Factors associated with co-morbidity of HIV and cervical cancer in Swaziland

By

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2015
Declaration

“I declare that the dissertation/thesis, which I hereby submit for the degree Master in Public Health at the University of Pretoria, is my own work and has not previously been submitted by me for a degree at another university”.

Ethics Reference No.: 309/2013
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Factors associated with co-morbidity of HIV and cervical cancer in Swaziland

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Summary

**Background** Human immune-deficiency virus makes it difficult for the body to fight the incidence and reoccurrence of human papillomavirus (HPV) infection which is associated with cervical cancer. People with HIV infection thus have a higher risk for cervical cancer. The objective of the study was to determine factors associated with co-morbidity of HIV and cervical cancer in Swaziland.

**Methods** A retrospective review was conducted at Mbabane Government Hospital, the national referral hospital in Swaziland. All histologically confirmed cervical cancer records from 2010 to 2012 with HIV status documentation were considered for analysis. Univariate logistic regression was used to determine the association between HIV and age, marital status, parity, cancer staging and treatment option. Multivariate logistic regression was used to establish the predictive model.

**Findings** It was found that out of 257 cervical cancer patients, 60\% (n=155) were HIV positive. Patients that were less than 49 years of age were 5.96 times (CI: 3.4 – 10.4) more likely to be HIV positive than HIV negative patients. Patients that were never married were 3.7 times more likely to be HIV positive than married patients (CI: 1.96 – 6.83). Patients that had parity of two and less were 3.7 times more likely to be HIV positive.

**Interpretation** In summary, the results of this study imply that age, parity and marital status are the main factors associated with comorbidity of HIV and cervical cancer in Swaziland. This calls for targeted screening of women particularly single women within 33 and 47 years old found positive.

**Funding** Self funded.

Introduction

Human immune-deficiency virus (HIV) and cervical cancer are serious public health problems in the Sub-Saharan region. It is known that HIV infection makes it difficult for the body to fight the incidence and reoccurrence of human papillomavirus (HPV) infection which is associated with cervical cancer.\textsuperscript{1-3} Therefore, HIV infected individuals have a higher risk of comorbidities than their uninfected peers.\textsuperscript{4-6} The link between HIV and cervical cancer was recognized in 1993 when the Centres for Disease Control (CDC) declared cervical cancer as an AIDS defining illness.\textsuperscript{7}

Cervical cancer is responsible for the annual deaths of 275 000 women in the world\textsuperscript{8} and also accounts for 43-3\% of all cancer among women in Swaziland.\textsuperscript{9}
Incidence Rates (ASIR) for cervical cancer in the world, Southern Africa, and Swaziland are 15.3, 26.8, and 50.0 per 100,000 respectively. Moreover, for the reproductive age group, Swaziland has the highest HIV prevalence in the world (26%). In Swaziland, the prevalence of HIV is higher in women than in men and it can be seen from the above that women in Swaziland have the highest ASIR for cervical cancer in the world. There is therefore a need to further investigate and identify the factors contributing to cervical cancer in women co-infected with HIV.

The International Federation of Gynaecology and Obstetrics (FIGO) broadly classify cervical cancer into four stages (Stage I, Stage II, Stage III, and Stage IV). Stage I and stage II are regarded as the early stages of infection where the cure rate is higher, while stage III and stage IV are regarded as advanced stages of infection.

Several factors, including cancer staging, are considered before providing treatment to cervical cancer patients. Early stages of cervical cancer are managed through surgical procedures, followed by chemo-radiation then palliative care as the disease progresses. Chemo-radiation has always been the major treatment option for patients with both early and advanced stages of the disease. However, comorbidity with HIV has complicated management of cervical cancer hence the need to further investigate the association with other factors in the Swazi context.

This study aims to establish the prevalence of HIV amongst cervical cancer patients, determine the factors that are associated with the occurrence of co-morbidity of cervical cancer, and also to compare the treatment outcomes of patients with this co-morbidity at the Mbabane Government Hospital in Swaziland.

Methods

Study design
This study employed a retrospective cross-sectional study design whereby all the records for confirmed cervical cancer patients in the gynaecology department at Mbabane government hospital between 1st January 2010 and 31st December 2012 were reviewed.

Hospital setting
During the study, MGH was the only national referral hospital designated for all health conditions and diseases except for tuberculosis and psychiatric cases. Patients that had an abnormal Pap smear result during screening in any of health facilities in the country were referred to the MGH, gynaecology department for further assessment. Cervical biopsy specimens were then taken and sent to the national referral laboratory, which was also within the same hospital, to confirm cancerous cells. In the presence of cancerous cells, the patients’ diagnosis was then recorded as CaCx or cervical cancer. The treatment of cervical cancer within this hospital was only limited to surgical procedures. If there was a need for chemotherapy and radiation, patients were referred to the Republic of South Africa.

Study population and sampling
The study targeted all patients that had confirmed cervical cancer records at Mbabane Government Hospital, gynaecology department. These records comprised inpatient and outpatient registers as well as patient files.
All cervical cancer patients recorded in the hospital source documents between 1st January 2010 and 31st December 2012 were included. On the contrary, all records recorded at the gynaecology department that were not cervical cancer cases and did not have documented HIV status were excluded from the study.

The study employed temporal sampling of all cervical cancer patients that met the inclusion criteria. Over a period of thirty six months; the sample size of the study was 257 patients.

**Data Collection**
All patient records such as registers, patient files and laboratory reports that were used by the department during the review period were used for data collection. The data was captured into Microsoft Excel 2010 and the variables that were measured were limited to age at diagnosis, marital status, parity, cancer staging, treatment option and treatment outcome.

**Data analysis**
Data was analysed using STATA (version12) statistical package. Simple frequency distributions were produced for all categorical variables. All analyses were done at the 5% significant level with 95% confidence interval (CI).

Univariate Logistic Regression was employed to establish the association between HIV and five risk factors: Age, Parity, Marital_status, Cancer_staging, and Treatment_Option. Multivariate Logistic regression was used to formulate the predictive model. All these explanatory variables were coded as categorical variables for the purpose of both logistic regression methods. Chi Square Test of association was then used to analyse the relationship between HIV status and treatment outcome.

Continuous variables were summarised by means, standard deviations. Data that was not normally distributed were summarised by median and range. Categorical variables were summarised as proportions followed by the used Chi Square test to establish the association between the categorical variables.

**Ethical considerations**
Approval was obtained from the Research Ethics Committee of the University of Pretoria, Research Ethics Committee of the Ministry of Health in Swaziland and the management of Mbabane government hospital, Swaziland.

Extraction of the data was done by the principal investigator to ensure confidentiality and consistency. Moreover, there were no patient identifiers such as names used in the final report.

**Results**
Figure 1 shows a summary of how the HIV prevalence amongst cervical cancer was established.
There were 695 cervical cancer records found for the period of 2010 to 2012. After removing double counting as a result of follow up visits, these records were equivalent to 399 patients that were histologically confirmed with cervical cancer within the review period. After excluding the patients without HIV status documentation, there were 257 patients available for analysis. The HIV prevalence was found to be 60% (n=155).

Table 1 summarises the characteristics of the 257 cervical cancer patients according HIV status.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV +</th>
<th>HIV -</th>
<th>Total</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Median (IQR)</td>
<td>(n =155) 40 (33 – 47)</td>
<td>(n = 102) 57 (40 – 67)</td>
<td>(n = 257) 43(35 – 59)</td>
<td>p &lt; 0·05</td>
</tr>
<tr>
<td>Parity Median (IQR)</td>
<td>(n = 100) 3 (2 – 5)</td>
<td>(n = 66) 5 (3 – 7)</td>
<td>(n = 166) 4 (2 – 6)</td>
<td>p &lt; 0·05</td>
</tr>
<tr>
<td>Marital status</td>
<td>Never married 61%</td>
<td>Married 39%</td>
<td></td>
<td>p &lt; 0·05</td>
</tr>
<tr>
<td>Cancer Stage</td>
<td>Stage 1 31%</td>
<td>Stage 2 16%</td>
<td>Stage 3 31%</td>
<td>Stage 4 22%</td>
</tr>
<tr>
<td>Treatment Option</td>
<td>Surgery 41%</td>
<td>chemo/radio 11%</td>
<td>palliative: 20%</td>
<td>unknown 28%</td>
</tr>
<tr>
<td>Treatment outcome</td>
<td>Follow up care 61%</td>
<td>chemo/radio referral 23%</td>
<td>Palliative 8%</td>
<td>Deceased 8%</td>
</tr>
</tbody>
</table>

The median age for all the cervical cancer patients was 43 years (IQR 41 to 45). On the other
hand, the median age for the HIV-seropositive women was 40 years (IQR 33 to 47), which was significantly lower (p < 0.05) compared with the median age for the HIV-seronegative women 57 years (IQR 40 – 67). The overall median parity was four (IQR 2 - 6), 50.8% were married and 49.2% of the patients were at Stage III and stage IV (advanced stage according to FIGO cancer staging). The proportion of advanced staging was insignificantly higher amongst seropositive women (p > 0.05). Most of the patients (43%) had received the surgical treatment option, compared to other treatment options. After receiving these treatment options 62.7% of the patients received further follow-up care, whilst 11.8% were deceased.

Figure 2 compares the different age distribution of cervical cancer patients, according to HIV status.

![Figure 2: Age distribution amongst cervical cancer patients, according to HIV status](image)

The youngest cervical cancer patient was 21 years old, whilst the oldest was 91 years old. Most of the young cervical cancer patients (less than 50 years) were found to be HIV positive as opposed to the HIV negative patients (p < 0.05).

Table 2 below shows the crude ratios from the univariate analysis of data obtained.

**Table 2: Univariate Analysis of categorical risk factors**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Category</th>
<th>OR</th>
<th>Chi2</th>
<th>P-Value</th>
<th>95 percent CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Young Old</td>
<td>5.9578</td>
<td>0.0000</td>
<td>p &lt; 0.05</td>
<td>3.4164 – 10.3898</td>
</tr>
<tr>
<td>Marital status</td>
<td>Never Married</td>
<td>3.6576</td>
<td>0.0000</td>
<td>p &lt; 0.05</td>
<td>1.9597 – 6.8266</td>
</tr>
<tr>
<td>Parity</td>
<td>Low parity</td>
<td>3.7196</td>
<td>0.0007</td>
<td>p = 0.002</td>
<td>1.6517 – 8.3763</td>
</tr>
<tr>
<td>Cancer stage</td>
<td>Advanced stage</td>
<td>1.3343</td>
<td>0.2780</td>
<td>0.279</td>
<td>0.7919 – 2.248</td>
</tr>
</tbody>
</table>

Patients that were less than 49 years of age were 5.96 times (CI: 3.4 – 10.4) more likely to be HIV positive than HIV negative patients. Patients that were never married were 3.7 times more likely to be HIV positive than married patients (CI: 1.96 – 6.83). Patients that had parity of two and less were 3.7 times more likely to be HIV positive.
Table 3 shows how the risks factors influenced the HIV status on cervical cancer patients after performing the multivariate analysis.

Table 3: Adjusted Odds Ratio for influence of HIV status on cervical cancer

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>Chi2</th>
<th>P-Value</th>
<th>95 percent CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>6.6019</td>
<td>0.0000</td>
<td>p &lt; 0.05</td>
<td>2.6675 – 16.3391</td>
</tr>
<tr>
<td>Marital status</td>
<td>2.8276</td>
<td>0.0000</td>
<td>0.019</td>
<td>1.1862 – 6.7403</td>
</tr>
<tr>
<td>Parity</td>
<td>1.5115</td>
<td>0.0007</td>
<td>0.442</td>
<td>0.5274 – 4.3321</td>
</tr>
<tr>
<td>Cancer stage</td>
<td>1.0254</td>
<td>0.2780</td>
<td>0.955</td>
<td>0.4256 – 2.4704</td>
</tr>
<tr>
<td>Treatment option</td>
<td>0.9324</td>
<td>0.6156</td>
<td>0.723</td>
<td>0.6328 – 1.37384</td>
</tr>
</tbody>
</table>

After adjusting for age, marital status, cancer stage and treatment option, patients that were less 50 years were 6.6 more likely to be HIV positive than the older patients. Patients that were never married were 2.8 times more likely to be HIV positive than the married patients. The association between HIV and parity in cervical cancer patients was no longer significant after adjusting for other variables (p = 0.442).

Figure 3 below, shows the comparison of treatment outcomes for HIV positive and HIV negative cervical cancer patients.

**HIV negative treatment outcomes**

- Follow up care: 68%
- Deceased: 10%
- Palliative: 9%
- Chemo/radio referral: 13%

**HIV positive treatment outcomes**

- Follow up care: 61%
- Deceased: 8%
- Palliative: 8%
- Chemo/radio referral: 23%

Figure 3: Comparison of treatment outcomes for HIV positive and HIV negative cervical cancer patients

There were more HIV positive patients referred for chemo/radiation therapy than HIV negative patients. However, the Chi square Test shows that there is no association between treatment option and HIV status (p = 0.269).

**Discussion**

The results for the univariate analysis revealed, even though not present when adjusted for
other variables, that parity is associated with the comorbidity of HIV and cervical cancer. Patients that had parity of less than three, had an increased odds of also being HIV infected (OR = 3.719576, p = 0.002). On the contrary, other studies have shown that high parity was associated with an increased risk of cervical cancer but this pattern has been reversed as a result of HIV infection. Jensen et al, further explains that parity is associated with cervical cancer provided there is persistent HPV infection, which is true for women that are HIV infected. This highlights the need to strengthen the provision of cervical cancer prevention services amongst women of reproductive age group, especially HIV infected.

This study also found that there was an association between age and the comorbidity of HIV and cervical cancer. As a result, cervical cancer patients that were HIV infected presented at a younger age compared to the HIV negative patients, which is similar to the findings by other studies. Moreover, Zhao et al found that HPV prevalence was highest in young to middle-aged women (30-34 years). There is therefore the urgency to initiate interventions for early diagnosis of cervical cancer at an earlier age for HIV positive patients.

Marital status was significantly associated with the comorbidity of HIV and cervical cancer since unmarried patients were 3.7 times (CI: 1.96–6.83) more likely to be HIV positive. Interestingly, other studies agree that being married contributes positively in the survival of cervical cancer patients. Patel et al also found that married women with early stage disease who did not receive radiation therapy had improved survival compared with single, separated/divorced, or widowed women. This highlights the importance of recognizing them to be at high risk and targeting all cervical cancer screening services to single women.

Limitations that were considered in this study include the fact there was a significant number of patients that had missing HIV status in the records. This gap was as a result of not routinely providing HIV test within the gynaecology department. This presents a missed opportunity and increases the likelihood for late diagnosis.

The total number of 399 cases found were less than the cases predicted in the protocol was attributable to the manual system used at the gynaecology department for recording cervical cancer cases. This system increased the chances of double counting patients coming for subsequent visits and inclusion non-confirmed biopsy cases. However, to minimize this limitation, all source documents were compared to ensure that only the unique and histologically confirmed cases were considered for analysis.

It is thus recommended for HIV care and treatment services to be integrated within the gynaecology department in order to improve the cervical cancer treatment outcomes for co-infected patients. Cervical cancer services also have been integrated into HIV service points. All National Guidelines should address the cervical cancer service provision to facilitate prevention and early diagnosis. It is high time that the country adopts other prevention strategies such as the HPV vaccine for primary school girls and the ‘see and treat’ for the community level.

In summary, the results of this study imply that age, parity and marital status are the main factors associated with comorbidity of HIV and cervical cancer in Swaziland. This calls for targeted screening of women particularly single women within 33 and 47 years old found positive.
Contributors

SNM is the principal investigator. She has contributed significantly to the conception, literature search, study design, collection and assembly of data, data analyses, interpretation and preparation of the report. AB contributed to preparation of the report and approved the final version.

Acknowledgement

We thank Loveness Dzikiti for her contribution to data management and data analysis, Andy Beke (coauthor) for guidance and helpful comments.
References

Articles


Appendix A: Ethics Approval letters
Appendix B: Guidelines to Authors
THE KINGDOM OF SWAZILAND

2nd July 2013

Dear Mrs. Sebentile Myeni

RE: YOUR REQUEST FOR PERMISSION TO CONDUCT A RESEARCH STUDY ON "FACTORS ASSOCIATED WITH MORBIDITY OF HIV AND CERVICAL CANCER IN SWAZILAND."

I refer to your dated 02 July 2013 requesting to be granted permission to obtain information on the above mentioned subject in our institution. I am pleased to inform you that the Hospital Management has accepted your request provided you received an official approval by Ministry of Health Ethics Committee. I would however appreciate it, if findings and recommendations could be communicated back to the hospital.

Thank you.

Yours sincerely,

DR. P. MAHALYANA
SENIOR MEDICAL OFFICER
FROM: The Chairman
Scientific and Ethics Committee
Ministry of Health
P. O. Box 5
Mbabane

TO: Sebentile Dlamini-Myeni

DATE: 23rd January 2014

REF: MH/599C

RE: Factors Associated with Co-morbidity of HIV and Cervical Cancer in Swaziland

The committee thanks you for your submission to the Swaziland Scientific and Ethics Committee on the protocol titled: Factors Associated with Co-morbidity of HIV and Cervical Cancer in Swaziland.

The committee finds no ethical or technical issues with this undertaking thus you are granted the permission to proceed with this undertaking.

You are requested to adhere to the specific topic and inform the committee through the chairperson of any changes that might occur in the duration of the documentation process which is not in this present arrangement.

The committee requests that you ensure that you submit the report of this documentation (Electronic and hard copy) and the data set to the Secretariat of the SEC committee. The committee further requests that you add the SEC Secretariat as a point of contact if there are any questions on 24047712/24045469.

The committee wishes you the best and await for copies of the best practice report.

Yours Sincerely,

Dr S.M. Zwane
DIRECTOR OF HEALTH SERVICES
(THE CHAIRMAN)

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The Research Ethics Committee, Faculty Health Sciences, University of Pretoria, complies with ICH-GCP guidelines and has US Federal wide Assurance:


Approval Certificate
New Application

Ethics Reference No.: 309/2013

Title: Factors associated with co-morbidity of HIV and cervical cancer in Swaziland.

Dear Mrs. S Myeni

The New Application as supported by documents specified in your cover letter for your research received on the 07/07/2013, was approved by the Faculty of Health Sciences Research Ethics Committee on the 28/10/2013.

Please note the following about your ethics approval:
- Ethics Approval is valid for 1 year.
- Please remember to use your protocol number (309/2013) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:
- The ethics approval is conditional on the receipt of 6 monthly written Progress Reports, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

Dr R Sommers, MBChB, MMed(Int), MPharmMed.
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee
University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles, Structures and Processes 2004 (Department of Health).

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• For more information about our policy, please visit http://cdn.elsevier.com/assets/pdf_file/0007/1111400/patient-consent-policy.pdf.

Signatures

At the external peer review stage you will need to send signed copies of the following statements:

• Authors’ contributions

• Conflicts of interest statements

• Statements of role, if any, of medical writer or editor

• Acknowledgments—written consent of cited individual

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Types of article and manuscript requirements

Please ensure that anything you submit to The Lancet follows the guidelines provided for each article type. For instruction on how to format the text of your paper, including tables, figures, panels, and references, please see our Formatting guidelines

Red section (Articles and Clinical pictures)

Articles

- The Lancet priorities reports of original research that are likely to change clinical practice or thinking about a disease (Lancet 2000; 356: 2-4)
- We offer fast-track peer review and publication of randomised controlled trials that we judge of importance to practice or research (see Fast-track publication)
- We invite submission of all clinical trials, whether phase 1, 2, 3, or 4 (see Lancet 2006; 368: 827-28). For phase 1 trials, we especially encourage those of a novel substance for a novel indication, if there is a strong or unexpected beneficial or adverse response, or a novel mechanism of action
- We encourage researchers to enrol women and ethnic groups into clinical trials of all phases, and to plan to analyse data by sex and by race
- Systematic reviews of randomised trials about diseases that have a major effect on human health also might warrant rapid peer review and publication
- Global public-health and health-policy research are other areas of interest to The Lancet
- We require the registration of all interventional trials, whether early or late phase, in a primary register that participates in WHO’s International Clinical Trial Registry Platform (see Lancet 2007; 369: 1909-11). We also encourage full public disclosure of the minimum 20-item trial registration dataset at the time of registration and before recruitment of the first participant (see Lancet 2006; 367: 1631-35). The registry must be independent of for-profit interest
- Reports of randomised trials must conform to CONSORT 2010 guidelines, and should be submitted with their protocols
- All reports of randomised trials should include a section entitled Randomisation and masking, within the Methods section
- Cluster-randomised trials must be reported according to CONSORT extended guidelines
- Randomised trials that report harms must be described according to extended CONSORT guidelines
- Studies of diagnostic accuracy must be reported according to STARD guidelines
- Observational studies (cohort, case-control, or cross-sectional designs) must be reported according to the STROBE statement, and should be submitted with their protocols
- We encourage the registration of all observational studies on a WHO-compliant registry (see Lancet 2010; 375: 348)
- Genetic association studies must be reported according to STREGA guidelines
- Systematic reviews and meta-analyses must be reported according to PRISMA guidelines
- To find reporting guidelines see: http://www.equator-network.org

All Articles should, as relevant:

- Be up to 3000 words with 30 references (the word count is for the manuscript text only)
- Include an abstract (semistructured summary), with five paragraphs (Background, Methods, Findings, Interpretation, and Funding), not exceeding 300 words. Our electronic submission system will ask you to copy and paste this section at the “Submit Abstract” stage
- For randomised trials, the abstract should adhere to CONSORT extensions: abstracts (see Lancet 2008; 371: 281-83)
- For intervention studies, the abstract should include the primary outcome expressed as the difference between groups with a confidence interval on that difference (absolute differences are more useful than relative ones). Important secondary outcomes can be included as long as they are clearly marked as secondary
- Use the SI system of units and the recommended international non-proprietary name (INN) for drug names. Ensure that the dose, route, and frequency of administration of any drug you mention are correct
- Use gene names approved by the Human Gene Organisation. Novel gene sequences should be deposited in a public database (GenBank, EMBL, or DDBJ), and the accession number provided. Authors of microarray papers should include in their submission the information recommended by the MIAME guidelines. Authors should also submit their experimental details to one of the publicly available databases: ArrayExpress or GEO
- Include any necessary additional data as part of your EES submission
- All accepted Articles should include a link to the full study protocol published on the authors’ institutional website (see Lancet 2009; 373: 992 and Lancet 2010; 375: 348)

Putting research into context

- From Aug 1, 2010, authors are invited to submit their research papers with a section in the Discussion that puts the results into context with previous work (see Lancet 2010; 376: 10-11). Authors should provide a panel explaining in brief how they arrived at their bottom line message
- The Discussion section should contain full description and discussion of the context. Authors are also invited to either report their own, up-to-date systematic review or cite a recent systematic review of other trials, putting their trial into context of the review

Research in context

Systematic review
This section should include a description of how authors searched for all the evidence. Authors should also say how they assessed the quality of that evidence—ie, how they selected and how they combined the evidence.

Interpretation
Authors should state here what their study adds to the totality of evidence when their study is added to previous work.

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Information for Authors
Clinical Pictures
- The ideal Clinical Picture provides visual information that will be useful to other clinicians.
- Clinical Pictures should be interesting, educational, and respectful of the patient. The Lancet is less interested in pictures that simply illustrate an extreme example of a medical condition.
- Authors must obtain signed informed consent for publication (see Patient and other consents). Do not use “blackout” bars or similar devices to anonymise patients: if you have taken consent appropriately, masking is not necessary.
- Use no more than 300 words, with no references.
- Currently, clinical pictures will be accepted as exclusive online only material, and subsequently indexed as e-pages. A random selection will go into the print journal as fillers when required. Pictures that are online only as well as those that are later published in print will be given a DOI and be submitted to the National Library of Medicine for PubMed listing.

Blue section (Comment, World Report, Perspectives, Correspondence, etc)

Editorial
Editorials are the voice of The Lancet, and are written in-house by the journal’s editorial-writing team and signed “The Lancet”

Comment
Most Comments are commissioned, but spontaneous Comments are welcome on a paper or other report or event within the past month or so, or in the near future
- Comments should be about 700 words and ten references
- The place to respond to something we have published is in our Correspondence section
- See Conflict of Interest guidelines for Comments

World Report
- The Lancet has a function as an international newspaper covering news about science, medicine, policy issues, and people.
- Most of the writers of World Report articles are professional journalists, but an important event in your country that might be of wider interest can be brought to the attention of our World Report editors via editorial@lancet.com

Perspectives
- Reviews of books and other media, Lifelines, and art of medicine pieces are often commissioned, but suggestions for contributions are welcome via editorial@lancet.com

Obituaries
- Obituaries are written by our team of professional journalists, but we invite suggestions from readers for people whom we should feature—remarkable individuals who are internationally renowned for their contributions to medicine.
- Please submit such suggestions within 3 weeks of an individual’s death via editorial@lancet.com

Correspondence
- We welcome correspondence on content published in The Lancet or on other topics of interest to our readers.
- Letters for publication in the print journal must reach us within 2 weeks of publication of the original item and should be no longer than 250 words.
- Letters of general interest, unlinked to items published in the journal, can be up to 400 words long.
- Correspondence letters are not usually peer reviewed (we rarely publish original research or Case Reports in this section), but the journal might invite replies from the authors of the original publication, or pass on letters to these authors.
- Only one table or figure is permitted, and there should be no more than five references and five authors.
- All accepted letters are edited, and proofs will be sent out to authors before publication.
- Some letters might be chosen for online-only publication.

Adverse drug reactions
- Reports of adverse drug reactions are peer reviewed and those we accept are published in the Correspondence section.
- Length must not exceed 800 words, with only one table or figure, and no more than five references. No more than five authors are permitted.

Department of Error
- Any substantial error in any article published in The Lancet should be corrected as soon as possible. Blame is not apportioned; the important thing is to set the record straight.
- The Lancet journals have a policy for types of errors that we do and do not correct. We will always correct any error affecting a non-proprietary drug name, dose, or unit, any numerical error in the results, or any factual error in interpretation of results.

Green section (Seminars, Reviews, Series, Viewpoints, etc)
Commissioned Seminars, Reviews, and Series
- Seminars are disease-oriented clinically focused overviews for the generalist, covering epidemiology, pathophysiology, diagnosis, management, and prevention; whereas Reviews have a narrower remit for a more specialised audience. We aim to provide comprehensive balanced Review papers for clinicians and researchers on topics that we judge to be of widespread interest.
- Complete transparency about the choice of material included is important to any Review paper. Therefore, all Seminars and Reviews, and some Series, should include a brief section entitled “Search strategy and selection criteria” stating the sources (including databases, MeSH and free text search terms and filters, and reference lists from journals or books) of the material covered, and the criteria used to include or exclude studies. Citations to papers published in non-peer-reviewed supplements are discouraged. Since these papers should be comprehensive, we encourage citation of publications in non-English languages. An example is shown below:
Seminars should be no more than 5000 words with a maximum of 140 references, and Reviews should be no more than 4500 words, with a maximum of 100 references. A 150-word unstructured summary should be included. These papers should include about five illustrations to aid the reader.

Hypotheses
- A hypothesis paper describes a substantial jump in thinking that is testable but not so easily testable that readers will wonder why you have not already done it. New data are not part of a hypothesis, but you must include a section on how to test your idea.
- Sharing a new idea takes courage and concision. If you cannot express your line of thought in 1500 words, 20 references, and a 150-word unstructured summary, it is not a hypothesis.

Other departments
- Much of The Lancet’s role in encouraging debate and opinion takes place in sections such as Public Health, Viewpoint, Essay, Reportage, and the Departments of Medical History, Ethics, Medicine and Art, and Literature and Medicine. 1500 words and 20 references are our general guidelines for papers in these sections.

Case Reports
- The ideal Lancet Case Report is of general, not specialist interest. It tells a clinical story of a difficult differential diagnosis in an engaging and concise manner, while respecting the dignity of the patient. Novelty is not essential, but at least one broadly useful learning point is. In general, those who have treated the patient should be part of the authorship.
- Present a diagnostic conundrum, and explain how you solved it. Tell us about the presentation, history, examination, investigations, management, and outcome. In your discussion, educate the reader.
- As a general rule, we do not usually publish reports purporting to show the effectiveness of medical interventions in single cases.
- Use no more than 600 words and 5 references. Explanatory and graphic pictures (up to a maximum of two) can be helpful.
- Consent for publication in print and electronically must be obtained from the patient or, if this is not possible, the next of kin before submission. See Patient and other consents.

Formatting guidelines
Language
- Manuscripts should be submitted in English. Authors writing in Chinese, Portuguese, or Spanish may wish to use the Webshop (http://webshop.elsevier.com/languageservices) to provide an English translation of their manuscript for submission.

Title page
- A brief title, author name(s), preferred degree (one only), affiliation(s), and full address(es) of the authors must be included. The name and address of the corresponding author should be separately and clearly indicated with email and telephone details.

Formatting of text
- Type a single space at the end of each sentence.
- Do not use bold face for emphasis within text.
- Use a comma before the final “and” or “or” in a list of items.
- Type decimal points midline (ie, 23.4, not 23.4). To create a midline decimal on a PC: hold down ALT key and type 0183 on the number pad, or on a Mac: ALT shift 9.
- Numbers one to ten are written out in words unless they are used as a unit of measurement, except in figures and tables.
- Use single hard-returns to separate paragraphs. Do not use tabs or indents to start a paragraph.
- Do not use the automated features of your software, such as hyphenation, endnotes, headers, or footers (especially for references). Please use page numbering.

References
- Cite references in the text sequentially in the Vancouver numbering style, as a superscripted number after any punctuation mark. For example: “...as reported by Saito and colleagues.”
- Two references are cited separated by a comma, with no space. Three or more consecutive references are given as a range with an en rule. To create an en rule on a PC: hold down CTRL key and minus sign on the number pad, or on a Mac: ALT Hyphen.
- References in tables, figures, and panels should be in numerical order according to where the item is cited in the text.
- Give any subpart to the title of the article. Journal names are abbreviated in their standard form as in Index Medicus.
- If there are six authors or fewer, give all six in the form: surname space initials comma.
- If there are seven or more give the first three in the same way, followed by et al.
- For a book, give any editors and the publisher, the city of publication, and year of publication.
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Search strategy and selection criteria
Data for this Review were identified by searches of MEDLINE, Current Contents, PubMed, and references from relevant articles using the search terms “sentinel node,” “breast cancer,” and “axilla.” Abstracts and reports from meetings were included only when they related directly to previously published work. Only articles published in English between 1980 and 2006 were included.
Information for Authors

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- Main heading for the web extra material should be in 12 point Times New Roman font **BOLD**
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- Main table heading should be in 10 point Times New Roman font **BOLD**
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Data
- SI units are required
- Numbers in text and tables should always be provided if % is shown
- Means should be accompanied by SDs, and medians by IQR
- Exact p values should be provided, unless p<0.0001

Drug names
- Recommended international non-proprietary name (rINN) is required

References
- Vancouver style—eg,


- Numbered in order of mention in Webappendix and numbered separately from references in the full paper

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- All images must have a minimum resolution of 300 dpi, width 107 mm
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Fast-track publication
- For research papers that are judged to warrant fast dissemination, which will usually be randomised controlled trials, The Lancet will publish a peer-reviewed manuscript within 4 weeks of receipt
- Systematic reviews of randomised trials about diseases that have a major effect on human health also might warrant rapid peer review and publication
- If you wish to discuss your proposed submission with an editor, please call one of the editorial offices in London (+44 [0] 20 7424 4943), New York (+1 212 633 3667), or Beijing (+86 10 852 08872)
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Protocol review

- The Lancet will assess protocols of various types of studies and will publish on our website summaries of those protocols that survive review
- It is best to submit your protocol before the start of the study; all trials should be registered
- We also make a commitment to seek peer review of any paper that reports the primary clinical data of a protocol that we have published (see Lancet 2008; 372: 189–190 and Lancet 2001; 357: 1819–20), and therefore encourage submission of such papers to The Lancet

How The Lancet handles your paper

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- Receipt of your paper will be acknowledged by an email containing a reference number, which should be used in all future communications

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- All Seminars, Series, Reviews, and other non-research material that we are interested in publishing will be checked by editors using CrossCheck (see Lancet 2011; 377: 281–82). We expect that such papers are written in a way that offers new thinking without recycling previously published text

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- Every Article, Case Report, Hypothesis, Seminar, and Review published in The Lancet has been peer reviewed. Occasional contributions (eg, Essays) are accepted without peer review
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