

## The Socio-Economic Cost of Vulvovaginal Atrophy (VVA) in Breast Cancer Survivors: An Italian Expert Consensus Statement On VVA Management

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### Abstract

**Background:** VVA (vulvo-vaginal atrophy) is a common condition in menopause. Recent data confirmed that VVA is more frequent and severe in patients treated for Breast Cancer (BC) with a relevant impact and burden of illness, along with significant additional economic and social costs.

**Methods:** This Consensus Document represents the collective opinions of an Italian Expert Panel on the clinical topic of VVA management. A Delphi Panel methodology was used: a first round of written questionnaires, followed by a face-to-face meeting with a facilitator and by two additional rounds of telephone interviews.

A US micro-costing study has been the reference for clinical results, while the US data were used to "benchmark" the Italian findings.

**Results:** Prevalence of VVA in Italy can be estimated in 115,000 cases out of 380,000 BC survivors. Approximately 76,000 of these cases would need treatment.

The Panel also confirmed an estimate of 4.25 additional cases/100/year of urinary tract infections (UTIs), of 3.68 additional cases of vulvovaginitis and of 6.97 cases of climacteric symptoms in BC patients with VVA.

In addition, as a potential consequence of VVA, 33.4 additional gynecological visits/100/year can be expected, along with 18.48 additional cancer screenings, 2.53 additional outpatient visits and 3.2 screenings for HPV. These findings translated

Binto an additional cost of over 12.5 million Euros/year for the NHS.

**Conclusions:** The VVA diagnosis is still an underestimated condition with a significant increase in costs compared to a control population matched for age that did not report VVA. This is essentially due to an increase in co-morbidities and resource utilization. Therefore, an adequate treatment could offset a significant amount of these costs

**Keywords:** Vulvo-vaginal Atrophy; VVA; Cost; Pharmacoeconomics; Consensus; Breast Cancer

## Introduction

Interventions to restore quality of life in cancer patients are becoming an important topic in the health-care policy worldwide. Knowing the cost of cancer treatment is crucial for managing health systems efficiently. Nowadays, the follow-up of oncological patients must consider the overall burden of cancers, which is linked not only to the incidence, prevalence and mortality, but also to significant disruption of daily living and potential disability [1-4].

Breast cancer (BC) is the most widespread female cancer with an estimated 2.3 million new cases in 2020. Recent statistics indicate a worldwide increased incidence rate of breast cancer diagnosis, while breast cancer mortality remains stable [5].

Therefore, an increased number of long-term breast cancer survivors (BCSs) experience the symptoms and complications caused by pharmacological and surgical interventions. Indeed, these patients frequently report symptoms linked to iatrogenic drug-induced menopause. The rapid endocrine changes, mainly related to the sharp decrease in estrogen levels, may induce hot flashes, night sweats, fatigue, insomnia, mood swing, arthropathies, as well as may have several consequences for women's health, including osteoporosis, cardio-metabolic risks and cognitive alterations. A very important aspect of quality of life is described in the new terminology "Genitourinary Syndrome in Menopause (GSM)", which includes disabling signs and symptoms previously named vulvovaginal atrophy (VVA) associated with sexual dysfunctions, vaginal and urinary infections, and urinary incontinence [6].

Vulvo-Vaginal Atrophy (VVA) is a symptomatic condition affecting more than 50% of all postmenopausal women [7-9] and the size of the problem is growing, since a great number of

women are expected to spend more than one third of their life in the postmenopausal state.

Patients undergoing iatrogenic menopause for cancer treatments such as BC patients show severe symptoms of VVA, even more after completion of their therapeutic oncological plan [10]. Up to 75% of BCSs suffer from one or more VVA symptoms. Indeed, women using endocrine therapy for breast cancer - like aromatase inhibitors - experience an extreme state of hypoestrogenism. Dryness may be exacerbated by superimposed infections, burning, itching, bleeding, leucorrhea, and dysuria.

In particular, young women undergoing adjuvant breast cancer therapy report a heavy impairment in several Quality of Life domains, including sexuality. Targeted support interventions are needed in this regard, since in more than 60% of these patients dyspareunia is present, alone or associated with other sexual dysfunctions [11,12].

Numerous studies describe the burden of disease and the impact of VVA on quality of life and relationship [13,9,14]. A recent pan-European cross-sectional study in postmenopausal women, including Italian patients, confirmed the negative impact of moderate to severe VVA, and a number of studies have shown that the clinical manifestations of VVA will be more relevant in patients with a history of BC [15].

The disparity between the high prevalence and the relatively infrequent clinical diagnosis of VVA is documented in medical practice and in several surveys [16]. This inaccuracy is thought to be primarily a consequence of patients' unwillingness and/or embarrassment to report symptoms to their health-care professionals (HCPs) along with some barriers during the consultation [11,12].

The result of this under-diagnosis is a chronic and progressive condition that may not be addressed for a considerable

period, and therefore may be more likely to undergo disease progression when left untreated). Considering the fact that VVA is a relevant problem for BCs, all efforts should be done to correctly inform HCPs about such condition and its related problems, as well as the different possible available treatments [17,18].

According to the most recent guidelines, local estrogen therapy (LET) is the standard of care for VVA symptoms in healthy women, but in BC patients particular caution should be used [17-19]. Lubricants and moisturizers are the first-line therapy, but they provide only poor benefit. Much debate is ongoing on the safety of prescription of LET, in particular very low dose estrogens or prasterone, while new drugs as the SERM ospemifene and some non-pharmacological therapies represent possible new approaches [20,21].

Women with VVA often suffer from associated comorbidities, leading to increased exploitation of healthcare resources. In fact, in a survey conducted on 9080 women aged 40-79 at baseline, a significantly higher proportion of women in the VVA cohort had a concomitant diagnosis of angina, osteoporosis, migraine, insomnia, or anxiety, or received estrogen supplementation or selective estrogen receptor modulators. Moreover, VVA had a significantly higher incidence of genitourinary conditions compared to controls [22].

Recently, we published a study analyzing such problem by means of the data collected by an Italian Delphi Panel that were compared with US epidemiological and costing data. We confirmed several key features of VVA, in particular those pertaining the urological and psychological implications of the condition in BC patients [23].

Since health-care interventions include many aspects with the potential to change over time, the evaluation of frequencies of screening, diagnostic tests and types of therapies have to be considered also from an economic point of view, in order to correctly evaluate the impact on overall costs of any therapeutic approach. The ultimate goal should be to improve the quality of life of BC patients.

The aim of this study was the gathering of an expert opinion on the management of VVA, by means of further analyzing the situation of VVA in Italy, with particular focus on the impact on health resources use.

Taking into account the current practice of diagnosis and treatment of VVA in Italian patients with a history of BC using a Delphi Panel approach, our aim was to provide a cost analysis of the VVA-related diagnostic methods and treatments.

The Panel had also the objective to collect information on the experience of participants with standard treatments for VVA and with new treatments such as ospemifene, considering also how these treatments are perceived in terms of their ability to reduce or eliminate the most important still unmet medical needs in the VVA population.

## Methods

The Consensus Group was organized and run using a modified Delphi design (24), where the possible responses are obtained from an external source and then submitted to the Panel. The Delphi technique provides a systematic method of gaining consensus from a group of experts through collecting and aggregating informed judgments over multiple iterations. The participants worked in a variety of Institutions. Every participant received the specific Institutional approval to participate to the study and the design of the study was approved by local Ethical Committees.

The centers, considered together, covered seventeen out of the 20 Italian regions, except for 3 areas (Valle D'Aosta, Trentino and Liguria).

A questionnaire was prepared and circulated by e-mail to all participants in the second half of November, 2016. The complete questionnaire is available upon request.

Responses were collected and analysed in the days preceding the session, which took place in Milano on November 24, 2016. The results of the analysis of the questionnaires were summarized in a series of tables and slides that were presented during the sessions as a starting point for the discussion.

Two additional rounds of follow-up interviews took place in January 2017 and in July 2017; the final analyses were completed in December 2018. The last round of reviews and updates was performed after the first publication was accepted (January 2020).

Participants were initially asked to review the results of a study conducted in the US on a health claims database (later

partially published by Bruyniks, 2017) [25,26] and to confirm whether or not the results described in the studied population could be applied also to the Italian patient population. Subsequently, clinical results were published in another paper [23].

This US case-control study compared women with VVA (regardless of a history of BC and treatment) and women without VVA. Controls were not “allowed” to have a diagnosis of VVA or hot flashes and were 1:1 matched for age with the cases. Controls were given the index date of the matched case patient and needed at least one year pre- and one-year post-index date observation. The study considered the most frequent events which showed the greatest difference between populations and their biological plausibility and was also used as a “benchmark” to evaluate Italian socio-economic results.

As far as the pharmaco-economic aspects were concerned, the calculation of the economic burden considered the cost - determined by means of the Italian DRG (Disease Related Group) - of any diagnostic and therapeutic interventions. DRG is the “umbrella” term that covers any of the payment categories that are used to classify patients for the purpose of reimbursing hospitals for each case in each category with a fixed fee, regardless of the actual costs incurred.

## Results

The four involved sites followed between 1200 and 3000 patients per year, of whom 23-50% had VVA and the percentage of patients with a history of BC varied from 3 to 50%.

The Panel, based on epidemiological and personal experience data, estimated that the prevalence of VVA in Italy is about 115,000 cases out of 380,000 BC survivors. Approximately 76,000 of these cases would need treatment. The Italian Delphi panel approach confirmed the findings of the analysis of the US database and the epidemiological and clinical point of view previously published [23].

The estimated expected increase in co-morbidity was 4.25 additional cases /100/yr of “urinary tract infections (UTIs)” and 1.96 of “urinary frequency” diagnoses.

There were 3.68 additional estimated cases of “vulvovaginitis” and 6.97 cases of “climacteric symptoms” in BC patients with VVA.

Finally, an increase, as a potential consequence of VVA, of 33.4 additional gynecological visits/100/year can be expected, along with 18.48 additional cancer screenings, 2.53 additional outpatient visits and 3.2 screenings for HPV.

In particular, the diagnostic and therapeutic interventions after the most frequent co-morbidities evaluated were summarized in Table 1

In order to evaluate the economic impact of the condition, the “*cost per event*” to the NHS, based on the US data confirmed by the Delphi Panel approach, was also estimated by using the existing DRG. Results are reported in Table 2.

If we consider the expected number of additional cases, we add up to a total cost to the NHS of over 12.5 million Euros according to the DRG, which is the “conventional” fixed amount used to reimburse reimbursing hospitals for each case in a category with a fixed fee regardless of the actual costs incurred (Table 3).

**Table 1:** Diagnostic and therapeutic interventions after one of the 14 most frequent co-morbidities is diagnosed

Co-morbidity/event	intervention	intervention 2	intervention 3	intervention 4	intervention 5	intervention 6
UTIs	urinoculture 1	antibiogram 1	antibiotic 1	urinoculture 2	antibiogram 2	antibiotic 2
Urinary frequency	urological visits	urinoculture	Antispasmodic	Urine test		
Gyn visits	gyn visit	Ultrasound				
Vulvovaginitis	gyn visits	vag smear	topical treat	test for fungi and bacteria		
Gen tract symptoms	gyn visit	Ultrasound	vag smear			
Cancer screening	Pap test 1	Pap test 2				
PM bleeding	ER visit	hysteroscopy	Pap smear	gyn visits(s)	Ultrasound	Curettage (in 80%)
Psych. unadjustment	counseling 1	counseling 2	counseling 3	counseling 4		
Climacteric symptoms	gyn visit	ultrasound				
Bone & cart. Disorders	MOC	bone resorption inhibitors				
Cystocele	intervention					
Outpatient Visits	spec. visit					
Stress incontinence	urol visit	ultrasound	urography			
Screen HPV	visit	colposcopy	lab test			

**Table 2:** Estimated cost “per occurrence” in Italy for the 14 most frequent co-morbidities and events

Event/co-morbidity	cost per episode
Urinary Tract Infections (UTIs)	86.24 €
Urinary frequency	91.14 €
Gynecological visits	64.04 €
Vulvovaginitis	39.12 €
Genitourinary tract symptoms	68.50 €
Cancer screening	104.96 €
Post Menopausal bleeding	560.86 €
Psych. unadjustment	77.48 €
Climacteric symptoms	64.04 €
Bone & Cartilage Disorders	211.82 €
Cystocele	3397.00€
Outpatient Visits	20.66 €
Stress incontinence	142.83 €
Screen for HPV	95.34 €

**Table 3:** Total cost per year to the NHS of co-morbidities in BCS/VVA patients

Co-morbidity/event	expected difference (cases/100/yr)	expected difference (cases/year)	Cost per event	Total cost of events
Urinary Tract Infections (UTIs)	4.25	3264	86.24 €	€ 281,520
Urinary frequency	1.96	1505	91.14 €	€ 137,207
Gynecological visits	33.40	25654	64.04 €	€ 1,642,895
Vulvovaginitis	3.68	2827	39.12 €	€ 110,575
Genitourinary tractsymptoms	3.38	2596	68.50 €	€ 177,836
Cancer screening	18.48	14194	104.96 €	€ 1,489,834
Post Menopausalbleeding	3.13	2404	560.86 €	€ 1,348,376
Psych. Unadjustment	10.00	7681	77.48 €	€ 595,116
Climacteric symptoms	6.97	5354	64.04 €	€ 342,844
Bone & Carilaget.Disorders	3.64	2796	211.82 €	€ 592,216
Cystocele	1.81	1390	3397.00 €	€ 4,722,655
Outpatient Visits	2.53	1943	20.66 €	€ 40,148
Stress incontinence	1.98	1521	142.03 €	€ 216,002
Dysuria	1.51	1160	35.48 €	€ 41,150
Osteoporosis	3.39	2604	211.82 €	€ 551,542
Leukorrhea	1.30	999	39.12 €	€ 39,062
Ovary Cysts	0.99	760	64.04 €	€ 48,697
Cervicitis	0.95	730	31.40 €	€ 22,912
Hematuria	1.74	1336	31.14 €	€ 41,618
Screen for HPV	3.20	2458	95.34 €	€ 234,335
			<b>Total cost</b>	<b>€ 12,676,541</b>

## Discussion

The results of this Panel confirm that VVA is a widespread and underdiagnosed condition, as it has been extensively published in the past decade and confirmed in our previous study; in particular, it shows the relevant economic and social impact of the VVA condition in BC patients.

The Panel consensus highlights that VVA may determine a relevant number of events and co-morbidities, which have a significant economic cost.

This is in line with the findings of the US study, which was used as a "benchmark" to evaluate the Italian situation in this regard.

This study started from an extended set of epidemiological data originated in the US using a Health Claims database, a very accurate and reliable source of information.

Due to the lack of epidemiological evidence in Italy and to the difficulties in organizing an "ad-hoc study", a Delphi Panel seemed an adequate preliminary approach to assess the situation in a semi-quantitative way and to guide future initiatives.

The Delphi Panel, which inherently reduces group-related bias as much as possible, was used in fact to "bridge" the US data and to evaluate its applicability to the Italian reality. The involved sites constituted a representative sample of the Italian patient population and of the diagnostic and treatment pathways applied in VVA patients with a history of BC.

Our Panel confirms the relevance of some comorbidities linked to the VVA condition in the Italian population, similarly to what was found in other countries, especially conditions pertaining to the “urological” and “psychological” domains [27]. In particular, we demonstrated the need to better explore urinary symptoms linked to vaginal atrophy as recent studies suggested [28].

At the same time, some conclusions of the US study have been modified or rejected, yielding a final picture that can be considered – with its similarities and differences- an adequate representation of the impact of VVA in BC patient in our country.

Indeed, the analysis of the impact of the underdiagnosed VVA-related diseases and their consequences from an economic point of view allow us to find how relevant the cost of the condition is for the Italian NHS.

Since VVA actually represents a relevant cost for the NHS, an effective treatment could therefore save a significant amount of resources to the NHS. In fact, this study highlights the importance of planning early and appropriate treatment of vaginal atrophy to improve whole women’s quality of life and to reduce the overall burden of illness on both patients and the NHS.

BC patients, as confirmed by our results, are more impacted by the consequences of the condition than the general VVA populations, since they cannot rely on LET. In these patients, the use of new therapies – such as e.g. SERMs like ospemifene – has a strong clinical rationale, even in light of the increasing evidence on their safety [29].

The Delphi technique is inherently limited by the fact that it is a forecasting approach that must be confirmed by further clinical studies.

It should be taken into account also the fact that US data was “bridged” to the Italian clinical reality, even though the approach used in the Panel tried to limit possible bias as much as possible.

The knowledge gained through this initiative, however, will be very useful in guiding treatment choices and in designing a future study, albeit a prospective epidemiological study should

be performed to obtain a definitive and quantitative answer. Indeed, there is a current lack of data on the social and pharmacoeconomic impact of the condition and whether its related to co-morbidities.

The availability of a more in-depth knowledge of the VVA management of BC patients in Italy may help the decision-making of health politics. In fact, knowing the cost of the failure of effective treatments enables to make a proper allocation of financial resources. On the other hand, knowing the cost of inaccurate diagnoses and treatments is important even for HCPs who, in addition to the traditional obligation to seek what is ‘best for the patient,’ should always be aware of the cost–benefit analysis attached to misunderstanding a given medical problem.

## Conclusions

A higher level of awareness about the frequency and possible clinical consequences of VVA, especially in BCS patients, would be beneficial to both patients and societies. That being so, a timely and appropriate treatment would avoid not only the significant impact this condition has on the life of patients and on their families, but would significantly reduce the financial burden to the NHS caused by diagnosis and treatment of the co-morbidities of VVA.

## Declarations

## Acknowledgments

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## Availability data

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. The Delphi Panel Report is available from the Corresponding Author upon reasonable request. The unpublished data from [26] is available from the authors upon reasonable request.

## Authors’ contributions

All authors participated in the face-to-face meeting.

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Nicoletta Biglia, Lino Del Pup, Paola Villa, Riccardo Masetti and Rossella E. Nappi contributed also in the second and third round follow-up and contributed to the preparation and redaction of the manuscript. Nicoletta Biglia originated also the report of the US trial used in the discussions.

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### **Compliance with ethical standards**

### **Ethics approval and consent to participate**

Every participant received the specific Institutional approval to participate to the study and the design of the study was approved by local Ethical Committees in accordance with the applicable regulations.

### **Conflict of interest**

The authors declare that they have no conflict of interest.

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