Epidemiologie von Krebserkrankungen in Subsahara Afrika: Populations-basierte Daten zu Inzidenz, Versorgung und Überleben mit Fokus auf das Prostatakarzinom

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Krebserkrankungen stellen mittlerweile weltweit eine der häufigsten Todesursachen dar. In Ländern mit niedrigem und mittlerem „Human Development Index“ lösen diese zunehmend Infektionserkrankungen als Haupttodesursache ab. Dies gilt für fast alle Länder Subsahara Afrikas, wo diese Entwicklung auf häufig schlecht finanzierte und überlastete Gesundheitssysteme trifft. Das Ziel dieser Arbeit war es einen ersten populations-basierten Einblick in die Versorgungssituation von Krebspatient*innen in Subsahara Afrika zu gewinnen. Der Fokus lag auf dem Prostatakarzinom, welches in Subsahara Afrika das häufigste Karzinom des Mannes ist. Des Weiteren wurden Studien zum Zervixkarzinom und Non-Hodgkin-Lymphom vergleichend hinzugezogen. Die Studien entstanden in Zusammenarbeit mit dem „African Cancer Registry Network“, einem Zusammenschluss von populations-basierten Krebsregistern aus Subsahara Afrika, welches als regionale Partnerorganisation der Internationalen Agentur für Krebsforschung fungiert. In der ersten Beobachtungsstudie beleuchteten wir die diagnostische Aufarbeitung, therapeutische Versorgung und das Überleben einer Zufallsstichprobe von Prostatakarzinom-Patienten und analysierten den Einfluss von unzureichender Therapie auf das Risiko zu Versterben. In der zweiten Studie werteten wir zeitliche Veränderungen der Inzidenz des Prostatakarzinoms in Registern mit mehr als 10 Jahren Registertätigkeit aus. In der dritten, vergleichenden Krebsregisterstudie berechneten wir das beobachtete Überleben und nutzten Daten der WHO um Schätzungen des relativen Überlebens, sowie des Einflusses von Alter, Krebsstadium und Human Development Index auf dieses zu erstellen. Die weiteren zwei Beobachtungsstudien explorierten die diagnostische Aufarbeitung des Non-Hodgkin-Lymphoms und des Zervixkarzinoms, wobei bei Letzterem zusätzlich die therapeutische Versorgung und das Überleben analysiert wurden.

Die durchgeführten Studien zeigen, dass die Häufigkeit des Prostatakarzinoms stetig, auch unabhängig von der demographischen Entwicklung zunahm (zwischen 2 und 10% jährlich). Die diagnostische Aufarbeitung war häufig inadäquat und die meisten Prostatakarzinom-Patienten wurden in einem späten Stadium diagnostiziert. Ebenso erhielt eine Vielzahl der Patienten keine, oder nur ungenügende Therapie (nur 17,5% kurativ therapiert), was zu einer, im internationalen Vergleich, niedrigen Überlebenszeit beitrug. Auch beim Non-Hodgkin-Lymphom und dem Zervixkarzinom zeigte sich eine unzureichende Versorgungssituation. Diese Ergebnisse lieferten die erste populations-basierte Evidenz in Bezug auf diese Fragestellungen und schaffen mögliche Datengrundlagen für gesundheitspolitische Entscheidungen und für die Verbesserung von an die lokalen Gegebenheiten angepassten Leitlinien.

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Inhaltsverzeichnis

1. Einleitung und Zielstellung

1.1. Krebserkrankungen weltweit

Krebserkrankungen zählen zu den führenden Todesursachen der Menschheit (World Health Institution, 2020). Weltweit erkrankten im Jahre 2018 laut Schätzungen der Internationalen Agentur für Krebsforschung (International Agency for Research on Cancer, IARC) 18,1 Millionen Menschen an Krebs (Ferlay et al., 2018). Die gleichen Schätzungen gehen davon aus, dass zu diesem Zeitpunkt 18% aller Frauen und 22% aller Männer bis zu ihrem 85. Lebensjahr eine Krebserkrankung entwickeln werden. Gleichzeitig wird ein weiterer Anstieg der Anzahl der Krebsneuerkrankungen um ca. 60% bis ins Jahr 2040 prognostiziert, welcher allein durch demographischen Wandel (Alterung und Wachstum der Bevölkerungen) bedingt ist und die Zu- bzw. Abnahme von spezifischen Risikofaktoren unbeachtet lässt (Ferlay et al., 2018). Dieser Anstieg wird laut Schätzungen in Ländern mit niedrigem oder mittlerem Human Development Index (HDI, siehe (United Nations Development Programme, 2019)) überproportional stattfinden. Es wird angenommen, dass sich die Fälle dort bis zum Jahre 2030 fast verdoppeln (Fidler et al., 2018).

1.2 Das Prostatakarzinom

Das Prostatakarzinom war mit geschätzt 1,28 Millionen Neuerkrankungen im Jahr 2018 weltweit die zweit häufigste Krebserkrankung bei Männern und die vierthäufigste des Menschen insgesamt (Ferlay et al., 2018). In Anbetracht dessen ist es erstaunlich, wie wenig wir, trotz großer Forschungsanstrengungen in der Vergangenheit und heute, nach wie vor über die Risikofaktoren dieser Erkrankung wissen.

Als gesicherte Risikofaktoren der Erkrankung gelten vor allem Alter, familiäre Belastung und Genmutationen, wie die Mutationen von BRCA1 oder BRCA2 Genen, sowie z.B. Mutationen, assoziiert mit dem Lynch-Syndrom. Zudem nennt die American Cancer Society auf ihrer Homepage „race“ bzw. ethnische Zugehörigkeit, sowie Geographie als weitere gut belegte Risikofaktoren (American Cancer Society, 2020). Andere Quellen, wie Cancer Research UK nennen z.B. nur ethnische Zugehörigkeit und zählen zusätzlich Hormonlevel und Übergewicht auf (Cancer Research UK, 2020). Die Deutsche Krebs Gesellschaft nennt neben Alter und familiärer Veranlagung ebenfalls Hormone sowie weitere Risikofaktoren wie Rauchen, Alkohol, sowie Ernährung und genetische Faktoren (Deutsche Krebsgesellschaft, 2018). Diese Divergenzen und Uneinigkeiten zeigen die bisher nach wie vor fehlenden kausalen Erklärungen für die Beobachtung, dass bei Afroamerikanern und Afrokariben (hier wird manchmal auch von afrikanischer Herkunft im Allgemeinen gesprochen) überproportional häufig ein Prostatakarzinom diagnostiziert wird und im Gegensatz dazu die altersstandardisierten Inzidenzraten von Menschen, die in asiatischen Ländern leben weltweit mit die niedrigsten sind (Ferlay et al., 2018). Studien aus den 90er Jahren aus den USA, die zeigen konnten, dass sich das

Risiko an Prostatakarzinom zu erkranken bei japanischen Migranten und ihren Nachfahren deutlich gegenüber dem Risiko der Ursprungspopulation in Japan erhöht hatte, führten zu der Annahme, dass Faktoren der Umwelt, insbesondere des Lebensstiles, eine Rolle spielen könnten (Shimizu et al., 1991). Heute gibt es folglich eine lange Liste von potenziellen Risikofaktoren, für die die Evidenzlage aber nach wie vor nicht eindeutig und empirisch unzureichend gesichert ist. Dazu zählen u.a. Ernährungsgewohnheiten, wie der Verzehr von Milchprodukten oder Calciumhaltigen Lebensmitteln, Übergewicht, sowie stattgehabte bzw. chronische Prostatitiden (American Cancer Society, 2020; World Cancer Research Fund/American Institute for Cancer Research, 2018). Insofern ist die Frage, ob das erhöhte Risiko für Prostatakarzinome bei Menschen mit afrikanischer Herkunft eher sozioökonomischen oder genetischen Ursachen entspringt oder auf den Lebensstil und Ernährung zurückzuführen ist, nach wie vor Gegenstand einer angeregten wissenschaftlichen Debatte.

Gut belegt ist jedoch der Einfluss von PSA (Prostata Spezifisches Antigen) Screening Programmen. Diese Art der Vorsorgeuntersuchung führte z.B. in den USA ab den 1980er Jahren zu einem enormen Anstieg der Inzidenzraten (Potosky et al., 1995), was seit den 2000er Jahren zu der bis heute anhaltenden Diskussion der Frage des Überlebensvorteils durch solch breit angelegte Screening Programme führte. Die heute existierenden Leitlinien und Empfehlungen zum Screening gehen weit auseinander. Es ist nach wie vor nicht eindeutig belegt, ob die stark gestiegenen 5-Jahresüberlebensraten durch früher erkannte Tumoren oder als Folge des Lead-time Bias zustande kommen. Außerdem wird unterschiedliche bewertet, dass die Überdiagnostizierung von eigentlich indolenten Karzinomen zu einer starken Einschränkung der Lebensqualität der Betroffenen führen kann. Aktuell empfehlen die meisten Leitlinien eine individuelle Entscheidungsfindung (Culp et al., 2020). Hier werden unter Beachtung der Risikofaktoren des Patienten gemeinsam mit der behandelnden Ärztin die Vor- und Nachteile des Screenings besprochen und anschließend entschieden, ob bei dem Patienten ein PSA-Wert als Screening-Test bestimmt wird.

In Bezug auf Diagnostik und Therapie ist die Evidenzlage jedoch eindeutiger und es existieren diverse Leitlinien mit klaren Empfehlungen. Die international meistgenutzten Leitlinien werden vom „National Comprehensive Cancer Network“ (NCCN) aus den USA erstellt. Diese empfehlen - wie fast alle anderen Leitlinien auch - als diagnostisches Vorgehen die Bestimmung des TNM-Stadiums, des PSA-Wertes und des Gleason Scores, sobald die Diagnose Prostatakarzinom gestellt wurde. Anhand dieser drei Faktoren lässt sich dann eine Einteilung in unterschiedliche Risikogruppen vornehmen, und unter Einbeziehung der Lebenserwartung des Patienten anschließend eine Therapie Empfehlung aussprechen (National Comprehensive Cancer Network (NCCN), 2020). Die gängigen kurativen Therapieoptionen des Prostatakarzinoms sind die radikale Prostatektomie, die externe Radiotherapie, sowie die Brachytherapie. Je nach Risikogruppe des Patienten wird zeitweise zu den nuklearmedizinischen Verfahren noch eine

Androgendeprivationstherapie (androgen deprivation therapie, ADT) hinzugefügt. Die kontinuierliche ADT ist ebenso der Gold-Standard in der Versorgung des metastasierten Prostatakarzinoms (NCCN, 2020). Da die Behandlung von Krebspatient*innen in den letzten Jahrzehnten zwar große Erfolge erzielen konnte, aber gleichzeitig immer technischer und kostenintensiver wurde, ist die Anwendung der heute international anerkannten Leitlinien gerade in Ländern mit mittlerem oder niedrigem HDI kaum umsetzbar. Um diesem Problem Rechnung zu tragen hat das NCCN für die wichtigsten Krebsentitäten im Jahre 2017 erstmals harmonisierte Leitlinien mit Empfehlungen speziell für Subsahara Afrika erstellt und publiziert. Diese wurden in Zusammenarbeit mit führenden Ärzt*innen der Region erarbeitet und sollen auch dort Therapien auf Basis von größtmöglicher Evidenz ermöglichen. Das Prinzip basiert hierauf auf der Empfehlung einer grundlegenden Therapie, welche möglichst in jedem Fall umgesetzt werden sollte und weiteren, fakultativen Therapieempfehlungen, die je nach Ressourcen umgesetzt werden können (NCCN, 2019).

1.3 Subsahara Afrika

Nach der von der Weltgesundheitsorganisation (World Health Organisation, WHO), bzw. von IARC genutzten Definition, umfasst Subsahara Afrika 46 von 54 afrikanischen Ländern. Laut Daten der Weltbank leben aktuell etwas mehr als eine Milliarde Menschen in der Region, die im Moment das schnellste Bevölkerungswachstum weltweit aufweist (World Bank Group, 2020). Es gibt Schätzungen, die davon ausgehen, dass sich die Bevölkerung bis 2050 verdoppeln wird, jedoch zeichnet sich auch dort schon seit Jahren ein deutlicher Rückgang der durchschnittlichen Geburten pro Frau ab. Im Jahre 2019 lag das Bruttoinlandsprodukt der gesamten Region mit ca. 1,75 Billionen US-Dollar bei weniger als der Hälfte des Deutschen (World Bank Group, 2020). Zwar hat sich die Lebenserwartung über die letzten Dekaden kontinuierlich erhöht, jedoch lag sie mit 61,3 Jahren im Jahre 2018 noch fast 20 Jahre unter der von Deutschland. Obwohl sich der Anteil der Kinder, die eine Grundschulausbildung erhalten, laut Schätzungen der Weltbank seit den 90er Jahren von ca. 70% auf fast 100% erhöht hat, so besucht doch nach wie vor nur jedes zweite Kind im Anschluss eine weiterführende Schule. Die häufigsten Todesursachen sind nach wie vor Infektionserkrankungen, wie AIDS, Malaria oder Tuberkulose, jedoch nimmt der Anteil an nicht-übertragbaren Erkrankungen (non-communicable diseases, NCDs) auch hier merklich zu (WHO, 2020). So gab es im Jahre 2018 nach GLOBOCAN Schätzungen 771.595 Krebsneuerkrankungen in Subsahara Afrika (Ferlay et al., 2018), wovon nach wie vor geschätzt jeder dritte Fall mit einer Infektionskrankheit in Verbindung gebracht werden kann (Parkin et al., 2020). Auf das Prostatakarzinom entfielen 9% aller Krebsneuerkrankungen, womit es bei Männern 22% aller Fälle ausmachte und somit in fast allen Ländern Subsahara Afrikas das am häufigsten diagnostizierte Karzinom des Mannes war (Ferlay et al., 2018).

1.4 Krebsregister und AFCRN

Die ersten populations-basierten Krebsregister entstanden im Europa und Nordamerika der

1940er und 1950er Jahre. Die zentrale Aufgabe von populations-basierten Krebsregistern war und ist es Krebsneuerkrankungen in ihrer Bezugspopulation zu dokumentieren und Inzidenzraten zu erstellen. Seit der ersten Ausgabe der IARC-Serie von „Cancer Incidence in Five Continents“ von Sir Richard Doll et al. im Jahre 1966 hat die Abdeckung der Weltbevölkerung durch populations-basierte Krebsregister stark zugenommen. Die neuste Ausgabe dieser Serie schließt 343 hochqualitative populations-basierte Krebsregister aus 65 Ländern weltweit ein und schätzt, dass damit 15% der Weltbevölkerung im Einzugsgebiet dieser Krebsregisters leben (Bray et al., 2017). Hand in Hand mit der steigenden Anzahl der Register ging eine Erweiterung der Funktionen und Registertätigkeiten einher. Hochqualitative Krebsregister sammeln heute eine Vielzahl von Variablen, die weit über die ursprünglichen demographischen Basisdaten hinausgehen (Parkin, 2006). Dadurch sind sie integraler Bestandteil der globalen Krebsüberwachung und tragen durch ihre Informationen über Krebsstadien, initialer Therapie, sozioökonomischen Status und Überleben zu den wissenschaftlichen Studien bei, die von den Verantwortlichen in Gesundheitssystemen weltweit zur Verbesserung der Versorgung konsultiert werden. Die Qualität der Register lässt sich anhand der Parameter Vergleichbarkeit, Validität, Aktualität und Vollständigkeit einschätzen (Bray & Parkin, 2009; Parkin & Bray, 2009). Das 2012 gegründete Afrikanische Krebsregister Netzwerk (African Cancer Registry Network, AFCRN) ist der Zusammenschluss einer Vielzahl von populations-basierten Krebsregistern auf dem afrikanischen Kontinent, mit dem Ziel, sowohl die Datenqualität, als auch die Populationsabdeckung zu verbessern (AFCRN, 2020). Das Netzwerk ist lokaler Partner der WHO-Unterorganisation IARC im Rahmen ihrer „Globalen Initiative zur Entwicklung von Krebsregistern“ („Global Initiative for cancer registry development“), in der Region Subsahara Afrika. IARC hilft bei Aus- und Weiterbildung des Registerpersonals, stellt Finanzierung und Expert*innenrat für Forschung bereit und nutzt ihrerseits die Registerdaten für eigene Analysen, wie z.B. GLOBOCAN (Ferlay et al., 2019). Zur Sicherung des Qualitätsstandards muss jedes Mitglied des AFCRN mindestens 70% der Krebsfälle in seinem Gebiet erfassen (für eine vorläufige Aufnahme reichen zunächst 50%) und als Arbeitsgrundlage das AFCRN Manual verwenden (AFCRN, 2020; Finesse et al., 2015). Zum Stand 30.06.2021 besteht das Netzwerk aus 32 populations-basierten Krebsregistern aus 30 verschiedenen Ländern in Subsahara Afrika.

1.5 Zielstellungen

Die aktuell sichtbare und sich in Zukunft noch verstärkende Zunahme der Krebsfälle in Subsahara Afrika mit der damit einhergehenden Verschiebung der Todesursachen weg von den Infektionserkrankungen, hin zu den NCDs, macht eine Neuausrichtung der lokalen und internationalen Gesundheitspolitik notwendig. Die WHO hat dieser Tatsache z.B. 2013 mit dem „Global Action Plan for the prevention and control of noncommunicable diseases 2013-2020“ Rechnung getragen. Ziel Nummer 6 hebt die Wichtigkeit der Überwachung der entscheidenden Faktoren und des Trends von nichtübertragbaren Erkrankungen sowie die Evaluation der

Fortschritte in ihrer Prävention und Kontrolle hervor (WHO, 2013). Ebenso haben die Vereinten Nationen in ihren 2015 veröffentlichten „sustainable development Goals“ (SDG) in Ziel Nummer 3.4 festgehalten, dass bis zum Jahr 2030 das vorzeitige Versterben aufgrund von NCDs um ein Drittel gesenkt werden soll (United Nations, 2015). Dies verdeutlicht noch einmal, wie wichtig eine ausreichend solide Datengrundlage für (Gesundheits-)politische Entscheidungen und Agenden ist. Jedoch gibt es nach wie vor wenig Gesundheitssystemdaten aus Subsahara Afrika, um den Status quo und die Fortschritte in Richtung der gesetzten Ziele zu beurteilen.

Das Ziel dieser Arbeit ist es, einen ersten populationsbasierten Einblick in epidemiologische Parameter sowie die Versorgungsrealität von Krebspatient*innen aus Ländern Subsahara Afrikas zu gewinnen und damit eine mögliche Grundlage für gesundheitspolitische Entscheidungen, oder für die Weiterentwicklung und Evaluation von regional-angepassten Leitlinien, wie beispielsweise den „NCCN harmonized Guidelines for sub-Saharan Africa“ (NCCN, 2019), zu schaffen. Der spezielle Fokus der Arbeit liegt hierbei auf dem Prostatakarzinom, jedoch wurde vergleichend auch das Management anderer Krebsentitäten beleuchtet.
Mit Bezug auf Subsahara Afrika wurden die folgenden Forschungsfragen beantwortet:

1. Wie häufig ist das Prostatakarzinom und gibt es zeitliche Veränderungen der Häufigkeit?
2. In welchen Stadien befinden sich die Patienten bei Diagnosestellung und findet eine leitliniengerechte diagnostische Aufarbeitung von Patienten mit Prostatakarzinom statt?
3. Welche Therapien erhalten Patienten mit Prostatakarzinom und wie gut ist die Leitlinienadhärenz?
4. Wie sind die beobachteten und relativen Überlebenswahrscheinlichkeiten von Patienten mit Prostatakarzinom?
5. Welchen Einfluss haben Stadium und Therapie, adjustiert für bekannte Prognosefaktoren, auf das beobachtete Überleben von Patienten mit Prostatakarzinom?
6. Welchen Einfluss haben Alter, Stadium und Human Development Index auf das relative Überleben von Patienten mit Prostatakarzinom?
7. Inwiefern gibt es Ähnlichkeiten der Versorgung von Patienten mit Prostatakarzinom im Vergleich zu Patient*innen mit Non-Hodgkin-Lymphomen oder Zervixkarzinomen?

In der nachfolgenden Diskussion möchte ich diese Fragen anhand meiner Forschungsarbeiten beleuchten und die Ergebnisse in den Kontext der internationalen Forschung zu diesem Thema setzen.

2. Zusammenfassung der Publikationen

Publikation 1:

Seraphin, T. P., Joko-Fru, W. Y., Hämmerl, L., Griesel, M., Mezger, N. C. S., Feuchtner, J., Adoubi, I., Egue, M., Okerosi, N., Wabinga, H., Hansen, R., Vuma, S., Lorenzoni, C., Buziba, N. G., Aynalem, A., Liu, B., Parkin, D. M., Jemal, A., & Kantelhardt, E. J. (2021c). Presentation, patterns of care, and outcomes of patients with prostate cancer in sub-Saharan Africa: A population-based registry study. *Cancer, 127(22), 4221-4232*. https://doi.org/10.1002/cncr.33818

Mein Beitrag als Autor:

Ich war wesentlich beteiligt an der Entwicklung von Ideen zu Konzept, Durchführung und Design der Studie. Ein Mitglied des Studienteams der MLU, bestehend aus 5 Doktorand*innen, besuchte jeweils 2-3 AFCRN-Register über mehrere Monate und koordinierte vor Ort die Datensammlung. Während meines fünfmonatigen Aufenthaltes in Côte d'Ivoire und Benin arbeitete ich hauptverantwortlich mit den lokalen Teams der Krebsregister zusammen, um die erforderlichen Patienten-Daten aus papierbasierten Akten der Bezugs-Krankenhäuser zu exzerpieren. Mir oblag maßgeblich die Analyse der Daten des Prostatakarzinoms aus den Rohdatensätzen aller eingeschlossenen Register. Ich war wesentlich beteiligt an der Interpretation und schrieb federführend das Manuskript.

Publikationen 2 und 3:

Seraphin, T. P., Joko-Fru, W. Y., Kamaté, B., Chokunonga, E., Wabinga, H., Somdyala, N. I. M., Manraj, S. S., Ogunbiyi, O. J., Dzamalala, C. P., Finesse, A., Korir, A., N'Da, G., Lorenzoni, C., Liu, B., Kantelhardt, E. J., & Parkin, D. M. (2021a). Rising Prostate Cancer Incidence in Sub-Saharan Africa: A Trend Analysis of Data from the African Cancer Registry Network. *Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, 30(1), 158–165.* https://doi.org/10.1158/1055-9965.EPI-20-1005

Seraphin, T. P., Joko-Fru, W. Y., Manraj, S. S., Chokunonga, E., Somdyala, N. I. M., Korir, A., N'da, G., Finesse, A., Wabinga, H., Assefa, M., Gnangnon, F. H. R., Hansen, R., Buziba, N. G., Liu, B., Kantelhardt, E. J., & Parkin, D. M. (2021b). Prostate cancer survival in sub-Saharan Africa by age, stage at diagnosis, and human development index: a population-based registry study. *Cancer Causes & Control, 32, 1001–1019.* https://doi.org/10.1007/s10552-021-01453-x

Mein Beitrag als Autor:

Im Rahmen dieser Publikationen war ich wesentlich beteiligt an der Entwicklung des Studienkonzepts und Designs, der Extraktion der Daten aus den Rohdatenbanken des AFCRN, sowie der Analyse und Interpretation der Ergebnisse. Ich schrieb den ersten Entwurf der Manuskripte und war in der Folge verantwortlich für die Koordination mit den Koautor*innen.

Publikationen 4 und 5:

Griesel, M., **Seraphin, T. P.,** Mezger, N. C. S., Hämmerl, L., Feuchtner, J., Joko-Fru, W. Y., Sengayi-Muchengeti, M., Liu, B., Vuma, S., Korir, A., Chesumbai, G. C., Nambooze, S., Lorenzoni, C. F., Akele-Akpo, M.-T., Ayemou, A., Traoré, C. B., Wondemagegnehu, T., Wienke, A., Thomssen, C., … Kantelhardt, E. J. (2021). Cervical Cancer in Sub-Saharan Africa: A Multinational Population-Based Cohort Study of Care and Guideline Adherence. *The Oncologist*, *26*(5), *e807–e816*. https://doi.org/10.1002/onco.13718

Mezger, N. C. S., Feuchtner, J., Griesel, M., Hämmerl, L., **Seraphin, T. P.,** Zietsman, A., Péko, J.-F., Tadesse, F., Buziba, N. G., Wabinga, H., Nyanchama, M., Borok, M. Z., Kéita, M., N'da, G., Lorenzoni, C. F., Akele-Akpo, M.-T., Gottschick, C., Binder, M., Mezger, J., … Kantelhardt, E. J. (2020). Clinical presentation and diagnosis of adult patients with non-Hodgkin lymphoma in Sub-Saharan Africa. *British Journal of Haematology*, *190*(2), 209–221. https://doi.org/10.1111/bjh.16575

Mein Beitrag als Autor:

Bei diesen Studien war ich beteiligt an der Entwicklung von Ideen zu Studienkonzept, Durchführung und Design. Wie bei Publikation 1 beschrieben wurden die von mir in den zwei besuchten Ländern zu Zervix-Karzinom, und NHL erhobenen Daten zur Auswertung genutzt. Zusammen mit den Koautor*innen kommentierte und revidierte ich die Manuskript Entwürfe der jeweiligen Erstautor*innen.

Förderungen im Rahmen meiner Promotion:

Während meiner Promotion erhielt ich Unterstützung im Rahmen der Stipendiatenförderung der Studienstiftung des Deutschen Volkes e.V. Ebenso erhielt ich ein Stipendium für einen 8-monatigen Forschungsaufenthalt im Rahmen des Internationalen Forschungsnetzwerkes HAL-OX (International Research Network Biology of Disease and Molecular Medicine; ZS/2016/08/80642) der Martin-Luther-Universität Halle-Wittenberg.

Publikationsteil

Publikation 1:

Seraphin, T. P., et al. (2021). Presentation, patterns of care, and outcomes of patients with prostate cancer in sub-Saharan Africa: A population-based registry study.

Cancer, 127(22), 4221-4232.

Publikation 2:

Seraphin, T. P., et al. (2021). Rising Prostate Cancer Incidence in Sub-Saharan Africa: A Trend Analysis of Data from the African Cancer Registry Network.

Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, *30(1), 158–165.*

Publikation 3:

Seraphin, T. P., et al. (2021). Prostate cancer survival in sub-Saharan Africa by age, stage at diagnosis, and human development index: a population-based registry study.

Cancer Causes & Control, 32, 1001–1019.

Publikation 4:

Griesel, M., et al. (2021). Cervical Cancer in Sub-Saharan Africa: A Multinational Population-Based Cohort Study of Care and Guideline Adherence.

The Oncologist, *26*(5), *e807–e816*.

Publikation 5:

Mezger, N. C. S., et al. (2020). Clinical presentation and diagnosis of adult patients with non-Hodgkin lymphoma in Sub-Saharan Africa.

British Journal of Haematology, *190*(2), 209–221.

Original Article

Presentation, Patterns of Care, and Outcomes of Patients With Prostate Cancer in Sub-Saharan Africa: A Population-Based Registry Study

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BACKGROUND: Although prostate cancer (PCa) is the most commonly diagnosed cancer in men of sub-Saharan Africa (SSA), little is known about its management and survival. The objective of the current study was to describe the presentation, patterns of diagnosis, treatment, and survival of patients with PCa in 10 countries of SSA. **METHODS:** In this observational registry study with data collection from 2010 to 2018, the authors drew a random sample of 738 patients with PCa who were registered in 11 population-based cancer registries. They described proportions of patients receiving recommended care and presented survival estimates. Multivariable Cox regression was used to calculate hazard ratios comparing the survival of patients with and without cancer-directed therapies (CDTs). **RESULTS:** The study included 693 patients, and tumor characteristics and treatment information were available for 365 patients, 37.3% of whom had metastatic disease. Only 11.2% had a complete diagnostic workup for risk stratification. Among the nonmetastatic patients, 17.5% received curative-intent therapy, and 27.5% received no CDT. Among the metastatic patients, 59.6% received androgen deprivation therapy. The 3- and 5-year age-standardized relative survival for 491 patients with survival time information was 58.8% (95% confidence interval [CI], 48.5%-67.7%) and 56.9% (95% CI, 39.8%-70.9%), respectively. In a multivariable analysis, survival was considerably poorer among patients without CDT versus those with therapy. **CONCLUSIONS:** This study shows that a large proportion of patients with PCa in SSA are not staged or are insufficiently staged and undertreated, and this results in unfavorable survival. These findings reemphasize the need for improving diagnostic workup and access to care in SSA in order to mitigate the heavy burden of the disease in the region. ***Cancer* 2021;127:4221-4232**.

KEYWORDS: Africa, population-based cancer registration, prostate cancer, staging, survival, treatment.

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INTRODUCTION

Prostate cancer (PCa) has become a major public health problem in sub-Saharan Africa (SSA).[1,2] According to GLOBOCAN 2018 estimates, PCa has the highest age-standardized incidence and mortality rates of all cancers in men in SSA; rates in parts of West Africa are among the highest in the world, and the rates have been rising all over the region during the last decades.[1,3] Studies on the uptake of screening show a lack of early-detection services and public awareness.[4,5] Accordingly, hospital-based studies reveal that most patients present with symptomatic disease and are diagnosed at late stages.[6] African American and Afro-Caribbean race has been associated with a more aggressive form of PCa and poorer outcomes in comparison with other population groups. This probably reflects a combination of germline susceptibility and socioeconomic and environmental factors.[7-10] The stage at presentation, the Gleason score, and the prostate-specific antigen (PSA) levels are the main factors influencing PCa survival. These factors are used by international guidelines for patient risk stratification and treatment decisions, with life expectancy taken into account. Adequate treatment, consisting of either curative approaches (eg, radical prostatectomy [RP] and external-beam radiation therapy [EBRT] with or without adjuvant androgen deprivation therapy [ADT]) or active palliative approaches (eg, ADT alone), has been shown to prolon

g patients' survival.[11,12]

However, the availability of these factors may be sparse in most African countries, and thus treatment decisions require local adjustment.[4] In 2017, the National Comprehensive Cancer Network (NCCN) for the first time released harmonized PCa treatment guidelines for SSA.[11] This study was designed to examine contemporary, population-based presentations, diagnoses, treatments, and outcomes of patients with PCa in 10 countries of SSA and how well management complied with guideline-recommended care.

MATERIALS AND METHODS

Study Design and Data Source

In our longitudinal, population-based, observational registry study, we assembled information from 11 population-based cancer registries (PBCRs) in 10 SSA countries (Fig. 1). We collected data on the presentation, diagnostic workup, patterns of care, and factors influencing survival of patients diagnosed with PCa between 2010 and 2015. The participating PBCRs included the Registre des Cancers d'Abidjan (Côte D'Ivoire), the Addis Ababa City Cancer Registry (Ethiopia), the Registre des Cancers du Mali (Bamako, Mali), the Registre des Cancers de Brazzaville (Congo), the Bulawayo Cancer Registry (Zimbabwe), the Cotonou Cancer Registry (Benin), the Eldoret Cancer Registry (Kenya), the Kampala Cancer Registry (Uganda), the Maputo Cancer Registry (Mozambique), the Nairobi Cancer Registry (Kenya), and the Namibian National Cancer Registry. All these registries are members of the African Cancer Registry Network (AFCRN), the African regional hub for the Global Initiative for Cancer Registry Development of the International Agency for Research on Cancer. Among the 31 AFCRN member registries from 21 countries in 2016 invited to participate in the study, the 11 aforementioned registries consented to participate in the study. The AFCRN research committee (March 2, 2016) and the respective registries' responsible bodies approved this study a priori. The PBCRs covered populations ranging from 653,000 (Bulawayo) to 4.4 million (Abidjan); they summed up to approximately 21.5 million.[1]

Spending time and making efforts feasible for the given setting, we assessed the prevalence of adequate care via medical records from a random sample. A minimal sample size of 700 would produce a 2-sided 95% confidence interval (CI) with a width equal to 0.075 if the sample proportion of patients with adequate care were 0.5. We drew a simple random sample of 60 to 100 patients per registry (*International Classification of Diseases, Tenth Revision* code C61) who were registered within a 2-year period (Supporting Table 1 and Supporting Fig. 1). For Cotonou and Addis Ababa, we used all patients registered because there were fewer than 60. Patients discovered to be duplicates in the database, patients who had relapses with a date of incidence before 2010, and patients falsely registered as having PCa were excluded. Patients with additional information for diagnostics, TNM stage, therapy, or outcomes were labeled the traced cohort and were further evaluated in Kaplan-Meier survival and Cox regression analyses.

Data Collection

The PBCRs collect information on sociodemographic, clinical, and pathological characteristics, therapy, and vital status according to AFCRN's *Standard Procedure Manual*.[13] Between September 2016 and May 2018, local staff from the PBCRs visited the health institutions to update the information of each randomly selected patient via medical charts and pathology reports. In cases without additional information traced, the patients or their relatives were called. The types of clinical data considered in

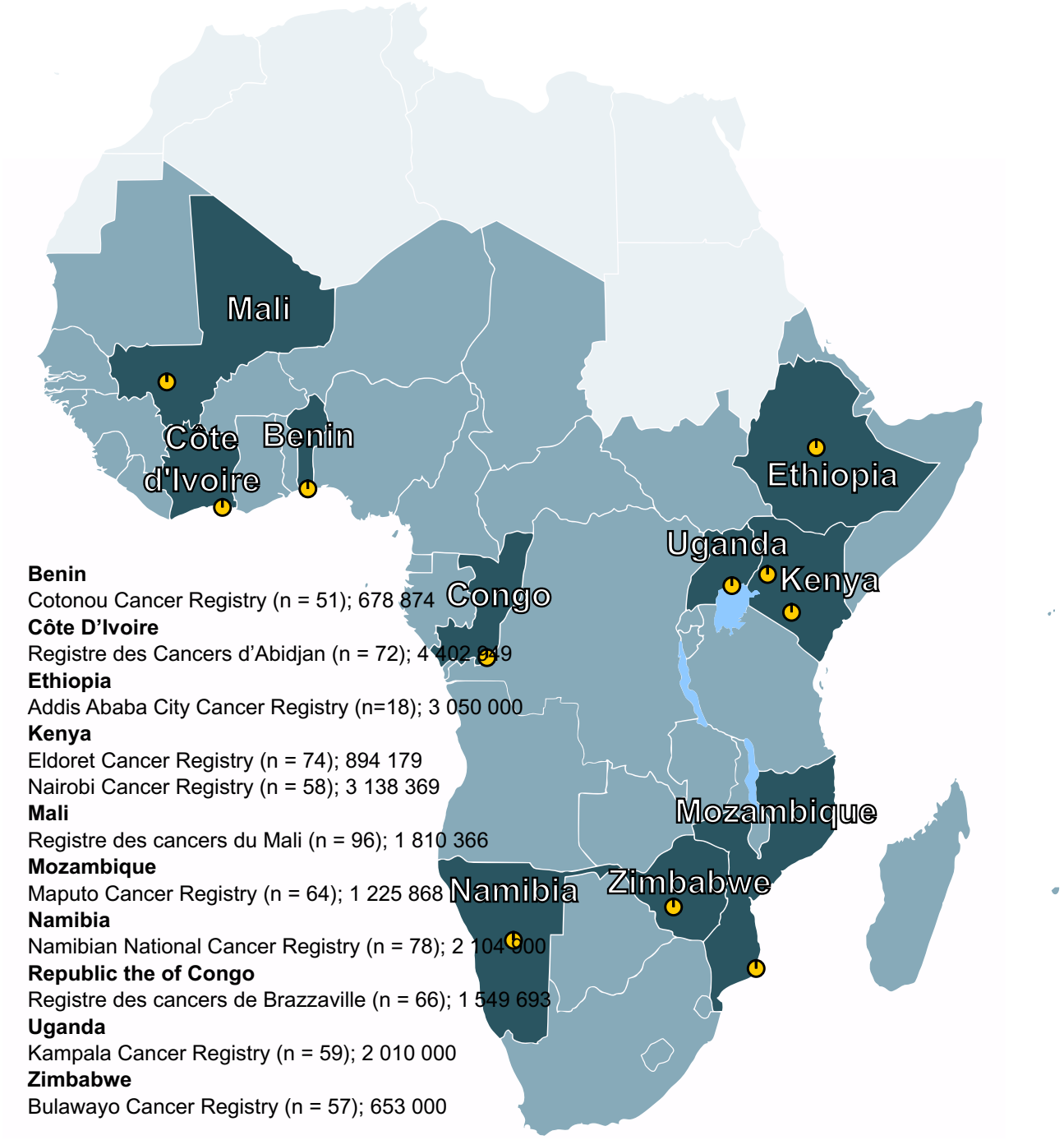

Figure 1. Countries of participating cancer registries. Countries of participating population-based cancer registries are highlighted along with the names of the registries, the number of included patients (n), and the population of each coverage area (persons).

our study included the following: PSA level at diagnosis, Gleason score, physical examination (ie, digital rectal examination [DRE]), imaging methods for staging, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and TNM stage. The types of treatment data included surgery, radiotherapy, and endocrine therapy. We classified these with respect to cancer-directed therapy (CDT): "curative approach" (RP and EBRT with a cumulative dose of at least 60 Gy in nonmetastatic patients), "any other approach with ADT" (ADT monotherapy or

ADT with transurethral resection of the prostate, EBRT with a cumulative dose of <60 Gy, or chemotherapy), "any other approach without ADT" (transurethral resection of the prostate, EBRT with a cumulative dose of <60 Gy, or chemotherapy), and "no CDT documented" (all other cases). When the TNM stage was not documented in the record, it was derived from clinical, pathological, or imaging information with Essential TNM and the American Joint Committee on Cancer prostate cancer staging system (eighth edition).[14,15] Accordingly, we considered the M stage to be M0 for all patients with no pathological or clinical suggestion of metastases. Patients with regional lymph node involvement documented (N1) were included in the metastatic subgroup for analysis, as were patients with an indication of lymph node involvement derived from clinical information, whereas Nx and N0 cases were included in the nonmetastatic group. We based our evaluation of the proportions of patients who received guideline-recommended diagnostic workup and care on the NCCN's harmonized guidelines for SSA (version 2.2017).[11]

Statistical Analysis

We used the Statistical Package for the Social Sciences (version 25) from IBM. We calculated overall survival (OS) by using the time between the date of diagnosis and the date of last known follow-up or death. We computed 1- to 5-year Ederer II age-standardized relative survival (ASRS) with Stata software (version 15) from StataCorp LLC, and we included World Health Organization life tables and adopted Corazziari et al's International Cancer Survival Standard 1 age standard for PCa.[16] We used the Kaplan-Meier method and a multivariable Cox proportional hazards model to analyze longitudinal data. We first assessed for the condition of "missing at random" (uninformative censoring) by performing a reverse Kaplan-Meier analysis. We restricted the Cox and Kaplan-Meier analyses to patients with survival longer than 3 months to allow time for the initiation of therapy and to account for bias from missing treatment through early death. In a sensitivity analysis, we studied other cutoffs. We estimated simple and multivariable hazard ratios (HRs). As covariates for adjusting the multivariable regression, we chose grouped parameters known to influence survival: TNM stage, Gleason score, PSA level at the date of diagnosis, ECOG PS, and age at diagnosis.[11] We followed Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for drafting this article.

RESULTS

A cohort of 693 patients (median age, 70 years; interquartile range, 64-77 years) with PCa (the total population-based cohort) was assembled from 11 PBCRs. Medical records for the extraction of additional sociodemographic and clinical data were located for 365 of the patients (52.7%; the traced cohort). For the remainder of the total population-based cohort, basic registry data could not be augmented because no additional information was retrieved by the original sources reporting the cancer diagnosis. The traced cohort (n = 365) represented 17.6% of the 2068 patients with PCa registered in the time period of random sampling in the included PBCRs (Supporting Table 1).

Patient Characteristics and Diagnostic Workup

In the traced cohort (n = 365), we identified 136 patients (37.3%) as metastatic (including 125 patients with M1 disease and 11 patients with N1 M0 disease) and 229 patients as nonmetastatic. For 55% of the traced cohort, there was no complete TNM stage documented. In the traced cohort (n = 365), 1 in 5 patients was diagnosed by clinical examination only, whereas a further 12% also had an elevated PSA level. The remaining two-thirds had pathological confirmation, with nearly all of those cases classified as adenocarcinoma. Additional patient characteristics are shown in Table 1 and Supporting Table 2. Figure 2 shows the availability of diagnostic information in our total population-based cohort (n = 693). In the nonmetastatic subgroup (n = 229), TNM stages with an unknown N status and a known N status were documented in 1 in 3 patients and in 1 in 9 patients, respectively. Thirty to forty percent of both subgroups had known PSA levels at diagnosis. We found that 26.2% of the patients had known histological confirmation of the primary but lacked documentation of the Gleason score. As for the nonmetastatic subgroup (n = 229), for 1 in 9 patients (11.2%), all 3 prognostic factors for risk stratification according to NCCN guidelines were found. Two in 5 patients in this subgroup had at least a documented T stage, which is used as a baseline parameter in the harmonized NCCN guidelines.[11] We found generally low rates of information from imaging. Furthermore, a small number of patients were assessed for ECOG PS.

Primary Treatment Approach

In the nonmetastatic subgroup (n = 229), 17.5% received curative-intent treatment: RP or EBRT (20 patients each). Of those patients having received EBRT, 13

TABLE 1. Patient Characteristics

Characteristic	Total Population-Based Cohort (n = 693)	Medical Records Not Available[a] (n = 328)	Traced Cohort[b] (n = 365)	Nonmetastatic Subgroup[c] (n = 229)	Metastatic Subgroup[d] (n = 136)
Age group, No. (%)					
15-54 y	35 (5.1)	16 (4.9)	19 (5.2)	10 (4.4)	9 (6.6)
55-64 y	150 (21.6)	54 (16.5)	96 (26.3)	61 (26.6)	35 (25.7)
65-74 y	234 (33.8)	98 (29.9)	136 (37.3)	79 (34.5)	57 (41.9)
75-84 y	178 (25.7)	82 (25.0)	96 (26.3)	65 (28.4)	31 (22.8)
≥85 y	43 (6.2)	25 (7.6)	18 (4.9)	14 (6.1)	4 (2.9)
Unknown age	53 (7.6)	53 (16.2)	0 (0.0)	0 (0.0)	0 (0.0)
Age, median (IQR), y	70 (64-77)	72 (64-79)	70 (63-76)	71 (62-76)	69 (63-75)
Year of diagnosis, No. (%)					
2010-2011	63 (9.1)	36 (11.0)	27 (7.4)	20 (8.7)	7 (5.1)
2012-2013	522 (75.3)	243 (74.1)	279 (76.4)	177 (77.3)	102 (75.0)
2014-2015	108 (15.6)	49 (12.5)	59 (16.2)	32 (14.0)	27 (19.9)
Highest basis of diagnosis, No. (%)					
Clinical investigation	153 (22.1)	81 (24.7)	72 (19.7)	52 (22.7)	20 (14.7)
PSA	55 (7.9)	10 (3.0)	45 (12.3)	15 (6.6)	30 (22.1)
Pathological confirmation ± PSA	432 (62.3)	184 (56.1)	248 (67.9)	162 (70.7)	86 (63.2)
Unknown basis	53 (7.6)	53 (16.2)	0 (0.0)	0 (0.0)	0 (0.0)
T stage, No. (%)					
T1 or T2			77 (21.1)	51 (22.3)	26 (19.1)
T3 or T4			72 (19.7)	38 (16.6)	34 (25.0)
Not documented			216 (59.2)	140 (61.1)	76 (55.9)
N stage, No. (%)					
N0			50 (13.7)	30 (13.1)	20 (14.7)
N1			23 (6.3)	0 (0.0)	23 (16.9)
Not documented			292 (80.0)	199 (86.9)	93 (68.4)
PSA at diagnosis, No. (%)					
<10 ng/mL			12 (3.3)	7 (3.1)	5 (3.7)
≥10 ng/mL and <20 ng/mL			7 (1.9)	5 (2.2)	2 (1.5)
≥20 ng/mL and <100 ng/mL			40 (11.0)	28 (12.2)	12 (8.8)
≥100 ng/mL			65 (17.8)	29 (12.7)	36 (26.5)
Not documented			241 (66.0)	160 (69.9)	81 (59.6)
Gleason score, No. (%)					
≤6			51 (14.0)	39 (17.0)	12 (8.8)
7			47 (12.9)	31 (13.5)	16 (11.8)
≥8			67 (18.4)	36 (15.7)	31 (22.8)
Not documented			200 (54.8)	123 (53.7)	77 (56.6)
Highest imaging for staging, No. (%)					
US only			102 (27.9)	72 (31.4)	30 (22.1)
X-ray with/without US			49 (13.4)	16 (7.0)	33 (24.3)
CT scan			31 (8.5)	8 (3.5)	23 (16.9)
MRI or bone scan			38 (10.4)	17 (7.4)	21 (15.4)
No imaging documented			145 (39.7)	116 (50.7)	29 (21.3)
ECOG PS, No. (%)					
≤1			67 (18.4)	48 (21.0)	19 (14.0)
≥2			94 (25.8)	35 (15.3)	59 (43.4)
Not documented			204 (55.9)	146 (63.8)	58 (42.6)

Abbreviations: CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; MRI, magnetic resonance imaging; PS, performance status; PSA, prostate-specific antigen; US, ultrasound.

[a]Part of the total population-based cohort for which medical records were not available.

[b]Part of the total population-based cohort for which medical records were available (additional clinical information).

[c]Subgroup of the traced cohort comprising all patients without a pathological or clinical suggestion of metastasis (M0), including patients with an unknown lymph node status (Nx M0).

[d]Subgroup of the traced cohort comprising all patients with a pathological or clinical suggestion of metastasis (M1), including all patients with a positive lymph node status (N1).

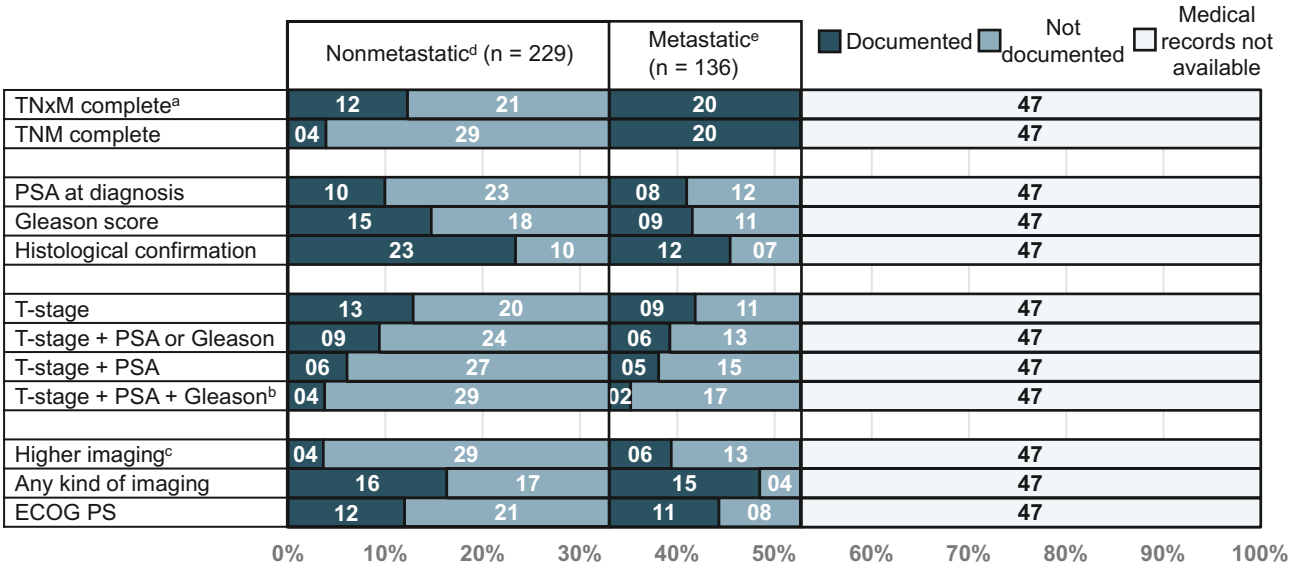

Figure 2. Availability of diagnostic information for patients with prostate cancer in the total population-based cohort (n = 693). [a]Nx included. [b]Main prognostic factors according to the 2017 National Comprehensive Cancer Network guidelines. [c]For example, computed tomography, magnetic resonance imaging, or a bone scan (used for staging). [d]The nonmetastatic subgroup (n = 229) comprised all patients without a pathological or clinical suggestion of metastasis (M0), including patients with an unknown lymph node status (Nx M0). [e]The metastatic subgroup (n = 136) comprised all patients with a pathological or clinical suggestion of metastasis (M1), including all patients with a positive lymph node status (N1). ECOG indicates Eastern Cooperative Oncology Group; PS, performance status; PSA, prostate-specific antigen.

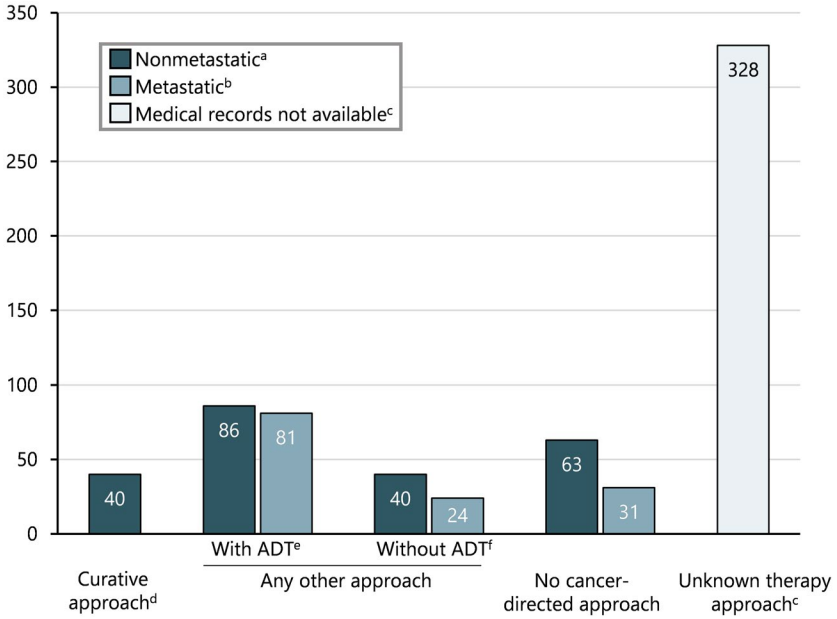

Figure 3. Primary treatment approach by identified M stage in the total population-based cohort (n = 693). [a]The nonmetastatic subgroup (n = 229) comprised all patients without a pathological or clinical suggestion of metastasis (M0), including patients with an unknown lymph node status (Nx M0). [b]The metastatic subgroup (n = 136) comprised all patients with a pathological or clinical suggestion of metastasis (M1), including all patients with a positive lymph node status (N1). [c]No medical records were available for the extraction of clinical data (n = 328). [d]Radical prostatectomy or external-beam radiation therapy with a potentially curative dose. [e]ADT monotherapy by surgical or medical castration or ADT by surgical or medical castration in combination with transurethral resection of the prostate or external-beam radiation therapy with a palliative dose or chemotherapy. [f]Transurethral resection of the prostate or external-beam radiation therapy with a palliative dose or chemotherapy without ADT. ADT indicates androgen deprivation therapy.

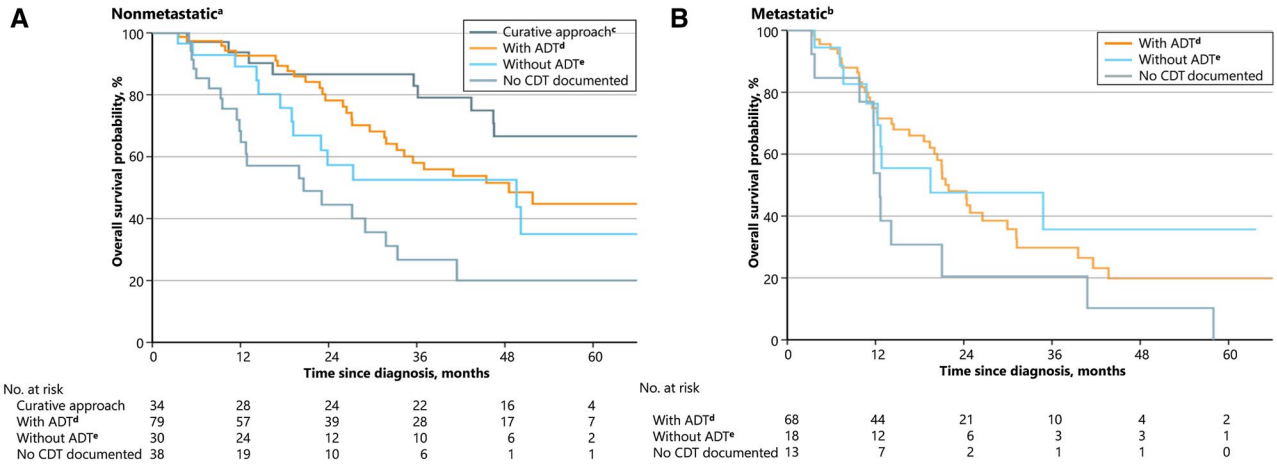

Figure 4. Overall survival of patients from the traced cohort with at least 3 months of survival stratified by M stage: differences according to the treatment approach. [a]These patients surviving at least 3 months from the nonmetastatic subgroup (n = 181) included all patients without a pathological or clinical suggestion of metastasis (M0), including patients with an unknown lymph node status (Nx M0). [b]These patients surviving at least 3 months from the metastatic subgroup (n = 99) included all patients with a pathological or clinical suggestion of metastasis (M1), including all patients with a positive lymph node status (N1). [c]Radical prostatectomy or external-beam radiation therapy with a potentially curative dose. [d]Any other approach with ADT by surgical or medical castration. [e]Any other approach without ADT such as transurethral resection of the prostate or external-beam radiation therapy with palliative doses. ADT indicates androgen deprivation therapy; CDT, cancer-directed therapy.

received concurrent ADT. In the nonmetastatic subgroup (n = 229), 82.5% did not receive a curative-treatment approach, with 27.5% receiving no CDT at all. The largest proportion of patients in the traced cohort (n = 365) received ADT at some point (nonmetastatic: 43.2%; metastatic: 59.6%) (Fig. 3). The ADT modalities for patients receiving any ADT were surgery (by bilateral subcapsular orchiectomy; n = 69), simple medical castration (with gonadotropin-releasing hormone agonists; n = 26), combined androgen blockade (n = 57), antiandrogen alone (mainly with bicalutamide; n = 23), and diethylstilboestrol (n = 8); 4 cases were unknown. For a quarter of the traced cohort (n = 365), no CDT was documented (Supporting Table 3).

Survival Analysis

In our total cohort (n = 693), survival data were available for 491 patients (183 deaths during observation; median follow-up, 9.3 months). The observed 1-, 3-, and 5-year OS rates were 73.3% (95% CI, 68.6%-78.0%), 42.6% (95% CI, 36.3%-48.9%), and 31.2% (95% CI, 24.5%-37.9%), respectively. The observed OS varied among the different PBCR areas (Supporting Fig. 2). The 1-, 3-, and 5-year ASRS was 82.2% (95% CI, 76.0%-86.9%), 58.8% (95% CI, 48.5%-67.7%), and 56.9% (95% CI, 39.8%-70.9%), respectively (Supporting Table 4A). When we looked at the outcomes of the traced cohort (n = 365) stratified by M stage, the observed 1-, 3-, and 5-year OS rates for the nonmetastatic subgroup (n = 229) were 82.8% (95% CI, 77.3%-88.4%), 53.7% (95% CI, 45.5%-61.9%), and 41.1% (95% CI, 32.1%-50.2%), respectively (Supporting Table 4B). For the metastatic subgroup (n = 136), they were 61.2% (95% CI, 52.2%-70.2%), 25.8% (95% CI, 16.4%-35.2%), and 14.7% (95% CI, 5.0%-24.5%), respectively. In the Kaplan-Meier analysis of patients in the traced cohort surviving at least 3 months (n = 280), who were stratified as nonmetastatic or metastatic, we found OS differences between management approaches: in this subgroup, nonmetastatic patients (n = 181) with curative- and noncurative-treatment approaches had better OS than patients with no CDT documented (Fig. 4A). Metastatic patients (n = 99) with any form of treatment approach had better OS than patients with no CDT documented (Fig. 4B).

Multivariable Analysis

In the Cox regression analysis of patients in the traced cohort surviving at least 3 months (n = 280), who were stratified as nonmetastatic or metastatic, we found some factors influencing the probability of survival (Supporting Table 5). In the nonmetastatic subgroup, a multivariable analysis showed that "no CDT documented" (HR, 3.86; 95% CI, 1.63-9.09) and "ECOG PS ≥ 2" (HR, 5.64; 95% CI, 2.46-12.94) were associated with a significantly

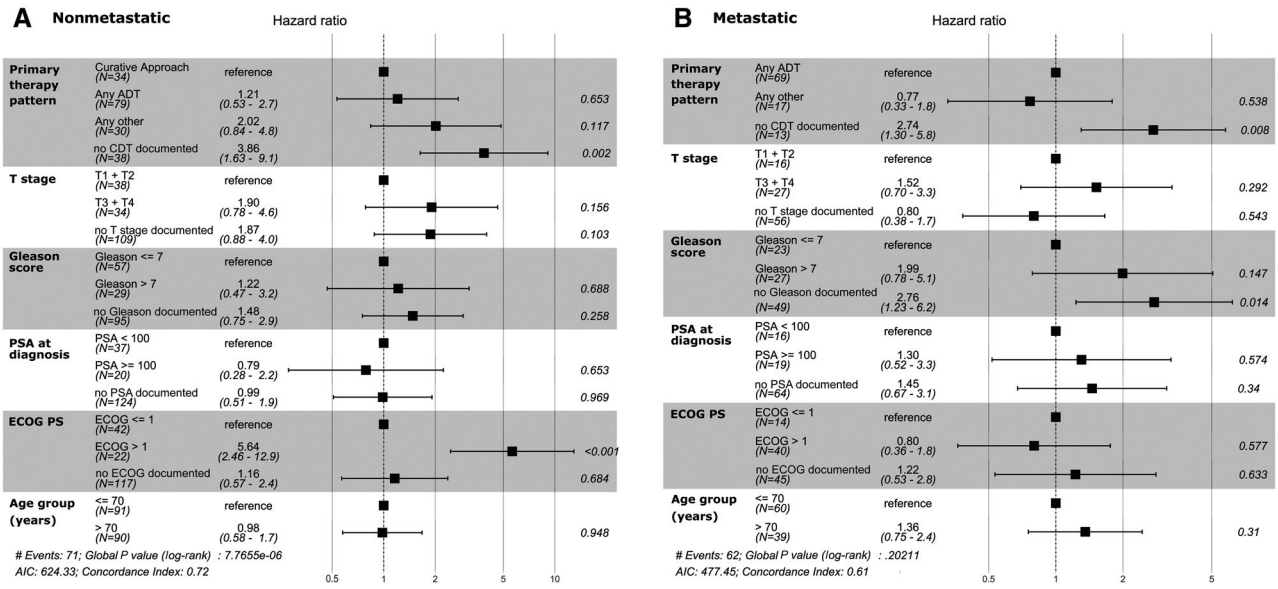

Figure 5. Forest plots showing the influence of primary treatment patterns on the survival of (A) patients with nonmetastatic prostate cancer[a] and (B) patients with metastatic prostate cancer.[b] The hazard ratios and 95% confidence intervals are the results of a multivariable Cox regression model adjusted for the T stage, Gleason score, PSA at diagnosis, ECOG PS, and age group. [a]These patients surviving at least 3 months from the nonmetastatic subgroup (n = 181) included all patients without a pathological or clinical suggestion of metastasis (M0), including patients with an unknown lymph node status (Nx M0). [b]These patients surviving at least 3 months from the metastatic subgroup (n = 99) included all patients with a pathological or clinical suggestion of metastasis (M1), including all patients with a positive lymph node status (N1). ADT indicates androgen deprivation therapy; AIC, Akaike information criterion; CDT, cancer-directed therapy; ECOG, Eastern Cooperative Oncology Group; PS, performance status; PSA, prostate-specific antigen.

increased risk of death (Fig. 5A). In the metastatic subgroup, a multivariable analysis showed "no CDT documented" (HR, 2.74; 95% CI, 1.30-5.80) and "no Gleason score documented" (HR, 2.76; 95% CI, 1.23-6.2) were associated with a significantly increased risk of death (Fig. 5B).

A reverse Kaplan-Meier analysis (testing for uninformative censoring) suggested that in nonmetastatic and metastatic patients, most covariates had a similar pattern of censoring over time (no difference in the reverse Kaplan-Meier analysis between covariates). Especially for treatment pattern, T stage, PSA at diagnosis, and ECOG PS, censoring was at random. In the nonmetastatic subgroup, Gleason score and age at diagnosis possibly were censored not at random. In the metastatic subgroup, both of these covariates were censored at random.

DISCUSSION

This study is, to our knowledge, the first to assess the status of diagnostics, treatments, and outcomes in a random sample of population-based patients with PCa from SSA. We found that patients with PCa presented at a late stage and lacked adequate diagnostic workup and treatment, and this led to unfavorable outcomes. A complete diagnostic workup for risk stratification, including the tumor stage, Gleason score, and PSA level, was documented for only 11% of the traced cohort (n = 365). We found that less than one-fifth of the nonmetastatic subgroup (n = 229) received therapy with curative intent. Nearly two-fifths of our traced cohort (n = 365) were diagnosed with metastatic disease. In this metastatic subgroup (n = 136), only two-thirds received ADT. In a multivariable analysis, a lack of CDT for nonmetastatic and metastatic patients was strongly associated with a higher risk of mortality.

Such a low proportion of patients with diagnostic workup and staging as required by treatment guidelines is an important limitation for adequate care. In high-income settings such as the United States, the stage is unknown for only 4% of patients with PCa, whereas it was unknown for 55% in our traced cohort.[17] Several factors may contribute to the high percentage of unknown stage information in SSA. The inadequacies of local health care systems, including an undersupply of diagnostic facilities and trained staff, are a well-known problem.[18,19] However, it is also likely that patients who might not be

able to pay for a treatment refrain from further diagnostic workup. Another challenge for PCa treatment in SSA is late presentation. Because the disease can remain asymptomatic for a long time, diagnosis at a late stage is common in settings without screening. At the time of our study, there were no general screening programs in any of the included countries; accordingly, most patients present with symptomatic disease (lower urinary tract symptoms and bone pain) and late-stage disease.[6] It is likely that this refers to most of the included patients with an unknown stage. In high-resource settings, PSA screening is part of an ongoing, controversial discussion, although most international guidelines recommend informed decision-making for or against screening that takes into account a patient's individual risk.[12,20] Generally, in high-income countries, routine PSA screening programs have led to a significant increase in patients with early-stage presentation.[21] Accordingly, in a Surveillance, Epidemiology, and End Results cohort from the United States, the proportion of metastatic PCa was reported to be only 6%.[17] This is in stark contrast to our traced cohort, in which more than 1 in 3 patients was known to have metastatic disease. However, a comparison of these 2 rates should be made with caution because PSA screening, starting in the 1980s in the United States, has hugely increased the total percentage of cases diagnosed at a very early stage.[22-24] Taking into account the lack of diagnostic workup in SSA, we think that the proportion of metastatic patients is likely to have been underestimated. Hospital-based studies from Nigeria and South Africa have reported the proportion of metastatic PCa at diagnosis to be approximately 50%, although hospital series from Ghana have reported a proportion similar to ours.[25-27] Early-detection programs at health facilities (DRE and targeted PSA screening in higher risk patients), together with educational programs for the population explaining the benefits of early treatment and countering the idea of a cancer diagnosis equaling death, need to be evaluated and could lead to a reduction in late-stage presentation and increase the utilization of curative-treatment approaches.

There are different treatment approaches to be considered according to the risk group, life expectancy, and patients' preferences. International guidelines propose a curative approach for all symptomatic, nonmetastatic patients.[11,12] The low proportion of curative-treatment approaches in our population-based cohort was also seen in previous hospital-based studies in SSA. For example, only 0% and 12% of patients with PCa from Nigeria and South Africa, respectively, were managed with a curative-treatment approach.[25,26] At the national radiotherapy center in Ghana, 56% of patients with nonmetastatic PCa received curative radiotherapy.[27] In our subgroup of patients with nonmetastatic PCa, 82% did not receive curative therapy, and more than 1 in 3 patients received ADT only without RP or EBRT. Reasons for the low proportion of curative-intent treatment in our study may include a lack of specialized surgeons/urologists in the region to perform adequate RP.[28] Furthermore, a lack of radiotherapy machines is a major barrier to the receipt of radiotherapy in the region[18,29] (Supporting Table 6). In contrast to our findings of relatively frequent use of ADT for nonmetastatic patients, international guidelines do not recommend the use of ADT as monotherapy for symptomatic, nonmetastatic PCa because studies have shown that the addition of adequate local therapy options improves survival significantly.[11,12] Nevertheless, in a low-resource setting and in the absence of more adequate CDT, substandard care such as bilateral orchiectomy for symptomatic nonmetastatic disease is an economically viable treatment option and may extend patients' survival and improve their quality of life.[30]

As expected in our cohort with many late-stage patients and substandard treatment, we found poor OS and ASRS. A lack of therapy was the second strongest predictor for an adverse outcome after a higher ECOG PS. Both nonmetastatic and metastatic patients without CDT had a 3-fold higher risk of death in comparison with patients receiving a curative treatment or ADT only. These results should be interpreted with caution because the current study is not a randomized trial of treatment, and other unmeasured prognostic factors (eg, comorbidity) may have influenced treatment allocations. Nevertheless, the outcomes of patients receiving substandard treatments such as ADT monotherapy for nonmetastatic disease were similar to those with optimal treatment. This suggests that any treatment, even with some guideline deviation, may still have a positive effect on outcomes. Our poor OS in the nonmetastatic group differs from the results observed in the radiotherapy center of Ghana, where a 5-year OS rate of 96% was found. The availability of radiotherapy and brachytherapy, as well as a selection bias of patients sent for curative therapy in Ghana, is almost certainly the reason.[27] CONCORD-3 found 5-year net survival rates of 58.7% and 37.8% for Nigeria (Ibadan) and South Africa (Eastern Cape), respectively.[31] Studies from Western countries, which include a large number of early-stage PCa cases on account of PSA screening, show very high survival rates for all stages: for example, in the United States, the 5-year ASRS is 98%, and even patients with PCa with regional lymph node involvement have

a 5-year relative survival rate of approximately 100%.[32] This dramatic difference in comparison with our cohort is probably a result of the broad availability of radiotherapy and surgical specialists, and a lead-time bias and overdiagnosis through general PSA testing surely play a role.[33] However, the incidence rates of PCa in the Surveillance, Epidemiology, and End Results cohort have declined steadily since 2007 and are now at the same level as they were before the PSA screening era.[17,34] There are tremendous scarcities of investment and resources in the countries included in this study according to comparisons of their health care indicators with those of the United States (Supporting Table 6).

There are some limitations to our study. First, we could not retrieve detailed information for 47% of our total population-based cohort. Besides a notable reduction in the cohort size for subgroup analyses, we consider this also to be an important secondary finding of our study. Overall, we assume that the majority of patients without detailed information did not receive a diagnostic workup or treatment, so no medical record was initiated. Therefore, the true population-based picture may even have a higher proportion of unstaged and untreated patients. We also believe that some records were lost at random because records are handwritten, the misspelling of names is common, and record-keeping systems are often poor. We also may have missed treated patients who had left the registration area to seek treatment elsewhere. However, such patients probably represent a small proportion of all patients because our study areas were major cities, which usually provide the best cancer care in countries. Second, our survival data may reflect some bias. The treatment effect was likely overestimated in the Cox regression analysis of our study: 1) treatment was not assigned at random (healthier patients were selected), 2) patients with early deaths did not receive therapy, 3) the date of diagnosis (and, therefore, the start of the survival time) had substantial variation due to delays of the system, and 4) the degree of guideline adherence was assessed only during the survival time and not before the survival time had started (an immortal time bias). To reduce these effects, we excluded patients surviving less than 3 months (avoiding early deaths and ensuring the start of therapy for 60% of the patients). Consequently, the analysis linking therapy to survival started 3 months after diagnosis. Third, because of the shortage in diagnostic workup, we might have underestimated the proportion of metastatic patients, and some of them were included in the nonmetastatic group; this resulted in poorer outcomes in this group. Consequently, we might have overestimated the proportion of nonmetastatic patients, and this potentially led to worse outcomes. Fourth, we were unable to apply detailed risk stratification of patients because of the lack of staging information. In a setting without screening, patients present with more advanced symptomatic disease. Therefore, we assumed that all patients needed treatment rather than active surveillance because an early-stage presentation was unlikely.

Despite these limitations, our study has several important strengths. First, the patients included in the study were a random sample of all patients with PCa recorded in the study populations and not just those being referred to specialist centers. Second, the study involved 11 populations from different parts of SSA and reflected broad ranges of socioeconomic and health systems in the region. Third, we were able to evaluate the impact of different treatment approaches—from guideline-compliant optimal therapy to "no CDT at all"—on survival, which never could have been assessed in a prospective trial for ethical reasons.

In conclusion, in this population-based cohort of SSA patients with PCa, we found that for most patients, adequate clinical workup information for the assignment of treatment recommendations was lacking, and curative approaches were underused. To improve the completeness of PCa staging, more clinical training and technical equipment (eg, ultrasound, computed tomography scanning, magnetic resonance imaging, and biopsy tools) are needed. This study further validates guideline development by demonstrating that improving diagnostic workup is the first step toward the implementation of guidelines (eg, the new harmonized NCCN guidelines for SSA). To reduce the high proportion of late-stage presentation, efforts should be put into raising awareness of the disease and targeted PSA screening for higher risk patients together with opportunistic DRE screening by care providers. More radiation facilities and, in the long term, well-trained urological surgeons, radio-oncologists, and clinical oncologists are needed to provide curative-treatment approaches and thus ameliorate the outcomes of patients with PCa in SSA.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Tobias Paul Seraphin: Study concept and design, data collection, statistical analyses, interpretation of the analyses, drafting of the manuscript, and critical review and modification of the manuscript. **W. Yvonne Joko-Fru:** Statistical analyses and critical review and modification of the manuscript. **Lucia Hämmerl:** Study concept and design, data collection, and critical review and modification of the manuscript. **Mirko Griesel:** Study concept and design, data collection, and critical review and modification of the manuscript. **Nikolaus C. S. Mezger:** Data collection and critical review and modification of the manuscript. **Jana Feuchtner:** Data collection and critical review and modification of the manuscript. **Innocent Adoubi:** Data collection and critical review and modification of the manuscript. **Marcel D. D. Egué:** Data collection and critical review and modification of the manuscript. **Nathan Okerosi:** Data collection and critical review and modification of the manuscript. **Henry Wabinga:** Data collection and critical review and modification of the manuscript. **Rolf Hansen:** Data collection and critical review and modification of the manuscript. **Samukeliso Vuma:** Data collection and critical review and modification of the manuscript. **Cesaltina F. Lorenzoni:** Data collection and critical review and modification of the manuscript. **Bourama Coulibaly:** Data collection and critical review and modification of the manuscript. **Sévérin W. Odzebe:** Data collection and critical review and modification of the manuscript. **Nathan G. Buziba:** Data collection and critical review and modification of the manuscript. **Abreha Aynalem:** Data collection and critical review and modification of the manuscript. **Biying Liu:** Data collection and critical review and modification of the manuscript. **Daniel Medenwald:** Interpretation of the analyses and critical review and modification of the manuscript. **Rafael T. Mikolajczyk:** Interpretation of the analyses and critical review and modification of the manuscript. **Jason A. Efstathiou:** Interpretation of the analyses, drafting of the manuscript, and critical review and modification of the manuscript. **Donald M. Parkin:** Study concept and design, data collection, drafting of the manuscript, and critical review and modification of the manuscript. **Ahmedin Jemal:** Study concept and design, data collection, interpretation of the analyses, drafting of the manuscript, and critical review and modification of the manuscript. **Eva J. Kantelhardt:** Study concept and design, data collection, statistical analyses, interpretation of the analyses, drafting of the manuscript, and critical review and modification of the manuscript. All authors substantially contributed to the manuscript, revised and approved the final version, and agreed to submit it for publication.

REFERENCES

1. 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;68:394-424. doi:10.3322/caac.21492
2. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. *Lancet Oncol*. 2012;13:790-801. doi:10.1016/S1470-2045(12)70211-5
3. Seraphin TP, Joko-Fru WY, Kamaté B, et al. Rising prostate cancer incidence in sub-Saharan Africa: a trend analysis of data from the African Cancer Registry Network. *Cancer Epidemiol Biomarkers Prev*. 2021;30:158-165. doi:10.1158/1055-9965.EPI-20-1005
4. Jemal A, Bray F, Forman D, et al. Cancer burden in Africa and opportunities for prevention. *Cancer*. 2012;118:4372-4384. doi:10.1002/cncr.27410
5. Baratedi WM, Tshiamo WB, Mogobe KD, McFarland DM. Barriers to prostate cancer screening by men in sub-Saharan Africa: an integrated review. *J Nurs Scholarsh*. 2020;52:85-94. doi:10.1111/jnu.12529
6. Jalloh M, Niang L, Ndoye M, Labou I, Gueye SM. Prostate cancer in sub Saharan Africa. *J Nephrol Urol Res*. 2013;1:15-20. doi:10.12970/2310-984X.2013.01.01.4
7. DeSantis CE, Siegel RL, Sauer AG, et al. Cancer statistics for African Americans, 2016: progress and opportunities in reducing racial disparities. *CA Cancer J Clin*. 2016;66:290-308. doi:10.3322/caac.21340
8. McGinley KF, Tay KJ, Moul JW. Prostate cancer in men of African origin. *Nat Rev Urol*. 2016;13:99-107. doi:10.1038/nrurol.2015.298
9. DeRouen MC, Schupp CW, Koo J, et al. Impact of individual and neighborhood factors on disparities in prostate cancer survival. *Cancer Epidemiol*. 2018;53:1-11. doi:10.1016/j.canep.2018.01.003
10. Krimphove MJ, Cole AP, Fletcher SA, et al. Evaluation of the contribution of demographics, access to health care, treatment, and tumor characteristics to racial differences in survival of advanced prostate cancer. *Prostate Cancer Prostatic Dis*. 2019;22:125-136. doi:10.1038/s41391-018-0083-4
11. NCCN Harmonized Guidelines for Sub-Saharan Africa: Prostate Cancer. Version 2.2017. National Comprehensive Cancer Network. Accessed June 25, 2018. https://www.nccn.org/global/what-we-do/harmonized-guidelines
12. Mottet N, van den Bergh RCN, Briers E, et al. EAU-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. EAU Guidelines Office; 2018.
13. Finesse AM, Somdyala N, Chokunonga E, Parkin DM, eds. Standard Procedure Manual for Population-Based Cancer Registries in Sub Saharan Africa. 2nd ed. African Cancer Registry Network. Published 2015. Accessed November 21, 2018. https://afcrn.org/index.php/resources2/53-standard-procedure-manual/131-sop
14. Amin MB, Greene FL, Edge SB, eds. AJCC Cancer Staging Manual. 8th ed. Springer; 2017.
15. Piñeros M, Parkin DM, Ward K, et al. Essential TNM: a registry tool to reduce gaps in cancer staging information. *Lancet Oncol*. 2019;20:e103-e111. doi:10.1016/S1470-2045(18)30897-0
16. Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. *Eur J Cancer*. 2004;40:2307-2316. doi:10.1016/j.ejca.2004.07.002
17. Noone A, Howlader N, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2015. National Cancer Institute; 2018.
18. Abdel-Wahab M, Bourque J-M, Pynda Y, et al. Status of radiotherapy resources in Africa: an International Atomic Energy Agency analysis. *Lancet Oncol*. 2013;14:e168-e175. doi:10.1016/S1470-2045(12)70532-6
19. Kanavos P. The rising burden of cancer in the developing world. *Ann Oncol*. 2006;17(suppl 8):viii15-viii23. doi:10.1093/annonc/mdl983
20. Prostate Cancer Early Detection: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Version 2.2018. National Comprehensive Cancer Network. Accessed December 16, 2018. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1459
21. Potosky AL. The role of increasing detection in the rising incidence of prostate cancer. *JAMA*. 1995;273:548. doi:10.1001/jama.1995.03520310046028
22. Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012;157:120-134. doi:10.7326/0003-4819-157-2-201207170-00459
23. Brawley OW. Trends in prostate cancer in the United States. *J Natl Cancer Inst Monogr*. 2012;2012:152-156. doi:10.1093/jncimonographs/lgs035
24. Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. *JAMA*. 2009;302:1685-1692. doi:10.1001/jama.2009.1498
25. Badmus TA, Adesunkanmi A-RK, Yusuf BM, et al. Burden of prostate cancer in southwestern Nigeria. *Urology*. 2010;76:412-416. doi:10.1016/j.urology.2010.03.020
26. Heyns CF, Fisher M, Lecuona A, van der Merwe A. Prostate cancer among different racial groups in the Western Cape: presenting features and management. *S Afr Med J*. 2011;101:267-270. doi:10.7196/SAMJ.4420

27. Asamoah FA, Yarney J, Awasthi S, et al. Contemporary radiation treatment of prostate cancer in Africa: a Ghanaian experience. *J Glob Oncol*. 2018;4:1-13. doi:10.1200/JGO.17.00234
28. Meara JG, Leather AJM, Hagander L, et al. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. *Lancet*. 2015;386:569-624. doi:10.1016/S0140-6736(15)60160-X
29. Efstathiou JA, Heunis M, Karumekayi T, et al. Establishing and delivering quality radiation therapy in resource-constrained settings: the story of Botswana. *J Clin Oncol*. 2016;34:27-35. doi:10.1200/JCO.2015.62.8412
30. Kingham TP, Alatise OI, Vanderpuye V, et al. Treatment of cancer in sub-Saharan Africa. *Lancet Oncol*. 2013;14:e158-e167. doi:10.1016/S1470-2045(12)70472-2
31. 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. *Lancet*. 2018;391:1023-1075. doi:10.1016/S0140-6736(17)33326-3
32. American Cancer Society. Cancer Facts & Figures 2018. American Cancer Society; 2018.
33. Barry MJ. Screening for prostate cancer—the controversy that refuses to die. *N Engl J Med*. 2009;360:1351-1354. doi:10.1056/NEJMe0901166
34. Jemal A, Fedewa SA, Ma J, et al. Prostate cancer incidence and PSA testing patterns in relation to USPSTF screening recommendations. *JAMA*. 2015;314:2054-2061. doi:10.1001/jama.2015.14905

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Rising Prostate Cancer Incidence in Sub-Saharan Africa: A Trend Analysis of Data from the African Cancer Registry Network

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ABSTRACT

Background: Prostate cancer is the leading cancer in men in sub-Saharan Africa (SSA) regarding incidence and mortality. Published data from a few registries in SSA suggest that the rates are still rising, but there is little comprehensive information on the time trends of prostate cancer incidence.

Methods: We analyzed registry data on 13,170 incident prostate cancer cases in men aged 40 years or above, from 12 population-based cancer registries in 11 SSA countries, with at least a 10-year time span of comparable data.

Results: We observed an increase in cumulative risks (CR) and age-standardized incidence rates (ASR) over time in all registries (statistically significant in all but one). The highest values of CR were found in Seychelles and Harare (Zimbabwe). The highest annual increase in the ASRs was seen in Seychelles and Eastern Cape (South Africa), whereas the lowest was seen in Mauritius. We mainly found a steady increase in incidence with age and during successive periods.

Conclusions: This analysis reveals that prostate cancer incidence rates are rising in many populations in SSA—often very rapidly—which is in contrast to recent observations worldwide. We acknowledge that the reasons are multifactorial and largely remain unclear, but believe that they are primarily associated with improvements in health care systems, for example, a broader use of prostate-specific antigen testing.

Impact: This study is the first to compare population-level data on time trends of prostate cancer incidence between multiple countries of SSA, presenting the different rates of increase in 11 of them.

Introduction

With an estimated 1.3 million new cases and 359,000 associated deaths, prostate cancer was the second most common cancer in men worldwide and the fifth leading cause of cancer-related death in 2018 (1).

Although prostate cancer incidence rates have been on the rise worldwide during the last decades, it has been reported that the trends have started to stabilize or even to decline in many countries in recent years (2, 3). This observation has been described to be more pronounced in high-income countries and is associated with changes in the recommendations concerning prostate-specific antigen (PSA) screening of asymptomatic men, and a subsequent decrease of its usage. Although men of African descent have been shown to be disproportionally affected by prostate cancer, and that it is the leading cause of cancer (and cancer-related deaths) among sub-Saharan African men, there is little information on the time trends of prostate cancer incidence in the region (4, 5). In Kampala (Uganda) Wabinga and colleagues (6) reported increasing trends for the period of 1991–2010 with an average annual percentage change (AAPC) of 5.2% (although they may have stabilized in the period 2008–2012; ref. 3). An AAPC of 6.4% has been observed in Harare (Zimbabwe; 1991–2010; ref. 7) and there has been a 2.5-fold increase in Maputo (Mozambique) in the period of 1956–2017 (8).

More population-based evidence is needed, to get a better insight into the burden of the disease in this region, to examine changes in incidence rates, anticipate future problems for local health care systems and possibly even help to better understand this disease, which affects so many men worldwide, but for which the etiology is still relatively obscure (9).

In this analysis, we describe and compare time trends in prostate cancer incidence rates for 12 populations from eleven sub-Saharan African countries, by examining data from population-based cancer registries of the African Cancer Registry Network (AFCRN).

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Materials and Methods

Data inputs

The African Cancer Registry Network (AFCRN; https://afcrn.org/) is the regional hub for cancer registration in sub-Saharan Africa (SSA) of the International Agency for Research on Cancer's (IARC) Global Initiative for Cancer Registry Development in Low- and Middle-Income Countries (GICR). The project's aim is to improve cancer surveillance in the region and thereby provide a solid basis for the planning and evaluation of local cancer control programs.

At the time of our study, 32 population-based cancer registries were members of the network. According to the network's membership criteria, a population-based cancer registry must achieve at least 70% coverage of their target population within 3 years of admission.

All registries collect data on incident cancer cases within their catchment population, usually by active methods. They enter the data electronically to the AFCRN's database, by using IARC's CanReg-5 software (10). Cancer site and histology are coded according to the International Classification of Diseases for Oncology (ICD-O) following the AFCRN's Standard Procedure Manual (11, 12).

We included 9 registries with at least 10 years of continuous data, during which period there appeared to have been no obvious changes in completeness of registration (13).

For Eastern Africa: Nairobi (Kenya, 2003–2014), Blantyre (Malawi, 1995–2009), Mauritius (2001–2016), Seychelles (2005–2018), Kampala (Uganda, 1991–2015), and Harare (Zimbabwe, 1990–2016).

For Southern Africa: Eastern Cape (South Africa, 1998–2015).

For Western Africa: Bamako (Mali, 1999–2018) and Ibadan (Nigeria, 1996–2010).

We also reviewed changes in incidence from 3 registries with recently published incidence rates, for which comparable data from older publications were available: Abidjan (Côte d'Ivoire, 1995–1998, 2012–2015); Bulawayo (Zimbabwe, 1963–1972, 2011–2015) and Maputo (Mozambique, 1956–1960, 2015–2017).

All other AFCRN registries did not meet our inclusion criteria.

The registries of Mauritius and the Seychelles cover national populations, that of Eastern Cape in South Africa a rural population, whereas the other registries all cover urban populations.

From January to March 2020, we extracted completely anonymized data on incident cases of prostate cancer (International Classification of Diseases, ICD-10 C61) from the AFCRN's database.

Annual estimates of the population-at-risk, by 5-year age group, for each registry area and time period were prepared, using national census data, and assuming a logarithmic growth (within age groups) between the censuses. For the period after the most recent census, we assumed a linear growth adding the average annual increase in numbers of cases (by sex and age group) for the years between the preceding censuses.

For Bulawayo (Zimbabwe), we included data only on the black (African) population, because historic data (for the 1960s) were available only for this racial group.

For a few registries, there were years with a known reduction of registration activities due to political or socio-economic circumstances. Those were the years 2015 for Bamako (Mali) 2007–2009 for Harare (Zimbabwe), and 1999 for Ibadan (Nigeria). We excluded these years from our analyses.

Data analysis

We used RStudio Version 1.2.5033 for data analyses (14). We estimated the proportions of prostate cancer cases registered only on the basis of information on a death certificate (death certificate only, DCO), on the basis of a histological or cytological examination (morphologically verified, MV), or on the basis of clinical examination/imaging with and without the additional evidence of an elevated PSA. These proportions can be used to indicate the data quality of a population-based cancer registry (15).

We included all incident prostate cancer cases (regardless of their basis of diagnosis, i.e., MV, DCO, or clinical) and grouped them by year and registry in 5-year age groups. Carcinoma of the prostate is very rare before age 40. Although there were around 0.7% of such cases in the datasets, they were omitted from analyses, because of concerns that they represented possible errors in coding (of site, or age). Because the population at risk data were often truncated at age group "75+," we also truncated our case grouping at age group "75+." We redistributed cases with missing age into the different age groups according to the distribution of the known cases.

We calculated age-specific and age-standardized incidence rates (ASR), together with cumulative risk (CR; 0–74), per registry and year. We used the world standard population to obtain the ASRs (16). We calculated the same parameters for three approximately even time periods per registry.

We examined temporal trends in annual ASR by using the Joinpoint Regression Software (17, 18). The maximum possible joinpoints in the model was set at three. For registries without continuous registration activities, we set the maximum possible joinpoints at zero. We report the AAPC over the whole time of examination, together with the 95% confidence intervals for each registry.

We present the trends of the annual ASRs graphically as centered 3-year moving averages.

We performed an exploratory Age-Period-Cohort analysis for Kampala (Uganda) and Harare (Zimbabwe), each of which contributed to four successive volumes of Cancer Incidence in Five Continents (CI5: http://ci5.iarc.fr/Default.aspx). For this analysis we used the "Rcan"-package, Version 1.3.81, for "R" from Laversanne and colleagues (19). Because there were very few cases in the age groups "40–44" and "45–49," resulting in very unstable rates, these age groups were omitted from the analyses.

Ethics

The AFCRN research committee approved this study (July 2019), as well as the respective registries. We conducted the study in accordance to the Declaration of Helsinki. The study used routinely collected, anonymized data, therefore no special ethical approval was needed.

Results

In **Fig. 1**, the registries (white circles) and their corresponding sub-Saharan African countries are highlighted. The table shows the national population (males) in 2010 and our estimates of the population of males in the areas covered by the registries, as a total, and a percentage of the national population (20).

The coverage of the national population for urban, non-national registries ranged from 1.7% in Ibadan (Nigeria) to 18.8% in Abidjan (Côte d'Ivoire). For the single rural registry of Eastern Cape (South Africa) it was around 2 %. Mauritius and Seychelles both have national registries.

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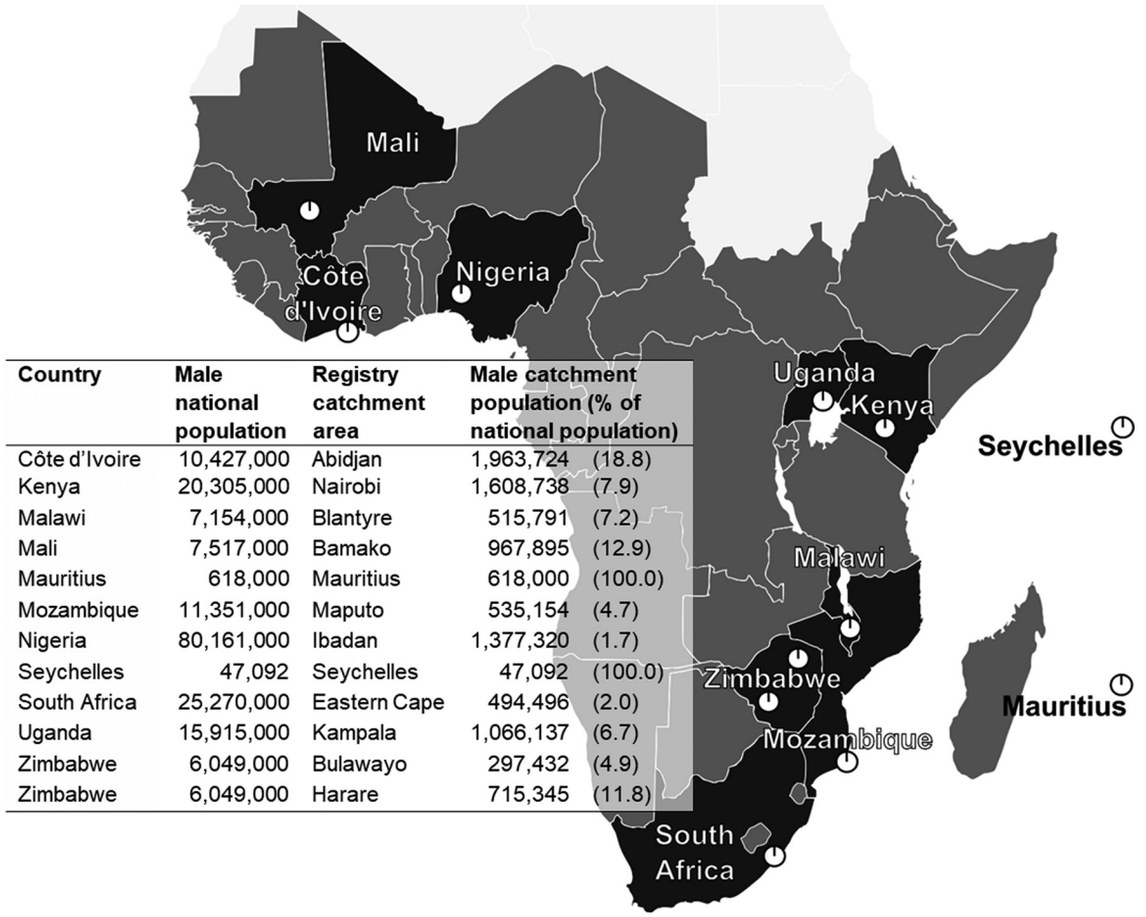

Country	Male national population	Registry catchment area	Male catchment population (% of national population)
Côte d'Ivoire	10,427,000	Abidjan	1,963,724 (18.8)
Kenya	20,305,000	Nairobi	1,608,738 (7.9)
Malawi	7,154,000	Blantyre	515,791 (7.2)
Mali	7,517,000	Bamako	967,895 (12.9)
Mauritius	618,000	Mauritius	618,000 (100.0)
Mozambique	11,351,000	Maputo	535,154 (4.7)
Nigeria	80,161,000	Ibadan	1,377,320 (1.7)
Seychelles	47,092	Seychelles	47,092 (100.0)
South Africa	25,270,000	Eastern Cape	494,496 (2.0)
Uganda	15,915,000	Kampala	1,066,137 (6.7)
Zimbabwe	6,049,000	Bulawayo	297,432 (4.9)
Zimbabwe	6,049,000	Harare	715,345 (11.8)

Figure 1.
Map of sub-Sahara Africa (Wikimedia Commons, 2019) and population of included registries. Included countries are in black; white circles indicate locations of registries; population estimates for the year 2010 are shown.

Table 1. Description of included registries.

Country	Registry catchment area	Time period	Number of cases	Basis of diagnosis[b]			Mean (median) age in years
				MV (%)	Clinical (%)	DCO (%)	
Côte d'Ivoire	Abidjan	1995–1998	193	79.3	20.7	0.0	68.1 (69)
		2012–2015	877	69.7	24.0	6.3	67.9 (68)
Kenya	Nairobi	2003–2014	1,655	73.6	22.2	4.2	68.3 (68)
Malawi	Blantyre	1995–2009	303	46.2	51.5	2.0	66.5 (66)
Mali	Bamako	1987–2017[a]	902	72.4	22.1	2.4	70.3 (70)
Mauritius	Mauritius	2001–2016	1,357	94.7	4.2	0.9	70.9 (72)
Mozambique	Maputo	1956–1960	10	n/a	n/a	n/a	n/a (n/a)
		2015–2017	342	80.2	5.3	14.5	67.8 (69)
Nigeria	Ibadan	1996–2010[a]	1,100	80.3	17.8	0.4	68.3 (69)
Seychelles	Seychelles	2005–2018	399	89.5	6.8	3.7	70.5 (71)
South Africa	Eastern Cape	1998–2017	735	59.0	41.0	0.0	70.8 (71)
Uganda	Kampala	1991–2015	1,749	51.9	46.8	1.3	69.9 (70)
Zimbabwe	Bulawayo	1963–1972	37	78	22	0.0	63.9 (62)
		2011–2015	359	54.0	37.4	8.6	74.1 (74)
	Harare	1990–2015[a]	3,162	69.2	16.5	14.3	72.0 (72)

Abbreviations: DCO, death certificate only; MV, morphologically verified.
[a]Some years excluded due to insufficient registration activities: Mali, Bamako: 2015; Nigeria, Ibadan: 1999; Zimbabwe, Harare: 2007–2009.
[b]In some registries, there were few cases with unknown basis of diagnosis; in those, the percentages do not sum up to 100%.

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Table 1 shows the registries (by sub-Saharan African region and country), as well as the time periods included in the analysis and corresponding numbers of cases. A total of 13,170 cases ages 40 or more were registered during a total of 24,300,079 person-years at risk [excluding the historic data from Maputo (Mozambique), because person-years at risk were not available].

The proportion of microscopically verified (MV%) prostate cancer cases ranged from 94.7% in Mauritius to 46.2% in Blantyre (Malawi).

For Harare, Zimbabwe and the recent period of Maputo (Mozambique), the proportion of DCO cases was around 15%, whereas in all other cases the proportion was below 8%.

Mean age at diagnosis ranged from 66.5 years in Blantyre (Malawi) to 72.0 years in Harare [Zimbabwe; although in Bulawayo (Zimbabwe), the mean age increased from 63.9 in the early period to 74.1 in the more recent period]. Excluding the few cases recorded as being <40 years of age, the mean age at diagnosis for all 12 populations was 70.1 years.

Table 2 shows age standardized incidence rates, as well as the number of cases, in three time periods for each registry with continuous data, as well as the AAPC of the ASRs over the whole period studied. For the registries with data from two (discontinuous) time periods, we show the number of cases and ASRs in each, and the estimated AAPC between them. CRs and ASRs varied widely between and within sub-Saharan African regions, but had increased over time in all registries (not statistically significant in Ibadan, Nigeria).

We observed the highest values of CR in Seychelles and Harare (Zimbabwe), where 1 in 9 and 1 in 10 men would develop prostate cancer by the age of 74 under exclusion of competing risks of death. The lowest CRs in the most recent periods are seen in Ibadan (Nigeria) and Mauritius.

The annual increase in the ASRs (AAPC) was highest in Seychelles and Eastern Cape (South Africa), at around 10% per year, and the lowest in Bulawayo (Zimbabwe) and Mauritius, as well as in Maputo (Mozambique).

Table 2. Cumulative risks, age-standardized incidence rates by registry and period of time, together with the average annual percentage change.

Country	Registry catchment area	Time period	Number of cases	Cumulative risk in %, 0–74 years (95% CI)	ASR (95% CI), cases per 100,000 person-years	AAPC of ASR (95% CI)
Côte d'Ivoire	Abidjan	1995–1998	193	2.8 (2.3–3.4)	21.1 (17.9–24.2)	3.8[a] (−0.3 to 8.1)
		2012–2015	877	4.4 (4.0–4.8)	35.6 (33.1–38.1)	
Kenya	Nairobi	2003–2006	363	4.0 (3.4–4.6)	32.6 (29.0–36.2)	4.4 (1.1–7.9)
		2007–2010	518	5.2 (4.6–5.9)	42.6 (38.7–46.5)	
		2011–2014	774	5.9 (5.3–6.5)	49.9 (46.2–53.6)	
Malawi	Blantyre	1995–1999	51	1.0 (0.6–1.3)	7.6 (5.5–9.8)	8.1 (3.2–13.2)
		2000–2004	120	2.2 (1.7–2.7)	16.8 (13.7–19.8)	
		2005–2009	132	2.4 (1.9–2.9)	17.1 (14.1–20.1)	
Mali	Bamako[b]	1987–1997	76	0.7 (0.5–0.9)	5.3 (4.1–6.6)	6.7 (4.9–8.5)
		1998–2007	201	1.1 (0.9–1.3)	9.6 (8.2–10.9)	
		2008–2017	625	2.3 (2.0–2.5)	19.0 (17.5–20.5)	
Mauritius	Mauritius	2001–2006	365	1.4 (1.2–1.6)	12.6 (11.3–13.9)	2.0 (0.2–3.8)
		2007–2011	403	1.5 (1.3–1.7)	13.2 (11.9–14.5)	
		2012–2016	589	1.8 (1.6–2.0)	15.5 (14.3–16.8)	
Mozambique	Maputo	1956–1960	10	n/a	9.2 (n/a–n/a)	2.6[a] (1.5–3.8)
		2015–2017	342	5.3 (4.6–6.1)	42.1 (37.6–46.6)	
Nigeria	Ibadan[b]	1996–2001	194	1.4 (1.1–1.6)	9.4 (8.0–10.7)	2.5 (−0.2 to 5.4)
		2002–2005	398	1.8 (1.5–2.0)	12.6 (11.3–13.9)	
		2006–2010	508	1.7 (1.5–1.9)	12.9 (11.7–14.0)	
Seychelles	Seychelles	2005–2009	67	4.6 (3.2–6.1)	38.0 (28.7–47.4)	10.3 (6.5–14.3)
		2010–2013	105	6.8 (4.9–8.8)	61.0 (49.2–72.8)	
		2014–2018	227	11.4 (9.3–13.4)	97.5 (84.6–110.3)	
South Africa	Eastern Cape	1998–2004	110	0.6 (0.5–0.8)	5.1 (4.1–6.0)	9.2 (6.7–11.8)
		2005–2010	185	0.9 (0.8–1.1)	8.9 (7.6–10.3)	
		2011–2017	440	2.1 (1.9–2.4)	17.4 (15.7–19.0)	
Uganda	Kampala	1991–1999	351	4.3 (3.7–4.9)	33.2 (29.7–36.8)	2.8 (1.7–4.0)
		2000–2007	528	5.5 (4.9–6.2)	41.9 (38.2–45.7)	
		2008–2015	870	6.7 (6–7.3)	53.4 (49.7–57)	
Zimbabwe	Bulawayo	1963–1972	37	1.3 (0.7–1.9)	18.8 (11.9–25.6)	2.3[a] (0.1–4.7)
		2011–2015	359	2.6 (2.1–3.1)	37.4 (33.3–41.5)	
	Harare[b]	1990–1998	696	4.5 (4.1–5.0)	40.3 (37.2–43.4)	5.0 (4.2–5.8)
		1999–2006	1,021	6.7 (6.2–7.3)	60.9 (57.1–64.6)	
		2010–2015	1,445	10.0 (9.2–10.8)	97.1 (92.1–102.2)	

Abbreviations: AAPC, average annual percentage change; ASR, age-standardized incidence rate; CI, confidence interval.

[a]Large time span without data between periods of observation.

[b]Some years excluded due to insufficient registration activities: Mali, Bamako: 2015; Nigeria, Ibadan: 1999; Zimbabwe, Harare: 2007–2009.

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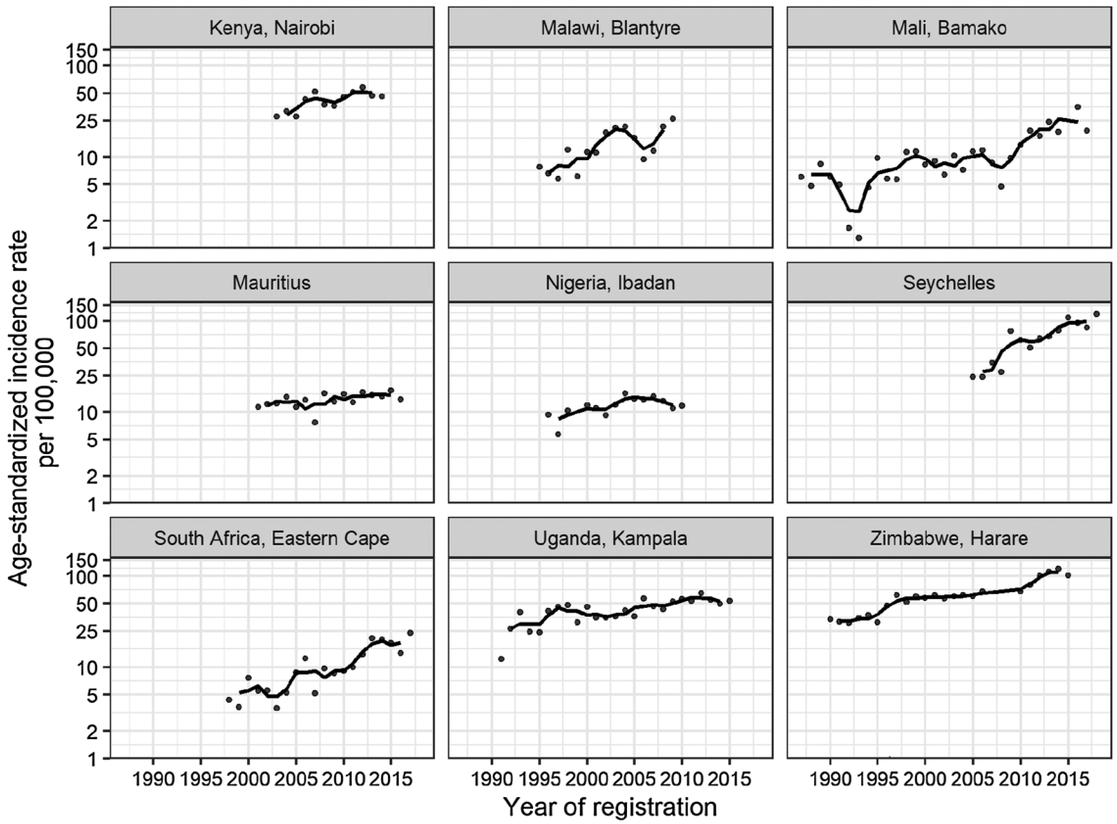

Figure 2.
Age-standardized incidence rate by registry and year of registration for registries with continuous data: Trend lines show 3-year moving averages, dots represent observed values.

Figure 2 shows annual ASRs in each registry, as well as a line representing three-year moving averages. We observe increasing incidence rates in all registries, with variation in the magnitude of the slopes between the registries.

The joinpoint analysis revealed that the trends are well explained for all registries by the simplest model without any joinpoints (see AAPCs in **Table 2** and Supplementary Fig. S1A and S1B).

Figure 3 depicts the age-specific incidence rates by registry for the same periods as in **Table 2**. Because case numbers in age groups below 50 years were very low, the corresponding rates are omitted from the graphs. Bulawayo (Zimbabwe) and Maputo (Mozambique) are also excluded because of the very sparse data in the older period.

We observe a steady increase in incidence with age, and the highest incidence rates in the oldest age group (with a few exceptions). For, Blantyre (Malawi), Bamako (Mali) and for the earliest periods in Ibadan (Nigeria), and Seychelles there are fluctuations in incidence. As well as being the result of small numbers [especially in younger age groups, and smaller registries (Blantyre (Malawi), Seychelles)], this relates to digit preference in given age of older men, with an excess of cases ages exactly 50, 60, and 70 (and corresponding higher rates in the age groups containing these digits; see Supplementary Fig. S2)

For all registries, these trends show an increase in age-specific incidence rates during these successive time periods, with, in general, a rather greater increase in older age groups.

Figure 4 shows trends of age-specific incidence rates by birth cohort and period of diagnosis in Harare (**Fig. 4A**) and Kampala (**Fig. 4B**). There is an increase in the age-specific incidence rates in both according to period of diagnosis and period of birth.

In Harare, the rate of increase is greater in the older age groups (as seen also in **Fig. 3**). In Kampala, there is more fluctuation in successive cohorts and the picture is not as clear as for Harare. For the most recent cohort of birth year and diagnosis (2011–2015), there seems to be a small decline in all age groups (except for the youngest).

Discussion

Prostate cancer incidence rates have been increasing in all 12 sub-Saharan African populations during the periods of observation [although the estimated annual 2.5% increase in Ibadan (Nigeria) was non-significant]. CR, age-standardized incidence rates, and the annual average percentage change varied up to 7-fold between the populations. The highest CRs and ASRs in recent periods were observed in the Seychelles and Harare (Zimbabwe). The lowest values were reported from Ibadan (Nigeria) and Mauritius. The Seychelles (2005–2018) and the rural area of Eastern Cape province in South Africa (1998–2017) have seen the steepest increases in the annual ASRs with an average annual increase of around 10%.

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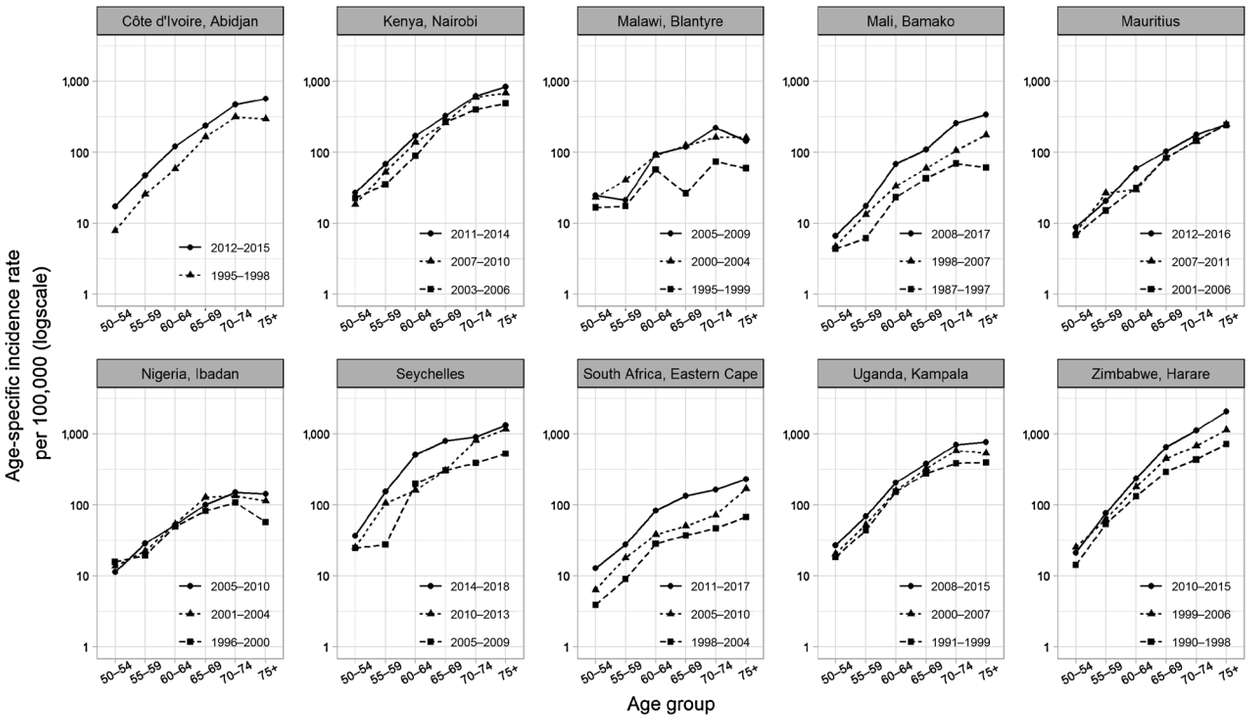

Figure 3.
Prostate cancer age-specific incidence rates by time period and registry.

In a recent international study of incidence rates in 44 countries (and mortality in 76), prostate cancer rates were found to have stabilized in most, and decreased in a few, since 2008–2012 (3). This is in contrast with our findings in SSA, where incidence has been rising, with decreases seen only in the most recent observation years of Ibadan (Nigeria; **Fig. 2**) and Kampala (Uganda; **Figs. 2** and **4**). The only population in common to the two studies was Kampala, where Culp and colleagues (3) observed stabilizing rates in the years 2008–2012 (non-significant AAPC), but a significant single trend with an annual percentage change of 1.8% during the period 1993–2012 (close to the single trend we found for the years 1991–2015).

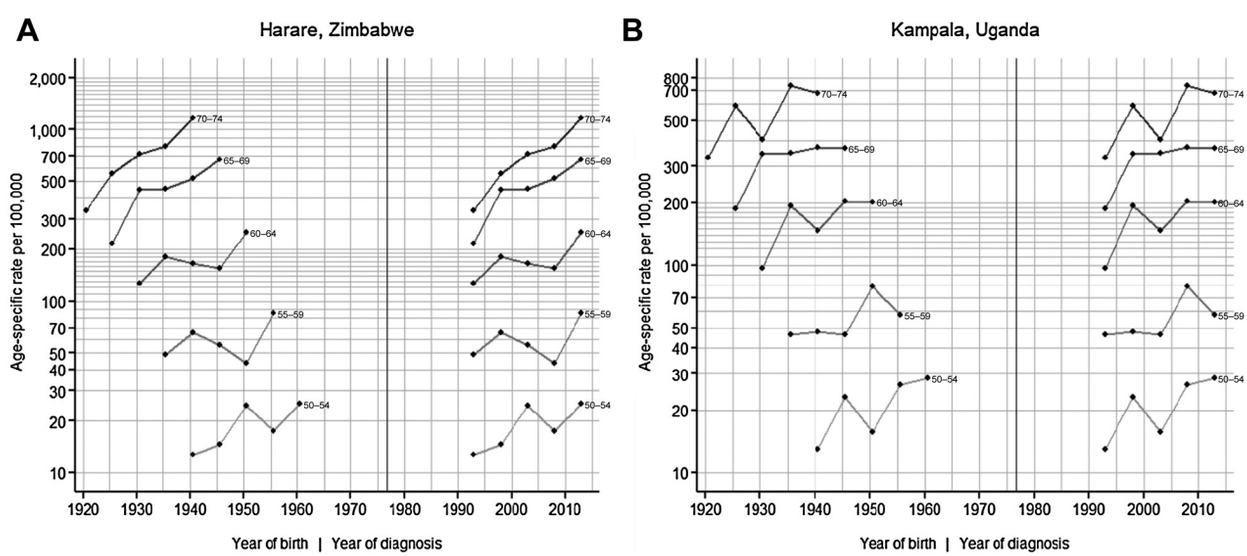

Figure 4.
Prostate cancer age-specific incidence rates by birth cohort and period of diagnosis in Harare (Zimbabwe; **A**) and Kampala (Uganda; **B**).

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Studies in migrants have suggested that environmental factors may affect prostate cancer risk. For example, in Japanese migrants to the United States and in particular in their descendants, an increase in their originally low risk of prostate cancer has been observed, leading to research on environmental or exogenous (lifestyle) factors, thought to be able to influence the prostate cancer risk (21). These factors comprise among others metabolic syndrome, obesity, body size, and dietary factors. However, apart from obesity and body size, the evidence is still poor and controversial (22–24).

Furthermore, the risks associated with these putative risk factors are not large, and it is unlikely that there has been a change in their prevalence large enough to account for such extensive increases in incidence. Rather, we believe that our results most likely reflect changes in the health care systems, linked to increasing socioeconomic development. Internationally, incidence of prostate cancer is higher in countries with higher socioeconomic development (25). In our study, the Seychelles has the highest human development index (HDI), followed by Mauritius (26). Although in the Seychelles, we observe correspondingly high ASRs of prostate cancer in the most recent period (97.5 per 100,000 men-years), Mauritius does not fulfil this criteria (15.5 per 100,000 men-years) and has one of the lowest ASRs of all countries under observation. We suggest that this might be due to a population of predominantly non-African ancestry, resulting in ASRs comparable with Asian countries with similar HDI like Malaysia or Thailand (1, 26). The biggest influence on reported incidence of prostate cancer has been the introduction of early detection programs through PSA testing in asymptomatic men (27, 28). However, in SSA, there has been no widespread general PSA screening activity. This is consistent with our observations that there have been no abrupt increases and successive declines, as for example, seen in the US, Canada, Australia or Sweden in the PSA screening era (2, 27, 29). Nevertheless, an *ad hoc* survey of AFCRN populations has confirmed that the PSA test is available in laboratories throughout Africa, and is widely used for diagnostic purposes, although there is no information on the trends in numbers of tests performed over time. It seems likely that at least some of the increase in incidence represents better detection (and diagnosis) of prostate cancers in middle-aged and elderly men with urinary symptoms.

In addition, there might also be an increase in the availability and consequently in the performance of trans-urethral resections of the prostate to treat urinary retention suspected to be caused by benign prostatic hyperplasia. This could lead to more incidental carcinomas and rising incidence rates, as has been described by Potosky and colleagues (30) for the United States in the pre-PSA screening era, during the years 1973 to 1986.

Limitations

The value of population-based cancer incidence data mainly relies on the accuracy of two parameters: First, the success of the registration activities, especially the completeness (and accuracy) of ascertainment of cancers in the targeted population. And second, the quality of the related population censuses and the derived population estimates.

This leads to the limitations of our descriptive study. Functioning cancer surveillance needs a relatively stable political and socioeconomic environment. Guaranteeing high levels of completeness and constancy in registration activities over a longer period of time are accordingly challenging in low-resource settings. For example, for Harare (Zimbabwe), there have been registration problems reported in the 2007–2009 period (7). We initially allowed for this by only including 12 of the 32 AFCRN registries, with the presumably most consistent data on prostate cancer incident cases reflected in relatively constant annual case registrations, as well as the coherence of indicators like MV% and DCO%. Although the rate of MV% varies widely from Blantyre (Malawi) with 46.2% (urban) to Mauritius (national) with 94.7%, this does not necessarily reflect any incompleteness—indeed, inclusion of clinically diagnosed (and DCO) cases is a means to maximize completeness (13), rather it reflects different access to, and use of, diagnostic services such as pathology and imaging (CT scans and MRI) in the registry areas.

We excluded years with a clear reduction in registration activities in the corresponding registries from our analyses. Likewise, we had to exclude recent data from Ibadan (Nigeria); because the most recent population census was performed in the year 2006 there has been some discussion about its accuracy, and post-censal estimates are even less secure.

Conclusions

This registry data analysis presents trends in overall and age-specific prostate cancer incidence rates in 12 populations of SSA. Overall, we observe rising trends, and believe that, although the reasons are multifactorial, they are primarily due to improvements in the healthcare system with, among others, a broader use of PSA testing. Taking account of the fact that cancer is a growing health problem in SSA and prostate cancer is the top cancer in men, in both incidence and mortality, more studies on the patterns of diagnosis, including the prevalence of PSA testing for diagnostic or early detection purposes, on genomic and environmental factors, as well as the maintenance and improvement of population-based cancer registration, would help to better understand the reasons behind this observation and might eventually enlighten some important questions on the etiology of this disease.

Authors' Disclosures

No disclosures were reported.

Disclaimer

The funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the article; or decision to submit the article for publication.

Authors' Contributions

T.P. Seraphin: Conceptualization, data curation, software, formal analysis, validation, investigation, visualization, methodology, writing–original draft, writing–review and editing. **W.Y. Joko-Fru:** Conceptualization, data curation, software, formal analysis, investigation, writing–review and editing. **B. Kamaté:** Resources, investigation, writing–review and editing. **E. Chokunonga:** Resources, investigation, writing–review and editing. **H. Wabinga:** Resources, investigation, writing–review and editing. **N.I.M. Somdyala:** Resources, investigation, writing–review and editing. **S.S. Manraj:** Resources, investigation, writing–review and editing. **O.J. Ogunbiyi:** Resources, investigation, writing–review and editing. **C.P. Dzamalala:** Resources, investigation, writing–review and editing. **A. Finesse:** Resources, investigation, writing–review and editing. **A. Korir:** Resources, investigation, writing–review and editing. **G. N'Da:** Resources, investigation, writing–review and editing. **C. Lorenzoni:** Resources, investigation, writing–review and editing. **B. Liu:** Data curation, project administration. **E.J. Kantelhardt:** Formal analysis, supervision, funding acquisition, validation, writing–original draft, project administration, writing–review and editing. **D.M. Parkin:** Conceptualization, resources, data curation, formal analysis, supervision, validation, methodology, writing–original draft, project administration, writing–review and editing.

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References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Global Cancer Observatory: cancer today. Lyon (France): International Agency for Research on Cancer; 2018 [cited 2020 Aug 4]. Available from: https://gco.iarc.fr/Today.
2. Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O, et al. International variation in prostate cancer incidence and mortality rates. Eur Urol 2012;61:1079–92.
3. Culp MBB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent global patterns in prostate cancer incidence and mortality rates. Eur Urol 2020;77:38–52.
4. Odedina FT, Akinremi TO, Chinegwundoh F, Roberts R, Yu D, Reams RR, et al. Prostate cancer disparities in Black men of African descent: a comparative literature review of prostate cancer burden among Black men in the United States, Caribbean, United Kingdom, and West Africa. Infect Agent Cancer 2009;4:1–8.
5. 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;68:394–424.
6. Wabinga HR, Nambooze S, Amulen PM, Okello C, Mbus L, Parkin DM. Trends in the incidence of cancer in Kampala, Uganda 1991–2010. Int J Cancer 2014;135:432–9.
7. Chokunonga E, Borok MZ, Chirenje ZM, Nyakabau AM, Parkin DM. Trends in the incidence of cancer in the black population of Harare, Zimbabwe 1991–2010. Int J Cancer 2013;133:721–9.
8. Lorenzoni CF, Ferro J, Carrilho C, Colombet M, Parkin DM. Cancer in Mozambique: results from two population based cancer registries. Int J Cancer 2020;14:1629–37.
9. Hayes VM, Bornman MSR. Prostate cancer in Southern Africa: does Africa hold untapped potential to add value to the current understanding of a common disease? J Glob Oncol 2018;4:1–7.
10. Ervik MJ. CanReg 5. Lyon (France): International Agency for Research on Cancer; 2019. Available from: http://www.iacr.com.fr/index.php?option=com_content&view= article&id=9:canreg5&catid=68&Itemid=445.
11. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, et al., editors. Basis of diagnosis. Int Classif Dis Oncol (ICD-O)- 3rd Ed., 1st Revis., 3rd ed. Geneva (Switzerland): World Health Organization; 2013:27. Available from: https://apps.who.int/iris/handle/10665/96612.
12. Finesse AM, Somdyala N, Chokunonga E, Parkin DM, editors. Standard procedure manual for population-based cancer registries in sub Saharan Africa. 3rd ed. Oxford (UK): African Cancer Registry Network; 2015. Available from: https://afcrn.org/index.php/resources2/53-standard-procedure-manual/131-sop.
13. Parkin DM, Bray F. Evaluation of data quality in the cancer registry: principles and methods Part II. Completeness. Eur J Cancer 2009;45:756–64.
14. RStudio Team. RStudio: Integrated Development for R. Boston: RStudio, Inc.; 2019. Available from: http://www.rstudio.com/.
15. 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;45:747–55.
16. Bray F, Colombet M, Mery L, Piñeros M, Znaor A, Zanetti R, et al. Cancer incidence in five continents, vol. XI (electronic version). Lyon (France): International Agency for Research on Cancer; 2017.
17. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;19:335–51.
18. National Cancer Institute. Joinpoint Regression Program. Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute; 2020. Available from: https://surveillance.cancer.gov/joinpoint/download.
19. Laversanne M, Vignat J. Rcan: Cancer Registry Data Analysis and Visualisation. Cancer Surveillance Unit, International Agency for Research on Cancer; 2019. Available from: https://cran.r-project.org/package=Rcan%0A.
20. UN. World Population Prospects 2019, Online Edition. Rev. 1. United Nations, Department of Economic and Social Affairs, Population Division (2019); 2019 [cited 2020 Apr 2]. Available from: https://population.un.org/wpp/Download/Standard/Population/.
21. Shimizu H, Ross R, Bernstein L, Yatani R, Henderson B, Mack T. Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. Br J Cancer 1991;63:963–6.
22. Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Parretta E, et al. Effect of metabolic syndrome and its components on prostate cancer risk: meta-analysis. J Endocrinol Invest 2013;36:132–9.
23. Eylert MF, Persad R. Management of Prostate Cancer. In: Bolla M, van Poppel H, editors. Br. J. Hosp. Med. Cham (Switzerland): Springer International Publishing; 2017. Available from: http://link.springer.com/10.1007/978-3-319-42769-0.
24. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and prostate cancer. London: WCRF; 2018. Available from: dietandcancerreport.org.
25. Wong MCS, Goggins WB, Wang HHX, Fung FDH, Leung C, Wong SYS, et al. Global incidence and mortality for prostate cancer: analysis of temporal patterns and trends in 36 countries. Eur Urol 2016;70:862–74.
26. United Nations Development Programme. Human Development Report 2019: beyond income, beyond Averages, beyond today - inequalities in human development in the 21st century. New York: United Nations; 2019.
27. Potosky AL, Miller BA, Albertsen PC, Kramer BS. The role of increasing detection in the rising incidence of prostate cancer. JAMA 1995;273:548–52.
28. Hankey BF, Feuer EJ, Clegg LX, Hayes RB, Legler JM, Prorok PC, et al. Cancer surveillance series: interpreting trends in prostate cancer part I: evidence of the effects of screening in recent prostate cancer incidence, mortality, and survival rates. JNCI J Natl Cancer Inst 1999;91:1017–24.
29. Zhou CK, Check DP, Lortet-Tieulent J, Laversanne M, Jemal A, Ferlay J, et al. Prostate cancer incidence in 43 populations worldwide: an analysis of time trends overall and by age group. Int J Cancer 2016;138:1388–400.
30. Potosky AL, Kessler L, Gridley G, Brown CC, Horm JW. Rise in prostatic cancer incidence associated with increased use of transurethral resection. JNCI J Natl Cancer Inst 1990;82:1624–8.

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ORIGINAL PAPER

Prostate cancer survival in sub-Saharan Africa by age, stage at diagnosis, and human development index: a population-based registry study

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Abstract

Objectives To estimate observed and relative survival of prostate cancer patients in sub-Saharan Africa (SSA) and to examine the influence of age, stage at diagnosis and the Human Development Index (HDI).

Patients and methods In this comparative registry study, we selected a random sample of 1752 incident cases of malign prostatic neoplasm from 12 population-based cancer registries from 10 SSA countries, registered between 2005 and 2015. We analyzed the data using Kaplan-Meier and Ederer II methods to obtain outcome estimates and flexible Poisson regression modeling to calculate the excess hazards of death

Results For the 1406 patients included in the survival analyses, 763 deaths occurred during 3614 person-years of observation. Of patients with known stage, 45.2% had stage IV disease, 31.2% stage III and only 23.6% stage I and II. The 1 and 5-year relative survival for the entire cohort was 78.0% (75.4–80.7) and 60.0% (55.7–64.6), while varying between the registries. Late presentation was associated with increased excess hazards and a 0.1 increase in the HDI was associated with a 20% lower excess hazard of death, while for age at diagnosis no association was found.

Conclusions We found poor survival of SSA prostatic tumor patients, as well as high proportions of late stage presentation, which are associated with inferior outcome. This calls for investment in health-care systems and action regarding projects to raise awareness among the population to achieve earlier diagnosis and improve survival.

Keywords Adenocarcinoma of the prostate · Population-based cancer registration · Africa · Survival · Cancer surveillance

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Introduction

According to GLOBOCAN estimates for the year 2018, prostate cancer was the top cancer in terms of age-standardized incidence rates in males in the majority of countries (118) worldwide and in nearly all of those in sub-Saharan African (SSA) (42) [1]. It is predicted, that just through demographic changes, the annual number of incident prostate cancer cases in Africa will more than double during the next 20 years [2]. In a recent analysis of time trends in prostate cancer incidence in sub-Saharan Africa, we showed that even adjusted for the effect of demographic changes the rates have been increasing annually by 2–10% during the last decade [3]. With a growth rate of 2% throughout the next two decades, the number of cases of prostate cancer will have more than tripled by 2040 [2]. Already today SSA countries are struggling to deal with the burden of cancer. Late presentation of prostate cancer patients has been described in several hospital-based studies while difficulties in access to adequate care of cancer patients in general is a well-known problem of SSA [4–9]. Although prostate cancer is estimated to be the number one cancer in terms of both numbers of cases and deaths in males in most SSA countries [1], there is little information on survival. The few hospital-based studies available have reported wide variations, but mainly poor survival from prostate cancer in SSA [8, 10, 11], yet those estimates have limited generalizability to the general population of the region. Population-based cancer registries originally simply monitored the occurrence of incident cancers, however "the activities of cancer registries have developed far beyond this to include studies of cancer cause and prevention, and to provide the information needed for the planning and evaluation of cancer-control programmes" [12].

Since 2012 the African Cancer Registry Network (AFCRN) has been the partner of the International Agency for Research on Cancer (IARC), facilitating population-based cancer registration in SSA as a regional hub of the Global Initiative for Cancer Registration (GICR) [13]. Data on survival from prostate cancer have been published from individual registries [14–17]. However, a broad and in depth analysis of the population-based survival of prostate cancer patients in SSA and an analysis of influencing factors is not available.

In this comparative registry study, we estimate 1-, 3- and 5-year observed and relative survival for 12 population-based cancer registries from 10 SSA countries and examine the influence of age, stage at diagnosis, and the Human Development Index [18].

Patients and methods

Study population

We obtained data from 12 population-based cancer registries from 10 SSA countries, all members of the African Cancer Registry Network (AFCRN, https://afcrn.org/): Cotonou (Benin), Abidjan (Côte d'Ivoire), Addis Ababa (Ethiopia), Eldoret (Kenya), Nairobi (Kenya), Mauritius, Namibia, Eastern Cape (South Africa), Seychelles, Kampala (Uganda), Bulawayo (Zimbabwe) and Harare (Zimbabwe). In 2016 we invited those registries that were members of AFCRN that were capable of providing follow-up data for a minimum of 3 years, and ideally 5 and the aforementioned agreed to participate. From each individual registry, we took a simple random sample from lists of incident prostate cancer cases (ICD-O-10: C61) in the AFCRN database, registered between 2005 and 2015. For Harare (Zimbabwe) we took one random sample of cases among black men and one of white men from the same period. Since active follow-up is resource intensive in this setting, the sample size for each registry was determined by the feasibility of obtaining follow-up information. If passive follow-up was used, a larger number of patients could be included.

Primary prostate cancer cases of at least 15 years of age were eligible for sampling. Recurrences and cases registered on the basis of a death certificate only (DCO) were excluded. We measured the follow-up time from the date of incidence to the date of last contact alive, to the date of death or to the closing date of the study for the corresponding registry, whichever occurred first.

Cases were excluded from survival analyses due to the following criteria: (1) Less than one day of follow-up time; (2) incoherent dates (i.e. the registered date of incidence lies after the date of last contact); (3) double registrations; (4) found not to be prostate cancer during the follow-up

process; (5) initially diagnosed before the study period of the registry (registered relapses); (6) unknown age.

Covariates

Vital status

We investigated vital status using means of active and passive follow-up. All registries, apart from Mauritius used active follow-up methods. In Mauritius, the follow-up was done passively, by linking the records to the death registry. In 2012, the completeness of this death registry was estimated to be 100% [19]. For verification, the registry performed active follow-up of 10% of the presumably living patients and found all of this 10% sample to be still alive on 31st December 2013. Accordingly, we assumed patients to be still alive, if they were not registered in the death registry.

In all other registries, active follow-up was performed, using medical records to determine the patient's vital status and date of last contact. For patients not known to have died, the registry staff augmented this information, if possible, with phone calls and sometimes home visits to the patients and their relatives. We censored patients "alive" at the date of last contact, if vital status (alive or dead) was unknown at the closing date (Appendix Fig. 3).

Stage at diagnosis

At the time of registration, the registry staff abstracted information on clinical stage at diagnosis. For most registries this included tumor-node metastasis (TNM) assessment. For some registries additional information was available on prostate specific antigen (PSA) levels at time of diagnosis and/or the Gleason Score. We used the AJCC Cancer Staging Manual 8th edition, of the American Joint Cancer Committee (AJCC) [20] to classify each prostate cancer case to one of the four stage groups (I–IV). Since for some patients only PSA level and/or Gleason score was available, a stage was assigned on the basis of this information alone, assuming the other risk factors to be at minimum level. Accordingly, we grouped all prostate cancer cases in one of the following groups: "Stage I–II", "Stage III, "Stage IV" and "Stage unknown". For the registries of Mauritius and Eastern Cape (South Africa) no stage information was available.

Basis of diagnosis

The registries code the most valid basis of diagnosis [21] they can find for each cancer patient. We grouped "Morphologically verified" cases as those with histopathological verification of the primary tumor (the majority), and a few cases with cytological diagnosis or histopathological verification of metastases.

Human development index

According to the United Nations Development Programme (UNDP), the Human Development Index (HDI) is a "composite index measuring average achievement in three basic dimensions of human development—a long and healthy life, knowledge and a decent standard of living" [22]. The HDI "is perhaps the most popular index used to assess countries' well-being levels across the globe" [18]. For those registries covering sub-national populations, we used the more precise Sub-national Human Development Index (SHDI) (https://globaldatalab.org/) [18] to allow for the wide differences of well-being within countries in SSA. For Namibia, where registry coverage is not complete at the national level, we estimated a weighted average HDI, based on the SHDI of the 13 regions of the country and the number of cases from each in the random sample. In order to compare between the registries, the HDI value of 2013 was chosen.

Statistical analyses

Observed survival

Following exclusion of ineligible cases (as described above), we estimated observed survival (OS) probabilities at 1, 3 and 5 years of follow-up, applying the semi-complete [23] approach. We plotted Kaplan–Meier (KM) curves of observed survival probabilities, as well as observed survival stratified by HDI group, age and stage group at diagnosis.

We used R, Version 3.6.3 [24] in the integrated development environment RStudio, Version 1.2.5033 [25] with the packages "survival" [26] and "survminer" [27].

The percentage of cases with morphological diagnosis (MV%) was calculated as an indicator of data quality [28]. We estimated the median follow-up time for all cases, including those with a known event of death.

Relative survival

To adjust for mortality due to causes of death other than prostate cancer, we calculated crude and age-standardized Ederer II relative survival (RS) at 1, 3 and 5 years of follow-up, using the "relsurv" package [29] for R. We obtained the national life tables as five-year age-specific death rates by calendar year, sex and country from the WHO Mortality database [30] and expanded them using a Poisson regression model implemented in the "rcsgen" [31] command for STATA 15, to obtain complete life tables by one year age group (more information in the Supplement). We performed direct age-standardization by applying the age-specific weights of the International Cancer Survival Standard-1 for prostate cancer [32], but, since the numbers of subjects in the upper and lower age groups of the standard were very small, when stratifying by registry, we used just three broad age groups: 15–64, 65–74, 75–99.

Estimation of average survival

We estimated average 5-year survival for the ten countries under observation, adjusting for the different size of the datasets from each country, using the method of Abdel-Rahman et al. [33]. In brief: we weighted the mean of the 5-year survival from each country by the number of prostate cancer patients included as a proportion of the total cases for that country, as estimated by GLOBOCAN 2018 [1]. This does not necessarily imply that regional survival estimates can be extrapolated to the national level.

Assessing loss to follow-up

We assessed the proportions of patients lost to follow-up (LFU) at 1, 3 and 5 years. Since these proportions were above 10%, and in such cases it is desirable to investigate if censoring is at random, we performed an "inverse" Cox proportional hazards model with LFU as the outcome and adjusted for age and stage at diagnosis for year 1 and year 5.

Assessing the potential of 5-year follow-up

For all registries (except Mauritius) the closing date for follow up was 31st December, 2017, so that we calculated the potential follow up period for each patient as the difference between the date of incidence and the closing date. If this period was greater than 5 years, we considered this patient to have a potential of 5-year follow-up.

Modeling excess hazards

We used univariable and multivariable Poisson regression models adjusted for stage group, HDI as a continuous variable and age group at diagnosis, splitting time into monthly intervals and using restricted cubic splines, to model excess hazards of death in RS framework for prostate cancer patients [34].

Results

Mauritius, Namibia and Seychelles had national population coverage, the registry in Eastern Cape (South Africa) covers a rural area and all other registries cover urban areas. From these 12 population-based cancer registries a total 1752 cases were randomly selected, representing a 44% of the total prostate cancer cases (after exclusion of death certificate only cases) registered within the study period (Table 1).

Table 1 shows, for each registry, the total number of prostate cancer patients from the catchment area during study period, the number (and %) of DCO cases (not eligible for the study sample), and the number of cases in the random sample (and sampling fraction). Also shown is the number (and percentage) of the cases in the random sample included for survival analysis, following exclusion on non-eligible cases, as described above, their mean age and the percentage of morphologically verified (MV) cases.

The sampling fraction ranged from 18% in Namibia, to 100% in six registries. The proportion of MV cases ranged from 42% in Kampala (Uganda) to 96% in Mauritius. Following exclusions, 1406 prostate cancer patients were included in the survival analysis, representing 80% of our random sample. During a total of 3613 person-years of observation, there were 763 deaths, and the individual

Table 1 Total number of prostate cancer cases registered, included and excluded, data quality indicator by population-based cancer registry

Country	Registry	HDI in 2013[1]	Period of diagnosis	Total of prostate cancer patients during study period	No. excluded due to DCO (%)	Random sample, (sampling fraction %)	Included for survival analyses, (fraction of random sample, %)	MV, %
Benin	Cotonou	0.580	2013–2014	54	0 (0)	54 (100)	43 (80)	53
Côte d'Ivoire	Abidjan	0.548	2013–2014	286	0 (0)	160 (56)	127 (79)	65
Ethiopia	Addis Ababa	0.653	2012	49	0 (0)	49 (100)	45 (92)	73
Kenya	Eldoret	0.546	2009–2013	177	7 (4)	75 (44)	23 (31)	74
	Nairobi	0.622	2009–2013	866	47 (5)	149 (18)	134 (90)	75
Mauritius	Mauritius	0.775	2005–2009	340	9 (3)	331 (100)	326 (99)	96
Namibia	Namibia	0.665[2]	2012–2013	443	0 (0)	80 (18)	35 (44)	74
Seychelles	Seychelles	0.782	2008–2013	140	10 (7)	130 (100)	119 (92)	95
South Africa	Eastern Cape	0.644	2008–2013	260	0 (0)	260 (100)	201 (77)	49
Uganda	Kampala	0.621	2009–2013	559	5 (1)	150 (27)	114 (76)	42
Zimbabwe	Bulawayo	0.623	2012–2013	135	21 (16)	60 (53)	50 (83)	54
	Harare (black)	0.599	2009–2013	905	168 (19)	200 (27)	148 (74)	91
	Harare (white)	0.599	2009–2013	66	12 (18)	54 (100)	41 (76)	93
Total			2005–2014	4280	279 (7)	1752 (44)	1406 (80)	75

DCO death certificate only, *MV* morphologically verified

[1]Human Development Index (http://hdr.undp.org/en/data and https://globaldatalab.org/), *Levels* Very High HDI (0.800–1.000), High HDI (0.700–0.799), Medium HDI (0.550–0.699), Low HDI (0.000–0.549)

[2]National weighted average (by No. of cases per subregion) of the subnational HDIs (https://globaldatalab.org/)

median time of follow-up was 1.78 years (Table 2), without excluding the deaths from the calculation. The HDI ranged from 0.546 in Eldoret (Kenya) to 0.782 in Seychelles.

The mean (SD) age at diagnosis was 70.5 (9.7) years, and ranged from 66.5 (9.1) years in Namibia, to 74.2 (9.8) in Eldoret (Kenya) (Table 2). Distribution of age by registry can be seen in Appendix Fig. 4. Age distribution of our cohort was compared with that of all prostate cancer cases in the target populations during the years concerned, and found to be representative. Information on stage was only available for 40.5% of patients from the 10 registries contributing staging information (i.e. excluding Mauritius and Eastern Cape, South Africa). Of patients with a known stage, 45.2% had stage IV disease, 31.2% stage III and only 23.6% stage I and II. The proportion of "Stage unknown" varied widely between the registries and ranged from 17% in Namibia, to 76% and 75% in the cohort of white and black men in Harare (Zimbabwe), respectively. The highest proportion of Stage I and Stage II disease was found in Namibia, Seychelles and Nairobi (Kenya), with 31%, 21% and 13%, respectively (Appendix Fig. 5).

Assessing Loss to follow-up

LFU was the highest during the first year; for the entire cohort it was 13%. The proportion of LFU in the first year ranged from 0 and 2% in Seychelles and Harare (Zimbabwe) blacks, to 49 and 36% in Cotonou (Benin) and Abidjan (Côte d'Ivoire). Our Cox model, adjusted for stage and age group, showed that censoring was at random at year one, as well as during the whole study period.

The registry cohorts from Cotonou (Benin) and Bulawayo (Zimbabwe) had no potential for a 5-year follow-up. Since only three patients from Addis Ababa had a potential of 5-year follow-up, we did not estimate 5-year survival for this registry. Nairobi (Kenya) had the lowest percentage of cases with a complete 5-year follow-up (51%), whereas Mauritius

Table 2 Patient characteristics: mean age at diagnosis, median years of follow-up and observed (all-cause) survival and loss to follow-up

Country	Registry	Mean age at diagnosis (SD), years	No. of cases included	Year 1			Year 2 and 3			Year 4 and 5		Median follow-up time (IQR), years
				No of deaths (%)[2]	LFU (%)[2]	Observed 1-year survival % (95% CI)	No of deaths (%)[2]	LFU (%)[2]	Observed 3-year survival % (95% CI)	No of deaths (%)[2]	Observed 5-year survival % (95% CI)	
Benin	Cotonou[1]	69.5 (9.8)	43	8 (19)	21 (49)	72 (57–91)	9 (64)	0 (0)	26 (12–54)	–	–	0.56 (1.68)
Côte d'Ivoire	Abidjan	68.0 (9.8)	127	20 (16)	46 (36)	78 (70–87)	30 (49)	5 (8)	37 (28–50)	5 (19)	30 (21–43)	0.79 (2.43)
Ethiopia	Addis Ababa[1]	67.7 (9.9)	45	17 (38)	3 (7)	60 (47–77)	11 (44)	7 (28)	29 (17–49)	–	–	1.11 (2.08)
Kenya	Eldoret	74.2 (9.8)	23	2 (9)	6 (26)	89 (75–100)	7 (47)	0 (0)	47 (29–78)	2 (25)	36 (19–67)	1.37 (3.14)
	Nairobi	67.4 (10.0)	134	18 (13)	41 (31)	83 (76–90)	11 (15)	14 (19)	69 (60–79)	7 (14)	58 (48–70)	1.52 (4.34)
Mauritius	Mauritius	71.5 (9.7)	331	73 (22)	0 (0)	78 (74–83)	73 (29)	0 (0)	56 (50–61)	30 (17)	46 (41–52)	4.08 (3.83)
Namibia	Namibia	66.5 (9.1)	35	5 (14)	3 (9)	85 (73–98)	4 (15)	6 (22)	70 (56–89)	1 (6)	66 (51–86)	2.84 (3.88)
Seychelles	Seychelles	70.8 (8.4)	119	21 (18)	0 (0)	82 (76–89)	29 (30)	3 (3)	58 (49–67)	17 (26)	41 (33–52)	3.34 (3.49)
South Africa	Eastern Cape	72.0 (10.1)	201	73 (36)	29 (14)	60 (54–68)	32 (32)	23 (23)	37 (30–46)	10 (23)	28 (21–37)	1.00 (2.64)
Uganda	Kampala	69.5 (9.0)	115	34 (30)	18 (16)	66 (57–76)	19 (31)	8 (13)	44 (35–56)	5 (14)	38 (29–49)	1.25 (3.78)
Zimbabwe	Bulawayo[1]	74.4 (8.1)	50	24 (48)	14 (28)	37 (24–56)	7 (58)	4 (33)	11 (4–34)	–	–	0.15 (0.91)
	Harare (black)	71.4 (9.7)	149	50 (34)	3 (2)	66 (59–74)	26 (27)	1 (1)	47 (40–56)	14 (21)	36 (29–45)	2.54 (4.25)
	Harare (white)	73.1 (8.3)	41	11 (27)	2 (5)	72 (59–87)	4 (14)	3 (11)	61 (47–79)	4 (19)	49 (35–69)	3.34 (4.06)
Total	Total	70.5 (9.7)	1406	355 (25)	186 (13)	72.1 (69.6–74.6)	262 (30)	74 (9)	49.2 (46.4–52.1)	96 (18)	39.1 (36.3–42.2)	1.78 (4.03)

CI confidence interval, *IQR* interquartile range, *LFU* loss to follow-up, *SD* standard deviation

[1]Registries without a potential of 5-year follow-up

[2]Percentages refer to the number at risk at the beginning of the time intervals of observation

and blacks from Harare (Zimbabwe) had the highest with 100% and 96%, respectively (Appendix Table 4).

Survival statistics for all ages by registry

For the whole study cohort, the observed Kaplan–Meier survival probability (95% CI) for prostate cancer patients was 72.1% (69.6–74.6) at year one, 49.2% (46.4–52.1) at year 3 and 39.1% (36.3–42.2) at year 5 (Fig. 1A, Table 2). The youngest age group had the highest observed survival (Fig. 1B). The 5-year observed survival probability was highest in Namibia and lowest in Eastern Cape (South Africa) (Table 2, Appendix Fig. 6).

The 1-, 3- and 5-year relative survival for the entire cohort was 78.0% (75.4–80.7), 62.9% (59.4–66.7) and 60.0% (55.7–64.6) (Appendix Fig. 7). The values varied by registry, with the highest values of 5-year relative survival found in Namibia, Nairobi (Kenya), in whites of Harare (Zimbabwe) and in Eldoret (Kenya). The lowest values of 5-year relative survival were found in Eastern Cape (South Africa) and in Kampala (Uganda).

Figure 2 shows the 1-, 3- and 5-year age-standardized relative survival (ASRS) in the different registries. At year 5 we found the highest values for Nairobi (Kenya) and white patients in Harare (Zimbabwe) and the lowest values for Eastern Cape (South Africa). The ASRS also varied within countries. E.g. in Zimbabwe at year 1, where the cohorts from the capital Harare had a better outcome than the cohort from Bulawayo. The ASRS also varied between the white and the black patients from Harare (Zimbabwe), with the whites having one of the best ASRS after 5 years and the blacks having one of the poorest. The ten countries under observation had an estimated average relative survival (taking into account the different sample sizes from each

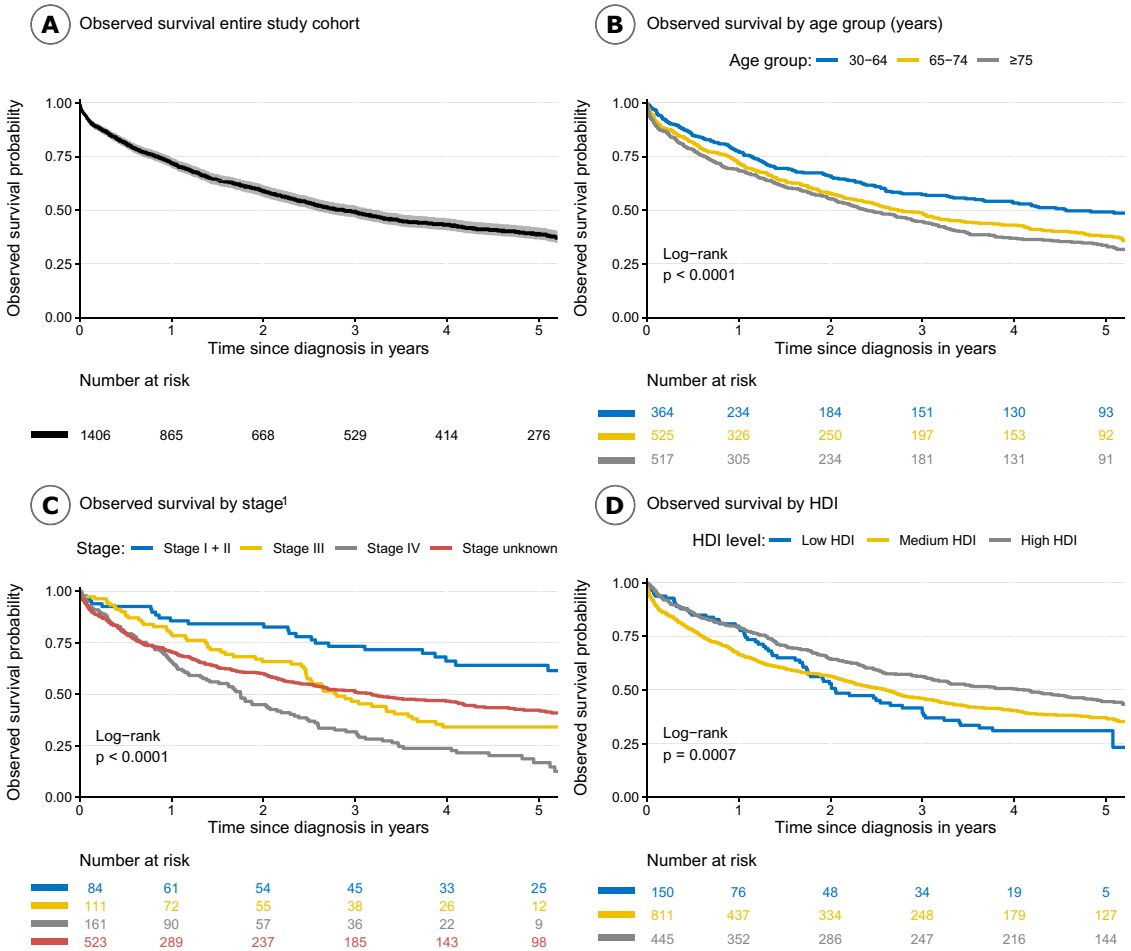

Fig. 1 Observed (all-cause) survival for the entire study cohort (**A**), by age group (**B**), by stage (**C**), and Human Development Index (HDI) (**D**), Source HDI (http://hdr.undp.org/en/data and http://globaldatalab.org/).

[1]Mauritius and Eastern Cape (South Africa) excluded, since no staging information was available

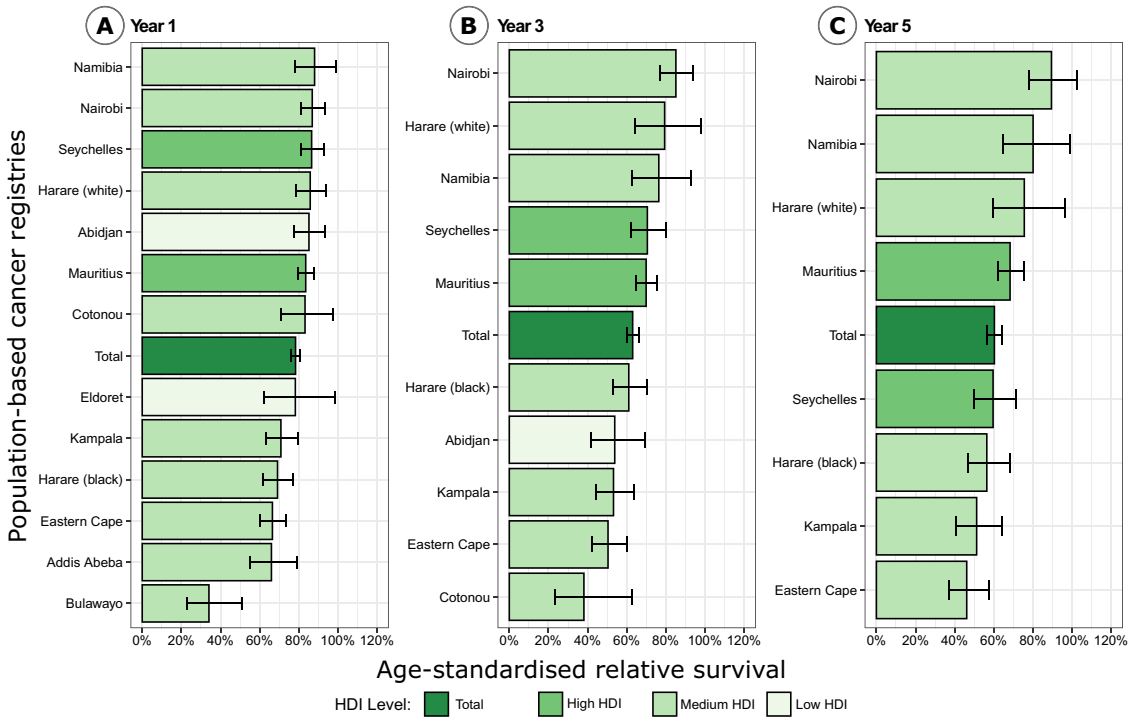

Fig. 2 Comparison of 1- (**A**), 3- (**B**) and 5-year (**C**) age-standardized relative survival with 95% confidence intervals (CI) by registry and Human Development Index (HDI)

country) of 73.1% (62.5–85.9) at year 1, 49.7% (36.9–69.0) at year 3 and 55.3 (42.1–73.2) at year 5. However, this sample was mainly from urban populations and is not representative for the whole of SSA.

Survival by age at diagnosis and registry

The oldest age group (>=75) had a significantly better relative survival probability than both younger groups (<65, 65–74) with 5-year RS point estimates (95% CI) of 74.9% (65.3–85.9), 56.1%(49.8–63.2) and 51.8% (45.7–58.7), respectively (Appendix Table 5). For most registries we observed the highest relative survival point estimates in the oldest age group at all three evaluated time points. This was not the case for Addis Ababa (Ethiopia) and Namibia, where the highest values were found in the younger age groups.

Survival by stage at diagnosis

We observed differing KM survival by stage at diagnosis for the entire cohort (Mauritius and Eastern Cape (South Africa) excluded). At five years, those with Stage I + II disease (64.0% [53.1–77.0]) had significantly higher point estimates than those with Stage III (34.1% [25.3–45.9]) and Stage IV disease (16.8% [10.7–26.3]) (Fig. 1C). This pattern was also observed in relative survival estimates for the entire cohort and within registries. The relative survival in each stage group, varied between the registries yet the confidence intervals were mainly wide and overlapping (Appendix Table 6).

Excess hazard ratio

Stage III and Stage IV at diagnosis were associated with a three- and sevenfold risk of death compared to Stage I + II at diagnosis (Table 3). When adjusting for age at diagnosis and HDI, we observed a similar independent association. An increase of the HDI by one decimal point (0.1) decreased the risk of death by 20% (95% CI: 9–30%) in our model, adjusted for age and stage at diagnosis. Age at diagnosis was not associated with the hazard of death in either the univariable or in the adjusted model. We did not find any evidence in our models for an interaction between age and stage at diagnosis.

Discussion

This comparative analysis—to our knowledge, the first of its kind from sub-Saharan Africa—evaluates the survival of prostate cancer patients from 10 different countries,

Table 3 Prostate cancer excess mortality hazard by age and stage at diagnosis and HDI

	No. of cases	Univariable analysis		Multivariable model[1]	
		Excess hazard ratio (95% CI)	*p* Value	Excess hazard ratio (95% CI)	*p* Value
Age at diagnosis (years)					
< 65	364	Reference		Reference	
65–74	525	1.17 (0.91–1.51)	0.213	1.19 (0.93–1.53)	0.173
75 +	517	0.85 (0.63–1.14)	0.281	0.92 (0.68–1.24)	0.584
Stage at diagnosis					
Stage I + II	84	Reference		Reference	
Stage III	111	3.18 (1.12–9.04)	0.030	2.83 (1.04–7.68)	0.042
Stage IV	161	6.93 (2.61–18.38)	< 0.001	6.16 (2.43–15.61)	< 0.001
Stage unknown	1050	3.70 (1.42–9.61)	0.007	3.51 (1.42–8.71)	0.007
HDI[2] (unit = 0.1)	1406	0.78 (0.68–0.89)	< 0.001	0.80 (0.70–0.91)	0.001

CI Confidence interval, *HDI* Human Development Index

[1]Adjusted for age at diagnosis, stage at diagnosis and sub-national HDI

[2]Human Development Index (http://hdr.undp.org/en/data and https://globaldatalab.org/)

incorporating data from 12 population-based cancer registries and assesses the influence of age, stage at diagnosis and Human Development Index. We used random sampling for inclusion of cases, although the size of the sampling fractions and accordingly the confidence intervals for our estimates varied between registries. The total sample of 1752 men included 44% of all patients registered with prostate cancer in the participating registries during the study period.

The survival estimates varied widely between registries and countries, as well as within countries and for Harare (Zimbabwe), between the racial groups. We found a 1-, 3- and 5-year observed (all-cause) survival (95% CI) for all 13 cohorts of prostate cancer patients of 72.1% (69.6–74.6), 49.2% (46.4–52.1) and 39.1% (36.3–42.2), respectively, while the ASRS was at 78.4% (76.2–80.6), 63.1% (60.1–66.1) and 60.3% (56.7–64.1), respectively. The ten countries under observation had an estimated average relative survival (taking into account the different sample sizes from each country) of 55.3 (42.1–73.2) at year 5. Nearly half of the patients with staging information had Stage IV disease. In flexible Poisson regression analysis, we found late stages of prostate cancer associated with increased excess hazards, compared to early stages and a 0.1 increase in the HDI to be associated with a 20% lower excess hazard of death. We did not find an association between age at diagnosis and the hazard of death in prostate cancer patients. It is possible that the lack of an association between hazard of death and age is due to confounding by stage; although this was adjusted for in the model, the adjustment would be far from complete, given the high proportion of cases with missing stage data.

The poor observed survival is to be expected given the advanced stage and age of prostate cancer patients (mean age 70.5 years in our study). Relative survival provides an estimate of the probability of surviving prostate cancer (excluding death from other causes), while comparisons between different series requires adjustment for age (if survival is related to age). Comparing our results of the ASRS to high income countries, like the US, Germany or the UK, where the 5-year age-standardized net survival in 2010–2014 was estimated to be at 97.4, 91.6 and 88.7% [14], respectively, we revealed that the average outcome of prostate cancer patients in SSA is rather poor. However, survival from prostate cancer in high income countries was much lower only a few decades ago. For example, in the US, the 5-year relative survival increased from 70% in the period of 1975–1979, to 99.3% in 1995–2000[35]. In the registry of Kampala (Uganda) the 5-year ASRS for prostate cancer patients was reported to be 46.9% during 1993–1997[16], while in our study it was at 51.2%. Data from Harare (Zimbabwe) from the same period showed a 3-year RS for black men of 27.1% and a 5-year survival for white men of 83.7% [17], respectively. In our study those estimates are at 59.9 and 76.8%, respectively. The survival of cancer patients is a product of a multitude of factors and it is therefore not easy to determine any single reason for the low survival of SSA prostate cancer patients, and for the variations we observe between and within countries. In high income countries, the implementation of routine and opportunistic screening for prostate cancer in asymptomatic men by prostate specific antigen (PSA) testing has been a major factor causing the very high survival currently observed, with much of the longer survival times being a consequence of the so called lead-time bias introduced through over-diagnosis of indolent cancers [36]. In SSA there are no systematic screening programs in place, and there are no data on the prevalence of opportunistic PSA testing. A few studies indicate that PSA screening

uptake is sparse in SSA [37, 38]. The rising incidence rates all over SSA in a recent trend analysis of population-based cancer registry data is believed to be linked to rising usage of PSA testing [3].

Another factor influencing the survival of prostate cancer patients is the stage at diagnosis. The majority of patients in our cohort were diagnosed at Stage III and Stage IV. This is in line with most (mainly hospital-based) studies from SSA [9, 39, 40]. The proportion of metastatic disease in high income countries is much smaller (6% in the USA for example [41]), than in our study, where nearly one in two patients (with known stage) was metastatic. As expected, late stage III and stage IV disease were associated with a higher excess hazard of death, even when adjusting for age and HDI.

It is likely that the high proportion of late stage disease is due to lack of awareness of the disease. Only 54% of 545 men in a cross-sectional study from Kampala ever heard about prostate cancer [42]. A recent review from Baratedi et al., similarly pointed towards lack of knowledge and a multitude of misconceptions about the disease. This study also identified lower education and socioeconomic status as barriers to prostate cancer screening on the patient level [43]. These factors are also known to influence the outcome of prostate cancer patients in general [44]. Since we had no information on individual socioeconomic status, we adjust for this on registry level using the HDI as covariate, which comprises information on life expectancy, education level and gross per capita income [18, 22]. We found a higher HDI to be associated with a reduction of the excess hazard of death. Since we modeled in a relative survival setting, which already adjusts for the influence of the background population's life expectancy, this association will be mainly driven by the influence of education level and gross per capita income. Regions with a higher gross domestic product are likely to have better health-care systems with better access to early detection and adequate treatment, as well as to post-treatment follow-up. A retrospective hospital-based study from South Africa found that patients wait an average of three months to receive the results of their prostate biopsy and to have their treatment planned [45]. It is estimated that 93% of the population of SSA have no access to timely, safe and affordable surgery and anesthesia [5]. A reason among others is likely to be that the region has the least surgical workforce worldwide [46].Shortcomings in the access to radiotherapy, as well as problems with the few functioning radiotherapy machines are a well-known problem in low income countries and especially in this region [4, 6, 47]. Yet a study from a tertiary referral center in Ghana showed that even in this setting the provision of adequate radiotherapy is possible and reports high 5-year observed survival rates (96%) of non-metastatic patients in their clientele [10].

It is possible also that there is a genetic component to the poor survival of men with prostate cancer in SSA. Men of African ancestry not only have been associated with a higher risk of developing prostate cancer, but also with more aggressive disease [48]. Nevertheless, the socioeconomic factors confounding this association are likely to be the principal reason for the racial survival disparities [49–51].

The differences we saw in 5-year relative survival between age groups, were not observed in our model—even in the multivariable (adjusted) analysis. Possibly the pattern observed in the pooled relative survival analysis is artificially influenced by the large proportion of patients in the oldest age group coming from Mauritius (67 of 181 patients at risk in years 4 and 5). Another reason is that relative survival estimation makes use of national lifetables, in which the mortality rates are too pessimistic for the background mortality of men with prostate cancer in the populations served by the registries. Most are in relatively affluent regions of their countries—the capital cities—which will artificially inflate the estimates of relative survival of our patients. Regionally stratified lifetables would reduce such bias, but are not readily available at the moment.

Stage was unknown for around 60% of patients from registries contributing stage information. Cancer registrars can only abstract staging information, if they are sufficiently trained, have access to medical records and if, after all, cancer stage had been assessed by physicians and was documented in the record. This problem is being addressed by the development of simplified staging protocols, which can be used by cancer registrars to allocate stage at diagnosis, in the absence of documented stage in the case record [52].

We used the HDI as a registry-level substitute covariate for unavailable patient-level socioeconomic data. Allocating socioeconomic status based on residential-level indices is now a very widely used technique, although it incorporates misclassification at the individual level [53], and, in our study, is also completely confounded with the actual cancer registry.

In order to minimize any potential bias due to incompleteness of registration, we only included AFCRN registries, which are evaluated as registering at least 70% of their target population [13]. Five of our registries (Eastern Cape, Harare, Kampala, Nairobi, and Seychelles) were included in Cancer Incidence in Five Continents during the relevant period [54]. Several studies have investigated aspects of registration practice to ascertain whether they can explain observed survival differences between countries, finding that particular registration differences are unlikely to impact greatly on survival differences [55]. A large number of patients were lost to follow up (LFU), especially during the first year of follow-up. The Cox-models suggest that LFU at year 1 and during the whole period, was not associated with age or stage and thus was considered to be random.

We analyzed data from 12 population-based cancer registries from 10 SSA countries, giving insight into the survival experience of prostate cancer patients in the general population. We show that survival of prostate cancer patients in SSA is generally poor, but differs widely between and also within different countries, while late stage disease and a lower Human Development index were associated with a substantially increased risk of death. More studies are needed to evaluate and adjust for the influence of patient-level socioeconomic factors, treatment and comorbidity. However, we believe that raising awareness of the disease in the general population to mitigate late stage presentation, as well as investments in training and equipment of health-care systems to improve the patterns of care would lead to a reduction of unnecessary early deaths from a disease that has rather good prognosis in more affluent regions of the world.

Appendix methods

Modeling of lifetables

Single year and 5-year-age abridged lifetables for the years 2000–2016 at national level was retrieved from the WHO Global Health Observatory. We obtained age-specific death rates, calculated from information on deaths among persons in the age group at age x during a given time period and the total person-years for the population in the same time period. A full description of the methods is available elsewhere: https://www.who.int/healthinfo/statistics/LT_method.pdf?ua=1.

The number of deaths and person-time by sex, year and country were used to estimate mortality rates using a Poisson regression and a flexible function to expand the abridged age groups (0–4, 5–9, 10–14 … 80 +) to single ages (0, 1, 2, 3, 4, 5 … 99). Briefly, we used the number of deaths and person-time by year and sex for each country separately. Smoothed age-specific mortality rates were derived using Poisson regression modeling by piecewise and spline function using eight knots with locations at ages 0–10 (three knots), 15–30 (three knots) and 50–85 + (two knots). The method chosen was fully described and explored by Rachet and colleagues (2015): https://bmcpublichealth.biomedcentral.com/track/pdf/10.1186/s12889-015-2534-3 (Figs. 3, 4, 5, 6, 7; Tables 4, 5, 6).

Table 4 Registries with potential for 5-year follow-up time

Country	Registry	Period of diagnosis	No. of cases included for survival analyses	No. of cases with potential of 5-year FU	No. of cases with complete (alive or dead) 5-year FU (%)	
					Alive	Dead
Côte d'Ivoire	Abidjan	2013–2014	127	47	1 (2)	25 (53)
Ethiopia	Addis Ababa	2012	45	3*	0 (0)	2 (67)
Kenya	Eldoret	2009–2013	23	17	4 (24)	7 (41)
	Nairobi	2009–2013	134	103	28 (27)	25 (24)
Mauritius	Mauritius	2005–2009	331	255	115 (45)	140 (55)
Namibia	Namibia	2012–2013	35	20	9 (45)	3 (15)
Seychelles	Seychelles	2008–2013	119	92	29 (32)	54 (59)
South Africa	Eastern Cape	2008–2013	201	113	17 (15)	77 (68)
Uganda	Kampala	2009–2013	115	103	23 (22)	51 (50)
Zimbabwe	Harare (black)	2009–2013	149	94	34 (36)	56 (60)
	Harare (white)	2009–2013	41	41	16 (39)	19 (46)
Total			1320	888	276 (31)	459 (52)

*Since there were only three cases, we did not assess 5-year survival for Addis Ababa (Ethiopia)

Table 5 Age-specific and age-standardized relative 1-, 3- and 5-year survival by registry

Registry	Year 1 RS				Year 1 ASRS
	< 65	65–74	> = 75	All ages	
Abidjan	83.8 (70.8–99.1)	77.7 (64.3–93.9)	94.8 (75.9–118.3)	85 (76.1–95)	85.2 (77.8–93.3)
Addis Ababa	76.8 (57.1–103.3)	55.8 (37.2–83.8)	60.6 (36.5–100.5)	63.4 (49.8–80.9)	66 (55.1–79.1)
Bulawayo	25.5 (7.1–91.3)	30.6 (13.9–67.6)	50 (30.7–81.4)	40.4 (26.6–61.5)	34.1 (22.7–51.1)
Cotonou	78 (54.7–111.2)	63.2 (40.1–99.7)	110.7 (86.7–141.5)	80.4 (63.8–101.2)	83.2 (70.9–97.7)
Eastern Cape	63.7 (50.2–80.8)	68.7 (56.7–83.2)	68.5 (57–82.4)	67.4 (59.9–75.7)	66.5 (60.1–73.6)
Eldoret	51.3 (19.3–136.7)	93.1 (74.9–115.8)	102.4 (102.4–102.4)	99.7 (85.1–116.8)	78.3 (62.3–98.4)
Harare (black)	67.1 (51.1–88.2)	74 (63.6–86.1)	67.2 (53.9–83.7)	70.8 (63.1–79.6)	69.1 (61.9–77.3)
Harare (white)	100.7 (100.7–100.7)	70.7 (50.3–99.3)	79.6 (60.2–105.1)	78.3 (64.6–95)	85.9 (78.5–94)
Kampala	75.6 (61.5–93)	65.7 (51.4–84)	69.2 (52–92.1)	69.7 (60.4–80.5)	70.9 (63.2–79.4)
Mauritius	82.7 (73.9–92.6)	85.7 (78.6–93.5)	82.6 (74.9–91.2)	84.3 (79.6–89.3)	83.6 (79.5–87.8)
Nairobi	91 (82.5–100.5)	76.7 (62.7–93.9)	91.1 (76.7–108.2)	86.8 (79.5–94.9)	86.9 (81–93.2)
Namibia	88.6 (73.2–107.3)	92 (74–114.3)	83.4 (57.5–121)	88.7 (76.7–102.6)	88.1 (78.2–99.2)
Seychelles	87.4 (75.8–100.9)	88 (77.7–99.6)	83.9 (72–97.9)	86.6 (79.7–94.1)	86.6 (80.9–92.6)
Total	79.5 (74.9–84.3)	75.9 (71.8–80.3)	79.2 (74.5–84.2)	78 (75.4–80.7)	78.4 (76.2–80.6)
Registry	Year 3 RS				Year 3 ASRS
	< 65	65–74	> = 75	All ages	
Abidjan	36.8 (21.6–62.5)	48.7 (32.3–73.4)	83.8 (48.7–144.3)	51.5 (38.6–68.8)	53.9 (41.9–69.3)
Addis Ababa	47 (24.3–90.9)	33.9 (17.2–66.7)	28.1 (9.5–83.4)	35 (21.1–58.1)	37.7 (26–54.6)
Bulawayo	–	33.6 (15.2–74.3)	–	15.4 (5.8–41.1)	–
Cotonou	41.1 (19.7–85.7)	–	72 (28.2–183.9)	37.2 (18.6–74.3)	–
Eastern Cape	45.8 (30.5–68.8)	53.9 (39.1–74.1)	53.8 (38.4–75.3)	51.5 (41.8–63.4)	50.5 (42.5–59.9)
Eldoret	-	82 (57.5–116.9)	47.6 (17.5–129.9)	60.1 (37.2–96.9)	-
Harare (black)	59.3 (42.8–82.2)	46.1 (34.5–61.5)	78.6 (61.3–100.8)	59.9 (50.5–70.9)	61.1 (53–70.4)
Harare (white)	81.2 (49.7–132.5)	70.2 (46.9–105.1)	85.9 (60.8–121.4)	79.7 (62.2–102.1)	79.4 (64.3–98)
Kampala	60 (43.9–82.1)	48.5 (33.1–71.2)	48.1 (28.8–80.6)	52.7 (41.8–66.4)	53.2 (44.3–64)
Mauritius	68.9 (58.1–81.7)	68.3 (58.8–79.4)	73 (61.5–86.7)	71.1 (64.6–78.4)	69.9 (64.6–75.7)
Nairobi	77.1 (63.6–93.6)	64.3 (47.4–87.1)	117.6 (99–139.6)	82 (71.5–94)	85.1 (77.1–94)
Namibia	85.4 (66.4–109.9)	84 (58.9–119.8)	55.7 (24.5–126.4)	81.7 (65–102.8)	76.4 (62.9–92.8)
Seychelles	70.9 (54.8–91.8)	67.1 (52.5–85.9)	73.4 (55.7–96.8)	70.7 (60.7–82.5)	70.6 (62.3–79.9)
Total	61.8 (56–68.2)	57.7 (52.5–63.5)	70.2 (63.2–77.9)	62.9 (59.4–66.7)	63.1 (60.1–66.1)
Registry	Year 5 RS				Year 5 ASRS
	< 65	65–74	> = 75	All ages	
Abidjan	–	–	76.3 (31.3–186.2)	55 (38.9–77.7)	–
Eastern Cape	41.6 (24.7–70)	50.9 (34.1–76)	48.1 (30.7–75.3)	48.2 (36.6–63.4)	46.2 (37–57.6)
Eldoret	–	68.1 (36.6–126.9)	47.6 (17.5–129.9)	75.6 (41.3–138.6)	–
Harare (black)	49.3 (31.7–76.8)	38.9 (27–56)	84.3 (59.8–118.8)	54.3 (43.5–67.9)	56.4 (46.7–68.2)
Harare (white)	81.2 (49.7–132.5)	52.4 (27.4–100.5)	90.6 (59.4–138.3)	76.8 (55.6–106.0)	75.6 (59.4–96.2)
Kampala	58.3 (41.5–81.8)	39.8 (24.3–65.3)	52.4 (27.4–100.1)	49.3 (37.5–64.8)	51.2 (40.9–64.1)
Mauritius	63.5 (51.7–77.9)	68.6 (57.3–82.2)	75 (60–93.9)	70.0 (62.1–79.0)	68.3 (62–75.3)
Nairobi	65.7 (49.8–86.7)	60.7 (39.8–92.8)	152.6 (121.4–191.8)	80.7 (66.9–97.5)	89.5 (78.2–102.3)
Namibia	90.8 (70.6–116.8)	88.9 (54.9–144.1)	55.7 (24.5–126.4)	88.4 (68.4–114.3)	80.1 (64.9–98.7)
Seychelles	55 (37.6–80.3)	54.6 (37.1–80.4)	71.4 (49.1–103.8)	59.4 (47.4–74.4)	59.6 (49.8–71.4)
Total	56.1 (49.8–63.2)	51.8 (45.7–58.7)	74.9 (65.3–85.9)	60 (55.7–64.6)	60.3 (56.7–64.1)

ASRS age-standardized relative survival, *RS* relative survival

Table 6 Relative survival (RS) by stage and registry

Registry	*n*	No. with known stage	No. Stage IV (%)	1 Year RS (95% CI)											
				Stage I+II	Stage III	Stage IV	Stage unknown	Stage I+II	Stage III	Stage IV	Stage unknown	Stage I+II	Stage III	Stage IV	Stage unknown
Abidjan	127	46	22 (48)	74 (38–142)	89 (70–112)	63 (44–91)	88 (79–99)	74 (38–142)	62 (33–116)	31 (14–70)	53 (37–75)	–	81 (43–151)	–	–
Addis Ababa	45	4	4 (100)	–	–	100 (100–100)	59 (45–78)	–	–	–	35 (22–58)	–	–	–	–
Bulawayo	50	19	10 (53)	–	54 (29–101)	32 (13–80)	38 (20–69)	–	–	16 (4–63)	–	–	–	–	–
Cotonou	43	31	13 (42)	110 (110–110)	105 (86–127)	35 (15–84)	97 (79–118)	–	41 (15–114)	–	87 (51–147)	–	–	–	–
Eldoret	23	12	6 (50)	100 (100–100)	100 (100–100)	70 (42–117)	113 (113–113)	62 (23–164)	100 (61–163)	58 (29–118)	27 (7–103)	–	128 (57–289)	58 (22–152)	27 (7–103)
Harare (black)	148	37	7 (19)	100 (100–100)	74 (57–96)	61 (34–109)	70 (61–80)	65 (29–147)	38 (21–69)	–	67 (57–80)	48 (13–172)	8 (2–35)	–	68 (55–84)
Harare (white)	41	10	3 (30)	100 (100–100)	73 (38–141)	38 (12–124)	80 (65–99)	100 (100–100)	73 (38–141)	38 (12–124)	78 (58–105)	100 (100–100)	46 (14–149)	–	81 (57–116)
Kampala	114	31	17 (55)	41 (20–83)	100 (100–100)	53 (33–85)	77 (67–89)	36 (15–84)	73 (27–194)	28 (11–67)	61 (49–78)	–	–	24 (8–72)	61 (47–79)
Nairobi	134	50	25 (50)	103 (103–103)	74 (48–114)	89 (75–106)	84 (74–95)	109 (109–109)	74 (48–114)	57 (36–90)	84 (71–99)	125 (125–125)	65 (34–124)	29 (11–78)	89 (73–109)
Namibia	35	29	15 (52)	100 (100–100)	101 (101–101)	81 (61–107)	70 (42–117)	114 (114–114)	101 (101–101)	55 (32–95)	61 (30–124)	128 (128–128)	127 (127–127)	46 (22–95)	61 (30–124)
Seychelles	119	87	39 (45)	94 (84–105)	95 (84–107)	80 (68–95)	79 (65–97)	97 (80–118)	78 (57–105)	45 (31–67)	75 (57–99)	95 (72–125)	83 (59–117)	27 (14–53)	48 (29–80)
Total	879	356	161 (45)	91 (83–100)	87 (78–96)	70 (62–78)	76 (72–81)	89 (78–103)	61 (49–76)	38 (30–49)	64 (58–71)	94 (79–113)	56 (42–76)	24 (15–37)	63 (56–71)

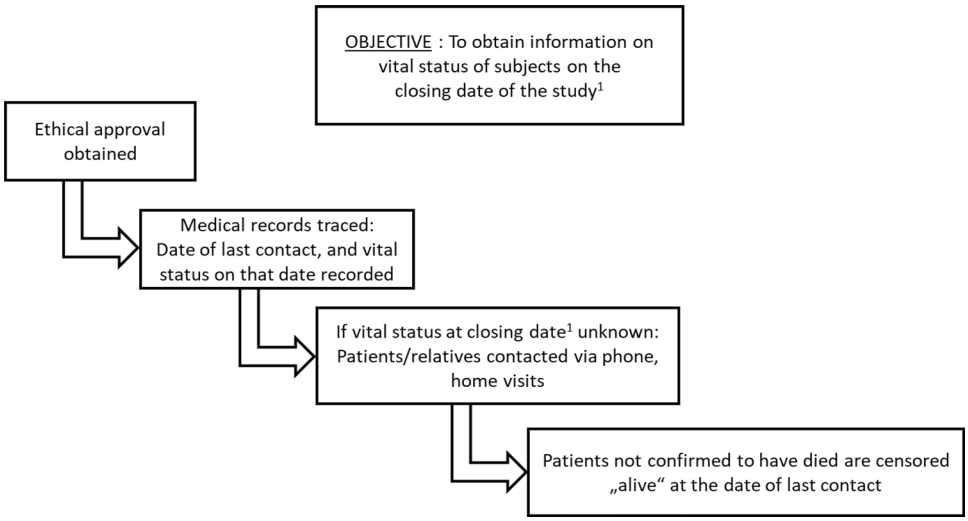

Fig. 3 Process of patient follow-up.[1]31st December, 2017, (for Mauritius: 31st December, 2013)

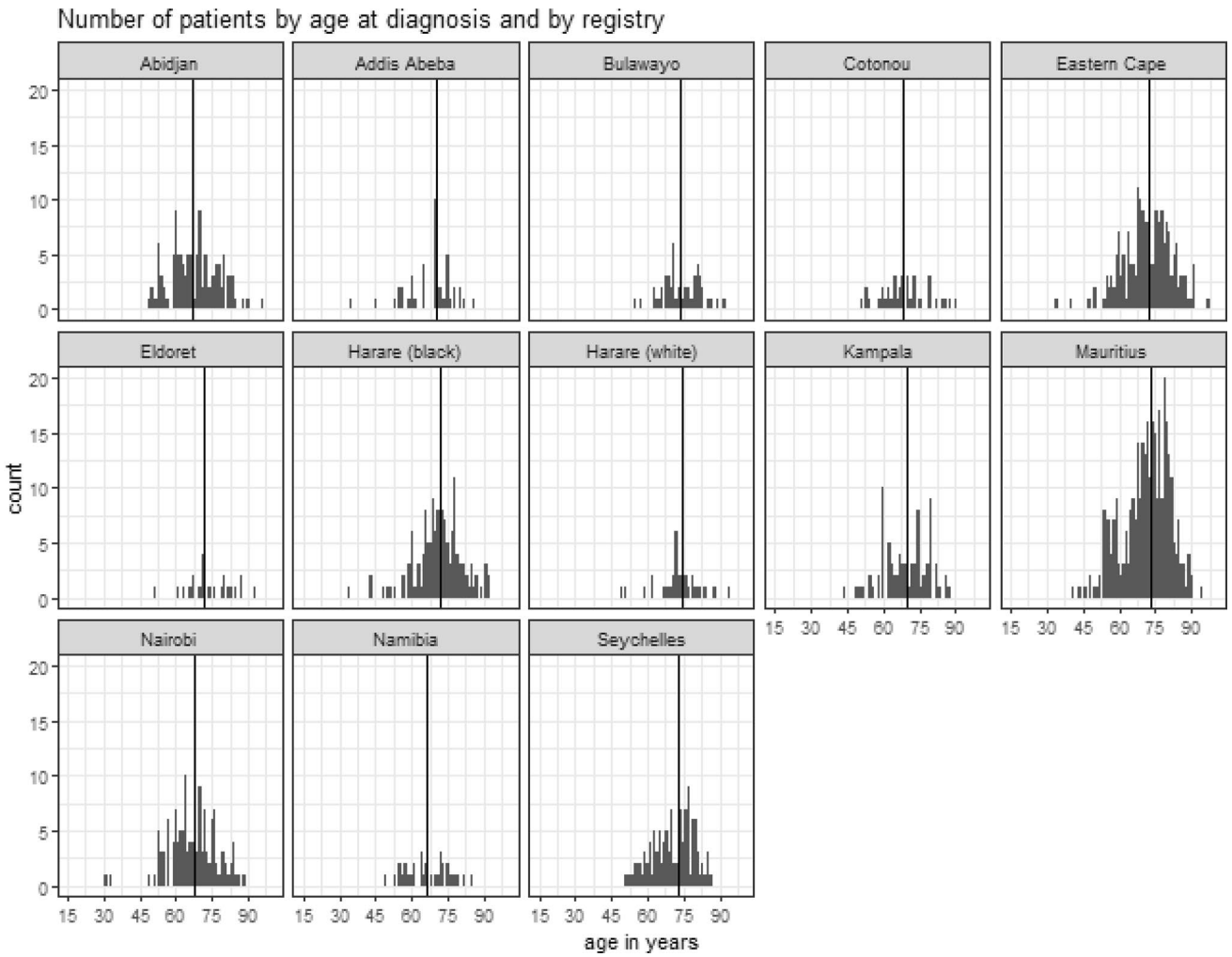

Fig. 4 Number of patients by age at diagnosis in years, by registry; black vertical lines indicate median age per registry

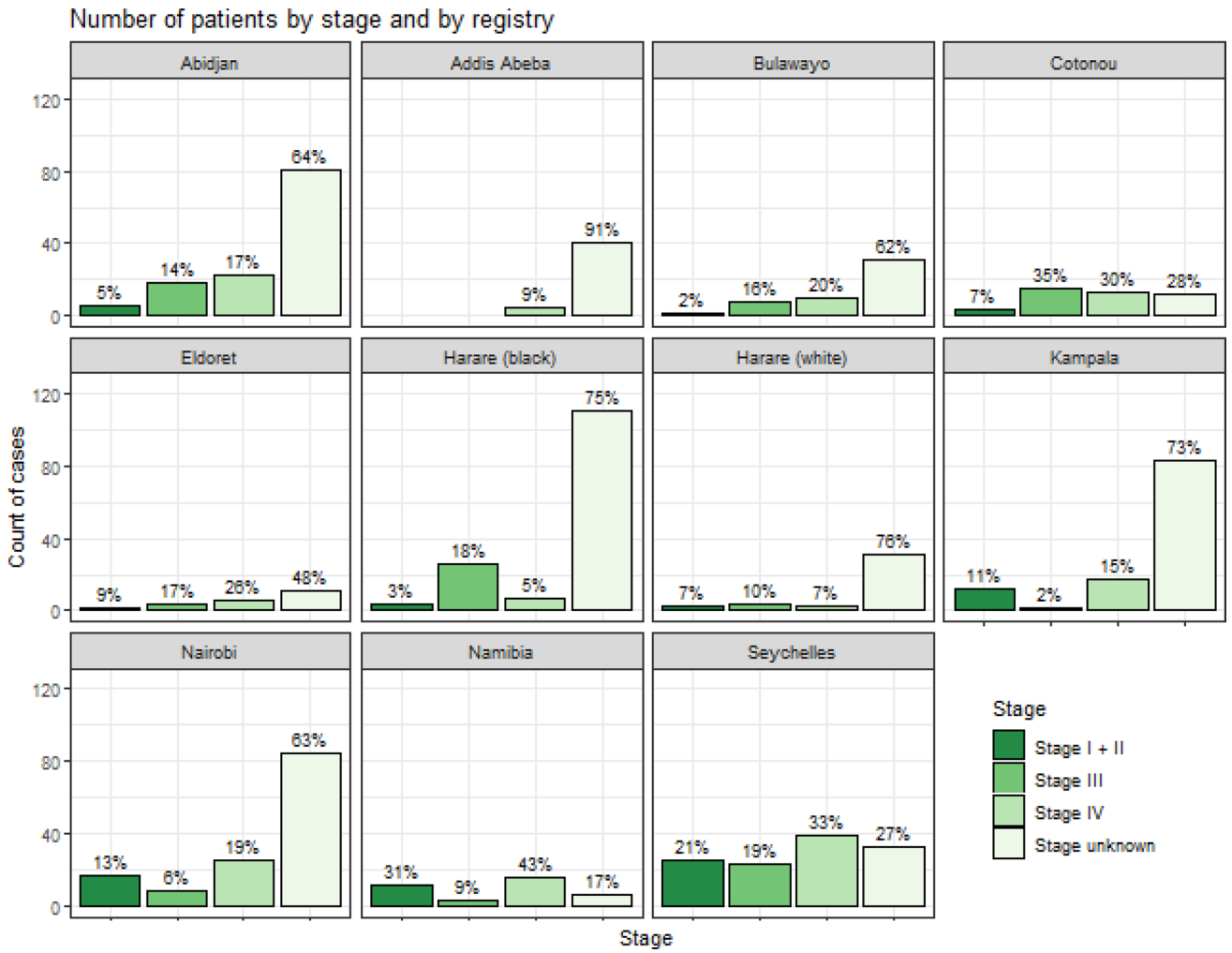

Fig. 5 Distribution of stage by registry (Mauritius and Eastern Cape (South Africa) excluded)

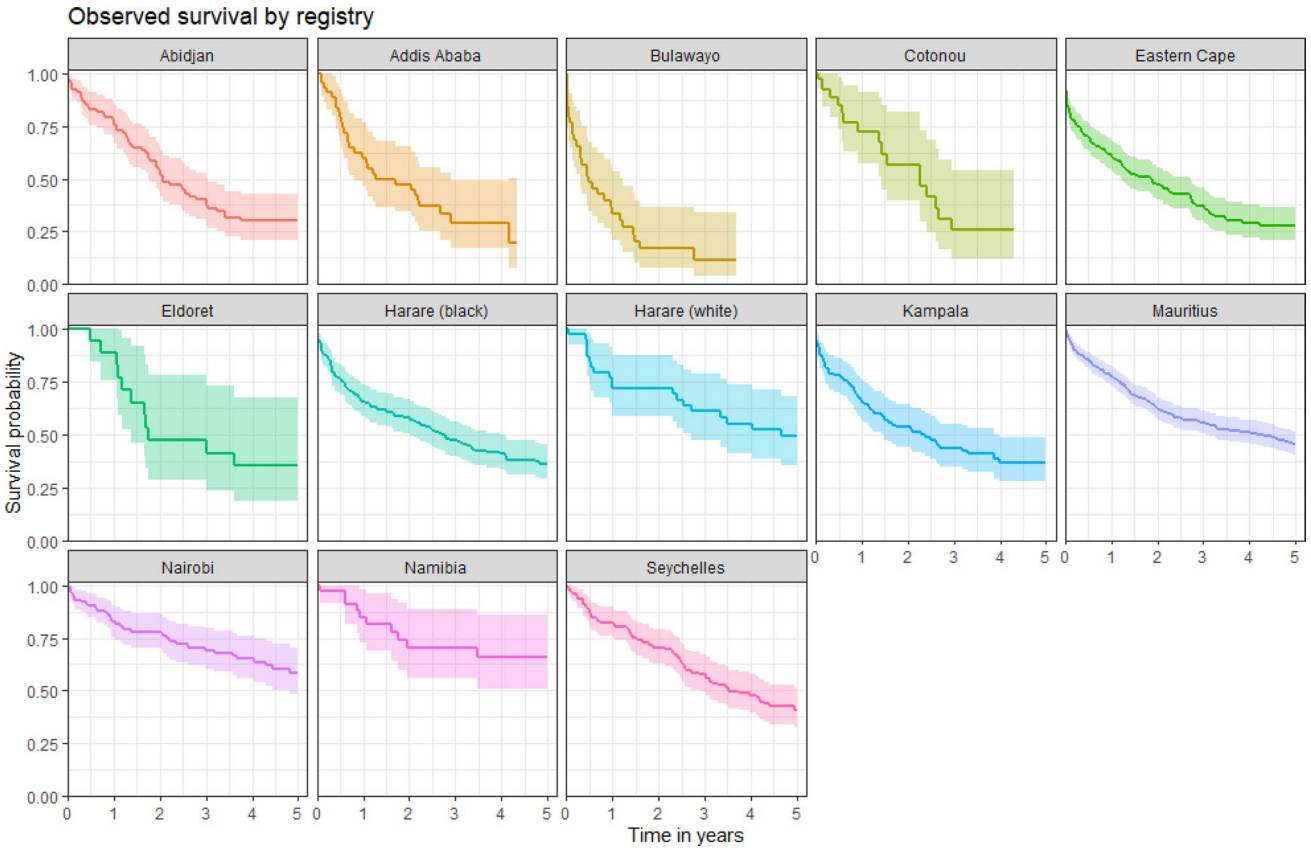

Fig. 6 Kaplan–Meier overall survival probabilities (95% confidence intervals) by registry

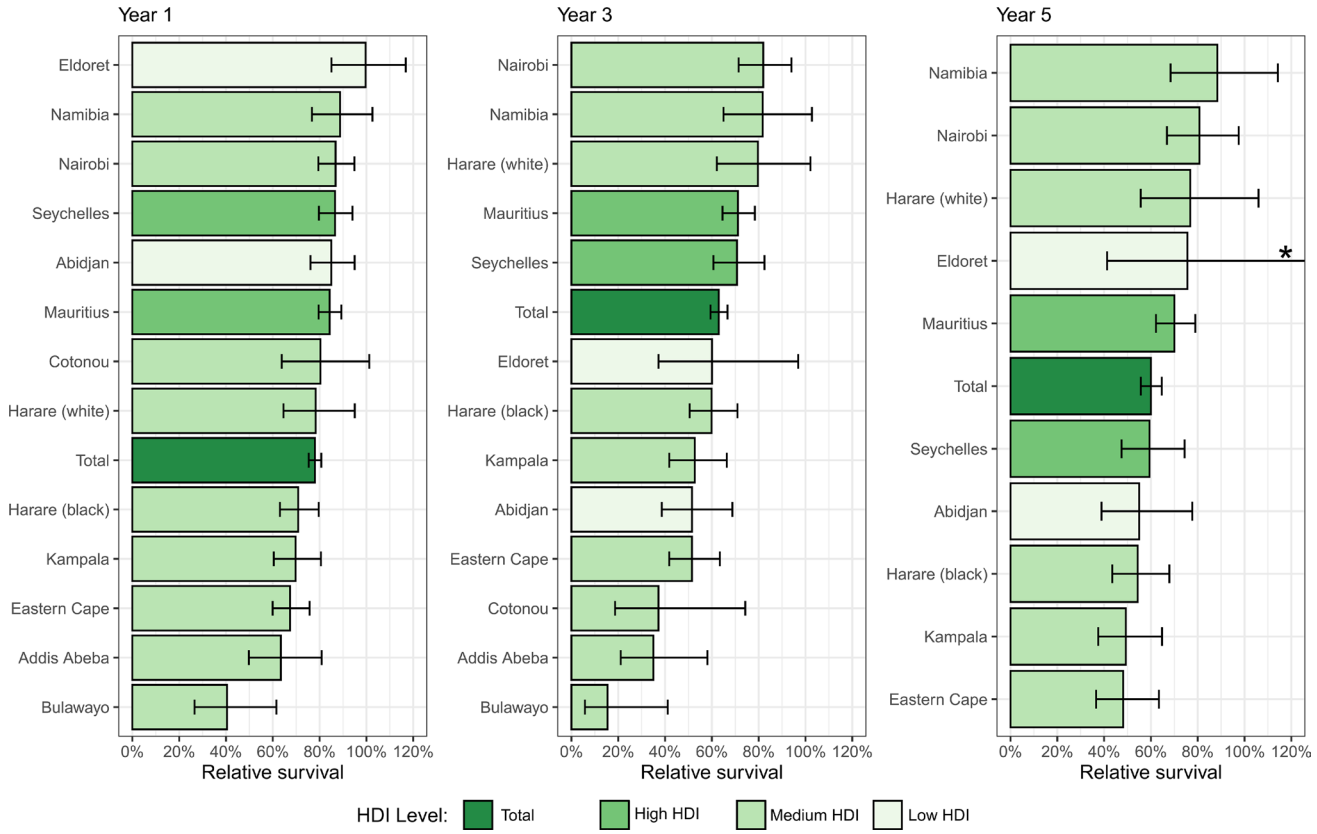

Fig. 7 1-, 3- and 5-year relative survival with 95% confidence intervals (CI) by registry and Human Development Index (HDI); *The upper limit of Eldoret's 95% CI is at 164%

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Author contributions T. P. S., E. J. K. and D. M. P. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Parkin, Joko-Fru, Seraphin; Acquisition of data: S., P., L., M., C., S., K., N., F., W., A., G., H., B.; Analysis and interpretation of data: S., P., J.-F., K.; Drafting of the manuscript: S., P., K.; Critical revision of the manuscript for important intellectual content: S., P., K., J.-F., M., C., S., K., N., F., W., A., G., H., B.; Administrative, technical, or material support: L.; Study supervision: P., K.

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Data accessibility The data that support the findings of this study are available from the corresponding author upon reasonable request, which will be evaluated by the AFCRN research committee. Details of the data application process are outlined on the AFRCN website (http:/afcrn.org/index.php/research/how-to-apply/76-research-collaborations).

Code availability The custom code used around the packages described in the methods section is available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare no potential conflicts of interest.

Ethical statement The AFCRN research committee approved this study (July 2019), as well as the respective registries. We conducted the study in accordance to the Declaration of Helsinki. The study used routinely collected, anonymised data, therefore no special ethical approval was needed.

References

1. Ferlay J, Colombet M, Soerjomataram I et al (2018) Global cancer observatory: cancer today. International Agency for Research on Cancer, Lyon, France. https://gco.iarc.fr/Today. Accessed 4 Aug 2020
2. Ferlay J, Ervik MJ, Lam F et al (2018) Global cancer observatory: cancer tomorrow. International Agency for Research on Cancer, Lyon, France. https://gco.iarc.fr/tomorrow. Accessed 4 Aug 2020
3. Seraphin TP, Joko-Fru WY, Kamaté B et al (2021) Rising prostate cancer incidence in Sub-Saharan Africa: a trend analysis of data from the African cancer registry network. Cancer Epidemiol Biomarkers Prev 30:158–165. https://doi.org/10.1158/1055-9965.EPI-20-1005
4. Atun R, Jaffray DA, Barton MB et al (2015) Expanding global access to radiotherapy. Lancet Oncol 16:1153–1186. https://doi.org/10.1016/S1470-2045(15)00222-3
5. Meara JG, Leather AJM, Hagander L et al (2015) Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. Lancet 386:569–624. https://doi.org/10.1016/S0140-6736(15)60160-X
6. Abdel-Wahab M, Bourque JM, Pynda Y et al (2013) Status of radiotherapy resources in Africa: an international atomic energy agency analysis. Lancet Oncol 14:e168–e175. https://doi.org/10.1016/S1470-2045(12)70532-6
7. Yamoah K, Beecham K, Hegarty SE et al (2013) Early results of prostate cancer radiation therapy: an analysis with emphasis on research strategies to improve treatment delivery and outcomes. BMC Cancer 13:23. https://doi.org/10.1186/1471-2407-13-23
8. Badmus TA, Adesunkanmi A-RK, Yusuf BM et al (2010) Burden of prostate cancer in southwestern Nigeria. Urology 76:412–416. https://doi.org/10.1016/j.urology.2010.03.020
9. Cassell A, Yunusa B, Jalloh M et al (2019) A review of localized prostate cancer: an African perspective. World J Oncol 10:162–168
10. Asamoah FA, Yarney J, Awasthi S et al (2018) Contemporary radiation treatment of prostate cancer in Africa: a Ghanaian experience. J Glob Oncol 4:1–13. https://doi.org/10.1200/JGO.17.00234
11. Magoha GA (2000) Management and survival in advanced prostate cancer in Nairobi. East Afr Med J 77:260–263. https://doi.org/10.4314/eamj.v77i5.46630
12. Parkin DM (2006) The evolution of the population-based cancer registry. Nat Rev Cancer 6:603–612
13. (2020) African Cancer Registry Network. https://afcrn.org/index.php/about-us. Accessed 9 Apr 2020
14. Allemani C, Matsuda T, Di Carlo V et al (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. Lancet 391:1023–1075. https://doi.org/10.1016/S0140-6736(17)33326-3
15. Sankaranarayanan R, Swaminathan R (2011) Cancer survival in Africa, Asia, the Caribbean and Central America. World Health Organization
16. Gondos A, Brenner H, Wabinga H, Parkin DM (2005) Cancer survival in Kampala, Uganda. Br J Cancer 92:1808–1812. https://doi.org/10.1038/sj.bjc.6602540
17. Gondos A, Chokunonga E, Brenner H et al (2004) Cancer survival in a southern African urban population. Int J Cancer 112:860–864. https://doi.org/10.1002/ijc.20471
18. Smits J, Permanyer I (2019) Data descriptor: the subnational human development database. Sci Data 6:1–15. https://doi.org/10.1038/sdata.2019.38
19. World Bank Group (2020) Completeness of death registration with cause-of-death information. https://data.worldbank.org/indicator/SP.REG.DTHS.ZS?locations=MU. Accessed 6 Aug 2020
20. Amin MB, Edge S, Greene F et al (2017) AJCC cancer staging manual, 8th edn. Springer International Publishing, New York
21. Fritz A, Percy C, Jack A, et al (2013) Basis of diagnosis. In: international classification of diseases for oncology (ICD-O)- 3rd edn. World Health Organization, Geneva
22. (2019) Human development report 2019 : beyond income, beyond averages, beyond today: inequalities in human development in the 21st century. United Nations Development Programme, New York
23. Brenner H, Swaminathan R (2011) Statistical methods for cancer survival analysis. In: Sankaranarayanan R, Swaminathan R, Lucas E (eds) Cancer survival in Africa, Asia, the Caribbean and Central America (SurvCan), IARC scientific publications, International Agency for Research on Cancer, World Health Organization. Lyon, France
24. R Core Team (2019) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/
25. RStudio Team (2020) RStudio: integrated development for R. RStudio, PBC, Boston, MA. http://www.rstudio.com/
26. Therneau TM, Grambsch PM (2000) Modeling survival data: extending the Cox model. Springer, New York
27. Kassambara A, Kosinski M, Biecek P (2019) Survminer: drawing survival curves using 'ggplot2'. https://rpkgs.datanovia.com/survminer/index.html
28. Bray F, Parkin DM (2009) Evaluation of data quality in the cancer registry: principles and methods. Part I: comparability, validity and timeliness. Eur J Cancer 45:747–755. https://doi.org/10.1016/j.ejca.2008.11.032
29. Perme MP, Pavlič K (2018) Nonparametric relative survival analysis with the R package relsurv. J Stat Softw 87(8):1–27. https://doi.org/10.18637/jss.v087.i08
30. World Health Institution Global Health Observatory (GHO) data. In: life tables. https://www.who.int/gho/mortality_burden_disease/life_tables/life_tables/en/
31. Lambert P (2008) RCSGEN: Stata module to generate restricted cubic splines and their derivatives. Statistical Software Components S456986, Boston College Department of Economics, revised 15 Sep 2015
32. Corazziari I, Quinn M, Capocaccia R (2004) Standard cancer patient population for age standardising survival ratios. Eur J Cancer 40:2307–2316. https://doi.org/10.1016/j.ejca.2004.07.002
33. Abdel-Rahman M, Stockton D, Rachet B et al (2009) What if cancer survival in Britain were the same as in Europe: how many deaths are avoidable? Br J Cancer 101(Suppl):S115–S124. https://doi.org/10.1038/sj.bjc.6605401
34. Dickman PW, Coviello E (2015) Estimating and modeling relative survival. Stata J Promot Commun Stat Stata 15:186–215. https://doi.org/10.1177/1536867X1501500112
35. Jemal A, Clegg LX, Ward E et al (2004) Annual report to the nation on the status of cancer, 1975–2001, with a special feature regarding survival. Cancer 101:3–27. https://doi.org/10.1002/cncr.20288

36. Potosky AL, Miller BA, Albertsen PC, Kramer BS (1995) The role of increasing detection in the rising incidence of prostate cancer. JAMA 273:548–552. https://doi.org/10.1001/jama.1995.03520310046028
37. Rebbeck TR, Zeigler-Johnson CM, Heyns CF, Gueye SM (2011) Prostate cancer screening, detection and treatment practices, among Sub-Saharan African urologists. African J Urol 17:85–91. https://doi.org/10.1007/s12301-011-0016-0
38. Ojewola RW, Oridota ES, Balogun OS et al (2017) Knowledge, attitudes and screening practices regarding prostatic diseases among men older than 40 years: a population-based study in Southwest Nigeria. Pan Afr Med J 27:151
39. Jalloh M, Niang L, Ndoye M et al (2013) Prostate Cancer in Sub Saharan Africa. J Nephrol Urol Res 1:15–20
40. Rebbeck TR, Devesa SS, Chang B-L et al (2013) Global patterns of prostate cancer incidence, aggressiveness, and mortality in men of African descent. Prostate Cancer 2013:1–12. https://doi.org/10.1155/2013/560857
41. Surveillance, Epidemiology, and End Results Program S (2020) SEER cancer stat facts: prostate cancer. https://seer.cancer.gov/statfacts/html/prost.html
42. Nakandi H, Kirabo M, Semugabo C et al (2013) Knowledge, attitudes and practices of Ugandan men regarding prostate cancer. African J Urol 19:165–170. https://doi.org/10.1016/j.afju.2013.08.001
43. Baratedi WM, Tshiamo WB, Mogobe KD, McFarland DM (2020) Barriers to prostate cancer screening by men in sub-Saharan Africa: an integrated review. J Nurs Scholarsh 52:85–94. https://doi.org/10.1111/jnu.12529
44. Coughlin SS (2019) A review of social determinants of prostate cancer risk, stage, and survival. Prostate Int 8:49–54. https://doi.org/10.1016/j.prnil.2019.08.001
45. Singh K, Abdel Goad EH, Ramklass SS (2015) Waiting times for prostate cancer diagnosis in KwaZulu-Natal. South Africa South African Med J 105:484. https://doi.org/10.7196/SAMJ.9192
46. Holmer H, Lantz A, Kunjumen T et al (2015) Global distribution of surgeons, anaesthesiologists, and obstetricians. Lancet Glob Heal 3:S9–S11. https://doi.org/10.1016/S2214-109X(14)70349-3
47. Zubizarreta E, Van Dyk J, Lievens Y (2017) Analysis of global radiotherapy needs and costs by geographic region and income level. Clin Oncol 29:84–92. https://doi.org/10.1016/j.clon.2016.11.011
48. McGinley KF, Tay KJ, Moul JW (2016) Prostate cancer in men of African origin. Nat Rev Urol 13:99–107. https://doi.org/10.1038/nrurol.2015.298
49. Chornokur G, Dalton K, Borysova ME, Kumar NB (2011) Disparities at presentation, diagnosis, treatment, and survival in African American men, affected by prostate cancer. Prostate 71:985–997. https://doi.org/10.1002/pros.21314
50. Krimphove MJ, Cole AP, Fletcher SA et al (2019) Evaluation of the contribution of demographics, access to health care, treatment, and tumor characteristics to racial differences in survival of advanced prostate cancer. Prostate Cancer Prostatic Dis 22:125–136. https://doi.org/10.1038/s41391-018-0083-4
51. DeRouen MC, Schupp CW, Koo J et al (2018) Impact of individual and neighborhood factors on disparities in prostate cancer survival. Cancer Epidemiol 53:1–11. https://doi.org/10.1016/j.canep.2018.01.003
52. Piñeros M, Parkin DM, Ward K et al (2019) Essential TNM: a registry tool to reduce gaps in cancer staging information. Lancet Oncol 20:e103–e111. https://doi.org/10.1016/S1470-2045(18)30897-0
53. Bryere J, Pornet C, Copin N et al (2017) Assessment of the ecological bias of seven aggregate social deprivation indices. BMC Public Health 17:86. https://doi.org/10.1186/s12889-016-4007-8
54. Wong MCS, Goggins WB, Wang HHX et al (2016) global incidence and mortality for prostate cancer: analysis of temporal patterns and trends in 36 countries. Eur Urol 70:862–874. https://doi.org/10.1016/j.eururo.2016.05.043
55. Rutherford MJ, Møller H, Lambert PC (2013) A comprehensive assessment of the impact of errors in the cancer registration process on 1- and 5-year relative survival estimates. Br J Cancer 108:691–698. https://doi.org/10.1038/bjc.2013.12

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Global Health and Cancer

Cervical Cancer in Sub-Saharan Africa: A Multinational Population-Based Cohort Study of Care and Guideline Adherence

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Cervical cancer • Sub-Saharan Africa • Population-based • Access to care • Radiotherapy • Survival

Abstract

Background. Cervical cancer (CC) is the most common female cancer in many countries of sub-Saharan Africa (SSA). We assessed treatment guideline adherence and its association with overall survival (OS).

Methods. Our observational study covered nine population-based cancer registries in eight countries: Benin, Ethiopia, Ivory Coast, Kenya, Mali, Mozambique, Uganda, and Zimbabwe. Random samples of 44–125 patients diagnosed from 2010 to 2016 were selected in each. Cancer-directed therapy (CDT) was evaluated for degree of adherence to National Comprehensive Cancer Network (U.S.) Guidelines.

Results. Of 632 patients, 15.8% received CDT with curative potential: 5.2% guideline-adherent, 2.4% with minor deviations, and 8.2% with major deviations. CDT was not documented or was without curative potential in 22%; 15.7% were diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage IV disease. Adherence was not assessed in 46.9% (no stage or follow-up documented, 11.9%, or records not traced, 35.1%). The largest share of guideline-adherent CDT was observed in Nairobi (49%) and the smallest in Maputo (4%). In patients with FIGO stage I–III disease (n = 190), minor and major guideline deviations were associated with impaired OS (hazard rate ratio [HRR], 1.73; 95% confidence interval [CI], 0.36–8.37; HRR, 1.97; CI, 0.59–6.56, respectively). CDT without curative potential (HRR, 3.88; CI, 1.19–12.71) and no CDT (HRR, 9.43; CI, 3.03–29.33) showed substantially worse survival.

Conclusion. We found that only one in six patients with cervical cancer in SSA received CDT with curative potential. At least one-fifth and possibly up to two-thirds of women never accessed CDT, despite curable disease, resulting in impaired OS. Investments into more radiotherapy, chemotherapy, and surgical training could change the fatal outcomes of many patients. ***The Oncologist*** 2021;26:e807–e816

Implications for Practice: Despite evidence-based interventions including guideline-adherent treatment for cervical cancer (CC), there is huge disparity in survival across the globe. This comprehensive multinational population-based registry study

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aimed to assess the status quo of presentation, treatment guideline adherence, and survival in eight countries. Patients across sub-Saharan Africa present in late stages, and treatment guideline adherence is remarkably low. Both factors were associated with unfavorable survival. This report warns about the inability of most women with cervical cancer in sub-Saharan Africa to access timely and high-quality diagnostic and treatment services, serving as guidance to institutions and policy makers. With regard to clinical practice, there might be cancer-directed treatment options that, although not fully guideline adherent, have relevant survival benefit. Others should perhaps not be chosen even under resource-constrained circumstances.

Introduction

Cervical cancer (CC) shows large differences in outcome globally depending on stage at presentation to the health system and access to high-quality care. Both may vary depending on individual patient factors and local or country-specific availability of diagnostic and treatment services. Assessing of treatment guideline adherence at the patient level and linking this to outcome is an established approach [1, 2]. This is a multinational, population-based study of the pattern and degree of adherence to guidelines of care, and its association with outcome, in patients with CC in sub-Saharan Africa (SSA).

The burden of CC is currently decreasing in high-income countries. For example, age-standardized annual incidence of CC in the U.S. fell to 7.4 in 100,000 in 2010–2014 from more than 40 in 100,000 in 1947–1948 largely because of wide dissemination of screening during this period [3]. In contrast, in SSA—without comprehensive screening—age-standardized incidence rates range from 26.8 in Central Africa to 43.1 in 100,000 in Southern Africa, with Zimbabwe even reporting 62.3 in 100,000 in 2018. Of the estimated 570,000 CC diagnoses and 311,000 cervical cancer deaths in the world in 2018, 112,000 (20%) of new diagnoses and 76,000 (24%) of the deaths occur in SSA [4], despite SSA accounting for only 9.4% of women older than 20 years worldwide [5].

Population-based data on stage at diagnosis are limited in SSA, and those that are available report a substantial proportion of cervical cancer cases diagnosed at late stages. For example, 30% of patients in Uganda presented with International Federation of Gynecology and Obstetrics (FIGO) stage III–IV disease, and 58% of patients in Zimbabwe presented with regional and metastatic disease [6, 7]. With a higher proportion of staged patients, but more selective by nature, recent hospital cohorts yield comparable stage patterns, for example, 81% with stage IIb–IV in a center in Addis Ababa, Ethiopia [8].

Similarly, population-based survival data for CC are limited, but a recently published large survey reports age-standardized relative survival (ASRS) of 69.8%, 44.5%, and 33.1% at 1, 3, and 5 years [9]. Additionally, there are premillennium cohorts that report 49% 5-year ASRS in Uganda and 45% 3-year ASRS in Zimbabwe [6, 7].

The situation of CC care in SSA from a health care infrastructure point of view can be gauged first from the gaps between calculated need and actual availability of radiotherapy services [10] and, secondly, from Global Surgery 2030's estimate that 93% of SSA's population does not have access to safe, timely, and affordable surgery [11]. In addition, although access to chemotherapy is increasing, it is still limited, and its safe administration is a major concern where there is a shortage of oncology personnel [12].

The consequences of these shortfalls in SSA health care systems have so far rarely been examined at an individual level. No previous study has described the pattern of CC care and guideline adherence using a population-based approach, nor has there been a longitudinal examination of the degree to which guideline adherence is linked to survival of patients with CC in SSA. This led to our main research questions: Firstly, what is the quality of CC therapy in SSA in terms of degree of guideline adherence? Secondly, to what extent is overall survival associated with therapy guideline adherence when adjusted for patient characteristics and stage?

With its multinational collection of registry data and multimodal evaluation of degree of therapy guideline adherence, the present study adds population-based evidence on status of CC care and outcomes in a SSA setting.

Materials and Methods

Study Design

This is a multinational retrospective population-based study, drawing patients from nine population-based cancer registries: Abidjan (Ivory Coast), Addis Ababa (Ethiopia), Bamako (Mali), Bulawayo (Zimbabwe), Cotonou (Benin), Eldoret (Kenya), Kampala (Uganda), Maputo (Mozambique), and Nairobi (Kenya). These registries cover populations between 800,000 (Cotonou) and four million (Abidjan) inhabitants. All are members of the African Cancer Registry Network (AFCRN), which since 2013 has coordinated sub-Saharan population-based cancer registries as the International Agency for Research on Cancer's regional hub [13].

Sources of Data and Study Population

After excluding cases registered based on a death certificate only, random samples of patients diagnosed with invasive cancers of the cervix (International Classification of Diseases-10 C53.x) between January 1, 2010, and June 30, 2016, were drawn within the sampling frame of the database of the African Cancer Registry Network. In Addis Ababa, we included all cases diagnosed from January to March 2012 and 2014. A sample size of 700 produces a two-sided 95% confidence interval with a width equal to 0.075 when the sample proportion of patients with adequate care is 0.500. We drew a simple random sample of 45 to 125 patients per registry (mean n = 75) to amount to 700 patients. For logistic reasons, it was impossible to include all patients diagnosed in that period. Follow-up was open for 7 years until December 31, 2017 (Fig. 1).

Data collection was integrated into registration work, based on the AFCRN Standard Procedure Manual Version 2 [14]. The databases of the participating registries include basic demographic and tumor characteristics (including basic

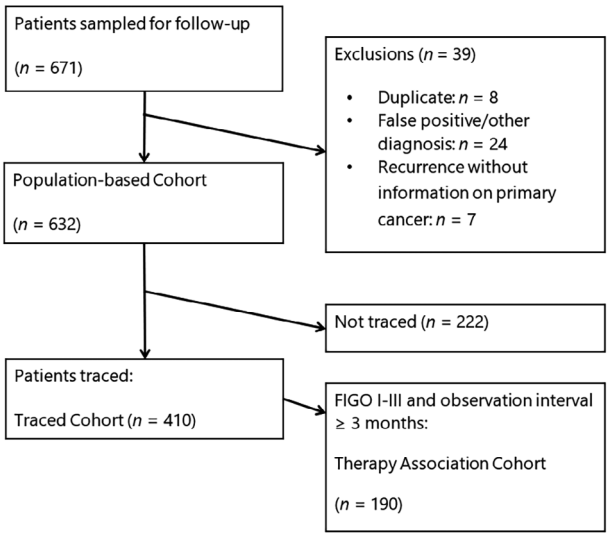

Figure 1. Trial flow diagram. Patients with hospital files found or successful telephone contact were considered to be traced. Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

staging) and, infrequently, basic initial treatment data. Clinical records of registered cases were traced via the source(s) recorded in the registry, information on date of diagnosis and stage was verified or updated, and any duplicates were excluded (Fig. 1). The registry records were updated with information on diagnostic procedures, treatment received, and patients' vital status. However, if this information could not be found in clinical records, we attempted to contact the patient or their relatives through all phone numbers available in the records and hospital information systems to ascertain treatment details and survival status. This also enabled us to inquire about within-country and international referral undocumented in the records. Cases for which a health record or additional information was found after this active follow-up are subsequently referred to as "traced cases" and "traced cohort."

Stage at diagnosis was obtained from physicians' clinical assessments in the records in line with FIGO's 2009 classification [15]; T1–T3 with radiologically or pathologically positive pelvic nodes were grouped as FIGO stage III. In some cases, clinical FIGO stage was amended by additional information from imaging or pathology findings in line with the abovementioned AFCRN Manual. Performance status at diagnosis as Eastern Cooperative Oncology Group (ECOG) score was collected. Four detailed aspects of cancer-directed therapy (CDT) were recorded: surgery, external beam radiation therapy (EBRT), brachytherapy, and chemotherapy. When details such as hysterectomy or radiotherapy dose were not further specified but the record reported "complete," we assumed the treatment was performed with adherence to guidelines as a necessary simplification.

Therapy Evaluation

U.S. National Comprehensive Cancer Network (NCCN) CC Guidelines 1.2010 (actually prepared for the high-income setting) reflected the optimum standard of CC care at the beginning of our study period [16]. These were in widespread use in low- and middle-income countries and parts of SSA and were therefore chosen as a point of reference [17, 18]. Physicians also used locally adapted guidelines, other guidelines, or adjusted treatment according to specific patient characteristics and resource limitations. Because of the retrospective nature of the study using real-world data, these factors were not captured in our analytical database. Still, we aimed to use NCCN Guidelines as standard to give an overall picture on access to care rather than a posteriori judging the individual treatment decisions. We compiled a scheme for evaluating degree of adherence (Table 1). Guideline adherence was assessed for cases known to be FIGO stage I–III. Each stage-dependent category includes key procedures and modalities required to reach a certain degree of adherence. Note that not all possible treatment variations were depicted, and possible overtreatment was not the focus of the study. "Guideline-adherent" was the minimum sufficient therapy recommended. Courses of chemotherapy alone, EBRT <45 Gy, and surgical intervention without removal of the tumor were defined as "CDT without curative potential."

Outcome

Outcome, in terms of date and vital status (alive/dead) at the last known contact, as recorded by the cancer registries, was verified and/or updated from the clinical records. When no information could be found, contact by telephone with the patient or next of kin was attempted. The precise cause of death, as certified by a medical practitioner, could rarely be determined.

Statistical Methods

Overall survival (OS) was estimated using the Kaplan-Meier method, and differences according to prognostic factors were assessed with the log rank test. ASRS was calculated for the traced cohort. Relative survival was determined using SAS macro "periodh" [19]. Because of the small number of patients per registry per year and because differences in baseline mortality of the age groups studied between the countries were small (see supplemental online Table 2) [20], only a single life table was created: World Health Organization life tables from the eight countries for the year 2013 as the median year of diagnosis of all patients were retrieved and the average calculated [20]. For age standardization the direct method and International Cancer Survival Standard 2 with its "broad age groups" were employed [21]. We assume that the small sample of cases (632) is representative of cervix cancer cases in sub-Saharan Africa and that the missing cases (35% of patients who cannot be traced; 2% of patients whose files that miss staging information) were missing at random. Extrapolation of therapy evaluation results for SSA was done by using simple multiplication with rounding to 1,000 and assuming representativeness and missing information at random.

To assess the association between treatment guideline adherence and survival, Cox multiple regression was employed for the therapy association cohort (follow-up $\geq$3 months, FIGO stage $\leq$III). The inclusion criteria were chosen to reduce survivorship bias. The assumption of

Table 1. Therapy evaluation scheme for patients with known FIGO stage

Therapy; FIGO stage	Guideline adherent (FIGO stage I–III applicable only)	Minor deviation (FIGO stage I–III applicable only)	Major deviation (FIGO stage I–III applicable only)	CDT without curative potential (FIGO stage I–III applicable only)	No CDT detected, FU <3 months (FIGO stage I–III applicable only)	No CDT detected, FU ≥3 months (FIGO stage I–III applicable only)
Curative primary surgery						
IA1	Excision with free margins, e.g., through conization, simple hysterectomy	—	Any cancer-directed surgery with possible tumor destruction, e.g., laser vaporization or cryotherapy	—	No CDT identified, but patient dead/ lost to FU <3 months after diagnosis	No CDT identified in patients with FU ≥3 months
IA2–IIA	(IA2: Modified) Radical hysterectomy + pelvic LAE	(IA2: Modified) Radical hysterectomy	Any less radical procedure for removal of tumor, e.g., simple hysterectomy	Any surgery with remaining parts of cervix/ primary tumor	No CDT identified, but patient dead/ lost to FU <3 months after diagnosis	No CDT identified in patients with FU ≥3 months
IIB	—	Radical hysterectomy + pelvic LAE	Radical hysterectomy	Any less radical surgery than radical hysterectomy	No CDT identified, but patient dead/ lost to FU <3 months after diagnosis	No CDT identified in patients with FU ≥3 months
Curative primary radiotherapy						
IB–III	EBRT ≥45 Gy + concurrent chemotherapy ≥2 cycles + brachytherapy ≥16.6 Gy	EBRT ≥45 Gy + brachytherapy ≥16.6 Gy	EBRT ≥45 Gy (with or without chemotherapy	EBRT <45 Gy or missing	No CDT identified, but patient dead/ lost to FU <3 months after diagnosis	No CDT identified in patients with FU ≥3 months
T1–3 N1	EBRT ≥45 Gy + concurrent chemotherapy ≥2 cycles + brachytherapy ≥16.6 Gy if primary is not resected	EBRT ≥45 Gy + brachytherapy ≥16.6 if primary is not resected	EBRT ≥45 Gy (with or without chemotherapy)	EBRT <45 Gy or missing	No CDT identified, but patient dead/ lost to FU <3 months after diagnosis	No CDT identified in patients with FU ≥3 months
Obligatory palliative care: IVA–IVB	Individual approaches with or without CDT, labeled "FIGO stage IV, any approach"					

Therapy was considered for evaluation if documented within 2 years and not indicated for relapse. References and considerations on which this scheme is based apart from National Comprehensive Cancer Network Guidelines version 1.2010 can be found in supplemental online Table 1.
Abbreviations: CDT, cancer-directed therapy; EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; FU, follow-up, observation after date of incidence; LAE, lymphadenectomy; N1, radiologically or pathologically involved pelvic lymph nodes.

proportionality of hazards was checked graphically and found to be satisfactory.

Ethics

The study protocol was approved by the AFCRN review committee (02.03.2016) and Halle University Review Board (votum no. 2019-009). The study group used anonymized secondary data, which were collected under existing regulations and national laws in the respective registries. Funding sources had no role in study design, collection, analysis, or interpretation of the data.

Results

The median age at diagnosis in our population-based cohort was 50 years. The most common stage was FIGO III, and the most common histology was squamous cell carcinoma (Table 2).

For the population-based cohort (n = 632) in general, we found that about one-eighth of patients had received some form of external beam radiotherapy (EBRT) and one-eighth some form of surgery. Information additional to that recorded by the cancer registries could not be found for 35% of the patients. Of the patients we could trace

(n = 410), more than half (or 31% of the total cases) lacked essential information for therapy evaluation. Guideline adherence of care varied according to FIGO stage group (supplemental online Table 3).

Quality and delay of radiotherapy were assessed. Only one-fifth of the traced cohort (n = 410) received primary EBRT. In detail, there were 73 nonsurgical patients, and of these 60 (82%) were staged FIGO I–III in need of curative EBRT with concurrent chemotherapy and subsequent brachytherapy [16]; of these latter 60 patients in need, 8 (13%) were documented as certainly incomplete. Furthermore, only 8 (13%) of 60 patients had brachytherapy as part of their treatment, and only 22 (37%) of 60 patients received concurrent chemotherapy. A median delay of 14 weeks (range, 1–73 weeks) between diagnosis and the start of EBRT was noted in 45 patients whose files had exact EBRT dates.

Radiation was also incomplete for 10 patients with node-positive disease who had received operations. Only three of them had documented EBRT after surgery, whereas four of the remaining seven patients with node-positive disease were observed for ≥12 months without EBRT.

Chemotherapy as the only CDT was seen in 66 (16%) of patients in the traced cohort, of whom there were 42 (64%) patients with FIGO stage I–III. Eighteen (43%) of these 42 patients were observed for more than 12 months without further CDT being documented.

Statements on guideline adherence and quality of care were possible for two-thirds of traced patients. Evaluation was impossible for one-third of traced patients because of lack of information on stage, early death, and observation less than 3 months. When we evaluated the degree of guideline adherence among the whole population-based cohort, the proportion of patients with known optimal guideline-adherent therapy came down to a total of only 5%; an additional 11% received therapy with curative potential showing minor or major deviations (Fig. 2). The proportions of guideline-adherent therapy were higher among patients with early stages compared with late-stage presentation (see supplemental online Table 3 and supplemental online Fig. 1). A total of 19% of patients certainly received therapy without curative potential or no therapy at all. In the worst-case scenario, that is, no further CDTs in the untraceable patients, this would mean that only 16% received any CDT with curative potential, whereas 67% of patients were receiving CDT without curative potential or no therapy at all. Additionally, 17% of patients were known FIGO stage IV in need of palliative care (Fig. 2).

We found large disparities in care within the populations of the different countries. Populations from centers with radiotherapy available (Addis Ababa, Kampala, and Nairobi) had higher proportions of patients with guideline-adherent therapy or minor and major deviations compared with those centers without radiotherapy facilities (Fig. 3).

Data come from eight countries only, but to highlight the possible broader implications of our findings, we extrapolated the findings of our cohort to all 112,000 estimated newly diagnosed cervical cancer cases each year in SSA [4]. This translated to 9,000 (8%) patients with FIGO stage I–III who received guideline-adherent care, 4,000 (4%) with FIGO stage I–III who received minor deviations and 15,000 (13%) major deviations, 19,000 (17%) with FIGO stage I–III who received CDT without curative potential, 19,000 (17%) more patients with FIGO stage I–III who did not receive any CDT though observed beyond 3 months, 18,000 (16%) patients with FIGO stage I–III who died or got lost to follow-up within 3 months of diagnosis and had no CDT documented, and

Table 2. Patient characteristics of the population-based cohort (n = 632)

Characteristics	*n* (%)
Age group (median: 50 years; IQR: 40–58 years; range 16–99 years)	
<40 years	143 (23)
40–59 years	335 (53)
≥60 years	154 (24)
Registry	
Abidjan, Ivory Coast	67 (11)
Addis Ababa, Ethiopia	92 (15)
Bamako, Mali	59 (9)
Bulawayo, Zimbabwe	55 (9)
Cotonou, Benin	37 (6)
Eldoret, Kenya	82 (13)
Kampala, Uganda	60 (9)
Maputo, Mozambique	122 (19)
Nairobi County, Kenya	59 (9)
HIV status	
Negative	78 (12)
Positive	82 (13)
Unknown	250 (40)
Not traced	222 (35)
ECOG performance	
ECOG 0–1	88 (14)
ECOG 2	61 (10)
ECOG 3–4	25 (4)
Unknown	236 (37)
Not traced	222 (35)
FIGO stage	
I	49 (8)
II	91 (14)
III (incl. T1–T3, pelvic N1)	123 (19)
IV	99 (16)
Unknown	48 (8)
Not traced	222 (35)
Histology	
Squamous cell carcinoma	443 (70)
Adenocarcinoma	40 (6)
Other	4 (1)
Carcinoma	41 (6)
Neoplasm, malignant	104 (16)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range.

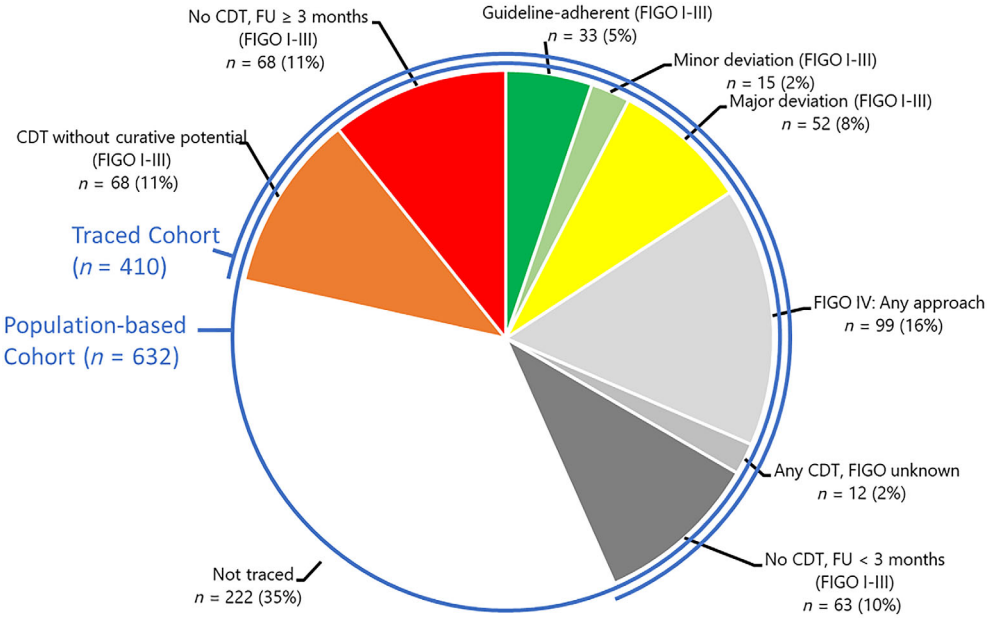

Figure 2. Therapy evaluation in the population-based cohort (*n* = 632). Evaluations refer to the therapy evaluation scheme in Table 1. Colors depict the degree of adherence: green indicates optimal, light green minor deviation, yellow major deviation, orange CDT without curative potential, and red no CDT. Light gray indicates patients with FIGO stage IV, middle and darker gray indicates missing stage or observation time, and no color indicates untraced patients. Patients with hospital files found or successful telephone contact were considered to be traced.
Abbreviations: CDT, cancer-directed therapy; FIGO, International Federation of Gynecology and Obstetrics; FU, follow-up (time of observation since diagnosis).

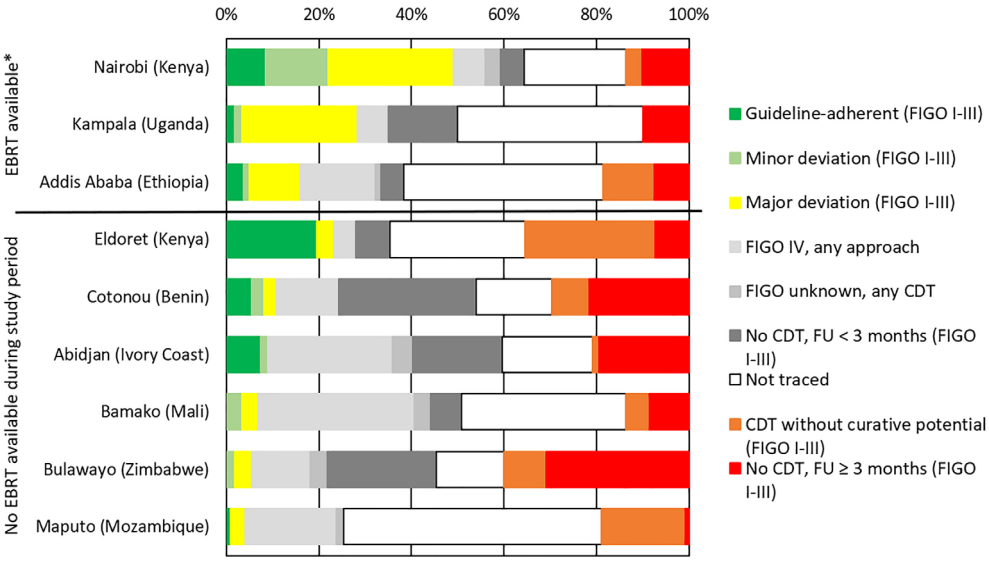

Figure 3. Therapy evaluation in the population-based cohort (*n* = 632) stratified by registry. Evaluations refer to the therapy evaluation scheme in Table 1. Colors depict the degree of adherence: green indicates optimal, light green minor deviation, yellow major deviation, orange CDT without curative potential, and red no CDT. Light gray indicates patients with FIGO stage IV, middle and darker gray indicates missing stage or observation time, and white indicates the proportion of untraced patients. *, Principal EBRT availability at the study site did not exclude overstrain or temporary breakdown of machines. EBRT in Bulawayo was nonfunctional during the whole study period.
Abbreviations: CDT, cancer-directed therapy; EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; FU, follow-up (time of observation since diagnosis).

28,000 (25%) patients who were diagnosed with FIGO stage IV and, hopefully, were subject to individualized care. Patients in the inconclusive categories "Not traced" (*n* = 222) and "Any CDT, FIGO unknown" (*n* = 12) were omitted at this point.

OS in the traced cohort (*n* = 410) at 1, 2, and 3 years was 74% (95% confidence interval [CI], 69.3%–78.7%), 51.3% (95% CI, 45%–57.6%), and 41.3% (95% CI, 34.6%–48%), respectively (Fig. 4). A total of 22 patients died within the first month (median at 7 days) after formal diagnosis.

One-, 3-, and 5-year ASRSs were 75.6% (95% CI, 70.9%–80.3%), 42.4% (95% CI, 35.5%–49.7%), and 28.7% (95% CI, 19.9%–37.5%). OS differed between FIGO stages I and II versus stages III and IV ($p < .001$). Three-year OS was similar for women with FIGO stage I and II cancer (60.8% and 58.2%) but considerably lower for women with FIGO stage III and IV cancer (27.8% and 17.8%) (supplemental online Fig. 2).

Multiple Cox regression analysis was done with adjustment for FIGO stage, age group, HIV status, and ECOG performance status among patients with known stage and more than 3 months' observation time. Lack of CDT was the variable most strongly associated with negative effect on survival. CDT without curative potential (hazard rate ratio [HRR], 3.88; 95% CI, 1.19–12.71) and no CDT (HRR, 9.43; 95% CI, 3.03–29.33) were associated with worse survival. Minor (HRR, 1.73; 95% CI, 0.37–7.37) and major deviations (HRR, 1.97; 95% CI, 0.59–6.56) were associated with somewhat worse survival. FIGO stage III (HRR, 2.21; 95% CI, 1.01–4.48) and HIV positivity (HRR, 2.00; 95% CI, 1.01–3.96) status were also associated with worse survival (Fig. 5).

To facilitate quantitative comparison with a 2005–2011 Australian cohort [22], we additionally analyzed a subcohort including only patients with FIGO stage I and II ($n = 111$). In this subcohort, adherence to guidelines was associated with a substantially better survival (HRR, 0.30; CI, 0.11–0.86).

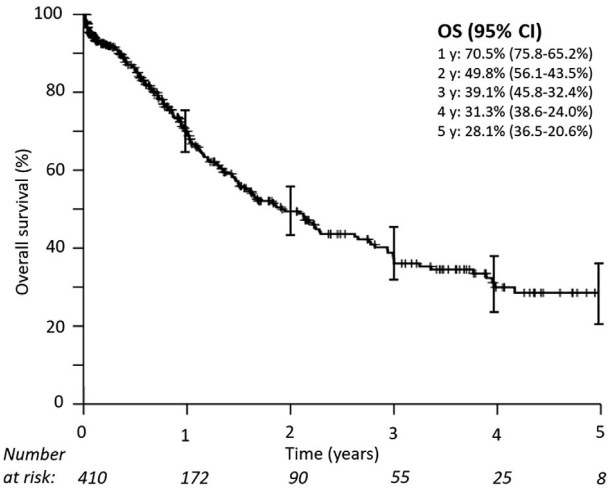

Figure 4. Overall survival in the traced cohort ($n = 410$). Median overall survival was 23 months. Patients with hospital files found or successful telephone contact were considered to be traced.
Abbreviations: CI, confidence interval; OS, overall survival.

Discussion

The most alarming finding in our population-based, cross-sectional assessment of NCCN Guidelines–recommended receipt of therapy in eight SSA countries was that for two-thirds of patients with CC, no documented CDT could be found despite thorough investigations, and in the worst-case scenario, these patients did not receive any CDT at all. Additionally, of the 37% patients with valid treatment evaluation, only half received CDT with curative potential. By country, the proportion of patients receiving CDT with curative potential varied from 4% in Maputo (Mozambique) to 49% in Nairobi (Kenya). But also, within countries we saw huge inequality. Our study was performed mainly in capital cities (exceptions: Eldoret and Bulawayo, both still major centers). All have tertiary referral oncology centers, which, however, were only partly equipped with radiotherapy facilities, and patients within population-based registry areas lived close to

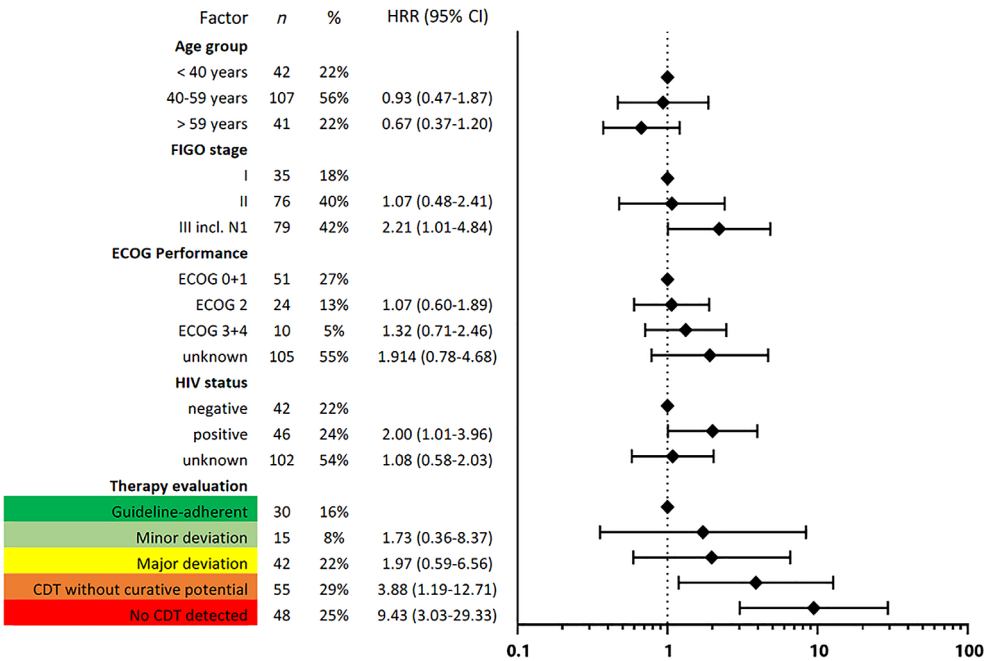

Figure 5. Results of multiple Cox regression for risk of early death in the therapy association cohort ($n = 190$) are shown: through inclusion criteria (FIGO stages I–III and follow-up ≥3 months), bias was reduced. Therapy evaluation refers to Table 1.
Abbreviations: CDT, cancer-directed therapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HRR, hazard rate ratio.

those centers. According to international recommendations, all centers had far too few radiotherapy facilities [23]. In this respect, we found that cancer centers in registry areas with EBRT available managed to provide CDT with curative potential to only 15%–49% of patients (Addis Ababa, Nairobi, and Kampala), whereas only 10% of patients in countries without radiotherapy facilities received CDT with curative potential—except Eldoret (Kenya) with 23%, where we know that a screening program is in place [24]. In general, economic, epidemiologic, and radiotherapy indicators confirm differences between the countries in our scope but also the backlog relative to Australia and the U.S., which we used for comparisons elsewhere in this report (supplemental online Table 4).

Excluding subjects with missing information, our estimated findings imply that only 28,000 of 112,000 annual patients with CC in SSA received CDT with curative potential [4]; 38,000 up to 56,000 received CDT without curative potential or no CDT. Approximately 28,000 patients presented in FIGO stage IV needing palliative care. These projections are optimistic because they assume that results in large city situations are generalizable to the whole population, including rural settings where access to therapy is likely to be worse.

In general, care of patients with CC requires specialized multimodal therapy with radiotherapeutic and surgical options. This applies to an even greater extent to patients with FIGO stage ≥II (86.5% of patients with staging information available). Given the patient pathways and observed treatment patterns, we assume that certain factors may have greatly reduced the proportion of patients receiving guideline-adherent care. The identified problems include a lack of specialized facilities and personnel for diagnosis [25], surgery [11], interrupted provision of chemotherapy drugs [12], and both individual poverty and lack of health insurance. The well-known and still widespread lack of EBRT and brachytherapy services has great impact and is also seen in our cohort [10]. Only 13% of patients with known FIGO stages I–III received primary EBRT and brachytherapy. This is comparable to findings from a population-based Ugandan cohort of 261 patients described 20 years ago (1995–1997): only 25% of patients with FIGO stages I–IV received primary EBRT and brachytherapy [6]. In contrast, in the Surveillance, Epidemiology, and End Results (SEER) program areas of the U.S., 59%–83% of patients with FIGO stages IB2–IVA received adequate radiotherapy in 1988–2009 [26]. Similarly, in Australia, treatment for patients with FIGO stages I–IVa was guideline adherent for more than half (54.1%) of the patients in 2005–2011 [22]. Our most important result of 16% strict guideline adherence among 190 patients (in the therapy association cohort; Fig. 5) is by far the lowest rate reported in the literature to this date.

This low adherence was associated with poor outcome. Analysis of survival showed 1-, 3-, and 5-year-ASRSs of 75.6%, 42.4%, and 28.7%. This survival is similar to Ugandan (81.4% and 49%) and Zimbabwean (66% and 44.9%) 1995–1997 population-based 1- and 3-year ASRS estimates, although the reference population for standardization slightly different [6, 7]. In contrast, the U.S. SEER estimate of 67.1% 5-year ASRS for the 2007–2013 period [27], taken as example of CC survival in a high-income country, is much higher. As expected, patients with FIGO stages I and II had considerably better outcome probabilities than those with FIGO stages III and IV. This should encourage education of health care workers to be able to recognize and interpret symptoms of CC and refer patients earlier.

Using the patient group with known FIGO stages I–III and ≥3 months' observation time, we analyzed the effect of known prognostic factors and degree of treatment completeness on outcome. In 2017, NCCN published Harmonized Guidelines specific to low-resource regions such as SSA [28]. These guidelines contain information on standard treatment, but also alternative options when resources are not available. The impact of an implementation of these NCCN Harmonized Guidelines for SSA obviously cannot be assessed in a randomized trial. The relationship between different degrees of therapy adherence and better survival observed in our study supports these guidelines' principles of recommending well-considered, specific deviations from maximum care if needed. Association of therapy with survival followed a dose-response effect, with the HRRs increasing with less guideline adherence. Treatment with minor deviations was associated with 1.7-times increased risk of death, major deviations were associated with a doubled hazard ratio, and "CDT without curative potential" and "no CDT" were associated with detrimental fourfold and ninefold higher hazards of death, respectively, compared with guideline-adherent treatment. As we do not expect extensive short-term improvements in CC care in SSA, we conclude that therapy with selected minor and major deviations (Table 1) such as recommended in the NCCN Harmonized Guidelines for SSA are justifiable options.

Treatment attempts without curative potential should be avoided, such as discontinuation of radiotherapy resulting in underdosing, chemotherapy only, surgery in patients with FIGO stage >IIb, or inappropriate surgery in patients with FIGO stage ≤IIb. We found that such practices were associated with a nearly fourfold risk of early death compared with guideline-adherent practices. It is also possible that they cause considerable morbidity as well as financial burden in patients and family members [29]. Of course, it is even less acceptable to see patients managed without any CDT in a curative situation, with risk of early death increased ninefold.

In patients with fully guideline-adherent treatments, the risk of early death was similar in our study (HRR, 0.30; 95% CI, 0.11–0.86; n = 111) compared with an Australian subcohort with FIGO stage I and II patients (HRR, 0.22; 95% CI, 0.07–0.75; n = 106) in 2005–2011 [22].

General limitations in our study include imprecise staging, poor documentation and record keeping, and early loss to follow-up [6–9, 30]. First, to assess completeness of therapy, we included patients from the population-based registries, among which there is no selection bias in contrast to hospital-based studies. Second, we assume there could have been a survivorship bias, because patients with aggressive disease and early death never had a chance to receive therapy and thus could have contributed to lower survival in the group without therapy. We also anticipated immortal-time bias for those patients receiving treatment. Therapy uptake might not have been at random but also might have been

linked to factors associated with outcome. To reduce inflation of therapy effects, we only included into regression analysis patients with survival of at least 3 months after diagnosis. Consequently, the analysis started 3 months after diagnosis [31]. Third, patients without any information were a large group of 35%. We decided not to make assumptions about therapy received and to present the data as unknown. Findings on stage pattern, number of patients left untreated, 1- and 3-year ASRSs, and proportion of HIV-positive patients were similar to previous studies from Ethiopia, Kenya, and Zimbabwe and reassuring as to the representativeness of our cohort [6–8]. Seeing a total of 22 among 410 patients in the traced cohort who died within the first month (median survival 7 days) shows that late presentation and late formal diagnosis is another reason for very short survival times in our cohort. Upcoming prospective studies from population-based cancer registries may result in more detailed information on therapy and outcome [32].

Conclusion

In this population-based study from eight African countries, up to two-thirds of patients with CC received treatment without curative potential or no therapy at all (worst-case scenario assuming those without documented information were left without therapy). Lack of therapy and advanced stage were associated with very low survival rates, similar to data reported 20 years ago from Uganda and Zimbabwe. Implementation of vaccination, early detection, and screening could reduce the total of 112,000 patients with CC and reduce the estimated 28,000 patients with incurable stage IV disease in the long term. More radiotherapy facilities are urgently needed for patients presenting with curative disease. Also, specialist gynecological surgeons need to be trained to mitigate the tragic outcome of up to 75,000 women presenting with curable disease but not receiving guideline-adherent or any treatment at all, who are thus left to suffer and die. Progress in surgical techniques managing even advanced and nodal-positive disease without radiotherapy could be of high importance for SSA [33].

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Disclosures

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References

1. Bach PB. Using practice guidelines to assess cancer care quality. J Clin Oncol 2005;23:9041–9043.

2. Kruk ME, Gage AD, Arsenault C et al. High-quality health systems in the Sustainable Development Goals era: Time for a revolution. Lancet Glob Health 2018;6:e1196–e1252.

3. Devesa SS, Silverman DT. Cancer incidence and mortality trends in the United States: 1935-74. J Natl Cancer Inst 1978;60:545–571.

4. Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

5. United Nations, Department of Economic and Social Affairs, Population Divison (2017). World Population Prospects: The 2017 Revision, custom data acquired via website. Available at: https://population.un.org/wpp/Publications/. Accessed February 18, 2019.

6. Wabinga H, Ramanakumar AV, Banura C et al. Survival of cervix cancer patients in Kampala, Uganda: 1995-1997. Br J Cancer 2003;89:65–69.

7. Chokunonga E, Ramanakumar AV, Nyakabau AM et al. Survival of cervix cancer patients in Harare, Zimbabwe, 1995-1997. Int J Cancer 2004;109:274–277.

8. Kantelhardt EJ, Moelle U, Begoihn M et al. Cervical cancer in Ethiopia: Survival of 1,059 patients who received oncologic therapy. ***The Oncologist*** 2014;19:727–734.

9. Sengayi-Muchengeti M, Joko-Fru WY, Miranda-Filho A et al. Cervical cancer survival in sub-Saharan Africa by age, stage at diagnosis and Human Development Index: A population-based registry study. Int J Cancer 2020;147:3037–3048.

10. Abdel-Wahab M, Zubizarreta E, Polo A et al. Improving quality and access to radiation therapy: An IAEA perspective. Semin Radiat Oncol 2017;27:109–117.

11. Meara JG, Leather AJM, Hagander L et al. Global Surgery 2030: Evidence and solutions for achieving health, welfare, and economic development. Lancet 2015;386:569–624.

12. Wilson BE, Jacob S, Yap ML et al. Estimates of global chemotherapy demands and corresponding physician workforce requirements for 2018 and 2040: A population-based study. Lancet Oncol 2019;20:769–780.

13. African Cancer Registry Network Web site. Available at http://afcrn.org/. Accessed December 29, 2018.

14. Finesse AM, Somdyala N, Chokunonga E, Parkin DM. Standard Procedure Manual for Population-Based Cancer Registries in sub-Saharan Africa. Version II, 2015. Available at: http://afcrn.org/resources/51-afcrndatabase/131-sop. Accessed July 31, 2017.

15. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynecol Obstet 2009;105:103–104.

16. National Comprehensive Cancer Network. Practice Guidelines in Oncology: Cervical Cancer. Version 1.2010. Plymouth Meeting, PA: National Comprehensive Cancer Network, 2009.

17. Kerr S, Jazieh AR, Kerr D. How useful are international treatment guidelines in low- and middle-income countries? J Glob Oncol 2017;3: 441–443.

18. Ismaila N, Salako O, Mutiu J et al. Oncology guidelines usage in a low- and middle-income country. J Glob Oncol 2018;4:1–6.

19. Brenner H, Gefeller O, Hakulinen T et al. period and periodh: Period Analysis of Survival Data, 2018. Available at: http://www.imbe.med.uni-erlangen.de/cms/software_period.html. Accessed January 2, 2019.

20. World Health Organization. Global Health Observatory Data Repository: Life tables by country. Available at: http://apps.who.int/gho/data/node.main.LIFECOUNTRY?lang=en. Accessed December 4, 2018.

21. Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. Eur J Cancer 2004;40:2307–2316.

22. Chiew KL, Chong S, Duggan KJ et al. Assessing guideline adherence and patient outcomes in cervical cancer. Asia Pac J Clin Oncol 2017;13:e373–e380.

23. Abdel-Wahab M, Bourque JM, Pynda et al. Status of radiotherapy resources in Africa: An International Atomic Energy Agency analysis. Lancet Oncol 2013:e168–e175.

24. Were E, Nyaberi Z, Buziba N. Perceptions of risk and barriers to cervical cancer screening at Moi Teaching and Referral Hospital (MTRH), Eldoret, Kenya. Afr Health Sci 2011;11:58–64.

25. Wilson ML, Atun R, DeStigter K et al. The Lancet Commission on diagnostics: Advancing equitable access to diagnostics. Lancet 2019;393: 2018–2020.

26. Han K, Milosevic M, Fyles A et al. Trends in the utilization of brachytherapy in cervical cancer in the United States. Int J Radiat Oncol Biol Phys 2013;87:111–119.

27. Howlader N, Noone AM, Krapcho M et al. SEER Cancer Statistics Review, 1975-2014. Available at: https://seer.cancer.gov/csr/1975_2014/. Accessed February 4, 2018.

28. National Comprehensive Cancer Network. NCCN Harmonized Guidelines for Sub-Saharan Africa: Cervical Cancer. Plymouth Meeting, PA: National Comprehensive Cancer Network, 2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cervical_harmonized-africa.pdf.

29. Moelle U, Mathewos A, Aynalem A et al. Cervical cancer in Ethiopia: The effect of adherence to radiotherapy on survival. ***The Oncologist*** 2018;23:1024–1032.

30. Allemani C, Matsuda T, Di Carlo V et al.; CONCORD Working Group. 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. Lancet 2018;391:1023–1075.

31. Suissa S. Immortal time bias in pharmacoepidemiology. Am J Epidemiol 2008;167:492–499.

32. Dereje N, Addissie A, Worku A et al. Extent and predictors of delays in diagnosis of cervical cancer in Addis Ababa, Ethiopia: A population-based prospective study. J Glob Oncol 2020;6: 277–284.

33. Höckel M, Wolf B, Schmidt K, et al. Surgical resection based on ontogenetic cancer field theory for cervical cancer: mature results from a single-centre, prospective, observational, cohort study. Lancet Oncol 2019;20(9):1316–1326.

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Clinical presentation and diagnosis of adult patients with non-Hodgkin lymphoma in Sub-Saharan Africa

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Summary

Non-Hodgkin lymphoma (NHL) is the sixth most common cancer in Sub-Saharan Africa (SSA). Comprehensive diagnostics of NHL are essential for effective treatment. Our objective was to assess the frequency of NHL subtypes, disease stage and further diagnostic aspects. Eleven population-based cancer registries in 10 countries participated in our observational study. A random sample of 516 patients was included. Histological confirmation of NHL was available for 76.2% and cytological confirmation for another 17.3%. NHL subclassification was determined in 42.1%. Of these, diffuse large B cell lymphoma, chronic lymphocytic leukaemia and Burkitt lymphoma were the most common subtypes identified (48.8%, 18.4% and 6.0%, respectively). We traced 293 patients, for whom recorded data were amended using clinical records. For these, information on stage, human immunodeficiency virus (HIV) status and Eastern Cooperative Oncology Group Performance Status (ECOG PS) was available for 60.8%, 52.6% and 45.1%, respectively. Stage at diagnosis was advanced for 130 of 178 (73.0%) patients, HIV status was positive for 97 of 154 (63.0%) and ECOG PS was ≥2 for 81 of 132 (61.4%). Knowledge about NHL subclassification and baseline clinical characteristics is crucial for guideline-recommended treatment. Hence, regionally adapted investments in pathological capacity, as well as standardised clinical diagnostics, will significantly improve the therapeutic precision for NHL in SSA.

Keywords: non-Hodgkin lymphoma, Sub-Saharan Africa, regional distribution, diagnostics, human immunodeficiency virus, public health.

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Introduction

Non-Hodgkin lymphoma (NHL) is the sixth most common type of malignant neoplasia in Sub-Saharan Africa (SSA), with incidence continuously rising and burden expected to double by 2040 (Parkin *et al.*, 2010; Chokunonga *et al.*, 2013; Bray *et al.*, 2018). NHL is a heterogeneous disease, with >80 subtypes identified (Swerdlow *et al.*, 2016). In SSA, infectious agents are important causes of lymphoma. A recent study reported that ~19.7% of NHL cases in SSA are attributable to infectious agents, with 12.7% of the cases related to human immunodeficiency virus (HIV) alone (Parkin *et al.*, 2019).

Non-Hodgkin lymphoma is aetiologically associated with Epstein–Barr virus (EBV) (Vockerodt *et al.*, 2015), human gammaherpesvirus 8 (Cesarman *et al.*, 1995), *helicobacter pylori* (Zucca *et al.*, 2014), human T-lymphotrophic virus 1 (Cook *et al.*, 2017), and malaria (Thorley-Lawson *et al.*, 2016), and epidemiologically associated with HIV (Grulich *et al.*, 2007; Shiels & Engels, 2012; Carbone *et al.*, 2014; Schonfeld *et al.*, 2016), even when controlled by antiretrovirals (Cesarman, 2013), and hepatitis C virus (Morton *et al.*, 2014; Miranda-Filho *et al.*, 2019). Other environmental, demographic, ethnic and lifestyle factors are likely to play an important role as well (Morton *et al.*, 2014). Identification of NHL subtype is crucial for specific therapy (Naresh *et al.*, 2011; Gopal *et al.*, 2012). In SSA, resources for diagnostic services and cancer care are limited, resulting in a high frequency of unclassified lymphoma and in poor clinical outcome (Gopal *et al.*, 2012; Mwamba *et al.*, 2012; Gopal *et al.*, 2016; Perry *et al.*, 2016b; Milligan *et al.*, 2018). The National Comprehensive Cancer Network (NCCN) developed resource-stratified guidelines on B cell lymphoma (Zelenetz *et al.*, 2019).

To date, data on quality of diagnostics have been published on hospital series only (e.g. Bateganya *et al.*, 2011; Naresh *et al.*, 2011; Wiggill *et al.*, 2011; Gopal *et al.*, 2016; Milligan *et al.*, 2018; Painschab *et al.*, 2019). The aim of the present study was to assess NHL subtype distribution and diagnostic services in a population-based cohort by collaborating with the African Cancer Registry Network (AFCRN). Data from registries in 10 countries were accessed for a retrospective analysis. Hence, the present study will help to provide a more complete picture of lymphoma diagnostics in SSA and contribute to improved diagnostic accuracy and patient management.

Patients and methods

Eleven population-based cancer registries (PBCRs) in 10 countries were selected as study centres, covering a population of ~21.5 million (Fig 1) (Parkin & Liu, 2019). These registries co-operate with oncological facilities, including hospitals and medical practices, in their respective registry areas from both the public and the private sector, and register all patients diagnosed with cancer in databases.

We included patients with NHL aged 15–99 years with International Classification of Diseases (ICD)-10 codes C82-C86 and C96 (April *et al.*, 2013) (Table S1) diagnosed between 2012 and 2013, extending the time period for some

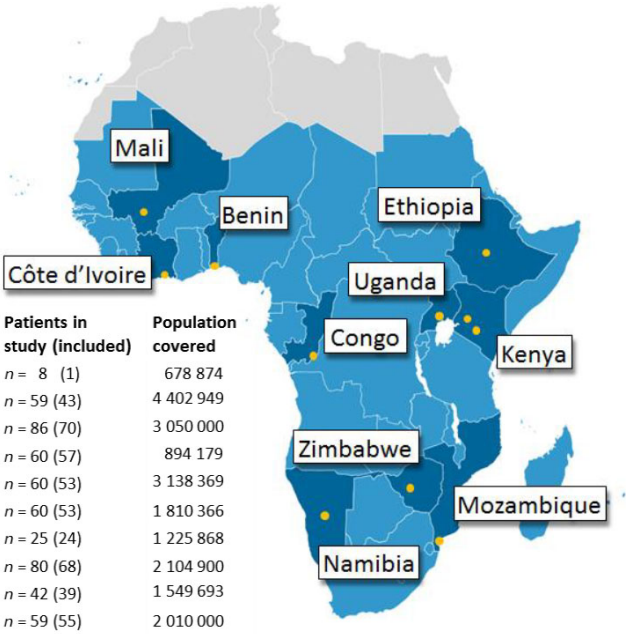
registries due to lack of patients. In total, 1068 patients were available in the registry databases. We assessed prevalence of adequate care from medical records among a random sample that could be assessed within feasible time and efforts in the given setting. We intended to draw conclusions for an SSA cohort, but not for individual registries. Therefore, no power was calculated for individual registries. A minimal sample size of 404 patients produces a two-sided 95% confidence interval with a width equal to 0.1 when the sample proportion of patients with adequate care is 0.500, which is the most conservative assumption. We assumed a drop-out rate of 33% and therefore aimed for 600 patients as our random sample. Thus, of 1068 patients available in registries, 599 patients (56.1%) were selected at random. In Brazzaville, Cotonou and Mozambique, all patients registered were included due to limited number of registered patients (Table I and Fig 2).

The AFCRN registry staff continuously retrieves information from hospital records and pathology reports (Am Finesse *et al.*, 2019). Data on sex and age, diagnosis and diagnostic modality are collected and coded according to current International Classification of Diseases for Oncology (ICD-O) standards (April *et al.*, 2013). To update the PBCR routine data, clinical records were re-evaluated. We considered registry data to be correct, unless the medical record gave differing information. Morphology was assessed from pathology reports, and, in the absence of definitive pathological diagnoses, those noted in clinical records were used.

A total of 41 diagnoses were reported according to Working Formulation classification (Rosenberg, 1982). For summary purposes, 11 diagnoses of '(diffuse) small cell NHL' were converted to 'low-grade NHL, unknown cellular lineage, not otherwise specified (NOS)' (ICD-O code 9591); and 23 diagnoses of '(diffuse) large cell NHL' were converted to 'high-grade NHL, unknown cellular lineage, NOS' (ICD-O code 9591). The remaining seven Working Formulation diagnoses were defined as NHL, NOS (unclassified NHL, ICD-O code 9591). Eight other patients pathologically diagnosed as low-grade NHL (three) and high-grade NHL (five) without any further classification were assigned to ICD-O code 9591, low-grade and high-grade, respectively. The diagnostic modality provided by registries, that is, histology, cytology, or clinical diagnosis without any specimen analysis, was amended if additional information on fine needle aspiration cytology (FNAC) or histological confirmation was found.

Furthermore, we traced data not available in PBCR databases: B symptoms, Eastern Cooperative Oncology Group Performance Status (ECOG PS), stage, HIV status and information on imaging. Stage was assessed in line with Lugano and Binet classification (Cheson *et al.*, 2014; Hallek, 2017). When stage had not been assigned in records, it was considered less advanced if no suggestion of disseminated nodal or extranodal involvement was found. When uncertain about primary or secondary extranodal lymphoma in advanced stages, we considered disease to be primary nodal rather than primary extranodal. Patients were considered to have 'traced clinical information' if information beyond the basic PBCR data was obtained from hospital and pathology records: Stage, B symptoms, ECOG PS, HIV status and imaging. For patients not traced, no information beyond the basic PBCR data was available.

For further analysis, patients were allocated to six groups: subclassified high-grade B cell NHL, subclassified low-grade B cell NHL, subclassified T cell NHL, otherwise subclassified



Population-based cancer registry	Patients in study (included)	Population covered
Benin – Cotonou	*n* = 8 (1)	678 874
Côte d'Ivoire – Abidjan	*n* = 59 (43)	4 402 949
Ethiopia – Addis Ababa	*n* = 86 (70)	3 050 000
Kenya – Eldoret	*n* = 60 (57)	894 179
Kenya – Nairobi	*n* = 60 (53)	3 138 369
Mali – Bamako	*n* = 60 (53)	1 810 366
Mozambique – Maputo	*n* = 25 (24)	1 225 868
Namibia – nation-wide	*n* = 80 (68)	2 104 900
Congo – Brazzaville	*n* = 42 (39)	1 549 693
Uganda – Kampala	*n* = 59 (55)	2 010 000
Zimbabwe – Bulawayo	*n* = 60 (53)	653 000

Fig. 1. Map of Sub-Saharan Africa (Wikimedia Commons, 2019). Countries and cities of participating population-based cancer registries are highlighted; together with number of patients in random sample drawn, number of patients included in the study and population covered in each registry area. [Colour figure can be viewed at wileyonlinelibrary.com]

Table I. Population-based cancer registries (PBCR) and study population characteristics.

PBCR (years observed)	Patients registered in PBCR during years observed, *n*	Population-based sample, *n* (% of patients registered in PBCRs during years observed)	Patients excluded, *n* (% of population-based sample)	Total cohort, *n*	Patients traced, *n* (% of total cohort)
Abidjan (2012–2013)	112	59 (52.7)	16 (27.1)	43	30 (69.8)
Addis Ababa (2012 and 2014)	103	86 (83.5)	16 (18.6)	70	33 (47.1)
Bamako (2012–2013)	61	60 (98.4)	7 (11.7)	53	20 (37.8)
Brazzaville (2011–2014)	42	42 (100)	3 (7.1)	39	6 (15.4)
Bulawayo (2012–2013)	198	60 (30.3)	7 (11.7)	53	36 (67.9)
Cotonou (2013–2014)	8	8 (100)	7 (87.5)	1	1 (100)
Eldoret (2012–2013)	68	60 (88.2)	3 (5.0)	57	21 (36.8)
Kampala (2012–2013)	94	59 (62.8)	4 (6.8)	55	40 (72.7)
Maputo (2014–2015)	25	25 (100)	1 (4.0)	24	17 (70.8)
Nairobi (2012–2013)	196	60 (30.6)	7 (11.7)	53	44 (83.0)
Namibia (2012–2013)	161	80 (49.7)	12 (15.0)	68	45 (66.2)
11 PBCRs (2011–2015)	1.068	599 (56.1)	83 (13.9)	516	293 (56.8)

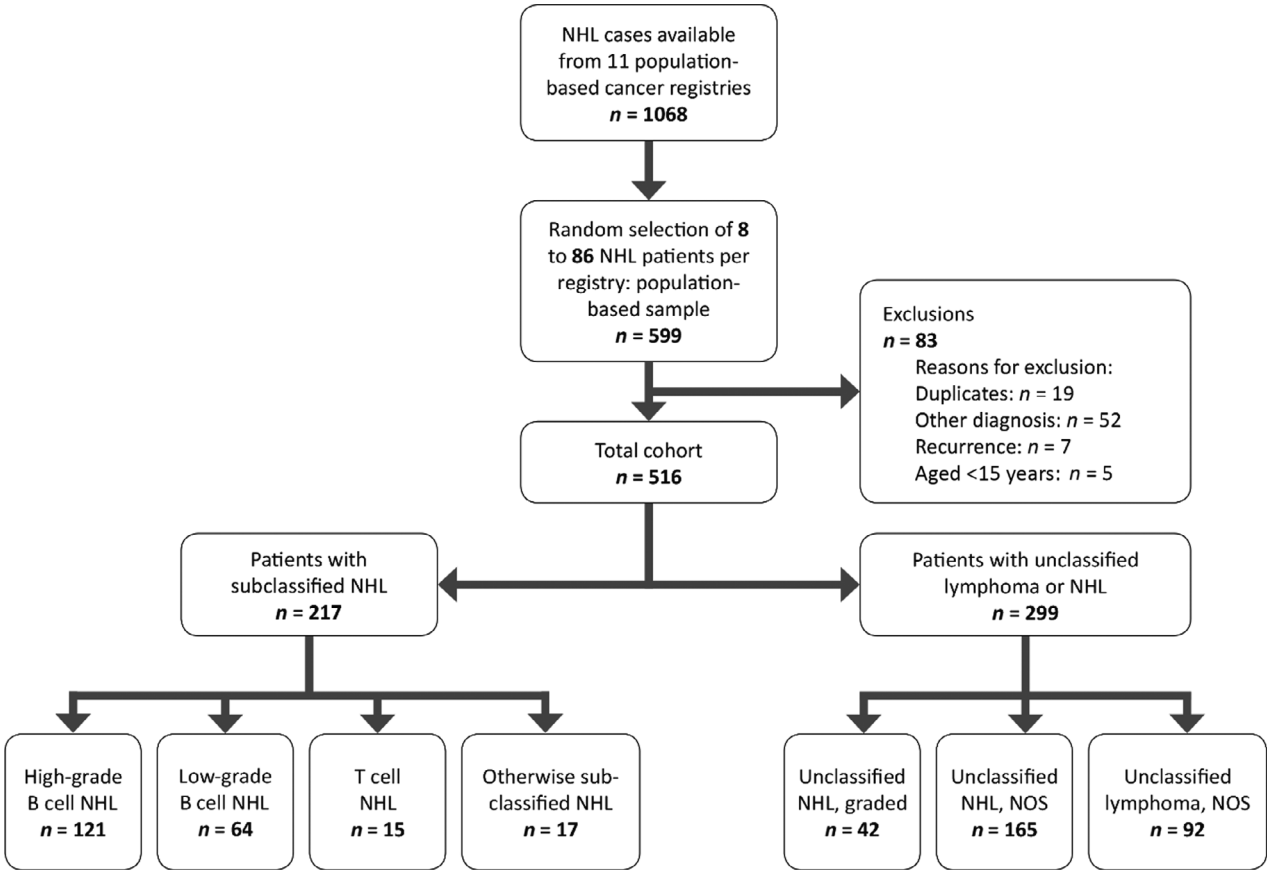


Fig. 2. Flowchart of study population. Stratified by non-Hodgkin lymphoma groups. NHL, non-Hodgkin lymphoma; NOS, not otherwise specified.

NHL, unclassified and graded NHL, and unclassified NHL or lymphoma, not graded (Table II).

According to NCCN guidelines harmonised for SSA (Zelenetz *et al.*, 2019), we established an evaluation scheme for quality of pathological diagnosis and completeness of clinical diagnostic criteria. We revised availability of NHL subclassification, information on grade for unclassified NHL and diagnostic modality. We were unable to evaluate

Table II. Proportions of morphological subtypes within the non-Hodgkin lymphoma groups.

Lymphoma classification	ICD-O morphology codes	Patients, *n* (%)
All subclassified NHL		**217 (42.1)**†
Subclassified high-grade B cell NHL		**121 (55.8)***
Diffuse large B cell	9680, 9684	106 (48.8)*
Burkitt	9687	13 (6.0)*
Precursor lymphoblastic B cell	9728	1 (0.5)*
Plasmablastic	9735	1 (0.5)*
Subclassified low-grade B cell NHL		**64 (29.5)***
CLL/SLL	9823, 9670	40 (18.4)
Follicular	9690, 9695, 9698	12 (5.5)*
Marginal zone	9710, 9689, 9699	7 (3.2)*
Mantle cell	9673	3 (1.4)*
Lymphoplasmacytic	9671	2 (0.9)*
Subclassified T cell NHL		**15 (6.9)***
Anaplastic large T/Null cell	9714	5 (2.3)*
Mature T cell, NOS	9702	3 (1.4)*
Mycosis fungoides	9700	3 (1.4)*
Angioimmunoblastic T cell	9705	1 (0.5)*
Precursor T cell lymphoblastic	9729	1 (0.5)*
Natural killer/T cell	9719	1 (0.5)*
Sézary syndrome	9701	1 (0.5)*
Otherwise subclassified NHL		**17 (7.8)***
Composite Hodgkin and non-Hodgkin lymphoma	9596	8 (3.7)*
Precursor cell lymphoblastic, unknown cellular lineage	9727	8 (3.7)*
Disseminated Langerhans cell histiocytosis	9754	1 (0.5)*
All unclassified lymphoma		**299 (57.9)**†
Unclassified, graded NHL		**42 (8.1)**†
High-grade B cell, NOS	9591	4 (0.8)†
Low-grade B cell, NOS	9591	2 (0.4)†
High-grade, unknown cellular lineage, NOS	9591	24 (4.7)†
Low-grade, unknown cellular lineage, NOS	9591	12 (2.3)†
Unclassified NHL or lymphoma, not graded		**257 (48.6)**†
Unclassified NHL, NOS	9591	165 (32.0)†
Unclassified NHL or HL, NOS	9590	92 (17.8)†
Total cohort		**516 (100)**†

CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; HL, Hodgkin lymphoma; ICD-O, International Classification of Diseases for Oncology; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified.

*Percentage of all subclassified NHL.

†Percentage of total cohort.

immunohistochemistry (IHC) diagnostics or cytogenetics due to lack of consistent data. Furthermore, we revised availability of Stage, B symptoms, ECOG PS, HIV status and any imaging. Biochemical evaluation such as lactate dehydrogenase, full blood count, comprehensive metabolic panel and International Prognostic Index were not consistently available either.

We adjusted the proportion of the age-groups within our younger cohort to that of the Surveillance, Epidemiology and End Results (SEER) cohort 1975–2016 (Howlader *et al.*, 2019) (age-standardisation) to compare the lymphoma subtype distribution irrespective of the age-effect with the SEER cohort. For statistical analysis, we used the Statistical Package for the Social Sciences (SPSS®), version 25 (SPSS Inc., IBM Corp., Armonk, NY, USA).

Use of secondary data and ethical approval was granted in accordance with each registry's regulations and by Martin-Luther-University Halle-Wittenberg. The study protocol is in line with the Declaration of Helsinki.

Results

A total of 516 patients from 11 registries ranging between one patient (Cotonou) and 70 patients (Addis Ababa) were included. Clinical and pathology records could be traced for 293 (56.8%). We were able to trace clinical records of 293 patients. Completeness of our data is shown in Fig S1. We amended the most valid base of diagnosis for 51 patients. For 36 patients with clinical or unknown base of diagnosis only registered, we found cytological diagnosis for seven, and histological diagnosis for 29. For 15 patients with cytological diagnosis registered, we found histological diagnosis and amended base of diagnosis accordingly. After reviewing clinical and pathological records, we amended pathological diagnosis for 59 patients, and identified Working Formulation diagnoses in 41 patients with unclassified NHL. Of these, 34 were assigned to either high- or low-grade NHL, the remaining seven patients to unclassified NHL, NOS.

For 299 patients of the total cohort (57.9%) no subclassification was identified. Among these, 207 (69.2%) were unclassified NHL (ICD-O code 9591). For the other 92 (30.8%), diagnosis did not include distinction between NHL and Hodgkin lymphoma [ICD-O code 9590 (Malignant lymphoma, NOS)]. For these, diagnosis of Hodgkin lymphoma can thus not be ruled out, although this is far less likely than NHL due to its relatively lower incidence in SSA (Bray *et al.*, 2018). Subclassification was identified for 217 patients of the total cohort (42.1%). The diagnoses in the 516 patients were confirmed histologically in 76.2%, with FNAC only in 17.3% and clinically without specimen analysis in 6.5%. Histologically diagnosed cases were subclassified in 186 of 366 (50.8%), cytologically diagnosed cases in 31 of 83 (37.3%). No clinically diagnosed cases were subclassified.

In Fig 3, quality of pathological diagnosis stratified by PBCRs is shown. According to NCCN guidelines harmonised for SSA, we defined diagnosis as most precise when NHL subclassification was available. Reliability of subclassification was considered better for histological confirmation than for FNAC confirmation only. In the absence of subclassification,

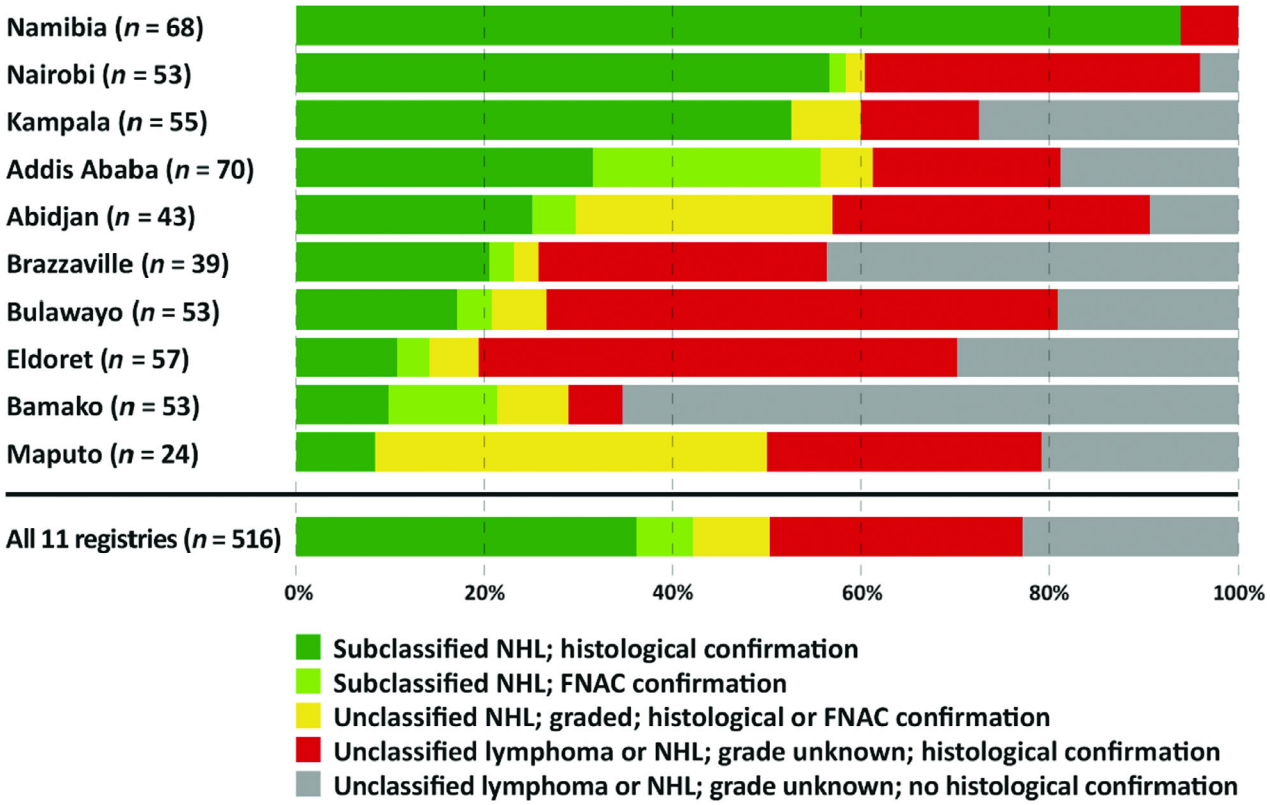


Fig. 3. Quality of pathological diagnosis. Stratified by population-based cancer registries, in order of quality of pathological diagnosis. With respect to non-Hodgkin lymphoma (NHL) subclassification, grade and diagnostic modality [according to National Comprehensive Cancer Network guidelines harmonised for Sub-Saharan Africa (Zelenetz *et al.*, 2019)]. Patients with morphologically ascertained diagnosis suitable for therapeutic decision-making (green and yellow): Patients with histopathological (dark green) or cytological (bright green) confirmation of subclassified NHL. Patients with unclassified but graded NHL (yellow). Patients with morphologically ascertained diagnosis not suitable for therapeutic decision-making (red): Patients with histological confirmation of lymphoma and neither subclassification nor grade. Patients with inconclusive diagnosis (white): Patients without histological confirmation of lymphoma and neither subclassification nor grade. (Cotonou was excluded from the figure due to small sample size, $n = 1$). FNAC, fine needle aspiration cytology. [Colour figure can be viewed at wileyonlinelibrary.com]

information on grade was deemed sufficient for basic therapy decision-making. For unclassified lymphoma with grade unavailable, histological confirmation of the disease was considered superior to other diagnostic modalities. In four registries, Namibia, Nairobi, Addis Ababa and Kampala, half or more NHLs were subclassified (94.1%, 58.5%, 55.7% and 52.7%, respectively). Bamako, Bulawayo, Eldoret and Maputo registries had the lowest proportion of NHLs subclassified (20.8%, 20.8%, 14.0% and 8.3%, respectively). Of the 299 unclassified cases, 123 (41.1%) were lacking histological confirmation.

Among the 217 subclassified NHLs, 20 subtypes were identified. We found a distribution of 55.8% high-grade B cell, 29.5% low-grade B cell, 6.9% T cell and 7.8% otherwise subclassified NHL. Diffuse large B cell lymphoma (DLBCL, ICD-O code 9680 and 9684) was the most common subtype (48.8%), followed by chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL, ICD-O code 9823 and 9670, 18.4%) and Burkitt lymphoma (BL, ICD-O code 9687, 6.0%). Rare entities such as various T cell NHL, primary central nervous system lymphoma (ICD-O code 9680), and extranodal unclassified lymphoma (ICD-O code 9590) suspicious of primary effusion lymphoma (ICD-O code 9678), were observed.

A moderate correlation between HIV prevalence in PBCRs and HIV-associated NHL was found (Table S2 and Fig S2). The proportion of HIV-associated NHL ranged between 38.5% and 89.1% in PBCRs with high HIV prevalence. For the remainder with lower prevalence, subtypes not associated with HIV were predominant.

Patients with high-grade B cell NHL had a median age of 43 years, patients with low-grade B cell NHL and T cell NHL were aged 52 and 56 years, respectively. When adjusting age-group proportions of our cohort to that of SEER, we found 41.4% DLBCL compared to SEER 27.8%, 25.4% for CLL/SLL compared to SEER 24.2% and 3.8% for BL compared to SEER 1.2% (Table S3).

Demographics, diagnostic modality and clinical presentation are shown in Table III. We found 88 of 473 NHLs to be primary extranodal lymphomas (18.6%) (Table S4).

Table III. Demographics, diagnostic modality and clinical presentation.

	High-grade B cell NHL	Low-grade B cell NHL	T cell NHL	All other lymphoma	Total cohort
Sex, *n* (%)					
Female	52 (41.6)	22 (33.3)	7 (46.7)	143 (46.1)	224 (43.4)
Male	73 (58.4)	44 (66.7)	8 (53.3)	167 (53.9)	292 (56.6)
Age, years					
Median (range) *n* (%)	43 (15–93)	52 (17–83)	56 (23–87)	42 (15–93)	45 (15–93)
15–39	50 (40.0)	15 (22.7)	4 (26.7)	133 (42.9)	202 (39.1)
40–59	56 (44.8)	24 (36.4)	5 (33.3)	119 (38.4)	204 (39.5)
≥60	19 (15.2)	27 (40.9)	6 (40.0)	58 (18.7)	110 (22.3)
Diagnostic modality, *n* (%)					
Histology	115 (92.7)	45 (73.8)	15 (100.0)	191 (68.2)	366 (76.2)
FNAC	9 (7.3)	16 (26.2)	0	58 (20.7)	83 (17.3)
Clinical	0	0	0	31 (11.1)	31 (6.5)
Unknown	1	5	0	30	36
Primary site involved, *n* (%)					
Nodal	97 (79.5)	36 (72.0)	8 (57.1)	244 (85.0)	385 (81.4)
Extranodal	25 (20.5)	14 (28.0)	6 (42.9)	43 (15.0)	88 (18.6)
Unknown	3	16	1	23	43
B symptoms*, *n* (%)					
No	9 (26.5)	2 (22.2)	2 (50.0)	6 (13.3)	19 (20.7)
Yes	25 (73.5)	7 (77.8)	2 (50.0)	39 (86.7)	73 (79.3)
Unknown	91	57	11	265	424
ECOG PS Score*, *n* (%)					
0 or 1	22 (40.7)	11 (64.7)	1 (33.3)	17 (29.3)	51 (38.6)
≥2	32 (59.3)	6 (35.3)	2 (66.7)	41 (70.7)	81 (61.4)
Unknown	59	49	12	252	384
Stage*, *n* (%)					
Early	22 (33.3)	4 (18.2)	3 (42.9)	19 (22.9)	48 (27.0)
Advanced	44 (66.7)	18 (81.8)	4 (57.1)	64 (77.1)	130 (73.0)
Unknown	59	44	8	227	338
HIV*, *n* (%)					
Negative	17 (29.8)	10 (76.9)	2 (66.7)	28 (34.6)	57 (37.0)
Positive	40 (70.2)	3 (23.1)	1 (33.3)	53 (65.4)	97 (63.0)
Unknown	68	53	12	229	362
Imaging*, *n* (%)					
CT/MRI/bone scan	17 (17.2)	4 (9.3)	2 (22.2)	13 (9.2)	36 (12.3)
X-ray and/or US	32 (32.3)	8 (18.6)	2 (22.2)	41 (28.9)	83 (28.3)
None	50 (50.5)	31 (72.1)	5 (55.6)	88 (62.0)	174 (59.4)
Unknown	26	23	6	168	223

CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FNAC, fine needle aspiration cytology; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; NHL, non-Hodgkin lymphoma; US, ultrasonography.

Stratified by high-grade B cell NHL [*n* = 125, including high-grade B cell NHL, not otherwise specified (*n* = 4)], low-grade B cell NHL [*n* = 66, including low-grade B cell NHL, not otherwise specified (*n* = 2)], T cell NHL (*n* = 15) and all other lymphoma (*n* = 310). Lugano Stage I, II, Binet Stage A and B were considered early disease, Lugano Stage III, IV and Binet Stage C advanced disease. We did not include patients with unknown clinical information in calculating percentage rates.

*Information for traced patients (*n* = 293) available only.

For 293 patients with clinical records traced, information on ECOG PS, B symptoms, Stage and HIV testing were available for 45.1%, 31.4%, 60.8%, and 52.6%, respectively. ECOG PS of ≥2 was documented in 61.4%, and 79.3% presented with B symptoms. In all, 73.0% were diagnosed with advanced Stage III or IV. HIV infection was documented for 63.0%. Imaging was done for 40.6%.

In Fig 4, quality of clinical diagnosis stratified by PBCRs is shown. According to NCCN guidelines harmonised for SSA, five clinical criteria are, among others, necessary for NHL diagnosis: ECOG PS, information on B symptoms, Stage, HIV status and any imaging done (Zelenetz *et al.*, 2019). Only 6.1% fulfilled all five criteria. On average 2.3 clinical criteria were available. Clinical diagnostics were most comprehensive in Kampala, with 9.1% meeting all five clinical criteria and on average 3.5 clinical criteria available. In Eldoret, Addis Ababa and Nairobi registries, clinical criteria were particularly lacking, with 1.7, 1.6 and 0.8 available on

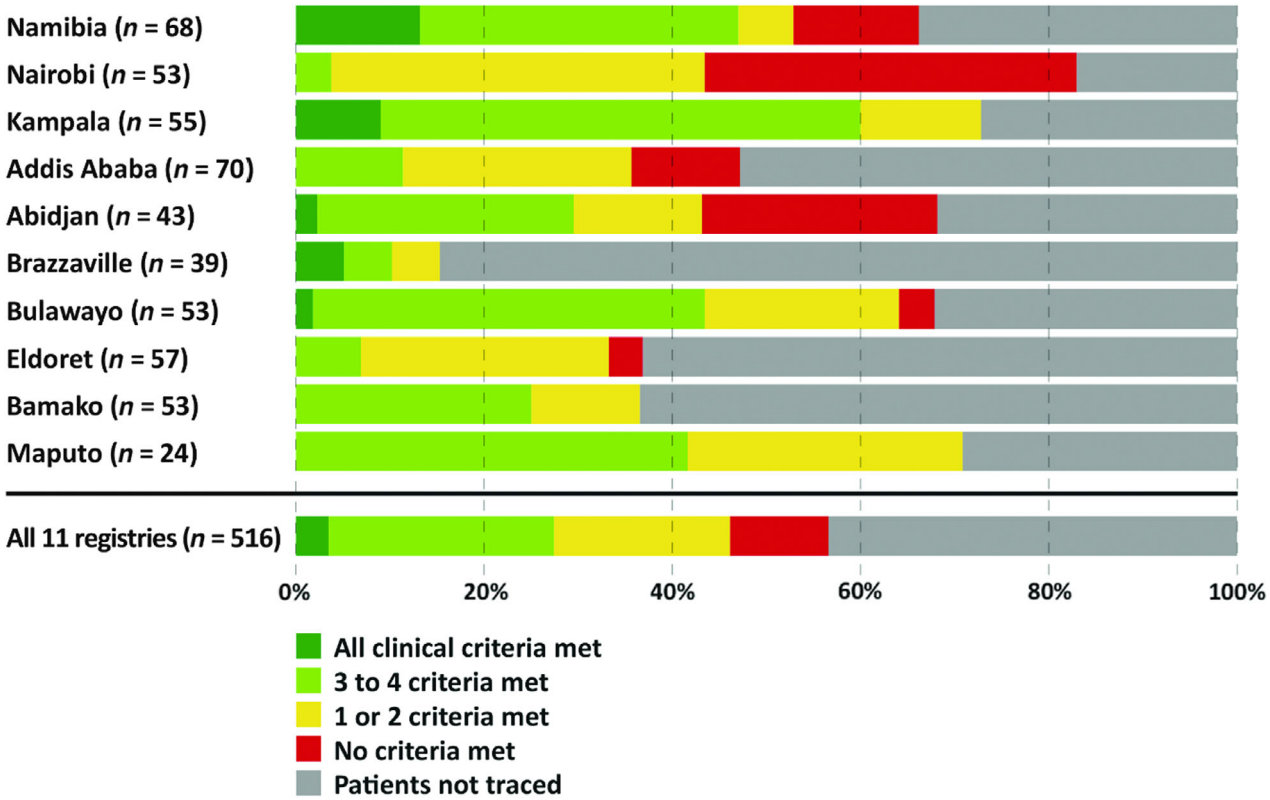


Fig. 4. Completeness of clinical diagnostic criteria. Stratified by population-based cancer registries, in order of Figure 3. With respect to information on Eastern Cooperative Oncology Group Performance Status, B symptoms, human immunodeficiency virus status, stage and any imaging [according to National Comprehensive Cancer Network guidelines harmonised for Sub-Saharan Africa (Zelenetz *et al.*, 2019)]. This information was only available for patients traced. (Cotonou was excluded from the figure due to small sample size, $n = 1$). [Colour figure can be viewed at wileyonlinelibrary.com]

average, respectively. Of the total cohort, 51.2% met two or fewer criteria only.

Discussion

Unclassified lymphoma cases and diagnostic modality

The NCCN has recognised the need to guide SSA physicians in resource-constrained settings and has published harmonised guidelines on a variety of B cell lymphomas (Zelenetz *et al.*, 2019). For the wide range of NHL entities, a broad spectrum of subtype-specific therapeutic algorithms has been designed. This requires NHL subclassification, as there are no recommendations on treatment of unclassified lymphoma. In this regard, the high proportion of 57.9% of unclassified lymphoma is striking. Distribution of unclassified lymphoma differed strongly among registries, ranging between Maputo (91.7%) and Namibia (5.9%). The varying quality of pathological diagnosis indicates that NHL diagnostic routine does not yet reach minimum standards for many patients. It is notable that for one in six patients, FNAC, and for one in 15 patients, clinical information only was the basis of the NHL diagnosis. Half of patients with NHL with histological confirmation had no subtype available, for patients with FNAC confirmation, the proportion was even higher (64.7%). The wide-spread use of FNAC in SSA has also been reported by others (Naresh *et al.*, 2011; Lemos *et al.*, 2018). FNAC is cheaper than core needle biopsy and much easier than surgical resection. However, as many investigators state, including the NCCN SSA guidelines, cytological diagnosis, let alone clinical presentation only, is deemed insufficient for NHL diagnosis except for CLL (Naresh *et al.*, 2011; Wilkins, 2011; Lemos *et al.*, 2018; Zelenetz *et al.*, 2019).

Biopsy material is mandatory for almost all kinds of pathological evaluation. Due to high cost and demanding infrastructure, IHC has yet to be facilitated in most SSA countries. Molecular genetics are practically unavailable. Consequentially, pathologists mostly rely on haematoxylin and eosin stains (Lemos *et al.*, 2018).

Hospital-based studies have reported much lower rates of unclassified lymphoma (13–14%) (Bateganya *et al.*, 2011; Milligan *et al.*, 2018). The severe lack of proper characterisation of lymphoma in our present cohort may be explained by lack of pathological infrastructure (Cainelli *et al.*, 2010; Wiggill *et al.*, 2013). Scarcity of trained personnel, especially

pathologists, is another major issue in SSA (Benediktsson *et al.*, 2007; Adesina *et al.*, 2013). In the Republic of Congo, for example, there is one pathologist available for the entire country with >4 million inhabitants (Jean-Félix Péko, 2019). The importance of correct classification of NHL remains an unmet need in SSA (Naresh *et al.*, 2011). Development and consistent implementation of resource-conserving guidelines on basic diagnostic procedures should be considered. The recent updates of the harmonised NCCN guidelines may lead to diligent and feasible subclassification algorithms for NHL in resource-constrained health systems. Hence, subtype-directed treatment could be enabled for a higher proportion of NHL. With limited resources, Malawian pathologists, for example, have reached concordance rates with American diagnoses of >90%, relying on basic cytology and histology services, a small IHC panel of nine antibodies and a telepathology conference (Montgomery *et al.*, 2016).

Subtypes of non-Hodgkin lymphoma

The relatively high percentage of high-grade B cell NHL (55.8%) observed in our present study confirms other studies from SSA (Naresh *et al.*, 2011; Wiggill *et al.*, 2011; Wiggill *et al.*, 2013; Patel *et al.*, 2015; Montgomery *et al.*, 2016; Perry *et al.*, 2016a; Milligan *et al.*, 2018). DLBCL (ICD-O code 9680 and 9684), BL (ICD-O code 9687), plasmablastic lymphoma (ICD-O code 9735), primary central nervous system lymphoma (ICD-O code 9680), and unclassified extranodal lymphoma suspicious of primary effusion lymphoma (ICD-O code 9678) were observed. All of these aggressive subtypes mentioned are associated with HIV (Re *et al.*, 2019), partly explaining their high proportion in our present study. However, in other parts of the resource-constrained world with much lower HIV prevalence than SSA, high-grade B cell NHLs are also known to be frequent. High-grade B cell NHL incidence is lower in the multicentric, population-based SEER study (31.3%) (Howlader *et al.*, 2019). This indicates that besides higher burden of further infectious diseases such as EBV (Crawford *et al.*, 2014), environmental and other factors such as demographics may play a role as well (Perry *et al.*, 2016a).

However, we could show that when age-adjusting our present cohort to the SEER cohort (Howlader *et al.*, 2019), proportions of DLBCL and BL remained lower in the SEER cohort (DLBCL adjusted: 41.4%, SEER: 27.8%; BL adjusted: 3.8%, SEER: 1.2%, respectively). HIV prevalence varied across the 11 participating PBCRs. Nairobi, Abidjan, Kampala, Namibia, Bulawayo and Maputo had high HIV prevalence (4.9–16.9%); whereas prevalence for the remaining PBCRs was much lower (1.7–4.1%) (National AIDS and STI Control Programme (NASCOP), 2012; United Nations Joint Programme on HIV/AIDS (UNAIDS), 2018; The Demographic and Health Surveys (DHS) Program, 2019). This affects proportions of HIV-associated lymphoma (89.1% in Namibia, 64.5% in Nairobi, 51.7% in Kampala *versus* 25.6% in Addis Ababa and 27.3% in Bamako). When testing for heterogeneity, Fig S2 shows that HIV prevalence in registries did moderately correlate with the respective proportion of HIV-associated NHL. There are numerous reasons that may increase or decrease the ratio of HIV-associated NHL in respective registries with varying HIV prevalence, including availability and reliability of detailed diagnosis, stigma of HIV-infected patients and quality of service for HIV patients.

The low frequency for CLL/SLL is consistent with other studies on NHL subtype distribution in SSA (Wiggill *et al.*, 2011; Perry *et al.*, 2016a) When age-adjusting to the SEER cohort, however, the proportion of CLL/SLL approximated the SEER proportion (CLL/SLL adjusted: 25.4%, SEER: 24.2%). Patients diagnosed with high-grade B cell NHL were diagnosed at a young age (median 43 years) compared to low-grade B cell NHL and T cell NHL patients (median age 52 and 56 years, respectively). The high burden of young patients diagnosed with aggressive NHL represents a socioeconomic threat and efficient treatment could reduce impact on SSA economies. Prospective, hospital-based studies in HIV-prevalent settings have shown that treatment for NHL can be safe, effective and feasible. The 1-year overall survival, regardless of NHL subtype, in Botswana was 53.7%. For DLBCL in Malawi, the 2-year progression-free survival was 34% (Milligan *et al.*, 2018; Painschab *et al.*, 2019)."

Clinical presentation

Patients with NHL in SSA present late, with nearly three-quarters diagnosed at advanced stage, almost two-thirds scoring an ECOG PS of ≥2, and four out of five suffering from B symptoms in our present cohort. Results are comparable to another retrospective, hospital-based study from the Uganda Cancer Institute (Bateganya *et al.*, 2011). The issue of late disease recognition due to lack of diagnostic resources, misdiagnosis (Buyego *et al.*, 2017), poor referral mechanisms, financial woes, low awareness and poverty may add to late presentation in the SSA tertiary hospital setting (Mwamba *et al.*, 2012). Even in Botswana, a middle-income country, duration between initial NHL symptoms and eventual diagnosis of NHL was 280 days on average (Milligan *et al.*, 2018). The proportion of primary extranodal disease was 18.6% in our present cohort. Even after carefully reviewing clinical records, our present data on extranodal organ manifestation of NHL may be confounded by primary nodal NHL infiltrating extranodal organs. Patients with extranodal lymphoma were possibly not diagnosed due to lack of comprehensive imaging such as computed tomography, let alone positron emission tomography, and absence of imaging in 59.4% of traced patients. However, in case of doubt, we assigned NHL as primary nodal rather than extranodal disease. Moreover, lack of imaging may also lead to understaged NHL within our present cohort, for which more sophisticated staging would have revealed even more advanced disease stages. A review has reported classification

of primary extranodal lymphoma to be inconsistent on a global scale (Vannata & Zucca, 2015), which may impede comparability with other studies in SSA. Mostly, these studies have reported higher proportions of extranodal disease; however, they did not specify whether extranodal disease was primary or secondary (Mwamba *et al.*, 2012).

In the absence of imaging procedures like ultrasonography, X-ray, and even less available higher-cost imaging procedures, thorough physical examination is essential. We found a high proportion of traced patients that lacked imaging and staging (59.4%, and 39.2%). Furthermore, lack of HIV testing in 139 patients (47.4% of 293) has to be noted. Due to these shortfalls, a median of only 2.3 of the five baseline non-pathological diagnostic criteria recommended by the harmonised NCCN guidelines were available. Stage, HIV status, and ECOG PS are key determinants for treatment. Improving completeness of patient examination could enhance personalised therapy decision-making and outcome.

Strengths and limitations of our study

The present study has several strengths. First, our initial total population-based cohort ($n = 599$) comprised 56.1% of all 1068 patients with NHL registered in the 11 PBCRs during the period of randomisation, of which we traced the clinical records of 293 patients. Second, the geographical variety of countries allows for an overview of patients with NHL with different ethnicities living in different socioeconomic settings, with both high and low HIV and malaria prevalence. Third, the patients were a random sample of all adult NHL cases, from both public and private institutions, treated or untreated, and we considered all bases of diagnosis, whether made histologically or solely clinically. The present study is, in fact, the first population-based overview of clinical presentation and diagnostics of patients with NHL in real-world SSA.

The present study also has several limitations. First, population-based cancer registries are limited by data quality (Parkin *et al.*, 2018). For example, 52 patients (8.7%) that were registered as NHL in the PBCR databases did not actually have a NHL diagnosis in their clinical records. For patients with traced clinical records (56.8%), we could amend these shortfalls and exclude such patients. Second, all of the PBCRs with the exception of Namibia cover urban populations and do not reflect experience in rural areas (Crocker-Buque & Pollock, 2015), but they provide the broadest image available of NHL patients' reality across the 10 countries participating. Third, we expect misclassified lymphoma in our present cohort. Deviations between diagnosis of general pathologists and expert haemato-pathologists are common in SSA, but occur also in high-income settings (Clarke *et al.*, 2004; LaCasce *et al.*, 2008; Chang *et al.*, 2014; Herrera *et al.*, 2014), including assignment to wrong cellular lineage (Armitage, 2013; Herrera *et al.*, 2014; Lage *et al.*, 2015) or even confounding benign and malignant disease (Wilkins, 2011; Ayers *et al.*, 2012; Masamba *et al.*, 2016; Buyego *et al.*, 2017). Two expert re-evaluations of lymphoma tissue in SSA have described diagnostic accuracy of 75% and 78%, respectively, reporting on poor tissue quality and frequent misdiagnoses (Naresh *et al.*, 2011; Ogwang *et al.*, 2011). Fourth, results on subtypes reported in our present study are hampered by different classification systems as outdated as the Working Formulation. We consider subtype distribution within our present cohort reliable nonetheless because we only considered outdated lymphoma subclassifications that allowed for obvious conversion to the current classification system. Fifth, a major issue to data analysis represented the rate of clinical records traced, 56.8%. We believe that clinical records were either, missing at random because of handwritten records, misspelling of names and inconsistent archive quality, or missing when records were not initiated in patients without clinical therapy. Even when clinical records could be assessed, we found a high proportion of missing data. However, this seems to be a general problem in the SSA setting as in a single-centred retrospective study and even in another multicentre prospective study, Stage was missing for 40% and 28% of patients, respectively (Bateganya *et al.*, 2011; Milligan *et al.*, 2018).

Conclusion

Our present pilot study describes NHL subtype distribution and diagnostic service received for patients on a population-level. As both pathological, as well as clinical diagnostics, are incomplete in most patients, thorough implementation of the NCCN guidelines harmonised for SSA remains challenging in many countries. Development of diagnostic algorithms emphasising feasibility in resource-constrained settings, improvement of laboratory infrastructure (especially IHC), and training of pathology and oncology workforce is required for more accurate diagnosis. Only then can sensible decision-making on guideline-adherent treatment be implemented for patients with NHL in SSA. The effect of such measures in real-world SSA should be monitored applying population-based research.

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Author contributions

All authors contributed to the contents and revised the article. Annelle Zietsman, Jean-Félix Péko, Fisihatsion Tadesse, Nathan G. Buziba, Henry Wabinga, Mary Nyanchama, Margaret Z. Borok, Mamadou Kéita, Guy N'da, Cesaltina F. Lorenzoni and Marie-Thérèse Akele-Akpo were responsible for the provision of data. Nikolaus C.S. Mezger and Eva J. Kantelhardt designed the study, did the data analysis, interpreted the data, and wrote the article. Cornelia Gottschick, Mascha Binder, Jörg Mezger, Ahmedin Jemal, Donald Maxwell Parkin and Claudia Wickenhauser did the data analysis, interpreted the data and wrote the article. Mirko Griesel, Lucia Hämmerl, Tobias P. Seraphin, Jana Feuchtner, interpreted the data.

Conflicts of interest

The authors declare no competing financial interests. Eva J. Kantelhardt has received travel support from Daiichy Sankyo.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Completeness of data. All areas relative to black rectangle (NHL patients registered, n = 1068). Red: pathological (cytological or histological) confirmation of NHL *only*; yellow: any clinical data on HIV, stage, ECOG PS B symptoms or imaging *only*; orange: *both* pathological confirmation of NHL *and* any clinical data present. For patients not traced (n = 223), only registry data on demographics and pathological diagnosis were available. For these, no data on clinical information on stage, HIV status etc. were available. ECOG PS, Eastern Cooperative Oncology Group Performance Status; NHL, non-Hodgkin lymphoma.

Fig S2. Correlation between HIV prevalence for PBCR and HIV-associated NHL among subclassified NHL. Correlation coefficient was r = 0,605 (p value = 0.064). HIV prevalence for 15-49 year old populations was extracted from online data bases (National AIDS and STI Control Programme (NASCOP), 2012; United Nations Joint Programme on HIV/AIDS (UNAIDS), 2018; The Demographic and Health Surveys (DHS) Program, 2019). PBCR, population-based cancer registry; NHL, non-Hodgkin lymphoma.

Table S1. ICD-10 codes included in study for patient selection (April *et al,* 2013).

Table S2. Proportion of HIV-associated non-Hodgkin lymphoma among subclassified non-Hodgkin lymphoma. Stratified by registry and HIV prevalence. HIV prevalence for 15-49 year old populations was extracted from online data bases (National AIDS and STI Control Programme (NASCOP), 2012; United Nations Joint Programme on HIV/AIDS (UNAIDS), 2018; The Demographic and Health Surveys (DHS) Program, 2019).

Table S3. Age-adjustment of non-Hodgkin lymphoma (NHL) subtypes found in our cohort to Surveillance, Epidemiology and End Results (SEER) cohort 1975-2016 (Howlader *et al,* 2019). Age 15-19 in our cohort (n=27) and 0-19 in SEER cohort (n=14.312) were excluded for analysis. Subsequently, unclassified NHL (International Classification of Diseases for Oncology (ICD-O) morphology code 9591 (April *et al,* 2013)) and unclassified lymphoma or NHL (9590) were excluded for our cohort (n=272) and for SEER (n=11.752) when calculating proportions.

Table S4. Primary extranodal lymphoma. Stratified by topographic categories (April *et al,* 2013) and lymphoma types.

References

Adesina, A., Chumba, D., Nelson, A.M., Orem, J., Roberts, D.J., Wabinga, H., Wilson, M. & Rebbeck, T.R. (2013) Improvement of pathology in sub-Saharan Africa. *The Lancet Oncology*, **14**, e152–e157.

April, F., Percy, C., Jack, A., Shanmugaratnam, K., Sobin, L., Parkin, D.M. & Whelan, S. (2013) International Classification of Diseases for Oncology. Third Edition. First Revision. http://apps.who.int/iris/bitstream/handle/10665/96612/9789241548496_eng.pdf;jsessionid=6D582B25CFBBF5C08F80E194A38F2023?sequence=1, 10 Sep 2019.

Armitage, J.O. (2013) The aggressive peripheral T-cell lymphomas: 2013. *American journal of hematology*, **88**, 910–918.

Ayers, L.W., Akin Abayomi, E., Adebamowo, C., Chumba, D.K., Iliyasu, Y., Naresh, K.N., NDung'u, J.R., Perner, Y., Stevens, W. & Tumwine, L.K. (2012) HIV/AIDS-related non-Hodgkin's lymphomas and confounders. Preliminary report of the Sub-Saharan Africa Lymphoma Consortium (SSALC). *Infectious agents and cancer*, **7**, P11.

Bateganya, M.H., Stanaway, J., Brentlinger, P.E., Magaret, A.S., Wald, A., Orem, J. & Casper, C. (2011) Predictors of survival after a diagnosis of non-Hodgkin lymphoma in a resource-limited setting. A retrospective study on the impact of HIV infection and its treatment. *Journal of acquired immune deficiency syndromes*, **56**, 312–319.

Benediktsson, H., Whitelaw, J. & Roy, I. (2007) Pathology services in developing countries. A challenge. *Archives of Pathology & Laboratory Medicine*, **131**, 1636–1639.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A. & Jemal, A. (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, **68**, 394–424.

Buyego, P., Nakiyingi, L., Ddungu, H., Walimbwa, S., Nalwanga, D., Reynolds, S.J. & Parkes-Ratanshi, R. (2017) Possible misdiagnosis of HIV associated lymphoma as tuberculosis among patients attending Uganda Cancer Institute. *AIDS research and therapy*, **14**, 13.

Cainelli, F., Tanko, M.N. & Vento, S. (2010) The challenge of lymphomas in sub-Saharan Africa. *The Lancet Oncology*, **11**, 610–611.

Carbone, A., Vaccher, E., Gloghini, A., Pantanowitz, L., Abayomi, A., de Paoli, P. & Franceschi, S. (2014) Diagnosis and management of

lymphomas and other cancers in HIV-infected patients. *Nature reviews. Clinical oncology*, **11**, 223–238.

Cesarman, E. (2013) Pathology of lymphoma in HIV. *Current opinion in oncology*, **25**, 487–494.

Cesarman, E., Chang, Y., Moore, P.S., Said, J.W. & Knowles, D.M. (1995) Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. *The New England journal of medicine*, **332**, 1186–1191.

Chang, C., Huang, S.-W., Su, I.-J. & Chang, K.-C. (2014) Hematopathologic discrepancies between referral and review diagnoses: a gap between general pathologists and hematopathologists. *Leukemia & lymphoma*, **55**, 1023–1030.

Cheson, B.D., Fisher, R.I., Barrington, S.F., Cavalli, F., Schwartz, L.H., Zucca, E. & Lister, T.A. (2014) Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *Journal of clinical oncology*, **32**, 3059–3068.

Chokunonga, E., Borok, M.Z., Chirenje, Z.M., Nyakabau, A.M. & Parkin, D.M. (2013) Trends in the incidence of cancer in the black population of Harare, Zimbabwe 1991–2010. *International journal of cancer*, **133**, 721–729.

Clarke, C.A., Glaser, S.L., Dorfman, R.F., Bracci, P.M., Eberle, E. & Holly, E.A. (2004) Expert review of non-Hodgkin's lymphomas in a population-based cancer registry: Reliability of diagnosis and subtype classifications. *Cancer epidemiology, biomarkers & prevention*, **13**, 138–143.

Cook, L., Melamed, A., Yaguchi, H. & Bangham, C.R. (2017) The impact of HTLV-1 on the cellular genome. *Current opinion in virology*, **26**, 125–131.

Crawford, D.H., Rickinson, A. & Johannessen, I. (2014) Cancer virus. The story of Epstein-Barr Virus. Oxford University Press, Oxford.

Crocker-Buque, T. & Pollock, A.M. (2015) Appraising the quality of sub-Saharan African cancer registration systems that contributed to GLOBOCAN 2008. A review of the literature and critical appraisal. *Journal of the Royal Society of Medicine*, **108**, 57–67.

Finesse, Am, Somdyala, N., Chokunonga, E. & Parkin, D.M. Standard Procedure Manual. For Population-Based Cancer Registries in sub-Saharan Africa. Version II. http://afcrn.org/resources/51-afcrndatabase/131-sop, 6 Sep 2019.

Gopal, S., Wood, W.A., Lee, S.J., Shea, T.C., Naresh, K.N., Kazembe, P.N., Casper, C., Hesseling, P.B. & Mitsuyasu, R.T. (2012) Meeting the challenge of hematologic malignancies in sub-Saharan Africa. *Blood*, **119**, 5078–5087.

Gopal, S., Fedoriw, Y., Kaimila, B., Montgomery, N.D., Kasonkanji, E., Moses, A., Nyasosela, R., Mzumara, S., Varela, C., Chikasema, M., Makwakwa, V., Itimu, S., Tomoka, T., Kamiza, S., Dhungel, B.M., Chimzimu, F., Kampani, C., Krysiak, R., Richards, K.L., Shea, T.C. & Liomba, N.G. (2016) CHOP Chemotherapy for Aggressive Non-Hodgkin Lymphoma with and without HIV in the Antiretroviral Therapy Era in Malawi. *PLoS ONE*, **11**, e0150445.

Grulich, A.E., van Leeuwen, M.T., Falster, M.O. & Vajdic, C.M. (2007) Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *The Lancet*, **370**, 59–67.

Hallek, M. (2017) Chronic lymphocytic leukemia. 2017 update on diagnosis, risk stratification, and treatment. *American journal of hematology*, **92**, 946–965.

Herrera, A.F., Crosby-Thompson, A., Friedberg, J.W., Abel, G.A., Czuczman, M.S., Gordon, L.I., Kaminski, M.S., Millenson, M.M., Nademanee, A.P., Niland, J.C., Rodig, S.J., Rodriguez, M.A., Zelenetz, A.D. & LaCasce, A.S. (2014) Comparison of referring and final pathology for patients with T-cell lymphoma in the National Comprehensive Cancer Network. *Cancer*, **120**, 1993–1999.

Howlader, N., Noone, Am, Krapcho, M., Miller, D., Brest, A., Yu, M., Ruhl, J., Tatalovich, Z., Mariotto, A., Lewis, C.H.S.,Feuer, E.J. & Cronin, K.A. (2019) SEER Cancer Statistics Review, 1975–2016. Based on November 2018 SEER data submission. https://seer.cancer.gov/csr/1975_2016/, 6 Sep 2019.

LaCasce, A.S., Kho, M.E., Friedberg, J.W., Niland, J.C., Abel, G.A., Rodriguez, M.A., Czuczman, M.S., Millenson, M.M., Zelenetz, A.D. & Weeks, J.C. (2008) Comparison of referring and final pathology for patients with non-Hodgkin's lymphoma in the National Comprehensive Cancer Network. *Journal of clinical oncology*, **26**, 5107–5112.

Lage, L.A.d.P.C., Cabral, T.C.d.S., Costa, R.d.O., Gonçalves, M.d.C., Levy, D., Zerbini, M.C.N. & Pereira, J. (2015) Primary nodal peripheral T-cell lymphomas: diagnosis and therapeutic considerations. *Revista brasileira de hematologia e hemoterapia*, **37**, 277–284.

Lemos, M.P., Taylor, T.E., McGoldrick, S.M., Molyneux, M.E., Menon, M., Kussick, S., Mkhize, N.N., Martinson, N.A., Stritmatter, A. & Randolph-Habecker, J. (2018) Pathology-Based Research in Africa. *Clinics in laboratory medicine*, **38**, 67–90.

Masamba, L.P.L., Jere, Y., Brown, E.R.S. & Gorman, D.R. (2016) Tuberculosis Diagnosis Delaying Treatment of Cancer: Experience From a New Oncology Unit in Blantyre, Malawi. *Journal of global oncology*, **2**, 26–29.

Milligan, M.G., Bigger, E., Abramson, J.S., Sohani, A.R., Zola, M., Kayembe, M.K.A., Medhin, H., Suneja, G., Lockman, S., Chabner, B.A. & Dryden-Peterson, S.L. (2018) Impact of HIV infection on the clinical presentation and survival of Non-Hodgkin lymphoma: a prospective observational study from Botswana. *Journal of global oncology*, **4**, 1–11.

Miranda-Filho, A., Piñeros, M., Znaor, A., Marcos-Gragera, R., Steliarova-Foucher, E. & Bray, F. (2019) Global patterns and trends in the incidence of non-Hodgkin lymphoma. *Cancer causes & control*, **30**, 489–499.

Montgomery, N.D., Liomba, N.G., Kampani, C., Krysiak, R., Stanley, C.C., Tomoka, T., Kamiza, S., Dhungel, B.M., Gopal, S. & Fedoriw, Y. (2016) Accurate real-time diagnosis of lymphoproliferative disorders in Malawi through clinicopathologic teleconferences. A model for pathology services in Sub-Saharan Africa. *American journal of clinical pathology*, **146**, 423–430.

Morton, L.M., Slager, S.L., Cerhan, J.R., Wang, S.S., Vajdic, C.M., Skibola, C.F., Bracci, P.M., de Sanjosé, S., Smedby, K.E., Chiu, B.C.H., Zhang, Y., Mbulaiteye, S.M., Monnereau, A., Turner, J.J., Clavel, J., Adami, H.-O., Chang, E.T., Glimelius, B., Hjalgrim, H., Melbye, M., Crosignani, P., Di Lollo, S., Miligi, L., Nanni, O., Ramazzotti, V., Rodella, S., Costantini, A.S., Stagnaro, E., Tumino, R., Vindigni, C., Vineis, P., Becker, N., Benavente, Y., Boffetta, P., Brennan, P., Cocco, P., Foretova, L., Maynadié, M., Nieters, A., Staines, A., Colt, J.S., Cozen, W., Davis, S., de Roos, A.J., Hartge, P., Rothman, N., Severson, R.K., Holly, E.A., Call, T.G., Feldman, A.L., Habermann, T.M., Liebow, M., Blair, A., Cantor, K.P., Kane, E.V., Lightfoot, T., Roman, E., Smith, A., Brooks-Wilson, A., Connors, J.M., Gascoyne, R.D., Spinelli, J.J., Armstrong, B.K., Kricker, A., Holford, T.R., Lan, Q., Zheng, T., Orsi, L., Dal Maso, L., Franceschi, S., La Vecchia, C., Negri, E., Serraino, D., Bernstein, L., Levine, A., Friedberg, J.W., Kelly, J.L., Berndt, S.I., Birmann, B.M., Clarke, C.A., Flowers, C.R., Foran, J.M., Kadin, M.E., Paltiel, O., Weisenburger, D.D., Linet, M.S. & Sampson, J.N. (2014) Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *Journal of the National Cancer Institute Monographs*, **2014**, 130–144.

Mwamba, P.M., Mwanda, W.O., Busakhala, N., Strother, R.M., Loehrer, P.J. & Remick, S.C. (2012) AIDS-related Non-Hodgkin's Lymphoma in Sub-Saharan Africa. Current status and realities of therapeutic approach. *Lymphoma*, **2012**.

Naresh, K.N., Raphael, M., Ayers, L., Hurwitz, N., Calbi, V., Rogena, E., Sayed, S., Sherman, O., Ibrahim, H.A.H., Lazzi, S., Mourmouras, V., Rince, P., Githanga, J., Byakika, B., Moshi, E., Durosinmi, M., Olasode, B.J., Oluwasola, O.A., Akang, E.E., Akenòva, Y., Adde, M., Magrath, I. & Leoncini, L. (2011) Lymphomas in sub-Saharan Africa–what can we learn and how can we help in improving diagnosis, managing patients and fostering translational research? *British journal of haematology*, **154**, 696–703.

National AIDS and STI Control Programme (NASCOP) (2012) Kenya AIDS Indicator Survey 2012. Adult Data Sheet - Population Reference Bureau. https://www.prb.org/kenya-aids-indicator-survey-adult-data/, 17 Jul 2019.

Ogwang, M.D., Zhao, W., Ayers, L.W. & Mbulaiteye, S.M. (2011) Accuracy of Burkitt lymphoma diagnosis in constrained pathology settings: importance to epidemiology. *Archives of Pathology & Laboratory Medicine*, **135**, 445–450.

Painschab, M.S., Kasonkanji, E., Zuze, T., Kaimila, B., Tomoka, T., Nyasosela, R., Nyirenda, R., Dhungel, B.M., Mulenga, M., Chikasema, M.,

Tewete, B., Mtangwanika, A., Chiyoyola, S., Mhango, W., Chimzimu, F., Kampani, C., Krysiak, R., Shea, T.C., Montgomery, N.D., Fedoriw, Y. & Gopal, S. (2019) Mature outcomes and prognostic indices in diffuse large B-cell lymphoma in Malawi: a prospective cohort. *British journal of haematology*, **184**, 364–372.

Parkin, D.M. & Liu, B. (2019) African Cancer Registry Network. https://afcrn.org/, 6 Sep 2019.

Parkin, D.M., Nambooze, S., Wabwire-Mangen, F. & Wabinga, H.R. (2010) Changing cancer incidence in Kampala, Uganda, 1991–2006. *International journal of cancer*, **126**, 1187–1195.

Parkin, D.M., Ferlay, J., Jemal, A., Borok, M., Manraj, S.S.N'da G.G., Ogunbiyi, F.J., Liu, B. & Bray F. (eds.) (2018) Cancer in Sub-Saharan Africa. International Agency for Research on Cancer, Lyon.

Parkin, D.M., Hämmerl, L., Ferlay, J. & Kantelhardt, E.J. (2019) Cancer in Africa 2018: the role of infections. *International journal of cancer*.

Patel, M., Philip, V., Omar, T., Turton, D., Candy, G., Lakha, A. & Pather, S. (2015) The impact of Human Immunodeficiency Virus infection (HIV) on lymphoma in South Africa. *Journal of Cancer Therapy*, **06**, 527–535.

Péko, J.-F. (2019) Scarcity of pathologists in the Republic of the Congo., Congo-Brazzaville.

Perry, A.M., Diebold, J., Nathwani, B.N., MacLennan, K.A., Müller-Hermelink, H.K., Bast, M., Boilesen, E., Armitage, J.O. & Weisenburger, D.D. (2016a) Non-Hodgkin lymphoma in the developing world: review of 4539 cases from the International Non-Hodgkin Lymphoma Classification Project. *Haematologica*, **101**, 1244–1250.

Perry, A.M., Perner, Y., Diebold, J., Nathwani, B.N., MacLennan, K.A., Müller-Hermelink, H.K., Bast, M., Boilesen, E., Armitage, J.O. & Weisenburger, D.D. (2016b) Non-Hodgkin lymphoma in Southern Africa: Review of 487 cases from The International Non-Hodgkin Lymphoma Classification Project. *British journal of haematology*, **172**, 716–723.

Re, A., Cattaneo, C. & Rossi, G. (2019) HIV and Lymphoma. From Epidemiology to Clinical Management. *Mediterranean Journal of Hematology and Infectious Diseases*, **11**, e2019004.

Rosenberg, S.A. (1982) National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. *Cancer*, 2112–2135.

Schonfeld, S.J., Erdmann, F., Wiggill, T., Singh, E., Kellett, P., Babb, C. & Schuz, J. (2016) Hematologic malignancies in South Africa 2000–2006. Analysis of data reported to the National Cancer Registry. *Cancer medicine*, **5**, 728–738.

Shiels, M.S. & Engels, E.A. (2012) Increased risk of histologically-defined cancer subtypes in HIV-infected individuals: clues for possible immunosuppression-related or infectious etiology. *Cancer*, **118**, 4869–4876.

Swerdlow, S.H., Campo, E., Pileri, S.A., Harris, N.L., Stein, H., Siebert, R., Advani, R., Ghielmini, M., Salles, G.A., Zelenetz, A.D. & Jaffe, E.S. (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*, **127**, 2375–2390.

The Demographic and Health Surveys (DHS) Program (2019) DHS data sets. https://dhsprogram.com/data/, 17 Jul 2019.

Thorley-Lawson, D., Deitsch, K.W., Duca, K.A. & Torgbor, C. (2016) The Link between Plasmodium falciparum Malaria and Endemic Burkitt's Lymphoma—New Insight into a 50-Year-Old Enigma. *PLoS Path*, **12**, e1005331.

United Nations Joint Programme on HIV/AIDS (UNAIDS) (2018) UNAIDS data 2018. https://www.unaids.org/en/resources/documents/2018/unaids-data-2018, 15 Jun 2019.

Vannata, B. & Zucca, E. (2015) Primary extranodal B-cell lymphoma. Current concepts and treatment strategies. *Chinese clinical oncology*, **4**, 10.

Vockerodt, M., Yap, L.-F., Shannon-Lowe, C., Curley, H., Wei, W., Vrzalikova, K. & Murray, P.G. (2015) The Epstein-Barr virus and the pathogenesis of lymphoma. *The Journal of pathology*, **235**, 312–322.

Wiggill, T.M., Mantina, H., Willem, P., Perner, Y. & Stevens, W.S. (2011) Changing pattern of lymphoma subgroups at a tertiary academic complex in a high-prevalence HIV setting. A South African perspective. *Journal of acquired immune deficiency syndromes*, **56**, 460–466.

Wiggill, T.M., Mayne, E.S. & Willem, P. (2013) Challenges in lymphoma diagnosis in HIV positive patients in the South African setting. *Transfusion and Apheresis Science*, **49**, 157–162.

Wilkins, B.S. (2011) Pitfalls in lymphoma pathology: avoiding errors in diagnosis of lymphoid tissues. *Journal of clinical pathology*, **64**, 466–476.

Zelenetz, A.D., Gordon, L.I., Abramson, J.S., Advani, R., Bartlett, N.L., Caimi, P.F., Chang, J.E. & Chavez, J.C. (2019) NCCN harmonized guidelines for Sub-Saharan Africa. *B-Cell lymphoma*. https://www.nccn.org/harmonized/default.aspx, 5 Sep 2019.

Zucca, E., Bertoni, F., Vannata, B. & Cavalli, F. (2014) Emerging role of infectious etiologies in the pathogenesis of marginal zone B-cell lymphomas. *Clinical cancer research*, **20**, 5207–5216.

3. Diskussion

3.1 Inzidenz

Die Verschiebung der Todesursachen von den Infektionserkrankungen hin zu den NCDs, welche sich schon seit Anfang des 20. Jahrhunderts in den sog. Industrienationen vollzog und aktuell auch in den Ländern mit niedrigem und mittlerem HDI zu beobachten ist, führt zu verstärkten Bemühungen der WHO sog. „Nationale Krebspläne“ als Mediatoren der Krebskontrolle weltweit zu implementieren. Dabei ist die Kenntnis der Häufigkeit von Krebserkrankungen in einer Bevölkerung ein grundlegender Pfeiler der Krebskontrolle und der Entwicklung und Ausrichtung solch eines Planes. Unsere Analyse offenbarte zwischen den Registern und Ländern stark variierende alters-standardisierte Inzidenzraten des Prostatakarzinoms. Die höchsten Raten fanden wir auf den Seychellen (zw. 2014 und 2018) und in Harare, Zimbabwe (zw. 2010 und 2015). Mit fast 100 Fällen pro 100 000 Personenjahre lag die Rate hier sogar etwas höher als in Deutschland im Jahr 2015 (91,7/100 000 Personenjahre) und nur knapp unter der durchschnittlichen Rate der USA in den Jahren 2013-2017 (109,8/100 000 Personenjahre) (German Centre for Cancer Registry Data, 2020; Surveillance, Epidemiology, and End Results Program, 2020).
In der ersten multizentrischen Analyse zu zeitlichen Veränderungen der Inzidenz des Prostatakarzinoms in Subsahara Afrika zeigten wir, dass es in den jeweils untersuchten Zeiträumen und Registern in allen zwölf eingeschlossenen Ländern zu einem jährlichen Anstieg der altersstandardisierten Inzidenzraten zwischen 2 und 10 % gekommen war (Seraphin et al., 2021a). In vielen Ländern weltweit lässt sich in unterschiedlichem Ausmaß ein entsprechender Trend über die letzten Dekaden beobachten (Zhou et al., 2016). Culp et. al berichteten in einer neueren Analyse entgegengesetzt dazu jedoch von hauptsächlich stagnierenden bzw. sogar sinkenden Raten in Ländern mit hohem HDI, in den letzten 5 Jahren des von ihnen untersuchten Zeitraums (~2009 – 2013) (Culp et al., 2020). In unserer Publikation stellen wir die Hypothese auf, dass eine Zunahme der Diagnostik, v.a. durch PSA Testungen bei symptomatischen Patienten und ggf. auch Inzidentalbefunde bei transurethralen Prostataresektionen, ähnlich wie in den USA in den 80er Jahren, verantwortlich für die ansteigende Inzidenz sein könnte (Potosky et al., 1990, 1995). Die Ursachen sind jedoch mit Sicherheit multifaktoriell und ggf. entzieht sich der eigentlich treibende Faktor bisher unserer Beobachtung. Unabhängig davon, was zu diesem Anstieg führt, ist jedoch hervorzuheben, dass falls sich dieser Trend auch nur mit der kleinsten errechneten Rate von jährlich 2% Inzidenzzunahme fortsetzen sollte, so käme es unter Zugrundelegung der GLOBOCAN Schätzungen fast zu einer Vervierfachung der Anzahl der Prostatakarzinom Neuerkrankungen in Afrika bis zum Jahre 2040 (Ferlay et al., 2018). Auch für andere Krebserkrankungen wurden kürzlich steigende Raten aus dieser Region berichtet. So fanden sowohl Joko-Fru et al. als auch Jedy-Agba et al. in ihren Analysen der Daten des AFCRN ebenfalls eine Zunahme der Häufigkeit des Mamma- bzw. des Zervixkarzinoms in fast allen inkludierten Krebsregistern (Jedy-Agba et al., 2020; Joko-Fru et al., 2020).

3.2 Versorgung

Um erwartete Zunahme der Häufigkeit zu antizipieren müsste schon heute eine verstärkte Allokation von Ressourcen in den Ausbau der für die Krebsversorgung zuständigen Bereiche der lokalen Gesundheitssysteme erfolgen. Jedoch bestätigten unsere Studien leider das auch medial häufig tradierte Bild der überforderten Gesundheitssysteme Subsahara Afrikas. Auf Basis von krankenhausbasierten Studien aus Subsahara Afrika ließ sich in der Vergangenheit schon ableiten, dass die diagnostische Aufarbeitung und anschließende therapeutische Versorgung von Krebspatient*innen in der Region mangelhaft zu sein scheint (Asamoah et al., 2018; Heyns et al., 2011; Jalloh et al., 2013). In unserer Therapie-Studie haben wir diese Beobachtung nun erstmals auf populationsbasierter Ebene publiziert. Wir legten dar, dass nur 11% der Prostatakarzinom-Patienten mit suffizientem Follow-up eine ausreichende Risikostratifizierung (Erhebung und Dokumentation von PSA-Wert, Gleason Score und TNM-Stadium) erhalten hatten (Seraphin et al., 2021c). Diese ist für die Therapie-Allokation nach internationalen Leitlinien unabdingbar. Ähnliche Schwierigkeiten in der Therapie-Allokation fanden wir bei Non-Hodgkin-Lymphom Patient*innen aus der Region, wo für 57% der Gesamtkohorte keine Subklassifikation des Non-Hodgkin-Lymphoms dokumentiert worden war (Mezger et al., 2020). Als eine der Ursachen ist z.B. der unzureichende Zugang zu pathologischer Versorgung zu nennen (Wilson et al., 2018). Eine Studie von Nelson et al. aus dem Jahre 2016 schätzt, dass in Subsahara Afrika im Schnitt ein*e Patholog*in pro eine Million Einwohner*innen vorhanden war (Nelson et al., 2016). In Deutschland lag der Vergleichswert bei ca. 20 zu eine Million Einwohner*innen (Bundesärztekammer, 2016). Besser stellte sich jedoch die Situation für die diagnostische Aufarbeitung des Zevixkarzinoms dar, wo nur bei 11% der nachverfolgbaren Kohorte das FIGO-Stadium unbekannt war und somit der wichtigste Parameter für eine Therapie Allokation zumeist erhoben worden war (Griesel et al., 2021).

Eine Gemeinsamkeit der von uns analysierten Krebsentitäten war die späte Vorstellung der Patient*innen im Gesundheitssystem. Von den Patient*innen mit bekanntem Krebsstadium befand sich die Mehrheit in Stadium III oder IV. Zervixkarzinom-Patientinnen befanden sich zu 30,0% in FIGO-Stadium III und zu 24,1% in FIGO-Stadium IV (Griesel et al., 2021). Bei 37% der Prostatakarzinom-Patienten in der Therapie-Studie waren zum Zeitpunkt der Diagnose Metastasen bekannt und in der etwas größeren Überlebens-Studie sogar bei fast 50% (Seraphin et al., 2021b; Seraphin et al., 2021c). Dies deckt sich auch mit Ergebnissen von krankenhausbasierten Studien aus der Region (Asamoah et al., 2018; Badmus et al., 2010; Heyns et al., 2011). Zum Vergleich: In den USA hatten laut „Surveillance, Epidemiology, and End Results (SEER)“ Datenbank in den Jahren 2011-2016 nur 6% der Prostatakarzinom-Patienten bereits eine Metastase bei Diagnosestellung (SEER, 2020). Eine der Ursachen für diese Beobachtungen ist mit großer Sicherheit das Fehlen von breit angelegten nationalen Früherkennungs- und Screening Programmen in den meisten Ländern. Auch wenn der Nutzen des

populationsweiten PSA-Screenings im Hinblick auf Lebensqualität und Gesamtüberleben (hier sei der sog. Lead-Time Bias erwähnt) nach wie vor äußerst kontrovers diskutiert wird, so zeigte sich doch z.B. in den USA in Phasen hoher Screening-Aktivität ein Rückgang der späten Stadien (Etzioni et al., 2008).
Hinzu kommen in Subsahara Afrika Hürden bei der Inanspruchnahme von jetzt schon angebotenen Früherkennungsuntersuchungen auf Patient*innen-Ebene. So berichtet eine Studie aus Uganda, dass nur 54% der 545 befragten Männer jemals vom Prostatakarzinom gehört hätten (Nakandi et al., 2013). Ein 2020 zu diesem Thema erschienener Review von Baratedi et al. identifiziert ebenfalls Unkenntnis der Erkrankung sowie eine Vielzahl von Irrglauben in Bezug auf das Prostatakarzinom als größte Hindernisse der Inanspruchnahme von opportunistischen Früherkennungsuntersuchungen. Es zeigte sich ebenso eine Abhängigkeit von der Höhe der Bildung und des sozioökonomischen Status (Baratedi et al., 2020). Beispielsweise für das Zervixkarzinom gibt es ebenso nur unzureichende Screening Programme, was auch hier als Ursache der späten Diagnosestellung gesehen wird (Sengayi-Muchengeti et al., 2020).

Die weitere Analyse der Versorgung ergab, dass nur ein Bruchteil der Malignompatient*innen in Subsahara Afrika eine adäquate Therapie erhielt. Nur 5% der Zervixkarzinom-Patientinnen erhielt leitliniengerechte Therapie und weitere 11% Therapie mit leichter bis starker Abweichung von den internationalen Empfehlungen (Griesel et al., 2021). Das Fehlen von ausreichend durchgeführter bzw. dokumentierter Diagnostik verhinderte im Falle des Prostatakarzinoms die für die Beurteilung der Behandlungsleitlinienadhärenz notwendige Risikostratifizierung der Patient*innen. Insofern ist es uns nicht möglich – wie ursprünglich geplant – für das Prostatakarzinom eine Aussage über den Grad der Implementation von internationalen Leitlinien in Bezug auf die Therapie zu treffen. Parallel zu den Ergebnissen der Zervixkarzinom-Studie blieb aber auch hier ein großer Teil der Patienten unbehandelt und nur ein kleiner Teil der Patienten in nicht-metastasiertem Stadium erhielt eine potentiell kurative Therapie (Seraphin et al., 2021c). Wie in den Publikationen diskutiert sind fehlendes Fachpersonal, eine mangelhafte technische Ausstattung sowie die Wartung und der Betrieb der vorhandenen Geräte bekannte Probleme der lokalen Gesundheitssysteme und kommen als Ursachen in Frage (Abdel-Wahab et al., 2013; Atun et al., 2015; Meara et al., 2015).

3.3 Überleben

Das Überleben von Krebspatient*innen ist, abgesehen von entitätsspezifischen Unterschieden abhängig von einer Vielzahl weiterer Faktoren. In der Regel lässt sich z.B. sagen, dass die Heilungs- bzw. Überlebenschancen umso größer sind, je früher ein Malignom erkannt wird. Weitere Faktoren sind Alter, sozioökonomischer und Versicherungsstatus, Fitnesszustand und Komorbiditäten der Patient*innen zum Zeitpunkt der Diagnose (American Cancer Society, 2019). Ebenso hat die Wartezeit bis zur ersten Therapie sowie die Therapie-Adhärenz und Nachsorge einen Einfluss.

Aufgrund der begrenzten Ressourcen unserer Studie sowie lokaler Gesundheitsdienstleister war es uns leider nicht möglich die Einflüsse all dieser Faktoren zu analysieren. In unserer Cox Regressionsanalyse der Therapie-Studie haben wir zumindest für die uns vorliegenden Faktoren adjustiert und konnten sowohl für nicht-metastasierte als auch für metastasierte Patienten mit Prostatakarzinom eine Assoziation von fehlender Therapie mit erhöhtem Risiko zu versterben im Vergleich zu adäquater Therapie nachweisen (HR= 3,86; 95%CI: 1,63 – 9,09, bzw. HR= 2,74; 95%CI: 1,30 – 5,80) (Seraphin et al., 2021c). Eine gleichgerichtete Assoziation zeigte sich auch in der multivariablen Analyse der Daten der Zervixkarzinom-Patientinnen (Griesel et al., 2021). Insofern wird deutlich, dass Patienten*innen unserer Kohorte durchaus von ihrer Krebstherapie profitieren konnten und auch trotz der häufig schwierigen Versorgungssituation vor Ort eine lebenszeitverlängernde Krebstherapie möglich erscheint. Wie schon zuvor erläutert ist jedoch der Anteil derer, die eine potenziell kurative Therapie erhielten Entitäten-übergreifend sehr gering.

Insofern ist es wenig überraschend, dass wir niedrige 1-, 3- und 5-Jahres-Überlebenswahrscheinlichkeiten der Krebspatient*innen aus Subsahara Afrika vorfanden. Das beobachtete 5-Jahresüberleben von Prostatakarzinom-Patienten aller Register zusammen lag in unserer Überlebens-Studie bei 39,1% (95%CI: 36,3 – 42,2). Unsere Analyse des relativen Überlebens (also der Vergleich des beobachteten Überlebens mit der angenommenen Hintergrundmortalität der Population aus der die Stichprobe stammt), offenbarte mit 60,0% (55,7 – 64,6) relativem 5-Jahresüberleben ebenfalls sehr niedrige Werte im internationalen Vergleich (Seraphin et al., 2021b). In den USA lag das relative 5-Jahresüberleben von Prostatakarzinom-Patienten in den 70er Jahren bei ca. 70% und seit 2000 bei fast 99%, während es in Deutschland im Jahre 2016 bei 89% lag (German Centre for Cancer Registry Data, 2020; Howlader et al., 2020). Daten zum relativen Überleben von Zervixkarzinom-Patientinnen aus teilweise überlappenden Populationen offenbarten ebenso ein niedriges Überleben im weltweiten Vergleich (Sengayi-Muchengeti et al., 2020).

Hierbei ist hervorzuheben, dass das relative Überleben von Prostatakarzinom-Patienten in Subsahara Afrika sich durchaus stark zwischen den untersuchten Populationen unterschied. In Namibia lag das relative 5-Jahresüberleben z.B. zw. 2012 und 2013 mit 88% (95%CI: 68,4 – 114,3) fast so hoch wie in Deutschland, wohingegen es in der Region Eastern Cape, Südafrika nur bei 48% (36,6 – 63,4) lag. Wir zeigten, dass ein niedriger HDI der Registerregion mit einer erhöhten Überschusssterblichkeit assoziiert war (Seraphin et al., 2021b). Insofern folgerten wir, dass eine weitere Verbesserung von Bildung und des Pro-Kopf Einkommens (als Surrogat der sozioökonomischen Situation) zu einer Verbesserung des Überlebens von Prostatakarzinom-Patienten beitragen könnte. Unsere Analyse weist zudem eine Assoziation zwischen späten Stadien und einer erhöhten Überschusssterblichkeit aus (Seraphin et al., 2021b). Wir sehen die Investition in Aufklärungs- und Früherkennungskampagnen als mögliches Mittel um eine Verschiebung hinzu frühen Stadien zu erreichen. Für mindestens ebenso wichtig halten wir die

Durchführung einer zumindest grundlegenden Therapie bei allen Patient*innen, wodurch sich das Überleben von Krebspatient*innen in Subsahara Afrika wahrscheinlich deutlich verbessern ließe.

3.4 Limitationen

Der Wert und die Aussagekraft von populationsbasierten Kennzahlen der Krebskontrolle, wie der durch uns berechneten altersstandardisierten Inzidenz oder die relative Überlebenswahrscheinlichkeit, sind hauptsächlich abhängig von zwei Faktoren. Zum einen der adäquaten Funktionsfähigkeit der Krebsregister selbst und zum anderen ein suffizientes Wissen über die Bezugspopulation der Krebsregister. Die Arbeit von Krebsregistern braucht einen stabilen politischen und sozioökonomischen Rahmen, um die notwendige und teils sehr komplexe Zusammenarbeit der verschiedenen Dienstleister im Gesundheitssektor zu ermöglichen, die notwendig ist, um die maximale Anzahl von Krebsfällen einer Population aufzunehmen. Um zeitliche Trends zu analysieren, muss dieser Rahmen zudem über einen längeren Zeitraum möglichst gleichbleibend sein, sodass Schwankungen der Registeraktivität nicht fälschlicherweise als Schwankungen der tatsächlichen Inzidenz interpretiert werden. Gerade in Subsahara Afrika ist dieser stabile Rahmen leider häufig nicht gegeben. Um diesem Sachverhalt Rechnung zu tragen, schlossen wir für die Inzidenzanalyse von 32 AFCRN Registern (mit - laut Statut - mindestens 70% Populations-Abdeckung) nur die zwölf ein, die wahrscheinlich die konsistentesten Daten hatten. Zusätzlich exkludierten wir Jahre mit bekannten Minderungen der Registeraktivität, wie z.B. bedingt durch soziopolitische Unsicherheiten in Harare, Zimbabwe von 2007 – 2009.
Eine weitere mögliche Fehlerquelle bei den Berechnungen der populations-basierten Raten erwächst durch die verwendeten Zensus der Bezugspopulationen. Hier muss darauf vertraut werden, dass die jeweiligen erstellenden Behörden der inkludierten Länder akkurat arbeiten und valide Zahlen liefern. Ähnlich ist bei der Bewertung des relativen Überlebens zu bedenken, dass in die Berechnungen expandierte „WHO-Lifetables“ als Hintergrundmortalität eingeflossen sind. Diese beruhen an sich schon häufig auf Schätzungen und sind für die von uns betrachteten Regionen leider nur auf nationaler Ebene erhältlich. Da die meisten der von uns in die Überlebens-Studie eingeschlossenen Register in den Hauptstädten bzw. wirtschaftlichen Zentren der Länder liegen, muss davon ausgegangen werden, dass dort die Hintergrundmortalität der Bezugspopulation wahrscheinlich etwas niedriger ist, als für das ganze Land gemittelt. Insofern überschätzen wir wahrscheinlich das relative Überleben der Krebspatient*innen sogar noch etwas. Falls diese verfügbar werden, könnten regional stratifizierte „Lifetables“ in zukünftigen Studien hier eine höhere Genauigkeit ermöglichen.
Sowohl in der Analyse als auch in der Interpretation und Bewertung der Therapie-Studien stellt der Anteil der nicht-verfolgbaren Patient*innen ein großes Problem bei allen Entitäten dar. Trotz größter Anstrengungen der Register vor Ort und Unterstützung durch Promovierende der Martin-Luther-Universität Halle-Wittenberg, war für 35% bis 47% der jeweiligen Stichproben keine weitere Information zu Stadium, Therapie und/oder Überleben zu ermitteln gewesen. Wir nehmen

an, dass ein Großteil der von uns nicht nachverfolgbaren Patient*innen erst gar nicht in die klinische Versorgung aufgenommen wurde, und sehen dies ebenfalls als wichtige Erkenntnis unserer Studien an. Wir können jedoch nicht gänzlich ausschließen, dass Patient*innen entweder im Ausland behandelt wurden oder ihre Akten aufgrund unzureichender Archivierungssysteme verloren gegangen sind.

3.5 Stärken

Trotz dieser Limitationen leisten unsere Studien einen grundlegenden Beitrag zur Schaffung von Datengrundlagen in dieser wissenschaftlich nach wie vor unterrepräsentierten Weltregion. Durch ihren Populations-Bezug geben unsere Studien einen bisher nicht vorhandenen Einblick in die Versorgungsrealität von Krebspatient*innen in Subsahara Afrika. Zudem liefern einige davon die ersten populationsbasierten Daten zu ihren jeweiligen Themen aus dieser Region. So sind wir unseres Wissens die ersten, die populationsbasiert sowohl über Diagnostik, Stadium und Therapie als auch über das (relative) Überleben und beeinflussende Faktoren berichten.
Außerdem ist zu berücksichtigen, dass der Studie zum relativen Überleben von Patienten mit Prostatakarzinom eine große Stichprobe (n=1406) zu Grunde lag (44% der in den eingeschlossenen Jahren registrierten Prostatakarzinom Fälle), was eine hohe externe Validität gewährleistet. Die Inzidenzanalyse ist die bisher einzige aus dieser Region, die sich speziell dem Prostatakarzinom widmet und darüber hinaus noch mehr als ein Register einschließt.

3.6. Fazit

In den dieser Dissertation zugrundeliegenden Studien zeigten wir, dass die Inzidenz des Prostatakarzinoms in Subsahara Afrika in den letzten Jahren stetig zugenommen hat und Patienten nicht ausreichend versorgt werden. Diese Tatsache bildete sich in unseren Studien durch die mangelhafte diagnostische Aufarbeitung der Patient*innen über alle untersuchten Entitäten hinweg ab. Wir sehen dies u.a. als möglichen Grund für die ebenso beobachtete fehlende Umsetzung von internationalen Therapieleitlinien, bei der nur ein Bruchteil der Patient*innen eine adäquate Therapie erhält. Die Ursachen hierfür sind aber mit Sicherheit multifaktoriell und weitere Forschung gerade in Bezug auf den Zugang zu Gesundheitsversorgung ist notwendig, um herauszufinden zu welchen Teilen die Probleme auf Ebene des gesamten Gesundheitssystems, der Gesundheitsdienstleister*innen, oder der Bevölkerung bzw. der Patient*innen liegen. Wir zeigten außerdem, dass die meisten Patient*innen in spätem Stadium diagnostiziert wurden und sich das – wie anzunehmen war – negativ auf das Überleben auswirkte. Gleiches konnten wir für das Fehlen von dokumentierter Therapie nachweisen. Unsere Studien liefern zum ersten Mal populationsbasierte Daten zum relativen Überleben von Prostatakarzinom-Patienten aus einer Vielzahl von Ländern Subsahara Afrikas und obwohl sich die Überlebensraten zwischen den Ländern erheblich unterschieden, so waren die Überlebensraten doch insgesamt eher niedrig im Vergleich zu anderen Weltregionen. Unserer Ansicht nach sind gerade im Hinblick auf die zukünftig zunehmende Last der

Krebserkrankungen in Subsahara Afrika weitere Investitionen notwendig: in Aufklärungs- und Früherkennungsprogramme, funktionierende und alle Menschen einbeziehende Krankenversicherungssysteme, in die Ausbildung von Gesundheitspersonal, Techniker*innen und Archivar*innen, als auch in die technische Ausstattung von Krankenhäusern und Laboren. Gleichzeitig ist weitere Forschung von Nöten, um den Ursachen unserer Beobachtungen und Ergebnisse weiter auf den Grund zu gehen. Neben den o.g. Studien zum Zugang zu Gesundheitsversorgung sind hier z.B. Untersuchungen zur Häufigkeit von PSA-Testung zu nennen.

Unsere Ergebnisse könnten in Folgestudien als Ausgangslage zur Bewertung des Erfolgs der dann etwaig implementierten harmonisierten NCCN Leitlinien dienen. Wir hoffen, dass unsere Studien weitere Evidenz liefern, die es lokalen Politiker*innen, Ärzt*innen, Patient*innenverbänden und NGOs ermöglicht ihre Forderungen mit mehr Nachdruck zu stellen und ihre Gesundheitspläne anzupassen, um dadurch Veränderungen anzustoßen, die in naher Zukunft zu einer Verbesserung der Versorgung und des Überlebens von Krebspatient*innen in Subsahara Afrika führt.

4. Literaturverzeichnis

Abdel-Wahab, M., Bourque, J. M., Pynda, Y., Izewska, J., Van der Merwe, D., Zubizarreta, E., & Rosenblatt, E. (2013). Status of radiotherapy resources in Africa: An International Atomic Energy Agency analysis. The Lancet Oncology, 14(4), e168–e175. https://doi.org/10.1016/S1470-2045(12)70532-6

African Cancer Registry Network. (2020). https://afcrn.org/index.php/about-us. Aufgerufen am: 04.09.2020

American Cancer Society. (2019). Cancer Treatment and Survivorship Facts and Figures 2019-2021. American Cancer Society

American Cancer Society. (2020). Prostate Cancer. Cancer.Org. https://www.cancer.org/cancer/prostate-cancer.html. Aufgerufen am: 05.08.2020

Asamoah, F. A., Yarney, J., Awasthi, S., Vanderpuye, V., Venkat, P. S., Fink, A. K., Naghavi, A. O., Abrahams, A., Mensah, J. E., Sasu, E., Tagoe, S. N. A., Johnstone, P. A. S., & Yamoah, K. (2018). Contemporary Radiation Treatment of Prostate Cancer in Africa: A Ghanaian Experience. Journal of Global Oncology, 4, 1–13. https://doi.org/10.1200/JGO.17.00234

Atun, R., Jaffray, D. A., Barton, M. B., Bray, F., Baumann, M., Vikram, B., Hanna, T. P., Knaul, F. M., Lievens, Y., Lui, T. Y. M., Milosevic, M., O'Sullivan, B., Rodin, D. L., Rosenblatt, E., Van Dyk, J., Yap, M. L., Zubizarreta, E., & Gospodarowicz, M. (2015). Expanding global access to radiotherapy. The Lancet Oncology, 16(10), 1153–1186. https://doi.org/10.1016/S1470-2045(15)00222-3

Badmus, T. A., Adesunkanmi, A.-R. K., Yusuf, B. M., Oseni, G. O., Eziyi, A. K., Bakare, T. I. B., Adetiloye, J. A., & Badmus, S. A. (2010). Burden of prostate cancer in southwestern Nigeria. Urology, 76(2), 412–416. https://doi.org/10.1016/j.urology.2010.03.020

Baratedi, W. M., Tshiamo, W. B., Mogobe, K. D., & McFarland, D. M. (2020). Barriers to Prostate Cancer Screening by Men in Sub-Saharan Africa: An Integrated Review. Journal of Nursing Scholarship, 52(1), 85–94. https://doi.org/10.1111/jnu.12529

Bray, F., Colombet, M., Mery, L., Piñeros, M., Znaor, A., Zanetti, R., & Ferlay, J. (2017). Cancer Incidence in Five Continents, Vol. XI (electronic version) Lyon: In International Agency for Research on Cancer.

Bray, Freddie, & Parkin, D. M. (2009). Evaluation of data quality in the cancer registry: Principles and methods. Part I: Comparability, validity and timeliness. European Journal of Cancer, 45(5), 747–755. https://doi.org/10.1016/j.ejca.2008.11.032

Bundesärztekammer. (2016). Ärztestatistik zum 31. Dezember 2016. https://www.bundesaerztekammer.de/ueber-uns/aerztestatistik/aerztestatistik-der-vorjahre/aerztestatistik-2016/gesamtzahl-der-aerzte/. Aufgerufen am: 20.08.2021

Cancer Research UK. (2020). Risks and causes. Prostate Cancer. https://www.cancerresearchuk.org/about-cancer/prostate-cancer/risks-causes. Aufgerufen am: 05.08.2020

Culp, M. B. B., Soerjomataram, I., Efstathiou, J. A., Bray, F., & Jemal, A. (2020). Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. European Urology, 77(1), 38–52. https://doi.org/10.1016/j.eururo.2019.08.005

Deutsche Krebsgesellschaft. (2018). Prostatakrebs - Ursache und Risikofaktoren. https://www.krebsgesellschaft.de/onko-internetportal/basis-informationen-krebs/krebsarten/prostatakrebs/ursachen-und-risikofaktoren.html. Aufgerufen am 05.08.2020

Etzioni, R., Gulati, R., Falcon, S., & Penson, D. F. (2008). Impact of PSA screening on the incidence of advanced stage prostate cancer in the United States: a surveillance modeling approach. Medical Decision Making : An International Journal of the Society for Medical Decision Making, 28(3), 323–331. https://doi.org/10.1177/0272989X07312719

Ferlay, J., Colombet, M., Soerjomataram, I., Mathers, C., Parkin, D. M., Piñeros, M., Znaor, A., & Bray, F. (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. https://doi.org/10.1002/ijc.31937

Ferlay, J., Colombet, M., Soerjomataram, I., Mathers, C., Parkin, D. M., Piñeros, M., Znaor, A., & Bray, F. (2019). Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. International Journal of Cancer, 144(8), 1941–1953. https://doi.org/10.1002/ijc.31937

Ferlay, J., Ervik, M. J., Lam, F., Colombet, M., Mery, L., Piñeros, M., Znaor, A., Soerjomataram, I., & Bray, F. (2018). Global Cancer Observatory: Cancer Tomorrow. Lyon, France: International Agency for Research on Cancer. https://gco.iarc.fr/tomorrow

Fidler, M. M., Bray, F., & Soerjomataram, I. (2018). The global cancer burden and human development: A review. Scandinavian Journal of Public Health, 46(1), 27–36. https://doi.org/10.1177/1403494817715400

Finesse, A. M., Somdyala, N., Chokunonga, E., & Parkin, D. M. (Hrsg.). (2015). Standard Procedure Manual for Population-Based Cancer Registries in sub Saharan Africa (3rd ed.). African Cancer Registry Network.

German Centre for Cancer Registry Data. (2020). Cancer in Germany 2015/2016 (12th ed.). Robert Koch Institut und Gesellschaft der epidemiologischen Krebsregister in Deutschland.

Griesel, M., Seraphin, T. P., Mezger, N. C. S., Hämmerl, L., Feuchtner, J., Joko-Fru, W. Y., Sengayi-Muchengeti, M., Liu, B., Vuma, S., Korir, A., Chesumbai, G. C., Nambooze, S., Lorenzoni, C. F., Akele-Akpo, M.-T., Ayemou, A., Traoré, C. B., Wondemagegnehu, T., Wienke, A., Thomssen, C., … Kantelhardt, E. J. (2021). Cervical Cancer in Sub-Saharan Africa: A Multinational Population-Based Cohort Study of Care and Guideline Adherence. The Oncologist, 26(5), e807–e816. https://doi.org/10.1002/onco.13718

Heyns, C. F., Fisher, M., Lecuona, A., & van der Merwe, A. (2011). Prostate cancer among different racial groups in the Western Cape: presenting features and management. South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde, 101(4), 267–270. https://doi.org/10.7196/samj.4420

Howlader, N., Noone, A. M., Krapcho, M., Miller, D., Brest, A., Yu, M., Ruhl, J., Tatalovich, Z., Mariotto, A., Lewis, D., Chen, H. S., Feuer, E. J., & Cronin, K. A. (Hrsg.). (2020). SEER Cancer Statistics Review, 1975-2017.

Jalloh, M., Niang, L., Ndoye, M., Labou, I., & Gueye, S. M. (2013). Prostate Cancer in Sub Saharan Africa. Journal of Nephrology and Urology Research, 1(1), 15–20. https://doi.org/10.12970/2310-984X.2013.01.01.4

Jedy-Agba, E., Joko, W. Y., Liu, B., Buziba, N. G., Borok, M., Korir, A., Masamba, L., Manraj, S. S., Finesse, A., Wabinga, H., Somdyala, N., & Parkin, D. M. (2020). Trends in cervical cancer incidence in sub-Saharan Africa. British Journal of Cancer, 123(1), 148–154. https://doi.org/10.1038/s41416-020-0831-9

Joko-Fru, W. Y., Jedy-Agba, E., Korir, A., Ogunbiyi, O., Dzamalala, C. P., Chokunonga, E., Wabinga, H., Manraj, S., Finesse, A., Somdyala, N., Liu, B., McGale, P., Jemal, A., Bray, F., & Parkin, D. M. (2020). The evolving epidemic of breast cancer in sub-Saharan Africa: Results from the African Cancer Registry Network. International Journal of Cancer, March, 1–11. https://doi.org/10.1002/ijc.33014

Meara, J. G., Leather, A. J. M., Hagander, L., Alkire, B. C., Alonso, N., Ameh, E. A., Bickler, S. W., Conteh, L., Dare, A. J., Davies, J., Mérisier, E. D., El-Halabi, S., Farmer, P. E., Gawande, A., Gillies, R., Greenberg, S. L. M., Grimes, C. E., Gruen, R. L., Ismail, E. A., … Yip, W. (2015). Global Surgery 2030: Evidence and solutions for achieving health, welfare, and economic development. The Lancet, 386(9993), 569–624. https://doi.org/10.1016/S0140-6736(15)60160-X

Mezger, N. C. S., Feuchtner, J., Griesel, M., Hämmerl, L., Seraphin, T. P., Zietsman, A., Péko, J.-F., Tadesse, F., Buziba, N. G., Wabinga, H., Nyanchama, M., Borok, M. Z., Kéita, M., N'da, G., Lorenzoni, C. F., Akele-Akpo, M.-T., Gottschick, C., Binder, M., Mezger, J., … Kantelhardt, E. J. (2020). Clinical presentation and diagnosis of adult patients with non-Hodgkin lymphoma in Sub-Saharan Africa. British Journal of Haematology, 190(2), 209–221. https://doi.org/10.1111/bjh.16575

Nakandi, H., Kirabo, M., Semugabo, C., Kittengo, A., Kitayimbwa, P., Kalungi, S., & Maena, J. (2013). Knowledge, attitudes and practices of Ugandan men regarding prostate cancer. African Journal of Urology, 19(4), 165–170. https://doi.org/10.1016/j.afju.2013.08.001

National Comprehensive Cancer Network (NCCN). (2019). Prostate Cancer. In NCCN (Ed.), NCCN Harmonized Guidelines for Sub-Saharan Africa (Version 2.). National Comprehensive Cancer Network (NCCN).

National Comprehensive Cancer Network (NCCN). (2020). Prostate Cancer. In NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) (Version 2.). National Comprehensive Cancer Network (NCCN).

Nelson, A. M., Milner, D. A., Rebbeck, T. R., & Iliyasu, Y. (2016). Oncologic Care and Pathology Resources in Africa: Survey and Recommendations. Journal of Clinical Oncology, 34(1), 20–26. https://doi.org/10.1200/JCO.2015.61.9767

Parkin, D. Max, & Bray, F. (2009). Evaluation of data quality in the cancer registry: Principles and methods Part II. Completeness. European Journal of Cancer, 45(5), 756–764. https://doi.org/10.1016/j.ejca.2008.11.033

Parkin, Donald M., Hämmerl, L., Ferlay, J., & Kantelhardt, E. J. (2020). Cancer in Africa 2018: The role of infections. International Journal of Cancer, 146(8), 2089–2103. https://doi.org/10.1002/ijc.32538

Parkin, Donald M. (2006). The evolution of the population-based cancer registry. In Nature Reviews Cancer (Vol. 6, Issue 8, pp. 603–612). https://doi.org/10.1038/nrc1948

Potosky, A. L., Kessier, L., Gridley, G., Brown, C. C., & Horm, J. W. (1990). Rise in prostatic Cancer Incidence Associated With Increased Use of Transurethral Resection. JNCI: Journal of the National Cancer Institute, 82(20), 1624–1628. https://doi.org/10.1093/jnci/82.20.1624

Potosky, A. L., Miller, B. A., Albertsen, P. C., & Kramer, B. S. (1995). The role of increasing detection in the rising incidence of prostate cancer. JAMA, 273(7), 548–552. https://doi.org/10.1001/jama.1995.03520310046028

Sengayi-Muchengeti, M., Joko-Fru, W. Y., Miranda-Filho, A., Egue, M., Akele-Akpo, M.-T., N'da, G., Mathewos, A., Buziba, N., Korir, A., Manraj, S., Lorenzoni, C., Carrilho, C., Hansen, R., Finesse, A., Somdyala, N. I. M., Wabinga, H., Chingonzoh, T., Borok, M., Chokunonga, E., … Parkin, D. M. (2020). Cervical cancer survival in sub-Saharan Africa by age, stage at diagnosis and Human Development Index: A population-based registry study. International Journal of Cancer, ijc.33120. https://doi.org/10.1002/ijc.33120

Seraphin, Tobias P, Joko-Fru, W. Y., Kamaté, B., Chokunonga, E., Wabinga, H., Somdyala, N. I. M., Manraj, S. S., Ogunbiyi, O. J., Dzamalala, C. P., Finesse, A., Korir, A., N'Da, G., Lorenzoni, C., Liu, B., Kantelhardt, E. J., & Parkin, D. M. (2021a). Rising Prostate Cancer Incidence in Sub-Saharan Africa: A Trend Analysis of Data from the African Cancer Registry Network. Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, 30(1), 158–165. https://doi.org/10.1158/1055-9965.EPI-20-1005

Seraphin, Tobias Paul, Joko-Fru, W. Y., Manraj, S. S., Chokunonga, E., Somdyala, N. I. M., Korir, A., N'Da, G., Finesse, A., Wabinga, H., Assefa, M., Gnangnon, F., Hansen, R., Buziba, N. G., Liu, B., Kantelhardt, E. J., & Parkin, D. M. (2021b). Prostate cancer survival in sub-Saharan Africa by age, stage at diagnosis, and human development index: a population-based registry study. Cancer Causes & Control, 32(9), 1001-1019. https://doi.org/10.1007/s10552-021-01453-x

Seraphin, Tobias Paul, Joko-Fru, W. Y., Hämmerl, L., Griesel, M., Mezger, N. C. S., Feuchtner, J. C., Adoubi, I., Egué, M. D., Okerosi, N., Wabinga, H., Hansen, R., Vuma, S., Lorenzoni, C., Coulibaly, B., Odzebe, S. W., Buziba, N. G., Aynalem, A., Liu, B., Medenwald, D., … Kantelhardt, E. J. (2021c). Presentation, patterns of care, and outcomes of patients with prostate cancer in sub-Saharan Africa: A population-based registry study. Cancer, 127(22), 4221-4232. https://doi.org/10.1002/cncr.33818

Shimizu, H., Ross, R., Bernstein, L., Yatani, R., Henderson, B., & Mack, T. (1991). Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. British Journal of Cancer, 63(6), 963–966. https://doi.org/10.1038/bjc.1991.210

Surveillance, Epidemiology, and End Results Program, S. (2020). SEER Cancer Stat Facts: Prostate Cancer. https://seer.cancer.gov/statfacts/html/prost.html. Aufgerufen am: 05.08.2020

United Nations. (2015). Transforming our world: the 2030 Agenda for Sustainable Development. New York. https://www.un.org

United Nations Development Programme. (2019). Human development report 2019 : beyond income, beyond averages, beyond today: inequalities in human development in the 21st century. In United Nations Development Program. United Nations Development Programme. https://doi.org/https://doi.org/10.18356/838f78fd-en

Wilson, M. L., Fleming, K. A., Kuti, M. A., Looi, L. M., Lago, N., & Ru, K. (2018). Access to pathology and laboratory medicine services: a crucial gap. The Lancet, 391(10133), 1927–1938. https://doi.org/10.1016/S0140-6736(18)30458-6

World Bank Group. (2020). World Bank Open Data. https://data.worldbank.org/. Aufgerufen am: 20.08.2020

World Cancer Research Fund/American Institute for Cancer Research. (2018). Diet, nutrition, physical activity and prostate cancer. In Continuous Update Project Expert Report 2018. https://doi.org/10.1108/nfs.2007.01737cab.032

World Health Institution. (2013). Global action plan for the prevention and control of noncommunicable diseases 2013-2020. World Health Organization.

World Health Institution. (2020). Global Health Estimates 2019: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2019. In The Global health Observatory.

Zhou, C. K., Check, D. P., Lortet-Tieulent, J., Laversanne, M., Jemal, A., Ferlay, J., Bray, F., Cook, M. B., & Devesa, S. S. (2016). Prostate cancer incidence in 43 populations worldwide: An analysis of time trends overall and by age group. International Journal of Cancer, 138(6), 1388–1400. https://doi.org/10.1002/ijc.29894

5. Thesen

1. Die alters-standardisierten Inzidenzraten des Prostatakarzinoms variierten stark zwischen den Ländern in Subsahara Afrika, mit den höchsten Werten in Harare (Zimbabwe) und den Seychellen und den niedrigsten Werten in Ibadan (Nigeria) und auf Mauritius.
2. Unabhängig von der demographischen Entwicklung stiegen die Inzidenzraten des Prostatakarzinoms jährlich zwischen 2 und 10% in den zwölf untersuchten Ländern Subsahara Afrikas.
3. Von den 365 gefundenen Patienten mit Prostatakarzinom der Zufallsstichprobe erhielten nur 11% eine (nach NCCN Leitlinien) ausreichende Diagnostik zur Risikostratifizierung. Von ihnen waren 37% zum Zeitpunkt der Diagnose bereits metastasiert. In der größeren Stichprobe der relativen Überlebensanalyse (n=1406) waren fast die Hälfte der Patienten mit bekanntem Tumorstadium dem AJCC/UICC Stadium IV zuzurechnen.
4. Nur ein Fünftel der nicht-metastasierten Prostatakarzinom-Patienten wurde mit kurativer Intention behandelt, während nur ca. zwei Drittel der metastasierten Patienten die von den NCCN Leitlinien empfohlene Androgendeprivationstherapie erhielt. In etwas mehr als der Hälfte der Fälle erfolgte diese chirurgisch durch bilaterale Orchidektomie.
5. Das (relative) Überleben von Prostatakarzinom-Patienten in Subsahara Afrika variierte stark zwischen den untersuchten Ländern und Registern. Die höchsten 3-Jahres Schätzungen des relativen Überlebens fanden wir in Nairobi (Kenia) und Namibia, die niedrigsten in Bulawayo (Zimbabwe) und Addis Abeba (Äthiopien). Insgesamt war das relative 3-Jahres Überleben mit 62,9% im internationalen Vergleich niedrig.
6. In der multivariablen Analyse des beobachteten Überlebens von Prostatakarzinom-Patienten war das Fehlen einer dokumentierten Karzinomtherapie im Vergleich zu einer kurativen bzw. palliativen Therapie stark mit einem höheren Risiko zu versterben assoziiert (HR, 3,86; 95%CI, 1,63- 9,09 bzw. HR, 2,74; 95%CI, 1,30- 5,80).
7. In der multivariablen Analyse des relativen Überlebens von Prostatakarzinom-Patienten waren ein spätes Krebsstadium sowie ein niedriger Human Development Index mit einem erhöhten Risiko zu Versterben assoziiert, während die Altersgruppe keine Rolle spielte.
8. Mangelhafte diagnostische Aufarbeitung für eine adäquate Therapieentscheidung zeigte sich ebenfalls in unserer Studie zum Non-Hodgkin Lymphom, wohingegen beim Zervixkarzinom nur in 11% der Fälle kein FIGO-Stadium zuweisbar war.
9. Patientinnen mit Zervixkarzinom präsentierten sich ebenfalls häufig in einem späten Krebsstadium und wurden inadäquat versorgt. Dies war ebenso im Vergleich zu adäquater Therapie mit einem höheren Risiko zu versterben assoziiert.

Erklärungen

(1) Ich erkläre, dass ich mich an keiner anderen Hochschule einem Promotionsverfahren unterzogen bzw. eine Promotion begonnen habe.

(2) Ich erkläre, die Angaben wahrheitsgemäß gemacht und die wissenschaftliche Arbeit an keiner anderen wissenschaftlichen Einrichtung zur Erlangung eines akademischen Grades eingereicht zu haben.

(3) Ich erkläre an Eides statt, dass ich die Arbeit selbstständig und ohne fremde Hilfe verfasst habe. Alle Regeln der guten wissenschaftlichen Praxis wurden eingehalten; es wurden keine anderen als die von mir angegebenen Quellen und Hilfsmittel benutzt und die den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht.

Düsseldorf, der 22. November 2022 Tobias Paul Seraphin

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