (first-degree relative or multiple family members) of BC increases the risk similar to a personal history of breast cancer or certain non-cancerous breast diseases such as atypical hyperplasia [72,73].

Moreover, older age and some genetic mutations, particularly in BRCA1, BRCA2, and p53 genes are strongly related with breast cancers, especially at younger ages [73,74].

Differences in BC incidence between developed and developing countries were probably associated with different modifiable factors [71] (Table 3).

Modifiable Factors for Breast Cancer	Increased Risk	Decreased Risk
Childbirth	Later	Prior
Parity	Nulliparity or Lower	Higher
Breastfeeding	Short or null	Long
Menarche	<12 years	≥12 years
Menopause	≤55 years	>55 years
Oestrogen exposure	Prolonged oral contraceptive or hormone replacement therapies	No hormonal therapies
Dietary habits	Diet rich of animal fat and proteins	Diet rich of fruit and vegetables (Mediterranean Diet)
Physical activity	Inactive	Active
Alcohol	High intake	Low or no intake
Weight	Overweight or obesity	Normal weight

Table 3. Risk and protective modifiable factors associated with breast cancer incidence.

With regard to modifiable risk factors, a prolonged exposure to endogenous oestrogens, early menarche (<12 years), late menopause (>55 years) or oral contraceptive and hormone replacement therapy, are all associated with an increased risk of BC [75,76].

Furthermore, some factors related to pregnancy such as late age at first childbirth or nulliparity increase the risk of a BC diagnosis, while breastfeeding is a protective factor [77]. Also, later first childbirth is associated with higher incidence rate of breast cancer [71].

High alcohol intake, overweight and obesity, unhealthy diet and physical inactivity are known risk factors as well [78–80]. A diet based mainly on a prevalent intake of vegetable fat and proteins and a limited intake of animal fat and proteins (such as reported by the principles of the Mediterranean Diet), was strongly associated with lower levels of endogenous estrogens in healthy postmenopausal women.

The dietary components of this diet more effectively decrease estrogen levels and could represent preventive measures for BC [81,82].

Moreover, previous treatment using radiation therapy to the chest or breasts (like for treatment of Hodgkin's lymphoma) has been also associated with BC insurgence [83].

5.2. Secondary Prevention: Breast Cancer Screening

Mammography is the elective screening modality recognized to reduce BC mortality [84]. Furthermore, particularly in a dense breast (typical of younger women), supplemental screening for BC with other imaging modalities such as ultrasonography should be considered [85,86].

An ecological study confirmed a positive association between the implementation of organized mammography screening programs (MSPs) and the reduction over the last decades of BC mortality rates throughout western European countries ranging from -1.5% to -5.4% (50–59), -0.2% to -8.1% (60–69) and 0% to -7.1% (70–79) [87].

Approximately 95% of the 67.5 million women aged 50 to 69, who the European Council recommended as an eligible age for BC screening, were screened in the European Union in 2016 [65]. These women were residents of member states that have adopted policies to plan and implement BC population-based screening programmes [65].

Specifically, among 13.1 million mammography tests performed, the overall detection rate for carcinoma in situ (CIS) and invasive breast cancers (defined as "malignancy detection rate") was of 6.2 per 1000 women screened in the age range 50–69 years, while for the age groups 45–49 years and 70–74 years the rate was of 4.3 and 9.5 per 1000, respectively [65].

An effective breast cancer screening program also increases the incidence of cancer detected at an early stage and decreases the incidence of cancer presenting at a later stage [88,89].

European guidelines suggest no screening for women aged 40 to 44 years, whereas the incidence of BC and mortality increases with age and the absolute health benefits are greater in women aged 45 to 49 than those aged 40 to 44 years [89].

Studies report that BC mortality rates are higher amongst women of more deprived areas who are less likely to attend breast cancer screening programmes [90].

For asymptomatic women aged 45 to 49 years without a high risk for BC, guidelines suggest a mammography screening every 2 or 3 years, while for women aged 50–69 a screening every 2 years, and lastly for women aged 70–74 every 3 years [89].

This data was confirmed in the 2017 Report of the European Commission about cancer screening, highlighting that the age range 50–69 years is the widest target for breast cancer screening recommended by the European Council (approximately 32 million women per year) and it is common to most of the national programmes of European countries [90].

The participation rate to screening programs in the entire EU in 2013 for the age group 50–69 years was 60.2% on almost 24 million total invitations, while for 45–49 years it was 68.9% and for 70–74 years 60.4% (on less than 1 million invitations each) [65].

Despite these results, there are still some barriers to a complete adhesion to breast screening programs such as lack of awareness and of correct information, misperceptions and wrong attitudes toward health, femininity and cancer prevention (often futile reasons such as forgetfulness, laziness, or lack of time) [91–93].

General practitioners could also play a role in such communication by providing scientifically sound information on breast cancer screening [94].

Novel technologies could help in the early diagnosis of BC and could integrate or substitute the actual procedures used in breast cancer screening [95,96].

Lastly, advanced technological methods such as next-generation targeted panel sequencing demonstrated a fundamental role for the evolution of future BC screening programs [97]. These most recent promising and accurate modern techniques of precision oncology are actually not available on a large scale and their role should be considered in cancer screening and diagnosis-related fields [98].

6. Conclusions

The review of the scientific literature allowed us to document an up-to-date epidemiological picture and at the same time to highlight the effectiveness of vaccination and screening in limiting the burden of the disease of cervical and breast cancers, two of the main preventable female tumours.

Among females, BC is the most commonly diagnosed cancer and the leading cause of cancer death, while CC ranks fourth for both incidence and mortality [99].

In particular, within gynaecologic cancers, the ones originating in the female reproductive organs, CC is in the top five of the main types of female tumours [99].

A number of common cancers among females, and above all cervical and breast neoplasia, have known means of prevention and/or early detection which can be applied in resource-appropriate settings [17]. To counteract the burden of the female cancers recalled, anti-HPV vaccination and preventive measures against risk factors represent the main primary prevention strategies, while mammography and cervical cancer screening are the most effective approaches.

On one side, the global burden of cancer among women is considerable but on the other, there is a significant potential to reduce morbidity and mortality due to female cancers, as well as to alleviate the economic impact of these diseases on individuals, families, and healthcare systems [1].

Moreover, dedicated prevention protocols should be considered to protect vulnerable populations like female migrants/refugees, considered at higher risk for CC incidence, whereas evidence suggests that women with a migration background of BC tend to acquire the same exposure risk of and are less likely to participate in mammography screenings than autochthonous women [100–102]. In the

future, preventive measures should be adopted to limit the burden of incidence and mortality of female cancers and be actively offered to the general population in developed and less developed countries.

The contrast of health inequalities should be considered a priority for international public health institutions by improving access to preventive interventions (such as HPV vaccination) or early diagnosis (such as cervical and breast cancer screening).

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