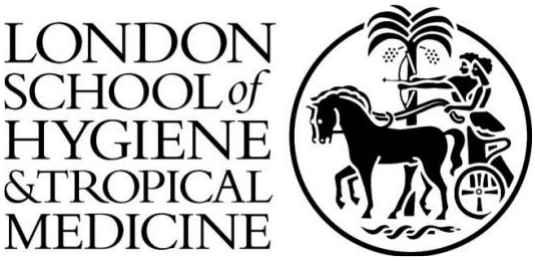

Cervical cancer in Saudi Arabia: trends and regional disparities in incidence and survival

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Declaration

I, Eman Alkhalawi, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:

Date: 8 February 2021

Dedication

I dedicate this work to my children Khalid and Dana, whose bravery has been inspiring.

Acknowledgment

First and foremost, I would like to thank my supervisors, Professor Michel Coleman, for his tireless dedication and generosity, and Dr. Claudia Allemani, for her guidance, encouragement, and support throughout. They have taught me so much beyond the science, including the value of kindness and collaboration.

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Abstract

In many countries, recent improvements in cervical cancer survival have mostly been modest. However, survival needs to be interpreted in the context of incidence and mortality in order to assess progress in cancer control. Further, survival by stage could help distinguish whether lower-than-expected survival is due to late-stage diagnosis or sub-optimal management, and to inform health policy.

Data on all women diagnosed with invasive cervical cancer during 2005-2016 were obtained from the Saudi Cancer Registry. Vital status and date of death if dead were ascertained by linking the registry records to vital registration data in the Ministry of Interior. Population counts by calendar year, sex, 5-year age group, region and nationality were obtained from the General Authority for statistics.

Age-standardised incidence rates were calculated for women diagnosed during 2005-2010 and 2011-2016. Age-standardised five-year net survival probabilities were estimated for the same periods by region and stage at diagnosis, and by region stratified by stage.

Incidence rates were lower than in most countries, and changed very little between 2005-2010 and 2011-2016 (1.66 to 1.76 per 100,000 women per year). Incidence was higher among non-Saudi than Saudi women, and in the three most populous regions.

Age-standardised 5-year net survival did not change in Saudi Arabia between 2005-2010 (59.2; 95%CI 52.7-65.7) and 2011-2016 (59.7; 54.7-64.6), or in any of the regions, except in Makkah, where there was a 19% increase in survival for women diagnosed during 2011-2016 compared to 2005-2010. Survival for women diagnosed at a distant stage was substantially lower in the Eastern Region than in other regions.

Cervical cancer incidence and survival have remained largely unchanged. Despite very low incidence in Saudi Arabia, it is difficult to predict the future burden of cervical cancer. Higher survival could be achieved by improving early diagnosis and access to high-quality treatment.

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Table of abbreviations

ASIR	Age-standardised incidence rate
ASMR	Age-standardised mortality rate
SCJ	Squamo-columnar junction
IARC	International Agency for Research on Cancer
CIN	Cervical Intraepithelial Neoplasia
HPV	Human Papillomavirus
WHO	World Health Organization
HSIL	High-grade squamous intra-epithelial lesion
LSIL	Low-grade squamous intra-epithelial lesion
ASCUS	High-grade squamous intraepithelial lesions atypical squamous cells of undetermined significance
ASC-H	Atypical squamous cells in which a high-grade squamous intraepithelial lesion cannot be excluded
MOH	Ministry of Health
FIGO	Federation of Gynaecology and Obstetrics
MOI	Ministry of Interior
MV	Morphologically verified
DCO	Death certificate only
SCR	Saudi Cancer Registry
NIC	National Information Center
KFSHRC	King Faisal Specialist Hospital and Research Center
MV%	morphologically verified
UNPD	United Nations Population Division
GBD	Global Burden of Disease
MCAR	Missing completely at random
MAR	Missing at random
MNAR	Missing not at random
NOS	Not otherwise specified

Chapter 1. Introduction

1.1 Global burden of cervical cancer

Cervical cancer is the seventh most common tumour in women, with an estimated 601,200 women newly diagnosed in 2017 and 259,700 women dying of the disease in that year[1,2] It accounts for about 3% of all cancer deaths in women. Age-standardised incidence rates (ASIR) range from 4.1 per 100,000 per year in Western Asia to over 40 in Southern and Eastern Africa.[3] Global variation in the estimates of age-standardised five-year net survival from cervical cancer is wide, from less than 40% in some African countries to over 70% in Northern Europe for women diagnosed during 2010-2014.[4] Consequentially, age-standardised mortality rates (ASMR) from cervical cancer vary largely across the world, ranging from less than 2 per 100,000 per year in North America, Australia and New Zealand to 30 per 100,000 per year in Eastern Africa.[3]

1.2 Rationale

Although relatively uncommon in Saudi Arabia and the Middle East in general, future projections of cervical cancer incidence are difficult to make because of lack of reliable data on past incidence trends and changes in lifestyle, most important being sexual behaviour. Based on current estimates of population growth and ageing and assuming that current incidence rates will remain constant, the number of cases in the Middle East and North Africa are expected to double from 2008 to 2030.[5]

Cervical cancer is one of the few cancers with a single predominant cause, namely persistent infection with one of several high-risk types of human papillomavirus (HPV).[6] This offers a clear target for preventive public health interventions. Screening methods are readily available, affordable and non-invasive. There is a consensus that the majority of cervical cancer deaths are preventable,[7] leading the WHO Director-General in 2018 to call for coordinated action globally to eliminate cervical cancer.[8] Following this aim, the WHO launched in November 2020 the global strategy to accelerate the elimination of cervical cancer as a public health problem, which was defined as achieving an incidence rate of less than 4 per 100,000 women per year globally. An interim target was set to be achieved by 2030 and sustained thereafter: to fully vaccinate 90% of girls by age 15, to screen 70% of women twice (by age 35 and again by age 45) using a high-performance test, and to

treat 90% of women with identified cervical pre-cancer and 90% of women with invasive cervical cancer.[9]

5-year survival for women diagnosed with cervical cancer between 1995 and 2004 in Saudi Arabia has been reported in the CONCORD-2 study.[10] More detailed analysis by tumour stage is important for interpretation of survival data, which is crucial to stimulate change in healthcare policy. Moreover, no research has yet been done to identify regional disparities in cancer outcomes in Saudi Arabia. Healthcare in Saudi Arabia is provided free of charge by different government sectors, but the concentration of oncologists and modern treatment facilities in major cities may pose a challenge to equitable access to treatment.[11,12]

Regional variation and time trends in incidence would provide information about cervical cancer risk factors and preventive strategies, while survival and mortality are outcome measures that would enable assessment of the effectiveness of the healthcare system in treatment and control, reflecting both availability of early diagnosis, thorough investigation and effective treatment.[13] That said, mortality has a direct relationship with incidence and it is a simple rate defined by the number of deaths due to a given cause during a calendar year divided by the mid-year population. Survival uses only cases as the denominator and is a better reflection of both access to early diagnosis and post-diagnostic management. It is important to report all three metrics when describing the burden of cancer.[14] Survival should be interpreted together with incidence and mortality when assessing progress in cancer control.[15] Examination of trends in incidence and survival by stage at diagnosis will help to determine both the effectiveness of diagnostic activity and the availability and efficacy of stage-appropriate treatment.

1.3 Aim

To provide up-to-date and detailed incidence, mortality and survival estimates for cervical cancer in Saudi Arabia.

1.4 Objectives

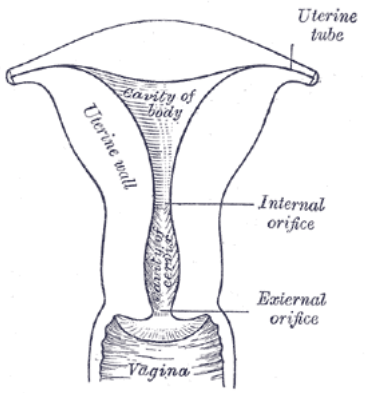
- To describe trends in incidence and mortality rates, and survival probability, for women diagnosed with cervical cancer in Saudi Arabia from 2005 to 2016.
- To explore cervical cancer incidence and survival trends by stage at diagnosis.

- To explore regional differences in cervical cancer incidence rates and 5-year net-survival in Saudi Arabia.
- To examine whether any regional discrepancies in survival are due to differences in the distribution of stage at diagnosis or in stage-specific survival.

Chapter 2. Cervical Cancer

2.1 Anatomy of the uterine cervix

Figure 1: Anatomy of the uterine cervix



Drake, R. L., Vogl, W., & Mitchell, A. W. M. (2012). Grays basic anatomy. Philadelphia, PA: Elsevier.

The cervix is the lower part of the uterus and is a canal leading to the vagina. Its upper and lower limits are referred to as the internal and external os, respectively (Figure 1). The external os separates the inner part (endocervix), lined by a single layer of glandular columnar epithelium, from the outer part (ectocervix), which is covered with non-keratinizing squamous epithelium. The external os and the ectocervix can be directly visualized on vaginal examination with a speculum. The boundary between the two epithelia is referred to as the squamo-columnar junction (SCJ). It is located at birth and in pre-pubertal girls at or close to the external os but migrates outwards during reproductive years to different extents under the effect of various factors, the most important being age and hormonal status. The boundary recedes into the endocervix in post-menopausal women. Through exposure to the acidic vaginal environment, the columnar epithelium undergoes a physiological transformation to squamous epithelium, giving rise to a new SCJ where the squamous tissue meets the columnar epithelium. This area between the original and the new location of the SCJ and where the columnar epithelium is replaced by squamous epithelium is defined as the transformation zone. The squamous cells in the transformation zone are susceptible to HPV infection, therefore 90% of cervical cancers are squamous cell carcinomas arising from the transformation zone and the remaining 10% are adenocarcinomas arising from the glandular columnar tissue of the endocervix.[7]

2.2 The role of Human Papillomavirus (HPV) in the development of cervical cancer

Over 170 HPV types have been identified. These are categorised into the alpha and beta genus; the alpha genus is further divided into cutaneous and mucosal types. Of the latter, epidemiological studies have found 18 types to be associated with cervical cancer (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82). These are now designated high-risk types. HPV16 and HPV18 alone are respectively responsible for an estimated 50% and 20% of cervical cancers globally.[16,17]

There is convincing evidence that HPV infection is not only the strongest risk factor, but is in fact a prerequisite for the development of the vast majority of cervical cancer.[6,17-19] A very strong association is observed between HPV prevalence and the incidence of cervical cancer in a particular geographic area.[18] In the International Agency for Research on Cancer (IARC) survey on prevalence of HPV DNA in invasive cervical cancer, retesting HPV-negative cervical cancer specimens with more sensitive methods, while excluding histologically inadequate samples, concluded that virtually all samples (99.7%) were positive for HPV DNA, in comparison to the initially reported 93% HPV positivity.[6,19] This was also confirmed in a case-control study in which HPV DNA was detected in 96.6% of squamous-cell cervical carcinoma specimens versus 15.6% of controls, yielding the extraordinarily high pooled odds ratio (OR) of 158 (95%CI 113-221) for the presence of HPV DNA in cases versus controls.[17] The small proportion of HPV negative cervical cancer has been explained by sample inadequacy and lower sensitivity of methods used (false negative), loss of HPV expression, or true HPV independent pathways to the development of cervical cancer.[20] These HPV-negative tumours tend to be mainly adenocarcinomas of gastric or endometroid type and are often diagnosed at later stage and have higher metastatic potential.[21]

HPV is by far not a sufficient cause for the development of cancer as most infections with carcinogenic types are transient and do not progress to cancer.[18,22] Different studies have shown HPV prevalence in the general population ranging between 6.2% and 31.6%.[23]

2.3 Risk factors for development of Cervical Intraepithelial Neoplasia (CIN) and natural history of their progression to cervical cancer

Persistent infection with high-risk HPV types is the major factor in the development of pre-cancerous lesions of the cervix. Several viral and host factors that contribute to HPV infection and persistence, the development of malignancy, or both, have been identified. The number of sexual partners of the woman or her male partner, age at first intercourse and co-infection with other sexually transmitted diseases increase risk of infection. While immune impairment and HPV type play a role in viral persistence and progression to malignancy (HPV16 having the highest risk of persistence). Cigarette smoking, oral contraceptive use, parity and lower socioeconomic status have also been associated with an increased risk of cervical cancer probably though various pathways.[24] The latency from carcinogenic HPV infection to development of precancerous lesions is estimated to be between 7 and 10 years.[25]

The cervical intraepithelial neoplasia (CIN) classification system is based on histological diagnosis and takes the natural history of lesions into account. CIN1 describes mild dysplasia with koilocytosis (characteristic cellular changes including nuclear enlargement, irregular nuclear membranes and perinuclear vacuoles), CIN2 describes moderate dysplasia and CIN3 includes severe dysplasia and carcinoma *in situ*.[7] The IARC working group on evaluation of carcinogenic risk of human papillomaviruses to humans considers CIN3 a surrogate for pre-cancer and CIN2 as a buffer zone.[25] Strictly speaking, pre-cancer is an intraepithelial lesion destined to progress to invasive cancer. However, non-oncogenic HPV types can also produce a microscopic picture of CIN2 which is not at risk of progression.[7]

For screening purposes, however, the WHO Bethesda cytological classification combines CIN2 and CIN3 into the broader grouping of high-grade squamous intraepithelial lesions (HSIL). This is due to the fact that it is not possible to differentiate the two based on cytology alone. Histological evaluation involves taking a tissue biopsy, preferably colposcopy-guided, by a trained expert. It is more invasive, and the equipment is not frequently available at the primary care level. In the Bethesda classification, CIN1 is categorised as low-grade squamous intra-epithelial lesion (LSIL) and the terms atypical squamous cells of undetermined significance (ASCUS) and atypical squamous cells in which a high-grade squamous intraepithelial lesion cannot be excluded (ASC-H) are assigned to lesser grades of cellular atypia.[7,26]

The majority of CIN2 lesions are transient; only a few progress to CIN3. Although many CIN3 lesions also regress, they are considered pre-cancerous and have a much higher risk of progression to carcinoma *in situ* and to a lesser degree, invasive cancer.[25] In a pooled analysis, the average probabilities of regression of CIN1, 2 and 3 were 57%, 43% and 32%, respectively. On the other hand, only 1%, 5% and 12% progressed to invasive cancer, respectively.[27]

2.4 Screening and treatment guidelines for precancerous lesions

Screening guidelines vary between countries and resource settings. The WHO recommends screening at least once for every woman between 30 and 49 years using HPV testing, cytology-based screening (Pap smear or liquid-based cytology) or visual inspection of the SCJ after applying acetic acid (VIA).[7] The choice of screening method depends on available equipment and financial and human resources. Where women are unlikely to return for colposcopy, a "screen and treat" approach using VIA and immediate treatment of suspicious lesions may be the most appropriate. Cytology-based screening has been the mainstay of screening for decades. It is a multi-step process involving sample collection, transport to the laboratory, cytological evaluation by pathologists, reporting results to healthcare providers and re-call of women with positive results for diagnosis and management. HPV testing is becoming more available and less expensive, and offers higher sensitivity, especially in settings where there is lack of trained healthcare providers and pathologists. Self-collection is also possible, which may be more convenient for both women and healthcare providers. In low-risk settings, HPV-testing could be used to reduce the number of cytological examinations, allowing them to be analysed centrally by more experienced pathologists, leading to improved performance of cytology.[28] Diagnostic tests include biopsy with or without colposcopy, which provides a magnified view of the cervix; or endocervical curettage. They are helpful to confirm and determine the extent of disease, but are not always available or appropriate, and should not be used if they are likely to cause loss to follow-up or to delay treatment.

The guidelines published by the Saudi Ministry of Health (MOH) in April 2014 recommend universal screening of women, starting three years after marriage up to 65 years of age, using HPV testing or cytology, followed by colposcopy and biopsy of positive results.[29] The guidelines do not specify a screening interval.

Treatment of CIN2 or higher lesions (CIN2+) aims to destroy or remove the abnormal tissue. Options consist of cryotherapy, which involves freezing the abnormal areas, Loop electrosurgical excision procedure (LEEP), which uses an electrically powered wire to cut and coagulate the lesion and the entire transformation zone, or cold knife conisation (CKC), involving the surgical removal of a cone-shaped portion of the endo- and ectocervix under spinal or general anaesthesia. The choice depends on provider training, availability of electricity and anaesthesia, and the need to treat during the screening visit ("screen and treat" approach). If cancer is suspected, the woman should not be treated with any of these methods, but should have a biopsy taken to confirm or rule out the diagnosis.[7]

The Saudi MOH guidelines recommend cryotherapy to treat CIN2+. These guidelines aim to reduce variability in clinical practice across the country and to reduce health inequities, taking the quality of available evidence as well as acceptability to key stakeholders (women, clinicians and policymakers) into account.[29]

2.5 Clinical features, diagnosis, staging and treatment of invasive cervical cancer

Cervical cancer is often asymptomatic in its early stages. Vaginal discharge and post-menopausal, post-coital or intermenstrual bleeding are the most common first symptoms. These might be ignored, especially if the discharge or bleeding is limited, until symptoms of more advanced disease manifest as the tumour invades locally (pain, haematuria, incontinence, constipation), spreads to lymph nodes (lower limb oedema or flank pain due to hydronephrosis) or causes weight loss, fatigue, and various metastatic symptoms.

Apart from Pap smear-detected disease, diagnosis may take place when visible abnormality is seen on examination of an asymptomatic woman attending screening or other gynaecological examination. More commonly, women will present with symptoms suggestive of cervical cancer. This is also the case in developed countries with free healthcare, like the UK. In a retrospective study of 148 women diagnosed with cervical cancer over the 4-year period 2007-2010 at the University Hospitals of Leicester, 66.4% were already symptomatic at diagnosis. Of those, 37.2% had stage I disease, in contrast to 100% of women who were asymptomatic at diagnosis.[30]

Following histopathological confirmation, the tumour stage is determined according to the International Federation of Gynaecology and Obstetrics (FIGO) classification (Table 1).[31] This is based on tumour size and the extent to which it has spread. Up until 2018, FIGO staging relied on clinical findings in order to preserve comparability across various

resource settings.[32] Pathology and advanced imaging findings could be used to guid treatment but not for formal FIGO staging. The 2018 update allowed the incorporation of surgical pathological and advanced imaging techniques if available. Diagnosis of stage IA disease is made on pathological examination of excised lesions with negative margins. For visible lesions (IB and higher), a biopsy confirmation is followed with clinical assessment which provides information on tumour size, lymph node status, and local or systemic spread. This may include imaging (chest X-ray, ultrasound, CT, MRI or positron emission tomography (PET)) and cystoscopy or sigmoidoscopy.

Table 1: Federation of Gynaecology and Obstetrics (FIGO) staging of cervical cancer (2018)

Stage I	Cervical carcinoma confined to the uterus (extension to corpus should be disregarded)
IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium; vascular space involvement, venous or lymphatic, does not affect classification
IA1	Measured stromal invasion of≤3.0 mm in depth and ≤7.0 mm in horizontal spread
IA2	Measured stromal invasion of>3.0 mm and not >5.0 mm, with a horizontal spread of≤7.0 mm
IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than IA2.
IB1	Clinically visible lesion <2.0 cm in greatest dimension
IB2	Clinically visible lesion ≥2 cm and <4.0 cm in greatest dimension
IB3	Clinically visible lesion ≥4 cm in greatest dimension
Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina
IIA	Without parametrial invasion
IIA1	Clinically visible lesion ≤4.0 cm in greatest dimension
IIA2	Clinically visible lesion >4 cm in greatest dimension
IIB	With parametrial invasion
Stage III	The tumour extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney
IIIA	Tumour involves lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney
IIIC	Involvement of pelvic and/or para-aortic lymph nodes
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
Stage IV	The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum.
IVA	Spread to adjacent organs
IVB	Spread to distant organs

The stage of the disease at diagnosis is the main determinant of treatment. Treatment options are also based on patient-related factors, including the woman's general health status and her desire to preserve fertility, and the resources available. For microinvasive disease (FIGO stages IA1 and IA2), treatment consists of conisation or hysterectomy (abdominal, vaginal or laparoscopic) alone. Radical hysterectomy is reserved for stages IB1 and IIA1 (clinically visible lesions ≤4 cm in greatest dimension). Locally advanced and grossly invasive cervical cancer (stage IB2–IVA) is treated with platinum-based chemoradiation. Palliative chemotherapy or radiotherapy are usually used for distant metastatic disease (stage IVB), with some exceptions where curative treatment may be appropriate when distant metastasis is limited.[33]

2.6 Role of screening and early diagnosis in cervical cancer prevention and survival

Invasive cervical cancer is preceded by years of preclinical precursor changes, which if detected early, can be treated by relatively simple procedures.[34] The primary aim of cervical cancer screening is to reduce the incidence of invasive cervical cancer by detection and removal of its precursors. A secondary aim is the early detection of cervical cancer that has already become invasive, in order to improve the prognosis and to reduce treatment cost and complications.[7] Stage at diagnosis is the single most important predictor of cervical cancer survival. In a Swedish nationwide population-based cohort, both screen-detected cancers and symptomatic cancers that present within screening intervals had a more favourable survival than symptomatic cancer overdue for screening, and this was largely attributable to FIGO stage at diagnosis.[35]

However, achieving high screening coverage may not always translate into improved survival on a population level when observing trends over time. High rates of detection and removal of slower growing pre-cancerous lesions could lead to the selective manifestation of more aggressive cancers, which has probably caused the plateau or even decline in survival seen in some countries with established screening programmes.[36] Nevertheless, countries with long-standing organised screening programmes have witnessed a clear fall in cervical cancer mortality.[37]

2.7 Role of the HPV vaccine

Two vaccines targeting the most prevalent HPV types were initially approved by the FDA for girls and women 9 to 26 years of age. Gardasil (Merck & Co, Inc., approved in 2006), a quadrivalent vaccine covering HPV types 6, 11, 16 and 18; and Cervarix (GlaxoSmithKline, approved in 2009), targeting HPV types 16 and 18. In the FUTURE II phase 3 randomised double-blinded trial, the quadrivalent vaccine demonstrated 98% efficacy in preventing HPV types 16 and 18 related CIN2+ or adenocarcinoma *in situ* in HPV-naïve women 15-26 years of age, with none of the participants in the intervention arm developing CIN2+ compared to 28 who developed CIN2+ in the control arm of the trial.[38] The efficacy of Cervarix was investigated in the PATRICIA trial, a double-blinded randomised controlled trial that included more than 18,000 women aged 15-25, which showed an efficacy of 92.9% in preventing CIN2+ lesions in HPV-naïve women. It also demonstrated some cross-protection against HPV types 31, 33, 45 and 52, and 58.[39] Both trials had a mean follow-up time of about three years.

More recently, a nonavalent HPV vaccine (Gardasil9; Merck Sharp & Dohme Corp., Whitehouse Station, New Jersey) targeting nine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) gained FDA approval in December 2014 for females aged 9 to 26 years and males aged 9 to 15 years. In an international, double-blinded randomised trial, the nonavalent vaccine demonstrated 97.1% efficacy in preventing HPV 31, 33, 45, 52 and 58-related high-grade cervical disease (CIN2+) in HPV naïve women after five years of follow-up compared to the quadrivalent vaccine.[40]

Early population-level data has also shown a significant reduction in the prevalence of HPV 16, 18, 31, 33, and 45 among vaccinated girls aged 13-19 and of CIN2+ among vaccinated girls aged 15-19 after 5-9 years of vaccination compared to pre-vaccination periods.[41]

Since population-level vaccination of girls only started in 2008/2009, long-term effectiveness data for the prevention of invasive cervical cancer through HPV vaccination are just emerging. Up to 10-years of registry-based follow-up of women enrolled in the PATRICIA trial resulted in no invasive cervical cancer occurrence in the vaccinated cohort while 4 women developed cervical cancer in the control cohort.[42] Similarly, 12-years of follow-up of the FUTURE II study participants, who have reached 30-37 years of age, showed sustained effectiveness of the quadrivalent vaccine, with none of the women

developing HPV 16 or HPV 18-related CIN2+ in comparison to an expected baseline incidence rate of 0.287 per 100 person-years in an unvaccinated cohort, as estimated from historical registry data.[43] A recent registry-based cohort study, which included over 1.6 million girls and women living in Sweden, showed an age-adjusted incidence rate ratio of 0.51 (95% 0.32-0.82) for invasive cervical cancer in vaccinated women compared to unvaccinated women. Adjusted for several socioeconomic and family characteristics, the incidence rate ratio for women who had been vaccinated before age 17 was 0.12 (95%CI 0.00-0.34).[44] A model-based analysis estimated that the bivalent and quadrivalent vaccines would reduce the number of invasive squamous cell carcinomas by 31.9% and 30.5%, respectively, over 70 years; while the nonavalent vaccine would be expected to reduce them by a further 4.8% and 6.6%.[45]

Based on available evidence, The WHO recommends universal vaccination of girls aged 9-14. Many countries have also introduced HPV vaccination of boys with the aims of reducing transmission and reducing the burden of HPV-associated head, neck, anal and penile cancers.[46]

Chapter 3. Literature review

The aim of the literature review was to identify any similar work that has been done and compile what is so far known about cervical cancer epidemiology in Saudi Arabia, and about regional differences in cervical cancer incidence, mortality and survival, including factors affecting those differences. Because a search for regional differences in cervical cancer incidence or mortality or survival in Saudi Arabia yielded no results in different databases, two separate search concepts were specified. The search was carried out using a combination of free text and subject headings adapted to each database. Where possible, language was restricted to English, Arabic and German. 82 Articles were included in the final literature review (Figure 2).

Literature was updated on 23 Sept 2020 in the on EMBASE and MEDLINE databases, using the same search terms and restricting results to those published in 2018 onwards. This added four articles to the final review.

Search strategy:

Concepts:

1- (cervical OR cervix) AND (cancer OR carcinoma OR neoplasm) AND (Incidence OR occurrence OR mortality OR “death rate” OR survival) AND ((Region* or geographic*) AND (Disparit* or inequal* or difference*))

2- (cervical OR cervix) AND (cancer OR carcinoma OR neoplasm) AND (Incidence OR occurrence OR mortality OR “death rate” OR survival) AND "Saudi Arabia"

Date of search: between 21/2/18 and 26/2/18

Time frame/ database coverage: no limits.

Records retrieved from databases:

BASE =25

Dissertations & Theses Global =14

EMBASE =365

Global Health =162

MEDLINE (Ovid®) =144

POPLINE =21

PubMed =60

SCOPUS =468

Web of Science =400

WHO Reproductive Health Library =3

Other (ethos-open grey-IMEMR-popline) =2

Sum =1661

Reasons for full texts exclusion:

Not reporting geographic disparities (for search 1) =58

Irrelevant geographic division (based on indigenous population, ethnicity, hospital capabilities, or environmental risk factors) =8

Recommendations, letters, reviews =24

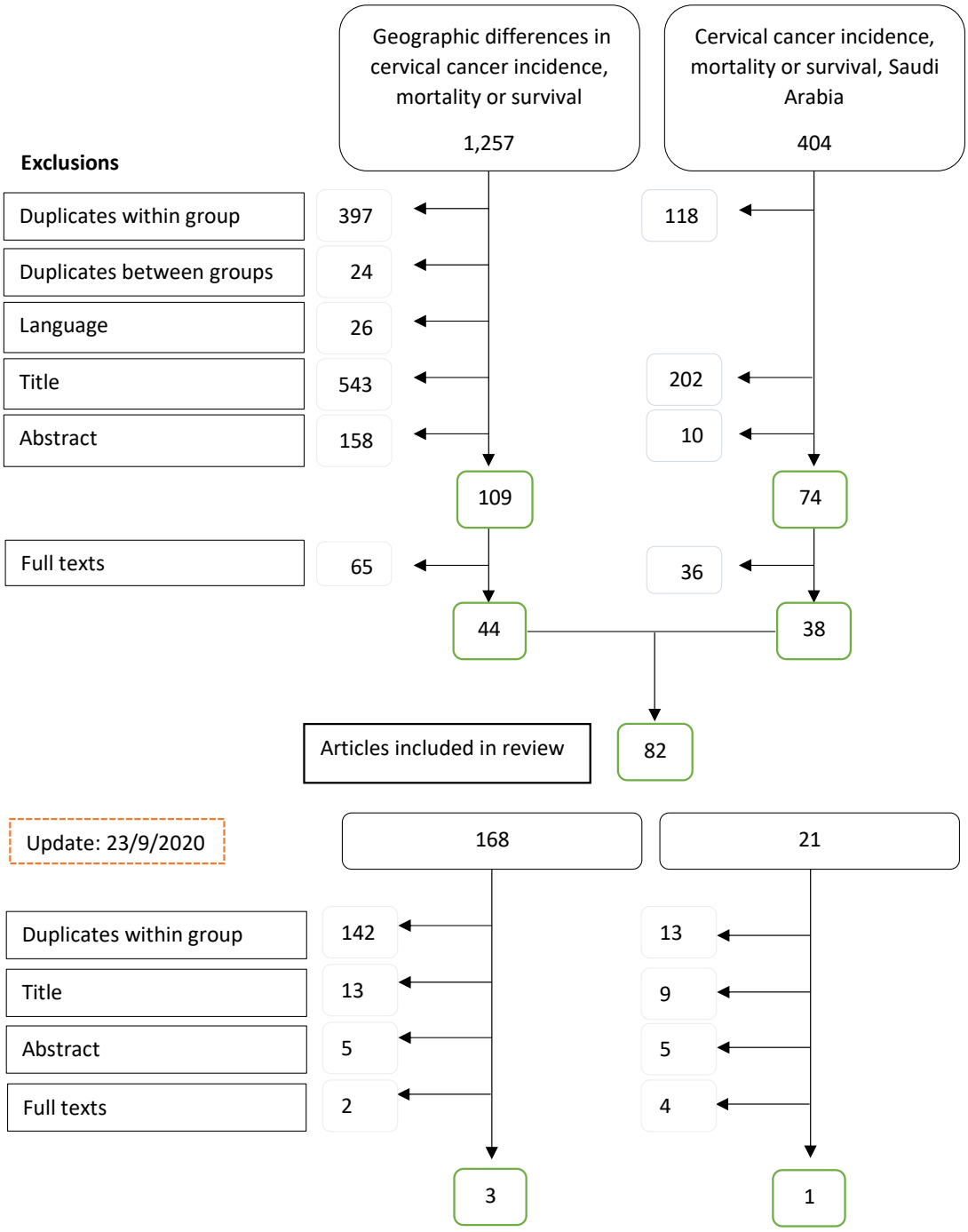
Repeated studies =2

Regional differences in cancers with no separate reporting of cervical cancer =3

Access to healthcare with no separate reporting for cervical cancer =1

Quality =5

Figure 2: Study selection flow chart



3.1 Cervical cancer incidence, survival and mortality trends and international disparities

Both the incidence of, and mortality from cervical cancer have been declining in most countries since the mid-20th century. This decline is mostly attributed to the increased use of screening. Some countries in Europe have witnessed an up to-16 fold reduction in incidence compared to the pre-screening era, despite a background of changing sexual patterns and a cohort-wise increased incidence in younger women.[3,47-49] Although some decline is seen in the world-wide age-standardised incidence and mortality rates of cervical cancer over the past three decades, there has been a 44% increase in the number of women diagnosed and a 38% increase in the number of deaths from the disease.[50] This was equally attributed to both population growth and ageing.[51] The decade between 2007 and 2017 has seen a world-wide average decline of 11.3% in years lost due to disability (YLD) rate of cervical cancer, but the absolute number of YLDs has risen by 9.4%.[52] Similarly, there was an estimated 7.2% decline in the rate of years of life lost (YLL) worldwide due to cervical cancer but an 18.8% increase in the YLL.

Not all countries have benefited equally from this decline in incidence and mortality. Cervical cancer is one of only three cancers where incidence showed an inverse relationship with a country's Human Development Index (HDI).[3,53] A clear increase in age-adjusted disability-adjusted life years (DALYs) lost due to cervical cancer per 100,000 population was seen with decreasing HDI among 184 countries.[54] Low- and middle-income countries (LMICs) have disproportionately high cervical cancer mortality rates in relation to their incidence, and 80% of cervical cancer deaths worldwide occur in LMICs.[55] The societal burden of cervical cancer is compounded by the relatively young age of its occurrence, with death at a young age being the overwhelming contributor to DALYs due to this disease.[54] In 79% of 185 countries included in the Global Cancer Observatory 2018 database, it ranked in the top three cancers affecting women younger than 45.[3]

Large international variation in cervical cancer standardised incidence ratios (the ratio of the observed age-standardised incidence rate in the country to the expected age-standardised incidence rate in a reference population, in this case the world incidence rate) exist, ranging from 13-570. But there is even greater variation in standardised mortality ratios, ranging from 16 to 804. It is the cancer with the largest variation in mortality between countries. This partially reflects risk factors prevalence but also stark inequalities in screening and management.[3]

Data from the US indicate that cancers of the uterine cervix and corpus were the only common cancers for which survival has remained largely unchanged since the early 1970s, despite a clear reduction in cervical cancer incidence and mortality.[56-58] In England, cervical cancer was the only one of six malignancies (oesophagus, stomach, colon, lung, breast, and cervix) for which no improvement in 1-year relative survival was observed during the period 1991-2006.[59] On the other hand, age-adjusted 5-year relative survival in Germany showed a 4.7% improvement from 2002 to 2006.[13]

International differences in cervical cancer survival remain wide. In about two-thirds of countries participating in CONCORD-3, 5-year net survival was between 50% and 70% for 2010-2014, while more extreme differences existed, ranging from 52% in Ecuador to 80% in Iceland. For some African and South American countries, 5-year survival was less than 40%, but these estimates were less reliable.[10] Although a modest increase in survival was seen over the 20 years 1995-2014 in some countries, the interpretation of such changes is complex given the potential of screening and early detection to change survival estimates in both directions. When cervical cancer is detected at an earlier stage, this could lead to more successful treatment and better survival, but also to an artificial increase in survival due to the diagnosis being brought forward in time in the absence of a true improvement in outcome (lead-time bias). On the other hand, survival may decrease when high screening coverage leads to the detection and removal of slower-growing precancerous and *in situ* lesions, leaving more aggressive interval tumours to be eventually diagnosed.[36]

3.2 Within-country disparities in cervical cancer

Disparities are seen on every level of the cervical cancer continuum, from risk factors exposure to screening, early diagnosis, incidence, survival and mortality. Various factors have been reported to influence these disparities. The focus of this literature review is on regional disparities, but there is a large body of literature showing socioeconomic and ethnic disparities; the three often overlap.

Incidence of preventable cancers such as melanoma, lung and cervical cancer was higher in rural and remote areas of Australia, with the age-standardised incidence rate (ASIR) for cervical cancer being 20%, 35% and 26% higher in outer regional, remote and very remote areas, respectively, compared to urban areas.[60] Cervical cancer was the only female cancer that had higher incidence in remote and disadvantaged areas of Queensland,

Australia.[61] Difference in the relative risk of death over five years in cancer patients diagnosed between 1992 and 1996 for the most remote (compared to more highly accessible) areas in New South Wales was highest for cervical cancer (crude RR=3.22; 95%CI 1.54–6.75, adjusted for age, sex and stage: RR=2.25; 95%CI 1.06–4.77).[62]

In an analysis including 1,594 women with cervical cancer from the New Zealand cancer registry, no association was found between rural residence and cervical cancer stage at diagnosis or hazard ratio (HR) of death due to cervical cancer during 1994-2005.[63] Travel time and distance to the nearest general physician (GP) showed no association with ever being screened, while showing a statistically non-significant trend towards increased odds of later stage diagnosis and HR of cervical cancer mortality during the study period. Distance to the nearest cancer centre was not associated with any of the outcomes.[64]

An urban excess of cervical cancer incidence has been observed in the Netherlands during 1989-1991 (RR=1.69; 95%CI 1.47-1.94 in the highest versus lowest level of urbanicity) and in Ireland during 1995-2007 (RR=1.48; 95%CI 1.35–1.62 in urban versus rural areas after adjusting for socioeconomic status). Organised cervical cancer screening is well established in both countries with good access for both urban and rural residents, and differences were attributed to higher smoking in urban areas, differences in sexual patterns, or migration of people with cancer to urban centres to seek specialised treatment, although the latter is unlikely as this urban excess was not seen with many of the other cancers examined.[65,66] In the period 1978-1982, higher cervical cancer ASIRs were seen in urban parts of Umbria region of Italy, while higher ASMRs were seen in rural parts, but these differences disappeared in 1998-2002.[67]

In Belgium and the Netherlands in the mid-1980s to 1990s, death from cervical cancer was the only cause amongst avoidable causes of death showing no difference between districts, or where differences were considered fully attributable to differences in incidence.[68,69] In Switzerland, cervical cancer mortality rates have dropped drastically over the 40 years from 1969 to 2010 in all age-groups, with no regional or rural-urban differences despite the country's diverse culture and self-governing cantonal healthcare.[70]

Higher mortality due to cervical cancer was seen in urban areas in Colombia after adjusting for age, region of residence, type of insurance and educational level. But the authors raise the possibility of under-reporting of cause of death in rural areas, and of cancer patients

moving to urban centres for treatment. Incidence data were not reported, making the differences in mortality difficult to interpret.[71]

Various studies from the USA showed higher incidence and mortality and poorer survival in rural and non-metropolitan areas. An ecological mediation analysis of SEER cervical cancer data from 612 counties (2009-2013) found a decrease in cervical cancer incidence rates as urbanicity increased. Socioeconomic status and primary care physician density were significant mediators, but the relationship remained significant after adjusting for them.[72] Data from 1950 to 2008 showed a 15% higher cervical cancer incidence and 20% higher mortality in rural areas compared to metropolitan areas. Survival differences were as wide as those seen between countries (50.8% 5-year survival in black, rural population versus 71% in white metropolitan population). Stage at diagnosis could not fully explain those differences.[73]

A nation-wide analysis of cancer incidence and mortality by the American Cancer Society reported that cervical cancer age-standardised mortality rates in the poorest counties were 2-fold higher than those in the most affluent counties, reflecting the widest between-county gap in mortality rates among all cancer types.[74]

Geographic clustering of advanced cervical cancer in Texas was explained by age, race/ethnicity, and contextual socioeconomic status but not spatial access to primary care physicians.[75]

For 934 women diagnosed at the University of Alabama at Birmingham during 2005-2015, both living in a rural area and distance from the nearest American College of Obstetricians and Gynecologists (ACOG) women's health provider were not associated with a higher risk of advanced stage cervical cancer, defined as stage II-IV (OR=1.19; 95%CI 0.91-1.56 for rural versus urban residence, OR=0.99; 95%CI 0.98-1.01 per mile of shorter distance to the nearest provider).[76] However, a retrospective cohort which included 390 cervical cancer patients diagnosed at the same centre between 1999 and 2011 found that women living more than 100 miles from the hospital received less radiotherapy and had worse overall survival (HR=1.68; 95%CI 1.11-2.54, unadjusted) despite similar distribution of stage and other risk factors.[77]

Two large studies from Texas including 7,232 and 11,212 women showed no association between rural residence and cervical cancer survival,[78] and between primary care physician spatial access and overall survival.[79] Geographic clusters of higher than

expected cervical cancer mortality were observed (HR=1.79; 95%CI 1.45-2.22), and these did not change much after adjusting for several individual and contextual factors (HR=1.61; 95%CI 1.31-1.98).[79] However, background mortality was not adjusted for, so it is not clear whether the clusters of lower survival in the cervical cancer population reflect higher death rates in that remote population in general.

Different results by urban-rural residence or other geographic variables seen between countries probably depend on various factors including screening intensity, completeness of ascertainment of incidence or mortality and differences in risk factor distribution; and probably also reflect complex interactions with other risk factors which are not always accounted for including educational level, socioeconomic status and access to high-quality healthcare. It seems that rural and remote area residents in the USA and Australia are at a disadvantage when it comes to cervical cancer incidence, survival and mortality which is not seen in Europe. This may be explained by the larger distances between cities in these two countries and differences in transportation systems. Therefore, access to healthcare may be more of a challenge for rural populations in the USA and Australia than in Europe.

3.3 Prevalence of HPV in healthy women and in cervical cancer specimens in Saudi Arabia

Prevalence studies of HPV in women from Saudi Arabia showed wide heterogeneity, with estimates between 5.9% and 31.6% for any type, 5%-43% for the high and intermediate risk types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68), and 9%-31.6% for HPV16 and HPV18 (3.3%-21.5% HPV16 alone, 1.4-15% mixed and 2.3-5.8% HPV18).[80-89] The most common type was HPV16, followed by HPV18 and HPV45. The variation between studies could be due to difference in settings (gynaecological clinics versus family medicine), intensity of cervical examinations in the centre (offering all eligible women versus only those who request it, are symptomatic or at high risk), inclusion criteria and detection methods (amplification versus hybridization techniques). Representativeness was probably an issue in all these studies which took place at a limited number of mostly specialised centres in Riyadh and Jeddah. Only one study mentioned participation rates, in which 70% of women were excluded. This was mainly due to refusal to take part (43%) which raises concerns of serious bias. Other reasons were pregnancy

(26%) and technical difficulties in sample collection (1%).[84] No population-based prevalence studies were found in the literature.

One study reported the seroprevalence of HPV6, 11, 16 and 18 IgG antibodies in 966 archived serum samples from healthy male and female blood donor and found it to be very low (1.7%). However, there are stringent criteria for blood donation which exclude potential donors with risky sexual behaviour. This may lead to an underestimation of HPV prevalence. Further, the four tested HPV subtypes are types included in HPV vaccines and antibodies in some samples could have therefore been generated by vaccination and not by natural infection. History of vaccination was unknown for the donors, many of whom were young.[85]

HPV was detected in 82% to 96% of cervical cancer specimens in Saudi Arabia. HPV16 was found in about two-thirds of samples, followed by HPV31, 18, 45 and 33 as a single infection. HPV18 was the second most common when considering mixed infection. Together, HPV16 and HPV18 comprised 79% of infections.[90-92]

3.4 Prevalence of abnormal cervical cytology in Saudi Arabia

fifteen studies from 12 tertiary and three secondary hospitals have described prevalence of abnormal cervical cytology between 1985 and 2017. Seven were located in Jeddah, five in Riyadh, two in the Eastern Region and one in the Southern Region. Proportions of smears with epithelial cell abnormalities ranged from 1.3% to 17.3%. The median proportion of abnormal smears was 4.5% while the median proportion of smears with invasive squamous cell carcinomas was 0.17%.[88,93-106] In the absence of organised population-based screening, it is difficult to draw a conclusion about prevalence of cervical cell abnormalities based on these findings, which may suffer biases due to the nature of the centre (secondary or oncology centre), reason for contact with a gynaecologist or general practitioner and undergoing a Pap smear, hospital eligibility (e.g. Saudi nationals or military) as well as study inclusion criteria. The age profile of participants varied widely, this is reflected in the up to 15-year difference in mean age at diagnosis of squamous cell carcinoma between studies.[93,105] Only one author reported excluding repeated smears for the same patient.[96] Some studies included all smears in the pathology department archives, while others were restricted to patients visiting gynaecologists or infertility clinics, and the reason for undergoing a Pap smear was not given. In a review of 10,659 Pap smears from women attending obstetrics and gynaecology clinics in Jordan, the incidence

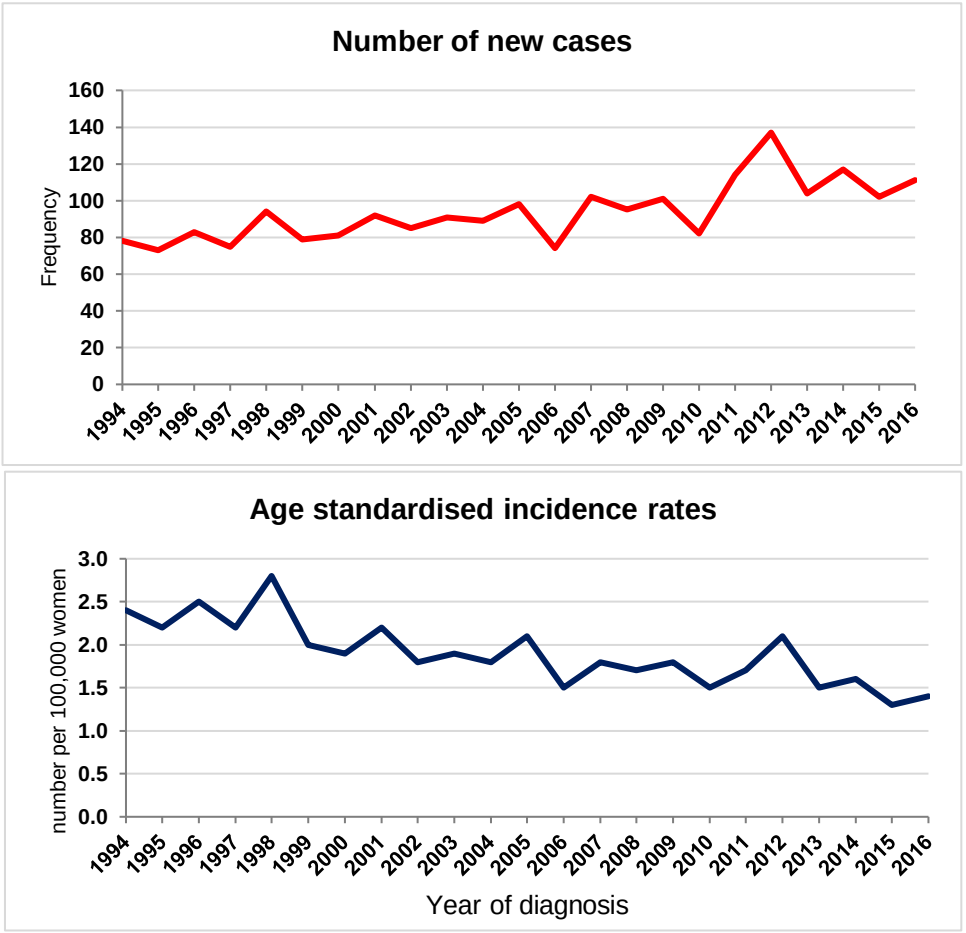
rate of cervical intraepithelial neoplasia (CIN) was much lower in those presenting for routine smears (49 per 100,000) than the total (114 per 100,000).[107] This reflects the low representativeness of hospital-based studies of cervical abnormalities.

Very few comparable Middle Eastern countries have population-based cervical cancer screening programmes. The screening programme in Turkey yielded 1.83% abnormal smears between 2001 and 2010 with a mean age of 45 years (standard deviation=12).[108] More recently, the Emirate of Abu Dhabi has introduced a screening programme starting at age 25. From a total of 4,593 screened women with a mean age of 39.5 years, the proportion of abnormal smears in the first year (2013) was 4.9%, while 0.05% showed malignancy, with a mean age of 45 years.[109]

3.5 Cervical cancer epidemiology in Saudi Arabia

The relative position of cervical cancer has been declining since the first report published by the Saudi Cancer Registry (SCR) in 2001, when it was the eighth and second most common cancer in Saudi and non-Saudi women of all ages, respectively.[110] In the latest report published for 2016, it became no longer one of the 10 most common cancers in Saudi women, though it remained the seventh most common cancer in non-Saudi women and ranked ninth among Saudi women aged 30-59. Cervical cancer made up 1.5% of cancers in Saudi women with an ASIR of 1.4 per 100,000 women, and 2.8% of all cancers in non-Saudi women, with an ASIR of 2.6 per 100,000 women.[111] GloboCan 2018 estimates for Saudi Arabia reported age-standardised incidence and mortality rates of 2.5 and 1.5 per 100,000 women, respectively.[112]

Figure 3: Number of new cases and age standardised incidence rates (per 100,000) of cervical cancer in Saudi females between 1994 and 2016.



data source: Saudi Cancer Registry, Cancer incidence reports

Data from the Saudi Cancer Registry between 1994 and 2016 (2001-2016 for non-Saudis) showed a mean of 94 and 54 new cervical cancer cases per year among Saudi and non-Saudi females, respectively, the latest published being 111 and 51 cases in 2016.[111] The ASIR has been slowly declining though the annual number of cases seems to be slightly increasing (Figure 3). This is consistent with international trends and reflects the growth and ageing of the population. Stage distribution was reported for 2002 only and included 26.9% localised, 39.8% regional, 10.8% distant and 22.6% unknown stage.[113]

3.6 Cervical cancer survival in Saudi Arabia

Age-standardised 5-year net survival from cervical cancer for women diagnosed during the calendar periods 1995-1999 and 2000-2004 was reported in CONCORD-2 at 62.2% (95%CI 50.6-73.8) and 65.6% (56.6-74.4) respectively. The SCR did not submit complete data for the calendar period 2005-2009.[10] There are no population-based stage-specific survival data published for cervical cancer in Saudi Arabia.

Four retrospective hospital-based studies of cervical cancer survival have been published. The earliest included 504 patients diagnosed and treated at King Faisal Specialist Hospital and Research Center (KFSHRC) in Riyadh between April 1975 and December 1993, of whom 410 received treatment with curative intent (radical surgery, radiation or a combination of both). The 5-year overall survival was 55% for all patients and 61% for those treated with curative intent. 5-year survival for stages 0 (in situ), I, II, III and IV, was 97%, 75%, 70%, 41% and 11% (4-year survival), respectively. While the stage-specific survival corresponded to that seen in developed countries, only 20% of patients were diagnosed with stage I disease, and 37%, 29% and 14% were diagnosed with stages II, III and IV, respectively. This is an unfavourable stage distribution in comparison to developed countries and is probably the main contributor to sub-optimal survival.[114]

More recently, a study from King Fahad Medical City, Riyadh, included 74 women with histologically confirmed locally advanced cervical cancer (66% IIB, 16% IIIA, 9% IIIB, and 8% IVA) receiving three-dimensional conformal radiotherapy with chemotherapy followed by high dose brachytherapy, between 2007 and 2012. 5-year overall survival was 64.5%.[115]

For 60 patients diagnosed between 2004 and 2010 and treated at the radiotherapy departments of KFSHRC and King Abdulaziz University Hospital in Jeddah, 4-year overall survival was 79%. Stage at diagnosis was 5% IB, 3% IIA, 69% IIB, 5% IIIA, 15% IIIB and 3% IVA.[116]

Between January 1999 and December 2017, 190 women with a mean age of 54 years were treated for cervical cancer at King Abdulaziz University Hospital in Jeddah. 19% were diagnosed at stage I, 49% at stage II, 18% at stage II and 14% at stage IV. Their 5-year overall survival was 32%, but the 18-year period included may mask any changes in stage distribution or survival over time.[117]

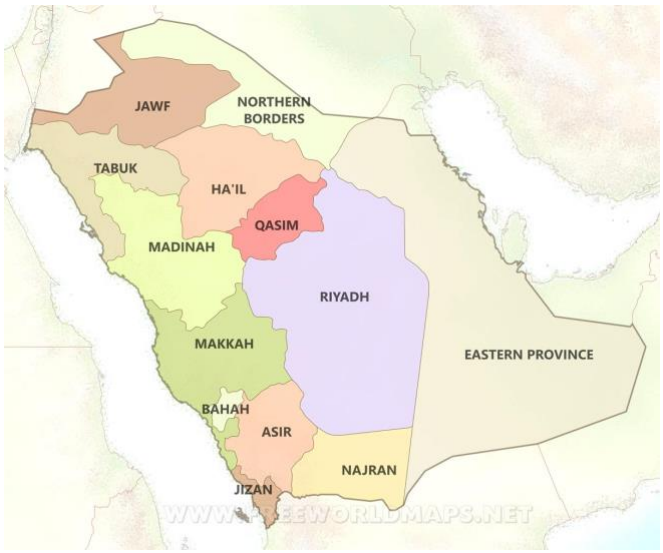
The four studies had different inclusion criteria, and all took place at tertiary referral centres often receiving more advanced cases but having the most advanced resources and experienced physicians.

Chapter 4. Healthcare and cancer control in Saudi Arabia

4.1 Demographics

The Kingdom of Saudi Arabia covers a total area of 2,149,690 km^2, occupying the majority of the Arabian Peninsula. It is divided into 13 administrative regions (Figure 4). Two-thirds (65.6%) of the population live in the three regions of Riyadh (25.5%), Makkah (25%) and the Eastern Region (15.1%).[118]

Figure 4: Administrative regions of Saudi Arabia.

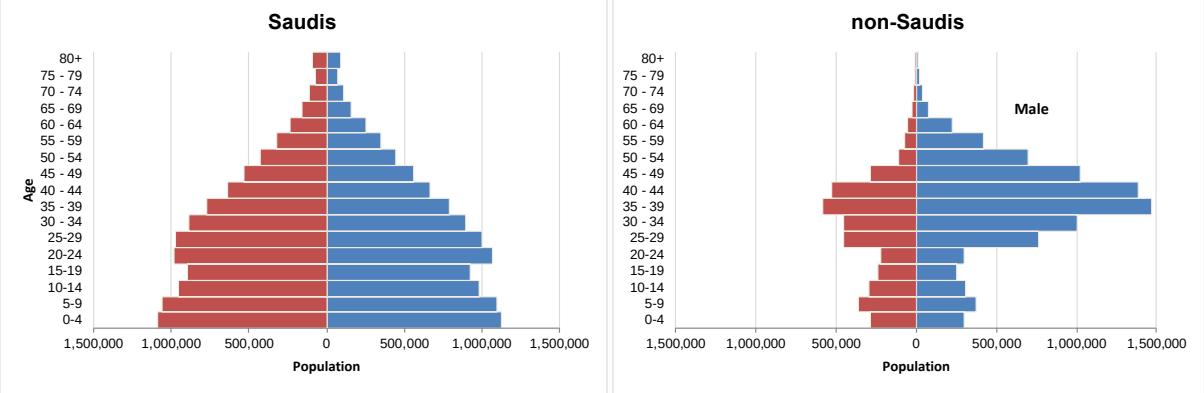


source:www.freeworldmaps.com

The combination of high fertility rates, increased life expectancy and migration has led to the population growing from 7 million (89% Saudis) in 1974 to over 34 million (63% Saudis) in 2019.[119,120] In 2016, the annual growth rate was 2.54% for the total population and 1.1% for Saudi nationals. The total fertility rate has declined steadily since the end of the 1970s from around 7.3 to 2.5 children per woman in 2016.[121] High fertility rates up until the end of the 20th century along with low infant mortality rates have led to a large population of women now occupying the age group at risk for cervical cancer (20-65 years).

The sex distribution of Nationals is fairly equal (50.9% female), while a large proportion of non-nationals is represented by males 25-44 years of age from Asian and Arab countries employed in various sectors (Figure 5).

Figure 5: Population pyramid for Saudis and non-Saudis, 2018 estimates. Data source: General Authority for Statistics



4.2 Vital statistics

Population counts are produced by means of periodic census, with counts for the intervening years being estimated by applying growth rates generated from the demographic surveys (1998, 2000, 2007, 2016). A comprehensive census has been carried out in 1974, 1992, 2004 and 2010. The next census was planned in 2020 but has been delayed due to the Covid-19 pandemic. The General Authority for Statistics publishes population counts by sex, 5-year age groups, administrative region and nationality (Saudi/non-Saudi).

When a person dies, the death must be certified by a physician and a death notification form is filled which includes national ID number, age, sex, the immediate and underlying causes of death and any other conditions contributing to the death. A copy of the death notification is given to the family of the deceased in order to register the death with the Department of Civil Status of the Ministry of Interior within 30 days. A death certificate is then issued, which is necessary for inheritance purposes. Burials can take place using only a copy of the death notification as burials traditionally take place within one or two days of a person's deaths.

The Ministry of Health (MOH) receives death notifications only from hospitals operating under it, and cause of death is coded centrally by the statistical department of the MOH. Annual mortality reports are produced by cause of death in crude categories (for example, external causes, cardiovascular, perinatal and neoplasms).

I obtained the complete 2016 MOH mortality database in which 45,686 deaths were recorded. Of those, only 2,076 were due to neoplasms (4.5%). The other four most commonly mentioned causes of death were “non-specific signs and symptoms” (33.6%),

"circulatory system illness" (14.4%), “factors affecting health status” (14.4%) and "accidents and external causes" (4.4%). This shows both an under-enumeration of deaths in the MOH mortality database compared to those reported from the census (over 80,000 deaths in 2010) and the low-quality of cause of death certification. This has also been reported in the Global Burden of Disease study,[2] In which the quality of death certification for the period 2010-2017 was rated as 2 on a scale of 0-5, and the percent well certified causes of death was 28.8%, completeness of death registration was estimated at 63%, and 55% of vital registration deaths were assigned to major garbage codes. Recent efforts for improving reporting of deaths and cause of death coding have been taking place though the introduction of an electronic reporting system (Balsam) in MOH hospitals in 2018 and running ICD-10 coding workshops.

Besides the MOH, other sources for death counts, include census, the family health survey, demographic surveys and municipality burial statistics. The official numbers published by the general authority for statistics rely on the first three. Burials tend to be largely under-recorded with the total number of those buried being approximately 30% lower than the deaths published by the statistical authority, and the number of men buried being approximately 70% higher than women. Data on deaths registered with the department of civil status are not publicly available.

4.3 Healthcare

Free healthcare is available to all Saudi nationals at primary, secondary and tertiary healthcare centres operated by the MOH. Several health services are funded and managed by government sectors other than the MOH: The Armed Forces medical services, Security Forces medical services, National Guard health services, Royal Commission for Jubail and Yanbu healthcare services, Saudi Arabian Oil Company (ARAMCO) hospitals and Ministry of Education. These are in general only accessible to employees of their sectors or by referral or royal decree, which is usually limited to Saudi nationals. University hospitals are an exception, in that any patient (including non-nationals) can be accepted as a teaching case. King Faisal Specialist Hospital and Research Center (KFSHRC) also receives separate government funding and is a referral centre in the two major cities of Riyadh and Jeddah. About 30% of cancer patients in the country are treated in the Riyadh hospital alone. Private hospitals and clinics can be attended by paying or insured patients; they vary widely in prices and infrastructure.

Altogether, there are 498 hospitals in the kingdom: 286 MOH, 48 other above mentioned government sectors and 164 private hospitals, providing 58%, 17% and 25% of hospital beds, respectively.[122] The Saudi Health Council was founded in 2002, with the aim to oversee and coordinate the various private and government health services, in order to increase efficiency and improve healthcare equity.

Despite the availability of free healthcare and modern facilities, there is inequitable distribution of health services between geographic areas,[11] which especially impacts those in rural and border areas with limited mobility: the elderly, young, disabled, and to an extent, women. Until 2018, women were officially banned from driving, which is the main mode of transport in the country. Another obstacle to seeking medical care is that even in urban centres, waiting times for diagnostic and treatment services in government hospitals may be very long.[123]

Non-nationals are required to have health insurance. Domestic employees can access MOH services as an exception, but cancer treatment may be limited to surgical excision and a certain number of chemotherapy cycles. In some cases, royal orders are issued for non-nationals to be treated at specialised government centres. There are also some charities which help cover their treatment costs.

The Council of Cooperative Health Insurance was established in 2014. It's role is to regulate insurance providers and set minimum coverage requirements, and has mandated the private sector to insure employees and their dependents.[124] Government employees and unemployed citizens will be covered by a national insurance scheme. This scheme will also cover health services beyond the private insurance limitations for citizens who hold private insurance.

Insurance companies are not required to reimburse the costs of screening or the HPV vaccine. The treatment of sexually transmitted infections is excluded from coverage according to the Council of Cooperative Health Insurance regulations.[124] Yearly insurance coverage limits of 500,000 Saudi Riyals (133,313 USD), and the lack of expensive imaging and radiotherapy equipment in private hospitals may pose a special challenge to cancer care in the private health sector. This could offset the advantage gained by less waiting time in contrast to government hospitals.

In the context of the national transformation programme, a plan towards corporatisation of governmental healthcare facilities is in place, in which five government holding companies

will be established and will oversee healthcare clusters in their geographic region (Central, Eastern, Western, Northern and Southern). Healthcare clusters will afterwards be matured to independent Accountable Care Organizations (ACOs). The aim is to improve access to health services, increase equity and efficiency and provide more effective primary care. Strengthening the role of primary care is expected to increase the utilisation of preventive and early diagnostic services, resulting in timelier referral. The ministry of health would take on a regulatory and legislative role over healthcare facilities in the country. Healthcare clusters will be financed through both a national health insurance scheme and private insurance.[125]

4.4 The Saudi Cancer Registry

The Saudi Cancer Registry (SCR) was established in 1992 and now operates under the umbrella of the Saudi Health Council. It is a population-based registry with national coverage, which started recording incident cancer cases in January 1994. In addition to the main office in Riyadh, five regional offices have been set up in the Central, Eastern, Western, Northern, and Southern regions. A ministerial decree in 1992 has made notification of every cancer diagnosis and death from cancer mandatory for all hospitals, clinics and laboratories. Maintaining a database of cancer diagnoses is required for hospitals treating cancer patients in order to obtain accreditation by the Saudi Central Board for Accreditation of Healthcare Institutions.[126] This insures the continued access of the registry to cancer patient records. All invasive neoplasms including non-melanoma skin cancer, haematological malignancies and cancer of unknown primary site are registrable (full list in appendix A).[127]

Active case-finding is carried out by trained registrars. It relies primarily on pathology reports, with other sources being cytology, radiology, radiotherapy, haematology and outpatient departments, as well as hospital death notifications. Many hospitals have information systems which are also used to provide a list of patients with a diagnosis of cancer. Some pathology departments keep a log of cancer diagnoses to facilitate registrars' access to patients' pathology reports. Registrars use the medical record number to retrieve the patient's file from which data are abstracted. These include personal details: name (first, father, grandfather and family name according to official documents, using standardised Latin spelling assigned to each Arabic name), nationality, ID number, date of birth, sex, marital status, address and telephone number; and tumour details (full date

of diagnosis defined as date of confirmation on pathology report, primary site, histology, behaviour, grade, stage, laterality and basis of diagnosis). Date of last contact, vital status and cause of death if dead (cancer or other) are recorded based on information available at the time of abstraction and are later updated if other sources for the same patient become available, including records from other hospitals, death notifications or death certificates.

Death notifications are usually kept in a dedicated department in hospitals. Cancer registrars manually search for death notifications with a mention of cancer. Additionally, Death certificates with a mention of cancer have been provided to the SCR by regional departments of vital statistics since 2005. These two sources are used to find missed cancer cases and to update the vital status of already registered patients. Consequentially, the availability of information on death in the registry is mostly limited to those with a mention of cancer on their death documents. The completeness of ascertainment is also dependent on physicians correctly documenting the cause of death. There is no formalised mechanism to follow up all cancer patients.

When the first mention of cancer is received on a death notification or certificate, the basis of diagnosis “death certificate only” (DCO) is assigned, and registry staff attempt to trace back the medical record with the first diagnosis after a 6-month wait period. A date of diagnosis preceding death is successfully traced within the region in about 80% of cases, in which case the basis and date of diagnosis will be updated. If no other source mentioning cancer is found from any region, the basis of diagnosis remains DCO and the date of diagnosis and date of death remain the same (Sameer Alkaifah, Saudi Cancer Registry Western Region senior registrar, personal communication, 13 March 2018).

The International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) coding for tumour topography (anatomical origin) and morphology (histology and behaviour), and SEER (Surveillance, Epidemiology and End Results) Summary Stage 2000 have been used for tumour coding and staging respectively since 2001. Where stage is recorded as TNM or FIGO classification, it is converted to SEER summary stage using the American Joint Committee on Cancer (AJCC) manual rules.[128] A computerised system (CanReg 4) is used to register cancer cases and check quality of the data, including flagging unfilled mandatory variables, first name-sex mismatch and invalid or rare combinations such as sex-topography. Data from the regional offices are sent to the main office of the registry in Riyadh, where further quality control measures are carried out including comparing the

number of cases from each region with the previous year, checking for duplicates by national ID, name and medical record number, as well as checking for duplicates in CanReg with at least 70% similarity, then combining any duplicates. Variables are checked again for invalid entries or combinations. Any suspected errors are sent back to the registrars in regional offices for correction. Finally, the central office checks for duplicates over the past five years.

The registry publishes annual cancer incidence reports describing age and regional distribution of cancer diagnosed in each calendar year. Incidence amongst nationals and non-nationals is reported separately due to the stark difference in demographic characteristics between the two groups. The registry currently publishes cancer incidence reports within three years of the registration year and aims to reduce the gap to one year.

Quality of registry data

An assessment of the registration process, and of the comparability, completeness and validity of the SCR data was carried out in 2013 by the International Network for Cancer Treatment and Prevention, which included visits to 16 hospitals across the five regions and examining registry data for the period 1994-2009.[129]

Completeness

This refers to the extent to which all of the incident cancer cases are included in the registry database. Incidence trends were steadily increasing over time with no significant fluctuation. Compared to neighbouring countries, age-standardised incidence rates (ASIRs) were the lowest in Saudi Arabia for both men and women for all cancers combined, but were similar to ASIRs for Oman and the United Arab Emirates. More notably, there were large regional discrepancies in ASIRs for all cancers combined, the highest being for Riyadh (117.5 per 100,000 males and 123.6 per 100,000 females) and the lowest for Jazan (30.7 per 100,000 males and 46.0 per 100,000 females). Prevalence of risk factors may largely vary between urban and rural areas. However, this discrepancy may partially result from misclassification of addresses for patients that were diagnosed and treated outside of their area of residence.

The age-specific curves for common cancers generally corresponded to what is expected for each site. The proportion of tumours that were morphologically verified (MV%) was relatively high for oesophagus (96.2%), liver (64.8%), pancreas (79.1%) and brain

(91.4%), for which clinical methods of diagnosis and imaging are often used. This might point to over-reliance on pathology reports for case finding.

Childhood cancer incidence is expected to be similar in different parts of the world and is therefore often used as an indicator for completeness of registration.[130] Age-specific incidence rates were within the reference range for boys, and slightly under the reference range for girls aged 5-14 years.

Validity

Validity points to the proportion of cases with a given characteristic in the registry that truly have it. The percentage of morphologically verified (MV%) diagnoses for all tumours has been consistently around 93% since 2005, but higher in earlier years. It was lower than 80% for liver, pancreas, unspecified digestive system cancers and leukaemias. The lowest MV% was observed in the age-group older than 80 (79.1% in males and 83.9% in females). Some regional variation was observed for MV%, the lowest was in the Northern region (80.9% in males and 89.0% in females) and the highest in Makkah region (96.0% in males and 97.6% in females).

The proportion of cases that were registered by death certificate only (DCO) increased from 0% in 1994 to 3.3% in 2000, then decreased to 2% in 2009 due to efforts to trace back the hospital records of death certificate notified tumours. It ranges from 0% for several sites to about 30% for acute undifferentiated leukaemia (C95). The highest percentage of diagnoses by DCO was in those older than 80 (9.5%).

Topography was unspecified for 4% of all registered tumours, the majority of which were metastasis of unknown primary. This proportion decreased slightly in the last three years examined (2006-2009) and increased with old age, reaching 7% for females older than 80.

The above-mentioned indices of validity were fairly consistent over time after the first few years of registration, and their age patterns seem to reflect diagnostic limitations in older age rather than deficits in the abstraction process. However, their values need to be interpreted in light of what is expected for the country's diagnostic infrastructure. Lack of a standard reference for comparison decreases their usefulness in assessing validity.[131]

One way to evaluate the completeness and validity of registry data is through reabstracting and recoding records from a given source and comparing them to registered data.[131] This was only done once in the past and for the first year of registration (1994) at KFSHRC in

Riyadh. The reported ascertainment proportion, which at the time relied on medical records only, was 68%, and major disagreement was found between the abstracted and re-abstracted data for stage (44%) and for histology and behaviour (26%).[132] Such issues are expected in the early years of a registry and additional sources of case finding have been in use since then such as radiology, outpatient clinics and death notifications.

Timeliness

When comparing the number of tumours in the 2009 cancer incidence report and tumours that were diagnosed during 2009 in the SCR database as of December 2012, a difference of 2-9% was observed for various common tumours, which reflects some late reporting. The assessment did not include individual cancers, but the number of women who were diagnosed with cervical cancer during 2009 as of 30 November 2018 in the SCR database (188) was 23.6% higher than the number reported in the 2009 cancer incidence report (152).[133] This may reflect more delayed reporting for cervical cancer or continued delay beyond the first three years.

4.5 Cancer control

The Gulf Center for Cancer Control and Prevention (GCCCP) was founded in 2011 and is based in KFSHRC in Riyadh. The scope of its work includes introducing cancer control strategies and evidence-based guidelines for cancer management, and supporting cancer research in the Gulf Cooperation Council (GCC) states (Saudi Arabia, the United Arab Emirates, Oman, Kuwait, Bahrain and Qatar). It has published a joint cancer control plan for the GCC states for the period 2016-2025 with the aim to reduce the burden of cancer and the associated human and financial cost through targeting various elements of the cancer control continuum. It states however, that individual states are encouraged to produce their national operational action plans according the their unique needs and resources.[134]

Primary prevention

The Gulf cancer control plan sets targets for several known cancer risk factors (overweight, physical activity, infections, environmental factors, diet and smoking). Tobacco consumption has increased by 12% in Saudi Arabia between 1996 and 2012,[135] but several anti-tobacco policies have been introduced in recent years, including indoor

smoking ban, plain packaging, health warnings, ban on advertising, cessation services and a large increase in tobacco tax in since 2017.[136]

Screening and early detection

The Saudi MOH has published screening guidelines for breast, colorectal and cervical cancer,[29,137,138] but there are currently no organised population-based screening programmes. The current fragmented health system and weak primary care mean there is often no clear path for individuals to seek the appropriate care they need. The efficiency and timeliness of cancer diagnosis and referral are also adversely affected by the complexity of this system.

Treatment and palliation

Ten governmental oncology centres provide specialised comprehensive care for cancer patients in Saudi Arabia:[139] five in Riyadh (King Faisal Specialist Hospital and Research Center, King Abdulaziz Medical City of the National Guard Hospital, King Fahad Medical City, Prince Sultan Medical Military City, and King Saud Medical City); three in Jeddah, the largest city of the Western Region (King Faisal Specialist Hospital and Research Center, King Abdulaziz Cancer Center (since 2010, the oncology centre was transferred to King Abdullah Medical City in Makkah and Jeddah), and Princess Noorah Oncology Center of the National Guard Hospital); and one in the Eastern Region (King Fahad Specialist Hospital). More recently, oncology centres have been launched in Makkah (King Abdullah Medical City, 2010) and Madinah (King Fahad Hospital, 2017).

Other major hospitals like ARAMCO hospital and some university and private hospitals provide treatment for cancer patients, but may lack services such as radiotherapy and palliative care.

Cancer care in rural areas is provided by general practitioners or non-specialised gynaecologists and surgeons. Patients who are referred to more specialised care may face logistical challenges such as in transport and housing. In a geographic information system analysis which mapped the city of residence for 45,532 individuals with registered cancers that were diagnosed between 1998 and 2004, approximately 40% lived more than a three-hour drive from the nearest city containing a specialist cancer centre, the median travel time was estimated to be 212 minutes. Those living in the Northern and Southern regions had the longest travel time (longer than five hours).[12]

Palliative care is mainly provided at the above-mentioned oncology centres. A recent pilot project carried out under the MOH model of care project provided primary health centre-based palliative care to 200 cancer patients and showed higher adherence to treatment and very high patient satisfaction.[140] The MOH plans to roll out the project over the next decade to cover more geographic areas.

An additional challenge cancer patients face is cancer treatment shortages, which has been reported to occur at least occasionally at all oncology centres in the country, and has led to treatment failure or relapse due to treatment delay or substitution.[139]

Rehabilitation and mental health services within the formal healthcare system are limited. Charities, civil society organisations and patient groups provide various types of material, psychological and spiritual support to cancer patients and cancer survivors.

Cervical cancer prevention and control

In 2013, the Saudi MOH introduced a 2-dose HPV vaccine schedule into its national immunisation programme, to be administered to girls at ages 11 and 12; and a 3-doses catch-up schedule given at 0, 1-2 and 6 months for females aged 15-26. However, availability of the vaccine has been limited mostly to private clinics and hospitals with high levels of resources such as KFSHRC and National Guard Hospitals (Dr. Fadia Albuhairan, personal communication, 15 November 2020). Of 450 Saudi women aged 18 to 57 who were randomly selected from gynaecology and primary care clinics in Riyadh, less than 1% had an HPV vaccine. Almost half the women were younger than 30 when the survey was conducted in 2018. Therefore, at least some of them belong to a cohort that was eligible for vaccination.[141] There are no published government data so far on HPV vaccine coverage in eligible girls and women.

Although the Saudi MOH recommends universal screening for ever-married women, there are no existing organised programmes for cervical cancer screening to date in Saudi Arabia. It's up to the healthcare provider to offer Pap smears and most smears take place opportunistically if eligible women present to a gynaecologist. Primary physicians have a limited but increasing role in offering and performing Pap smears. In a survey of 500 eligible women in Jeddah in 2008 with a median age of 42 years (range 18-66), only 16.8% had ever had a Pap smear and a little over half of those stated that their physician offered it. It does not mention how many had undergone it routinely versus as an investigation due to a complaint.[142] Similarly, of 450 women surveyed in Riyadh in 2018 (mean age 33), only

26% had ever undergone a Pap smear test.[141] Of 200 eligible female physicians surveyed in 2009, (70 gynaecologists and 130 non-gynaecologists), only 28.5% had undergone Pap smears themselves and only 61.4% of gynaecologists reported ever recommending it to patients.[143] In the nationally representative World Health Survey Plus conducted in Kuwait, Oman, Saudi Arabia and the UAE in 2008, only 7% of 2,746 eligible women in Saudi Arabia received a Pap smear within recommended intervals for their age (within the past 3 years for women 25-49 years and within the past 5 years for women 50-64 years).This was the lowest among the included countries. Women living in urban areas were twice as likely to have had a Pap smear within the recommended interval. Higher educational level was also associated with Pap smear uptake while wealth was the strongest predictor: 10% of women in the high wealth category and 2.5 % of women in the low wealth category received a Pap smear within the recommended interval.[144]

Barriers to prevention and early diagnosis

While some women prefer or insist on being examined by a female physician, this wish can usually be granted. Shame and shyness from discussing symptoms like vaginal bleeding, especially with a male relative, lack of awareness about the potential significance of such symptoms and of the availability and benefits of screening might delay presenting to a healthcare provider.[142] The belief that cancer is an incurable disease, and superstition that “seeking out or speaking of such serious diseases” could attract ill fate, may also lead women to ignore their symptoms and reject the offer of a Pap smear. In the case of cervical cancer, the fact that the causative agent is a sexually transmitted virus makes it challenging to educate women in order to make an informed decision about HPV vaccination and screening, especially in a conservative society where it is generally assumed that premarital and extramarital sexual relations are rare. The lack of adolescent health platforms may pose a challenge to reach high coverage for the HPV vaccine.[145]

Changing risk factors

The number of lifetime sexual partners is the most important predictor of persistent high-risk HPV infection.[25] In a survey of 400 women who have been ever married (married, divorced or widowed) attending family medicine or gynaecology clinics between November 2013 and November 2015, 12% reported having had more than one lifetime sexual partner. Due to cultural sensitivity, never married women could not be included in this survey. Further, their husbands’ sexual history is unknown, and polygyny is practiced by

some men in Saudi Arabia. In the same survey, 30% of the women were smokers.[87] However, in the nationally representative Saudi Health Information Survey conducted in 2014, only 1.5% of women older than 15 were current smokers, with an average of 3.7 cigarettes consumed a day among those who smoked.[146] Age of marriage in Saudi Arabia has been increasing. In the 2016 demographic survey, over 30% of ever-married women aged 45 and more reported that their first marriage was before age 19, while only 17% of ever-married women aged 25-35 were married by age 19. Previous marriages of the husband may also play a role in risk of exposure to HPV. Of the ever-married surveyed population, only 3% of women, but 13% of men, were married more than once.[147] It is unknown whether delaying marriage could lead to an increase in premarital sex. Women are delaying pregnancy and having less children on average,[121] which may reduce the risk of cervical cancer.

Chapter 5. Principles of cancer incidence, survival and mortality

Incidence, survival and mortality are complementary indicators that help to assess the cancer burden in a given population. In order to reach a comprehensive understanding of the effectiveness of cancer control measures, any change, or lack thereof, in survival should be interpreted together with incidence and mortality.

5.1 Incidence

Cancer is unique among major chronic diseases in that data on the occurrence of disease have been available from population-based registries for many countries, in some cases for more than 60 years. These datasets enable the calculation of incidence rates and trends.

The incidence rate is defined as the number of new cases occurring over a given period, typically a year, in a defined population, divided by the person-years at risk:

$$incidence\ rate = \frac{number\ of\ new\ cases\ of\ disease\ in\ a\ period}{person\ years\ at\ risk}$$

In a stable population, the mid-year population can be used as an approximation for the person-years at risk. Cancer incidence rates are usually expressed per 100,000 persons per year. In the case of cervical cancer, the population at risk is the general female population.

Incidence rates are important in identifying risk factors for a disease and allocating preventive services. Monitoring trends in incidence help to plan for future healthcare demands.

5.2 Survival

In longitudinal studies where subjects are followed-up from a defined starting point (for example, diagnosis) up to the event of interest (for example, death or loss to follow-up), survival analysis allows for the estimation of event rates that may not be constant over time.

Survival can be expressed in terms of the hazard *h(t)*, the instantaneous rate at time *t,* or the survivor function *S(t)*, which is the probability that an individual will survive up to a given time *t* after diagnosis. The cumulative hazard rate over the duration of the study

gives the hazard function, also known as the cumulative hazard *H(t)*, which has a direct mathematical relationship with the survival function:

$$S(t) = e^{-H(t)} \quad \text{or equivalently:}$$

$$H(t) = -\log(S(t))$$

If a person is known to have survived up to a certain point in time, but whose survival past that point is unknown, they are censored, i.e., they only contribute their follow-up time to the point when they are censored. This occurs when the person is lost to follow-up, experiences a competing event that precludes the event of interest from being observed, or does not experience the event of interest by the end of the follow-up time. Censoring is said to be non-informative if the probability of being censored is independent from the probability of experiencing the event of interest.

Because the risk of death usually varies with time since diagnosis, it is useful to display a survival curve graphically in a step function where there is a drop every time an event is observed. Patients who are censored do not cause a drop in the curve, but are removed from the population at risk in the next interval. As a summary statistic, survival is reported as a proportion surviving for a defined duration (usually 1 or 5 years).

Survival is classically estimated using the Kaplan-Meier method, which is a non-parametric method calculating the probability of surviving up to a given time (for example, 5 years) as the product of the conditional probabilities of individuals surviving over successive small-time intervals, given that they survived up until that time.

Population-based cancer survival

Examining cancer survival on a population level enables the assessment of the overall performance of the healthcare system in managing cancer, including timely diagnosis and effective treatment. It relies on having high quality registry data covering the whole population of a defined geographic area. The population at risk is those diagnosed with the cancer of interest. The date of diagnosis is the starting point for follow-up.

In terms of years of follow-up used to estimate cancer survival, two main approaches are used: the cohort approach uses the actual observed survival experience of a cohort of patients until the end of the desired follow-up (for example, 5 years), and only cohorts with a potentially full follow-up time are included in the analysis. A variation of this approach is the complete approach, where all the available years of diagnosis are included and cohorts

without the full follow-up experience are censored. An alternative "period" approach was proposed to predict survival when not all cancer patients have been followed for the desired time (for example, at 5 years since diagnosis). This approach uses the most up-to-date data and draws on the survival experience of individuals diagnosed in earlier years who are still alive in the calendar period of interest and for whom the full follow-up time has been observed. Thus, the conditional survival probabilities from individuals diagnosed during successive years are multiplied. Survival in this case is observed for a 5-year period of follow-up rather than a 5-year cohort. This has the advantage of including the most recent years of diagnosis and it was argued by the authors that this "period" analysis produces estimates closer to the true survival experience than the complete approach when the cohort is eventually followed for the full duration of interest.[148]

In registries where follow-up is obtained by passive linkage to the death index, it is often the case that the follow-up is more recent than the available years of cancer registration, especially when cancer registration is carried out manually. In this case a "hybrid" approach can be used, which includes elements of the cohort and period analysis.[149]

Net survival

In population-based cancer survival, we are interested in isolating the hazard of death due to cancer in order to compare the survival experience between different settings or monitor progress over time, whilst taking account of background mortality in the population. This can be estimated in two different settings: “Cause-specific” and “relative”.

In a cause-specific survival setting, deaths attributable to cancer are the event of interest, while deaths due to any other cause are censored. Survival is usually estimated using the Kaplan-Meier method. It requires both the correct attribution of cause of death by the reporting physician and appropriate coding of the underlying cause of death. Determining whether the cause of death in a cancer patient is their cancer is challenging and may be subjective, since cancer and its treatments can affect many of the body's systems and cancer often occurs in elderly people with pre-existing comorbidities. Moreover, it cannot account for the informative censoring by other causes of death which is problematic when it differs between populations being compared. This informative censoring also increases in older age groups.

The relative survival setting compares the survival experience of the cancer population to that of the general population, that is, the observed versus the expected survival. Thus,

aiming to estimate the excess deaths in the cancer population compared to the age- and sex-matched general population. However, because cancer is not the only cause of death in cancer patients and death from other causes precludes death from cancer (competing risks), and because the hazard of death from other causes varies between populations and increases with age, the ratio of survival observed in the cancer population to that of the general population, known as the relative survival ratio, is not an appropriate measure to compare survival between populations or over time. Therefore, an estimator must be used that addresses these issues.

Net survival is the cumulative probability of surviving up to a given time since diagnosis, after correcting for background mortality. The population background mortality is given by life tables of all-cause death rates by a set of covariables, usually single year of age, sex, and calendar year, which are available from government census data. For this purpose, the Pohar-Perme estimator is used. It is a non-parametric estimator which gives an unbiased estimate of net survival because it takes account of differences in mortality due to causes other than the cancer of interest (background mortality) between the populations being compared, and of the increase in competing risks of death in older age. It achieves this by giving individual weights to each failure and censoring time which are equal to the inverse of the expected probability of surviving up to this time.[150] In other words, it is the cumulative product of the partial probabilities of survival, weighted by the inverse probability of an individual being alive in the population.

Estimation of net survival requires the following assumptions:[150]

1- Time to death due to the disease and time to death in the population are conditionally independent, given a set of covariables (age, sex). i.e., within each demographic stratum, time to death in the cancer population does not depend on time to death in the population.
2- Non-informative censoring.
3- That the disease is rare. Since the life tables are derived from the general population including individuals with the cancer of interest, the assumption is that their effect on the overall all-cause mortality rates is negligible.

5.3 Mortality

Cancer mortality data are obtained from cause of death certification where the underlying cause of death is recorded by a physician as cancer. This information is routinely collected

by the ministry of health in a country or region. Mortality rate refers to the number of deaths due to a given cause divided by the mid-year population at risk.

$$mortality\ rate = \frac{number\ of\ deaths\ due\ to\ the\ disease\ in\ a\ period}{person\ years\ at\ risk}$$

As with incidence, the denominator for cervical cancer mortality is the general female population. The mortality rate is usually expressed per 100,000 population per year.

Mortality has the advantage of not being affected by biases caused by changes in diagnostic procedures in the same way that incidence and survival are.

Although reducing mortality is the ultimate goal of cancer control strategies, mortality rates per se are not the best indicator of progress in cancer control. First, because mortality for many cancers, including cervical cancer closely mirrors incidence patterns. Incidence is a reflection of risk factors which a person is exposed to years or decades earlier. Due to long latency, preventive measures are only expected to manifest years later. Second, mortality is affected by survival of patients diagnosed in previous years, and this backscatter in time varies with time, and increases as survival improves. Thus, it is difficult to interpret, and it is not as sensitive to changes in diagnosis and treatment.

5.4 Age standardisation

For many cancers, incidence and mortality rates increase by 100-fold or more over the adult age span. Because the age profile of populations varies geographically and over time, it is necessary to age-standardise these metrics to enable meaningful comparisons. For cervical cancer, incidence rates change less markedly with age, but standardisation for age is still required to enable comparison of all-ages rates over time and between populations.

For incidence and mortality, we use the direct standardisation method applying the weights from the Segi-Doll world standard population to the age-specific rates.[151] The world standard population was introduced by Segi (1960)[152] and then modified by Doll et al. (1966) for the first volume of *Cancer Incidence in Five Continents* (Table 2).[151] The Segi-Doll world standard population is still used in order to enable continuous comparison between countries and regions and over time.

Table 2: Age distribution of the Segi-Doll world standard population

Age group	Standard population weight
0-4	12,000
5-9	10,000
10-14	9,000
15-19	9,000
20-24	8,000
25-29	8,000
30-34	6,000
35-39	6,000
40-44	6,000
45-49	6,000
50-54	5,000
55-59	4,000
60-64	4,000
65-69	3,000
70-74	2,000
75-79	1,000
80-84	500
85+	500
Total	**100,000**

For survival, it is necessary to use cancer population weights because we estimate survival within a cancer population, for which the age profile differs markedly from that of the general population. The International Cancer Survival Standard (ICSS) weights have been derived from analysing over one million adult cancer patients included in the EUROCARE-2 study, using multivariable methods to derive the smallest number of sets of standard weights. Three broad cancer age-incidence patterns were identified: (1) cancers for which incidence increases with age; (2) cancers for which incidence is fairly constant with age; (3) cancers mainly affecting young adults. For cervical cancer, ICSS group 2 is used (Table 3).[153]

Table 3: International cancer survival standard (ICSS) weights, group 2

Age group	Standard cancer patient population weights group 2
15–44	0.28
45–54	0.17
55–64	0.21
65–74	0.20
75+	0.14
Total	**1.00**

Chapter 6. Methods

6.1 Data sources

Registry data

Cervical cancer records for the whole period of data availability (1994-2016), including in situ cancer were obtained from the Saudi Cancer Registry (SCR) (n=4,071; 1,841 diagnosed in 1994-2004 and 2,330 in 2005-2016) via the CONCORD file transmission utility.[154] The dataset included full date of birth, date of diagnosis, date of last known vital status, administrative region and city/town of residence, diagnosis and referral; as well as nationality, tumour stage (SEER Summary Stage 2000) grade, morphology, behaviour and cause of death if a death notification or death certificate was received (cancer, other or unknown).

Ethical approval was obtained from the London School of Hygiene and Tropical Medicine prior to data transfer (Appendix D. Ethical approval).

Population counts and life tables

The general authority for statistics provided death counts and mid-year population counts for the years 2004, 2007, 2010 and 2016 by nationality (Saudi/ non-Saudi), 5-year age groups (0-4 to 80+) and administrative region. These data were collected during the 2004 and 2010 census and the 2007 and 2016 demographic surveys. Death counts rely on recall of deaths which occurred in the household over the past 12 months. Based on the census and demographic surveys, the SCR produced population counts for the years 2005-2016 by 5-year age groups, which I used to estimate incidence and mortality.

I calculated all-cause mortality rates by age group and administrative region for Saudi and non-Saudi females. However, the mortality rates were irregular especially for non-Saudis, older age groups and for regions with smaller populations.

The United Nations Population Division (UNPD) publishes population and mortality estimates in the World Population Prospects. The same above-mentioned sources for Saudi Arabia were utilised but estimates were adjusted for under-enumeration of the population and for under-5 and old age mortality. Internal consistency by age and sex and over time was ensured, as well as between demographic components (fertility, mortality

and migration) and the population. Some years were prioritised due to fluctuation in the reported data.

The Institute of Health Metrics and Evaluation (IHME) also publishes life tables in the context of the Global Burden of Disease study (GBD).[155] In order to produce life tables for Saudi Arabia, it uses various data sources including the Ministry of Health mortality database, United Nations Statistics Division (UNSD), census data from the Central Department of Statistics and Information (now the General Authority for Statistics) demographic bulletin. It corrects for lower completeness of death ascertainment in women and extremes of age, employing complex modelling methods.

I used UNPD life tables in the net survival estimation because, apart from the adjustment for under-enumeration at extremes of age, the age-specific mortality rates were similar to those I calculated from the census data. The death rates from the GBD study were lower especially in younger age groups. The CONCORD Central Analytic Team obtained life tables of all-cause mortality rates by single calendar year, sex and 5-year age groups for Saudi Arabia from the UNPD and interpolated them and extended them to age 99 years with the Elandt-Johnson method in order to have mortality rates by single year of age.[156]

6.2 Linkage to death records

For the purpose of survival analysis, a passive follow-up method was used to obtain a woman's vital status and date of death if dead. Based on women's unique national identification (ID) numbers, registry records were linked to the vital registration database of the National Information Centre of the Ministry of Interior (NIC) on 29 August 2019.

Non-nationals are a group largely made up of those working on limited contracts. Many return to their home countries after a diagnosis of cancer due to visa and medical treatment restrictions, making follow-up difficult. Also, obtaining accurate life table data for this population is challenging given their unsteady in- and out-migration. Therefore, I limited the survival analysis to Saudi nationals.

I further restricted the analysis to women diagnosed during 2005-2016 because ID number was not a mandatory field in the cancer registry before 2005, and it was only available for 32% of women diagnosed during 1994-2004.

Of 1,477 records, 1,199 (81%) had at least one complete (10-digit) national ID number. 31 women had two ID numbers in their records. This was explained by tumour registrars

finding more than one ID number in a woman's medical record, one of which probably belongs to an accompanying husband or relative. All available ID numbers were submitted to the NIC. Vital status and date of death if dead were requested, as well as sex, date of birth and complete name (the first name of the woman and of her father and grandfather, and the family name) in order to cross-check with registry records. All name checks were carried out by registry staff in order to protect the identities of the women. Linkage was successful for 1,193 ID numbers corresponding to 1,191 registry records. Eighty-three of the ID numbers belonged to males in the NIC. This eliminated 29 of the second ID numbers in records with two IDs. For the remaining two records, the correct ID number was selected based on matching names and dates of birth. The remaining 54 IDs belonging to males were therefore considered to be wrong ID numbers (Figure 6). For women with missing, incomplete or wrong ID numbers, date of last known vital status from the registry was used in the survival analysis. There were 20 women who were dead according to registry follow-up but alive in NIC records. I used NIC follow-up for these women in order for the method to remain consistent.

Six further records had names that partially or completely did not match between registry and NIC records. Registry follow-up was used if more that one of the four names did not match (n=4). There was a much higher proportion of mismatch in dates of birth between registry and NIC records, ranging between 1 day and 24 years (Figure 7). Only 44% had perfectly matching dates of birth, while 67% had differences within 2 days, 86% within 1 year and 97% within 5 years. Many of the elderly in Saudi Arabia do not know their dates of birth or only know them roughly, therefore the mid-year date was assigned to the majority of those born in the 1970s and earlier. In addition, the conversion from the locally used Hijri lunar calendar to the Gregorian calendar could lead to differences of a few days. Dates of birth from the registry were used for all analyses.

Figure 6: Women included in the survival analysis

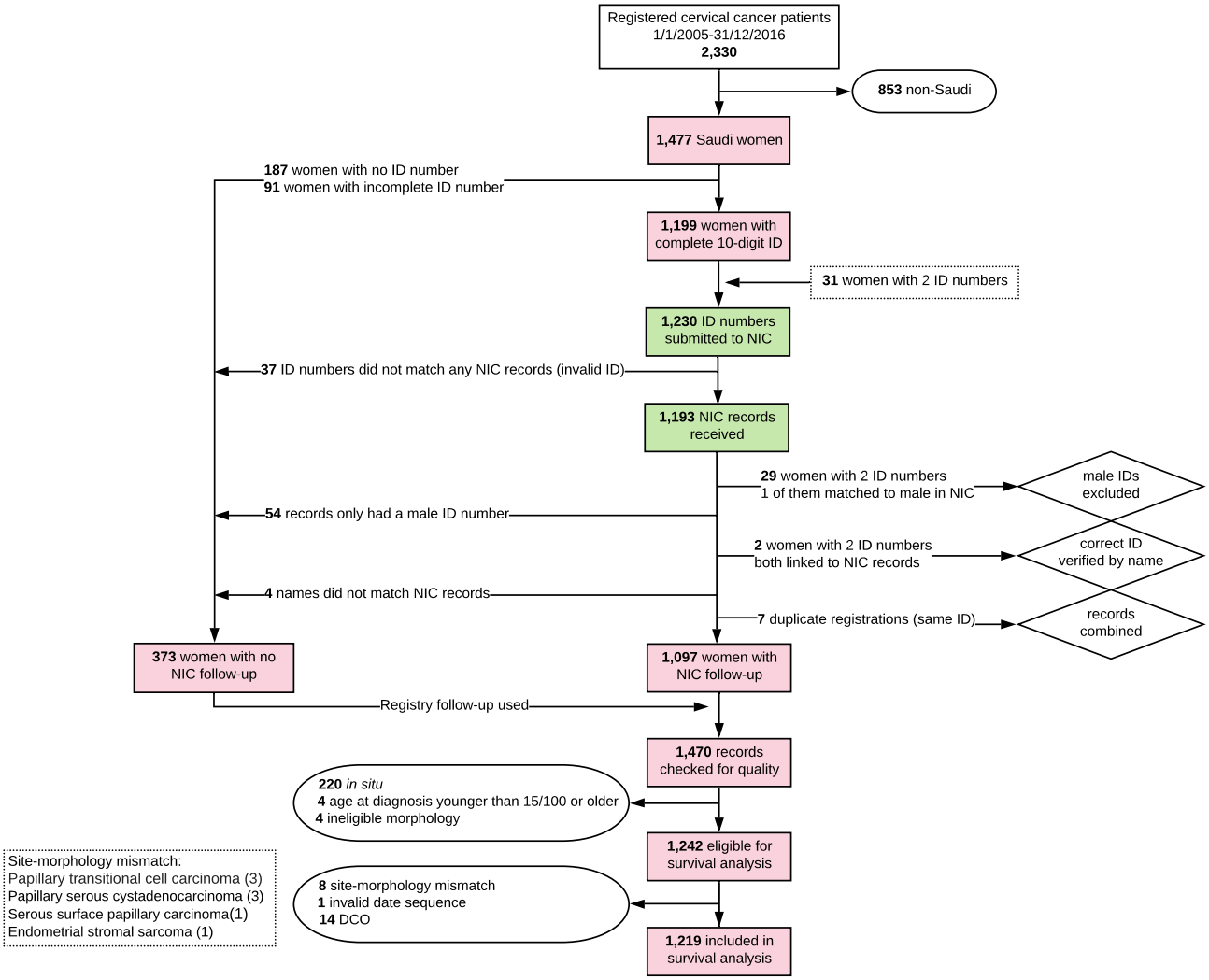
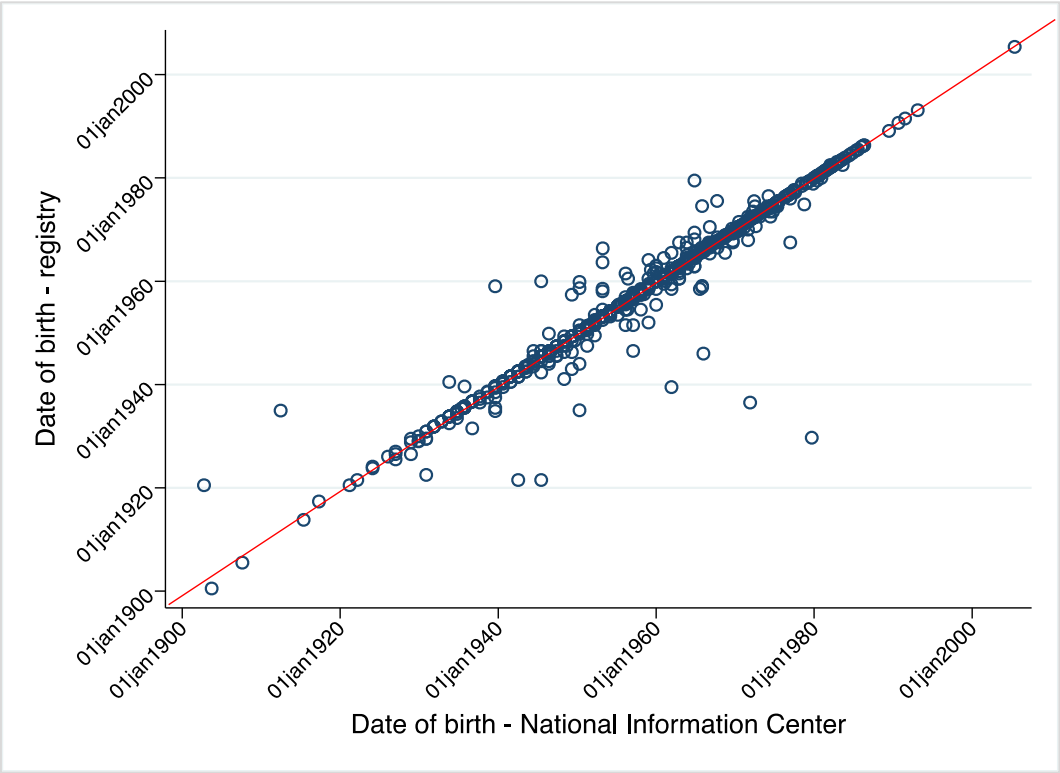


Figure 7: Correlation between dates of birth recorded in the Saudi Cancer registry and the Ministry of Interior



6.3 Data quality

A total of 1,470 records were checked for CONCORD eligibility criteria. Patients were eligible for survival analysis if they had a complete date of birth, diagnosis and death if dead, were 15-99 years of age at diagnosis and if they had an invasive primary tumour with an eligible morphology and topography code. Further, patients were excluded from the analysis if registered based on death certificate only, or had inconsistent age, sex, morphology or site combinations, including age less than 20 for cervical cancer (Appendix B, Annex table 1 for full exclusion table). Of the 1,242 women eligible for survival analysis, 1,219 were included in the survival analysis (98.1%) (Figure 6).

Further quality indicators were examined according to the CONCORD protocol (Annex table 2).[4,157] Of the women included in the survival analysis, 99.7% had microscopically verified tumours and 1.2% had non-specific morphology. Follow-up was censored within 5 years of diagnosis for 34% of women. Two percent had died within 30 days of diagnosis. The distribution of the day and month of birth showed around a 15% excess of women having their day of birth documented as the first of the month and their month of birth as July. The first of July is assigned by the government to those who's date of birth is unknown. Date of diagnosis was fairly evenly distributed over the year, while the date of

last known vital status clustered on the 29th of August, which was the date of record linkage (29 August 2019) (Appendix figure 1).

For calculation of incidence, non-Saudis and women with unknown vital status, women registered by death certificate only, and records with invalid date of death or an invalid date sequence which involved date of death were included. Women with carcinoma in situ were excluded (n=306). Eight women were excluded for incomplete date of birth or date of diagnosis, 8 for age younger than 15 or older than 99 years, 2 for age-morphology mismatch (Embryonal rhabdomyosarcoma) 11 for site-morphology mismatch (for example, Papillary serous cystadenocarcinoma, Papillary transitional cell carcinoma, Large-cell carcinoma) and one because the date of diagnosis preceded her date of birth. Seventeen duplicate registrations were combined, and 21 non-Saudi women were excluded because they were international patients, leading to a total of 1,957 women. For 10 women, the region of residence was unknown (6 Saudi and 4 non-Saudi women), and these were excluded from regional analysis.

6.4 Statistical analysis

Incidence rates

Incidence rates by five-year age group were calculated for the two calendar periods 2005-2010 and 2011-2016 by region of residence and by stage at diagnosis. Age-standardised incidence rates were then derived for each period and region/stage as the sum of the weighted age-specific incidence rates:

$$\sum_i w_i d_i / y_i$$

Where the subscript *i* indicates age group, d_i is the number of women diagnosed in age group *i*, y_i is the number of person-years at risk (approximated by sum of the mid-year female populations over the period in age group *i*), and w_i is the weight given to age group *i*, i.e. the proportion of individuals in that age group in the world standard population.

Estimation of net survival

Five-year net survival probabilities and their 95% confidence intervals were estimated for women diagnosed during the two calendar periods 2005-2010 and 2011-2016, both for the whole population and for each of the three main administrative regions (Riyadh, Makkah and the Eastern Region) and the other ten regions combined. This was to ensure

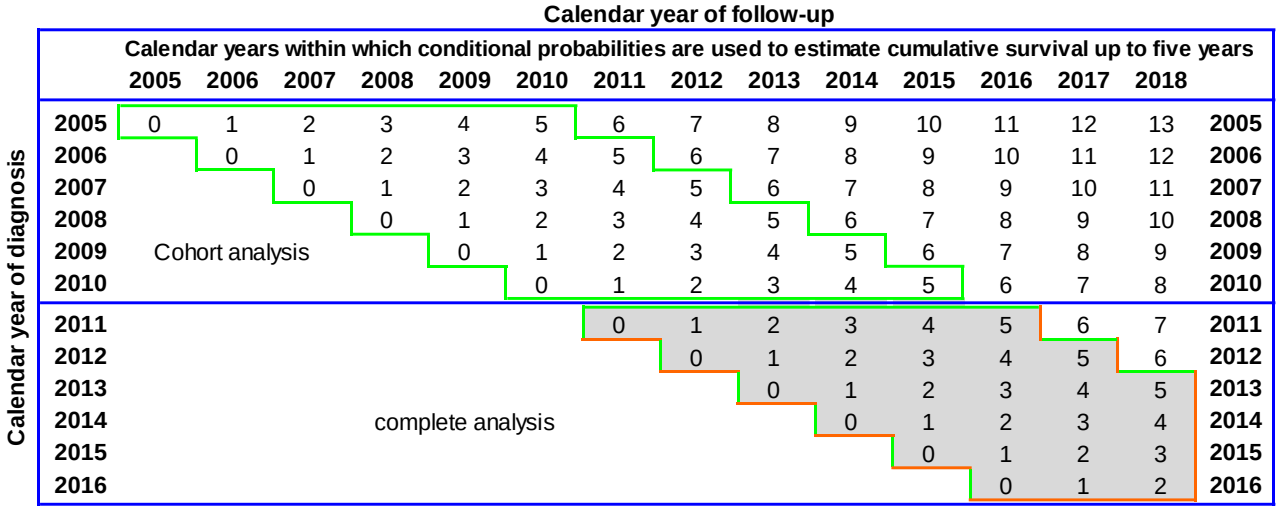
that enough women were available for robust estimation of survival in each category, given the small population of these ten regions.

Probabilities were estimated with the Pohar-Perme estimator[150] in Stata IC 16 version 1, using the program *stns*.[158] Life tables of all-cause mortality rates in the Saudi Arabian female population were utilised to correct for background mortality. Death due to any cause was the event of interest. Women who were alive on 31 December 2018 were censored. For the 291 (24%) women for whom ID number was not available, their follow-up time was censored at the last known vital status recorded by the registry, if they were known to be alive at that date. The date of death in the registry, obtained from the death notification or death certificate, was used for women known to be dead.

A cohort approach was followed for the period of diagnosis 2005-2010 for which at least 5 years of potential follow-up were available for all women. For the period 2011-2016, a complete approach was used, where those diagnosed in calendar years for which 5 years of follow-up are not available (2014-2016) were censored at the closing date (Figure 8).

One- and five-year net survival was estimated for each calendar period, and by region of residence and stage at diagnosis. Where at least 10 women were available for analysis in each age group, estimates were produced for each of five age groups (15–44, 45–54, 55–64, 65–74, and 75-99 years) and an age-standardised summary estimate was derived using the International Cancer Survival Standard (ICSS) group 2 weights.[153] If fewer than 10 women were at risk for a single age group, they were combined with the women in the adjacent age group and the resulting survival estimate was assigned to both age groups, which were then used for age standardisation. If fewer than 10 women were at risk in two or more age groups, I only present the unstandardised estimate for all ages combined. Survival estimates for all women were not age-standardised if fewer than 50 women were at risk in a given analysis stratum. Further, estimates were not age-standardised if, for at least one of the age groups with 10 or more women, the last event occurred before 6 months for 1-year estimates or before 3 years for 5-year estimates, and some women are still alive at the end of follow-up. This was done in order to obtain robust estimates, based on past experience from the CONCORD programme.

Figure 8: Structure of survival analyses



Imputation of missing data on stage

Data on stage at diagnosis were missing for 11.3% of the women included in the survival analyses. This proportion was relatively low, but the option to impute missing stage was explored, because missing data can reduce efficiency and may introduce bias in the estimation of survival.

In order to address missing data appropriately, the mechanism of missing data, and any associations between the variable with missing data and other variables in the data set that may be predictive of its values should be explored.

The mechanisms that underlie missing data fall into three conventional categories. In situations where the data are considered to be missing completely at random (MCAR), the probability that an observation is missing is not dependent on any other variables in the data set, or on the outcome. In this case, the exclusion of observations (in this case, tumour records) with missing data will not bias estimates of the outcome, but they may lead to loss in statistical power, because of the smaller number of records that can be included in the analyses.

Data are described as missing at random (MAR) when cases with incomplete data (here, data on stage at diagnosis) do differ in respect to the distribution of their values from those with complete data, but the chances of stage data being missing are independent of the underlying value, which is unknown, given other variables that are fully observed, or the outcome. An example is when records of elderly patients are more likely to have missing stage information and these patients are also more likely to have advanced stage, but the

true distribution of stage amongst those with missing values for stage is similar to that in patients in the same age group for whom stage is fully observed.

Under the assumption that data for a given variable (in this case stage) are missing at random, multiple imputation of the missing values is a practical way to address the problem, by “filling the gaps” in the records with missing data. The approach is to obtain a value for the missing variable in a given record from the distribution of observed data for that variable, conditional on data from other variables. Thus, the stage at diagnosis in a woman of a given age, region of diagnosis and with a tumour of given grade can be imputed from the distribution of stage among women whose records are complete for these variables.

The observed data are then combined with the imputed data to construct a complete dataset, in which there are no longer any missing data. This process is repeated several times, typically 5-20 times, to obtain a number of complete datasets.

Data are missing not at random (MNAR) when the chance of data being missing depends on their unseen value, even given observed variables,[159] for example if the main reason for missing stage was that women were directly referred to palliative care, typically with very advanced disease, but without investigation to determine the stage. Exclusion of these women could bias the estimation of survival for women with advanced disease, and thus for all women combined. Estimation under a MNAR assumption is complex and requires specifying the selection mechanism or how the distribution of the variable with missing data given fully observed variables differs between observations that do and do not have missing data.[159]

The mechanism of missing data cannot be formally proven, but the association between missingness of stage and observed data for other variables can provide some indication of the mechanism.

Missing data on stage are often not missing completely at random: missing data are more likely in women with advanced disease, in women who are medically unfit for staging or where investigation to determine the stage are deemed irrelevant for treatment decisions because the woman is receiving palliative care.[160]

Missing stage in these data was associated with age older than 75, Region of residence (one of the regions other than Riyadh, Makkah and the Eastern Region), region of

diagnosis (Regions other than Riyadh and the Eastern Region), shorter follow-up time and less death during the follow-up period (Table 4, Table 6).

Table 4: Association between missingness of stage and observed variables (univariable) (n=1,219)

Variable	Odds Ratio	95% CI	P-value
Age (years)	1.02	(1.00 - 1.03)	0.016
20-44	1		
45-54	0.98	(0.60 - 1.58)	0.921
55-65	1.00	(0.58 - 1.71)	0.988
65-74	1.39	(0.78 - 2.45)	0.264
75+	2.18	(1.20 - 3.96)	0.010
Region of residence			
Riyadh	1		
Makkah	1.43	(0.83 - 2.46)	0.203
Eastern	1.04	(0.54 - 2.02)	0.908
Other	3.10	(1.87 - 5.15)	<0.001
Region of diagnosis			
Riyadh	1		
Makkah	2.32	(1.45 - 3.73)	<0.001
Eastern	1.42	(0.70 - 2.90)	0.336
Other	9.78	(5.88 - 16.24)	<0.001
Follow-up time (days)	0.9998	(0.9997 - 0.9999)	0.023
Vital status (dead)	0.75	(0.38 - 0.85)	0.006
Grade (n=878)			
I	reference		
II	0.57	(0.28 - 1.15)	0.118
III	0.74	(0.36 - 1.49)	0.497
IV	1.23	(0.77 - 2.92)	0.702

The strongest determinant of missing stage was being diagnosed in regions other than the three main regions of Riyadh, Makkah or the Eastern Region, followed by living in one of those regions.

Where stage at diagnosis was known, advanced stage (regional spread with lymph node involvement, with or without direct extension or distant metastasis) was associated with region of residence, region of diagnosis, older age at diagnosis and higher grade (Table 5, Table 6).

Table 5: Association between advanced stage at diagnosis and other observed variables (univariable) (n=1,081)

Variable	Odds Ratio		P-value
Age (years)	1.02	(1.00 - 1.02)	0.002
20-44	reference		
45-54	0.91	0.66 - 1.26)	0.578
55-65	1.23	(0.86 - 1.77)	0.249
65-74	1.80	(1.20 - 2.72)	0.005
75+	1.65	(1.01 - 2.72)	0.045
Region of residence			
Riyadh	reference		
Makkah	0.60	(0.43 - 0.84)	0.003
Eastern	1.17	0.81 - 1.69)	0.405
Other	1.21	(0.86 - 1.70)	0.269
Region of diagnosis			
Riyadh	reference		
Makkah	0.54	(0.40 - 0.72)	<0.001
Eastern	0.85	(0.57 - 1.25)	0.407
Other	0.26	(0.14 - 0.48)	<0.001
Grade (n=799)			
I	reference		
II	1.81	(1.05 - 3.12)	0.033
III	2.50	(1.44 - 4.32)	0.001
IV	3.12	(1.35 - 2.93)	0.007

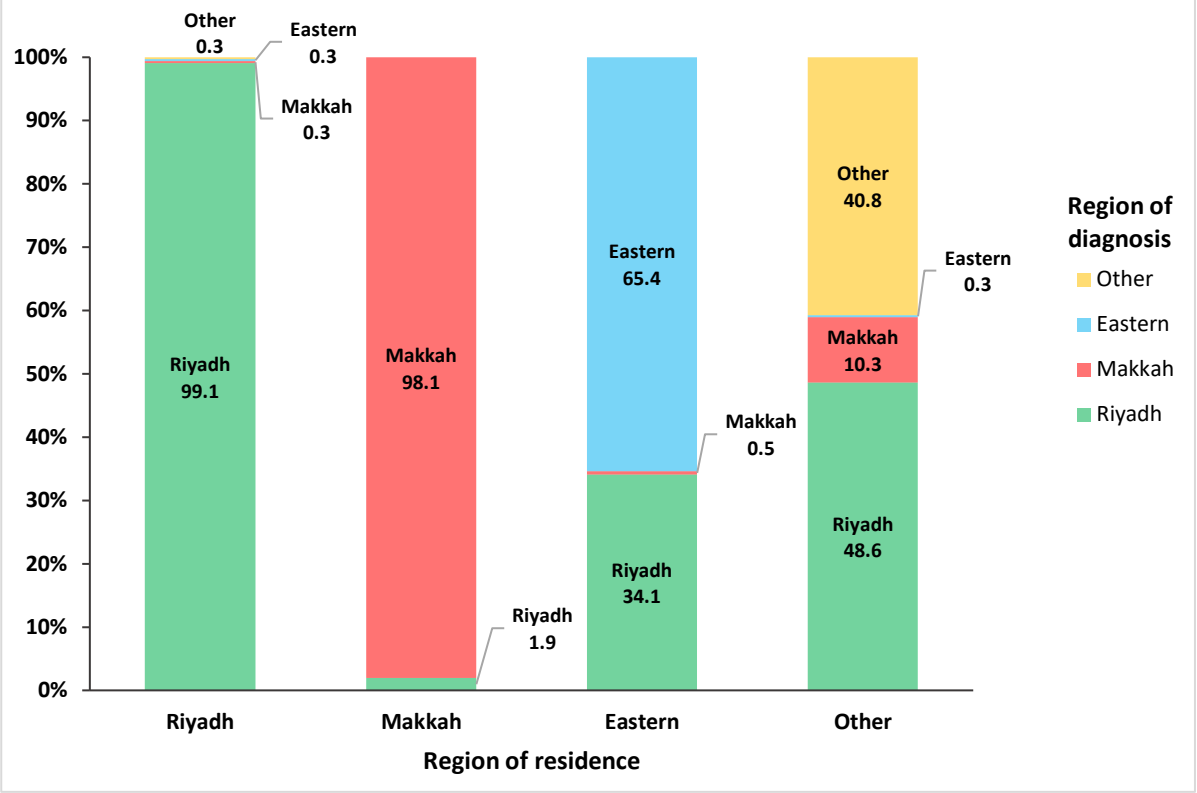
Given the observed data, being diagnosed in Makkah or “other” regions was associated with higher odds of missing data on stage at diagnosis (OR=2.32 for Makkah and 9.78 for other regions, p<0.001) but also lower odds of advanced stage among women for whom the data were available (OR=0.54 for Makkah and 0.26 for other regions, p<0.001). This suggests that women for whom data on stage were missing may have been those with more advanced disease.

Table 6: Characteristics of women and tumour grade by stage at diagnosis

	Early stage		Advanced stage		Unknown stage	
	N	%	N	%	N	%
Age						
15-44	217	59.62	110	30.2	37	10.2
45-54	223	61.6	103	28.5	36	9.9
55-64	131	55.3	82	34.6	24	10.1
65-74	70	45.2	64	41.3	21	13.6
75-99	44	43.6	37	36.6	20	19.8
Region of residence						
Riyadh	183	57.4	113	35.4	23	7.2
Makkah	237	65.7	88	24.4	36	10.0
Eastern	115	53.7	83	38.8	16	7.5
Other	147	46.1	110	34.5	62	19.4
Region of diagnosis						
Riyadh	295	53.2	229	41.3	31	5.6
Makkah	241	62.0	101	26.0	47	12.1
Eastern	79	55.6	52	36.6	11	7.8
Other	69	52.7	14	32.5	48	36.6
Period of diagnosis						
2005-2010	317	58.8	166	30.8	56	10.4
2011-2016	368	54.1	230	33.8	82	12.1
Grade						
I	66	67.4	20	20.4	12	12.2
II	237	60.0	130	32.9	28	7.1
III	177	51.6	134	39.1	32	9.3
IV	18	43.9	17	41.5	6	14.6
Unknown	187	54.8	95	27.9	59	17.3

The marked difference in the odds ratio of missing stage between women living in one of the peripheral regions and women who were diagnosed in them can be explained by the large proportion of women living in these regions who were diagnosed in Riyadh. While virtually all women living in Riyadh and Makkah region were diagnosed in the same region they lived in, almost half of the women living in the ten peripheral regions were diagnosed in Riyadh and 10% were diagnosed in Makkah region. Further, over one third of women living in the Eastern Region were diagnosed in Riyadh (Figure 9). This is not surprising given the geographic proximity between the two regions (about 400 km).

Figure 9: Proportion (%) of women diagnosed with invasive cervical cancer in each of the four regions for each region of residence



Of all women diagnosed in the ten peripheral regions, 37% did not have information on stage. This proportion was reduced to 20% when women had a second referral hospital documented by the registry (Table 7), but the proportion of missing stage was only reduced in women who were referred to Makkah or Riyadh (none were referred to the Eastern Region) and remained at 39% for women referred within the ten peripheral regions.

Table 7: Proportion of women with missing stage for each region of diagnosis for all women and for women with a second referral hospital

	N	All women		N	Women who were referred	
Region of diagnosis		**Missing stage**	**(%)**		**Missing stage**	**(%)**
Riyadh	555	31	(5.6)	357	11	(3.1)
Makkah	389	47	(12.1)	225	19	(8.4)
Eastern	142	11	(7.8)	85	3	(3.5)
Other	131	48	(36.6)	59	12	(20.3)
Total	1,217	137	(11.3)	726	45	(6.2)

Conventionally, multiple imputation and estimation of the outcome are carried out in a one-step approach using parametric methods. Multiple imputation of missing values for variables that will be used to estimate net survival in various strata of the data has not

been frequently addressed. I used a multinomial logistic model to impute stage where it was missing. I generated five imputed datasets, using a model that included the Nelson-Aalen estimate of the cumulative hazard, the event indicator (death), and dummy variables for grade, age group and region of diagnosis[161]. The five resulting complete datasets had very similar stage distributions (Table 8).

Table 8: Stage distribution in the imputed datasets

Imputation	localised		regional		distant		Total
	N	(%)	N	(%)	N	(%)	N
Complete observations	378	(34.97)	480	(44.40)	223	(20.63)	1,081
1	437	(35.88)	534	(43.84)	247	(20.28)	1,218
2	433	(35.55)	536	(44.01)	249	(20.44)	1,218
3	442	(36.29)	528	(43.35)	248	(20.36)	1,218
4	448	(36.78)	519	(42.61)	251	(20.61)	1,218
5	441	(36.21)	533	(43.76)	244	(20.03)	1,218

I estimated age-standardised net survival for each of the complete datasets by stage and calendar period of diagnosis, at one and five years after diagnosis. We then combined the point estimates of survival and their variance, using Rubin's rule,[162] to obtain a single pooled point estimate of net survival ($\overline{NS}$) using the formula:

$$\overline{NS} = \frac{1}{k}\left(\sum_{i=1}^{k} NS_i\right)$$

where *i* indexes the imputation up to *k*, the number of imputations. This represents the mean of the survival estimates from the *k* complete data sets after imputation.

The mean of the variances of these survival estimates, the “within-imputation” variance (*W*) is given by:

$$W = \frac{1}{k}\left(\sum_{i=1}^{k} {SE^2}_i\right)$$

where SE is the standard error of the survival estimate from each imputed dataset.

Further, the between-imputation variance (*B*) is calculated as:

$$B = \frac{\sum(NS_i - \overline{NS})^2}{k-1}$$

This accounts for the extra uncertainty in the variance of the pooled estimate that arises from the missing data.

The total variance is the sum of B and W corrected for the number of imputations:

$$VAR = W + \left(1 + \left(\frac{1}{k}\right)\right) B$$

The 95% confidence intervals of the pooled estimate after multiple imputation are then derived conventionally for a normal distribution as: $\overline{NS} \pm 1.96\sqrt{VAR}$

Effect of stage on variation in survival by region of residence

I estimated net survival for women of all ages by region of residence and stage at diagnosis without age standardisation, in order to avoid small numbers in older age groups. Although older women tended to be diagnosed at a more advanced stage (Figure 10), the comparability of estimates between regions is not expected to be compromised since the age distribution between regions was similar (p for chi^2=0.64, 12 degrees of freedom) (Figure 11).

Figure 10: Age distribution (%) of Saudi women diagnosed with cervical cancer between 2005 and 2016, by stage at diagnosis (n=1,219)

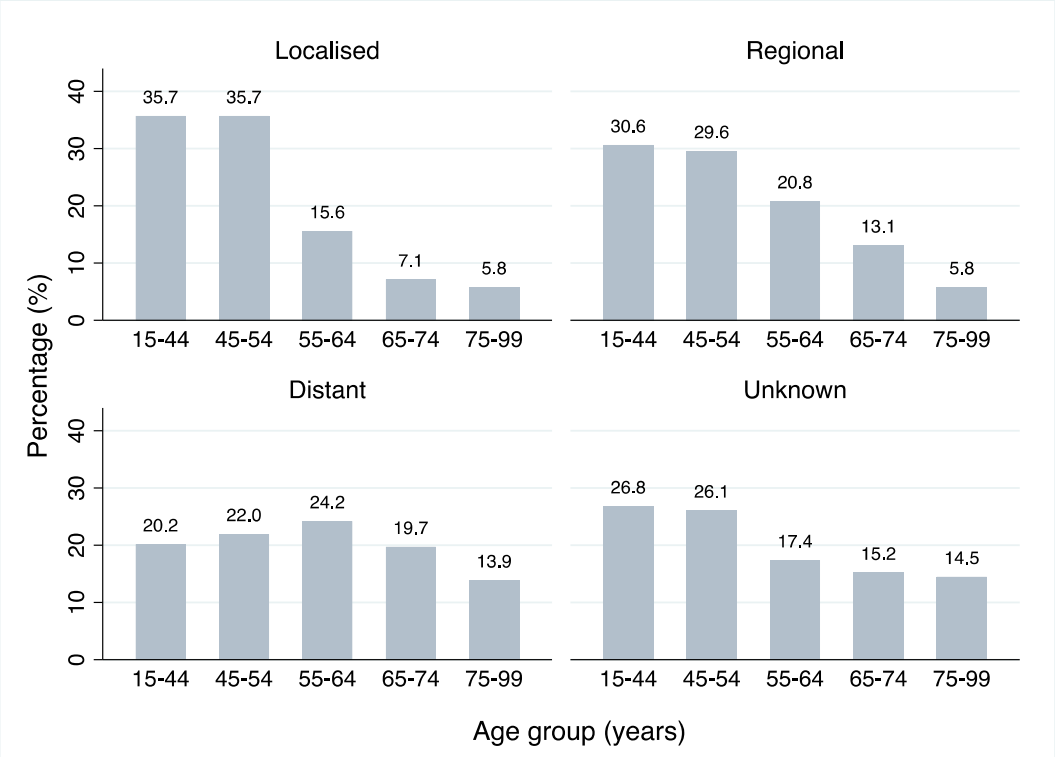
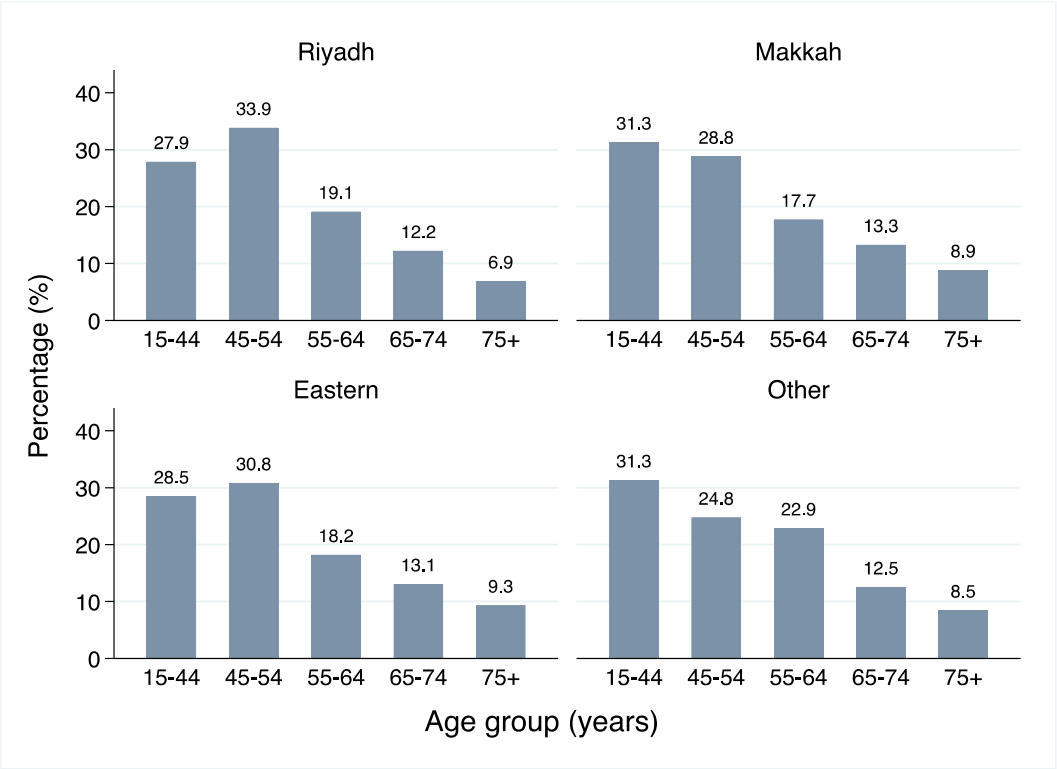


Figure 11: Age distribution (%) of Saudi women diagnosed with cervical cancer between 2005 and 2016, by region of residence (n=1,213)



Sensitivity analysis

In order to explore whether censoring the follow-up time for women without an available ID number could bias the survival estimates, net survival was estimated while restricting the analysis to women with NIC follow-up, which required an ID number.

In order to explore whether the complete approach used for women diagnosed during 2011-2016, who were followed up to 31 December 2018, could bias the evaluation of survival trends, survival was also estimated for women diagnosed during 2005-2010 while censoring the follow-up at 31 December 2012, i.e., restricting the follow-up duration to be the same as that used for women diagnosed during 2011-2016.

Net survival estimates using life tables produced by the Global Burden of Disease study were compared to those obtained using UNPD life tables.

Mortality rates

Given the clear under-enumeration of deaths that were attributed to cervical cancer in the MOH mortality database, I instead used deaths due to cancer in women registered with cervical cancer as the numerator for mortality. These were obtained primarily from death certificates and death notifications with a mention of cancer, and were either used to

update the vital status of women already existing in the registry or as a primary source for case finding, and can therefore be considered an independent source of cervical cancer mortality data.

I included women who were diagnosed with invasive cervical cancer from 1994 onwards and had died from cancer between 2005 and 2016 (n=326). I further excluded two women who were younger than 20 at the time of death and one who was an international patient. I calculated mortality rates by age at death (five-year age groups) for the two calendar periods 2005-2010 and 2011-2016, and separately for Saudi and non-Saudi women. I derived age-standardised mortality rates in the same way as age-standardised incidence rates. I did not estimate mortality by region because there were too few deaths and because the region a woman lived in at the time of diagnosis may differ from the one she died in and be less relevant at the time of death.

Chapter 7. Results

7.1 Study population characteristics

During the period 2005-2016, 2,313 women were diagnosed with cervical cancer (1,470 Saudis and 843 non-Saudis) of whom 1,957 had invasive disease eligible for inclusion in incidence calculation and 1,219 were included in the survival estimation. A further 306 women were registered with carcinoma *in situ*.

The mean age at diagnosis for invasive cancer was 51.4±13.3 years. Non-Saudis were four years younger on average (Table 10). This may partially reflect the population distribution of non-Saudi women who are mostly of employment age (Figure 5), but the proportion of non-Saudi women diagnosed at younger age tends to be higher than that of Saudi women (Figure 12, Table 10). The age-specific incidence rates for non-Saudi women were higher at every age group than those for Saudi women (**Error! Reference source not found.**). The unusually high incidence rates in women aged 75-79 may reflect an under-enumeration of the non-Saudi population in that age group or misclassification of women aged 75-79 as being over 80 in the census (Table 9). Given the more plausible age distribution of women diagnosed in the registry (Figure 12), it seems the registry documents age more accurately than the census.

While 26% of Saudi women lived in Riyadh region, 45% were diagnosed there and only about half the proportion living in one of the ten peripheral regions were diagnosed in those regions. These large differences between region of residence and region of diagnosis were not apparent in non-Saudi women. Non-Saudi women had a smaller proportion of in situ tumours (10.2%) than Saudi women (14.9%). A higher percentage of non-Saudi women were diagnosed at localised stage, but they had almost double the proportion of unknown stage (23% versus 12%). This difference was larger in the earlier period 2005-2010. The proportion of women registered as dead by registry follow-up was much lower for non-Saudi women. Ninety-nine percent of women had a histologically verified diagnosis. Characteristics of the women included in the survival analysis did not differ from those of Saudi women included in incidence (Table 10,Table 11).

Figure 12: Age distribution of Saudi and non-Saudi women diagnosed with invasive cervical cancer in 2005-2016 (n=1,957)

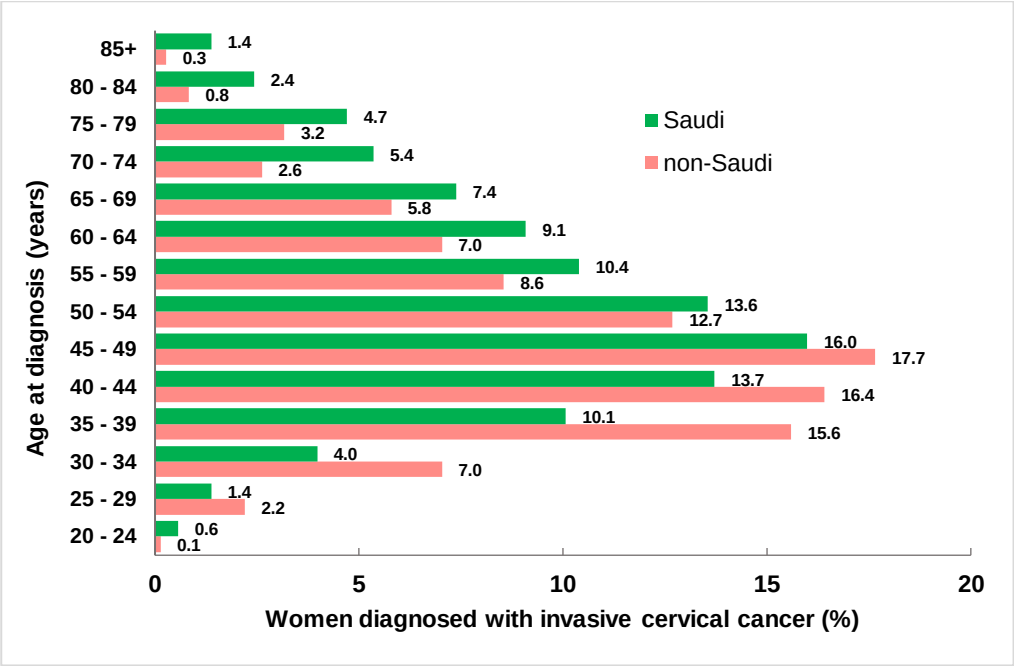


Figure 13: Age-specific incidence rates for invasive cervical cancer in Saudi and non-Saudi women (n=1,957), by calendar period.

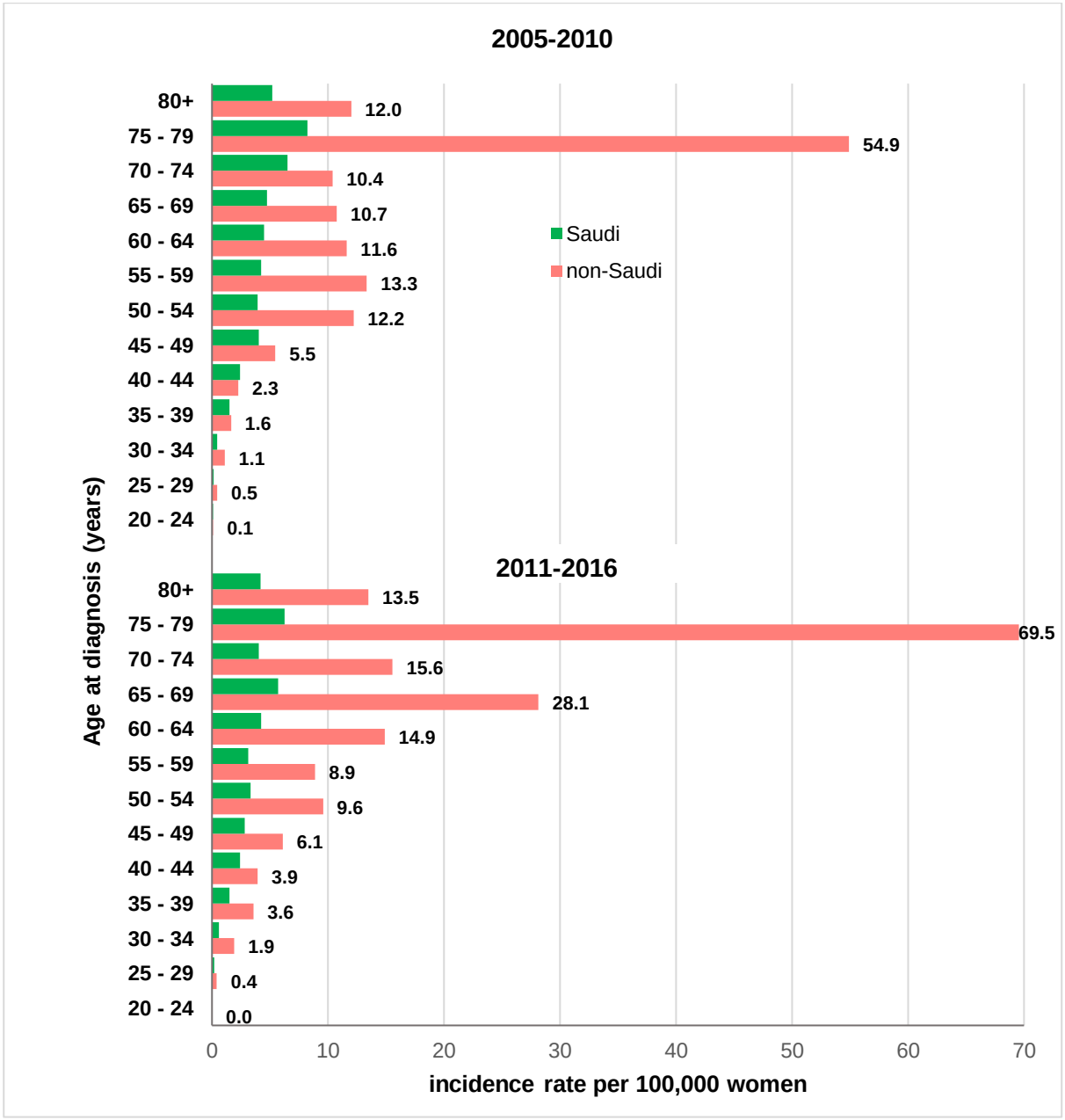


Table 9: Population counts and number of women diagnosed with invasive cervical cancer in each 5-year age group

	Saudi				non-Saudi			
	2005-2010		2011-2016		2005-2010		2011-2016	
Age group	Population	n	Population	n	Population	n	Population	n
20 - 24	5,091,022	1	5,553,048	6	723,479	0	1,082,624	1
25 - 29	5,042,146	10	5,487,974	7	1,466,043	6	2,193,810	10
30 - 34	4,561,534	28	4,965,737	21	1,457,582	28	2,181,149	24
35 - 39	3,970,635	59	4,320,091	65	1,873,654	67	2,803,776	46
40 - 44	3,318,964	81	3,614,293	88	1,708,721	67	2,556,954	58

45 - 49	2,740,968	77	2,985,082	120		917,396	56	1,372,803	75
50 - 54	2,183,876	73	2,378,254	94		344,896	33	516,101	63
55 - 59	1,654,520	52	1,801,606	76		225,444	20	337,351	45
60 - 64	1,220,986	52	1,329,560	60		161,286	24	241,343	28
65 - 69	838,538	48	911,118	43		99,494	28	148,894	16
70 - 74	593,181	24	645,016	42		64,254	10	96,161	10
75 - 79	382,194	24	414,449	34		15,818	11	23,679	13
80+	480,750	20	522,207	27		22,277	3	33,351	4
	32,079,314	549	34,928,435	683		9,080,344	353	13,587,996	393

Table 10: Characteristics of women diagnosed with invasive cervical cancer during the calendar period 2005-2016 (n=1,957)

	Saudi						Non-Saudi					
	2005-2010		2011-2016		All periods		2005-2010		2011-2016		All periods	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
Age	52.5	13.7	53.3	13.6	**52.9**	**13.6**	47.97	12.4	49.3	12.1	**48.7**	**12.2**
	n	%	n	%	n	%	n	%	n	%	n	%
Region of residence												
Riyadh	145	26.4	173	25.3	**318**	**25.8**	92	27.2	88	22.7	**180**	**24.8**
Makkah	157	28.6	204	29.9	**361**	**29.3**	187	55.3	202	52.2	**389**	**53.7**
Eastern	94	17.1	123	18.0	**217**	**17.6**	25	7.4	50	12.9	**75**	**10.3**
Other	150	27.3	180	26.4	**330**	**26.8**	32	9.5	45	11.6	**77**	**10.6**
Unknown	3	0.6	3	0.4	**6**	**0.5**	2	0.6	2	0.5	**4**	**0.6**
Region of diagnosis												
Riyadh	249	45.4	305	44.7	**554**	**45.0**	97	28.7	98	25.3	**195**	**26.9**
Makkah	171	31.2	218	31.9	**389**	**31.6**	186	55.0	205	53.0	**391**	**53.9**
Eastern	57	10.4	87	12.7	**144**	**11.7**	22	6.5	47	12.1	**69**	**9.5**
Other	71	12.9	72	10.5	**143**	**11.6**	31	9.2	37	9.6	**68**	**9.4**
International	1	0.2	0	0.0	**1**	**0.1**	0	0.0	0	0.0	**0**	**0.0**
Unknown	0	0.0	1	0.2	**1**	**0.1**	2	0.6	0	0.0	**2**	**0.3**
Stage												
Localised	153	27.9	226	33.1	**379**	**30.8**	114	33.7	194	50.1	**308**	**42.5**
Regional	234	42.6	245	35.9	**479**	**38.9**	91	26.9	84	21.7	**175**	**24.1**
Distant	98	17.9	127	18.6	**225**	**18.3**	43	12.7	32	8.3	**75**	**10.3**
Unknown	64	11.7	85	12.5	**149**	**12.1**	90	26.6	77	19.9	**167**	**23.0**
Grade												
Grade I	38	6.9	60	8.8	**98**	**8.0**	20	5.9	32	8.3	**52**	**7.2**
Grade II	192	35.0	205	30.0	**397**	**32.2**	99	29.3	141	36.4	**240**	**33.1**
Grade III	136	24.8	206	30.2	**342**	**27.8**	100	29.6	95	24.6	**195**	**26.9**
Grade IV	23	4.2	18	2.6	**41**	**3.3**	20	5.9	25	6.5	**45**	**6.2**
Unknown	160	29.1	194	28.4	**354**	**28.7**	99	29.3	94	24.3	**193**	**26.6**
Basis of diagnosis												
Pathology	532	96.9	673	98.5	**1,205**	**97.8**	336	99.5 0	384	99.3	**720**	**99.3**
Clinical/imaging	2	0.4	2	0.3	**4**	**0.3**	1	0.3 0	1	0.3	**2**	**0.3**
Death certificate only	10	1.8	4	0.6	**14**	**1.1**	0	0	1	0.3	**1**	**0.1**
Unknown	5	0.9	4	0.6	**9**	**0.7**	1	0.3	1	0.3	**2**	**0.3**
Proportion dead by registry follow-up	124	22.6	110	16.1	**234**	**19.0**	22	6.5	30	7.75	**52**	**7.2**
Total	549		683		**1,232**		338		387		**725**	

SD: Standard deviation

Table 11: Characteristics of Saudi women included in the survival analysis (n=1,219)

	2005-2010		2011-2016		All periods	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age	52.7	13.59	53.73	13.47	52.8	13.52
	n	**%**	**n**	**%**	**n**	**%**
Region of residence						
Riyadh	145	26.90	174	25.59	319	26.17
Makkah	157	29.13	204	30.00	361	29.61
Eastern	92	17.07	122	17.94	214	17.56
Other	142	26.35	177	26.03	319	26.17
Unknown	3	0.56	3	0.44	6	0.49
Region of diagnosis						
Riyadh	249	46.20	306	45.00	555	45.53
Makkah	171	31.73	218	32.06	389	31.91
Eastern	55	10.20	87	12.97	142	11.65
Other	63	11.69	68	10.00	131	10.75
Unknown	1	0.19	1	0.15	2	0.16
Stage						
Localised	153	28.39	225	33.09	378	31.01
Regional	234	43.41	246	36.18	480	39.38
Distant	96	17.81	127	18.68	223	18.29
Unknown	56	10.39	82	12.06	138	11.32
Grade						
I	38	7.05	60	8.82	98	8.04
II	191	35.44	205	30.15	396	32.49
III	136	25.23	207	30.44	343	28.00
IV	23	4.27	18	2.65	41	3.36
Unknown	151	28.01	190	27.94	341	27.97
Basis of diagnosis						
Pathology	533	98.89	674	99.12	1,207	99.02
Clinical/imaging	2	0.37	2	0.29	4	0.33
Unknown	4	0.74	4	0.59	8	0.66
Censored within 5 years of diagnosis	130	24.1	284	41.7	414	34.00
Total	539		680		1,219	

SD: Standard deviation

The proportion of women who were found to be dead after linkage to the National Information Center (NIC) records was consistently higher than the proportion who were registered as dead by the Saudi Cancer Registry (SCR) in every region and period, and was more than double the proportion previously captured by the SCR (Table 12).

Table 12: Proportion of Saudi Women included in survival analysis who were dead by linkage to the National Information Center (NIC) and by registry follow-up for each calendar period of diagnosis and region of residence (n=1,213)

	NIC						Registry					
	Period						Period					
	2005-2010			2011-2016			2005-2010			2011-2016		
Region	n	dead		n	dead		n	dead		n	dead	
		n	%		n	%		n	%		n	%
Riyadh	102	43	42.2	144	59	41.0	145	33	22.8	174	31	17.8
Makkah	108	58	53.7	175	64	36.6	157	30	19.1	204	38	18.6
Eastern	67	36	53.7	102	53	52.0	92	20	21.7	122	24	19.7
Other	100	49	49.0	139	56	40.3	142	31	21.8	177	16	9.0
Total	377	186	49.3	560	232	41.4	536	114	21.3	677	109	16.1

Regional distribution of stage

The proportion of women diagnosed at localised stage increased from 2005-2010 to 2011-2016 in the three main regions. This increase in localised stage was minimal in the 10 other regions where more women were still being diagnosed at regional stage in 2011-2016. Of women with a documented stage at diagnosis, Makkah had the highest proportion of localised stage and the lowest proportion of distant stage. A higher percentage of women had an unknown stage in the other 10 regions compared to the three main regions (Figure 14, Figure 15). The regional distribution of stage in the imputed datasets was similar to that of known stage, with Makkah having the highest proportion of localised stage and lowest proportion of distant stage in both periods (Figure 16).

Figure 14: Stage distribution of invasive cervical cancer (2005-2016) for women living in Riyadh, Makkah, Eastern or one of the ten remaining administrative regions. n=1,947 (10 women had missing region of residence)

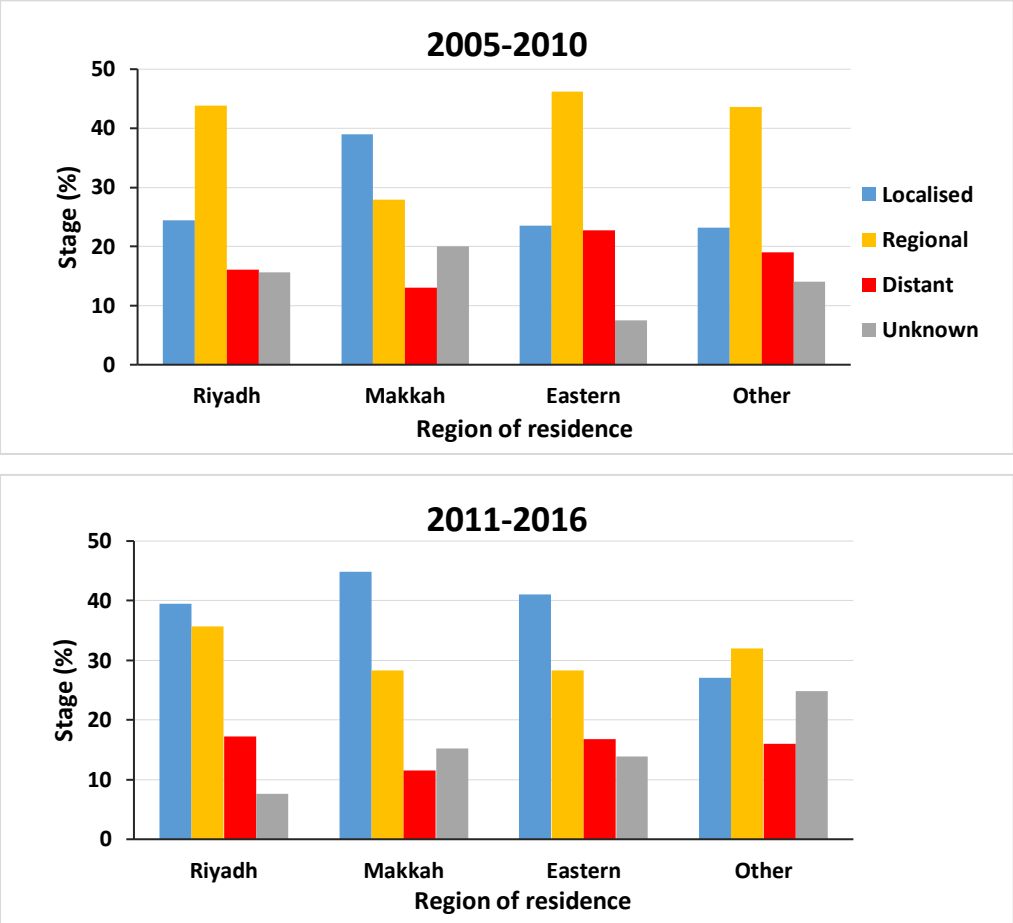
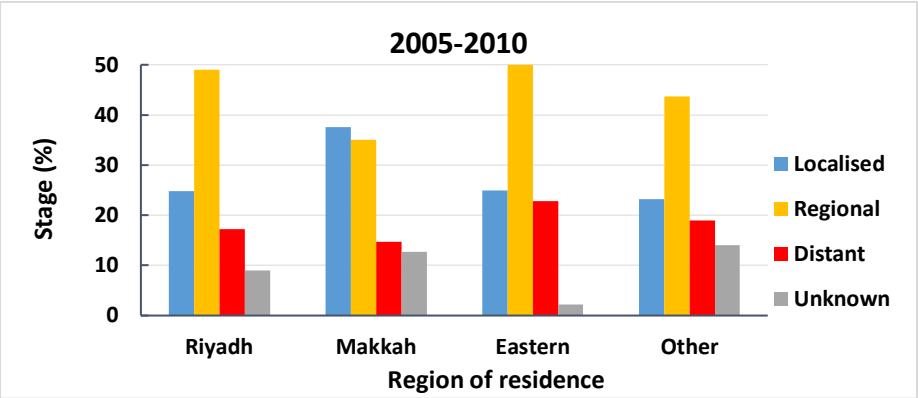


Figure 15: Stage distribution of invasive cervical cancer (2005-2016) for Saudi women included in survival analysis and living in Riyadh, Makkah, Eastern or one of the 10 remaining administrative regions (n=1,213) (region was missing for 6 women)



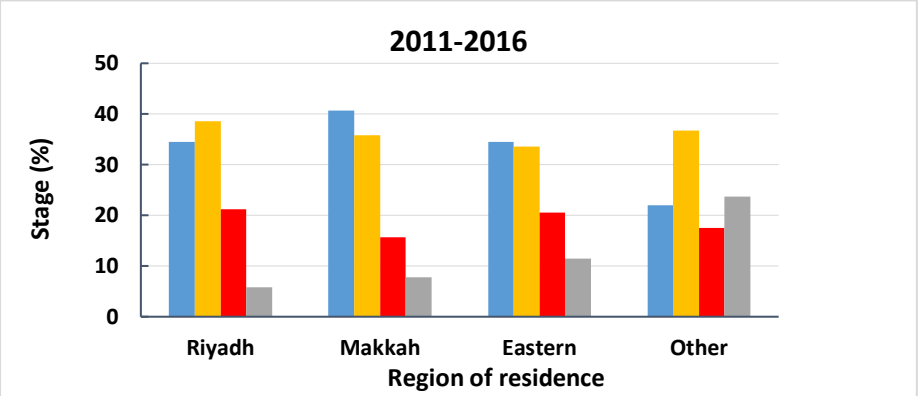
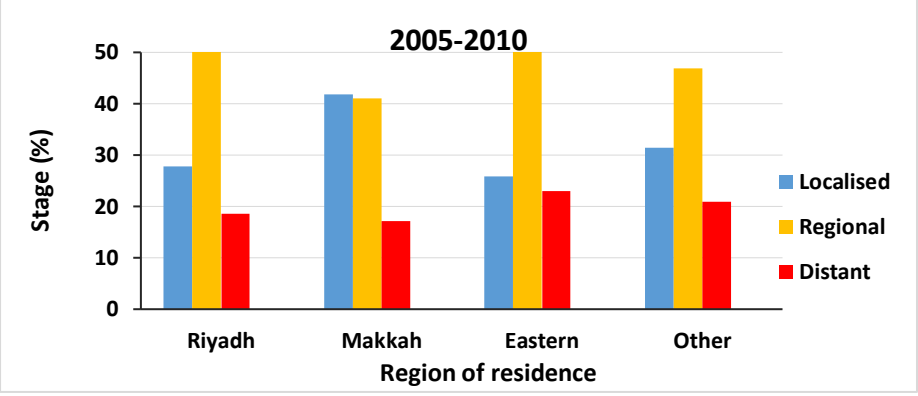
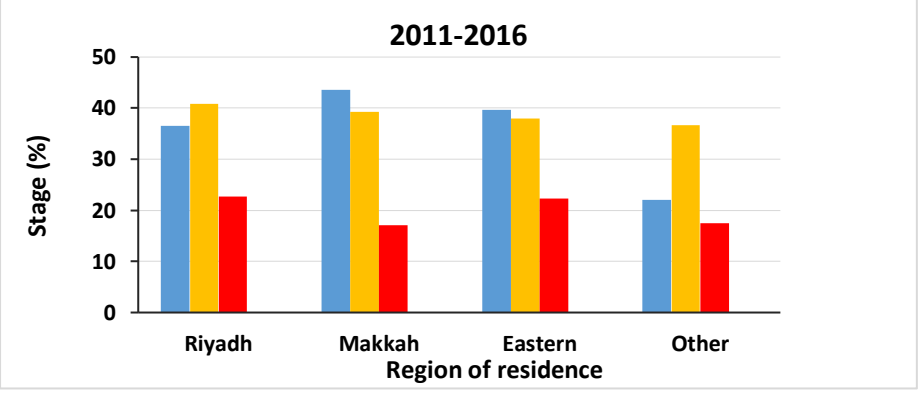


Figure 16: Stage distribution of invasive cervical cancer (2005-2016) for Saudi women included in the survival analysis and living in Riyadh, Makkah, Eastern or one of the 10 remaining administrative regions using the combined data from the five imputed datasets (n=6,065)





Time trend of stage at diagnosis

Over the 12 years examined, there has been an increase in the proportion of women diagnosed at localised stage and a decrease in those with unknown stage. After 2012, localised overtook regional as the most common stage at diagnosis (Figure 18). A similar trend was seen for Saudi women included in the survival analysis (Figure 18)

Figure 17: Stage distribution by year of diagnosis for all women diagnosed with invasive cervical cancer in Saudi Arabia during 2005-2016 (n=1,957)

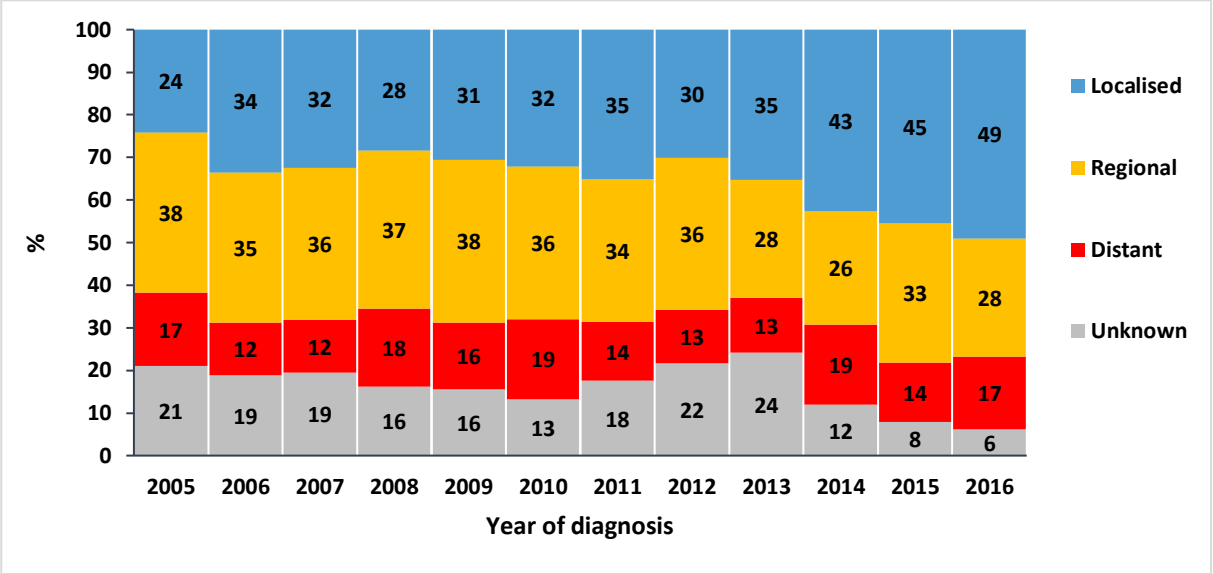
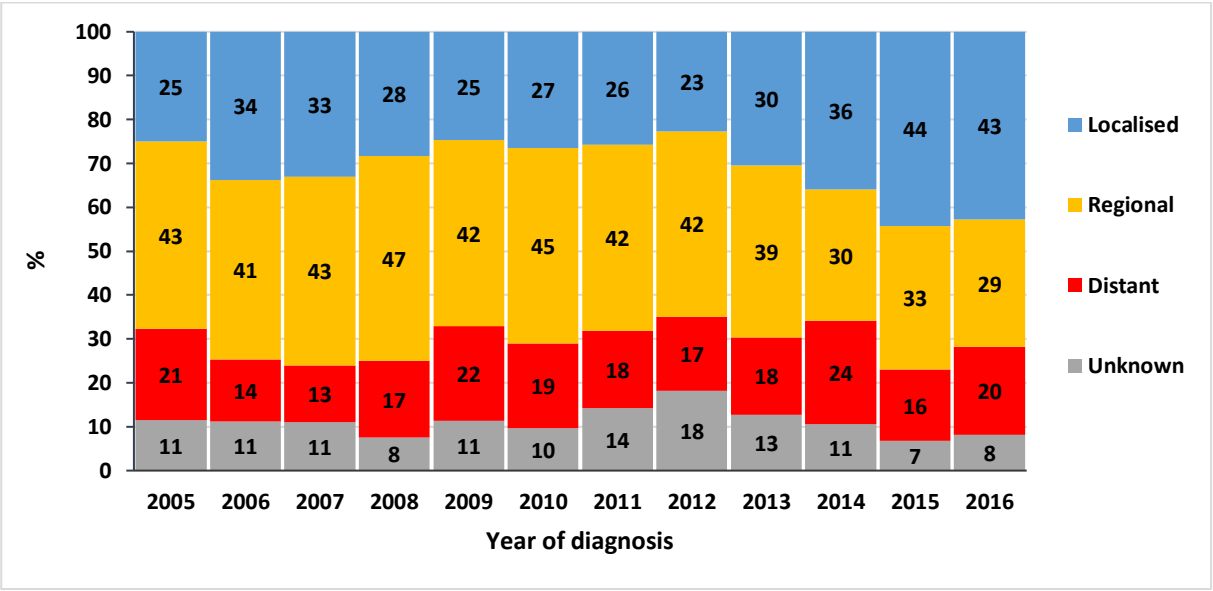


Figure 18: Stage distribution by year of diagnosis for Saudi women included in the survival analysis (n=1,219)



7.2 Age-standardised incidence rates

The age-standardised incidence rate (ASIR) for invasive cervical cancer in women of all nationalities was 1.66 and 1.76 per 100,000 women per year in 2005-2010 and 2011-2016, respectively.

By region of residence

The ASIR of invasive cervical cancer varied between regions and was higher in the three main regions than the ten peripheral regions. Makkah region had the highest ASIRs in both periods. There was no remarkable change in ASIR between the two periods (Table 13).

Table 13: Crude and age-standardised incidence rates (ASIRs) for invasive cervical cancer by region for all nationalities (n=1,947).

	2005-2010				2011-2016			
	N	crude	ASIR	95% CI	N	crude	ASIR	95% CI
All	902	1.37	1.66	(1.55 - 1.78)	1,076	1.40	1.76	(1.65 - 1.87)
Riyadh	237	1.51	2.10	(1.78 - 2.41)	261	1.41	1.93	(1.66 - 2.20)
Makkah	344	2.04	2.32	(2.05 - 2.58)	406	2.01	2.42	(2.17 - 2.68)
Eastern	119	1.25	1.68	(1.34 - 2.01)	171	1.57	2.20	(1.84 - 2.57)
Other	182	0.75	0.88	(0.75 - 1.02)	223	0.82	0.98	(0.84 - 1.11)
Asir	32	0.63	0.73	(0.47 - 0.99)	45	0.79	0.97	(0.68 - 1.27)
Baha	10	0.88	0.81	(0.29 - 1.33)	9	0.72	0.67	(0.22 - 1.12)
Hail	9	0.57	0.75	(0.22 - 1.27)	16	0.90	1.17	(0.56 - 1.78)
Jazan	13	0.36	0.39	(0.17 - 0.60)	18	0.45	0.48	(0.25 - 0.71)
Jouf	12	1.10	1.52	(0.62 - 2.42)	17	1.38	1.92	(0.95 - 2.90)
Madinah	46	1.02	1.14	(0.79 - 1.49)	52	1.00	1.18	(0.85 - 1.52)
Najran	13	1.01	1.33	(0.56 - 2.10)	12	0.82	1.04	(0.41 - 1.67)
Northern	3	0.36	0.59	(0.00 - 1.27)	7	0.75	0.96	(0.22 - 1.71)
Qassim	27	0.91	1.14	(0.68 - 1.61)	34	1.01	1.25	(0.79 - 1.71)
Tabuk	17	0.84	1.11	(0.56 - 1.67)	13	0.58	0.83	(0.33 - 1.33)

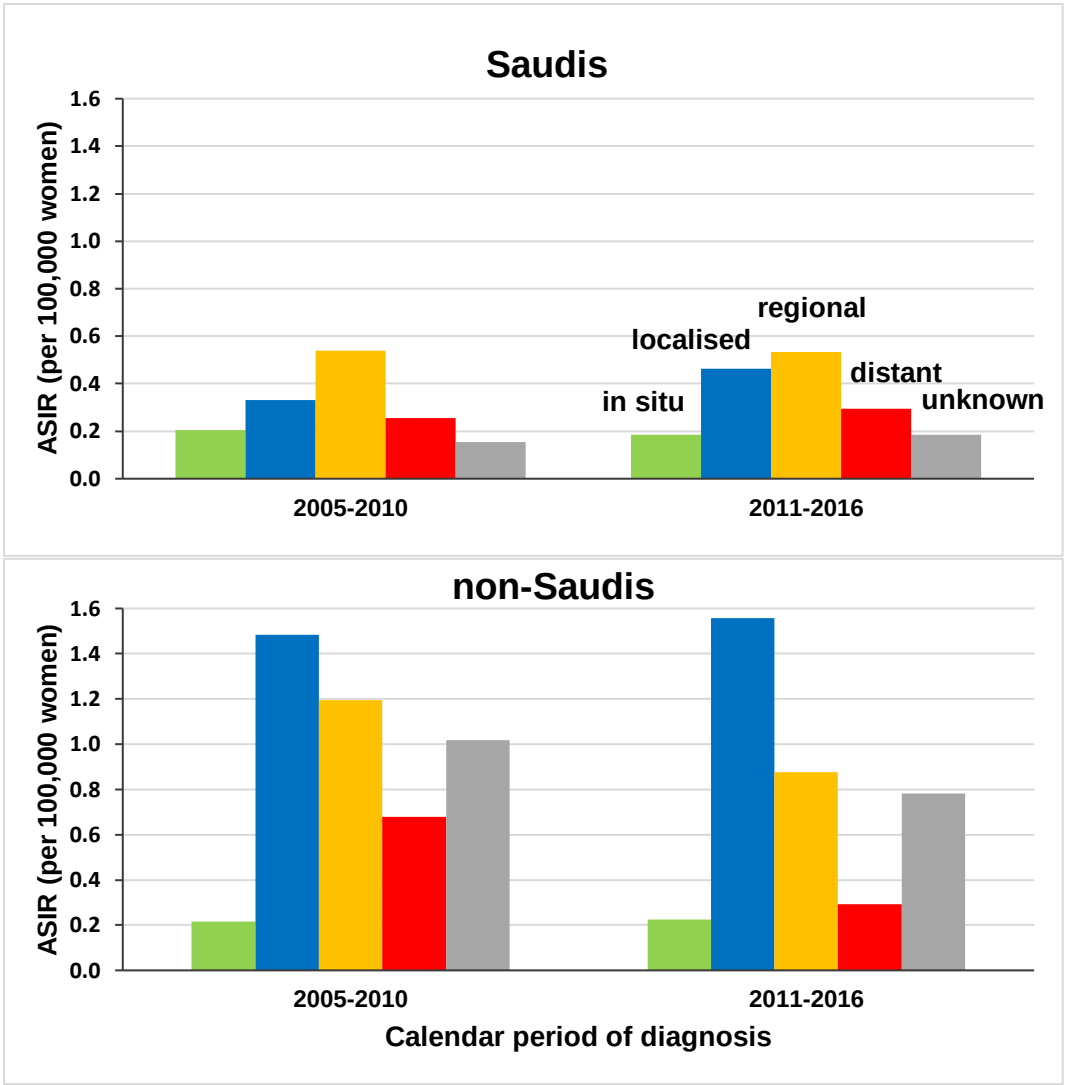
By nationality and stage

ASIRs of invasive cervical cancer in non-Saudi women were higher for each stage of invasive cancer than those in Saudi women, and especially for unknown stage. ASIR for cervical carcinoma in situ was slightly lower for non-Saudis. There was no remarkable change between the two periods 2005-2010 and 2011-2016 (Table 14, Figure 19).

Table 14: Crude and age-standardised incidence rates of invasive cervical cancer by calendar period, nationality and stage (n=2,262)

		2005-2010				2011-2016			
		n	crude	ASIR	95% CI	n	Crude	ASIR	95% CI
Saudi	In situ	59	0.21	0.20	(0.17 - 0.24)	61	0.19	0.19	(0.15 - 0.22)
	All invasive	**549**	**1.04**	**1.28**	**(1.17 - 1.40)**	**683**	**1.19**	**1.47**	**(1.36 - 1.60)**
	Localised	153	0.29	0.33	(0.28 - 0.39)	226	0.39	0.46	(0.40 - 0.52)
	Regional	243	0.44	0.54	(0.47 - 0.61)	245	0.43	0.53	(0.46 - 0.60)
	Distant	98	0.19	0.25	(0.20 - 0.31)	127	0.22	0.29	(0.24 - 0.35)
	Unknown	64	0.12	0.15	(0.11 - 0.19)	85	0.15	0.19	(0.14 - 0.23)
Non-Saudi	In situ	17	0.31	0.22	(0.14 - 0.29)	20	0.23	0.22	(0.14 - 0.31)
	All invasive	**338**	**2.74**	**4.38**	**(3.71 - 5.05)**	**387**	**2.04**	**3.48**	**(3.00 - 3.96)**
	Localised	114	0.91	1.48	(1.07 - 1.89)	194	1.02	1.56	(1.25 - 1.86)
	Regional	91	0.75	1.19	(0.86 - 1.53)	84	0.45	0.88	(0.63 - 1.13)
	Distant	43	0.34	0.68	(0.39 - 0.97)	32	0.17	0.29	(0.16 - 0.43)
	Unknown	90	0.73	1.02	(0.72 - 1.31)	77	0.40	0.78	(0.53 - 1.03)

Figure 19: Age standardised incidence rates (ASIR) by stage at diagnosis for Saudi and non-Saudi women



7.3 Survival

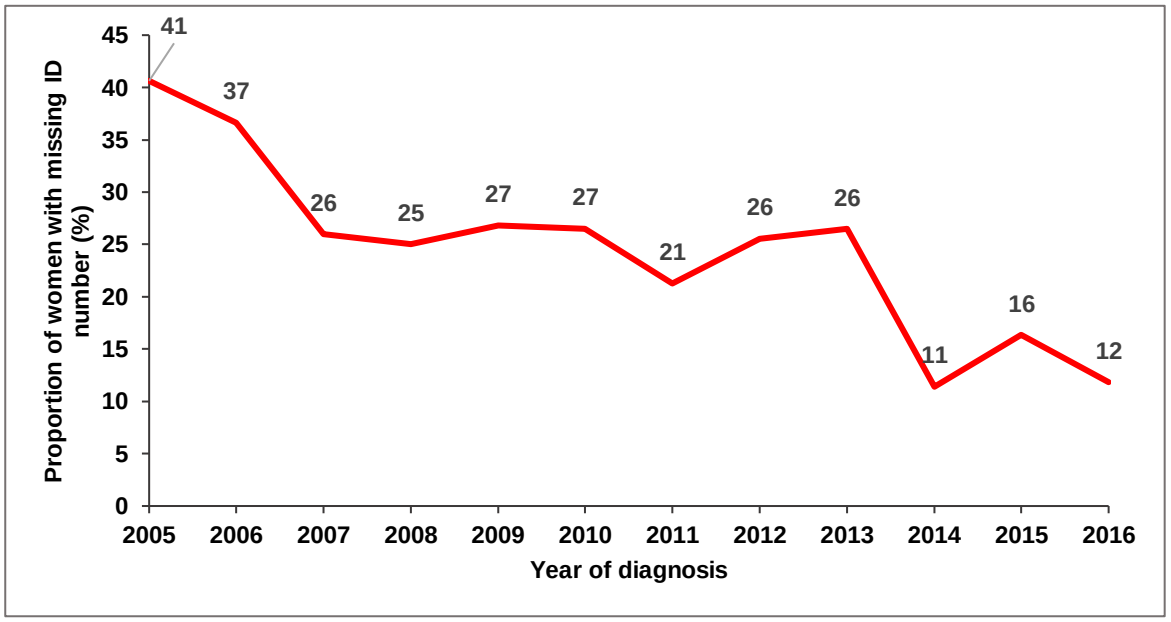
Linkage to death records

Seventy-six percent of women included in the survival analysis had a valid national ID number enabling NIC follow-up. The proportion of women with information on national ID number increased over the study period (Figure 21), but women living in the 10 peripheral regions had the least increase, leading to a lower proportion of available ID numbers in the period 2011-2016. In both periods, less than half the women *diagnosed* in those 10 regions had an ID number (Table 15). More women diagnosed at localised stage and women with unknown stage had missing ID numbers. The age difference between women with and without NIC follow-up was not statistically significant (mean age was 53 for women with, and 54.2 for women without NIC follow-up, p=0.17).

Table 15: Number and proportion (%) of women included in survival analysis who had NIC follow-up data by calendar period, region of residence, region of diagnosis and stage at diagnosis.

	2005-2010			2011-2016			All periods		
		NIC follow-up			NIC follow-up			NIC follow-up	
	n	n	%	n	n	%	n	n	%
Region of residence									
Riyadh	145	102	70.3	174	144	82.8	319	246	77.1
Makkah	157	108	68.8	204	171	83.8	361	279	77.3
Eastern	92	66	71.7	122	100	82.0	214	166	77.6
Other	142	99	69.7	177	133	75.1	319	232	72.7
Total	536	375	70.0	677	548	81.0	1,213	923	76.1
Region of diagnosis									
Riyadh	249	190	76.3	306	267	87.3	555	457	82.3
Makkah	171	121	70.8	218	182	83.5	389	303	77.9
Eastern	55	36	65.5	87	69	79.3	142	105	73.9
Other	63	30	47.6	68	32	47.1	131	62	47.3
Total	538	377	70.1	679	550	81.0	1,217	927	76.2
Stage at diagnosis									
Localised	153	93	60.8	225	177	78.7	378	270	71.4
Regional	234	182	77.8	246	216	87.8	480	398	82.9
Distant	96	70	72.9	127	110	86.6	223	180	80.7
Unknown	56	32	57.1	82	48	58.5	138	80	58.0
Total	539	377	69.9	680	551	81.0	1,219	928	76.1

Figure 20: Proportion (%) of women with missing ID by year of diagnosis



Age-specific net survival

Net survival decreased with increasing age at diagnosis for women diagnosed at 55 or older, and especially for those 65 and older (Figure 21, Table 16). Survival at one year since diagnosis was very similar in each age group for women diagnosed during 2005-2010 and 2011-2016, but was difficult to compare at five years due to the small number of women in older age groups (Table 17).

Figure 21: Age-specific net survival probabilities using ICSS (international Cancer Survival Standard) age groups for Saudi women diagnosed with invasive cervical cancer in the 12-year period 2005-2016

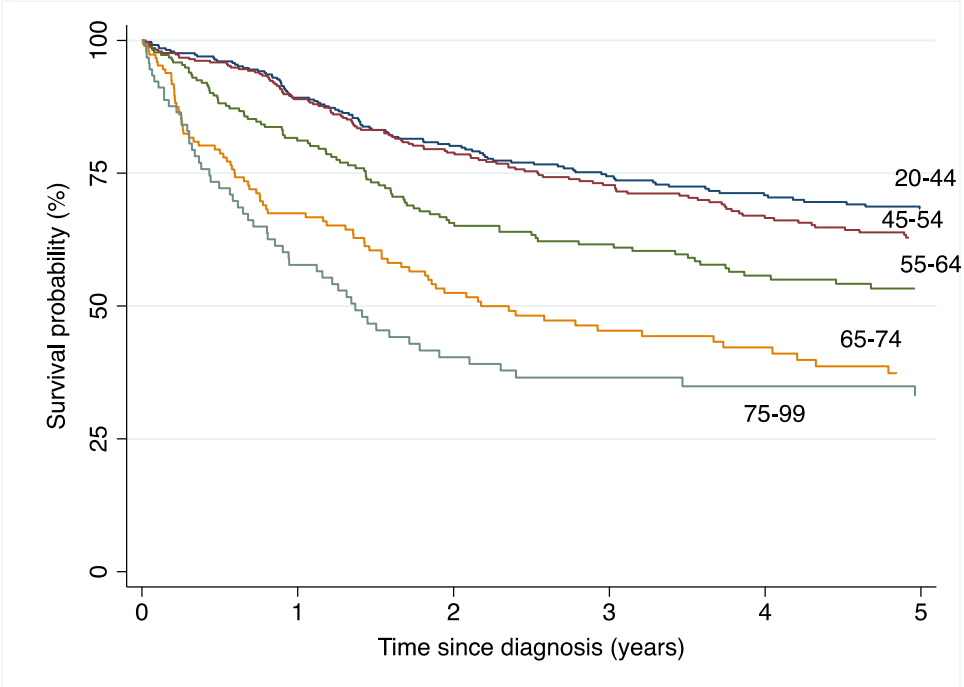


Table 16: 1- and 5- year net survival by ICSS age groups for Saudi women diagnosed with cervical cancer during 2005-2016 (n=1,219)

Age	N	1-year net survival		5-year net survival	
15-44	364	89.2	(85.8 - 92.6)	68.7	(62.9 - 73.7)
45-54	362	88.9	(85.5 - 92.3)	63.6	(57.2 - 68.6)
55-64	237	81.2	(75.8 - 86.5)	52.8	(45.9 - 60.7)
65-74	155	67.5	(59.7 - 75.3)	39.1	(28.5 - 46.3)
75+	101	57.8	(47.3 - 68.2)	30.1	(22.7 - 43.5)

Table 17: Number of women at risk at the beginning of each year of follow-up in each ICSS age group

	Year of follow-up				
age group	1	2	3	4	5
15-44	364	282	239	196	171
45-54	362	281	235	187	153
55-64	237	158	119	102	76
65-74	155	88	64	44	36
75+	101	48	32	23	19
Total	1219	857	689	552	455

Time trends in age-standardised net survival

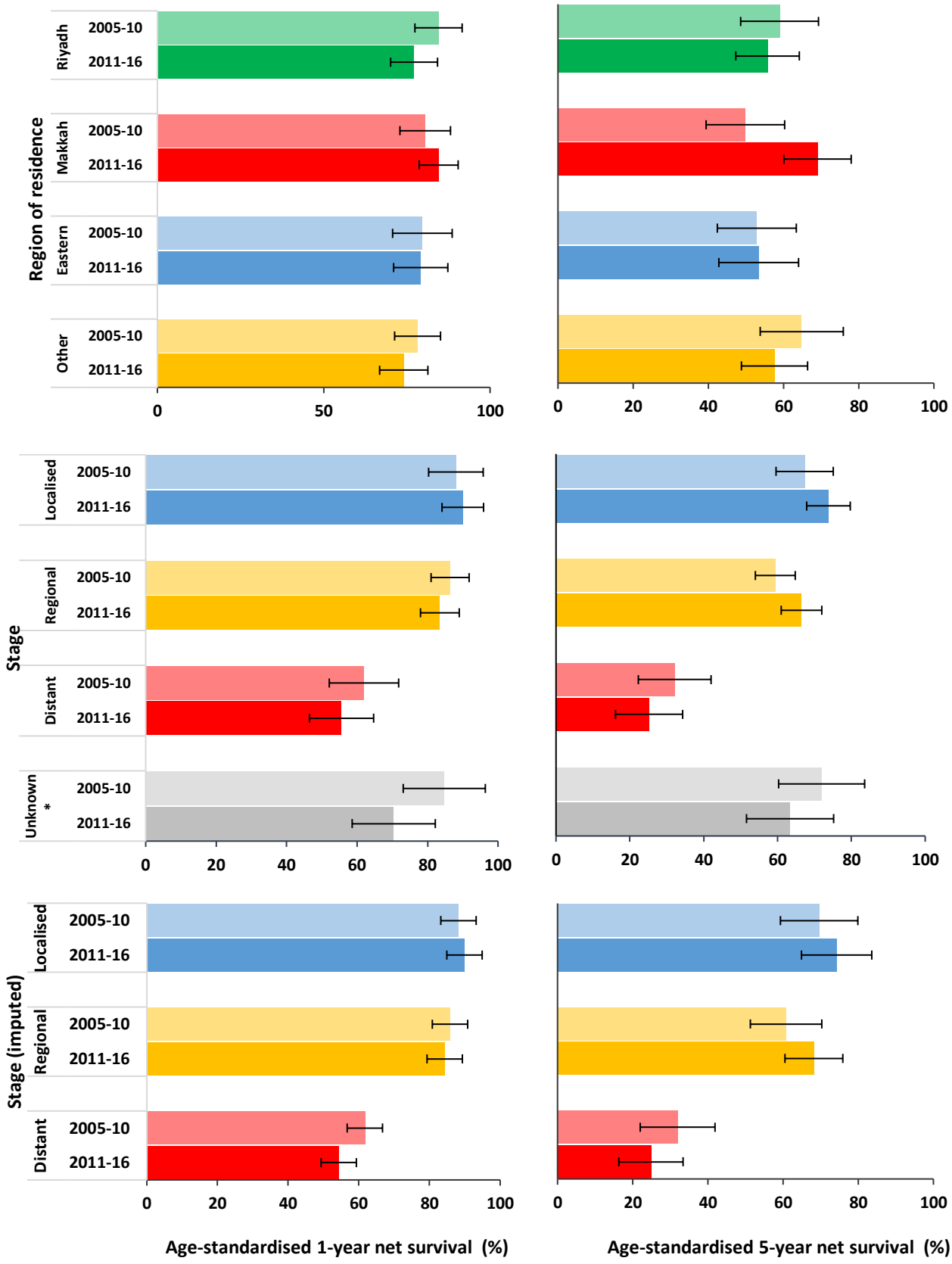
From 2005-2010 to 2011-2016, age-standardised net survival did not change for all Saudi women and all stages combined. Women living in Makkah region moved from having the lowest 5-year net survival during 2005-2010 (49.9%; 95%CI 39.4-60.3) to the highest during 2011-2016 (69.1; 60.1-78.0), while survival of women living in Riyadh, the Eastern Region and the other 10 regions remained the same or decreased slightly. There was a small increase in 5-year net survival for localised and regional stage and decline for distant stage and unknown stage. Survival for women with unknown stage was similar to that for women diagnosed at a localised or regional stage. Stage-specific net survival did not change after imputing unknown stage (Table 18, Figure 22).

Table 18: Age-standardised 1- and 5-year net survival estimates, with 95% confidence intervals (CI), by region of residence and stage at diagnosis, in 2005-10 and 2011-16.

	Calendar period	n	1-year net survival	5-year net survival
	2005-10	539	81.0 (76.8 - 85.2)	59.2 (52.7 - 65.7)
	2011-16	680	79.4 (75.8 - 83.0)	59.7 (54.7 - 64.6)
Region of residence				
Riyadh	2005-10	145	84.5 (77.4 - 91.6)	59.0 (48.6 - 69.3)
	2011-16	174	77.1 (70.1 - 84.2)	55.8 (47.3 - 64.2)
Makkah	2005-10	157	80.5 (72.9 - 88.1)	49.9 (39.4 - 60.3)
	2011-16	204	84.6 (78.7 - 90.4)	69.1 (60.1 - 78.0)
Eastern	2005-10	92	79.6 (70.7 - 88.6)	52.9 (42.4 - 63.4)
	2011-16	122	79.1 (71.0 - 87.3)	53.4 (42.8 - 64.0)
Other	2005-10	142	78.2 (71.3 - 85.1)	64.8 (53.8 - 75.9)
	2011-16	177	74.1 (66.8 - 81.3)	57.6 (48.8 - 66.4)
Stage				
Localised	2005-10	153	88.1 (80.3 - 95.8)	67.4 (57.3 - 77.5)
	2011-16	225	90.0 (84.1 - 95.9)	73.8 (63.5 - 84.1)
Regional	2005-10	234	86.4 (81.0 - 91.8)	59.4 (49.7 - 69.0)
	2011-16	246	83.5 (78.0 - 89.0)	66.5 (58.8 - 74.3)
Distant	2005-10	96	61.9 (52.1 - 71.8)	32.1 (22.2 - 42.0)
	2011-16	127	55.6 (46.5 - 64.7)	25.2 (16.6 - 33.8)
Unknown	2005-10*	56	84.8 (73.1 - 96.4)	72.0 (56.7 - 87.4)
	2011-16	82	70.4 (58.6 - 82.2)	63.4 (49.9 - 77.0)
Stage (Imputed) [§]				
Localised	2005-10	879	88.2 (80.7 - 95.8)	69.6 (59.3 - 79.9)
	2011-16	1304	89.9 (84.2 - 95.7)	74.3 (64.9 - 83.6)
Regional	2005-10	1282	85.8 (80.5 - 91.1)	60.8 (51.3 - 70.3)
	2011-16	1376	84.3 (78.9 - 89.6)	68.2 (60.5 - 75.9)
Distant	2005-10	529	61.7 (52.2 - 71.3)	32.0 (22.0 - 41.9)
	2011-16	720	54.3 (45.1 - 63.6)	24.9 (16.3 - 33.4)

*unstandardised
[§] n is the total from five imputations

Figure 22: Age-standardised 1- and 5-year net survival trends by stage at diagnosis and region of residence for women diagnosed with invasive cervical cancer during the calendar periods 2005-2010 and 2011-2016.



*unstandardised

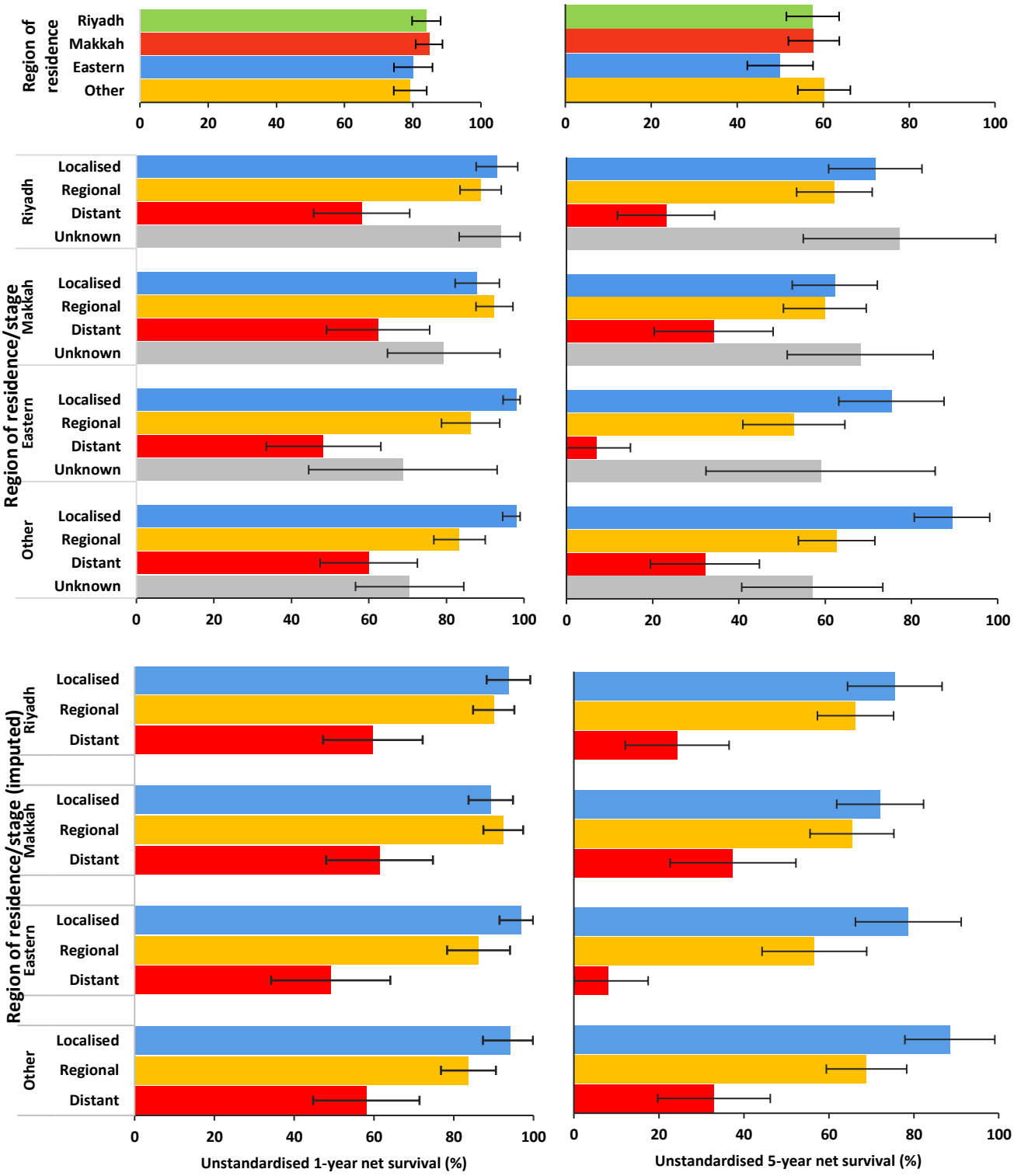
Net survival by region and stage

Unstandardised stage-specific net survival for women diagnosed during the 12-year period 2005-2016 was similar between regions except for distant stage, for which 5-year net survival in the Eastern region was remarkably lower than that in all other regions (Table 19, Figure 23). When including unknown stage as a category using the unimputed dataset, there was no difference in net survival for women with unknown stage between regions.

Table 19: Stage-specific 1- and 5-year unstandardised net survival estimates, with 95% confidence intervals (CI), by region of residence for women diagnosed with invasive cervical cancer during 2005-2016.

		N	1-year net survival	5-year net survival
Region				
	Riyadh	319	84.0 (79.8 - 88.2)	57.6 (51.5 - 63.7)
	Makkah	361	84.8 (80.9 - 88.7)	57.8 (51.9 - 63.8)
	Eastern	214	80.1 (74.5 - 85.8)	50.0 (42.4 - 57.7)
	Other	319	79.3 (74.4 - 84.1)	60.2 (54.1 - 66.3)
Region and stage				
Riyadh	Localised	96	93.0 (87.7 - 98.4)	71.6 (60.8 - 82.5)
	Regional	138	88.8 (83.5 - 94.1)	62.1 (53.4 - 70.9)
	Distant	62	58.1 (45.7 - 70.5)	23.1 (11.8 - 34.4)
	Unknown	23	94.1 (83.3 - 105.0)	77.2 (54.9 - 99.5)
Makkah	Localised	142	87.9 (82.2 - 93.7)	62.2 (52.4 - 72.1)
	Regional	128	92.4 (87.6 - 97.2)	59.9 (50.3 - 69.5)
	Distant	55	62.4 (49.1 - 75.7)	34.1 (20.3 - 47.9)
	Unknown	36	79.3 (64.8 - 93.8)	68.1 (51.2 - 85.0)
Eastern	Localised	65	98.2 (94.6 - 101.7)	75.4 (63.2 - 87.6)
	Regional	87	86.2 (78.7 - 93.7)	52.7 (40.9 - 64.6)
	Distant	46	48.3 (33.5 - 63.1)	7.0 (0.0 - 14.8)
	Unknown	16	68.8 (44.4 - 93.1)	58.9 (32.4 - 85.5)
Other	Localised	72	98.1 (94.5 - 101.7)	89.4 (80.7 - 98.2)
	Regional	127	83.4 (76.7 - 90.0)	62.7 (53.8 - 71.5)
	Distant	58	59.9 (47.4 - 72.5)	32.1 (19.5 - 44.8)
	Unknown	62	70.5 (56.5 - 84.5)	57.0 (40.6 - 73.4)
Region and imputed stage				
Riyadh	Localised	100	93.6 (88.1 - 99.1)	75.1 (63.7 - 86.5)
	Regional	152	89.5 (84.1 - 94.9)	64.9 (55.7 - 74.2)
	Distant	67	59.0 (46.4 - 71.6)	23.9 (11.9 - 35.9)
Makkah	Localised	156	88.9 (83.1 - 94.7)	70.5 (59.6 - 81.3)
	Regional	142	93.2 (88.3 - 98.1)	62.6 (52.2 - 72.9)
	Distant	63	63.7 (50.1 - 77.3)	38.9 (23.4 - 54.4)
Eastern	Localised	74	98.7 (95.1 - 100.0)	79.1 (66.4 - 91.7)
	Regional	93	87.2 (79.5 - 94.8)	56.2 (43.6 - 68.7)
	Distant	47	49.6 (34.4 - 64.8)	7.9 (0.0 - 16.6)
Other	Localised	104	98.7 (95.1 - 100.0)	94.2 (85.0 -100.0)
	Regional	147	84.2 (77.4 - 90.9)	67.8 (58.2 - 77.4)
	Distant	68	60.6 (47.9 - 73.2)	34.3 (20.8 - 47.7)

Figure 23: 1- and 5-year unstandardised net survival estimates by region of residence and stage at diagnosis for women diagnosed with invasive cervical cancer during 2005-2016.



Sensitivity analysis

Restriction to women with NIC follow-up

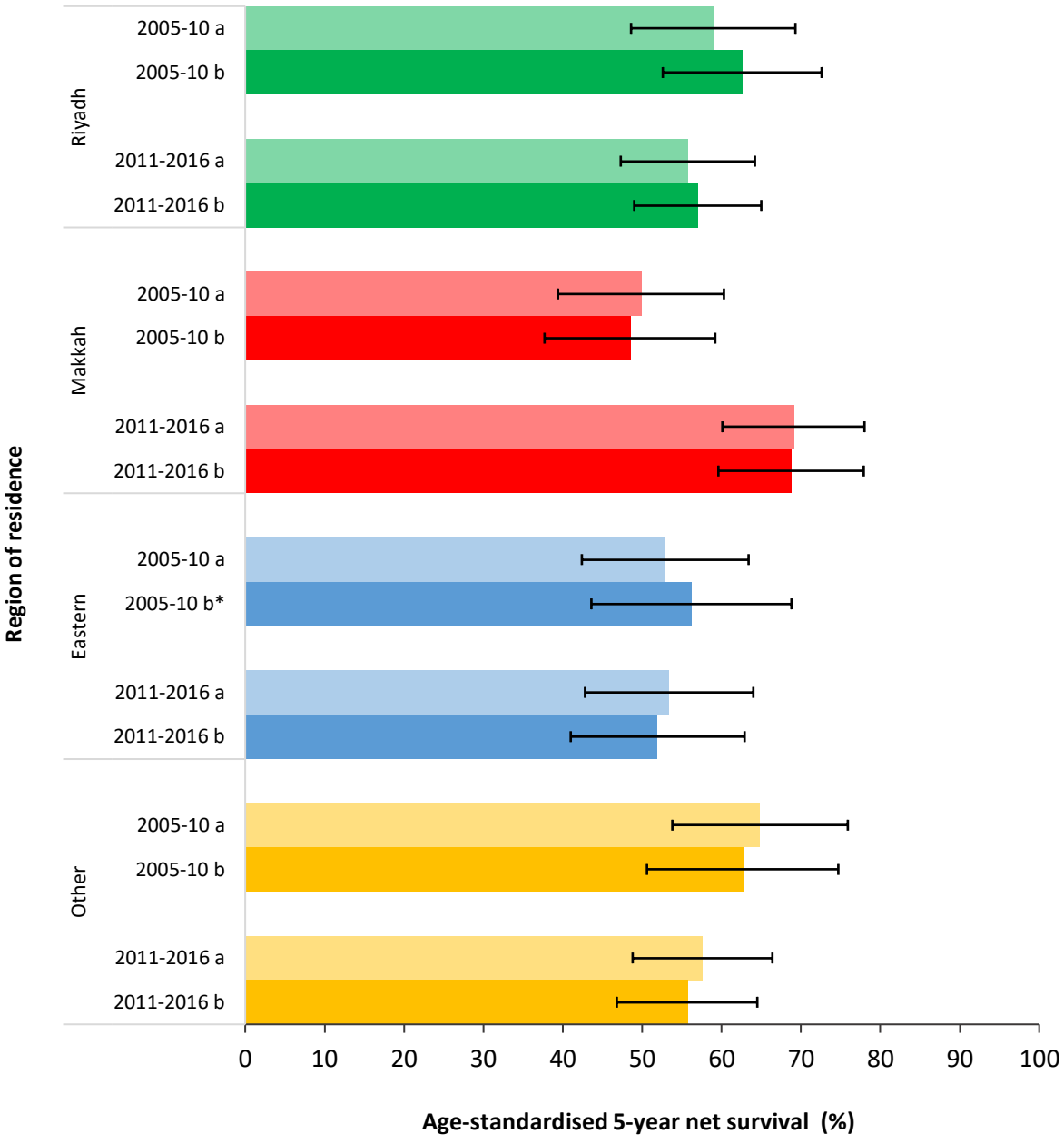
Restricting the analysis to the 928 women with NIC follow-up did not change the results for any of the regions, with the largest difference being a 3.6% absolute increase for Riyadh in 2005-2010 (Table 20, Figure 24).

Table 20: 1- and 5-year age-standardised net survival estimates, with 95% confidence intervals (CI), by region of residence and stage at diagnosis for women with NIC follow-up (n=928).

	Calendar period	n	1-year net survival	5-year net survival
	2005-10	377	80.5 (76.8 - 85.2)	58.6 (51.8 - 65.5)
	2011-16	551	79.2 (75.8 - 83.0)	59.6 (54.5 - 64.8)
Region of residence				
Riyadh	2005-10	102	87.6 (82.3 - 92.9)	62.6 (52.6 - 72.6)
	2011-16	144	78.0 (71.6 - 84.4)	57.0 (49.0 - 65.0)
Makkah	2005-10	108	80.5 (72.7 - 88.2)	48.5 (37.7 - 59.2)
	2011-16	171	83.7 (77.5 - 89.8)	68.8 (59.6 - 77.9)
Eastern	2005-10*	66	79.4 (69.5 - 89.3)	56.2 (43.6 - 68.8)
	2011-16	100	78.3 (69.7 - 86.8)	51.9 (41.0 - 62.9)
Other	2005-10	99	77.2 (69.5 - 84.8)	62.7 (50.6 - 74.7)
	2011-16	133	72.7 (64.8 - 80.5)	55.7 (46.8 - 64.5)
Stage				
Localised	2005-10*	93	91.2 (85.1 - 97.3)	78.0 (68.2 - 87.8)
	2011-16	177	90.4 (84.2 - 96.6)	74.2 (63.6 - 84.8)
Regional	2005-10	182	86.2 (80.1 - 92.2)	60.4 (50.3 - 70.4)
	2011-16	216	83.2 (77.5 - 88.8)	66.5 (58.6 - 74.4)
Distant	2005-10*	70	63.9 (52.5 - 75.3)	33.5 (22.1 - 45.0)
	2011-16	110	54.0 (44.3 - 63.6)	23.3 (14.8 - 31.8)
Unknown	2005-10*	32	81.6 (68.2 - 95.0)	67.5 (50.9 - 84.1)
	2011-16*	48	70.1 (56.8 - 83.4)	66.0 (50.1 - 82.0)

*unstandardised

Figure 24: Age standardised 5-year net survival, with 95% confidence intervals (CI). (a) using NIC follow-up complemented with registry follow-up (b) restricted to NIC follow-up.

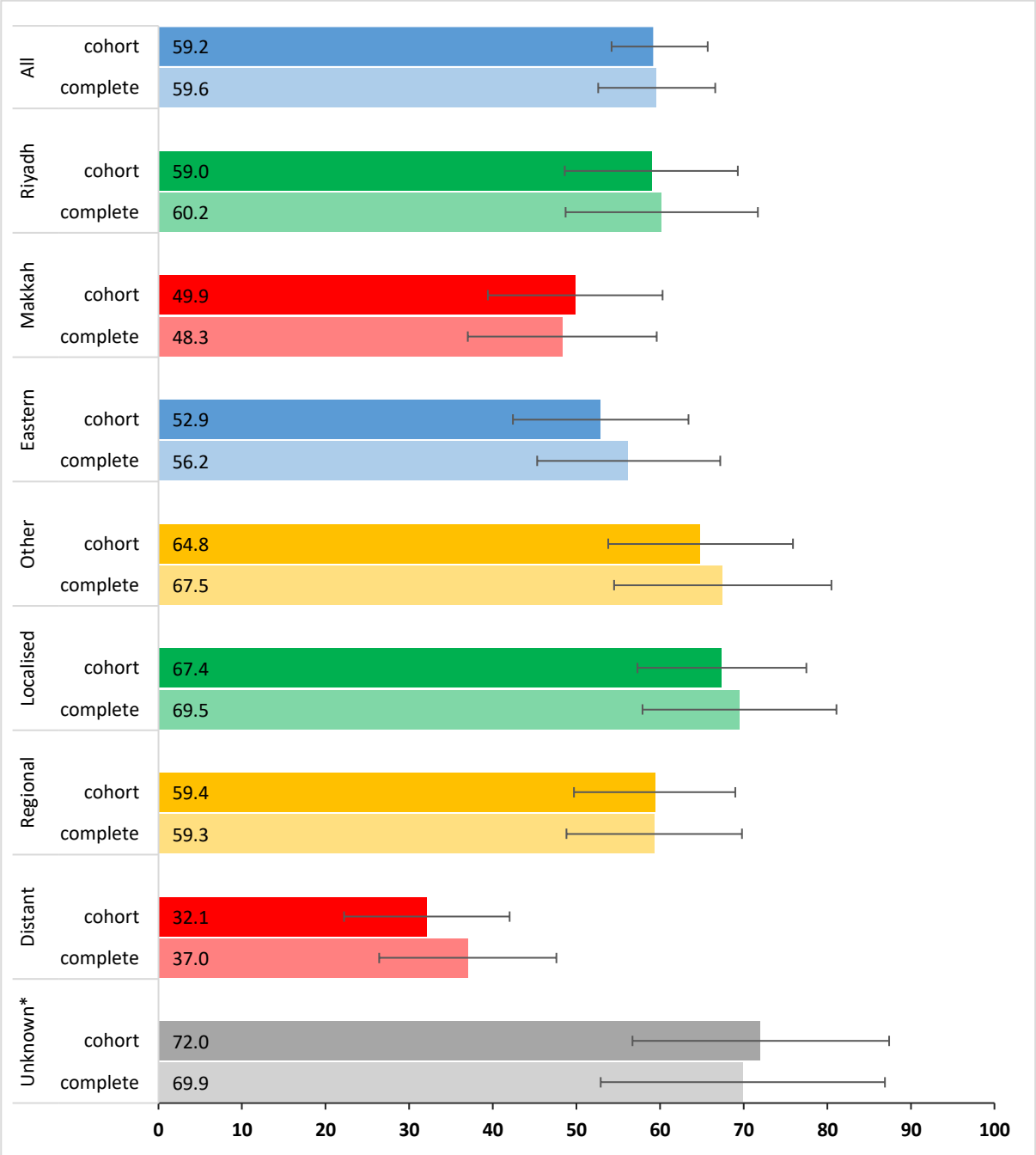


*unstandardised

Censoring survival time at 31 December 2012 for women diagnosed during 2005-2010

Using a complete approach for women diagnosed during 2005-2010 while censoring follow-up until 31 December 2012 did not change the survival estimate for all ages combined compared to the cohort approach, but was 5% higher for women diagnosed at a distant stage (Figure 25).

Figure 25: Effect of censoring survival time at 31/12/2012 on 5-year age-standardised survival estimates for women diagnosed during 2005-2010



Cohort: 5 years follow-up for all women
Complete: survival time censored at 31 December 2012

Age-standardised net survival using Global Burden of disease life tables

One and 5-year age-standardised net survival estimates were slightly lower when using life tables for Saudi Arabia obtained from the Global Burden of Disease study. The difference was less than 1% for all 1-year net survival estimates and the largest difference was 3.3% for women diagnosed at localised stage during 2005-2010 (Table 21).

Table 21: Age-standardised 1- and 5-year net survival, 95% confidence intervals (CIs), for women diagnosed with invasive cervical cancer in Saudi Arabia during 2005-2011 using Global Burden of Disease life tables (n=1,219)

		N	1-year net survival	5-year net survival
	2005-10	539	80.6 (76.5 - 84.8)	56.5 (50.7 - 62.4)
	2011-16	680	79.1 (75.5 - 82.7)	58.2 (53.5 - 62.9)
Region of residence				
Riyadh	2005-10	145	84.2 (77.1 - 91.2)	58.2 (48.3 - 68.2)
	2011-16	174	76.9 (70.0 - 83.9)	55.2 (46.9 - 63.4)
Makkah	2005-10	157	80.2 (72.7 - 87.8)	47.9 (38.3 - 57.5)
	2011-16	204	84.1 (78.4 - 89.9)	66.6 (58.2 - 75.0)
Eastern	2005-10	92	79.3 (70.4 - 88.2)	52.4 (42.1 - 62.7)
	2011-16	122	78.9 (70.8 - 87.0)	52.3 (42.1 - 62.5)
Other	2005-10	142	77.9 (71.0 - 84.8)	61.3 (51.3 - 71.2)
	2011-16	177	73.9 (66.7 - 81.1)	57.0 (48.4 - 65.5)
Stage				
Localised	2005-10	153	87.6 (80.0 - 95.3)	66.9 (56.9 - 76.8)
	2011-16	225	89.6 (83.8 - 95.4)	71.1 (61.8 - 80.4)
Regional	2005-10	234	86.2 (80.8 - 91.6)	56.1 (47.4 - 64.7)
	2011-16	246	83.2 (77.8 - 88.6)	65.3 (57.9 - 72.7)
Distant	2005-10	96	61.6 (51.9 - 71.4)	31.7 (21.9 - 41.5)
	2011-16	127	55.4 (46.3 - 64.4)	24.5 (16.1 - 32.9)
Unknown	2005-10*	56	84.7 (73.1 - 96.3)	71.6 (56.4 - 86.9)
	2011-16	82	70.1 (58.4 - 81.9)	62.9 (49.4 - 76.3)

*unstandardised

7.4 Age-standardised mortality rates

A total of 323 women were included in mortality estimates. The mean age at death was 58±14.4. The number of women dying of cervical cancer was very similar over the periods 2005-2010 and 2011-2016 for both Saudi and non-Saudi women. Crude and age-standardised mortality rates were also similar over the two calendar periods of mortality (Table 22).

Table 22: Crude and age-standardised mortality rates (ASMR) from invasive cervical cancer (n=323)

	2005-2010					2011-2016				
	N	Crude	ASMR	95% CI		N	Crude	ASMR	95% CI	
				upper	lower				upper	lower
Saudi	134	0.25	0.34	(0.28 -	0.40)	135	0.23	0.32	(0.27 -	0.38)
Non-Saudi	25	0.19	0.59	(0.31 -	0.87)	29	0.15	0.28	(0.14 -	0.42)

Chapter 8. Discussion

In this thesis, I have described the characteristics of women diagnosed with cervical cancer in Saudi Arabia during 2005-2016 and examined incidence and survival trends by stage at diagnosis and region of residence; I have also explored age-standardised mortality rates over the same period. I have included both Saudi and non-Saudi women with registered cervical malignancies in the incidence and mortality rates, but since it was not possible to obtain data on follow-up for vital status for non-Saudi women, survival analyses have been restricted to Saudi women.

Stage at diagnosis has moved over time towards a more favourable distribution with localised becoming the predominant stage after 2012. With 39% of women diagnosed at localised stage in 2016, this is still somewhat lower than the proportion seen in high-income countries with established screening programmes, such as the UK (Northern Ireland) during 2010-2017 (54% localised) and the US during 2010-2016 (44% localised).[163,164] A similar increase in localised stage over time was seen in the United Arab Emirates (UAE) from 15.6% during 2003-2007 to 38.3% in 2008-2012. For other countries of the Gulf Cooperation Council (GCC), a large proportion of missing stage made it difficult to observe trends.[165] Between 2000 and 2013, 43% of women diagnosed with cervical cancer in Jordan were diagnosed at localised stage, but stage was unknown for 28%.[166]

The shift from regional to localised stage over time was minimal in the ten peripheral regions of Saudi Arabia. The proportion of women whose stage at diagnosis was unknown also remained high in these regions, suggesting that women living in those regions did not benefit as much as women in more populous regions from improved timeliness and thoroughness of diagnosis. This may be due to a lower degree of awareness among women living in these regions or a lack of clinical resources. Women's educational attainment is positively associated with higher cervical cancer screening uptake and earlier stage diagnosis.[78,167,168] In a nationally representative survey of women in Kuwait, Oman, Saudi Arabia and the UAE, women with secondary and college education were more likely to have a Pap smear within recommended intervals.[144] While 49%, 50% and 52% of females aged 10 years and older in Riyadh, Makkah and the Eastern region have a secondary school education or a higher level of attainment, only 42% had the equivalent educational level in the other ten regions. In almost all regions, the most frequently given reason for not enrolling in school was marriage or pregnancy, followed by helping in the

household.[169] However, these statistics include girls aged 10 to 17 who have not yet had the chance to complete secondary education. They also include cohorts of women who did not have access to formal schooling, which only became widely available for girls in the early 1960s. The age distribution is very similar between regions, with girls in the age group 10-19 years making up 25-26% of the female population and women 65 years or older making up only 3-4%. The reported figures therefore underestimate the proportion of women who have completed secondary education, but they are still useful for comparison between regions.

Early-stage diagnosis is the most important determinant of cervical cancer survival, but early diagnosis can also allow young women diagnosed with stage I cervical cancer to be offered the option of fertility-sparing surgery. Preserving fertility is a crucial outcome to consider, especially with a disease that affects relatively young women in societies that value having children very highly. In this study population, half the women were in what is considered child-bearing age (younger than 50). Desire to spare fertility may pose a challenge to effective treatment for gynaecological cancers, and it is a source of psychological stress for the woman. Additionally, diagnosis at an early stage is even more crucial in settings with less access to specialised treatment centres that offer radiotherapy, since radiotherapy is part of the treatment of choice (chemoradiation) for locally advanced tumours.[33]

Incidence rates of cervical cancer

The patterns of age-specific incidence rates are consistent with those seen in low-resource settings, where they continue to rise up to age 69 years. In high-resource countries, incidence rates tend to peak around age 40, which may reflect the removal of pre-cancerous (dysplastic) or pre-invasive (in situ) lesions detected at screening. The higher prevalence of hysterectomy in some high-income countries may also contribute to the lower incidence in older age.[3]

Age-standardised incidence rates (ASIR) remained similar throughout the period 2005-2016. The annual incidence rates for all Saudi and non-Saudi women combined (1.66 and 1.76 per 100,000 women during 2005-2010 and 2011-2016, respectively) derived from these data are similar to those reported in *Cancer Incidence in Five Continents* for 2008-2012, which only included data from Riyadh.[170] These rates are about 30% lower than the Globocan estimates for Saudi Arabia in 2018 (2.5 per 100,000 women). The registry has

not yet published data for 2018 and the estimates are projections, based on a range of assumptions and use the incidence data for 2003-2012, applied to the 2018 United Nations resident population estimates.[171]

The age-standardised incidence rates for cervical cancer in Saudi Arabia are similar to those in neighbouring countries such as Jordan, Palestine, Egypt, Iran, Iraq and Yemen.[166,171] The ASIRs for Saudi nationals are lower than the incidence rates among nationals of other GCC states.[165] Low ASIRs in Saudi Arabia and the region in general are most likely attributable to the low prevalence of premarital and extramarital sex, for religious and cultural reasons. Very little is known about the prevalence of extramarital sex in Saudi Arabia and whether it is increasing, or the number of life-time sexual partners for women and men. A survey of 225 male preparatory college students aged 15-20 years in 2012 revealed that 31% had engaged in premarital sexual activity at least once.[172] Of 5,377 men and women presenting to primary care with symptoms suggestive of sexually transmitted infections during 2009, only 8.6% reported having sex outside marriage. However, the questionnaires were completed at the primary health centre and were not anonymous, which may have led to under-reporting.[173] Of 400 women aged 22-80 years who attended routine cervical examination in Riyadh from November 2013 to November 2015, only 12% reported having had more than one life-time sexual partner, and only 4% had more than three.[87] The prevalence of high-risk HPV strains is also difficult to determine in the absence of population-based prevalence studies, or HPV testing in the context of screening programmes. Despite lack of empirical evidence, it is generally believed that sexual behaviours that would increase the risk of HPV infection are now being more frequently adopted among Saudi women due to globalisation, increased travel, and internet and social media use.[174] However, later age at marriage, delayed childbearing and decreasing parity are also factors that could reduce the risk of cervical cancer,[175] along with increasing uptake of Pap-testing. There is evidence of increasing age of first marriage and celibacy among women in Arab countries, including Saudi Arabia, since the second half of the 20th century. While this trend is associated with a reduction in early childbirth and multiparity, the interval between menarche and marriage could increase the risk of pre-marital sex without access to sexual health services.[176,177] Male circumcision also plays a protective role in HPV transmission and is very widely practiced in Saudi Arabia and other Muslim-majority countries.[25]

For all nationalities combined, Riyadh, Makkah and the Eastern Region had higher ASIRs than the ten other regions, and ASIRs were the highest in Makkah in both periods, 2005-2010 and 2011-2016. Makkah has the largest non-Saudi population in the country (48% of women according to the 2010 census),[118] and the proportion of non-Saudis among women with cervical cancer was higher than in other regions (52%). The ASIR among Saudi women living in Makkah was similar to that in Riyadh.

Non-Saudi women had higher incidence rates than Saudi women in every age group, and higher ASIRs at every stage of invasive cervical cancer. Lower socioeconomic status is associated with increased risk of cervical cancer, and many of the non-Saudi residents are working in unskilled, low-paying jobs (for example, domestic helpers). Countries with lower Human Development Index also generally have higher cervical cancer incidence rates.[53] The 746 non-Saudi women in this study population held 50 different nationalities, but half of them came from the Philippines, Indonesia, Yemen and Somalia, followed by smaller numbers from Syria, Sudan, Ethiopia, Eritrea, Nigeria, Chad, Sri Lanka, Pakistan, India and Palestine. This reflects a mix of the numbers of resident women from these countries and the risk profile of the countries the women come from. For example, the estimated ASIRs for cervical cancer for the Philippines, Indonesia and Somalia for 2018 are 14.9, 23.4 and 24.0 per 100,000 women respectively, while the estimated ASIR is low in Yemen (1.9 per 100,000). But Yemeni nationals constitute one of the largest group of expatriates and migrants in Saudi Arabia. Employment-related migration has been recognised as increasing the risk of sexually transmitted infections due to several factors. These include demographics, since many migrant workers are young and single, or move to the host country alone; lack of skills and restrictive employment policies, which may push women towards sex work; and loss of social pressure to conform to the sexual norms in their society of origin.[178] Further, studies of sexual networks have shown clustering of sexual relations by ethnicity.[179] This could mean that women born in Saudi Arabia but who identify with high-risk ethnicities could carry a similar risk of cervical cancer to those ethnic backgrounds. Data from the United Kingdom suggest that young women living in deprived areas are less likely to be vaccinated against HPV or to attend cervical screening, which may compound inequalities in cervical cancer incidence.[180]

Net survival

Age-standardised net survival at one and five years since diagnosis for all Saudi women diagnosed with cervical cancer did not change between 2005-2010 and 2011-2016.

Survival was similar for women diagnosed during these two periods in all regions except Makkah, where the 5-year net survival probability increased by 19%, from the lowest survival among regions during 2005-2010 (49.9%) to the highest survival during 2011-2016 (69.1%). There was a small decline in survival in 2011-2016 compared to 2005-2010 in Riyadh and in the ten peripheral regions.

Five-year survival was lower than that reported for Saudi Arabia in CONCORD-2 for women diagnosed during 1995-1999 (62.2%; 95%CI 50.6-73.8%) and 2000-2004 (65.6%; 56.8-74.4%).[10] However, those estimates were flagged as being less reliable due to the very high proportion of women with censored survival times (75.9%). The data submitted for CONCORD-2 contained “registry follow-up” (page 40), which is obtained through a mix of active methods (search in patient records) and passive methods (receipt of death notifications and death certificates with a mention of cancer). The registry aims to capture deaths of all registered patients, regardless of the cause of death, but the method is inherently biased towards finding deaths that have been attributed to cancer, while follow-up is censored at the date of last contact at which a woman was known to be alive. This is often a short time after diagnosis, which is why the proportion of women with a censored survival time was so high. By contrast, linkage to the National Information Center (NIC) mortality records, although it was only achieved for 74% of women, substantially reduced the proportion of women with censored survival time, to 24% for those diagnosed during 2005-2010 and 42% for 2011-2016.

The age-standardised 5-year net survival estimates for cervical cancer in Saudi women were similar to those in countries in Western Asia reported in CONCORD-3, such as Turkey during 2005-2009 (59.2%; 95%CI 56.5-61.9) and 2010-2014 (60.7%; 58.1-63.3), Jordan during 2010-2014 (56.4%; 48.2-64.6), Kuwait during 2010-2014 (56.6%; 44.2-69.0), Qatar during 2005-2009 (55.5%; 35.3-76.0) and 2010-2014 (63.5%; 44.2-82.8). Survival estimates were also similar to those in some Eastern European countries, but lower than estimates for most countries in Western and Northern Europe.[4]

A lack of improvement or even a decline in cervical cancer survival has been seen in some countries after the introduction of widespread cervical cancer screening, due to the removal of slower-growing precancerous lesions. More aggressive lesions, some of which carry a worse prognosis, selectively form and progress to invasive cancer within screening intervals. However, this is unlikely to be why survival has not improved in Saudi Arabia, since there is no organised screening programme and uptake of opportunistic Pap smears

has been quite low, with only about 7.6% of women aged 25-49 having had a Pap smear within the recommended intervals for their age.[144]

Interpreting survival estimates in the light of the stage distribution could help understand changes, or lack thereof, in survival patterns. The proportion of women diagnosed at a localised stage increased, while the proportion diagnosed at a regional stage declined. However, there was no change in the proportion of women diagnosed at a distant stage in all regions combined. The probability of surviving up to five years was similar for women diagnosed at a localised or regional stage, while women diagnosed at a distant stage had much lower survival.

The large improvement in survival in Makkah, in contrast to the lack of improvement in other regions, cannot be explained by discrepancies in follow-up between regions, or a deficit in follow-up in Makkah Region during the later calendar period (2011-2016). A decline in the proportion of women with missing ID numbers was seen in all regions, but women living in Makkah Region had the highest proportion of missing ID numbers in 2005-2010 and the lowest during 2011-2016 (Table 15). Also, the proportion of women who had died in Makkah, as determined by registry follow-up (Table 12), was similar to that in other regions, which makes it unlikely that the registry was failing to capture deaths in Makkah during 2011-2016. Finally, the increase in survival in Makkah, and lack thereof in all other regions, was not much altered when the analysis was restricted to women with more complete (NIC) follow-up (Table 20). Among women with a known stage at diagnosis, the proportion diagnosed at a localised stage was the highest in Makkah in both periods, and there was very little change in the stage distribution, whereas the increase in localised stage was much larger for Riyadh and the Eastern region (Figure 14). Thus, the increase in survival in Makkah Region cannot be attributed to improvements in early detection. There have been no changes to treatment guidelines during 2005-2016, and such changes would be expected to apply to all regions. The oncology centre at King Abdulaziz hospital in Jeddah was moved in 2010 to the newly founded King Abdullah Medical City, with treatment centres in Jeddah and Makkah. This led to the availability of more advanced treatment and an increased treatment volume. The oncology centre at the King Abdullah Medical City became the first specialised cancer centre in the Western Region functioning under the Ministry of Health (MOH), and in 2015, became the first of three centres of integrated oncology and palliative care in Saudi Arabia designated by ESMO (European Society for Medical Oncology), followed by the King Faisal Specialist Hospital and

Research Center in Riyadh (2018) and the King Fahad Specialist Hospital in the Eastern Region (2019). The presence of this oncology centre at King Abdullah Medical City under the Ministry of Health (MOH) may have led to more equitable access, efficient referral and timely treatment, translating into improved survival.

A small decrease in survival was seen in Riyadh and the ten peripheral regions. The complete approach used to estimate 5-year net survival during 2011-2016 could give rise to lower survival estimates due to censoring the follow-up of women diagnosed in 2014, 2015 and 2016.[181] However, the lower survival seen in Riyadh and the ten peripheral regions was also seen for 1-year survival, for which a cohort approach was possible for all years of diagnosis. The sensitivity analysis limiting follow-up until 31 December 2012 for women diagnosed during 2005-2010, and thus making the estimates comparable to those for women diagnosed during 2011-2016, did not show any consistent difference from the cohort analysis. Higher availability of national ID numbers in the SCR records during later years has probably led to improved death ascertainment, but restricting the analysis to women with NIC follow-up did not alter the findings. Improvement in completeness and timeliness of death reporting to the department of civil status may offer a better explanation for this reduction in survival. A fine was imposed in 2015 for failure to notify deaths within 30 days, and electronic death notification was also introduced in MOH hospitals in 2016, and is now being rolled out to other hospitals. In the data with imputed stage, there was no change in the proportion of distant stage, except for Riyadh, where it increased by 4%, which may also explain the observed decrease in survival in that region.

Age-standardised five-year net survival increased slightly between 2005-2010 and 2011-2016 for localised and regional stage, but fell for women diagnosed at a distant stage, both before and after imputation of unknown stage. Together with the lack of improvement in survival for all stages combined, despite the increase in the proportion of localised stage, this pattern could be attributable to stage migration, or the so-called "Will Rogers phenomenon".[182] When staging practices improve over time, some tumours that have intermediate survival and were previously classified as localised are later classified as regional, leading to an apparent improvement in survival for both stages. This possibility is supported by the increase from 7% to 18% in the proportion of women with lymph node extension among women diagnosed at a regional stage. Stage migration was shown to occur for cervical cancer in a study that compared stage distribution before and after applying the FIGO 2018 criteria, which incorporate advanced imaging findings.

Improvements in the detection of lymph node extension was stated as the main reason for stage migration in cervical cancer, while the detection of occult metastasis accounted for a small increase of distant stage. The authors did not observe any improvement in survival for women with distant metastasis after upstaging of tumours found to have occult metastasis. This suggests that distant metastasis, even when clinically occult, has a poor prognosis.[183]

There was an increase in the ratio of localised to regional stage during the period 2011-2016. This is not consistent with stage migration, which would produce a shift in the opposite direction. It is possible, however, that for women who were diagnosed at a localised stage during 2011-2016, better documentation of stage more than compensated for the shift towards more regional stage that may have arisen from improved diagnostics, leading to a net increase in the proportion of women with localised stage. The category "unknown stage" comprises a mixture of women diagnosed at various stages. Therefore, if more women who had a localised underlying stage, and who would not previously have been assigned a stage, were appropriately assigned to their correct stage at diagnosis in 2010-2016, this would lead to an increase in the proportion of women diagnosed at localised stage and a reduction of that sub-set of women in the pool of women with unknown stage. This could also explain the decline in survival for women with unknown stage during 2011-2016.

Compared to stage-specific relative survival reported by the US National Cancer Institute for the period 2010-2016 and net survival by stage reported by CONCORD-3 for US women diagnosed during 2009-2014,[184] net survival was lower in Saudi women diagnosed at a localised stage but higher for women diagnosed at a regional and distant stage (Table 23). The proportion of women with unknown stage was higher among Saudi women than US women, and survival for women with unknown stage was higher among Saudi women than US women. This, together with the lower survival for Saudi women diagnosed at a localised stage, may point to some of the women with unknown stage having a localised underlying stage with a good prognosis. However, imputation of missing stage in the Saudi data did not lead to an increased survival estimate for women diagnosed at a localised stage.

Table 23: Stage distribution (%) and stage-specific age-standardised 5-year survival (%) in the US (SEER registries: Surveillance, Epidemiology and End Results program and CONCORD-3) and in Saudi Arabia

	US-SEER 2010-16*		US-CONCORD 2009-14§		Saudi Arabia 2011-16	
	Stage (%)	5-year relative survival (%)	Stage (%)	5-year net survival (%)	Stage (%)	5-year net survival (%)
Localised	44	91.8	43	86.9	33	73.8
Regional	36	57.6	37	56.4	36	66.5
Distant	16	16.8	14	18.7	18	25.2
Unknown	4	49.7	6	55.0	12	63.4
All stages		**66.1**		**62.4**		**59.7**

* Based on data from SEER 18, 18 population-based registries covering 27.8% of US population.
§ 41 population-based cancer registries covering 85% of the US population.

Stage-specific unstandardised 1- and 5-year net survival was similar between regions except for the Eastern Region, where 5-year net survival for distant stage was substantially (16% to 27%) lower than that in all other regions. However, this was based on 46 observations only. Five-year net survival for women living in the Eastern Region, who were diagnosed at regional stage, also was between 6.4% and 11.6% lower than in Riyadh, Makkah and the ten peripheral regions.

Restricting the analysis to the 928 women with National Information Center (NIC) follow-up did not change the results for any of the regions or for any stage at diagnosis.

When comparing the proportion of women who have died as ascertained through registry follow-up and through linkage to the NIC records, among women for whom data on both are available, it is clear that more than half of the deaths are not captured by registry follow-up. Of the women with NIC follow-up, 44.3% were dead, according to government records. However, when including all women, i.e. those with and without NIC follow-up, and complementing the follow-up data with information available from the registry for women who could not be followed up at NIC because of a missing or incorrect ID number, the proportion of women known to have died fell to 36.8%, because only 13% of women for whom registry follow-up was used were known to be dead. However, these women only contributed their follow-up time until the date of their last known vital status, which was often the date when their data were abstracted for the registry. This amounted to 272 of 4,456 years of follow-up (for 5 years survival), only 6% of the total follow-up time. Therefore, using registry follow-up in this context does not seem to bias the results.

It is not clear what proportion of follow-up can be complemented using registry follow-up without compromising validity. In total, 24% of women only had registry follow-up. But there was variation by region and stage, with 27.3% of women living in the ten peripheral regions

and 58% of women with unknown stage only having registry follow-up. The proportion of women for whom only registry follow-up was available fell from 30% during 2005-2010 to 19% during 2011-2016.

Using Global Burden of Disease (GBD) life tables gave slightly lower net survival estimates. This is because the modelled mortality rates for the general female population were lower than those produced by the United Nations Population Division (UNPD). Data sources for the GBD study were less clear and partially relied on the Ministry of Health, which only collects mortality data from its own hospitals. In their census data, the General Authority for Statistics groups the population 80 years and older in a single age group. Mortality rates up to age 99 years are therefore extrapolated, and may vary between estimations.

Data on stage at diagnosis were imputed for the 11% of women for whom they were missing. This is a relatively small proportion, and neither the stage distribution nor the stage-specific survival estimates changed from the complete-case analysis. Because between-imputation variance was taken into account, in addition to within-imputation variance, the gain in precision from the increased number of observations in each stratum of age, stage and calendar period after the imputation of missing stage was offset by the addition of the between-imputation variance.

A limitation of exploring the missing data mechanism and the process of multiple imputation in the current dataset is the lack of data on comorbidity and treatment. Comorbidity may partially explain the association between age and stage missingness but could also be an independent determinant of missing stage if a person's health status makes them unfit for clinical procedures that are used to determine stage.[185]

The strongest predictor of missing stage in this context was region of diagnosis. Thirty seven percent of women diagnosed in one of the ten peripheral regions had an unknown stage. This proportion was only 20% for the subset of women who had a second referral hospital as a source of information, but the proportion of women with missing stage only became lower for women who were referred to Riyadh or Makkah regions. This suggests that missing information on stage is strongly related to the access a woman has to more advanced medical facilities available in the three main regions.

Being diagnosed in one of the ten peripheral regions was also associated with less advanced stage. This may be caused by under-staging due to lack of advanced imaging modalities. If true, this could bias the multiple imputation results.

Mortality rates of cervical cancer

Age-standardised mortality rates for Saudi women (0.34 and 0.32 per 100,000 women per year in 2005-2010 and 2011-2016, respectively) and non-Saudi women (0.59 and 0.15 per 100,000 women per year in 2005-2010 and 2011-2016, respectively) were lower than the Global Cancer Observatory estimates for 2018 (2.1 per 100,000 women) and Global Burden of Disease estimates for the years 2005-2016 (about 1.3 per 100,000 women per year).[51,171]

I used what I believe to be the most reliable and most complete source of mortality data currently available in Saudi Arabia. The stability of the number of deaths over the two periods 2005-2010 and 2011-2016 indicates consistent collection of these data, and the lack of change in mortality rates is in line with the unchanged incidence and survival over the period 2005-2016. But given the known shortcomings of cause of death reporting in Saudi Arabia, the numbers reported may nevertheless underestimate the true mortality, especially for non-Saudi women. The ratio of the number of Saudi women to non-Saudi women who died of cervical cancer was more than double that seen for incidence. Such under-ascertainment of deaths among non-Saudis is expected, given that many of them return to their countries upon diagnosis.

Deaths available in the Saudi Cancer registry (SCR) were from women diagnosed since 1994, the first year of registration, which is 12 years earlier than the first year included in mortality estimates. Any deaths that occurred in 2005 or later among women diagnosed earlier than 1994 would not be captured. Of the 323 women who died of cervical cancer during 2005-2016, 15.5% had been diagnosed before 2005 but none had been diagnosed in 1994 or 1995, suggesting that capturing deaths among women diagnosed since 1994 is sufficient for estimating cervical cancer mortality.

Additional considerations

The utilisation of a population-based cancer registry with national coverage, and statutory cancer registration, theoretically ensures access to every single cancer patient's record and gives a picture of the true survival of women with cervical cancer in Saudi Arabia, which has previously only been reported from the limited number of studies that included

women who were treated in tertiary centres. However, low numbers of registry staff may pose a challenge to timely and complete registration. The active nature of case finding also relies on the meticulousness of tumour registrars. There is no system in place for the SCR to ensure complete ascertainment of cases.

The overall incidence of cancer in Saudi Arabia is low. Under-registration cannot be excluded, but the assessment carried out in 2013 by the International Network for Cancer Treatment and Research (INCTR) did not detect any major issues pointing towards low completeness.[129] Assuming near-complete registration, the low incidence of all cancers could be due to two causes. First, the number of cancers may be truly low. Cancers generally take decades to develop (induction period) and the incidence rates we see today are to a large degree arising in a generation that was not exposed to the same set of risk factors that exist today. Smoking prevalence is moderate in men (23.7%) and extremely low in women (1.5%), with an overall prevalence of 12%. It is even lower (6.5%) in the those over the age of 65 years.[186] Alcohol consumption is increasingly recognised as a major contributor to cancers of the breast, colorectum and upper gastrointestinal tract. Of all cancers worldwide, 3.6% were attributable to alcohol consumption and this proportion is even higher in Europe,[187] while only 0.5% of cancers in Saudi Arabia were attributable to alcohol.[188]

The second reason for low incidence may be under-diagnosis. Many cancers have a long pre-clinical phase (latent period), and when a person becomes symptomatic, their health-seeking behaviour may be affected by cultural, psychological and logistical factors, including ease of access to healthcare. Competing health issues may divert both the patient’s and the physician's attention away from seemingly trivial complaints like perimenopausal bleeding, and the person may die of other causes before being diagnosed with cancer. This is less likely to occur for solid tumours that arise in non-vital organs and are not rapidly lethal, and these patients may be expected to present to a physician in due course unless they die of another cause prior to diagnosis. For example, the age-standardised mortality rate from transport accidents in 2015 was 28 per 100,000 population, significantly higher than in most high-income countries. Since autopsies are rarely carried out in Saudi Arabia, tumours that have not come to medical attention during a person's lifetime would not be captured. The lower age-standardised incidence rates seen in peripheral regions could be due to both lower incidence and under-diagnosis.

The effect of any incompleteness in cancer registration on survival estimates would depend on the underlying reason for under-registration. The high percentage of morphologically verified tumours in the SCR may point to over-reliance of registrars on pathology reports. Since cervical cancer is a pathological diagnosis at any disease stage, it is unlikely that this preferential use of pathology reports would lead to selective detection of one stage over another and that it might therefore bias survival estimates for all stages combined. Under-staffing of regional offices has been an issue that may affect thoroughness of case-finding, because it has led to less frequent visits to remote areas and smaller clinics. Cervical specimens from smears or cone biopsies that are performed in private clinics and polyclinics are usually sent to larger laboratories or hospitals. It is thus very likely that they would be captured, even if registrars did not visit these clinics and the women were not referred to a hospital.

Completeness of registration should be evaluated by independent ascertainment of cases from a sample of sources for a defined period of diagnosis, and comparison to those cases with the registry's records. Quantification of death certificate-initiated cancers for which no information was received within the following six-month waiting period and for which trace-back was initiated, leading to a previously missed hospital record, would also give an indication of thoroughness of routine case-finding.[130]

The mortality-to-incidence ratio is a metric that has been used to assess the completeness of cancer registration by comparing the number of deaths from a given cancer in a given year or period, obtained from the vital registration system, with the number of new registrations of the same cancer in that period. However, this was not possible in Saudi Arabia, because the cause of death is often given only as "cancer", and there is a major deficiency in the documentation of specific cancers as a cause of death. For example, in the 2016 MOH mortality database, only eight deaths were attributed to cervical cancer, and a further 47 to malignant neoplasm of the uterus, part unspecified. In contrast, 29 deaths due to cancer were identified from the registry data in the same year among women diagnosed with cervical cancer at some point since 1994. In such a setting, the mortality-to-incidence ratio is likely to be an indicator of the completeness of death registration, or the accuracy of certification or coding of the underlying cause of death, rather than an indicator of the completeness of cancer registration.[189]

During 2005-2016, around 120 and 160 women were diagnosed yearly with a cancer of the cervix or the body of the uterus, respectively, while 24 tumours on average were

registered yearly as “uterus, not otherwise specified (NOS)”. Due to the anatomic proximity of the two topographies, some clinical misclassification of stage II or higher cervical cancer (extending to the body of the uterus) as uterine cancer is possible. However, squamous cell morphology was recorded in only 1% and 3%, respectively, of tumours registered as cancer of the uterine corpus (C54) or uterus NOS (C55). This indicates that the vast majority of tumours at both these sites are indeed of uterine, and not cervical origin. However, it is more difficult to assess whether adenocarcinomas of the cervix are sometimes misclassified as uterine cancer. In many cases, the origin of adenocarcinomas with unclear topography can only be determined by immunohistochemistry. Such testing is not always performed, and the registry does not collect information on it. Adenocarcinomas generally have a worse prognosis, especially if they are HPV-negative.[21] However, any misclassification of these tumours as uterine cancer is unlikely to affect survival estimates, because HPV- negative cervical cancers are rare,[20] and the morphological distribution of cervical cancer in the dataset (69.2% squamous cell carcinoma, 21.6% adenocarcinoma 9.2% other or unspecified) is in line with what is expected (adenocarcinomas make up 10-25% of cervical cancers in developed countries with established screening programmes).[190]

About a quarter of tumours registered as uterus NOS were diagnosed at a distant stage, and another quarter had an unknown stage, compared to only 13% at distant stage and 12% with an unknown stage for cancer of the uterine corpus. Only 80% of tumours registered as uterus NOS were diagnosed by histology of the primary tumour, compared to 98% for uterine corpus cancers. Most notably, 11% of uterus NOS tumours were registered based on death certificate only. These characteristics are likely to lead to ambiguity and probably contributed to assigning some of the tumours to the NOS category. Therefore, the topography code uterus NOS may include women with both cancer of the uterine corpus and cervix who have a worse prognosis.

A major advantage of net survival for population-based survival estimates is that information on the cause of death is not required, because it is often unavailable or unreliable. However, it relies on the completeness of death registration. There are no formal estimates of the completeness of death reporting to the Department of Civil Status. Since hospital death notifications are sufficient for burial, and it is the responsibility of the relatives of the deceased to report the death to the Department of Civil Status in order to issue a death certificate, some degree of under-reporting and late reporting is possible. A

common observation in statistics published from census and survey data and from burial statistics in Saudi Arabia is the lower numbers of deaths that are reported for women than men, even in Saudis, for whom the sex distribution is fairly equal. This discrepancy may be due to counting non-Saudis as Saudis, given the large excess of non-Saudi men. Additionally, deaths in women and children may go unreported because they are less likely to have assets or money in bank accounts that would require a death certificate to be distributed as inheritance. Neglecting to report deaths can also occur due to lack of knowledge, difficult access to a reporting centre, or may even be deliberate in order to continue to collect pension money. Efforts to counteract late and non-reporting of deaths have included media campaigns to increase awareness of the necessity and process of notification, introducing fines for late reporting and an electronic death reporting system in MOH hospitals. This would theoretically guarantee the immediate notification of all deaths if they occur in hospital, or if the deceased is taken to hospital. Fifty-four percent of deaths in the 2016 MOH mortality database occurred out of hospital, which suggests that such deaths are regularly captured by the MOH.

Twenty women were reported as alive from the NIC records but dead in the registry records, despite matching names in the two databases. Eleven of these women were diagnosed at a distant stage, one of whom was 90 years old at the closing date, having a survival time of 14 years since diagnosis. Two women were diagnosed at localised stage and were aged 96 and 98 years at the closing date, with a survival time of 8 and 13 years, respectively. It is possible that some or all of these women have died and that their deaths were not notified to the Department of Civil Status. Another possible explanation is that non-Saudi women who were uninsured have used other women's IDs in order to receive medical care. Not all women in Saudi Arabia hold a photo ID, and a family card with the name and national ID number is sufficient for hospital use. In order to keep the method consistent, the vital status from linkage to the NIC was used when available, provided that the name and sex matched between the SCR and NIC records.

Survival time was censored for 34% of women. Censoring in the context of this study involves two mechanisms: the first is that the ID number is missing from the patient’s record, leading to censoring at the date of last contact. According to registry staff, a missing ID number is more common among women treated in private hospitals, which do not require patients to present identification. In this case, ID numbers would be missing at random, leading to non-informative censoring. Women admitted as an emergency may

also not be requested to show identification. In this scenario they would be expected to present with more advanced disease, but in fact, there was a higher proportion of localised stage among women with missing ID numbers (37%) than women with available ID numbers (29%), which supports the suggestion that many of them had early disease that could be treated in private hospitals. Some ID numbers were invalid due to recording errors, which occur randomly. Attempts to trace back missing IDs were unsuccessful, due to the workload of registry staff. Like stage, missing ID number is strongly associated with being diagnosed in regions other than Riyadh, Makkah and the Eastern Region, which may indicate that a missing ID number is related to poorer documentation practices in patient records in peripheral regions, and is not due to patient or disease characteristics that are relevant to survival. The second reason for censoring is that the woman was alive at the date of record linkage, and with less than five years of follow-up. This was the case for women diagnosed in 2014, 2015 and -2016, and is a form of non-informative censoring.

I used life tables for Saudi Arabia that have been published by the UNPD because high-quality death rates were not available. These life tables are for all nationalities, and they may therefore inaccurately reflect the background mortality of the women included in the survival analyses, which include only Saudi citizens. They are also not region-specific. Although every attempt was made to acquire death counts by sex, age, region and nationality from the government vital registration records, this was not possible due to the lack of a process for researchers or individuals to request data from the Ministry of Interior or Department of Civil Affairs. The SCR was also unsuccessful at requesting these data. Despite this shortcoming, the relative survival setting has been shown to be more robust to violations in the assumptions of life tables than the cause-specific setting is to misclassification in the cause of death.[191]

Region of diagnosis may be a more important determinant of survival than region of residence. However, exploring survival by region of diagnosis was not feasible because fewer women were diagnosed in one of the ten peripheral regions, especially in the older age strata. While 319 (27%) women lived in one of these regions, only 131 women (11%) were diagnosed there. Moreover, for over half the women who were diagnosed in the ten peripheral regions, only registry follow-up was available. This would probably have led to overestimation of their survival due to the high proportion of women for whom follow-up time is censored in registry follow-up. The region to which a woman is referred, which may also be an important determinant of survival, was only available for 60% of women.

Therefore, survival could not be compared between regions of referral. Whether centralised cancer care leads to better cancer outcomes than in decentralised care settings is an important question that has produced different results in various countries. Cancer survival by region of diagnosis and region of referral in Saudi Arabia could be usefully explored with other, more common tumours.

Estimating survival by stage at diagnosis is valuable in explaining survival differences between regions and over time. However, advances in diagnostic methods or differences in the available technology between regions could lead to some women who would have been diagnosed in earlier years or in lower-resource regions at a less advanced stage being classified later or in higher-resource regions at a more advanced stage. This may be falsely interpreted as progress in stage-specific survival (due to the stage migration phenomenon) or may mask differences in the stage distribution between regions, and consequentially, in stage-specific survival between regions. Diagnostic criteria that were used at the time of diagnosis or the diagnostic procedures a particular woman had undergone are not available from the registry records and therefore cannot be accounted for.

Survival was one of the variables used in the multiple imputation model to predict stage. A higher proportion of women living in the ten peripheral regions only had registry follow-up. If survival for these women was overestimated due to higher loss to follow-up, some of them would have been assigned to a lower stage than their true (but unknown) stage. The resulting stage distribution, and therefore, the stage-specific survival by region, may be biased. Estimating survival by region and stage using unimputed data and restricting to NIC follow-up was not possible due to small numbers.

Although it has not been possible to examine patterns of survival from cervical cancer in non-Saudi women, some understanding of their experience with the disease can be obtained by exploring other characteristics. Incidence rates are much higher in each age group than for Saudi women, which reflects the patterns of incidence in many of the countries from which these women have immigrated into Saudi Arabia. For cervical cancers of known stage, the tumours in non-Saudi women are more often diagnosed at a localised stage and less often at a regional or distant stage than for Saudi women. However, the proportion of cervical cancers with unknown stage in non-Saudi women (23%) is almost double that in Saudi women (11%). Unknown stage was imputed for Saudi women using various variables, including survival, as predictors in the multiple imputation

model. This was not possible for non-Saudi women due to lack of follow-up data. The resulting complete stage distribution for Saudi women leads us to believe that unknown stage is to a large extent missing completely at random. However, it is possible that unknown stage has a different mechanism in non-Saudis. For example, women with early-stage cancer who are fit to travel may leave the country as soon as they receive the diagnosis and before their tumour can be fully staged. But it is also generally observed that stage is more likely to be missing for those with advanced tumours and comorbidities making them unfit for staging.[160,185]

The proportion of *in situ* tumours in non-Saudi women was half of that in Saudis, indicating that they may have less access to early diagnostic tests, or less awareness of their availability and importance. Several studies from Saudi Arabia have described women's knowledge and awareness of cervical cancer, its risk factors and its prevention, but none of these studies reported results separately for non-Saudis, and some were restricted to Saudi nationals.[142,143,192-194]

A large proportion of Saudi women living in the Eastern region and the ten peripheral regions were diagnosed in Riyadh or Makkah. Non-Saudi women living in those regions appear to be less likely to travel to Riyadh or Makkah for diagnosis. This may reflect a discrepancy in mobility among non-Saudi women, due to economic factors or lack of the social and family support which would enable them to move to other regions for medical care. Movement from smaller towns or villages to larger cities within a given region is not explored here because the small number of women diagnosed with cervical cancer disables any such comparison on a more granular scale.

Non-Saudis make up about one third of the general population and of the population of women with cervical cancer, but little is understood about their experience with healthcare and with cancer care specifically. In a multi-centre study of patients who presented with acute coronary syndrome, non-Saudi patients had a significantly longer median symptom-to-door time (175 versus 130 minutes), were less likely to undergo percutaneous coronary interventions and suffered higher hospital mortality, cardiogenic shock and heart failure, after adjustment for age and sex.[195] Of 335 women with breast cancer who were treated at King Abdulaziz University Hospital in Jeddah between 2009 and 2017, Non-Saudi women had double the odds of Saudi women for undergoing mastectomy versus breast-conserving therapy after adjusting for age and several tumour characteristics (e.g. size, stage, grade and oestrogen, progesterone and HER2 receptor status).[196] Using registry

follow-up to estimate survival for non-Saudi women would not have been a feasible option because it is generally incomplete, and could be especially low for non-Saudi women. This is reflected in the low proportion of non-Saudi women who are known to be dead from registry follow-up, especially during the period 2005-2010 (Table 10). Therefore, survival for Saudi and non-Saudi women cannot be usefully compared, even if the analysis were restricted to registry follow-up for both groups. Loss to follow-up could be due to those women returning to their home country after being diagnosed. In contrast, migration among Saudis is rare, and despite some Saudis seeking treatment for cancer in other countries, citizens who die abroad will in most cases be buried in Saudi Arabia, which ensures that their death is registered. Loss to follow-up by the registry could also be caused by a woman abandoning her treatment. Various factors may put non-Saudi women at risk of treatment discontinuation, including lack of social support, limited insurance coverage or the requirement to cover part of the treatment cost in government hospitals.

I explored the possibility of deriving mortality estimates from deaths due to cancer that occurred among women who were diagnosed with cervical cancer and whose death was captured by the registry. The registry held more records of women certified as having died of cervical cancer than the cause-specific mortality database at the Ministry of Health. Even so, as for incident cases, the completeness of ascertainment of deaths from cancer by the registry cannot be ensured. Regardless of the data sources, the completeness of mortality estimates can only be as good as the quality of cause of death attribution by the reporting physician, which has been documented as quite low in Saudi Arabia, even though it is higher for cancer than other causes of death.[197,198]

Chapter 9. Summary and recommendations

Summary

Monitoring population-based cancer survival is crucial to evaluate the effectiveness of cancer care in a country or region and thus to support cancer control planning. Population-based cancer registries with national coverage provide data on all malignant neoplasms diagnosed in the country. They reflect the real-world population experience and outcomes of a cancer diagnosis, irrespective of the inclusion criteria applied in clinical studies and stringent treatment regimens.

Net survival provides a robust method which enables comparison of cancer survival between populations and over time, whilst taking due account of differences in the risks of death from competing causes (background mortality), which increase in older age. Estimating net survival was made possible by linking cancer registry records to information on each woman's vital status in the Ministry of Interior records, which ensures virtually complete ascertainment of all-cause mortality. Although linkage could not be achieved for one-quarter of women included in the survival analysis, more than double the number of deaths were captured through this method compared to registry follow-up alone. This halved the proportion of women with censored survival time compared to CONCORD-2.

I examined cervical cancer incidence rates and net survival probabilities by stage for women diagnosed with cervical cancer in Saudi Arabia between 2005 and 2016. I also explored regional differences in cervical cancer incidence and survival, and examined stage-specific survival by region of residence.

Age-standardised incidence rates (ASIRs) for cervical cancer in Saudi Arabia are generally very low on a global scale, but are higher in non-Saudi women and women living in the three most populous regions of Saudi Arabia: Makkah, Riyadh and the Eastern Region. No change in incidence was observed over the twelve years 2005-2016. There was a shift towards a higher proportion of women being diagnosed at a localised stage during the calendar period 2011-2016 compared to 2005-2010 in the three most populous regions, but not in the other ten peripheral regions.

Age-standardised 5-year net survival probabilities are similar to those in other countries in Western Asia for which survival estimates are available. No change was seen in age-standardised 1- and 5-year net survival between 2005-2010 and 2011-2016, except in

Makkah Region, where 5-year net survival increased by 19%, from the lowest among regions in 2005-2010 to the highest in 2011-2016. There was a small increase in age-standardised 5-year net survival among women diagnosed at a localised or regional stage, and a decrease in survival for women diagnosed at a distant stage and among women with an unknown stage. This pattern may indicate more accurate staging practices in recent years, leading to stage migration. Stage-specific survival estimates during the 12-year period 2005-2016 were similar in all regions except for the Eastern Region, where survival for distant stage was substantially lower.

Restricting the survival analysis to women with available ID numbers, which enabled their records to be linked to the National Information Centre database to ascertain their vital status, did not change the survival patterns by stage at diagnosis or by geographic region; neither did using alternative life tables obtained from the Global Burden of Disease study.

Recommendations

Public health recommendations

The availability of HPV vaccines in Saudi Arabia has been limited, despite their licensing since 2013. Further, a large cohort of unvaccinated women is entering the age group at risk for cervical cancer. Raising awareness of early signs and symptoms of cervical cancer could increase the proportion of tumours detected at an earlier stage, allowing for surgical management, which is more widely accessible than chemoradiation. Increasing the uptake of cervical screening through high-quality organised screening programmes with national coverage would help reduce the incidence of invasive cervical cancer. It could also further increase the proportion of women who are diagnosed at a localised stage by detection of pre-symptomatic cancer. This would ultimately reduce morbidity and mortality from the disease, and help to achieve higher survival levels as seen in many other high-income countries.

Implementing a systematic screening programme entails inviting women who are eligible according to the Ministry of Health (MOH) guidelines. Home HPV testing may offer a culturally sensitive, accessible and feasible screening option given the low HPV prevalence in Saudi Arabia and the wide geographic spread of cities.[199] This would, however, require a system for swab transport and collection, and recall of women with positive tests. Any planned screening programme should be preceded by a pilot programme and accompanied by a system for monitoring and evaluation. An informed

decision to participate should be encouraged through clear and honest communication, which addresses the misconceptions about cancer and screening. It may be useful to identify higher-risk groups of women who would benefit from more frequent screening, for example migrant workers coming from high-incidence countries.

The limited availability of HPV vaccines, primarily in private and high-resource government settings, raises concerns about equity. Uptake of Pap smears is higher among those women in Saudi Arabia with higher income and education,[144] which may further compound inequities in cervical cancer incidence and outcomes. National guidelines for preventive and early diagnostic programmes should be developed, and led by the MOH, along with mechanisms to ensure equitable access and allocation of resources.

Research recommendations

It is difficult to predict the future burden of cervical cancer in Saudi Arabia from existing data. Studies are needed to shed light on current patterns of sexual behaviour, and on the uptake of HPV vaccines and Pap smears. HPV prevalence studies should be representative of the general population, and not limited to a specific region or centre.

Studies carried out to understand women's knowledge about cervical cancer symptoms, and their attitudes towards early diagnostic testing, have so far been limited to single hospitals, universities or regions. Representative cross-sectional studies to compare levels of awareness between regions would probably help elucidate the persistence of delayed diagnosis in the peripheral regions. Further, exploring barriers to both early diagnosis and effective treatment is essential. Efforts are already under way to encourage women to undergo cervical screening, but ensuring timely referral and adequate treatment for women who screen positive is the ultimate goal of early diagnosis.

The population-based cancer registry provides a unique opportunity for exploring patterns of patient movement between regions, cities and hospitals, as well as differences between Saudis and non-Saudis in referral for diagnosis and treatment. Using larger datasets for more common cancers, such as breast or colorectal cancer, would be more appropriate for this purpose.

Data quality recommendations

ID numbers were missing for many women, and of those for whom they were available, a substantial proportion had incomplete or incorrect ID numbers, or numbers that belonged

to men. The Saudi Cancer Registry (SCR) is working to build its own programme for tumour registration. Incorporating ID verification in the programme would be the most effective way to ensure correct recording of ID numbers during abstraction. The Saudi ID number contains a check digit (a digit added to the end of a string of numbers that is computed from the other digits in the string). This characteristic could be utilised to verify the correctness of each ID number at data entry. As a minimal requirement, the cancer registry programme should only accept complete 10-digit ID numbers. While CanReg is still being used, verifying ID numbers at the time of carrying out other regular quality checks centrally could allow for routine correction of ID numbers along with other variables. "Yakeen" is a new service launched by Elm, a company that manages the government's digital security. It allows instant verification of identity, matching ID numbers with official records, and it could therefore be used by the registry for this purpose. Data from Saudi Arabia could not be used in the third cycle of the CONCORD programme, due to the large proportion of records for which linkage to the individual's vital status, based on their ID number and date of birth, had failed. Verifying ID numbers should rely on matching names, not dates of birth, which often differ between hospital records and government records. Since four names are recorded in official records (first name, father's name, grandfather's name, and family name), and women do not take their husband's names after marriage, names are in most instances highly reliable. A downside to using names is that they need to be manually cross-checked, since names are recorded in Latin letters in CanReg but in Arabic in government records.

Obtaining follow-up for the vital status of registered cancer patients from the National Information Centre (NIC) is a lengthy process. Unfortunately, it is likely to become even more difficult, because the NIC has recently been transferred to the Presidency of State Security. The SCR has succeeded in ensuring statutory access to all cancer patients' records, and has since treated these with confidentiality and shared data responsibly. Similar legislation to allow continuous updates of the vital status of registered cancer patients, in addition to the residency status for non-Saudis, would enable timely monitoring of survival patterns. This would be especially effective when the reporting of deaths in hospital becomes automated.

In a survey of population-based cancer registries in the Eastern Mediterranean Region in 2020, led by the International Agency for Research on Cancer, the SCR did not provide information on the use of cancer registry data in various areas of cancer control. This

indicates a disconnect between registry staff, researchers and policymakers.[200] Utilising the full potential of the SCR data would produce policy-relevant research, bring clinicians' attention to the existence of the registry and encourage them to make use of the available data. This would also attract political recognition of the importance of maintaining and improving the registry, which currently suffers a perennial shortage of staff and resources. Periodic assessment and transparent reporting of quality indicators could identify areas for improvement, and it would be expected to increase confidence in the registry data.

After ensuring high completeness and quality of the data currently collected by the SCR, expanding the scope of the data to include variables such as dates of referral and start of treatment, as well as the type of treatment, could be valuable in monitoring the quality of cancer care. These variables could also be used in more detailed analyses of the patterns of care and survival. Looking beyond survival, these data could support the establishment of survivorship research, which is essential to evaluate the full scope of cancer services.

Cause-specific mortality is an important metric to assess the burden of disease and to monitor progress in public health interventions. Mortality data have so far been of very low completeness and quality in Saudi Arabia. This weakness should be addressed by expanding the coverage of mortality data collection to non-MOH hospitals, training physicians to assign the cause of death appropriately, and making these data publicly accessible.

Constructing regional life tables for Saudi Arabia from population and death counts may more accurately reflect the background mortality for each region, and therefore improve the reliability and public health utility of net survival estimates. This would require facilitating access to vital registration data. Access to data from various government sectors has been a challenge throughout this project.

In its global strategy for the elimination of cervical cancer as a public health problem, WHO has emphasised the need for high-quality population-based surveillance systems, to evaluate progress towards this goal. It highlights the role of population-based cancer registries in monitoring cervical cancer incidence and survival by stage at diagnosis, and stresses the importance of these metrics for planning cancer services and evaluating the delivery of cancer care, through comparison of survival estimates between regions and countries. Vital registration systems with accurate cause-of-death data are also essential

to monitor cervical cancer mortality trends, which enable the evaluation of screening programmes.[9]

The current elimination goal is to reduce cervical cancer incidence to below 4 per 100,000 women per year in all countries, through defined targets for HPV vaccination, screening and treatment of precancerous lesions. But in countries such as Saudi Arabia, where incidence is already below the WHO target, the strategy may need to be redefined according to their context. Given the high priority the elimination of cervical cancer has been accorded on the global health agenda, it is crucial for Saudi Arabia to join the effort to further reduce the burden of cervical cancer and eliminate inequalities along the cervical cancer continuum.

References

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**(10159): 1789-858.
2. GBD Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**(10159): 1736-88.
3. Arbyn M, Weiderpass E, Bruni L, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob Health* 2020; **8**(2): e191-e203.
4. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *The Lancet* 2018; **391**(10125): 1023-75.
5. Vaccarella S, Bruni L, Seoud M. Burden of human papillomavirus infections and related diseases in the extended middle east and North Africa Region. *Vaccine* 2013; **31**(S6): G32-G44.
6. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999; **189**(1): 12-9.
7. World Health Organization. Comprehensive Cervical Cancer Control, A guide to essential practice. Second ed: World Health Organization; 2014.
8. Dr Tedros Adhanom Ghebreyesus, WHO Director-General. Cervical cancer: an NCD we can overcome. Geneva: World Health Organization; 2018.
9. World Health Organization. Global strategy to accelerate the elimination of cervical cancer as a public health problem. Geneva; 2020.
10. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet* 2015; **385**(9972): 977-1010.
11. Ministry of Health. Statistical year book, Kingdom of Saudi Arabia. Riyadh; 2016.
12. Al-Ahmadi K, Al-Zahrani A, Al-Ahmadi S. Spatial Accessibility to Cancer Care Facilities in Saudi Arabia. Esri Health GIS Conference. Cambridge, MA, USA; 2014.
13. Chen T, Jansen L, Gondos A, et al. Survival of cervical cancer patients in Germany in the early 21st century: a period analysis by age, histology, and stage. *Acta Oncol* 2012; **51**(7): 915-21.
14. Ellis L, Woods LM, Estève J, Eloranta S, Coleman MP, Rachet B. Cancer incidence, survival and mortality: explaining the concepts. *Int J Cancer* 2014; **135**(8): 1774-82.
15. Cho H, Mariotto AB, Schwartz LM, Luo J, Woloshin S. When do changes in cancer survival mean progress? The insight from population incidence and mortality. *J Natl Cancer Inst Monogr* 2014; (49): 187-97.

16. Ghittoni R, Accardi R, Chiocca S, Tommasino M. Role of human papillomaviruses in carcinogenesis. *ecancer medical science* 2015; **9**: 526.

17. Muñoz N, Bosch FX, de Sanjose S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003; **348**(6): 518-27.

18. Muñoz N. Human papillomavirus and cancer: the epidemiological evidence. *J Clin Virol* 2000; **19**(1): 1-5.

19. Bosch FX, Manos MM, Munoz N, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. *J Natl Cancer Inst* 1995; **87**(11): 796-802.

20. Tjalma W. HPV negative cervical cancers and primary HPV screening. *Facts, views & vision in ObGyn* 2018; **10**(2): 107-13.

21. Nicolás I, Marimon L, Barnadas E, et al. HPV-negative tumors of the uterine cervix. *Mod Pathol* 2019; **32**(8): 1189-96.

22. Rodriguez AC, Burk R, Herrero R, et al. The natural history of human papillomavirus infection and cervical intraepithelial neoplasia among young women in the Guanacaste cohort shortly after initiation of sexual life. *Sex Transm Dis* 2007; **34**(7): 494-502.

23. de Sanjose S, Diaz M, Castellsague X, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. *Lancet Infect Dis* 2007; **7**(7): 453-9.

24. Holly EA. Cervical intraepithelial neoplasia, cervical cancer, and HPV. *Annu Rev Public Health* 1996; **17**: 69-84.

25. IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. Human Papillomaviruses. Lyon, France: International Agency for Research on Cancer; 2007.

26. Nayar R, Wilbur DC. The Pap test and Bethesda 2014. *Cancer Cytopathol* 2015; **123**(5): 271-81.

27. Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol* 1993; **12**(2): 186-92.

28. Agorastos T, Dinas K, Lloveras B, et al. Human papillomavirus testing for primary screening in women at low risk of developing cervical cancer. The Greek experience. *Gynecol Oncol* 2005; **96**(3): 714-20.

29. Sagr E, Kushi AA, Salem H, et al. Clinical practice guideline on the screening and treatment of precancerous lesions for cervical cancer prevention. Riyadh: Ministry of Health, The Saudi Center for Evidence Based Health Care; 2014.

30. Myriokefalitaki E, Potdar N, Barnfield L, Davies Q, Moss EL. Cervical cancer still presents symptomatically 20 years after the introduction of a structured national screening programme. *Cytopathology* 2016; **27**(4): 229-36.

31. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. *International Journal of Gynecology & Obstetrics* 2018; **143**(S2): 22-36.

32. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet* 2009; **105**(2): 103-4.

33. Cibula D, Potter R, Planchamp F, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer. *Virchows Arch* 2018; **472**(6): 919-36.

34. Vink MA, Bogaards JA, van Kemenade FJ, de Melker HE, Meijer CJ, Berkhof J. Clinical progression of high-grade cervical intraepithelial neoplasia: estimating the time to preclinical cervical cancer from doubly censored national registry data. *Am J Epidemiol* 2013; **178**(7): 1161-9.

35. Andrae B, Andersson TM, Lambert PC, et al. Screening and cervical cancer cure: population based cohort study. *BMJ* 2012; **344**: e900.

36. Gatta G, Lasota MB, Verdecchia A. Survival of European women with gynaecological tumours, during the period 1978-1989. EUROCARE Working Group. *Eur J Cancer* 1998; **34**(14): 2218-25.

37. Laara E, Day NE, Hakama M. Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes. *Lancet* 1987; **1**(8544): 1247-9.

38. Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007; **356**(19): 1915-27.

39. Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009; **374**(9686): 301-14.

40. Huh WK, Joura EA, Giuliano AR, et al. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial. *Lancet* 2017; (1474-547X (Electronic)).

41. Drolet M, Bénard É, Pérez N, Brisson M. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *Lancet* 2019; **394**(10197): 497-509.

42. Lehtinen M, Lagheden C, Luostarinen T, et al. Ten-year follow-up of human papillomavirus vaccine efficacy against the most stringent cervical neoplasia end-point-registry-based follow-up of three cohorts from randomized trials. *BMJ Open* 2017; **7**(8): e015867.

43. Kjaer SK, Nygård M, Dillner J, et al. A 12-Year Follow-up on the Long-Term Effectiveness of the Quadrivalent Human Papillomavirus Vaccine in 4 Nordic Countries. *Clin Infect Dis* 2018; **66**(3): 339-45.

44. Lei J, Ploner A, Elfström KM, et al. HPV Vaccination and the Risk of Invasive Cervical Cancer. *N Engl J Med* 2020; **383**(14): 1340-8.

45. Van de Velde N, Boily MC, Drolet M, et al. Population-level impact of the bivalent, quadrivalent, and nonavalent human papillomavirus vaccines: a model-based analysis. *J Natl Cancer Inst* 2012; **104**(22): 1712-23.

46. World Health Organization. Human papilloma virus vaccines: WHO position paper. 2017; **19**(92): 241-68.

47. Gustafsson L, Ponten J, Bergstrom R, Adami HO. International incidence rates of invasive cervical cancer before cytological screening. *Int J Cancer* 1997; **71**(2): 159-65.

48. Bray F, Loos AH, McCarron P, et al. Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. *Cancer Epidemiol Biomarkers Prev* 2005; **14**(3): 677-86.

49. Levi F, Lucchini F, Negri E, Boyle P, La Vecchia C. Cancer mortality in Europe, 1990-1994, and an overview of trends from 1955 to 1994. *Eur J Cancer* 1999; **35**(10): 1477-516.

50. Institute of Health Metrics and Evaluation. Global Health Data Exchange. http://ghdx.healthdata.org/gbd-results-tool (accessed 29/9/2020).

51. Global Burden of Disease Cancer Collaboration. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2016: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol* 2018; **4**(11): 1553-68.

52. Vos T, Abajobir AA, Abbafati C, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *The Lancet* 2017; **390**(10100): 1211-59.

53. Fidler MM, Soerjomataram I, Bray F. A global view on cancer incidence and national levels of the human development index. *Int J Cancer* 2016; **139**(11): 2436-46.

54. Soerjomataram I, Lortet-Tieulent J, Parkin DM, et al. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. *Lancet* 2012; **380**(9856): 1840-50.

55. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**(2): 87-108.

56. Qualters JR, Lee NC, Smith RA, Aubert RE. Breast and cervical cancer surveillance, United States, 1973-1987. *Morbidity and Mortality Weekly Report* 1992; **41**(SS-2): 1-15.

57. Mokdad AH, Dwyer-Lindgren L, Fitzmaurice C, et al. Trends and patterns of disparities in cancer mortality among US Counties, 1980-2014. *JAMA* 2017; **317**(4): 388-406.

58. Jemal A, Ward EM, Johnson CJ, et al. Annual Report to the Nation on the Status of Cancer, 1975-2014, Featuring Survival. *J Natl Cancer Inst* 2017; **109**(9).

59. Walters S, Quaresma M, Coleman MP, Gordon E, Forman D, Rachet B. Geographical variation in cancer survival in England, 1991-2006: An analysis by cancer network. *J Epidemiol Community Health* 2011; **65**(11): 1044-52.

60. Australian Association of Cancer Registries. Cancer in Australia: an overview , 2006. Cancer Series No 37 Catalog No CAN 32. Canberra: Australian Institute of Health and Welfare; 2007. p. 88-9.

61. Mengersen KL, Baade PD. Identification of area-level influences on regions of high cancer incidence in Queensland, Australia: A classification tree approach. *BMC Cancer* 2011; **11**(311).

62. Jong KE, Smith DP, Yu XQ, O'Connell DL, Goldstein D, Armstrong BK. Remoteness of residence and survival from cancer in New South Wales. *Med J Aust* 2004; **180**(12): 618-22.

63. Brewer N, Pearce N, Jeffreys M, White P, Ellison-Loschmann L. Demographic differences in stage at diagnosis and cervical cancer survival in New Zealand, 1994-2005. *J Womens Health* 2009; **18**(7): 955-63.

64. Brewer N, Pearce N, Day P, Borman B. Travel time and distance to health care only partially account for the ethnic inequalities in cervical cancer stage at diagnosis and mortality in New Zealand. *Aust N Z J Public Health* 2012; **36**(4): 335-42.

65. Schouten LJ, Meijer H, Huveneers JAM, Kiemeney LALM. Urban-rural differences in cancer incidence in the Netherlands, 1989-1991. *Int J Epidemiol* 1996; **25**(4): 729-36.

66. Sharp L, Donnelly D, Hegarty A, et al. Risk of Several Cancers is Higher in Urban Areas after Adjusting for Socioeconomic Status. Results from a Two-Country Population-Based Study of 18 Common Cancers. *Journal of Urban Health-Bulletin of the New York Academy of Medicine* 2014; **91**(3): 510-25.

67. Minelli L, Stracci E, Cassetti T, et al. Urban-rural differences in gynaecological cancer occurrence in a central region of Italy: 1978-1982 and 1998-2002. *Eur J Gynaecol Oncol* 2007; **28**(6): 468-72.

68. Levêque A, Humblet PC, Lagasse R. Atlas of 'avoidable mortality' in Belgium 1985-1989. *Arch Public Health* 1999; **57**(1-2): 1-87.

69. Treurniet HF, Looman CWN, Van Der Maas PJ, Mackenbach JP. Variations in 'avoidable' mortality: A reflection of variations in incidence? *Int J Epidemiol* 1999; **28**(2): 225-32.

70. Herrmann C, Ess S, Thurlimann B, Probst-Hensch N, Vounatsou P. 40 years of progress in female cancer death risk: A Bayesian spatio-temporal mapping analysis in Switzerland. *BMC Cancer* 2015; **15**(666).

71. Bermedo-Carrasco S, Waldner CL. The role of socio-demographic factors in premature cervical cancer mortality in Colombia. *BMC Public Health* 2016; **16**(981): 1-13.

72. Moss JL, Liu BM, Feuer EJ. Urban/rural differences in breast and cervical cancer incidence: the mediating roles of socioeconomic status and provider density. *Womens Health Issues* 2017; **27**(6): 683-91.

73. Singh GK. Rural-urban trends and patterns in cervical cancer mortality, incidence, stage, and survival in the United States, 1950-2008. *J Community Health* 2012; **37**(1): 217-23.

74. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; **69**(1): 7-34.

75. Zhan FB, Lin Y. Racial/Ethnic, Socioeconomic, and Geographic Disparities ofCervical Cancer Advanced-Stage Diagnosis in Texas. *Womens Health Issues* 2014; **24**(5): 519-27.

76. Powell TC, Dilley SE, Bae S, Straughn JM, Kim KH, Leath CA. The Impact of Racial, Geographic, and Socioeconomic Risk Factors on the Development of Advanced-Stage Cervical Cancer. *J Low Genit Tract Dis* 2018; **22**(4): 269-73.

77. Barrington DA, Dilley SE, Landers EE, et al. Distance from a Comprehensive Cancer Center: A proxy for poor cervical cancer outcomes? *Gynecol Oncol* 2016; **143**(3): 617-21.

78. Eggleston KS, Coker AL, Williams M, Tortolero-Luna G, Martin JB, Tortolero SR. Cervical cancer survival by socioeconomic status, race/ethnicity, and place of residence in Texas, 1995-2001. *J Womens Health* 2006; **15**(8): 941-51.

79. Lin Y, Schootman M, Zhan FB. Racial/ethnic, area socioeconomic, and geographic disparities of cervical cancer survival in Texas. *Applied Geography* 2015; **56**: 21-8.

80. Al-Muammar T, Al-Ahdal MN, Hassan A, Kessie G, Dela Cruz DM, Mohamed GE. Human papilloma virus-16/18 cervical infection among women attending a family medical clinic in Riyadh. *Ann Saudi Med* 2007; **27**(1): 1-5.

81. AlObaid A, Al-Badawi IA, Al-Kadri H, et al. Human papillomavirus prevalence and type distribution among women attending routine gynecological examinations in Saudi Arabia. *BMC Infect Dis* 2014; **14**: 643.

82. Al-Ahdal MN, Al-Arnous WK, Bohol MF, et al. Human papillomaviruses in cervical specimens of women residing in Riyadh, Saudi Arabia: a hospital-based study. *J Infect Dev Ctries* 2014; **8**(3): 320-5.

83. Gazzaz FB. Molecular testing of human papillomavirus in cervical specimens. *Saudi Med J* 2007; **28**(12): 1810-8.

84. Bondagji NS, Gazzaz FS, Sait K, Abdullah L. Prevalence of high-risk human papillomavirus infections in healthy Saudi women attending gynecologic clinics in the western region of Saudi Arabia. *Ann Saudi Med* 2013; **33**(1): 13-7.

85. Mousa M, Al-Amri SS, Degnah AA, et al. Prevalence of human papillomavirus in Jeddah, Saudi Arabia. *Ann Saudi Med* 2019; **39**(6): 403-9.

86. Turki R, Sait K, Anfinan N, Sohrab SS, Abuzenadah AM. Prevalence of human papillomavirus in women from Saudi Arabia. *Asian Pac J Cancer Prev* 2013; **14**(5): 3177-81.

87. Alhamlan FS, Khayat HH, Ramisetty-Mikler S, et al. Sociodemographic characteristics and sexual behavior as risk factors for human papillomavirus infection in Saudi Arabia. *Int J Infect Dis* 2016; **46**: 94-9.

88. AlBabtain FA, Hussain AN, Alsoghayer SA, Alwahbi OA, Almohaisen N, Alkhenizan AH. The yield of pap smears and its characteristics in a community based setting in Saudi Arabia. *Saudi Med J* 2020; **41**(6): 661-5.

89. Ali MAM, Bedair RN, Abd El Atti RM. Cervical high-risk human papillomavirus infection among women residing in the Gulf Cooperation Council countries: Prevalence, type-specific distribution, and correlation with cervical cytology. *Cancer Cytopathol* 2019; **127**(9): 567-77.

90. Al-Badawi IA, Al-Suwaine A, Al-Aker M, et al. Detection and genotyping of human papilloma virus in cervical cancer specimens from Saudi patients. *Int J Gynecol Cancer* 2011; **21**(5): 907-10.

91. Alsbeih G, Raef A, Al-Harbi N, Venturina LA, Tulbah A, Balaraj K. Prevalence and genotypes' distribution of human papillomavirus in invasive cervical cancer in Saudi Arabia. *Gynecol Oncol* 2011; **121**(3): 522-6.

92. Alsbeih G, Al-Harbi N, El-Sebaie M, Al-Badawi I. HPV prevalence and genetic predisposition to cervical cancer in Saudi Arabia. *Infect Agent Cancer* 2013; **8**(1): 15.

93. Abdullah LS. Pattern of abnormal Pap smears in developing countries: a report from a large referral hospital in Saudi Arabia using the revised 2001 Bethesda System. *Ann Saudi Med* 2007; **27**(4): 268-72.

94. Al-Jaroudi D, Hussain TZ. Prevalence of abnormal cervical cytology among subfertile Saudi women. *Ann Saudi Med* 2010; **30**(5): 397-400.

95. Al-Kadri HM, Kamal M, Bamuhair SS, Omair AA, Bamefleh HS. Prevalence and characteristics of abnormal Papanicolaou smear in Central Saudi Arabia. *Saudi Med J* 2015; **36**(1): 117-22.

96. Altaf FJ, Mufti ST. Pattern of cervical smear abnormalities using the revised Bethesda system in a tertiary care hospital in Western Saudi Arabia. *Saudi Med J* 2012; **33**(6): 634-9.

97. Altaf FJ. Pattern of cervical smear cytology in the western region of Saudi Arabia. *Ann Saudi Med* 2001; **21**(1-2): 94-6.

98. Balaha MH, Al Moghannum MS, Al Ghowinem N, Al Omran S. Cytological pattern of cervical Papanicolaou smear in eastern region of Saudi Arabia. *J Cytol* 2011; **28**(4): 173-7.

99. El Dosoky M, Ismail N, Dagastani M. Preinvasive cervical carcinoma in Saudi Arabia. *Lancet* 1995; **345**(8950): 650.

100. El-Mahalli AA. Incidence and risk factors of abnormal cervical cytology in a university hospital - Saudi Arabia. *Saudi Journal for Health Sciences* 2015; **4**(1): 104-10.

101. Elhakeem HA, Al-Ghamdi AS, Al-Maghrabi JA. Cytopathological pattern of cervical Pap smear according to the Bethesda system in Southwestern Saudi Arabia. *Saudi Med J* 2005; **26**(4): 588-92.

102. Haroon S, Cui M. Role of pap smear in early diagnosis of cervical cancer- a case study of women in Saudi Arabia. *Life Science Journal* 2012; **9**(2): 1027-36.

103. Jabbar FAA, Al-Meshari AA, Wong SS, Ramia S, Abdul-Hafeez M. Prevalence of carcinoma in situ and squamous dysplasia of the uterine cervix in Riyadh, Saudi Arabia. *Ann Saudi Med* 1988; **8**(1): 5-13.

104. Jamal A, Al-Maghrabi JA. Profile of Pap smear cytology in the Western region of Saudi Arabia. *Saudi Med J* 2003; **24**(11): 1225-9.

105. Mufti ST, Altaf FJ. Changing pattern of epithelial cell abnormalities using revised bethesda system. *Iranian Journal of Basic Medical Sciences* 2014; **17**(10): 779-84.

106. Nasser H, AlAyyaf M, Atallah A, et al. Eleven-year review of data on Pap smears in Saudi Arabia: We need more focus on glandular abnormalities! *Ann Saudi Med* 2017; **37**(4): 265-71.

107. Dajani YF, Maayta UM, Abu-Ghosh YR. Cervical intraepithelial neoplasia in Jordan: A ten year retrospective cytoepidemiologic study. *Ann Saudi Med* 1995; **15**(4): 354-7.

108. Sengul D, Altinay S, Oksuz H, Demirturk H, Korkmazer E. Population-based cervical screening outcomes in turkey over a period of approximately nine and a half years with emphasis on results for women aged 30-34. *Asian Pac J Cancer Prev* 2014; **15**(5): 2069-74.

109. Zaabi MA, Muqbali SA, Sayadi TA, et al. Age specific cytological abnormalities in women screened for cervical cancer in the Emirate of Abu Dhabi. *Asian Pac J Cancer Prev* 2015; **16**(15): 6375-9.

110. National Cancer Registry. Cancer Incidence Report Saudi Arabia 2001. Riyadh: Ministry of Health, 2005.

111. Saudi Cancer Registry. Cancer Incidence Report Saudi Arabia 2016. Riyadh, 2019.

112. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **0**(0): 3-31.

113. Saudi Cancer Registry. Cancer Incidence Report Saudi Arabia 2002. Riyadh, 2007.

114. Manji MF, Pradhan D, El-Senoussi M, et al. Carcinoma of cervix, the King Faisal Specialist Hospital & Research Center experience--the need for screening for cervical cancer in developing countries. *Eur J Gynaecol Oncol* 1999; **20**(5-6): 412-5.

115. Al Asiri M, Tunio M, Al Hadab A, et al. Five-year outcome of concurrent radiotherapy and chemotherapy in Saudi women with locally advanced cervical cancer: Single-institution experience. *Ann Saudi Med* 2013; **33**(4): 327-33.

116. El Sayed ME, Bahadur YA, Hassouna AH, et al. Outcome of cervix uteri cancer patients: Clinical treatment results and toxicity profile in a retrospective study from Saudi Arabia. *Asia Pac J Clin Oncol* 2017; **13**(5): e364-e72.

117. Anfinan N, Sait K. Indicators of survival and prognostic factors in women treated for cervical cancer at a tertiary care center in Saudi Arabia. *Ann Saudi Med* 2020; **40**(1): 25-35.

118. General Authority for Statistics. The general population and housing census, 2010.

119. General Authority for Statistics. The general population and housing census, 1974.

120. General Authority for Statistics. Population estimates, 2019.

121. The World Bank. Total Fertility rate, Saudi Arabia. https://data.worldbank.org/indicator/SP.DYN.TFRT.IN?contextual=default&locations=SA&name_desc=false (accessed 25/04/2019).

122. Ministry of Health. Statistical year book. 2019.

123. Almalki M, Fitzgerald G, Clark M. Health care system in Saudi Arabia: an overview. *East Mediterr Health J* 2011; **17**(10): 784-93.

124. Council of Cooperative Health Insurance. Cooperative health insurance document. Riyadh 2017. p. 11-3.

125. Ministry of Health. Introductory guid to the national transformation programme in the health sector. Riyadh, Saudi Arabia: Ministry of Health; 2018.

126. Royal Court. Royal affirmation of the Saudi Health Council. resolution nr. 3/67. Riyadh: Royal Court; 2016.

127. Saudi Cancer Registry. Cancer Incidence Report Saudi Arabia 2014. Riyadh, 2017.

128. American Joint Committee on Cancer. AJCC 7th Ed Cancer Staging Manual. Seventh ed. Chicago, IL: Springer.

129. Dimitrova N, Znaor A. International Network for Cancer Treatment and Research: Report On The Saudi Cancer Registry, 2013.

130. Parkin DM, Bray F. Evaluation of data quality in the cancer registry: principles and methods Part II. Completeness. *Eur J Cancer* 2009; **45**(5): 756-64.

131. Bray F, Parkin DM. Evaluation of data quality in the cancer registry: principles and methods. Part I: comparability, validity and timeliness. *Eur J Cancer* 2009; **45**(5): 747-55.

132. Al-Zahrani A, Ali B, Al-Hamdan N, Mohamed G. Completeness and validity of cancer registration in a major public referral hospital in Saudi Arabia. *Ann Saudi Med* 2003; **23**(1-2): 0256-4947.

133. Al-Eid HS, Garcia AD. Cancer Incidence Report Saudi Arabia 2009. 2012.

134. Gulf Center for Cancer Control and Prevention, Gulf Health Council. The Gulf Cooperation Council cancer control plan 2016-2025.

135. Al-Othman SH, A.; Alhomoud, S.; Alkhenizan, A.; Khoja, T.; Al-Zahrani, A. Tackling cancer control in the Gulf Cooperation Council Countries. *The Lancet Oncology* 2015; **16**(5): e246-e57.

136. World Health Organization. WHO report on the global tobacco epidemic., 2019.

137. Ministry of Health. Use of Screening Strategies for Detection of Breast Cancer. Kingdom of Saudi Arabia: The Saudi Center for EBHC Clinical Practice Guideline, 2014.

138. Alsanea N, Almadi MA, Abduljabbar AS, et al. National Guidelines for Colorectal Cancer Screening in Saudi Arabia with strength of recommendations and quality of evidence. *Ann Saudi Med* 2015; **35**(3): 189-95.

139. AlAzmi AA, Jastaniah W, Alhamdan HS, et al. Addressing cancer treatment shortages in Saudi Arabia: results of a national survey and expert panel recommendations. *JCO global oncology* 2020; **6**: 476-85.

140. Alshammary SA, Punalvasal Duraisamy B, Salem L, Altamimi A. Integration of palliative care into primary health care: Model of Care experience. *Cureus* 2020; **12**(6): e8866.

141. Aldohaian AI, Alshammari SA, Arafah DM. Using the health belief model to assess beliefs and behaviors regarding cervical cancer screening among Saudi women: a cross-sectional observational study. *BMC Womens Health* 2019; **19**(1): 6.

142. Sait KH. Attitudes, knowledge, and practices in relation to cervical cancer and its screening among women in Saudi Arabia. *Saudi Med J* 2009; **30**(9): 1208-12.

143. Sait KH. Knowledge, attitudes, and practices regarding cervical cancer screening among physicians in the Western Region of Saudi Arabia. *Saudi Med J* 2011; **32**(11): 1155-60.

144. So VHT, Channon AA, Ali MM, et al. Uptake of breast and cervical cancer screening in four Gulf Cooperation Council countries. *Eur J Cancer Prev* 2018.

145. Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. *The Lancet* 2019; **393**(10167): 169-82.

146. Ministry of Health. Health Information Survey, 2014.

147. General Authority for Statistics. Demography Survey 2016.

148. Brenner H, Gefeller O, Hakulinen T. Period analysis for 'up-to-date' cancer survival data: theory, empirical evaluation, computational realisation and applications. *Eur J Cancer* 2004; **40**(3): 326-35.

149. Brenner H, Rachet B. Hybrid analysis for up-to-date long-term survival rates in cancer registries with delayed recording of incident cases. *Eur J Cancer* 2004; **40**(16): 2494-501.

150. Pohar-Perme M, Stare J, Estève J. On estimation in relative survival. *Biometrics* 2012; **68**(1): 113-20.

151. Doll R, Payne P, Waterhouse J. Cancer Incidence in Five Continents: Springer-Verlag Berlin Heidelberg; 1966.

152. Segi M. Cancer mortality for selected sites in 24 countries (1950–57). Sendai, Japan: Department of Public Health, Tohoku University School of Medicine.; 1960.

153. Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. *Eur J Cancer* 2004; **40**(15): 2307-16.

154. CONCORD-3 protocol - Annex 3. https://csg.lshtm.ac.uk/wp-content/uploads/2016/05/filesend.pdf (accessed 4 Februray 2016).

155. GBD Mortality Collaborators. Global, regional, and national age-sex-specific mortality and life expectancy, 1950-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**(10159): 1684-735.

156. Elandt-Johnson RC, Johnson NL, Statistiker M. Survival models and data analysis: Wiley Online Library; 1980.

157. CONCORD-3 protocol - Annex 1.

158. Clerc-Urmès I, Grzebyk M, Hédelin G. Net Survival Estimation with Stns. *The Stata Journal* 2014; **14**(1): 87-102.

159. Carpenter JR. Multiple imputation and its application. 1 ed. Chichester, West Sussex: John Wiley & Sons; 2013.

160. Nur U, Shack LG, Rachet B, Carpenter JR, Coleman MP. Modelling relative survival in the presence of incomplete data: a tutorial. *Int J Epidemiol* 2010; **39**(1): 118-28.

161. Falcaro M, Carpenter JR. Correcting bias due to missing stage data in the non-parametric estimation of stage-specific net survival for colorectal cancer using multiple imputation. *Cancer Epidemiol* 2017; **48**: 16-21.

162. Rubin DB. Multiple Imputation for Nonresponse in Surveys: John Wiley & sons; 1987.

163. Cancer Research UK. Cervical cancer incidence statistics. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/cervical-cancer/incidence#heading-Three (accessed 8/7/2020.

164. National Cancer Institute. Cancer Stat Facts: Cervical Cancer. https://seer.cancer.gov/statfacts/html/cervix.html (accessed 8/7/2020.

165. Alkhalawi E, Al-Madouj A, Al-Zahrani A. Cervical Cancer Incidence and Trends among Nationals of the Gulf Cooperation Council States, 1998-2012. 2019; (2078-2101 (Print)).

166. Sharkas G, Arqoub K, Khader Y, et al. Trends in the Incidence of Cervical Cancer in Jordan, 2000-2013. *J Oncol* 2017; **2017**.

167. Akers AY, Newmann SJ, Smith JS. Factors Underlying Disparities in Cervical Cancer Incidence, Screening, and Treatment in the United States. *Curr Probl Cancer* 2007; **31**(3): 157-81.

168. Singh GK, Miller BA, Hankey BF, Edwards BK. Persistent area socioeconomic disparities in U.S. incidence of cervical cancer, mortality, stage, and survival, 1975-2000. *Cancer* 2004; **101**(5): 1051-7.

169. General Authority for Statistics. Education and training survey 2017.

170. Cancer Incidence in Five Continents, Vol. XI (electronic version)2017. https://ci5.iarc.fr (accessed.

171. Global Cancer Observatory. 2018. http://gco.iarc.fr/ (accessed 8/7/2020).

172. Raheel H, Mahmood MA, BinSaeed A. Sexual practices of young educated men: implications for further research and health education in Kingdom of Saudi Arabia (KSA). *Journal of Public Health* 2012; **35**(1): 21-6.

173. Kabbash IA, Al-Mazroa MA, Memish ZA. Evaluation of syndromic management of sexually transmitted infections in Saudi Arabia. 2011; **4**(2): 73-9.

174. Horanieh N, Macdowall W, Wellings K. Abstinence versus harm reduction approaches to sexual health education: views of key stakeholders in Saudi Arabia. *Sex Education* 2019; **20**(4): 425-40.

175. Babay ZA, Addar MH, Shahid K, Meriki N. Age at menarche and the reproductive performance of Saudi women. *Ann Saudi Med* 2004; **24**(5): 354-6.

176. Rashad H, Osman M. Nuptiality in Arab countries: changes and implications. In: Hopkins NS, ed. The New Arab Family. Cairo: American University in Cairo Press; 2003: 20-50.

177. DeJong J, Jawad R, Mortagy I, Shepard B. The sexual and reproductive health of young people in the Arab countries and Iran. *Reprod Health Matters* 2005; **13**(25): 49-59.

178. Bosch FX, Burchell AN, Schiffman M, et al. Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia. (Special Issue: Prevention of cervical cancer: progress and challenges on HPV vaccination and screening.). *Vaccine* 2008; **26**(Supplement 10): K1-K16.

179. Prah P, Copas AJ, Mercer CH, Nardone A, Johnson AM. Patterns of sexual mixing with respect to social, health and sexual characteristics among heterosexual couples in England: analyses of probability sample survey data. *Epidemiol Infect* 2015; **143**(7): 1500-10.

180. Beer HH, S.; Brophy, S.; Rahman, M. A.; Waller, J.; Paranjothy, S. Does the HPV vaccination programme have implications for cervical screening programmes in the UK? *Vaccine* 2014; **32**(16): 1828-33.

181. Brenner H, Hakulinen T. Advanced Detection of Time Trends in Long-term Cancer Patient Survival: Experience from 50 Years of Cancer Registration in Finland. *Am J Epidemiol* 2002; **156**(6): 566-77.

182. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985; **312**(25): 1604-8.

183. Grigsby PW, Massad LS, Mutch DG, et al. FIGO 2018 staging criteria for cervical cancer: Impact on stage migration and survival. *Gynecol Oncol* 2020; **157**(3): 639-43.

184. Matz M, Weir HK, Alkhalawi E, Coleman MP, Allemani C, The US CONCORD Working Group. Disparities in cervical cancer survival in the United States by race and stage at diagnosis: an analysis of 138,883 women diagnosed from 2001 to 2014 (CONCORD-3). 2020.

185. Di Girolamo C, Walters S, Benitez Majano S, et al. Characteristics of patients with missing information on stage: a population-based study of patients diagnosed with colon, lung or breast cancer in England in 2013. *BMC Cancer* 2018; **18**(1): 492-.

186. Ministry of Health. Health Information Survey, 2013.

187. Boffetta P, Hashibe M, La Vecchia C, Zatonski W, Rehm J. The burden of cancer attributable to alcohol drinking. *Int J Cancer* 2006; **119**(4): 884-7.

188. Kulhánová I, Znaor A, Shield KD, et al. Proportion of cancers attributable to major lifestyle and environmental risk factors in the Eastern Mediterranean region. *Int J Cancer* 2019.

189. Ellis L, Belot A, Rachet B, Coleman MP. The Mortality-to-Incidence Ratio Is Not a Valid Proxy for Cancer Survival. *J Glob Oncol* 2019; **5**: 1-9.

190. Tavassoli FA, Devilee P, editors. Pathology and Genetics, Tumours of the Breast and Female Genital Organs. Lyon: IARC Press; 2003.

191. Schaffar R, Rachet B, Belot A, Woods LM. Estimation of net survival for cancer patients: Relative survival setting more robust to some assumption violations than cause-specific setting, a sensitivity analysis on empirical data. *Eur J Cancer* 2017; **72**: 78-83.

192. Malibari SS. Knowledge about Cervical Cancer among Women in Saudi Arabia. 2018; **70**(10): 1819-25.

193. Al-Darwish AA, Al-Naim AF, Al-Mulhim KS, Al-Otaibi NK, Morsi MS, Aleem AM. Knowledge about cervical cancer early warning signs and symptoms, risk factors and vaccination among students at a medical school in Al-Ahsa, Kingdom of Saudi Arabia. *Asian Pac J Cancer Prev* 2014; **15**(6): 2529-32.

194. Al-Shaikh GK, Almussaed EM, Fayed AA, et al. Knowledge of Saudi female university students regarding cervical cancer and acceptance of the human papilloma virus vaccine. *Saudi Med J* 2014; **35**(10): 1223-30.

195. AlFaleh HF, Al Shamiri MQ, Ullah A, et al. Disparities in health care delivery and hospital outcomes between non-Saudis and Saudi nationals presenting with acute coronary syndromes in Saudi Arabia. *PLoS One* 2015; **10**(4): e0124012.

196. Al-Gaithy ZK, Yaghmoor BE, Koumu MI, Alshehri KA, Saqah AA, Alshehri HZ. Trends of mastectomy and breast-conserving surgery and related factors in female breast cancer patients treated at King Abdulaziz University Hospital, Jeddah, Saudi Arabia, 2009-2017: A retrospective cohort study. *Annals of medicine and surgery (2012)* 2019; **41**: 47-52.

197. Binsaeed AA, Al-Saadi MM, Aljerian KA, et al. Assessment of the accuracy of death certification at two referral hospitals. *J Family Community Med* 2008; **15**(1): 43-50.

198. Ansary LA, Esmaeil SA, Adi YA. Causes of death certification of adults: an exploratory cross-sectional study at a university hospital in Riyadh, Saudi Arabia. *Ann Saudi Med* 2012; **32**(6): 615-22.

199. Perehudoff K, Vermandere H, Williams A, et al. Universal cervical cancer control through a right to health lens: refocusing national policy and programmes on underserved women. *BMC Int Health Hum Rights* 2020; **20**(1): 21.

200. Znaor A, Fouad H, Majnoni d'Intignano F, et al. Use of cancer data for cancer control in the Eastern Mediterranean Region: Results of a survey among population-based cancer registries. *Int J Cancer* 2020.

Appendix A. Registrable neoplasms in the SCR

Site	ICD-10
Mouth	C01-C02
Salivary Glands	C07-C8
Tonsil	C09
Other oropharynx	C10
Nasopharynx	C11
Hypopharynx	C12-C13
Pharynx Unspecified	C14
Oesophagus	C15
Stomach	C16
Small intestine	C17
Colon	C18
Rectum	C19-C20
Anus	C21
Liver	C22
Gall bladder	C23-24
Pancreas	C25
Nose, sinuses, etc.	C30-31
Larynx	C32
Lung	C33-C34
Other thoracic organs	C37-C38
Bone	C40-C41
Melanoma of skin	C43
Other skin	C44
Mesothelioma	C45
Kaposi sarcoma	C46
Connective, Soft tissue	C47; C49
Breast	C50
Vulva	C51
Vagina	C52

Site	ICD-10
Cervix uteri	C53
Corpus uteri	C54
Uterus unspecified	C55
Ovary	C56
Other female genital	C57
Placenta	C58
Penis	C60
Prostate	C61
Testis	C62
Other male genital	C63
Kidney	C64
Renal pelvis	C65
Ureter	C66
Bladder	C67
Other urinary organs	C68
Eye	C69
Brain, Nervous system	C70-C72
Thyroid	C73
Adrenal gland	C74
Other endocrine	C75
Hodgkin Disease	C81
Non-Hodgkin lymphoma	C82-C85; C96
Immunoproliferative dis.	C88
Multiple Myeloma	C90
Lymphoid Leukaemia	C91
Myeloid Leukaemia	C92-C94
Leukaemia unspecified	C95
Other & unspecified	other

Appendix B. Data quality control by calendar period of diagnosis

Annex table 1: The number and proportion of Saudi women diagnosed with cervical cancer between 2005 and 2016 and are ineligible for, or excluded from survival analysis, and reasons for exclusion.

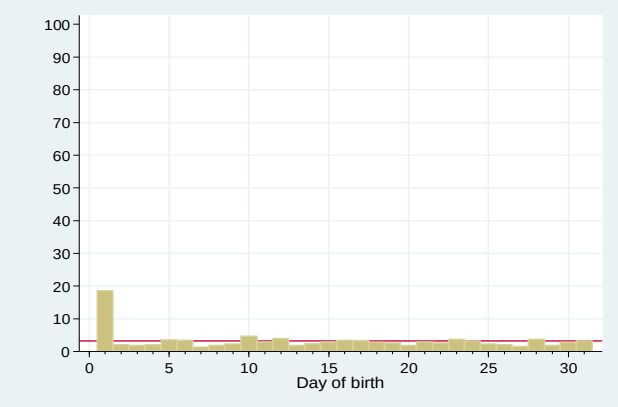
	2005-2010			2010-2016			All periods 2005-2016		
	Records	**Patients**	**%**	**Records**	**Patients**	**%**	**Records**	**Patients**	**%**
Total submitted	**669**	**669**	**100.0**	**801**	**801**	**100.0**	**1470**	**1470**	**100.0**
Incomplete date(s)	0	0	0.0	0	0	0.0	0	0	0.0
In situ neoplasm	113	113	16.9	107	107	13.4	220	220	15.0
Benign or uncertain behaviour	0	0	0.0	0	0	0.0	0	0	0.0
Metastatic from another primary site	0	0	0.0	0	0	0.0	0	0	0.0
Ineligible morphology	1	1	0.1	3	3	0.4	4	4	0.3
Ineligible topography	-	-	-	-	-	-	-	-	-
Age at diagnosis <15 or 100+ years	4	4	0.6	0	0	0.0	4	4	0.3
Not eligible		**118**	**17.7**		**110**	**13.7**		**228**	**15.5**
Patients who are eligible for survival analysis		**551**	**100.0**		**691**	**100.0**		**1242**	**100.0**
Vital status unknown	0	0	0.0	0	0	0.0	0	0	0.0
Sex unknown	0	0	0.0	0	0	0.0	0	0	0.0
Sex-site error	0	0	0.0	0	0	0.0	0	0	0.0
Site-morphology mismatch	61	2	0.4	67	6	0.9	128	8	0.6
Age-site mismatch	2	0	0.0	0	0	0.0	2	0	0.0
Age-morphology mismatch	0	0	0.0	0	0	0.0	0	0	0.0
Age-site-morphology mismatch	-	-	-	-	-	-	-	-	-
Invalid date(s) or date sequence	0	0	0.0	1	1	0.1	1	1	0.1
Death certificate only	10	10	1.8	4	4	0.6	14	14	1.1
Autopsy only	0	0	0.0	0	0	0.0	0	0	0.0
Duplicate registration	0	0	0.0	0	0	0.0	0	0	0.0
Synchronous tumours	0	0	0.0	0	0	0.0	0	0	0.0
Multiple primary same site	1	0	0.0	0	0	0.0	1	0	0.0
Total exclusions		**12**	**2.2**		**11**	**1.6**		**23**	**1.9**
Patients included in analyses		**539**	**97.8**		**680**	**98.4**		**1219**	**98.1**

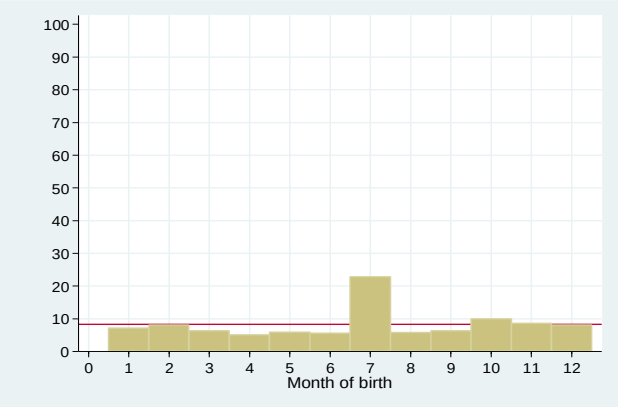
Annex table 2: The number and proportion of Saudi women diagnosed with cervical cancer between 2005 and 2016 to be included in survival analysis for which the tumour was microscopically verified, of non-specific morphology; the patient was lost to follow-up; or follow-up was censored within 5 years of diagnosis.

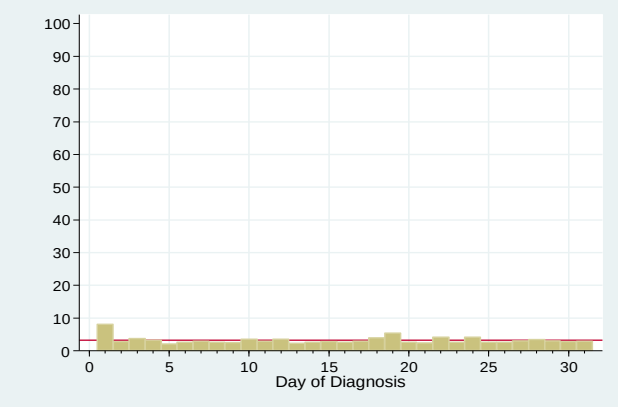
	No.	%
Patients included in analyses	1219	100
Microscopically verified	1215	99.7
Non-specific morphology	15	1.2
Censored within 5 years of diagnosis		
Diagnosed 2005-10	130	24.1
Diagnosed 2011-16*	284	41.7
Death within 30 days	24	2

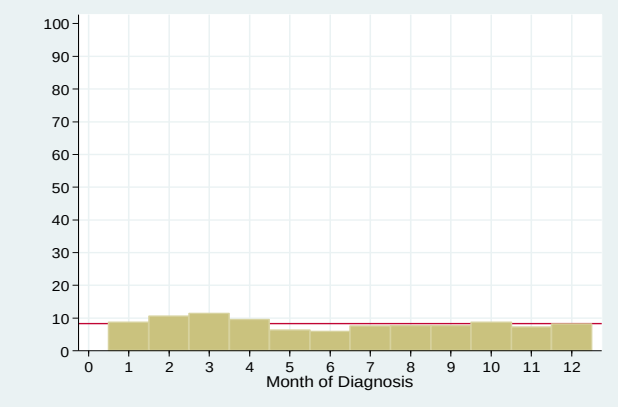
* Censored before 31 Dec 2018

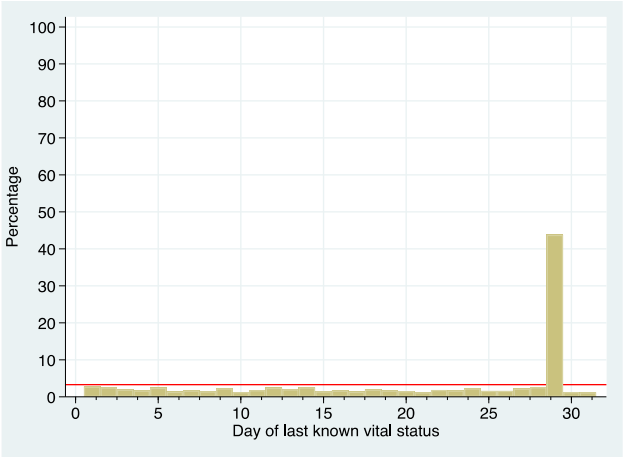
Appendix figure 1: Distribution of the day and the month of the dates of birth, diagnosis and last known vital status

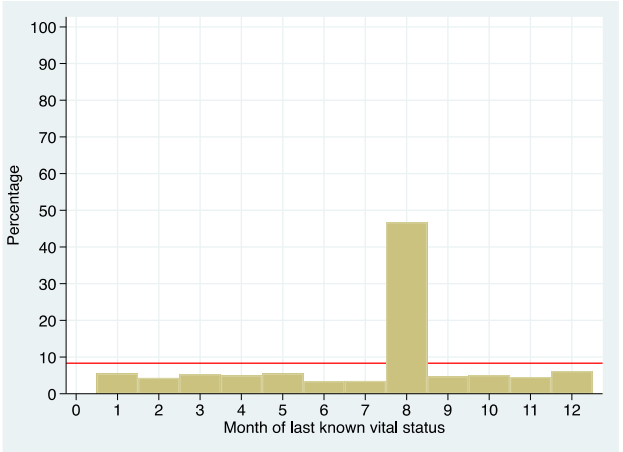












Appendix C. Articles included in literature review

Table 1: Literature review 1: Geographic differences in cervical cancer incidence, mortality or survival.

	First author	Year	Title	Region	Notes
1	Bray	2005	Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening	Europe	• Effectiveness of cervical cancer screening against the background of changing risk in 13 European countries with incidence data from 1953-2000. • Changing risk trends in Europe have been affected by screening and sexual behaviours, responsible for the decline in period risk and increase in cohort risk, respectively. • The decline in several European countries is a consequence of screening programmes, organised programmes in Nordic countries and UK having the clearest effect. • Cohort related increase in risk especially in younger generations with unmet screening-related decline.
2	Ferlay J	2013	GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet].	International	Age standardised incidence and mortality rates.
3	Gustafsson	1997	International incidence rates of invasive cervical cancer before cytological screening	International	• Data from 28 populations (CI5). • Pre-screening incidence rates up to 16-fold higher than recent post-screening rates but same age curve shape: rapid increase, peak, slower decline/plateau. • Shift towards younger age with time was seen in some countries.
4	Levi	1999	Cancer mortality in Europe, 1990-1994, and an overview of trends from 1955 to 1994	Europe	• Decline in uterine including cervical cancer mortality trend during 1955-1994, most probably due to introduction of cervical cancer screening.
5	Qualters	1992	Breast and cervical cancer surveillance, United States, 1973-1987	USA	Decline in cc incidence and mortality 1973-87. 1987 incidence was 8.2/100000 and mortality 3/100000.
6	Mokdad	2017	Trends and patterns of disparities in cancer mortality among US Counties, 1980-2014	USA	• Population attributable factor for risk factor (HPV)=1, (second is lung 0.9) • Though mortality rate has steadily gone down, cervical cancer 5-y relative survival has remained largely unchanged (about 67%)

	First author	Year	Title	Region	Notes
					• large differences in county level mortality rate (range 0.6 - 5.2/100000)
7	Vos	2017	Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016	international	• GBD from 195 countries. • Estimated 186,000 YLDs due to cervical cancer in 2016, with 9.4% increase in number despite 11.3 % decrease in ASR between 2006 and 2016.
8	Fidler	2016	A global view on cancer incidence and national levels of the human development index	international	• Cervical cancer one of 3 cancers with ASR negatively associated with HDI with a clear trend across the 4 HDI categories (along with kaposi sacrcoma and other pharynx in women). • A substantial decrease in cervical cancer was observed across HDI level, decreasing from 30.0 to 8.6 per 100,000 in low to very high HDI regions, respectively. • ASRs were very scattered within Low and Medium HDI countries (very low in Yemen).
9	Soerjomataram	2012	Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions	international	• Age adjusted DALYs due to cc was estimated at 82/100,000 in MENA, which is only slightly higher than that of north America and western Europe and very close that of Very high HDI countries. • Inversely related to HDI. • Premature death (YLL) was the overwhelming contributor to age adjusted DALYS due to cc. it contributed to more premature deaths than breast cancer in 23 countries.
10	Torre	2015	Global cancer statistics, 2012	international	Incidence and mortality in world regions and more and less developed countries.
11	Allemani	2015	Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2)	international	Wide differences in cervical cancer survival.

	First author	Year	Title	Region	Notes
12	Allemani	2018	Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries	international	• Wide differences in cervical cancer survival. • Slight improvement in survival over the past 20 years.
13	Laara	1987	Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes	Europe (Nordic countries)	Direct association between screening coverage and mortality reduction witnessed in the 20th century.
14	Senno	2015	Spatial Distribution and Sociodemographic Composition of High-Grade Cervical Lesion Clusters in Connecticut 2008-2013	USA (Connecticut)	• The incidence of HGCL has significantly declined from 2009-2013 in the 20-29 age group (14.6% in 20-24 and 2.8% in 25-29) but not in the older age group reflecting effect of vaccination.
15	Jong	2004	Remoteness of residence and survival from cancer in New South Wales	Australia (New South Wales)	• Survival analysis • Diagnosed 1992-1996. • Relative excess risk of death over 5 years for the most geographically remote category (vs highly accessible category) was highest for cervical cancer (crude RER 3.22 (95% CI, 1.54–6.75) adjusted 2.25 (95% CI, 1.06–4.77), probably reflecting contribution of screening and treatability of early detected tumours.
16	Mengersen	2011	Identification of area-level influences on regions of high cancer incidence in Queensland, Australia: A classification tree approach	Australia (Queensland)	• 1998-2007, n = 186,075. • Area-level factors mostly associated with cancer incidence. • Cervical cancer had higher incidence in remote areas (only cancer besides male lung) and most disadvantaged areas. • Interaction with areas with high indigenous population.
17	Lynge	1984	Regional differences in smear-taking activity and cervical cancer incidence in Denmark 1943-1982	Denmark	• Previous geographic differences in cc incidence between Copenhagen and Western Jutland have disappeared. This is attributable to smear taking activity.

	First author	Year	Title	Region	Notes
18	Melan	2017	Epidemiology and survival of cervical cancer in the French West-Indies: Data from the Martinique cancer registry (2002–2011)	The Caribbean	• Population based cancer registry. 2002-11, n=1253 (947 in situ, 306 ICC). • ASIR, mortality, and survival • 5-year OS=55%, median survival 6.5 y. HR of death for stage 3 and 4 vs 1 and 2 was 4 , • survival was related mostly to stage (HR=3.53), then SES and location (north vs centre-south) (HR 1.5)
19	Levêque	1999	Atlas of 'avoidable mortality' in Belgium 1985-1989	Belgium	• 1985-89 • Among 20 causes of avoidable deaths, no statistically significant heterogeneity in SMR for cervical cancer (and body of uterus) between 43 districts.
20	Treurniet	1999	Variations in 'avoidable' mortality: A reflection of variations in incidence?	Netherlands	• 1984-1994. • Significant regional mortality variations were found for cervical cancer (RR=0.82-1.32). • Of 16 causes of avoidable death, cervical cancer was the only disease where regional variation in avoidable mortality was fully explained by variation in incidence (regional differences in mortality disappeared after adjusting for incidence).
21	Zhan	2014	Racial/Ethnic, Socioeconomic, and Geographic Disparities of Cervical Cancer Advanced-Stage Diagnosis in Texas	USA (Texas)	• 1995-2008 • Found geographic clustering of advanced cervical cancer. • Could be explained by age, race/ethnicity, SES, and the percentage of African Americans in a census tract. • Differences in spatial access did not explain racial/ethnic and contextual-level SES disparities of cervical cancer advanced stage diagnosis in this study.
22	Seamon	2011	Cervical cancer survival for patients referred to a tertiary care center in Kentucky	USA (Kentucky)	• 2001-2010. • Prognostic factors influencing cervical cancer survival in patients referred to the University of Kentucky (complete or partial treatment or coordination of therapy).

	First author	Year	Title	Region	Notes
					• Race, residence (Appalachian region), insurance status, months between last normal cervical cytology and diagnosis, histology, tumour grade, and location of primary radiation treatment (Appalachian/non-Appalachian) showed no association with survival. • Stage, comorbid risk factors and unemployment was correlated with overall survival. • Conclusions: Residence and location of treatment centre are not an important factor in cervical cancer survival when a tertiary cancer centre can oversee and coordinate care.
23	Aponte-Gonzalez	2012	The impact of under-recording on cervical cancer-related mortality rates in Colombia: an equity analysis involving comparison by provenance	Columbia	Cervical cancer mortality was found to be higher in urban areas, but underreporting was inversely correlated with mortality.
24	Vatanasapt	1995	Cancer Incidence in Thailand, 1988-1991	Thailand	Cervical cancer most common cancer in females with little regional variation
25	Brewer	2009	Demographic differences in stage at diagnosis and cervical cancer survival in New Zealand, 1994-2005	New Zealand.	• 1994-2005,1594 cases • NZ has an organized population wide screening program. • little evidence of geographic (urban vs rural) differences in stage at diagnosis (OR 1.02, 95% CI 0.671.53) and HR of death from cervical cancer over 5 years (Cox proportional hazard)(1.03, 95% CI 0.70–1.50) • Adjustment for age, year of diagnosis, stage ethnicity and SES did not change outcome.
27	Lin	2015	Racial/ethnic, area socioeconomic, and geographic disparities of cervical cancer survival in Texas	USA, Texas	• 1995-2005, 11,212 women with cervical cancer • Cervical cancer specific overall 5-year survival using passive follow up. • Individual level factors: race/ethnicity, age at diagnosis, year of diagnosis, grade, stage and treatment. • Contextual (census tract level variables): demographics, health insurance expenditure, behavioural factors, urbanisation, spatial access to PCP and gynaecologists.

	First author	Year	Title	Region	Notes
					• Race/ethnicity, SES and geography associated with survival. • OS was slightly lower (54% vs 58%) in the higher vs lower spatial access to quartile. • Geographic clusters HR only decreased slightly after adjusting for all the covariates.
28	Walters	2011	Geographical variation in cancer survival in England, 1991-2006: An analysis by cancer network	UK, England	• Compares selected cancers relative survival (1991-2006) across UK cancer networks. • Geographic inequalities in survival (north worse than south), but some reduction in survival inequality between networks over time periods. • Age adjusted 1-year survival (adjusted for age, sex, region and deprivation using life tables) improved by up to 10 percentage points for all cancers analysed over the period 1991-2006, with the exception of cervical cancer. This may be explained stage migration: over 85% screening coverage achieved since 1998, leading to dramatic decline in incidence. Most tumours happen in women who haven't been screened or are particularly aggressive.
29	Brewer	2012	Travel time and distance to health care only partially account for the ethnic inequalities in cervical cancer stage at diagnosis and mortality in New Zealand	New Zealand	• Diagnosed 1994-2005, follow up until end of 2005? • Travel time and distance to nearest GP were only weakly associated stage at diagnosis HR 1.67 (0.95-2.94) and 1.37 (0.78-2.40) for the highest quartile, respectively; and cc mortality 1.32 (0.79-2.19) and not associated with cervical cancer screening.
30	Barrington	2016	Distance from a Comprehensive Cancer Center: A proxy for poor cervical cancer outcomes?	USA (Alabama)	• Retrospective cohort of patients treated at a single centre. • Those living >100 miles away had lower median OS (66 vs 99 months), worse OS by Cox PH. (HR=1.68, 95% CI 1.11–2.54).(not clear whether it was adjusted for age, BMI, race, smoking status and histology and stage)

	First author	Year	Title	Region	Notes
					• Received less radiotherapy and more "other" may be due to delays in treatment due to transportation problems.
31	Eggleston	2006	Cervical Cancer Survival by Socioeconomic Status, Race/Ethnicity, and Place of Residence in Texas, 1995-2001	USA (Texas)	• 7232 cc cases, Texas cancer registry, 1995-2001. • Cox PH model by stage. • Zip-code level rural residence was not associated with cervical cancer specific survival in any stage. • Stage adjusted zip-code level SES was associated with survival (adjusted HR=2 in lowest vs highest quintile)
32	Minelli	2007	Urban-rural differences in gynaecological cancer occurrence in a central region of Italy: 1978-1982 and 1998-2002	Italy.	Incidence of cervical cancer was higher in urban regions in the period 1978-82 then similar afterwards, author explains this by more wide spread screening later. Mortality was higher (non-significant) in rural.
33	Moss	2017	Urban/Rural Differences in Breast and Cervical Cancer Incidence: The Mediating Roles of Socioeconomic Status and Provider Density	USA	• 2009-13 • Data source: SEER data (SES), 2010 census (ethnicity), 2010 Area Health Resource File (PCP concentration), Small Area Estimates for Cancer Risk Factors & Screening Behaviours (screening), USDA (9 point urbanicity score for each county). • Method: Ecological mediation analyses. • As urbanicity increased, age standardised cervical cancer incidence rates decreased. • SES and PCP density were significant mediators, changing the main effect by 82 and 32% respectively. • Percentage whites and pap screening levels did not contribute to the relationship (pap history was a mediator in the preliminary but not complex mediation analysis). After controlling for all 4 variables, the relationship between urbanicity and cervical cancer incidence was weaker but remained significant.
34	Australian Institute of Health and Welfare & Australasian	2007	Cancer in Australia: an overview , 2006	Australia	• 2001-2003.

	First author	Year	Title	Region	Notes
	Association of Cancer Registries.				• Preventable cancers such as cervical cancer have higher incidence in rural and remote areas: by 20%, 35%, and 26%, in outer regional, remote and very remote areas respectively.
35	Schouten	1996	Urban-rural differences in cancer incidence in the Netherlands, 1989-1991	Netherlands	• 1989-1991. • Excess in cervical cancer incidence in urban areas (RR=1.69 CI 1.47, 1.94) with linear trend. Potential reasons: tobacco, sexual patterns, migration to urban centres.
36	Sharp	2014	Risk of Several Cancers is Higher in Urban Areas after Adjusting for Socioeconomic Status. Results from a Two-Country Population-Based Study of 18 Common Cancers	Ireland	• 1995-2007 • RR for cervical cancer incidence 1.48 (1.35–1.62) for urban vs rural after adjusting for SES. • Organised cervical screening has been in place since the 1980s. • There is no difference in screening uptake between urban and rural areas in the UK and it is mostly done by a GP. • Urban–rural variations could also arise as a result of people with cancer moving to urban areas to seek management in specialised centres, smoking (20% higher in urban) and HPV patterns.
37	Singh	2012	Rural-urban trends and patterns in cervical cancer mortality, incidence, stage, and survival in the United States, 1950-2008	USA	• Disparities between metropolitan and non-metropolitan areas in cervical cancer. • Mortality rates 1950 - 2007. • Incidence, stage and survival for 2000-2008. • Sharp overall decline in incidence and mortality. • Non-metropolitan had higher mortality in small urban (15%) and rural areas (20%) vs metropolitan. Non-metropolitan had a higher likelihood of advanced stage at dx (non-significant) • Blacks had double the mortality. • Higher incidence in small urban (6%) and rural (15%) areas. • 5-y survival: 51% non-metropolitan black, 60% for metropolitan black, and 71% for white metropolitan.

	First author	Year	Title	Region	Notes
					• Worse mortality and survival persisted after controlling for stage.
38	Benard	2007	Cervical cancer incidence in the United States by area of residence, 1998-2001	USA	• 1998-2001. 39,946 cases (SEER). • Rural had higher rates than suburban or metropolitan across ethnic, SE groups and within localized stage, despite age and race interaction. No area difference was seen in those over 45. • Increase among younger women. • Peak at 40-44 years. • No differences in stage at diagnosis were seen between urban and rural areas (but were seen for race)
39	Hopenhayn	2008	Variability of cervical cancer rates across 5 Appalachian States, 1998-2003	USA	• 1998-2003 • Among Appalachian states, rural counties were at higher risk of cervical cancer.
40	Blake	2017	Making the case for investment in rural cancer control: An analysis of rural cancer incidence, mortality, and funding trends	USA	• SEER • 14% and 13% higher incidence and mortality in rural vs metropolitan counties, respectively. • No consensus on definition of rurality within USA.
41	Chen	2016	Cancer Statistics in China, 2015	China	• Data source: national cancer registry of china (combined data from 72 registries). Covers 6.5% of population. • Data from 2009-11 was used for incidence and mortality estimation for 2015. A subset of longer standing registries was used for trends (2000-11). • Strong increase in incidence (annual percentage change (APC) 15.6 for 2000-2007) and slower increase in mortality (APC 5.9). • Incidence higher in urban areas. Estimated for 2015: 53200 vs 45700 new cases in 2015) but mortality higher in rural (urban 13600 rural 16900). No ASR • 1/5 ever had pap, vaccine not licenced.

	First author	Year	Title	Region	Notes
42	Herrmann	2015	40 years of progress in female cancer death risk: A Bayesian Spatio-temporal mapping analysis in Switzerland	Switzerland	• Mortality rate dropped drastically during 1969-2010 (up to 6 time reduction) with no appreciable regional differences with respect to urban and rural or geographic access to care. Switzerland is an affluent country with universal access despite cantons being self-governing in terms of health care and the diverse culture.
43	Bermedo-Carrasco	2016	The role of socio-demographic factors in premature cervical cancer mortality in Colombia	Colombia	• Cervical cancer deaths 2005-13 obtained from National Administrative Department of Statistics by year. • Risk factors including rural/urban residence extracted from mortality record • Age 20-49 selected (n=5093), stratified by 5 y age groups. Outcome: age group specific cervical cancer death counts. • IRR for cervical cancer mortality was higher for urban than in rural areas after accounting for the effects of age, region of residence, and type of insurance or educational level. • May be explained by those diagnosed moving to larger cities and dying there (or lower incidence, only provide mortality and no survival data).
44	Baldwin	2012	Receipt of Recommended Radiation Therapy Among Rural and Urban Cancer Patients	USA, 8 states	• Adjusted rates of radiation therapy receipt were similar for rural and urban patients overall (66.1% vs 68.2%; difference not significant), and for each stage of cervical cancer (urban/rural: 91/90% for stage I, 85/86% for stage II, 80/71% for stage IV)

Table 2: literature review 2: Cervical cancer incidence, mortality or survival, Saudi Arabia.

	Author	Year	Title	Category	Notes
1	Al-Ahmadi	2013	Spatial autocorrelation of cancer incidence in Saudi Arabia	Cervical cancer epidemiology	• Studying the clustering of cancers: cervical cancer was clustered in the eastern region. • Spatial association between various cancers: • The weakest association was between cervical and other common types of cancer. But highest for prostate.

	Author	Year	Title	Category	Notes
					• The strongest association was between cervical and lung cancer. • Other: Cancer management is offered free of charge to all Saudi patients, including those who may need further treatment abroad. It is therefore unlikely for a Saudi citizen to seek treatment outside the national healthcare system. • Although major cancer treatment centres are located in the major regions (Riyadh, Makkah, and Eastern regions), cancer detection and diagnosis is usually made at the secondary healthcare centres, which are widely spread to cover all geographic regions of the country. • While inequitable access to an advanced healthcare system for cancer patients from remote areas is expected, authors believe that this would have negative impacts on the treatment outcome rather than on cancer detection.
2	Sebai	1989	Cancer in Saudi Arabia	Cervical cancer epidemiology	• Cervical cancer was the 6th most seen cancer in females in KFSH in 1979-84 in terms of crude relative frequency (4.6% of female cancers) • Breast cancer patients presented relatively late. On average 6 months after start of symptoms. • General attitude of fatalism
3	Stirling	1979	Malignant neoplasms in Saudi Arabia	Cervical cancer epidemiology	• Cervical cancer ranked 7th overall. 4.2% (42/1000 cancer cases) • Ranked 2nd after breast in females in life threatening malignancies.
4	Taylor	1963	Cancer in Saudi Arabia	Cervical cancer epidemiology	• Very low incidence of gynaecological tumours may reflect women's resistance to examination.
5	Al Nsour	2012	Breast and cervical cancer screening among women in Jordan: Findings from the behavioural risk factor surveillance system - 2007	comparable countries, screening	• Data from the third Jordan Behavioural Risk Factor Surveillance System (2007) among a nationally representative sample of Jordanian women aged >35 years (n=1,157). • Mean age 50. • Association between cervical cancer screening and socio-demographic characteristics was assessed by logistic regression. • Income had the strongest association with screening followed by geography, age and working status. • 28% of ever-married women have ever undergone pap-smear.

	Author	Year	Title	Category	Notes
					• Highest in 35-44 year olds lowest in 65+, and higher in women with higher income (OR increased with income up to 4, strongest predictor) education, and who worked (NS). • Primary source of health was private sector (OR 1.5). • Women in the south were significantly less likely to undergo screening compared to north and middle (OR=0.43).
6	Dajani	1995	Cervical intraepithelial neoplasia in Jordan: A ten year retrospective cyto-epidemiologic study	comparable countries	• 1982-1991 • 10,659 females attending obstetrics and gynaecology clinics in Jordan. 4,048 (38%) were for routine check-up, 3519 (33%) had gynaecologic complaint(s) and 3,092 (29%) had no specific reason stated. • Incidence of CIN much lower in those presenting for routine pap and vs total (49/100,000 vs 114/100,000).
7	Al-Hamdan	2009	Incidence of cancer in Gulf Cooperation Council countries, 1998-2001	comparable countries	• Data: Gulf Centre for Cancer Registration (GCCR). 1998-2001, active and passive population based cancer registration of nationals. Health surveys (Family Health Survey): smoking and reproductive factors. • Incidence: crude and ASR (world standard population), population estimated at 1 Jan 2000 by 5-year age category. • Cancer in males more than females in Saudi Arabia and Oman , ASR highest in Qatar and Bahrain for males and females and lowest in Saudi Arabia and UAE. • Bahrain and Kuwait have the highest smoking. • Between 3% and 12% of women aged 40–44 years had their first child before the age of 15 years, compared to only around 2% of those aged 15–19 years. • Saudi has the youngest population. • Incomplete registration of the elderly? • Bahrain X7 lung cancer compared to Saudi (long smoking history and higher rates)
8	Ben Khaial	2014	Cervical cancer in north-eastern Libya: 2000-2008	comparable countries	• Data source: major oncology clinic. 74 cases cervical cancer over 9 years. • Mean age 53. • 65% presented in stage III and IV.

	Author	Year	Title	Category	Notes
					• 83% and 13% were positive for HPV-16 and 18 respectively. • Highest incidence was observed in the 45–54
9	Kapila	2006	Changing spectrum of squamous cell abnormalities observed on Papanicolaou smears in Mubarak Al-Kabeer Hospital, Kuwait, over a 13-year period	comparable countries	• Source: Mubarak Alkabeer hospital (tertiary hospital serving 25 hospitals and 17 clinics). 1992-2004. • Age and nationality retrieved for those with abnormalities diagnosed 2000-2004 for age specific analysis and was restricted to Kuwaitis. • Results: 86,434 smears over a 13-year period. • 4.3% abnormal. (96% satisfactory, ASCUS 2.2%, AGUS 0.8%, LSIL 1%, HSIL 0.2%, cc 0.1%, slightly over half of them SSC with a mean age of 48 (28-80). • Increase in ASCUS and AGUS % over the period. Reduction in LSIL and HSIL. LSIL highest in 25-34 year olds. peak age for HSIL 25-34
10	Kulhánová	2017	Profile of cancer in the Eastern Mediterranean region: The need for action	comparable countries	• GLOBOCAN 2012 data were used to estimate cancer incidence and mortality by country, cancer type, sex and age in 22 EMR countries. • Cervical cancer ranks second or third after breast in 10 of 22 countries. • 100% increase in cancer expected over the coming 2 decades. The highest in WHO regions.
11	Sengul	2014	Population-based cervical screening outcomes in turkey over a period of approximately nine and a half years with emphasis on results for women aged 30-34	comparable countries;	• frequency of cervical cytological abnormalities January 2001- April 2010 at the Early Cancer Screening, Diagnosing and Education Center Giresun Prof. Dr. A. İlhan Ozdemir State Hospital, Turkey. • Department of pathology reports and corresponding patient records. • Results: of 32,578 pap-smears, 95.7% were satisfactory. • cervical cytological abnormality was 1.83% (n=598), with ASCUS in 1.18%, LSIL in 0.39, HSIL in 0.16%, AGUS in 0.07%, squamous cell carcinoma in 0.02%, and adenocarcinoma in 0.006%. • 9.5% of abnormal findings were in women aged 30-34 (n=57) (but not highest age specific rates) which would have been missed according to old guidelines of starting at age 35. mean age ± SD of women having the abnormal cervical cytology (45.3±12.5)

	Author	Year	Title	Category	Notes
12	Sharkas	2017	Trends in the Incidence of Cervical Cancer in Jordan, 2000-2013	comparable countries	• 2000-2013, Jordan Cancer registry. • ASR= 2/100,000. Mean age 50. • Decreased after 2006 but remained constant 2008-13.
13	Zaabi	2015	Age specific cytological abnormalities in women screened for cervical cancer in the Emirate of Abu Dhabi	comparable countries	• Aim: prevalence of cervical abnormalities in the year of introduction of screening programme, using liquid based cytology, and age specific abnormalities. • Data: retrospective SKMC hospital (public referral centre where all collected samples are sent), Abu Dhabi, Jan-Dec 2013 and electronic health records. • Results: total screened=4,593, mean age =39.5. 97% satisfactory, with 225 (4.89%) abnormal smears, (ASCUS) 114 (2.48% of total), ASC-H (0.1%), LSIL (1.56%) HSIL (0.58%) cancer (0.04%), glandular (0.1%). abnormalities highest in the >61 age group. mean age for cervical cancer was 45.
14	Al-Badawi	2011	Detection and genotyping of human papilloma virus in cervical cancer specimens from Saudi patients	HPV in cervical cancer	• 1997-2007. • 100 cervical cancer and CIS specimens randomly selected from pathology department at KFSHRC, Riyadh. HPV detected with PCR. • Results: 90 cases analysed. HPV detected in 95.5%. HPV-16 (63.4%), followed by HPV18 (11.1%), HPV45 (4.5%), HPV33 (3.3%), and HPV-31, HPV52, HPV53, HPV58, HPV59, and HPV66 (2.2%)
15	Alsbeih	2013	HPV prevalence and genetic predisposition to cervical cancer in Saudi Arabia	HPV in cervical cancer	100 cervical cancer patients, 82 were HPV positive. Mean age 49. Most common genotypes were HPV16 (71%), 31 (7%), and 18, 45, 73 (4% each)
16	Alsbeih	2011	Prevalence and genotypes' distribution of human papillomavirus in invasive cervical cancer in Saudi Arabia	HPV in cervical cancer	• 100 paraffin-embedded cervical tumours at KFSHRC, Riyadh • 89% HPV+. The most common genotypes were 16 (65.2%), 31 (7.9%), 45 (6.7%), 18 (3.4%. but 10% when considering double infection). 16+18 formed 79% of infections. • Only 40% from central region. Rest referred mainly from eastern region (30%). Bimodal distribution (41-45, 46-60).

	Author	Year	Title	Category	Notes
17	Abdullah	2007	2007Pattern of abnormal Pap smears in developing countries: a report from a large referral hospital in Saudi Arabia using the revised 2001 Bethesda System	Abnormal cytology	• 5590 smears between 1995 and 2005, 77% negative, 4.6 % had cervical epithelial abnormalities, 0.37% SCC, 0.25% adenocarcinoma. • Referral centre most probably leading to higher results than even opportunistic screening. • Only Saudis. Usually as part of post-partum follow up or gynaecological complaint. • Mean age for SCC was 59, younger for lower grade lesions.
18	Al-Jaroudi	2010	Prevalence of abnormal cervical cytology among subfertile Saudi women	Abnormal cytology	• 241 sub-fertile women in tertiary centre, mean age 40 (49% participation). • 2.9% epithelial cell abnormality. ASCUS 42.8%, ACS-H 14.3% LSIL 28.5% AGS 14.3% ;
19	Al-Kadri	2015	Prevalence and characteristics of abnormal Papanicolaou smear in Central Saudi Arabia	Abnormal cytology	• Case control, department of obstetrics and gynaecology and histopathology, Riyadh, 2008-2011. • All pap-smears reviewed according to Bethesda 2001. • Abnormal cytology in 841 of 19,650 (4.3%)
20	el Dosoky	1995	Preinvasive cervical carcinoma in Saudi Arabia	Abnormal cytology	• 1,515 cervical smears taken between 1985 and 1994 at KKNGH, Jeddah. • 25-60 years, routine on request or minor complaints (% not given). • 14 ICC detected, all in late stage (age 35-80), none had previous smear. • 2 severe, 4 moderate, 8 mild dysplasia (total 1.26%).
21	Jamal	2003	Profile of Pap smear cytology in the Western region of Saudi Arabia	Abnormal cytology	• Retrospective, KAAUH, 1984-2000,. • 22,089 pap smears. • 1.7% abnormal pap. 0.28% CIN1 0.2% CIN2 0.12% CIN3 0.09% malignancy, 0.39 ASCUS. 0.16 AGUS, 1.17 SCC, 0.03% adenocarcinoma. (mean ages for each given)
22	Nasser	2017	Eleven-year review of data on Pap smears in Saudi Arabia: We need more focus on glandular abnormalities!	Abnormal cytology	• 2006-16, n= 19,759 • Riyadh Regional Laboratory at King Saud Medical City. • 1.98% abnormal pap. mean age 39 • 0.23% HSIL, 0.08% SCC, 0.02% AIS, 0.14% adenocarcinoma.

	Author	Year	Title	Category	Notes
23	Altaf	2001	Pattern of cervical smear cytology in the western region of Saudi Arabia	Abnormal cytology	• King Khalid NGH retrospective 1990-1997 pap-smears; 3,088 samples • 3.14% abnormal. • HSIL: 17 (0.55%) • Invasive squamous cell: 4 (0.13%)
24	Altaf	2012	Pattern of cervical smear abnormalities using the revised Bethesda system in a tertiary care hospital in Western Saudi Arabia	Abnormal cytology	• Jeddah, KAUH and Alkhadrah lab, all smears 2005-2009, n=7,297 • Retrospectively reviewed and reclassified (Bethesda) • Epithelial cell abnormalities: 17.3%, ASCUS: 9.3% (mean age 40), ASC-H: 0.8% (42) LSIL: 2.7% (47), HSIL: 0.9% (45), SCC: 0.06% (46) AGSUG: 3.20%, GC favouring neoplasm: 0.10%, endometrial favouring neoplasm: 0.08%. Repeat pap within short interval excluded.
25	Balaha	2011	Cytological pattern of cervical Papanicolaou smear in eastern region of Saudi Arabia	Abnormal cytology	• 2003-2012, n=1,171. Retrospective. • maternity hospital, eastern region (Alahsa) • ECA: 4.95%, ASCUS: 2.99% (45), ASC-H: 0.60%, LSIL: 0.09%, HSIL: 0.68%, SCC: 0.34%, AGCUS: 0.09%.
26	El. Mahalli	2015	Incidence and risk factors of abnormal cervical cytology in a university hospital - Saudi Arabia	Abnormal cytology	• Case-control. 2004–2013. • University hospital Al-khobar. • Cases=63 (Saudi women with positive result and contact data), controls=375. Mean age for cases was 45.97 ± 8. • Over 10 years, 1.8% (129) had abnormal results (CIS, ASCUS, AGUS, and ICC). • Higher risk in: IUD, older age, repeated pregnancies. Lower risk: condom use, previous pap.
27	Elhakeem	2005	Cytopathological pattern of cervical Pap smear according to the Bethesda system in Southwestern Saudi Arabia	Abnormal cytology	• 1994-2003, n=2,100. Retrospective • King Fahad Hospital, Albaha (the major referral hospital). • ECA: 7.90%, ASCUS: 2.8% (age peak incidence 30-39), ASC-H: 0.19 (40-49), LSIL: 1.3% (50-59), HSIL: 0.7% (40-49), SCC: 0.3% (50-59), endometrial favouring neoplasm: 0.09%.

	Author	Year	Title	Category	Notes
28	Haroon	2012	Role of pap smear in early diagnosis of cervical cancer- a case study of women in Saudi Arabia	Abnormal cytology	• 1/2009-1/2011, n=1475, prospective? • King Abdulaziz hospital and Oncology Centre, Jeddah. • ECA: 2.57%, ASCUS: 0.27%, LSIL: 1.02%, HSIL: 0.88%, SCC: 0.20% • First pap-smear for 83%, 79% of smears were done when presenting for gynaecological complaint. • Methods not clear. • All performed by the same physician.
29	Mufti	2014	Changing pattern of epithelial cell abnormalities using revised Bethesda system	Abnormal cytology	• 1/2000-10/2012, n=15,805. Retrospective. • KAUH, Jeddah. • ECA: 14.50%, ASCUS7.1%(39), ASC-H: 1.08%(43), LSIL2.2%(45), HSIL0.86%(46) SCC: 0.05%(45), AGCUS: 2.4%(46), GC favouring neoplasm: 0.09%(53), endometrial favouring neoplasm: 0.01% (56)
30	Jabbar	1988	Prevalence of carcinoma in situ and squamous dysplasia of the uterine cervix in Riyadh, Saudi Arabia	Abnormal cytology	• 1983-1986, 2,476 Saudi women. Mean age 28.Prospective. • KKUH gynaecology department. • 97.6% normal cytology. • Atypical squamous cells were detected in 2.4%. • 1.9% mild dysplasia, 0.2% moderate, 0.1% severe. No CIS or CC. • Low-income group of women had a slightly larger number of atypical squamous cells as compared to other income groups, smokers had higher risk.
31	Al-Shahrani	2017	Cancer Incidence Report Saudi Arabia 2014	Saudi cancer incidence reports	• Incidence by age and region.
32	Saudi Health Council	2002	Cancer Incidence Report Saudi Arabia 2002	Saudi cancer incidence reports	• Cervical cancer 8th for Saudi females of all ages. 4th among non-Saudi females • Morphology distribution, incidence by region, highest: Tabuk, Najran, Qassim, Eastern. • mean age 51 (youngest 20) • Stage distribution: 10.8% distant, 26.9% localised, 39.8% regional, 22.6% unknown.

	Author	Year	Title	Category	Notes
33	Saudi Health Council	2011	Cancer Incidence Report	Saudi cancer incidence reports	• Incidence by age and region.
34	Alhamlan	2016	Sociodemographic characteristics and sexual behaviour as risk factors for human papillomavirus infection in Saudi Arabia	STDs and sexual behaviour	• 400 Women attending family medicine and gynaecology departments for cervical examination at KFSHRC 2013-2015. Excluded those who did not complete the questionnaire. • HPV type distribution varied with age, and declined with age, associated with smoking, number of lifetime sexual partners. • 17% were HPV positive. 16% in those with 1 lifetime sexual partner. • 30% smokers. • Average age of first intercourse was 21.5 and median 20. • 12% had more than 1 lifetime sexual partner.
35	Saudi Health Council	2007	Cancer Incidence and Survival Report, Saudi Arabia 2007	survival	• SCR has started collecting death certificates for cancer cases in 2005 • 5-year overall survival 1994-2004 for Saudis for the 14 most common cancers: Breast, Colorectal, Non Hodgkin Lymphoma (NHL), Thyroid, Leukaemia, Liver, Lung, Hodgkin Disease, Stomach, Skin, Prostate, Urinary Bladder, Corpus Uteri, and Ovary. • Record linkage of 10 digit national number with the National Information Centre (NIC), Ministry of Interior through Al-Elm Information Security Company. Out of 15,484 case, Al-Elm company were able to match 5,141 patients whose names in Arabic correlated exactly with the 10-digit national ID number.
36	Manji	1999	Carcinoma of cervix, the King Faisal Specialist Hospital & Research Center experience--the need for screening for cervical cancer in developing countries	cervical cancer survival	• Retrospective, cervical cancer cases diagnosed April 1975-december 1993 at KFSHRC, Riyadh. • Ages 20-90 (median 50). • Of 504 patients, 410 received treatment with curative intent (radical surgery, radiation or both). • Overall 5-year survival was 55%, and 61% for those treated with curative intent. • Stage distribution: 20% I, 37% II, 29% III, 14% IV.

	Author	Year	Title	Category	Notes
					• 75% stage I ,70% stage II , 41% stage III, 11 % stage IV (4 years) Stage specific survival was similar to developed countries but 2/3 presented in advanced stage.
37	El Sayed	2017	Outcome of cervix uteri cancer patients: Clinical treatment results and toxicity profile in a retrospective study from Saudi Arabia	cervical cancer survival	• 2004-2010, N=60. • King Faisal Specialist Hospital and Research Center, Jeddah and King Abdulaziz University Hospital, Jeddah. Retrospective chart review. • 69% presented in stage IIB, 23% higher (15% III, 3% IV) and 8 % lower (5% IB, 3% IIA) • 78% received Cisplatin + radiotherapy. • Median follow-up period was 24 months (range: 6–77 months). • Mean survival time 65 months. • The 2- and 4-year overall survival (OS) was 82% and 79%. Disease free survival: 80% and 69%. Treatment and complication results and predictors of survival given.
38	Al Asiri	2013	Five-year outcome of concurrent radiotherapy and chemotherapy in Saudi women with locally advanced cervical cancer: Single-institution experience	cervical cancer survival	• 2007-2012, retrospective. King Fahad Medical City , Riyadh • 74 patients with histologically proven locally advanced cervical cancer (IIB-IVA) receiving three-dimensional conformal radiotherapy with concurrent chemotherapy followed by high dose rate brachytherapy. • Median follow-up period = 60 months (range, 8-66). • Median age of = 52.3 years (32-78). • 66% stage IIB. • The 5-year disease-free and overall survival was 75.7% and 64.5%.

Appendix D. Ethical approval

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Observational / Interventions Research Ethics Committee

Mr eman alkhalawi

LSHTM

23 January 2018

Dear Mr eman alkhalawi

Study Title: Cervical Cancer in Saudi Arabia: Regional Disparities in Incidence, Mortality and Survival

LSHTM Ethics Ref: 14739

Thank you for your application for the above research project which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant. **Approved documents**

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Protocol / Proposal	research protocol	12/01/2018	1
Investigator CV	CV-EmanAlkhalawi	12/01/2018	1
Local Approval	ethical-concord	15/01/2018	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

Professor John DH Porter

Chair

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