Krebs in Subsahara-Afrika mit Fokus auf das kolorektale Karzinom und infektiöse Krebsursachen: Epidemiologie, Überleben und leitliniengerechte Therapie - Eine Analyse multizentrischer populationsbasierter Krebsregisterdaten

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Krebserkrankungen sind weltweit in den meisten Ländern die häufigste oder zweithäufigste Ursache für vorzeitige Sterblichkeit. In den Ländern des globalen Südens, insbesondere in Subsahara-Afrika (SSA), wurde jedoch bis zum Beginn des 21. Jahrhunderts der Bekämpfung von Infektionserkrankungen höchste Priorität eingeräumt, so dass in regionalen wie internationalen gesundheitspolitischen Betrachtungen die Krebserkrankungen nur eine untergeordnete Aufmerksamkeit fanden. Mit den Erfolgen der Priorisierung der Infektionserkrankungen – bei Prävention und Behandlung von Erkrankungen wie Malaria, Tuberkulose, Hepatitis oder AIDS – rücken nun aber auch Krebserkrankungen verstärkt ins Blickfeld gesundheitspolitischer Akteure. Gleichzeitig führen demographische Veränderungen wie Bevölkerungswachstum und -alterung und eine zunehmende Verbreitung des sogenannten „westlichen Lebensstils“ mit Adipositas, Bewegungsmangel, Rauchen und ungesunder Ernährung zum tatsächlichen Anstieg der Prävalenz von zahlreichen Krebsentitäten, wie dem kolorektalen Karzinom (CRC). Jedoch ist bisher die Datenlage ungenügend.

Ziel der vorliegenden Arbeit war es zunächst, anhand von populationsbasierten Daten Aussagen zur Versorgungsgüte von Krebspatienten in SSA zu treffen. Das Hauptaugenmerk lag auf der Evaluation und Korrelation von Überlebensrate und leitliniengerechter Therapie. In Zusammenarbeit mit dem afrikanischen Krebsregisternetzwerk wurden Daten von 653 Patienten mit CRC in 10 verschiedenen Ländern in SSA erhoben und ausgewertet. Es zeigte sich, dass nur 3,1% der Patienten mit nicht metastasierter Erkrankung eine leitliniengerechte Behandlung erhielten. Das Risiko vorzeitig zu sterben lag bei Patienten ohne Krebsbehandlung 3,49-mal höher als bei denen, die eine leitliniengerechte Therapie oder eine Behandlung mit nur geringfügigen Abweichungen erhielten und war bei Patienten aus Ländern mit niedrigem „Index für menschliche Entwicklung“ (Human Development Index – HDI) um den Faktor 1,67 höher als bei Patienten mit mittlerem HDI (→ Publikation 1). Vergleichend wurden vier weitere Krebsentitäten hinzugezogen, die in der Region am häufigsten auftreten (Mamma-, Cervix-, und Prostatakarzinom, Non-Hodgkin-Lymphom). Hier konnten ebenfalls besorgniserregende Mängel in der Versorgung der Patienten mit entsprechenden Auswirkungen festgestellt werden. (→ Publikation 2-6). Bei der Verlagerung der Aufmerksamkeit von Infektions- zu Krebserkrankungen sollte aber nicht übersehen werden, dass Infektionen wegen ihrer karzinogenen Rolle – auch in SSA – nicht aus dem Fokus geraten dürfen. Deshalb wurden epidemiologische Daten erhoben, um diesen Zusammenhang näher zu beleuchten. Die Schätzungen für SSA im Jahr 2018 deuten darauf hin, dass 28,7% der gesamten Krebsfälle auf Infektionen zurückzuführen waren. Besonders virale Erreger waren für diesen hohen Anteil verantwortlich, während andere Faktoren wie Helicobacter pylori-Infektionen und Schistosomiasis eine untergeordnete Rolle spielten (→ Publikation 7). In einer weiteren Studie verwendeten wir ebenfalls populationsbasierte Daten der afrikanischen Krebsregister, um die Verteilung des Auftretens von Plattenepithelkarzinomen der Konjunktiva (SCCC) und des Burkitt-Lymphoms (BL) in Afrika zu untersuchen. Die geografische Verteilung von SCCC korrelierte 2018 mit der Verbreitung von HIV/AIDS und unterstreicht die dringende Notwendigkeit von Aufklärung. Ebenfalls legt die geografische Verteilung von BL in Verbindung mit Malariaendemien nahe, dass das Epstein-Barr-Virus (EBV) und Malaria als Ko-Faktoren bei der Entstehung eine entscheidende Rolle spielen. (→ Publikation 8,9). Insgesamt kann aus den Studienergebnissen gefolgert werden, dass der wachsenden Zahl an Krebserkrankungen in SSA bei bisher ungenügender Versorgungsqualität nur mit einer holistischen Gesundheitspolitik effektiv begegnet werden kann. Dazu gehören Infektionsprävention, Impfprogramme und Screening, sowie eine verbesserte Behandlungszugänglichkeit.

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Abkürzungsverzeichnis

AIDS	Acquired Immunodeficiency Syndrome (Erworbenes Immunschwächesyndrom)
AFCRN	African Cancer Registry Network (Afrikanisches Krebsregisternetzwerk)
ASR	Age-Standardized Rate (Altersstandardisierte Inzidenzrate)
BL	Burkitt-Lymphom
CI	Confidence Interval (Konfidenzintervall)
CRC	Colorectal Carcinoma (Kolorektales Karzinom)
EBV	Epstein-Barr-Virus
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique (Internationale Föderation für Gynäkologie und Geburtshilfe)
HBV	Hepatitis-B-Virus
HCV	Hepatitis-C-Virus
HDI	Human Development Index (Humaner Entwicklungsindex)
HHV-8	Humanes Herpes-Virus 8
HIV	Humanes Immundefizienz-Virus
HP	Helicobacter pylori
HPV	Humanes Papillomavirus
HTLV-1	Humanes T-lymphotropes-Virus 1
IARC	International Agency for Research on Cancer (Internationale Agentur für Krebsforschung)
INCTR	International Network for Cancer Treatment and Research (Internationales Netzwerk für Krebsbehandlung und -forschung)
MRT	Magnetresonanztomographie
NCCN	National Comprehensive Cancer Network
NCD	Non-Communicable diseases (Nichtübertragbare Krankheiten)
NHL	Non-Hodgkin-Lymphom
PET-CT	Positronenemissionstomographie
PSA	Prostataspezifisches Antigen
SCCC	Squamous Cell Carcinoma of the Conjunctiva (Plattenepithelkarzinom der Bindehaut)
SDG	Sustainable Development Goals (Ziele für nachhaltige Entwicklung)
SSA	Subsahara-Afrika
TNM	Tumor-Nodes-Metastasis (Staging-System)

1 Einleitung und Zielstellung

1.1 Das kolorektale Karzinom und NCCN Guidelines

Weltweit traten im Jahr 2020 schätzungsweise 19,3 Millionen neue Krebsfälle auf. Das kolorektale Karzinom (CRC) ist mit 10 % der neu diagnostizierten Fälle (in absoluter Zählung etwa 1,9 Millionen Fälle) die dritthäufigste Krebsart bei beiden Geschlechtern und steht mit 9,4% an zweiter Stelle der krebsbedingten Todesursachen (Sung et al., 2021). Es wird erwartet, dass die Anzahl der CRC-Diagnosen bis 2040 aufgrund des demographischen Wandels auf 3,2 Millionen ansteigen wird (Morgan et al., 2023). Zu den sogenannten änderbaren Risikofaktoren von CRC zählen Übergewicht, Typ-2-Diabetes, bestimmte Ernährungsgewohnheiten (hoher Fleischkonsum, wenig Gemüse), Rauchen und Alkoholkonsum. Nicht änderbar sind die Faktoren aus Alter, Geschlecht, ethnischer Zugehörigkeit, familiärer Vorbelastung und genetischen Syndromen wie Lynch-Syndrom und familiäre adenomatöse Polyposis. Einige seltene erbliche Zustände wie das Peutz-Jeghers-Syndrom und cystische Fibrose erhöhen ebenfalls das Risiko (American Cancer Society, 2020). In Subsahara-Afrika (SSA) gewinnt das CRC trotz seiner relativen Seltenheit in der Gesamtbevölkerung absolut gesehen an Bedeutung, insbesondere in städtischen Gebieten, in denen zunehmend westliche Lebensweisen und Ernährungsgewohnheiten angenommen werden (Katsidzira et al., 2017). Allerdings ist die epidemiologische Datenlage weiterhin sehr spärlich, nur wenige Studien beziehen ihre Daten aus populationsbasierten Registern und gerade über zeitliche Trends liegen häufig keine Informationen vor. Dennoch kann aus den wenigen existierenden Studien eine eindeutige Tendenz abgeleitet werden. In Harare (Zimbabwe) betrug die altersstandardisierte Inzidenzrate (Age-Standardized Rate; ASR), bezogen auf die Jahre 1991-1995 bei Männern 8,1 pro 100000 und 8,2 bei Frauen; im Jahr 2010 stieg sie auf 14,9 bei Männern und 14,2 bei Frauen (Chokunonga et al., 2013). In Kampala (Uganda) lag die ASR pro 100.000 bei 7,8 bei Männern und 5,2 bei Frauen in den Jahren 1991–1995 und erhöhte sich auf 8,8 pro 100.000 bei beiden Geschlechtern in den Jahren 2006–2010 (Wabinga et al., 2014). Im Vergleich dazu lag die ASR in Deutschland im Jahr 2022 bei 25,7 pro 100.000 für beide Geschlechter, in Dänemark lag sie gar bei 48,1 pro 100.000 (Bray et al., 2024). Gründe für den Anstieg der Inzidenz von CRC in SSA können einerseits im Zusammenhang mit der Verbesserung bei Diagnostik und Zugang zum Gesundheitssystem gesehen werden (Katsidzira et al., 2017). Andererseits – und möglicherweise in einem bedeutenderen Ausmaß – liegt die Inzidenzzunahme in der sozio-ökonomischen Entwicklung begründet (Fidler et al., 2016). Damit einher geht ein vereinfachter Zugang zu günstigem „Junkfood“ mit erhöhtem Verzehr von Fett, Zucker und

tierischen Produkten, eine Abnahme der körperlichen Aktivität, steigende Raten von Adipositas und die Zunahme von Nikotinabusus (Stevens et al., 2012; Dickson, 2016; Arnold et al., 2017). Eine populationsbasierte retrospektive Studie von Katsidzira et al. in Harare (Zimbabwe) fand eine ungewöhnlich hohe Inzidenz von CRC bei jungen Erwachsenen, was teilweise dem häufigeren Vorkommen von muzinösen und Siegelringzellkarzinomen in der schwarzen Bevölkerung anzulasten ist. Insgesamt vermuten die Autoren, dass der Anstieg der CRC-Inzidenz in SSA wahrscheinlich unterschätzt wird, da neue Krebsfälle in der Region weiterhin unterdiagnostiziert und unterberichtet sind (Katsidzira et al., 2016).

Die Leitlinien des NCCN (National Comprehensive Cancer Network) für CRC bieten evidenzbasierte Empfehlungen für die Behandlung von Patienten mit Darm- und Rektumkrebs. Sie gelten als globaler Standard in der onkologischen Versorgung und decken alle Aspekte der Patientenbehandlung ab – von der Prävention über das Screening bis hin zu Therapie und Nachsorge. Die Leitlinien werden regelmäßig aktualisiert, um die neuesten wissenschaftlichen Erkenntnisse abzubilden (Winn et al., 1996). Vor einigen Jahren wurden erstmals harmonisierte NCCN-Leitlinien für SSA entwickelt, um den besonderen Herausforderungen in ressourcenarmen Umgebungen gerecht zu werden. Diese Leitlinien berücksichtigen auf pragmatische Weise die eingeschränkte Verfügbarkeit von medizinischen Ressourcen und die Notwendigkeit, eine effektive Versorgung mit knappen Mitteln zu gewährleisten (Anderson, 2020; Mutebi et al., 2020). Für Rektumkarzinome empfehlen sie unter anderem eine transabdominelle oder transanale lokale Resektion im Stadium I sowie eine neoadjuvante Chemotherapie kombiniert mit Strahlentherapie im Stadium II und III (Benson et al., 2018b). Bei resektablem Kolonkrebs sollte eine Kolektomie durchgeführt werden, bei der mindestens 12 Lymphknoten entfernt werden. Für T4b-Tumoren oder lokal nicht resektable Kolonkarzinome wird eine neoadjuvante Chemotherapie empfohlen (Benson et al., 2018a). Patienten mit kolorektalem Karzinom im Stadium IV sollten eine (Radio-)Chemotherapie erhalten, wobei eine chirurgische Resektion je nach Tumoreigenschaften und Gesundheitszustand des Patienten in Betracht gezogen wird. Für nicht operable Tumoren im Stadium IV kann eine Strahlentherapie in einer Einzeldosis eine Behandlungsoption sein (Benson et al., 2018a, 2018b). Hinsichtlich diagnostischer Möglichkeiten empfehlen die harmonisierten Leitlinien für SSA das Zurückgreifen auf Ultraschall und Röntgen, wenn fortgeschrittene Bildgebungsmethoden wie (PET-)CT (Positronenemissionstomographie) oder MRT (Magnetresonanztomographie) nicht verfügbar sind (Benson et al., 2018a, 2018b).

1.2 Infektiöse Krebsursachen

Schon am Ende des 19. Jahrhunderts wurde eine Verbindung zwischen infektiösen Erregern und der Entwicklung von Krebs vermutet. Askanazy veröffentlichte im Jahr 1900 seine Überlegungen zum Zusammenhang von Infektionen mit Distomum felineum, einem parasitären Plattwurm und dem Auftreten von Leberkrebs in Ostpreußen (Askanazy, 1900). Einige Jahre später gelang Peyton Rous der experimentelle Nachweis von Tumor-induzierenden Viren bei Hühnern. Rous konnte zeigen, dass ein Sarkom durch die Injektion einer filtrierten zellfreien Flüssigkeit aus einem Tumor auf andere Hühner übertragen werden konnte. Diese Flüssigkeit enthielt kein festes Tumorgewebe, sondern ein Virus, das später als Rous-Sarkom-Virus bekannt wurde (Rous, 1911; Zinsser et Tang, 1927). Anfang der 1960er Jahre systematisierte Denis Burkitt das Auftreten eines endemisch und überwiegend im Kindesalter vorkommenden malignen Lymphoms in Ostafrika und stellte dabei fest, dass dieses nur in Zonen mit hoher Malaria-Inzidenz auftrat (Burkitt, 1962a). Diese Beobachtung führte zur Hypothese, dass eine chronische Infektion in Verbindung mit der geschwächten Immunabwehr durch Malaria das Krebsrisiko erhöhte. Kurze Zeit später wurde das EBV (Epstein-Barr-Virus) mit der damals neu entwickelten Technik der Immunfluoreszenz in den Malignom-Zellen entdeckt und damit die Ursache des sogenannten Burkitt-Lymphoms nachgewiesen (Epstein et al., 1964). Seither wurden zahlreiche weitere Infektionserreger als für den Menschen potentiell karzinogen identifiziert. Die Internationale Agentur für Krebsforschung (International Agency for Research on Cancer; IARC) stuft elf infektiöse Erreger als Gruppe-1-Karzinogene ein. Dazu zählen unter anderem Helicobacter pylori (HP), humanes Papillomavirus (HPV), Hepatitis-B-Virus (HBV), Hepatitis-C-Virus (HCV), Humanes T-lymphotropes-Virus 1 (HTLV-1) und Humanes Herpes-Virus 8 (HHV-8) (International Agency for Research on Cancer, 2012). HP, HPV, HBV und HCV sind nach einer Schätzung von de Martel et al. zusammen für mehr als 90% der im Jahr 2018 aufgetretenen infektionsbedingten Krebserkrankungen weltweit verantwortlich (de Martel et al., 2020). Obwohl bereits frühere Studien zeigten, dass in SSA eine signifikante Anzahl der Krebserkrankungen auf Infektionen zurückzuführen ist (Pisani et al., 1997; Parkin, 2006b; de Martel et al., 2012; Plummer et al., 2016), wurden von der Arbeitsgruppe „Global Burden of Disease“ erstaunlicherweise auch in ihrem Übersichtspapier für das Jahr 2021 Infektionen nicht als Risikofaktor für Erkrankungen aller Art (darunter Krebserkrankungen) aufgeführt (Brauer et al., 2024). Um die Relevanz von infektiösen Erregern – insbesondere auf dem afrikanischen Kontinent – zu unterstreichen, nutzen wir in unserer Studie nationale Schätzungen zu in Afrika neu aufgetretenen Krebsfällen, die 2018 von der IARC im Rahmen der „GLOBOCAN“-Reihe publiziert wurden, um den Anteil verschiedener Krebsentitäten,

die ursächlich auf infektiöse Erreger zurückzuführen waren, abzubilden. Beispielhaft sollen im Anschluss zwei Entitäten, deren Auftreten mit viralen Infektionen in Verbindung gebracht werden, näher beleuchtet werden: Das Plattenepithelkarzinom der Bindehaut (Squamous Cell Carcinoma of the Conjunctiva; SCCC) ist in SSA relativ häufig. Templeton berichtete vor mehr als 50 Jahren von einer hohen Inzidenz in Uganda (Templeton, 1973), einige Zeit später wurde ein Zusammenhang mit UV-Strahlung vermutet (Newton et al., 1996; Sun et al., 1997). Auffälliger ist jedoch der deutliche Zusammenhang mit HIV/AIDS-Infektionen. HIV-infizierte Personen haben ein 5- bis 10-fach höheres Risiko, ein Plattenepithelkarzinom der Konjunktiva zu entwickeln (Ateenyi-Agaba, 1995; International Agency for Research on Cancer, 2011; Gichuhi et al., 2013). Als zweite Entität betrachten wir das Burkitt-Lymphom (BL), eine hochaggressive Form des B-Zell-Lymphoms, die erstmals in den 1950er Jahren bei Kindern in Afrika beschrieben wurde (Burkitt, 1962b). Es ist durch eine schnelle Tumorproliferation und eine charakteristische chromosomale Translokation gekennzeichnet, bei der das MYC-Onkogen aktiviert wird, was zu unkontrolliertem Zellwachstum führt. BL tritt weltweit auf und wird in die drei Hauptformen „endemisch, sporadisch und immunschwächeassoziiert“ eingeteilt, wobei letztere vor allem bei HIV-positiven Patienten beobachtet wird (Diebold J et al., 2001). Weder zu SCCC noch zu BL gab es bisher systematische populationsbezogene epidemiologische Schätzungen, um fundierte Aussagen hinsichtlich Inzidenz und Verteilung in Bezug auf andere Infektionskrankheiten auf dem afrikanischen Kontinent treffen zu können.

1.3 Populationsbasierte epidemiologische Studien und Krebsregister im Allgemeinen

In der Resolution der World Health Assembly “Cancer prevention and control in the context of an integrated approach“ wurden die Mitgliedsstaaten ausdrücklich aufgefordert*, “to collect high-quality population-based incidence and mortality data on cancer, for all age groups by cancer type, including measurements of inequalities, through population-based cancer registries, household surveys and other health information systems*, *in order to guide policies and plans*” (Seventieth World Health Assembly, 2017). Im Gegensatz zu klinischen Studien, die sich auf spezifische Patientengruppen konzentrieren, erfassen populationsbasierte Studien Daten aus der gesamten Bevölkerung oder, weitaus häufiger, einer repräsentativen Stichprobe davon. Dies ermöglicht es, Ergebnisse auf die gesamte Bevölkerung zu übertragen, was insbesondere in der Krebsforschung von großer Bedeutung ist. Die Krankheitslast kann durch die Messung von Inzidenz, Prävalenz und Mortalität von Krebserkrankungen in verschiedenen Bevölkerungsgruppen besser verstanden und mit anderen Populationen

verglichen werden. Bei der Betrachtung der Aufgaben von Krebsregistern auf Ebene einer Klinik, eines pathologischen Instituts oder einer Population fällt auf, dass diese sehr unterschiedlich sind und komplementär zueinanderstehen. Während die ersten beiden genannten essentiell bei der Erfüllung von administrativen und klinischen Aufgaben sind, gelingt es nur mit populationsbasierten Krebsregistern, ein (weitgehend) unverzerrtes Bild der aktuellen Krebsbelastung und deren Veränderungen im Laufe der Zeit zu zeichnen (Bray et al., 2014). Die Beobachtung von Trends über längere Zeiträume ist unerlässlich für die Planung von Gesundheitsressourcen, nationalen und internationalen Krebskampagnen und Präventionsstrategien (Parkin, 2008). Die systematische Erfassung von Daten zu allen Krebserkrankungen in definierten Bevölkerungsgruppen begann in der ersten Hälfte des 20. Jahrhunderts in Nordamerika und Europa. Seitdem ist die Anzahl sogenannter Krebsregister stetig gewachsen. Lag der Schwerpunkt zunächst vor allem darauf, die Inzidenz von unterschiedlichen Tumorentitäten zu berechnen, erweiterten die meisten Krebsregister ihren Aufgabenbereich und erhoben Informationen zur Tumorhistologie, zum Stadium bei der Diagnose, zur Art der Behandlung sowie zum Überleben der Patienten (Parkin, 2006a).

In Ländern mit niedrigem und mittlerem Einkommen sind Meldesysteme für Geburts- und Sterberegister oft unzuverlässig, gar nicht vorhanden oder den Registern nicht zugänglich, weshalb eine Reihe von Registern auf aktive Follow-Up-Methoden zurückgreifen (Bray et al., 2014). Dennoch ist und bleibt der Verlust an Nachverfolgung („Loss to Follow-Up“) eine der wichtigsten Ursachen für eingeschränkte Qualität und Aussagekraft – selbst in Registern, die in Ländern mit hohem Einkommen verortet sind. Dieser Umstand ist wesentlich, denn selbst eine geringe Unterschätzung von Todesfällen kann zu einer signifikanten Überschätzung des Langzeitüberlebens führen, wie eine Simulationsstudie auf Basis von Daten aus dem finnischen Krebsregister zeigt (Brenner & Hakulinen, 2009).

1.4 Das Afrikanische Krebsregister Netzwerk

Das Afrikanische Krebsregister Netzwerk (African Cancer Registry Network, AFCRN) wurde offiziell 2012 gegründet, nachdem es seit 2009 als Projekt des Krebsregisterprogramms des Internationalen Netzwerks für Krebsbehandlung und -forschung (International Network for Cancer Treatment and Research; INCTR) existierte. Finanziert wird es durch den INCTR Challenge Fund, eine in Großbritannien registrierte Wohltätigkeitsorganisation (Registrierungsnummer 1079181), die Gelder für INCTR-Projekte sammelt. Der Challenge Fund erhält gezielte Spenden, die speziell zur Förderung von Krebsregisteraktivitäten in Ländern mit niedrigem und mittlerem Einkommen vorgesehen sind (Stefan et al., 2017). In das AFCRN werden lediglich populationsbasierte

Register aufgenommen, die zum Zeitpunkt der Aufnahme mindestens 50% der Zielbevölkerung abdecken. Innerhalb von drei Jahren müssen mindestens 70% der Krebsfälle in den Erfassungsgebieten dokumentiert sein (African Cancer Registry Network, 2022). Ziel des AFCRN ist es, die Erfassung von Krebsfällen in SSA effizienter zu gestalten, indem es eine fachkundige Analyse aktueller Probleme sowie technische, finanzielle und wissenschaftliche Unterstützung zur Beseitigung identifizierter Hindernisse bietet. Mittel- und langfristig sollen die von den Registern generierten Ergebnisse als grundlegender Bestandteil von gesundheitspolitischen Diskursen und Entscheidungen dienen. Das Netzwerk umfasst aktuell 31 populationsbasierte Krebsregister in 22 Ländern Subsahara-Afrikas und steht in enger Kooperation mit der Internationalen Agentur für Krebsforschung (African Cancer Registry Network, 2024). 86% der Länder in der Region haben Krebsregister in ihre gesundheitspolitischen Programme aufgenommen und die WHO-Region Afrika verzeichnete zwischen 2010 und 2015 den schnellsten Anstieg an Krebsregistern weltweit (Romero et al., 2018).

1.5 Zielstellung

Angesichts des zunehmenden Anteils an nichtübertragbaren Krankheiten (non-communicable diseases, NCDs) in SSA ist eine umfassende Erhebung und Analyse von Daten zu Krebserkrankungen unerlässlich. Die Daten des AFCRN tragen dazu bei, die gesundheitspolitischen Maßnahmen und die Ressourcenverteilung in der Region zu verbessern. Ziel der vorliegenden Arbeit ist es, einen Überblick über die epidemiologischen Trends von CRC in SSA zu geben mit Fokus auf die Evaluation der Therapiequalität sowie den Krankheitsverlauf und die Überlebensrate der Patienten. Wir nutzten dazu Daten aus 11 regionalen, bevölkerungsbasierten Krebsregistern in SSA, darunter Abidjan (Elfenbeinküste), Addis Abeba (Äthiopien), Bamako (Mali), Brazzaville (Kongo), Bulawayo (Simbabwe), Cotonou (Benin), Eldoret (Kenia), Kampala (Uganda), Maputo (Mosambik), Nairobi (Kenia) und Namibia. Diese Register sind Teil des AFCRN. Unsere Hauptstudie umfasst zwischen 60 und 100 zufällig ausgewählte Patienten pro Register, die zwischen 2011 und 2015 mit CRC diagnostiziert wurden. Insgesamt wurden 653 Patienten in die Studie aufgenommen. Demografische und klinische Daten wurden aus den Registern nach dem AFCRN-Standardverfahren erhoben (African Cancer Registry Network, 2022), während weitere Informationen zu Diagnose, Behandlung und Überleben aus medizinischen Unterlagen, Telefoninterviews und Hausbesuchen gewonnen wurden (Hämmerl et al., 2023). Analog dazu werden die vier in der Region am häufigsten auftretenden Krebsentitäten (Mamma-, Zervix- und Prostatakarzinom, Non-Hodgkin-Lymphom) untersucht und

ausgewertet (Joko-Fru et al., 2018; Mezger et al., 2020, Griesel et al., 2021; Seraphin et al., 2021; Mezger et al., 2023).

Trotz der zunehmenden und berechtigten Aufmerksamkeit auf NCDs in SSA wird nicht der anhaltend große Anteil von infektiös bedingten Krebsarten außer Acht gelassen. Es wird ein Überblick über die epidemiologische Entwicklung zu infektiös bedingten Krebsentitäten in Afrika gegeben (Parkin et al., 2020) und schließlich werden beispielhaft epidemiologische Daten zu BL und SCCC vorgestellt, um deren geografische Verteilung in Bezug auf infektiöse Erreger zu beleuchten (Hämmerl et al., 2019a; Hämmerl et al., 2019b).

Konkret stand die Beantwortung folgender Forschungsfragen im Fokus der vorliegenden Arbeit:

1. In welchem Umfang werden die Therapieempfehlungen der NCCN-Leitlinien in SSA umgesetzt, und wie beeinflusst dies die Überlebensrate der CRC-Patienten?
2. Welche Rolle spielen sozioökonomische Faktoren, wie der humane Entwicklungsindex (Human Development Index; HDI), bei der Überlebensrate von CRC-Patienten in SSA?
3. Inwiefern gibt es Gemeinsamkeiten in der Diagnostik, Behandlung und den Überlebensraten von Brust-, Gebärmutterhals- und Prostatakarzinomen und Non-Hodgkin-Lymphomen (NHL) in SSA?
4. Wie groß ist der Anteil der Krebserkrankungen, die durch infektiöse Erreger in SSA verursacht werden, und welche Rolle spielen Impfprogramme bei der Prävention?
5. Welche Zusammenhänge mit dem Auftreten verschiedener Infektionskrankheiten lassen sich bei der systematischen Analyse der Inzidenz von SCCC und BL in Afrika ableiten?

2 Diskussion

2.1 Überleben und leitliniengerechte Therapie

Wie hoch die Belastung einer Gesellschaft durch eine Krebsentität ist, drückt sich im Wesentlichen durch drei Parameter aus: Inzidenz, Mortalität und Überlebensrate. Die Krebsinzidenz, also die Anzahl der jährlichen Neuerkrankungen in einer bestimmten Region, sowie die Mortalität werden als Rate pro 100.000 Personen gemessen. Das Krebsüberleben wird aus Inzidenz und Mortalität geschätzt und liefert zuverlässigere Informationen über die Effizienz des Gesundheitssystems inklusive Zugang zu Früherkennung und Behandlung, wenn die Schätzwerte aus bevölkerungsbasierten Krebsregistern stammen (Lambert et al., 2012). Bisher standen nur begrenzt Daten zu Überleben und Evaluation der Therapieleitlinien von Patienten mit CRC in SSA zur Verfügung. Von den wenigen vorhandenen Publikationen evaluierte keine die Therapieadhärenz in Übereinstimmung mit den harmonisierten NCCN Leitlinien, die Anfang 2018 für SSA entwickelt worden waren, um den unterschiedlichen Ressourcen in der Region Rechnung zu tragen.

In unserer Studie auf der Grundlage von 11 populationsbasierten Krebsregistern in SSA stellten wir fest, dass das Gesamtüberleben der Patienten mit CRC schlecht war. Es lag nach 1, 2 und 3 Jahren bei 70,9 % (95% CI, 65,5%–76,3%), 55,2 % (95% CI, 49%–61,4%) und 45,3 % (95% CI, 38,9%–51,7%) und unterschied sich statistisch signifikant je nach Stadium bei Diagnosestellung und nach Beginn der Therapie. Bei Patienten ohne dokumentiertes Stadium lag das 2-Jahres-Überleben bei 50,5 % (95% CI, 33,7%–67,3%) (Hämmerl et al., 2023). Es ist davon auszugehen, dass viele der Patienten, zu denen keine Informationen gefunden werden konnten (Klinikakte, Follow-Up), sich bereits in einem weit fortgeschrittenem Krebsstadium befanden, und/oder keine adäquate Diagnostik und Therapie erhielten (Hämmerl et al., 2023). Insgesamt befinden sich unsere Ergebnisse im Einklang mit bisherigen Studien zu Überlebensraten von CRC-Patienten in SSA, selbst wenn diese auf Fallserien, Erfahrungsberichten einzelner Akteure und Daten von Klinikregistern basierten. Eine retrospektive Analyse von Agyemang-Yeboah et al am Komfo Anokye Teaching Hospital in Kumasi (Ghana) untersuchte 221 Patienten mit CRC, die dort zwischen 2009 und 2015 diagnostiziert wurden, und fand ebenfalls sehr niedrige Überlebensraten. Die Überlebensraten im 1., 2., 3. und 4. Jahr betrugen 64% (95% CI: 56,2–71,1), 40% (95% CI: 32,2–50,1), 21% (95% CI: 11,4–30,6) und 16% (95% CI: 8,9–26,9). Die Autoren führten die niedrigen Überlebensraten vor allem auf die späte Diagnosestellung in fortgeschrittenem Krankheitsstadium zurück (Agyemang-Yeboah et al., 2018). Eine Arbeitsgruppe der Internationalen Agentur für Krebsforschung verglich die Überlebensraten von Patienten mit

CRC aus 27 bevölkerungsbasierten Krebsregistern in 14 Ländern in Afrika, Asien, der Karibik und Zentralamerika und bestätigte, dass diese in Ländern SSAs extrem niedrig waren im Vergleich zu asiatischen und zentralamerikanischen Ländern. In Ländern wie Gambia und Uganda lag die 5-Jahres-Überlebensrate bei weniger als 8%, verglichen mit 60% in Korea, wobei insgesamt nur von drei Ländern in SSA populationsbasierte Daten für die Analyse zur Verfügung standen (Sankaranarayanan et al., 2011). Die Überlebensraten für CRC in westlichen Ländern sind generell deutlich höher als in SSA, beziehungsweise verbesserten sich im Laufe der letzten Jahrzehnte drastisch. Beispielsweise stieg die 5-Jahres-Überlebensrate in den USA zwischen 1975 und 2001 von 49,8 % auf 65,1 % (Jiang et al., 2021). Verbesserungen der CRC-Prognose in entwickelten Ländern werden hauptsächlich durch fortschrittlichere Diagnose- und Staging-Methoden, verbesserte chirurgische Techniken und präoperative Strahlentherapien erreicht. Auch der breite Einsatz von Screeningprogrammen und eine damit verbundene Diagnosestellung in frühen Krankheitsstadien wirkt sich auf die Verbesserung der Prognose aus. In SSA hingegen bleibt die Überlebensrate niedrig, was auf mehrere Faktoren zurückzuführen ist: Ein mangelndes Bewusstsein für CRC in der Bevölkerung und beim Gesundheitspersonal, das Fehlen von Screening-Programmen (Fidler & Bray, 2018; Irabor, 2017), schlechtere chirurgische Behandlungen (Chawla et al., 2018), Engpässe bei Chemotherapie und Bestrahlung sowie Verzögerungen bei der Versorgung und hohe Kosten für Diagnostik und Behandlung (Alkire et al., 2015). Dies führt häufig dazu, dass Patienten ihre Behandlung abbrechen, weil sie sich diese nicht leisten können. Auch innerhalb Europas gibt es erhebliche Unterschiede in den Überlebensraten; osteuropäische Länder wie Estland, Litauen und Polen weisen deutlich schlechtere Überlebensraten auf, – und auch diese Diskrepanz steht in einem klaren Zusammenhang mit dem sozioökonomischen Status und dem Zugang zu medizinischer Technologie (Baili et al., 2015). Screening-Programme spielen hier eine entscheidende Rolle; sie wurden in vielen entwickelten Länder seit den späten 1980er Jahren eingeführt. Aber viele Regionen weltweit profitieren immer noch nicht ausreichend von diesen Maßnahmen (Jiang et al., 2021). Vor der Einführung einer nationalen Krebspräventionspolitik in Entwicklungsländern sollte die Krebssterblichkeit im Verhältnis zur Sterblichkeit durch Infektionskrankheiten und nicht übertragbare Krankheiten bewertet werden. In armen Entwicklungsländern wie in SSA ist die Priorität der Krankheitsprävention aufgrund der hohen Todesrate durch Infektionskrankheiten und Atemwegsinfektionen anders gelagert. Es gibt Potenzial zur Krebsprävention in Entwicklungsländern durch primäre Präventionsmaßnahmen, die sich auf Lebensstil- und Umweltfaktoren konzentrieren, sowie durch Verbesserungen in der Früherkennung und Behandlung. Eine nationale

Präventionspolitik, die sich auf Krebsrisiken konzentriert, könnte das Bewusstsein für diese Risiken erhöhen und die Akzeptanz von Früherkennungsmaßnahmen wie Massen-Screenings steigern (Lambert et al., 2012).

In unserer Therapie- und Outcomestudie erhielten lediglich 3 % der Darmkrebspatienten in den Stadien I–III eine leitliniengerechte Behandlung, und 20 % wurden mit geringen Abweichungen von den Leitlinien behandelt. Der Anteil der Patienten mit nicht metastasiertem CRC, die eine adäquate Behandlung erhielten, inklusive Behandlungen mit geringfügigen Abweichungen, lag zwischen 2% in Kampala (Uganda) und 29,7% in Namibia. Abweichungen von den Leitlinien hatten signifikante Auswirkungen auf das Überleben (Hämmerl et al., 2023). Beispielsweise resultierte eine geringere Anzahl entfernter Lymphknoten bei Operationen, was ein etablierter prognostischer Faktor ist (Le Voyer et al., 2003; Chang et al., 2007; Ghukasyan et al., 2023), in schlechteren Überlebenschancen. Dies verdeutlicht, dass radikale chirurgische Eingriffe auch in ressourcenarmen Umgebungen eine entscheidende Rolle bei der kurativen Behandlung von CRC spielen können. Auch hinsichtlich der Therapiequalität finden sich in der Literatur ähnliche Ergebnisse, wobei bis dato noch keine umfangreiche Studie in populationsbasiertem Setting publiziert wurde. Eine prospektive Studie, die an fünf nigerianischen Kliniken durchgeführt wurde, ergab, dass etwa 30 % der Patienten nicht die empfohlene chirurgische Therapie erhielten, rund die Hälfte nicht das empfohlene Chemotherapie-Regime und 96 % keine Strahlentherapie, selbst wenn diese als optimale Behandlung galt. Das Gesamtüberleben derjenigen Patienten, die die leitliniengerechte Therapie erhielten, war signifikant besser (24 Monate gegenüber 8 Monaten) (Sharma et al., 2020). Auch eine Untersuchung von Dakubo et al. in Ghana mit 350 Fällen zeigte, dass 36 % der Patienten keine Operation erhielten, hauptsächlich aufgrund von Inoperabilität, finanziellen Einschränkungen und dem Wunsch der Patienten, eine Kolostomie zu vermeiden (Dakubo et al., 2011). Eine retroprospektive Kohortenstudie in Kampala (Uganda), die 247 Darmkrebspatienten zwischen 2008 und 2018 analysierte, zeigte Überlebensraten von 65,2 % nach einem Jahr, 42,0 % nach zwei Jahren und 33,3 % nach drei Jahren. Insgesamt erhielten nur 65 Patienten (26,3 %) eine Kombination aus kurativer Operation und adjuvanter Chemotherapie, während lediglich 3 Patienten mit Rektumkarzinom eine postoperative Strahlentherapie erhielten (Wismayer et al., 2022).

Gründe für die unzureichende Leitlinientreue konnten in unserem retrospektiven Studiendesign nicht systematisch ermittelt werden. Sie umfassen aber wahrscheinlich einerseits mangelnde (Gesundheits)-bildung in der Bevölkerung, fehlenden Zugang zum Gesundheitssystem – vor allem in ländlichen Gebieten, und andererseits Stigmatisierung onkologischer Erkrankungen (Chalya et al., 2013). Ein weiterer entscheidender Faktor ist die

unzureichend vorhandene Gesundheitsinfrastruktur, die sich in einem Mangel an Onkologen, Chirurgen und Krebsmedikamenten sowie den hohen Kosten für Krebsbehandlungen widerspiegelt. Laut der Lancet Commission on Global Surgery haben über 95 % der Bevölkerung in Zentral-, Ost- und West-SSA keinen Zugang zu sicherer, bezahlbarer und rechtzeitiger chirurgischer Versorgung (Alkire et al., 2015). Darüber hinaus arbeiten nur 19 % aller Chirurgen in Ländern mit niedrigem und mittlerem Einkommen, während in diesen Regionen aber 48 % der Weltbevölkerung leben (Holmer et al., 2015).

Auch auf dem Gebiet der Strahlentherapie konnte unsere Studie erhebliche Mängel aufzeigen, obwohl diese eine entscheidende Rolle bei der Behandlung von Rektumkarzinomen spielt. Nur 17 % der von uns erfassten nicht metastasierten Fälle (absolut: 63 Patienten) erhielten überhaupt Strahlentherapie (Hämmerl et al., 2023). Dies steht im Zusammenhang mit der geringen Verfügbarkeit von Strahlentherapiegeräten auf dem afrikanischen Kontinent, wo im Jahr 2014 lediglich fünf der zehn von uns untersuchten Länder Onkologiezentren mit Strahlentherapiekapazität hatten (Abdel-Wahab et al., 2013). Tatsächlich verfügt Afrika weltweit über die am schlechtesten entwickelten Strahlentherapieressourcen, mit durchschnittlich weniger als einem Bestrahlungsgerät pro einer Million Menschen. Trotz leichter Verbesserungen in den letzten zehn Jahren bleibt die Versorgungslage unzureichend (Zubizarreta et al., 2017; Christ et al., 2023).

Die NCCN-Harmonisierten Leitlinien für SSA für Darmkrebs wurden erst 2018 veröffentlicht, also nach der Diagnose und Behandlung der Patienten in dieser Studie (2011–2015). Daher dienen unsere Daten als eine Art „Maßstab *vor* der Leitlinie“ und können als Ausgangspunkt für zukünftige Untersuchungen herangezogen werden, um den Fortschritt bei der Leitlinientreue und die daraus resultierende Verbesserung der Krebsversorgung seit der Einführung der NCCN-Leitlinien für SSA zu bewerten. Unsere Studie betont daher die Notwendigkeit einer frühzeitigen Krebsdiagnose. Behandlungen in frühen Stadien sind nicht nur effektiver hinsichtlich Morbidität und Mortalität, sondern haben sich auch als kosteneffizienter erwiesen als alle Therapien in fortgeschrittenen Stadien (Ralaidovy et al., 2018).

2.2 Abhängigkeit des Überlebens vom Human Development Index

Bei der epidemiologischen Entwicklung von CRC hinsichtlich Inzidenz und Mortalität zeigt sich global ein klares Muster in Bezug auf den HDI: In Ländern mit mittlerem bis hohem HDI – wie Brasilien, Polen oder China – steigen sowohl die Inzidenz als auch die Mortalität stark an. In Ländern mit hohem HDI, wie Singapur oder Kanada, nimmt die Inzidenz weiter zu, während die Mortalität abnimmt. In Ländern mit sehr hohem HDI, wie Australien, Japan

oder Frankreich, sinken sowohl Inzidenz als auch Mortalität (Jiang et al., 2021). Wir nutzten den HDI als Indikator für die Ressourcenverfügbarkeit in den von uns untersuchten Ländern in SSA und kategorisierten die Länder basierend auf den Werten von 2014 (United Nations Development Programme, 2015) in solche mit niedrigem HDI (<0,5) und mittlerem HDI (0,5 bis <0,8). Länder mit hohem oder sehr hohem HDI waren nicht eingeschlossen.

In unserer Studie zu Überleben und Therapie an Patienten mit CRC in SSA konnten wir zeigen, dass das Sterberisiko bei Patienten in Ländern mit niedrigem HDI 1,67-mal höher war (95%, 1,07–2,62) im Vergleich zu Patienten in Ländern mit mittlerem HDI (Hämmerl et al., 2023). Unterstrichen werden unsere Ergebnisse durch eine Publikation von Gullikson et al., bei deren Gesamtkohorte mit 1448 CRC-Patienten es teilweise Überschneidungen zu unserer Studienpopulation gab. Das beobachtete Überleben betrug insgesamt 72,0 % nach einem Jahr, 50,4 % nach drei Jahren und 43,5 % nach fünf Jahren. Schlechtere Überlebenschancen waren hier ebenfalls mit einem niedrigen HDI assoziiert. So war das Sterberisiko für Patienten aus Ländern mit mittlerem HDI 1,6-mal höher, während es in Ländern mit niedrigem HDI sogar 2,7-mal höher war, verglichen mit Ländern, die einen hohen HDI aufweisen (Gullickson et al., 2021). Der HDI kann laut verschiedenen Studien als grober Indikator für die zunehmenden globalen Ungleichheiten bei Krebsbelastung, Mortalität und den Ergebnissen herangezogen werden (Fidler & Bray, 2018). Auch die Generalversammlung der Vereinten Nationen trug dieser Erkenntnis Rechnung, als sie 2015 Ziele für nachhaltige Entwicklung (Sustainable Development Goals; SDG) formulierte und feststellte, dass Länder mit niedrigem Einkommen besonders anfällig für die wachsende globale Krebsbelastung sind (United Nations General Assembly, 2015). Im Jahr 2009 gründete sich die *Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries,* in der führende Vertreter der globalen Gesundheits- und Krebsversorgungsgemeinschaften für eine verbesserte Ressourcenallokation in armen Ländern zusammenarbeiten (Farmer et al., 2010). Unsere Ergebnisse unterstreichen die dringende Notwendigkeit, mehr Ressourcen für die Krebsversorgung in SSA, insbesondere in den Ländern mit niedrigem HDI, bereitzustellen. Die Stärkung der Gesundheitssysteme ist entscheidend, um den Zugang zu Prävention, Früherkennung und adäquater Behandlung zu verbessern (Hämmerl et al., 2023).

2.3 Vergleichende Studien mit häufigen Krebsentitäten in SSA

Auch in Bezug auf andere häufige Krebsentitäten in SSA, die wir in unseren Studien untersuchten, konnten erhebliche Lücken in der Versorgung aufgezeigt werden. Von den 693 untersuchten Patienten mit Prostatakarzinom hatten 37,3% bereits Metastasen zum Zeitpunkt

der Diagnosestellung, und nur 11,2% durchliefen eine vollständige diagnostische Abklärung zur Risikoeinschätzung (Erhebung und Dokumentation des Prostataspezifischen Antigens (PSA-Wert), des Gleason-Scores und des Tumor-Nodes-Metastasis-Stadiums (TNM-Stadium)), welche unabdingbar für eine leitliniengerechte Therapie ist. 17,5% der Patienten mit nicht-metastasiertem Prostatakrebs erhielten eine kurative Behandlung, während 27,5% keinerlei tumorspezifische Therapie erhielten (Seraphin et al., 2021). Und auch von den 809 untersuchten Patientinnen mit Mamma-Karzinom erfüllten nur 20% der Fälle die minimalen diagnostischen Kriterien, um gemäß den NCCN Harmonized Guidelines behandelt zu werden. Bei 72,5% der Frauen war der Hormonrezeptorstatus unbekannt, und 50,9% der Frauen mit Brustkrebs im Stadium I–III erhielten eine unzureichende oder gar keine tumorspezifische Therapie (Joko-Fru et al., 2021). Für eine Evaluation der Therapieadhärenz fehlte bei der Analyse von Brust- und Prostatakrebs ein zu großer Anteil der für die Therapieallokation notwendigen Diagnostik, so dass die anfangs geplante Aussage über den Grad der Umsetzung der NCCN-Leitlinien nicht getroffen werden konnte (Seraphin et al., 2021; Joko-Fru et al., 2021). Schwierigkeiten in der diagnostischen Aufarbeitung fanden wir auch bei Patienten mit NHL. Bei 58% der Gesamtkohorte ließ sich keine Subklassifikation des NHLs finden (Mezger et al., 2020). Ohne eine genaue Klassifizierung sind jedoch weder Diagnose noch Behandlung durch das klinische Team möglich. In der Folge konnte nur bei 4,1 % der Patienten der Beginn einer leitliniengerechten Therapie identifiziert werden, bei weiteren 9,5 % der Patienten der Beginn einer Therapie mit geringfügigen Abweichungen (Mezger et al., 2023). Als entscheidender ursächlicher Faktor für diese Mängel gilt eine Unterversorgung durch Pathologielabore in der Region (Wilson et al., 2018). In einer Studie von Nelson et al. wurden Pathologen aus 26 Ländern SSAs hinsichtlich der pathoonkologischen Infrastruktur befragt. Im Schnitt standen nur ein bis zwei Pathologen pro 1 Million Einwohner zur Verfügung (Nelson et al., 2016) – im Vergleich beträgt die Dichte der Pathologen pro 1 Million Einwohner in Nordamerika 48,8, in Europa 26,1, in Südamerika 17 und in Asien 6,8, so dass für den afrikanischen Kontinent ein extremer Mangel konstatiert werden muss (Bychkov & Fukuoka, 2022). Lediglich zum Zervixkarzinom konnten wir hinsichtlich der diagnostischen Situation bei unseren Studien bessere Ergebnisse feststellen, wo bei 89 % der Kohorte mit Follow-Up ein Stadium gemäß der Klassifikation der Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) dokumentiert war. In der therapeutischen Versorgung des Zervixkarzinoms stellte sich jedoch wiederum ein äußerst negatives Bild dar: 15,8% der untersuchten Patientinnen erhielten eine kurative Therapie, wobei nur 5,2% leitliniengerecht behandelt wurden, 2,4% mit geringfügigen und 8,2% mit erheblichen Abweichungen von den Leitlinien. Bei den Patientinnen im Stadium I–III führte

eine nicht kurative oder fehlende Behandlung zu deutlich schlechteren Überlebenschancen. Somit konnten wir feststellen, dass bis zu zwei Drittel der Frauen keine adäquate Therapie erhielten, obwohl die Krankheit in einem heilbaren Stadium diagnostiziert wurde (Griesel et al., 2021).

2.4 Krebserkrankungen und infektiöse Erreger in Afrika

In unserer Studie zum Anteil der Krebserkrankungen in Afrika, die durch Infektionserreger verursacht werden, kamen wir zu dem Ergebnis, dass im Jahr 2018 in SSA etwa 221.500 Fälle (28,7 %) auf Infektionserreger zurückzuführen waren (Parkin et al., 2020). Im Vergleich dazu geht man in Westeuropa nur von einem Anteil von etwa 15% an Infektionsbedingten Krebsfällen aus (de Martel et al., 2020). Unsere Studie zeigt, dass in Afrika der Großteil der infektionsbedingten Krebsfälle von viralen Infektionen wie Hepatitis B, Hepatitis C und HPV verursacht wird. Nur ein geringer Anteil (2,7%) ist dem im Rest der Welt relevanteren Bakterium Helicobacter pylori zuzuschreiben (Parkin et al., 2020). Im Vergleich zu früheren Schätzungen ist der Anteil infektionsbedingter Krebserkrankungen in SSA leicht gesunken, was möglicherweise mit der Zunahme von Krebsarten wie Mamma- und Prostatakrebs zusammenhängt. Außerdem könnte der Rückgang der geschätzten Zahlen auf die Abnahme der Fallzahlen einiger wichtiger infektionsbedingter Krebserkrankungen wie Kaposi-Sarkom und Leberkrebs zurückzuführen sein (Parkin et al., 2020). Die Prävention infektionsbedingter Krebserkrankungen in Afrika wird durch Impfprogramme unterstützt, insbesondere gegen HBV und HPV. Trotz Fortschritten bleibt die Etablierung der HPV-Impfung in vielen Regionen Afrikas eine Herausforderung, vor allem wegen kultureller Barrieren und logistischer Probleme bei der Zielbevölkerung. Die Behandlung von HCV bleibt aufgrund der hohen Kosten schwer zugänglich (Dakurah et al., 2021). Zusätzlich zu Impfprogrammen könnte eine frühzeitige Erkennung durch Screening-Programme die Krebsbelastung erheblich verringern, was sich in Ländern mit mittlerem und hohem Einkommen zeigen lässt, wo solche Screening-Programme bereits Realität sind (International Agency for Research on Cancer, 2005). Bei der koordinierten Umsetzung solcher Maßnahmen, die die Krebsbelastung aufgrund von Infektionen signifikant senken können, kann die Implementierungsforschung helfen, indem sie die Einführung und Ausweitung solcher Programme unterstützt und einzelne Maßnahmen nach ihrem tatsächlichen Erfolg evaluiert (Rositch, 2020). Trotz zahlreicher Fortschritte bleibt es eine globale Herausforderung, die Lücke zwischen wissenschaftlicher Evidenz und praktischer Umsetzung in der Krebsbekämpfung zu schließen, insbesondere in ressourcenarmen Ländern.

Beispielhaft für Krebserkrankungen, die mit infektiösen Erregern assoziiert sind, haben wir auf Grundlage der Daten der afrikanischen Krebsregister untersucht, in welchem Zusammenhang die Inzidenz von SCCC – eine relativ häufige Krebsentität in Afrika – mit den Fallzahlen bei der HIV-Epidemie steht; dafür haben wir die Inzidenzraten für 26 Länder in SSAs und 5 Länder Nordafrikas berechnet. Wir kamen zu dem Ergebnis, dass 2018 etwa 6.200 neue Fälle von SCCC in Afrika auftraten, vorrangig in SSA und mit ähnlicher geografischer Verteilung wie die Verbreitung von HIV. Die höchsten Inzidenzraten stellten wir in Botswana, Namibia, Malawi, Mosambik, Sambia, Simbabwe und Eswatini fest, alles Länder mit hoher HIV-Prävalenz (Hämmerl et al., 2019a). Auch beim BL, einer weiteren relativ häufigen Krebserkrankung, die vor allem im Kindesalter und in tropischen Regionen Afrikas auftritt, existierten bisher keine systematischen Untersuchungen zur Inzidenz und genauen geografischen Verteilung. Das BL ist stark mit Infektionen durch das EBV und Malaria assoziiert (Carbone et al., 2008; International Agency for Research on Cancer, 2013). Für 2018 schätzen wir, dass 3900 neue Fälle von BL in Afrika auftraten, davon etwa 81% bei Kindern im Alter zwischen 0 und 14 Jahren. Die höchsten Inzidenzraten stellten wir in Ländern wie Malawi (6,2 pro 100.000), Kamerun (2,1), Uganda (1,4) und Sambia (1,3) fest. Unsere Ergebnisse bestätigen die seit langem vermutete geographische Verteilung und zeigen, dass diese weitgehend durch die Endemizität der Falciparum-Malaria beeinflusst wird. Eine frühe Co-Infektion mit EBV ist zudem ein relevanter ätiologischer Faktor in mehr als 80 % der Fälle (Hämmerl et al., 2019b).

2.5 Limitationen und Stärken der Studien

Die Limitationen unserer Therapie- und Outcome-Studien ergeben sich vorrangig aus der Methodik (retrospektives Studiendesign). Das Loss-to-Follow-Up unterschied sich zwar nach Tumorentität und Land, war aber insgesamt auf hohem Niveau. Besonders in der hier im Fokus stehenden Analyse zu Patienten mit CRC konnten für einen erheblichen Anteil (fast 50%) der von den Krebsregistern ausgegeben Fälle keinerlei Informationen zu Diagnostik, Therapie oder Outcome in den klinischen Akten gefunden werden. Bei denjenigen Patienten wiederum, zu denen wir klinische Daten ausfindig machen konnten, erschwerten häufig unpräzises Staging, schlechte und lückenhafte Dokumentation und frühes Loss-to-Follow-Up die Datenanalyse. Viele Patienten wurden möglicherweise gar nicht erst in die klinische Versorgung aufgenommen oder aber ihre Daten sind aufgrund mangelhafter Archivierungssysteme verloren gegangen. Eine andere Erklärungsmöglichkeit für den hohen Anteil von Patienten, zu denen keine klinischen Informationen gefunden werden konnten, ist eine Überweisung zu onkologischen Zentren im Ausland – allerdings dürfte diese Option

aufgrund der hohen Kosten nur den wohlhabendsten Patienten vorbehalten sein und nur einen sehr geringen Prozentsatz der zensierten Daten ausmachen. Wir betrachten also den außerordentlich hohen Anteil an fehlenden Daten und die dadurch begrenzte Aussagekraft zu Diagnostik und Therapie nicht nur als einschränkenden Faktor dieser Studie, sondern auch als wichtiges Teilergebnis, das die besorgniserregende Situation der Versorgung von Patienten mit CRC in SSA unterstreicht (Hämmerl et al., 2023). Eine weitere Limitation, die all unseren Studien gemein ist, liegt in der Tatsache begründet, dass wir unsere Daten aus populationsbasierten Krebsregistern beziehen. Krebsregistern ist jedoch trotz des repräsentativen Charakters anzulasten, dass sie vorrangig städtische Bevölkerungen abdecken. Dies kann zu Verzerrungen bei der Schätzung von Inzidenzen führen. Beispielsweise ist die Malaria-Übertragungsintensität in ländlichen Gebieten höher. Somit könnten unsere Schätzwerte für BL-Fälle in Afrika eine Unterschätzung der tatsächlichen Zahlen darstellen (Hämmerl et al., 2019b).

Trotz der genannten Einschränkungen erachten wir unsere Studien als einen wesentlichen Fortschritt in der Datenlage für eine wissenschaftlich noch immer unterrepräsentierte Region. Durch den populationsbasierten Ansatz ermöglichen sie erstmals einen detaillierten und repräsentativen Einblick in die tatsächliche Versorgungssituation von Patienten mit den am häufigsten auftretenden Krebsentitäten in SSA. Die von uns gewählte äußerst aufwändige Methode des aktiven Follow-Ups erweitert die Daten aus den populationsbasierten Krebsregistern um wertvolle Daten zu Behandlung und Überlebensstatus. Dadurch konnten wir erstmals multizentrische repräsentative Studien zur Therapieevaluation diverser Krebsentitäten in SSA vorstellen und eine Grundlage für Folgeuntersuchungen liefern.

2.6 Fazit

Das Fazit unserer Studien zeigt deutlich die drängenden Herausforderungen im Bereich der Krebsversorgung in SSA auf. Zum ersten Mal wurde untersucht, inwieweit die Behandlung von Patienten mit CRC in SSA den NCCN-harmonisierten Leitlinien entspricht und inwiefern die Überlebensraten eine Abhängigkeit vom HDI aufweisen. Darüber hinaus analysierten wir auch Therapie und Outcome von Patienten mit Zervix-, Mamma- und Prostatakarzinom sowie NHL auf populationsbezogener Basis. Trotz der steigenden Krankheitslast ist die Versorgungslage in SSA deutlich unzureichend. Es bestehen erhebliche Lücken in Früherkennung, Diagnose und Behandlung; selbst Patienten ohne Metastasen – also in potentiell kurativen Krankheitsstadien – erhalten oftmals keine adäquate leitliniengerechte Therapie. Dies alles trägt maßgeblich zu einer niedrigen Überlebensrate bei. So liegt das

Überleben von CRC-Patienten in unserer Kohorte nach drei Jahren bei nur etwa 45%. Ein weiterer wichtiger Aspekt, der zur schlechten Prognose von Krebspatienten in SSA beiträgt, ist der fehlende Zugang zu angemessener medizinischer Infrastruktur, was mit einem Mangel an Pathologielaboren, an Chirurgen und Onkologen, sowie mit der begrenzten Verfügbarkeit von lebensrettenden Behandlungen wie Strahlentherapie und Chemotherapie korreliert. Der HDI erwies sich als zuverlässiger Indikator für die Überlebenschancen, wobei CRC-Patienten in Ländern mit niedrigem HDI ein signifikant höheres Sterberisiko hatten. Trotz der schwierigen Bedingungen in SSA konnten die positiven Effekte und das Potential einer leitliniengerechten Behandlung aufgezeigt werden: Patienten, die eine Therapie entsprechend den NCCN-Leitlinien erhielten, hatten eine deutlich bessere Überlebenschance. Dies deutet darauf hin, dass selbst unter den prekären Bedingungen in SSA die Leitlinien eine effektive Basis für Therapieentscheidungen darstellen können. Doch trotz dieser Bemühungen bleibt die Implementierung solcher Leitlinien in der Praxis oft schwierig. Das fehlende Bewusstsein für Krebs in der Bevölkerung und bei Gesundheitspersonal, hohe Behandlungskosten und die Abhängigkeit von veralteter oder unzureichender medizinischer Technologie sowie der Mangel an spezialisierten Fachkräften, wie Chirurgen und Onkologen, tragen weiterhin zur Diskrepanz zwischen evidenzbasierter Praxis und tatsächlicher Versorgung bei. Während der globale Fokus der Krebsprävention auf Tabakkontrolle, gesunder Ernährung, körperlicher Aktivität und der Reduzierung schädlichen Alkoholkonsums liegt, konnten wir in unserer Studie zeigen, dass Infektionen in Afrika weiterhin eine sehr wichtige Ursache für Krebs darstellen. Dies sollte sich in den Präventionsstrategien in stärkerem Maße widerspiegeln. Fortschritte im Bereich der Impfprogramme, besonders gegen HPV, wären also vielversprechend, jedoch bleiben logistische und kulturelle Barrieren bestehen, die den breiten Einsatz von Impfungen bisher behindern. Zudem sind selbst kostengünstige Behandlungsoptionen, wie die HCV-Therapie, für viele Menschen in der Region unerschwinglich. Um die Krebsbelastung in SSA effektiv zu reduzieren, bedarf es einer umfassenden und koordinierten Strategie, die auf Früherkennung, Prävention und angemessene Therapie abzielt. Es müssen Synergien zwischen verschiedenen Gesundheitsbereichen gefördert werden, um den Zugang zur Versorgung zu verbessern und die Überlebenschancen zu erhöhen. Nur durch einen systematischen Ansatz, der sowohl auf nationaler als auch globaler Ebene unterstützt wird, kann die Lücke zwischen wissenschaftlicher Evidenz und praktischer Anwendung schrittweise geschlossen und die Krebssterblichkeit in der Region langfristig gesenkt werden.

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Thesen

1 Die Überlebensrate der von uns untersuchten Patienten mit CRC in SSA betrug nach 1 und 3 Jahren 70,9 % (95 % CI, 65,5 %–76,3 %) bzw. 45,3 % (95 % CI, 38,9 %–51,7 %). In Übereinstimmung mit der Literatur zeigte sich ein schlechtes Gesamtüberleben, was vorrangig auf die späte Diagnosestellung in fortgeschrittenen Krankheitsstadien sowie die unzureichende therapeutische Versorgung zurückzuführen ist.

2 Nur 3 % der Patienten mit CRC in den Stadien I–III erhielten eine leitliniengerechte Therapie entsprechend den harmonisierten NCCN-Leitlinien für SSA; 20,6 % erhielten eine Behandlung mit geringfügigen Abweichungen, 31,7 % eine Behandlung mit größeren Abweichungen, und 35,1 % erhielten keinerlei tumorspezifische Behandlung.

3 Abweichungen von den Leitlinien hatten statistisch signifikante Auswirkungen auf das Überleben. Das Sterberisiko bei Patienten mit CRC, die keine gezielte Krebstherapie erhielten, war 3,49-mal höher (95 % CI, 1,83–6,66) als bei Patienten, die eine leitliniengerechte oder eine Behandlung mit geringfügigen Abweichungen erhielten. Eine geringere Anzahl entfernter Lymphknoten bei Operationen hatte ein schlechteres Gesamtüberleben zur Folge, was die Bedeutung von radikalen chirurgischen Eingriffen in ressourcenarmen Settings unterstreicht.

4 Laut unserer Analysen kann der HDI als Indikator für die Überlebensrate von CRC-Patienten in SSA dienen, wobei Patienten in Ländern mit niedrigem HDI ein 1,67-mal höheres Sterberisiko hatten als in Ländern mit mittlerem HDI.

5 Bei anderen häufigen Krebsentitäten in SSA zeigten sich erhebliche Mängel in der diagnostischen und therapeutischen Versorgung. Nur 11,2 % der Patienten mit Prostatakarzinom und 20 % der Patienten mit Mammakarzinom durchliefen eine ausreichende diagnostische Abklärung; bei fast zwei Drittel der Patienten mit NHL war keine Subklassifikation dokumentiert. Eine Ausnahme stellte die Diagnostik beim Zervixkarzinom dar, wo bei 89 % der Patientinnen ein FIGO-Stadium detektiert wurde. Die Evaluation der Therapie ergab, dass nur ein geringer Prozentsatz der Patienten leitliniengerecht behandelt wurde (4,1% bei NHL und 5% bei Zervixkarzinom). Im Falle des Prostata- und Mammakarzinoms war eine fundierte Beurteilung der Therapieadhärenz aufgrund der unzureichend durchgeführten oder dokumentierten Diagnostik nicht möglich; der hohe Anteil der Patienten ohne tumorspezifische Therapie ließ jedoch auf eine besorgniserregende Unterversorgung schließen.

6 Im Jahr 2018 waren etwa 28,7 % der Krebserkrankungen in SSA durch Infektionserreger bedingt, wobei Hepatitis B, Hepatitis C und HPV für den Großteil der krebsauslösenden Infektionen verantwortlich waren. Impfprogramme sind entscheidend, um diese Belastung zu reduzieren.

7 Die Inzidenz von BL war in unseren Schätzungen für das Jahr 2018 in den Teilen SSAs hoch, in denen Plasmodium falciparum-Malaria verbreitet ist. Ein zusätzlicher ätiologischer Faktor stellte das EBV in mehr als 80 % der Fälle dar.

8 In Bezug auf SCCC schätzten wir, dass im Jahr 2018 etwa ein Drittel aller Fälle in Afrika HIV-assoziiert waren. Die höchsten Inzidenzraten stellten wir in Ländern mit hoher HIV-Prävalenz fest, was die Notwendigkeit für Präventionsmaßnahmen in der Region unterstreicht.

Publikationsteil

Überblick über die Veröffentlichungen und Anteil der Doktorandin an den Publikationen

Publikation 1:

Hämmerl, L., Mezger, N. C. S., Seraphin, T. P., Joko-Fru, W. Y., Griesel, M., Feuchtner, J., Gnahatin, F., Gnangnon, F. H. R., Okerosi, N., Amulen, P. M., Hansen, R., Borok, M. Z., Carrilho, C., Mallé, B., Ahoui Apendi, C., Buziba, N. G., Seife, E., Liu, B., Mikolajczyk, R., Parkin, D. M., … Jemal, A. (2023). *Treatment and Survival Among Patients With Colorectal Cancer in Sub-Saharan Africa: A Multicentric Population-Based Follow-Up Study.* Journal of the National Comprehensive Cancer Network : JNCCN, 21(9), 924–933.e7. https://doi.org/10.6004/jnccn.2023.7041

Mein Beitrag als Autorin:

Ich war wesentlich beteiligt an der Entwicklung von Ideen zu Konzept, Durchführung und Design der Studie. Während meines fünfmonatigen Aufenthaltes in Mali und Mosambik war ich hauptverantwortlich für die Erhebung der Daten aus papierbasierten Akten und koordinierte, unterstützt von den lokalen Teams der Krebsregister, die Follow-Up-Untersuchungen per Telefon. Im Anschluss analysierte ich die Daten aus den Rohdatensätzen aller eingeschlossenen Register. Ich war hauptverantwortlich für die Interpretation der Ergebnisse und schrieb federführend das Manuskript.

Publikationen 2,3,4,5 und 6:

Seraphin, T. P., 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., Mikolajczyk, R. T., … Kantelhardt, E. J. (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. https://doi.org/10.1002/cncr.33818

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., Parkin, D. M., … 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

Joko-Fru, W. Y., Griesel, M., Mezger, N. C. S., **Hämmerl, L.**, Seraphin, T. P., Feuchtner, J., Wabinga, H., N'da, G., Mathewos, A., Kamaté, B., Nsonde Malanda, J., Gnangnon, F. H. R., Chesumbai, G. C., Korir, A., Lorenzoni, C., Zietsman, A., Borok, M. Z., Liu, B., Thomssen, C., McGale, P., … Kantelhardt, E. J. (2021). *Breast Cancer Diagnostics, Therapy, and Outcomes in Sub-Saharan Africa: A Population-Based Registry Study.* Journal of the National Comprehensive Cancer Network : JNCCN, 20(13), 10.6004/jnccn.2021.7011. https://doi.org/10.6004/jnccn.2021.7011

Mezger, N. C. S., **Hämmerl, L.**, Griesel, M., Seraphin, T. P., Joko-Fru, Y. W., Feuchtner, J., Zietsman, A., Péko, J. F., Tadesse, F., Buziba, N. G., Wabinga, H., Nyanchama, M., Chokunonga, E., Kéita, M., N'da, G., Lorenzoni, C. F., Akele-Akpo, M. T., Mezger, J. M., Binder, M., Liu, B., … Kantelhardt, E. J. (2023). *Guideline Concordance of Treatment and*

Outcomes Among Adult Non-Hodgkin Lymphoma Patients in Sub-Saharan Africa: A Multinational, Population-Based Cohort. The oncologist, 28(11), e1017–e1030. https://doi.org/10.1093/oncolo/oyad157

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., Jemal, A., … 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 Autorin:

Analog zur Publikation 1 war ich bei diesen Studien im Vorfeld maßgeblich an der Entwicklung von Ideen zu Studienkonzept, -durchführung und -design beteiligt. Die von mir in Mali und Mosambik erhobenen Daten zu Mamma-, Zervix- und Prostatakarzinom sowie NHL wurden von den jeweiligen Erstautor:innen zur Auswertung genutzt. Nach Erstellung der Manuskripte durch die Erstautor:innen war ich an der Überarbeitung und Revision der Publikationen beteiligt.

Publikationen 7,8 und 9:

Parkin, D. 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

Hämmerl, L., Ferlay, J., Borok, M., Carrilho, C., & Parkin, D. M. (2019). *The burden of squamous cell carcinoma of the conjunctiva in Africa.* Cancer epidemiology, 61, 150–153. https://doi.org/10.1016/j.canep.2019.06.007

Hämmerl, L., Colombet, M., Rochford, R., Ogwang, D. M., & Parkin, D. M. (2019). *The burden of Burkitt lymphoma in Africa.* Infectious agents and cancer, 14, 17. https://doi.org/10.1186/s13027-019-0236-7

Mein Beitrag als Autorin:

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. Außerdem schrieb ich den ersten Entwurf der Manuskripte.

Förderungen im Rahmen meiner Promotion:

Während meiner Promotion erhielt ich für die Auslandsaufenthalte finanzielle Unterstützung im Rahmen der Stipendiatenförderung des Cusanuswerks (Bischöfliche Studienförderung).

Originalpublikationen

Publikation 1:

Hämmerl, L., et al (2023). Treatment and Survival Among Patients With Colorectal Cancer in Sub-Saharan Africa: A Multicentric Population-Based Follow-Up Study. *Journal of the National Comprehensive Cancer Network, 21(9):924-933.e7*

Publikation 2:

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 3:

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 4:

Joko-Fru, W.Y., et al (2021). Breast Cancer Diagnostics, Therapy, and Outcomes in Sub-Saharan Africa: A Population-Based Registry Study. *Journal of the National Comprehensive Cancer Network, 20(13).*

Publikation 5:

Mezger, N. C. S., et al (2023). Guideline Concordance of Treatment and Outcomes Among Adult Non-Hodgkin Lymphoma Patients in Sub-Saharan Africa: A Multinational, Population-Based Cohort. *Oncologist, 28(11):e1017-e1030.*

Publikation 6:

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.

Publikation 7:

Parkin D.M., et al (2020). Cancer in Africa 2018: The role of infections. *International Journal of Cancer; 146(8):2089-2103.*

Publikation 8:

Hämmerl L., et al (2019). The burden of squamous cell carcinoma of the conjunctiva in Africa. *Cancer Epidemiology, 61:150-153*

Publikation 9:

Hämmerl L., et al (2019). The burden of Burkitt lymphoma in Africa *Infectious Agents and Cancer, 14:17.*

Hämmerl L, Mezger NCS, Seraphin TP, Joko-Fru WY Griesel M, Feuchtner J, Gnahatin F, Gnangnon FHR, Okerosi N, Amulen MP, Hansen R, Borok MZ , Carrilho C, Mallé B, Ah Clausina AA, Buziba NG, Seife E, Liu B, Mikolajczyk R, Parkin DM, Kantelhardt EJ, Jemal A. **Treatment and survival among colorectal cancer patients in sub-Saharan Africa: A multicentric population-based follow-up study.** J Natl Compr Canc Netw vol. 21,9 (2023): 924-933.e7. doi:10.6004/jnccn.2023.7041.

Volltext: https://jnccn.org/view/journals/jnccn/21/9/article-p924.xml

Abstract

Background: The burden of colorectal cancer (CRC) is increasing in Sub-Saharan Africa (SSA). However, little is known about CRC treatment and survival in the region.

Methods: A random sample of 653 patients with CRC diagnosed from 2011 to 2015 was obtained from 11 population-based cancer registries in SSA. Information on clinical characteristics, treatment, and/or vital status was obtained from medical records in treating hospitals for 356 (54%) of the patients ("traced cohort"). Concordance of CRC treatment with NCCN Harmonized Guidelines for SSA was assessed. A Cox proportional hazards model was used to examine the association between survival and human development index (HDI).

Results: Of the 356 traced patients with CRC, 51.7% were male, 52.8% were from countries with a low HDI, 55.1% had colon cancer, and 73.6% were diagnosed with nonmetastatic (M0) disease. Among the patients with M0 disease, however, only 3.1% received guideline concordant treatment, 20.6% received treatment with minor deviations, 31.7% received treatment with major deviations, and 35.1% received no treatment. The risk of death in patients who received no cancer-directed therapy was 3.49 (95% CI, 1.83-6.66) times higher than in patients who received standard treatment or treatment with minor deviations. Similarly, the risk of death in patients from countries with a low HDI was 1.67 (95% CI, 1.07-2.62) times higher than in those from countries with a medium HDI. Overall survival at 1 and 3 years was 70.9% (95% CI, 65.5%-76.3%) and 45.3% (95% CI, 38.9%-51.7%), respectively.

Conclusions: Fewer than 1 in 20 patients diagnosed with potentially curable CRC received standard of care in SSA, reinforcing the need to improve healthcare infrastructure, including the oncology and surgical workforce.

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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See editorial on pages 4131-4132, this issue.

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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

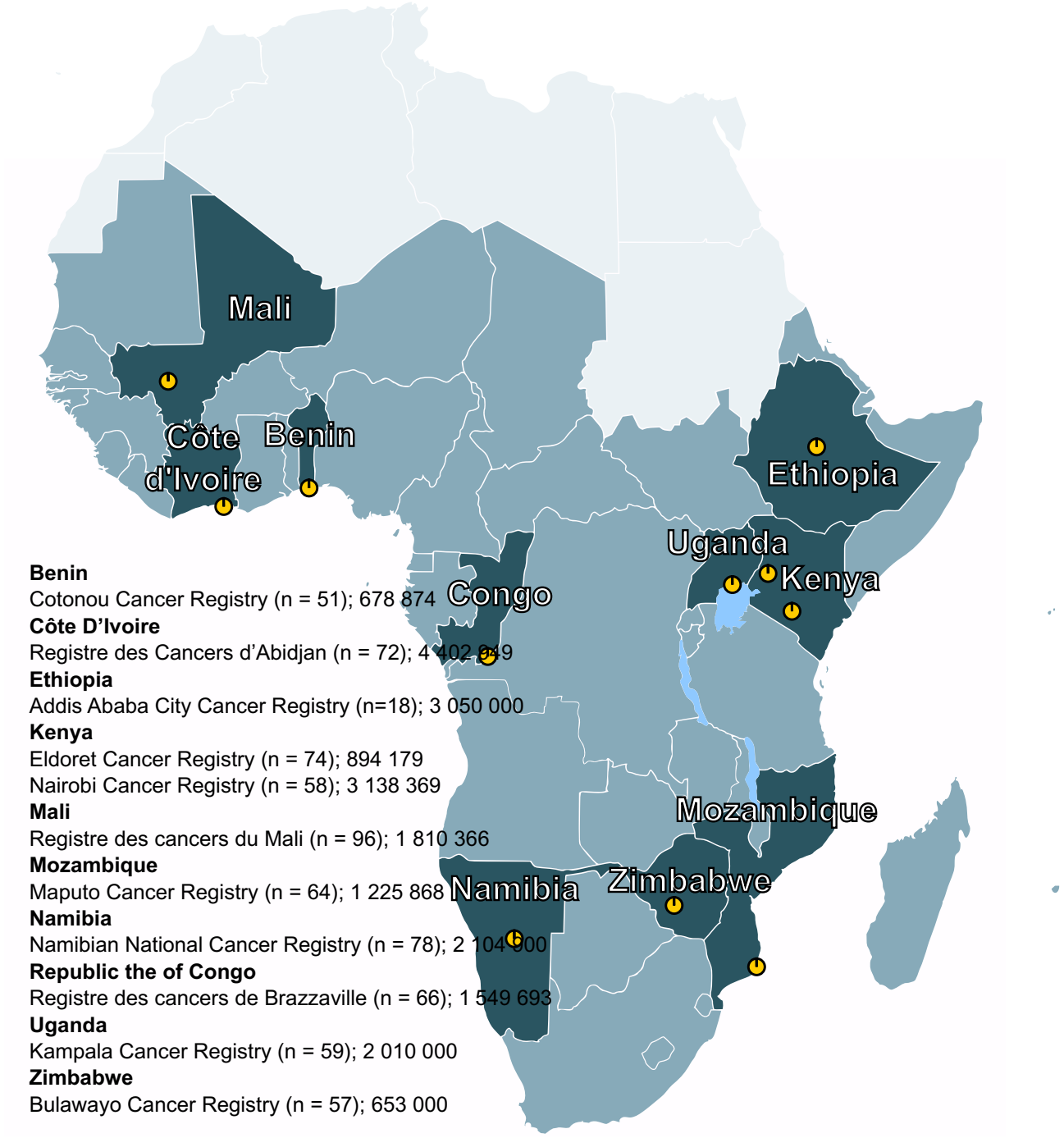

Figure 1. Countries of participating cancer registries. Countries of participating population-based cancer registries are highlighted along with the names of the registries, the number of included patients (n), and the population of each coverage area (persons).

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).

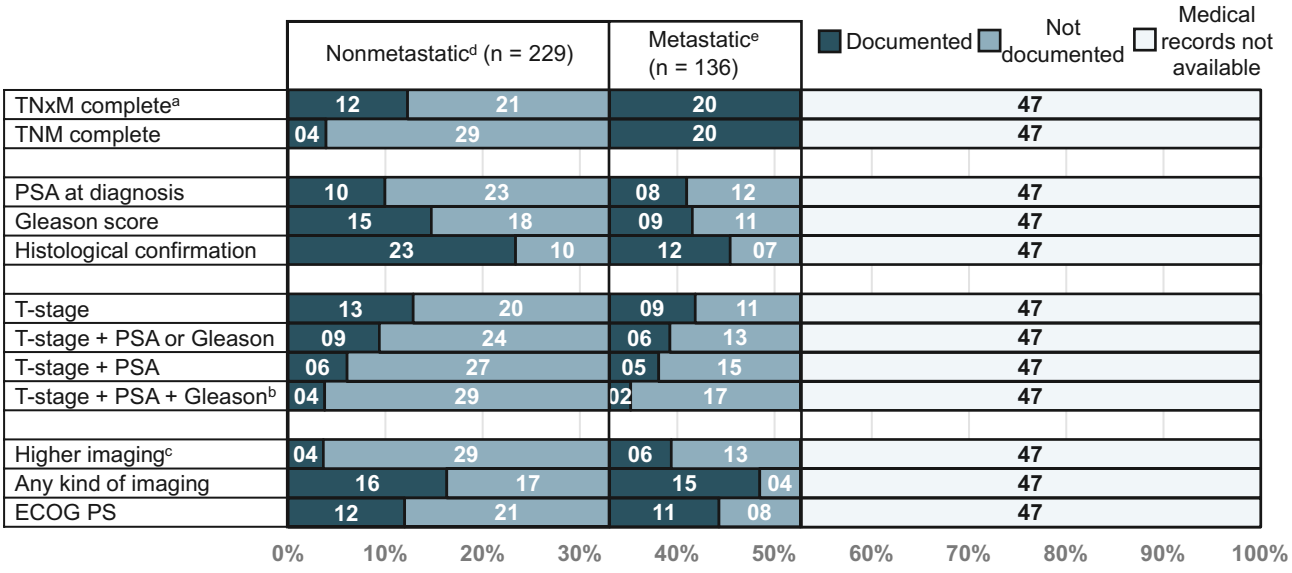

Figure 2. Availability of diagnostic information for patients with prostate cancer in the total population-based cohort (n = 693). [a]Nx included. [b]Main prognostic factors according to the 2017 National Comprehensive Cancer Network guidelines. [c]For example, computed tomography, magnetic resonance 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.

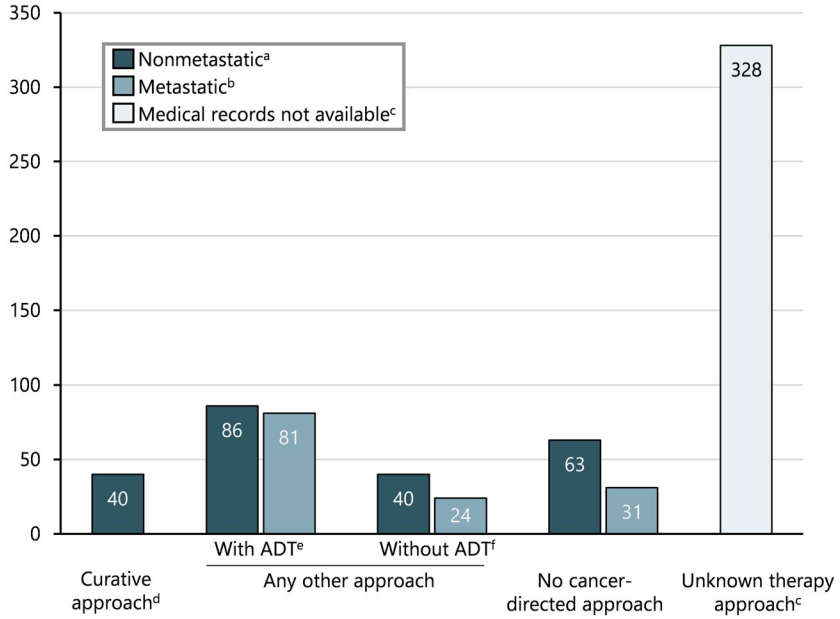

Figure 3. Primary treatment approach by identified M stage in the total population-based cohort (n = 693). [a]The nonmetastatic subgroup (n = 229) comprised all patients without a pathological or clinical suggestion of metastasis (M0), including patients with an unknown lymph node status (Nx M0). [b]The 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.

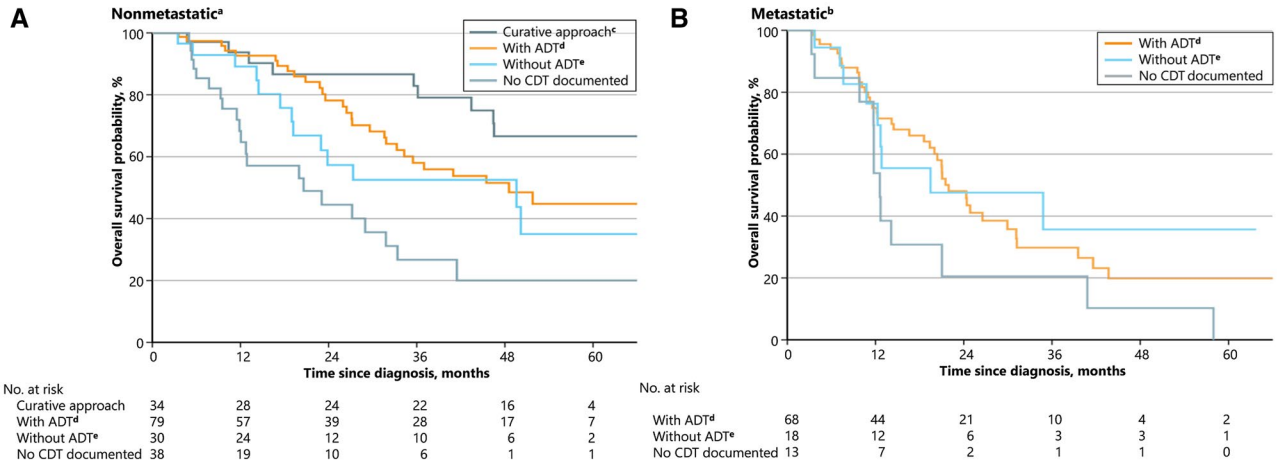

Figure 4. Overall survival of patients from the traced cohort with at least 3 months of survival stratified by M stage: differences according to the treatment approach. [a]These patients surviving at least 3 months from the nonmetastatic subgroup (n = 181) included all patients without a pathological 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

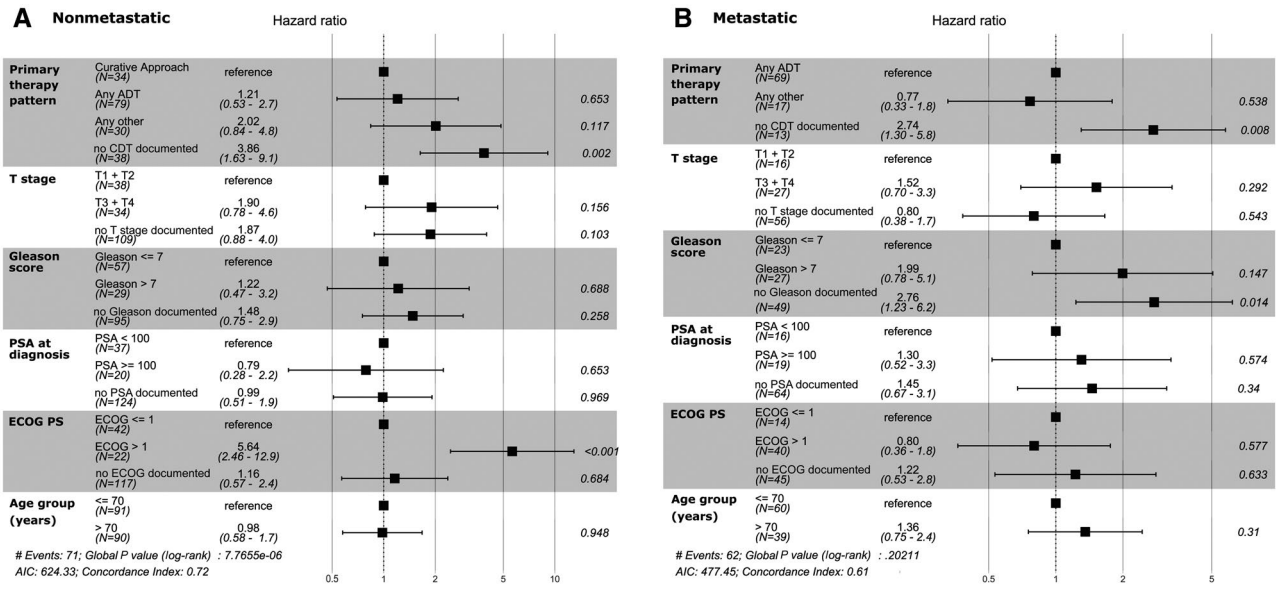

Figure 5. Forest plots showing the influence of primary treatment patterns on the survival of (A) patients with nonmetastatic prostate cancer[a] and (B) patients with metastatic prostate cancer.[b] The hazard ratios and 95% confidence intervals are the results of a multivariable Cox regression model 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.

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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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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

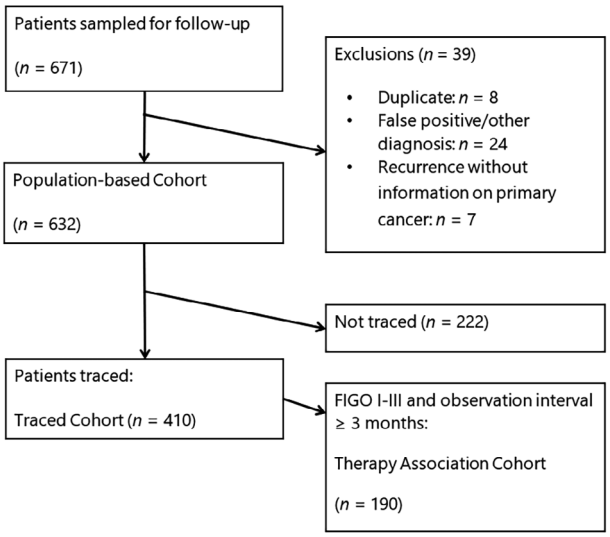

Figure 1. Trial flow diagram. Patients with hospital files found or successful telephone contact were considered to be traced. Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

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.

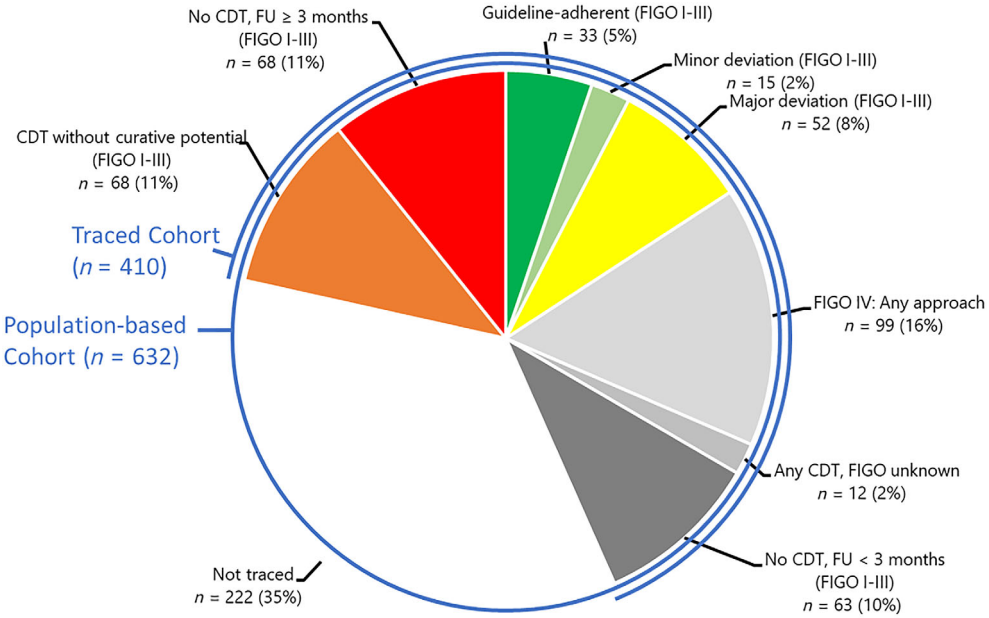

Figure 2. Therapy evaluation in the population-based cohort (*n* = 632). Evaluations refer to the therapy evaluation scheme in Table 1. Colors depict the degree of adherence: green indicates optimal, light green minor deviation, yellow major deviation, orange CDT without curative potential, and red no 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).

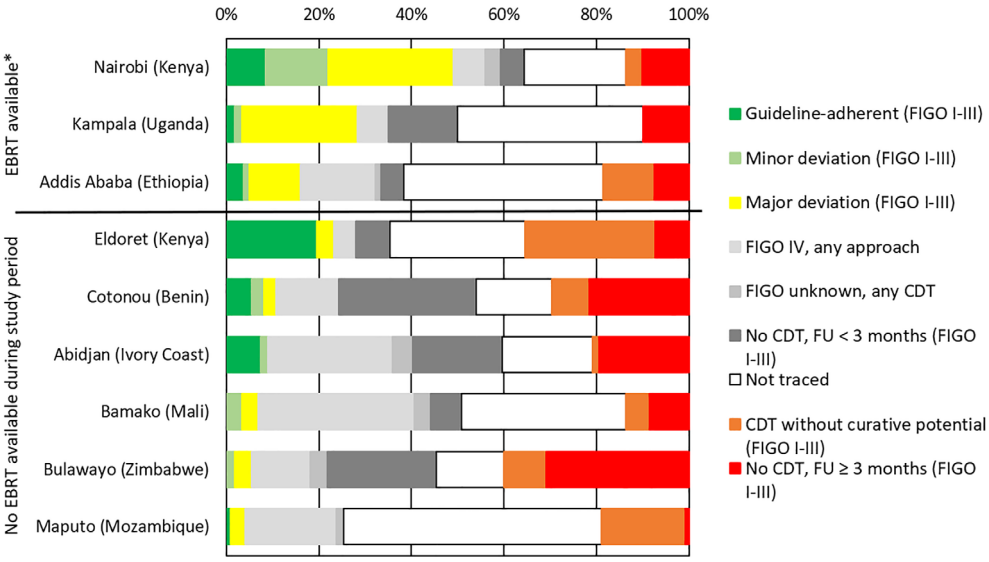

Figure 3. Therapy evaluation in the population-based cohort (*n* = 632) stratified by registry. Evaluations refer to the therapy evaluation scheme in Table 1. Colors depict the degree of adherence: green indicates optimal, light green minor deviation, yellow major deviation, orange CDT without curative 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).

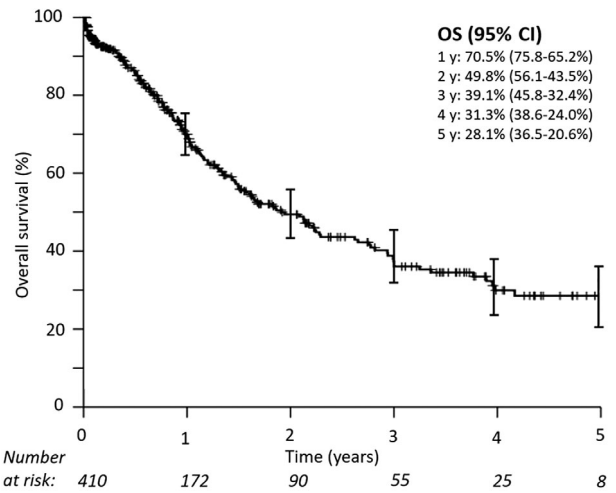

Figure 4. Overall survival in the traced cohort ($n = 410$). Median overall survival was 23 months. Patients with hospital files found or successful telephone contact were considered to be traced.
Abbreviations: CI, confidence interval; OS, overall survival.

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

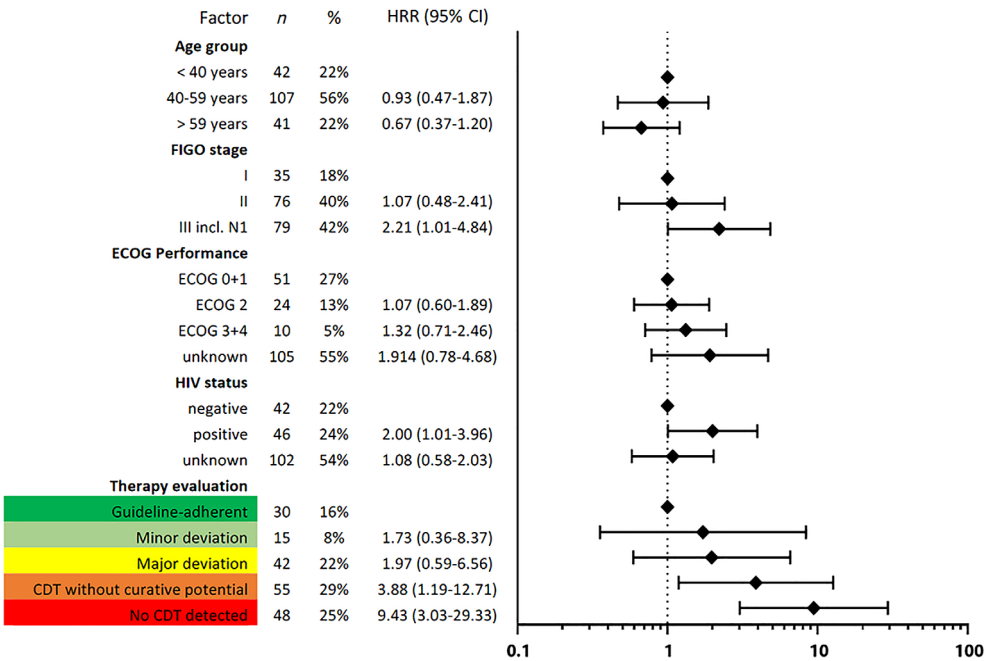

Figure 5. Results of multiple Cox regression for risk of early death in the therapy association cohort ($n = 190$) are shown: through inclusion criteria (FIGO stages I–III and follow-up ≥3 months), bias was reduced. Therapy evaluation refers to Table 1.
Abbreviations: CDT, cancer-directed therapy; CI, 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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Abstract

Background: Breast cancer (BC) is the most common cancer in sub-Saharan Africa (SSA). However, little is known about the actual therapy received by women with BC and their survival outcome at the population level in SSA. This study aims to describe the cancerdirected therapy received by patients with BC at the population level in SSA, compare these results with the NCCN Harmonized Guidelines for SSA (NCCN Harmonized Guidelines), and evaluate the impact on survival.

Methods: Random samples of patients with BC (≥40 patients per registry), diagnosed from 2009 through 2015, were drawn from 11 urban population-based cancer registries from 10 countries (Benin, Congo, Cote d'Ivoire, Ethiopia, Kenya, Mali, Mozambique, Namibia, Uganda, and Zimbabwe). Active methods were used to update the therapy and outcome data of diagnosed patients ("traced patients"). Excess hazards of death by therapy use were modeled in a relative survival context.

Results: A total of 809 patients were included. Additional information was traced for 517 patients (63.8%), and this proportion varied by registry. One in 5 traced patients met the minimum diagnostic criteria (cancer stage and hormone receptor status known) for use of the NCCN Harmonized Guidelines. The hormone receptor status was unknown for 72.5% of patients. Of the traced patients with stage I-III BC (n=320), 50.9% received inadequate or no cancer-directed therapy. Access to therapy differed by registry area. Initiation of adequate therapy and early-stage diagnosis were the most important determinants of survival.

Conclusions: Downstaging BC and improving access to diagnostics and care are necessary steps to increase guideline adherence and improve survival for women in SSA. It will also be important to strengthen health systems and facilities for data management in SSA to facilitate patient follow-up and disease surveillance.

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Original Article

Guideline Concordance of Treatment and Outcomes Among Adult Non-Hodgkin Lymphoma Patients in Sub-Saharan Africa: A Multinational, Population-Based Cohort

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Abstract

Background: Although non-Hodgkin lymphoma (NHL) is the 6th most common malignancy in Sub-Saharan Africa (SSA), little is known about its management and outcome. Herein, we examined treatment patterns and survival among NHL patients.

Methods: We obtained a random sample of adult patients diagnosed between 2011 and 2015 from 11 population-based cancer registries in 10 SSA countries. Descriptive statistics for lymphoma-directed therapy (LDT) and degree of concordance with National Comprehensive Cancer Network (NCCN) guidelines were calculated, and survival rates were estimated.

Findings: Of 516 patients included in the study, sub-classification was available for 42.1% (121 high-grade and 64 low-grade B-cell lymphoma, 15 T-cell lymphoma and 17 otherwise sub-classified NHL), whilst the remaining 57.9% were unclassified. Any LDT was identified for 195 of all patients (37.8%). NCCN guideline-recommended treatment was initiated in 21 patients. This corresponds to 4.1% of all 516 patients, and to 11.7% of 180 patients with sub-classified B-cell lymphoma and NCCN guidelines available. Deviations from guideline-recommended treatment were initiated in another 49 (9.5% of 516, 27.2% of 180). By registry, the proportion of all patients receiving guideline-concordant LDT ranged

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from 30.8% in Namibia to 0% in Maputo and Bamako. Concordance with treatment recommendations was not assessable in 75.1% of patients (records not traced (43.2%), traced but no sub-classification identified (27.8%), traced but no guidelines available (4.1%)). By registry, diagnostic work-up was in part importantly limited, thus impeding guideline evaluation significantly. Overall 1-year survival was 61.2% (95%CI 55.3%-67.1%). Poor ECOG performance status, advanced stage, less than 5 cycles and absence of chemo (immuno-) therapy were associated with unfavorable survival, while HIV status, age, and gender did not impact survival. In diffuse large B-cell lymphoma, initiation of guideline-concordant treatment was associated with favorable survival.

Interpretation: This study shows that a majority of NHL patients in SSA are untreated or undertreated, resulting in unfavorable survival. Investments in enhanced diagnostic services, provision of chemo(immuno-)therapy and supportive care will likely improve outcomes in the region.

Implications for Practice

Although advances in care have tremendously improved non-Hodgkin lymphoma (NHL) outcomes, disparities in uptake of treatment still confine survival across the globe. While NHL is a common disease in Sub-Saharan Africa, little is known about its treatment and survival. Our multinational, population-based study aimed to assess the current quality of care and survival in 10 countries. Patients across the region presented at late stages, with poor ECOG performance status, and lacked subtyping. Absence of any therapy was identified in some 3 in 5 patients, and non-guideline-concordant therapy in 6 of 7, with all factors associated with unfavorable survival. Our study shows that many NHL patients are unable to access high-quality diagnostic and treatment services, providing a baseline for targeted investments. With regard to clinical practice, we underline the importance of NHL grading and subtyping, patient-centered treatment mindful of possible side effects, and relevance of therapy completion.

Introduction

Non-Hodgkin lymphoma (NHL) is the 6th most common type of malignant neoplasia in Sub-Saharan Africa (SSA).[1,2] Incidence is continuously rising and by 2040 the number of new cases per year is expected to nearly double to more than 60 000.[3-5] Many subtypes of NHL are treatable with good outcomes, with a 5-year survival rate of 73.2% for patients in the United States.[6] In SSA, however, resources for cancer care are limited.[7-10] Therefore, the National Comprehensive Cancer Network (NCCN) developed Harmonized Guidelines on a variety of B-cell lymphoma subtypes for resource-stratified use in the region.[11] In this context, identification of NHL subtype is crucial for specific therapy, however, a high frequency of unclassified lymphoma has been reported across the region.[8-10]

Previous studies on NHL treatment patterns in SSA were hospital-based studies, with high proportion of late-stage and aggressive diseases,[8,10,12-16] limited treatment options, and poor survival.[10,17-22] The aim of our study was to assess the application of NHL treatment according to NCCN harmonized guidelines in this region and to identify factors influencing survival using a multi-national, real-world cohort within the African Cancer Registry Network (AFCRN, https://afcrn.org).

Methods

Study Setting

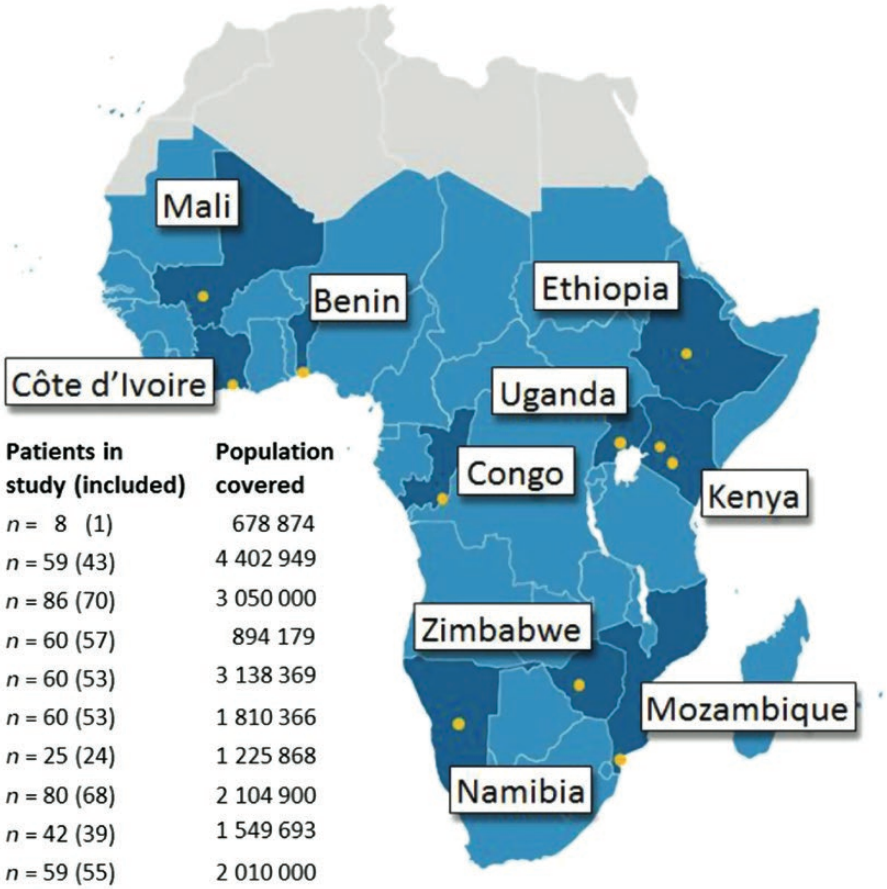
In 2014, AFCRN coordinated 23 regional population-based cancer registries (PBCRs) as International Agency for Research on Cancer's regional hub in SSA.[23] Of these, 11 registries in 10 countries consented to serve as study centers, covering a population of roughly 21.5 million (Fig. 1). We included NHL patients aged 15 and above with B-cell and T-cell lymphoma as well as unclassified lymphoma (International Classification of Diseases-10 codes C82–C96 and C96) and diagnosed between 2011 and 2015. Hodgkin lymphoma and pediatric lymphoma aged 14 and below were not included. Power was calculated for the entire cohort but not for individual sites: A minimal sample size of 404 patients produces a 2-sided 95% CI with a width equal to 0.1 when the sample proportion of patients with adequate care is 0.500. We assumed a drop-out rate of 33% and therefore aimed for 600 patients. Of 1068 patients available, a study population of 599 patients (56.1%) was thus selected at random.

Data Collection

As previously described in detail, registry staff continuously retrieve information on demographics, diagnosis including NHL subtype, and vital status from hospital records.[24] Occasionally, data on treatment modalities (eg, chemotherapy yes/no) are collected. To complement PBCR routine data, clinical records were re-evaluated to collect information on patterns of care. Lymphoma morphology registered was verified and amended by assessing pathology reports, and, in the absence of definitive pathological diagnoses, those noted in clinical records were used.[24] Stage was assessed in line with Lugano and Binet classifications.[26,27] When the stage had not been assigned in records, it was considered less advanced if no suggestion of disseminated nodal or extranodal involvement was found. Vital status was assessed by follow-up calls. Patients were considered "traced" if information beyond PBCR data (eg, detailed information on clinical diagnostics (such as ECOG performance status (PS) or HIV status) and/or lymphoma-directed treatment (such as chemotherapy regimen administered or radiotherapy) and/or survival status) was obtained from hospital records and/or follow-up calls. Patients were considered "not traced" if no information beyond PBCR data were available. Follow-up was open for 7 years until April 31, 2018.

Therapy Evaluation

For NHL subtypes with NCCN Harmonized Guidelines for SSA[11] available, we established an evaluation scheme assessing completion of first-line therapy and adherence to guidelines. For therapy evaluation, patients were allocated to 3 groups: sub-classified NHL with guidelines available, sub-classified NHL without guidelines available, and unclassified NHL. NCCN Harmonized Guidelines for SSA were available for diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia/small lymphocytic lymphoma



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

Figure 1. Map of Sub-Saharan Africa.[24,25] Countries and cities of participating population-based cancer registries are highlighted. On the left, the numbers included in the random sample are shown along with the covered population in the registry area. For details see also Supplementary Table S2.

(CLL/SLL), Burkitt (BL), follicular (FL), marginal zone, and lymphoplasmacytic lymphoma. For these subtypes, "guideline concordance" was defined as NCCN's harmonized "generally available standard of care." "Deviation from guidelines" was defined, again according to NCCN, as "regional options that may be considered when availability precludes standard of care." Non-guideline concordant lymphoma-directed therapy (LDT) was defined "any other therapy." As an example, for DLBCL, NCCN recommends rituximab (R) + cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP). Deviation from guidelines in DLBCL was thus defined as CHOP without rituximab. Other chemotherapy regimens were labeled as any other therapy. Concerning guideline-concordant therapy *completion* for DLBCL, at least 5 cycles of RCHOP or 3 cycles of RCHOP + radiotherapy in stage I or II were necessary for therapy to be considered complete. For completion of guideline-deviating therapy in DLBCL, the same number of cycles for CHOP was necessary. Concerning guideline concordance of treatment for indolent NHL, NCCN guidelines allow for a variety of chemo(immuno-)therapeutic agents. However, due to the heterogeneous nature of eg, CLL/SLL and FL, NCCN does not specify a minimum number of cycles. Thus, any number of cycles of chemo(immuno-)therapy was accepted regarding the completeness of guideline-concordant therapy (for details on therapy evaluation see Supplementary Table S1). Patients with clinical records traced, but without any information on LDT were labeled as "no therapy." For presentation of therapy evaluation, patients not traced without PBCR information on LDT were grouped separately. Both for subtypes without guidelines available and for unclassified NHL, application of guidelines was not feasible. We differentiated between polychemo(immuno-)therapy (PCT) vs. "any other therapy" vs. "no therapy," considering sole radiotherapy without chemo(immuno-)therapy as "any other therapy." Similarly, we labeled sole splenectomy and other operations in stage I lymphoma as "any other therapy," but regarded all other operations as supportive care and therefore defined these as "no therapy."

Statistical Analysis

For statistical analysis, IBM SPSS Statistics (version 25) was used. For longitudinal data, Kaplan-Meier's method and multivariable Cox proportional hazard model were used. First, we assessed for the condition of "missing at random" (uninformative censoring) by performing reverse Kaplan-Meier's analysis. We then restricted the analysis to patients with the survival of at least 1 month to allow time for initiation of therapy and to account for bias from missing treatment through early death. Kaplan-Meier's method accounted for further loss to follow up. For survival analysis, we grouped patients traced without indication of LDT and patients not traced, assuming that patients not traced despite our efforts did not receive any LDT. We estimated simple and multivariable hazard

ratios (HR), and computed 1- to 3-year age-standardized overall survival using the "popEpi" package for R software, while adopting Corazziari et al's ICSS 1 age standard.[28]

Ethical Consideration

The study protocol was approved by the AFCRN research committee (March 2, 2016) and the Martin-Luther-University, Halle Ethical Review Board, and it was in line with the Declaration of Helsinki. Anonymized secondary data were collected from each participating registry under existing regulations and national laws of the respective registries.

Role of the Funding Source

Funders had no role in study design, collection analysis, and interpretation of data, in writing of the report, and in decision to submit the paper for publication.

Results

Of 599 patients, 516 patients were included (Fig. 2). A total of 83 patients had to be excluded due to duplicates, other diagnoses, recurrence, or not meeting the age inclusion criteria. Additional information, eg, on treatment and/or survival was obtained for 293 patients ("traced," 56.8%, Supplementary Table S2).

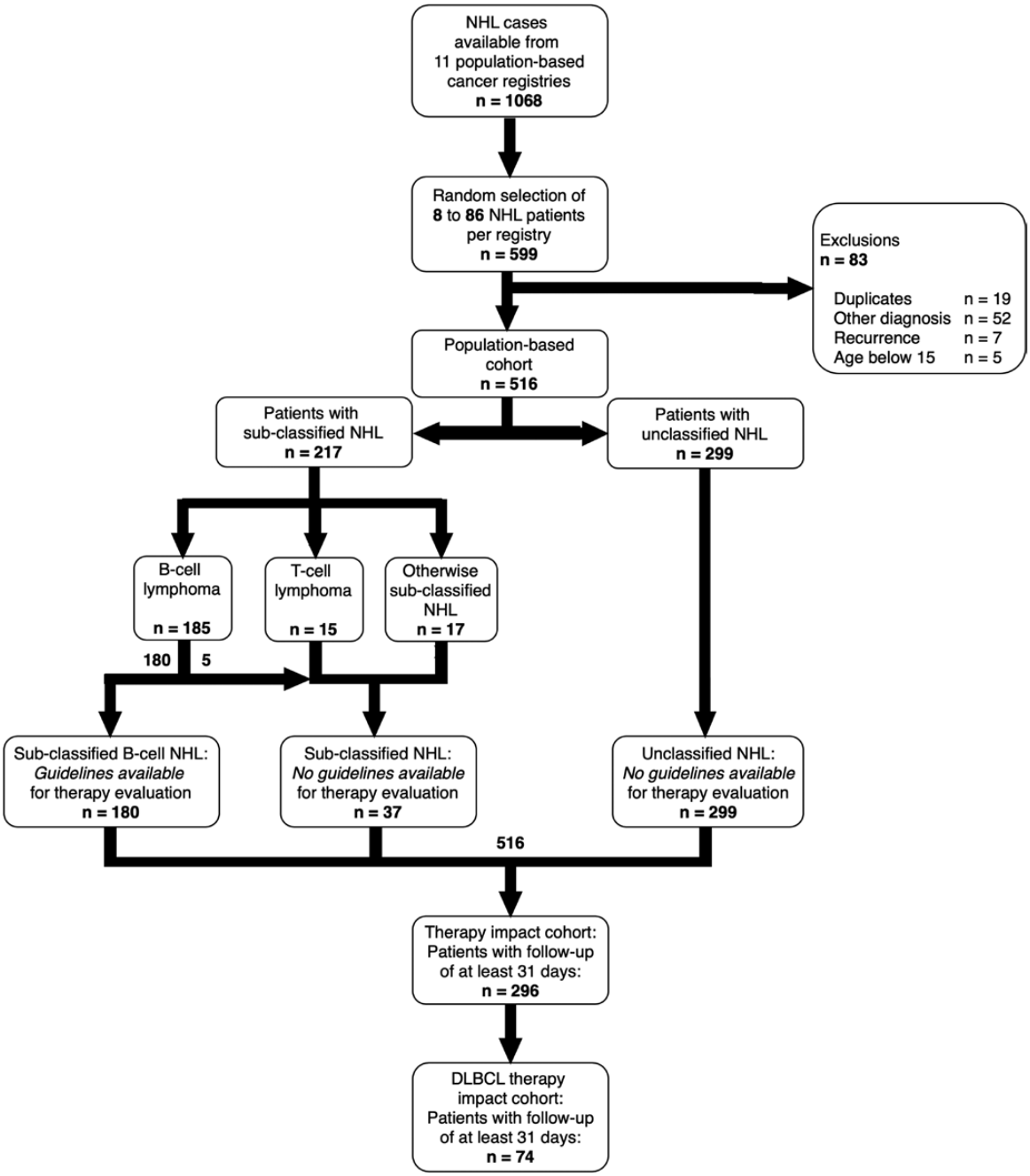


Figure 2. Flow chart of the study population. NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma.

Baseline and Diagnostic Characteristics

Patient characteristics have been published elsewhere in detail.[24] Median age was 45 years and 43.4% of patients were female. ECOG PS of 2 or worse was documented in 61.4%, and 79.3% presented with B symptoms. Advanced stage, defined as Lugano stages III and IV and as Binet C for CLL/SLL, was diagnosed in 73.0%. Of 154 tested patients, 63.0% were HIV positive (Supplementary Table S3). In 85.3% combined antiretroviral therapy had been initiated prior to diagnosis of NHL. Sub-classification was documented in 217 patients (42.1) while 299 NHL (57.9%) remained unclassified. By registry, proportion of sub-classified NHL ranged from 94.1% in Namibia to 8.3% in Maputo.[24] Of all sub-classified lymphoma, 121 were high-grade (55.8%) and 64 low-grade B-cell lymphoma (29.5%), 15 T-cell lymphoma (6.9%), and 17 otherwise sub-classified NHL (7.8%) (Supplementary Table S4).

Therapy

Any systemic therapy was documented in 187 of all 516 patients (36.2%). For these, first-line chemo(immuno-)therapy consisted of CHOP (-related) and cyclophosphamide, vincristine, and prednisone (COP) (-related) protocols in 62.0% and 10.7%, respectively. Rituximab was the only immunotherapy agent identified and administered in 20 of 187 (10.7%). Patients received a median of 6 cycles of first-line systemic therapy (interquartile range: 3–6 cycles). Among all 83 patients receiving a minimum of 6 cycles of systemic therapy, 49 had sub-classified NHL and 34 unclassified NHL. Overall, 2 patients received second-line systemic therapy. Of the 195 patients with any LDT initiated (37.8%), radiotherapy was identified in 34 cases, and lymphoma-directed surgery in 28 (Table 1). For details, see Supplementary Table S5.

Guideline Concordance

Of all 516 patients, 180 patients with sub-classified NHL and guidelines available were eligible for therapy evaluation. Namely, patients diagnosed with DLBCL (48.8% of all 217 sub-classified NHL), CLL/SLL (18.8%), BL (6.0%), FL (5.5%), marginal zone (3.2%), and lymphoplasmacytic lymphoma (1.0%) were evaluated with respect to concordance with the NCCN guidelines harmonized for SSA.[11] Of these 180 cases, we found both initiation and completion of guideline-recommended treatment for 21 patients (11.7%) (Fig. 3A and 3B). Initiation of guideline-deviating therapy was found for another 49 (27.2%), of which 35 (19.4%) managed to complete respective therapies. No therapy could be identified for 86 of 180 cases (47.8%, including patients not traced). For the remaining 37 patients with sub-classified NHL, predominantly T-cell and otherwise sub-classified NHL, no harmonized guidelines were available. Further, no guidelines were available for the 299 patients with unclassified NHL.

Disparities Within and Between Registries

Within and between the PBCR cohorts, we found huge disparities in therapy initiation, ranging from patients without any treatment to patients treated in concordance with guidelines. For example, 11.6% of patients in Abidjan initiated guideline-concordant therapy or a deviation thereof, while in 72.1% no treatment was documented. Similarly, in Bamako and Brazzaville only 15.4% and 12.8% had any treatment documented, respectively (Fig. 4A). The largest proportion of patients with any treatment initiated was found in Nairobi (71.7%) followed by Addis Ababa (57.1%). In Namibia, the largest proportion of patients completed therapy concordantly with guidelines (30.8%), for Maputo and Bamako, none were treated in concordance with guidelines—with only 11 sub-classified NHL cases in Bamako (20.8%) and 2 cases in Maputo (8.3%) (Fig. 4B). Radiotherapy was identified in patients from 4 registries only, Addis Ababa, Kampala, Nairobi, and Namibia.

Survival

Any follow-up information was available for 384 patients. For all patients, median follow-up and survival were 6 and 20 months, respectively. Observed 1- and 3-year overall survival (OS) was 61.2% (95% CI, 55.3%-67.1%) and 37.2% (30.5%-43.9%) (Fig. 5A), respectively, varying substantially between the different PBCR areas: 1-year-OS was highest for patients in Addis Ababa (76.3%) and worst for patients in Bulawayo (37.5%) (Supplementary Table S6). The 1-and 3-year age-standardized overall survival was 62.3% (95%CI, 52.9%-70.4%) and 32.9% (22.1%-44.2%), respectively. As for median survival of subtypes, we found 48 months in DLBCL (n = 110), 29 months in CLL/SLL (n = 40), 8 months in BL (n = 13), 9 months in FL (n = 12), and 15 months in unclassified lymphoma (Fig. 5B). Differences in survival with respect to any therapy initiation in all NHL were rather small (Fig. 5C), but better survival was found in patients completing at least 5 cycles of chemo(immuno-)therapy (Fig. 5D). In DLBCL, both any therapy initiation as well as completion of guideline-recommended treatment were associated with better survival (Fig. 5E and 5F). Kaplan-Meier estimates for clinical characteristics and further association of guideline-concordant treatment with improved survival are shown in Supplementary Fig. S1.

Factors Associated With Outcome

In unadjusted Cox proportional hazards modeling, mortality of the cohort (follow-up at least 30 days, n = 296) was associated with ECOG PS, presence of B symptoms, missing assessment of B symptoms, advanced or missing stage, and somewhat associated with lack of subtype. Mortality was also associated with receipt of less than 5 cycles of any chemo(immuno-)therapy and lack of treatment. For DLBCL (n = 74), we found mortality associated with age of 60 and older, absent staging, and lack of guideline-concordant therapy or absence of any therapy. Notably, for neither cohort HIV status was associated with mortality (Supplementary Table S7).

In adjusted Cox proportional hazards modeling controlling for selected parameters in all NHL patients, worse survival remained (somewhat) associated with worse ECOG PS, advanced stage, B symptoms, less than 5 cycles of any chemo(immuno-)therapy, and absence of any therapy (Fig. 6A). For DLBCL patients only, absent staging and initiation of therapy other than guideline-recommended and absence of any therapy remained (somewhat) associated with worse survival in multivariate Cox regression (Fig. 6B).

Reverse Kaplan-Meier analysis suggested that in all NHL patients as well as in the DLBCL cohort, some covariates had a similar pattern of censoring over time: for sex, site involved, and HIV status, censoring appeared at random. NHL patients

Table 1. Treatment modalities in the population-based cohort (*n* = 516).

Chemo(immuno-)therapy regimen	Patients (*n*)	% of all receiving systemic therapy	Cycles applied	Patients (*n*)	% of therapy evaluation cohort	Cycles applied, median
CHOP and similar	116	62	5 or more	71	38	6
			4 or less	34	18.2	2
			Unknown # of cycles	11	5.9	n/a
COP and similar	20	10.7	5 or more	10	5.3	6
			4 or less	9	4.8	2
			Unknown # of cycles	1	0.5	n/a
Other polychemo(immuno-)therapy regimen	8	4.3	5 or more	3	1.6	7
			4 or less	5	2.7	3
Monotherapy	15	8	5 or more	3	1.6	6
			4 or less	5	2.7	4
			Unknown # of cycles	7	3.7	n/a
Unknown regimen	28	15	5 or more	5	2.7	6
			4 or less	2	1.1	3
			Unknown # of cycles	21	11.2	n/a
Any systemic therapy	187	100	5 or more	92	49.2	6
			4 or less	55	29.4	2
			Unknown # of cycles	40	21.4	n/a
Radiotherapy dose applied		% of all receiving radiotherapy				
Thirty gray or more	17	48.1				
Less than 30 gray	7	22.2				
Unknown dose	10	29.6				
Any radiotherapy	34	100				
Surgery type		% of all receiving surgery				
Splenectomy and stage I lymphnode resection	5	17.9				
Other surgery (diagnostic/palliative/unspecified)	23	82.1				
Any lymphoma-directed surgery (including diagnostic surgery, excluding biopsies)	28	100				
Any lymphoma-directed therapy	195	37.8 (of population-based cohort, n = 516				

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; COP, cyclophosphamide, vincristine, prednisone.

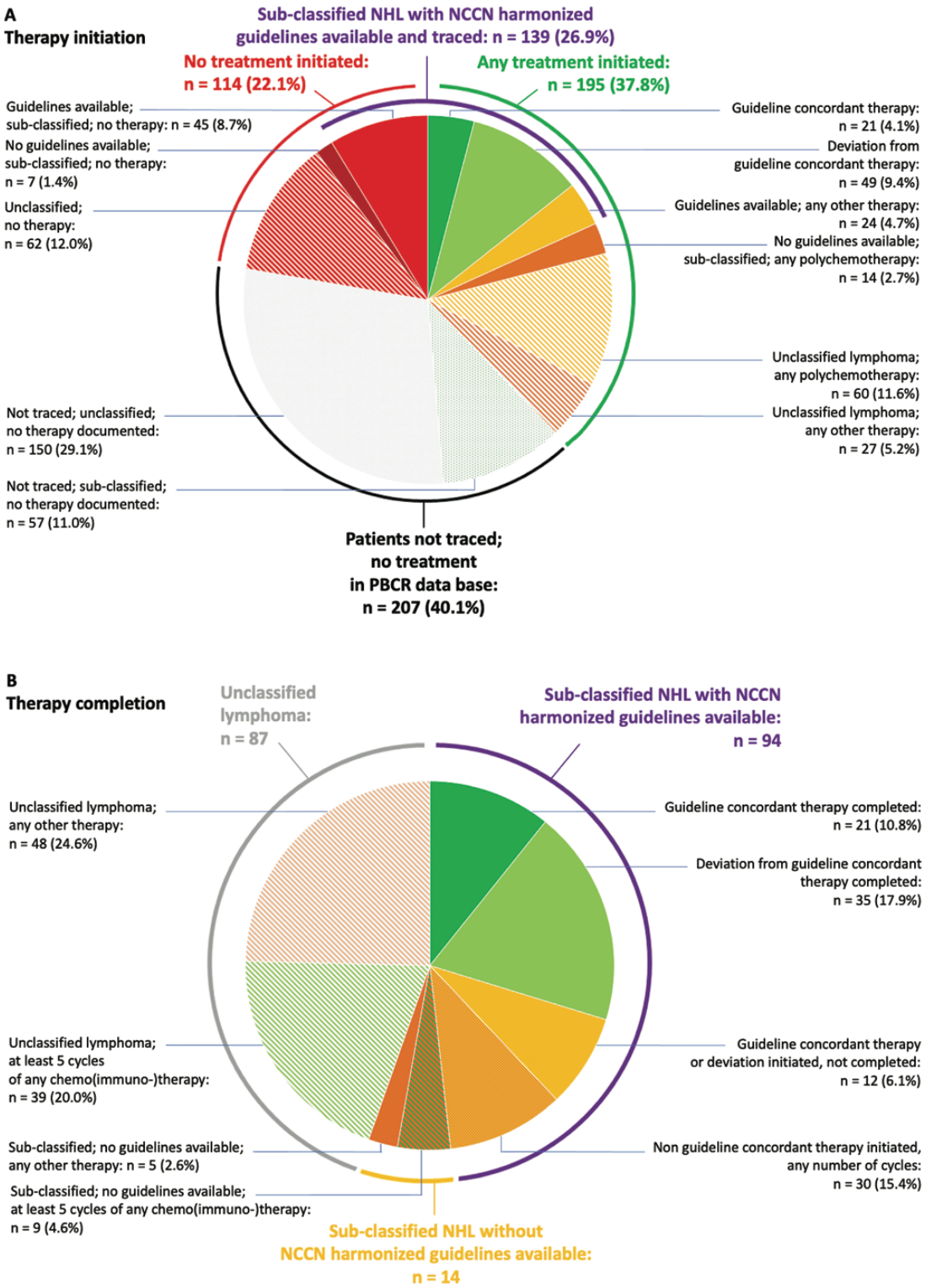


Figure 3. Evaluation of guideline concordance. (**A**) Depicts evaluation of therapy *initiation* in the population-based cohort (n = 516). Percentages refer to the proportion of all patients in cohort. (**B**) Depicts evaluation of therapy *completion* in all patients with any treatment documented (n = 195 (37.8% of total cohort)). The groups marked in green depict patients completing at least 5 cycles of chemo(immuno-)therapy. Percentages refer to proportion of all patients with any treatment documented. Evaluation refers to "therapy evaluation scheme" in Supplementary Table S1. PBCR, population-based cancer registry.

with ECOG PS of 1 or better versus others, early-stage versus others, lack of B symptoms, sub-classified NHL as well as completion of at least 5 cycles of any chemotherapy versus others, had less censoring. For DLBCL patients, ECOG PS of 1 or better, any staging, and initiation of guideline-concordant therapy equally had less censoring.

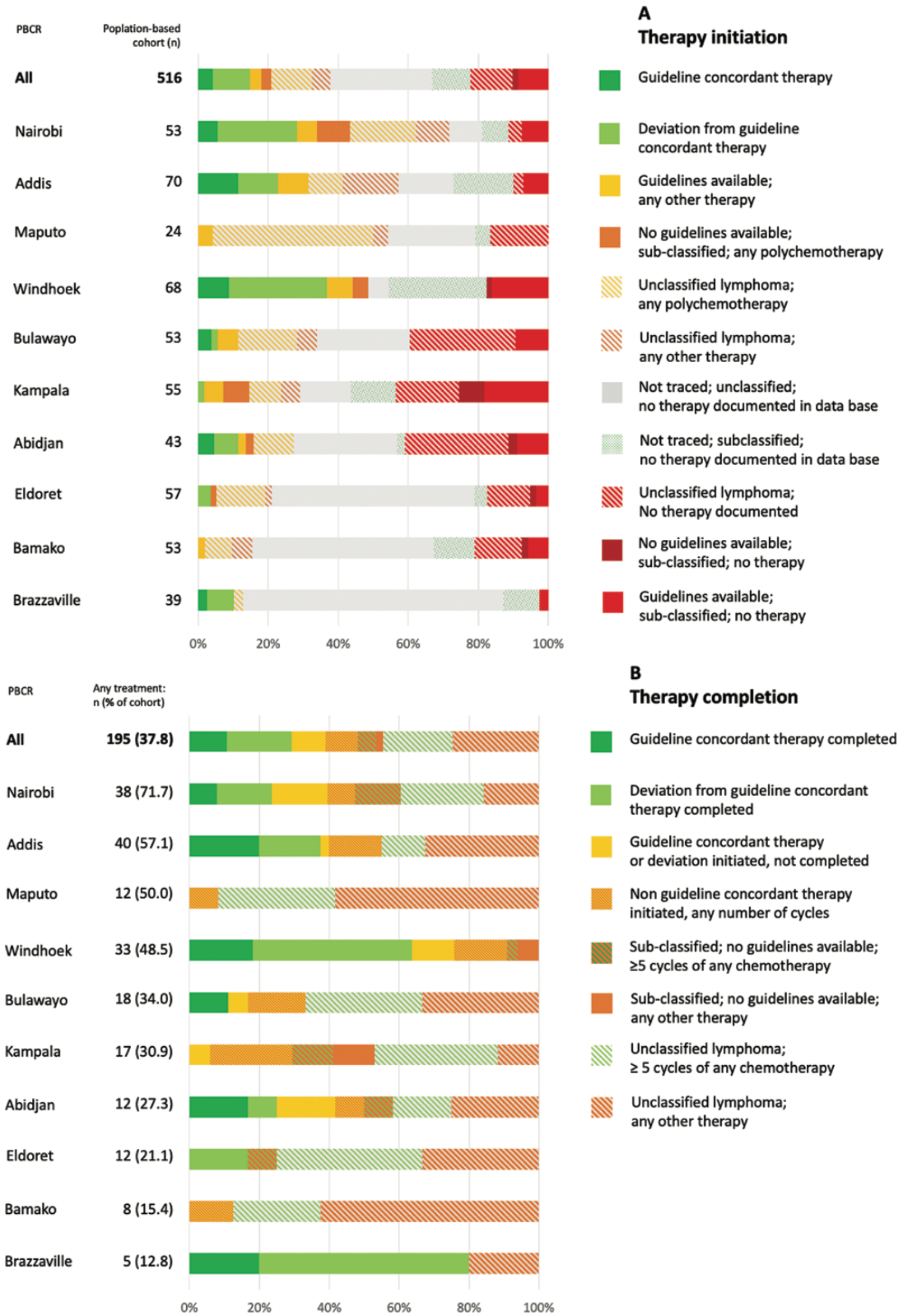


Figure 4. Stratification of evaluation of guideline concordance by population-based cancer registries. (**A**) Depicts evaluation of therapy *initiation* within the population-based cohort (n = 516). Percentages refer to proportion of all patients in respective population-based cancer registries. (**B**) Depicts evaluation of therapy *completion* among all patients with any treatment documented (n = 195 (37.8% of total cohort)). Percentages refer to proportion of all patients with any treatment documented in respective population-based cancer registries. Evaluation refers to "Therapy evaluation scheme" in Supplementary Table S1. Cotonou was excluded from figure due to small patient number (n = 1). PBCR, population-based cancer registry.

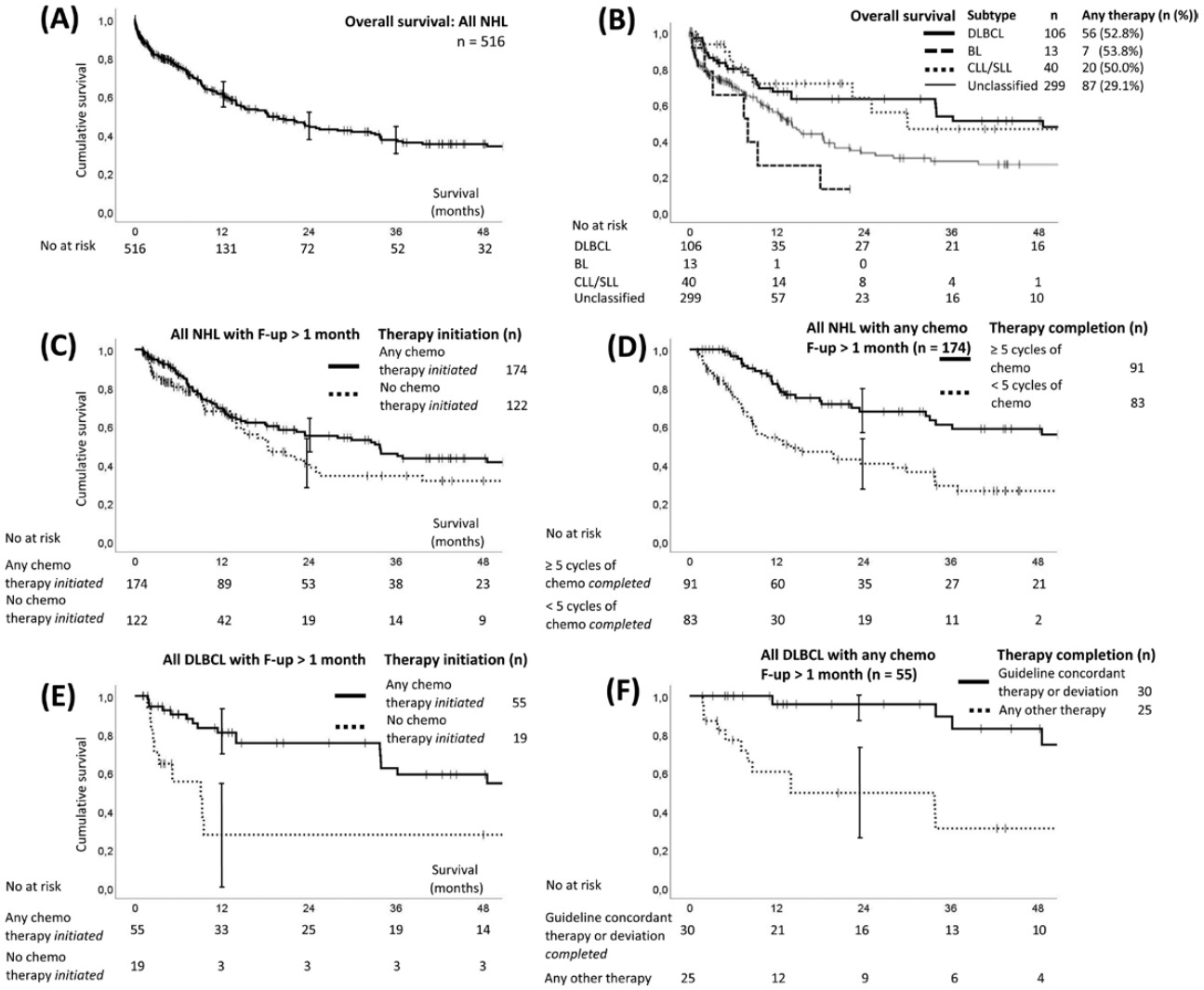


Figure 5. Survival by Kaplan-Meier estimates. (**A**) Overall survival of population-based cohort (n = 516); 95% CI indicated for 12, 24, and 36 months. (**B**) Overall survival of population-based cohort stratified by different subtypes and unclassified lymphoma. (**C**) Survival of population-based cohort with at least 1 month of survival (n = 296) with respect to therapy initiation and (**D**) those surviving at least 1 month that initiated any chemotherapy (n = 174), with respect to completion of chemo(immuno-)therapy cycles. (**E**) Survival of DLBCL with at least 1 month of survival (n = 74) with respect to therapy initiation and (**F**) DLBCL patients surviving at least 1 month that received any chemo(immuno-)therapy (n = 55) with respect to therapy completion concording with NCCN guidelines harmonized for Sub-Saharan Africa. No, Number; DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; F-up, follow-up.

Discussion

This study represents, to our knowledge, the first population-based multinational investigation on treatment and survival in adult non-Hodgkin lymphoma patients in Sub-Saharan Africa. Our objective was to evaluate guideline-concordance of therapy and survival in real-world patients. The main results of our study were: (1) The proportion of patients treated was low and guideline-concordant therapy was initiated in very few patients. (2) Survival of our study population was poor, while guideline-concordant treatment was associated with improved outcomes. (3) Treatment and survival of NHL patients varied considerably within and between the population-based cancer registries included.

(1) A concerning finding is the small share of NHL patients that received guideline-concordant care. Roughly summarized, NCCN Harmonized Guidelines for SSA recommend intensified chemotherapy regimen plus rituximab for the predominant aggressive subtypes such as DLBCL and BL as well as for advanced FL and MZL, and monotherapy for CLL/SLL.[11] However, only 13.1% of patients in our population-based cohort initiated guideline-concordant treatment or therapy with some deviation. As reported previously by our group in detail, one important factor attributing to this strikingly low proportion is the absence of sub-classification in more than half of patients (57.9%) and hence failure to apply guideline-concordant therapy.[24] Our results stress the importance of diagnostic work-up in NHL. Uniform treatment approaches disregarding subtype of lymphoma appear common in the region, eg, administration of oral polychemotherapy or (R-)CHOP for any NHL.[10,22,29] Only in recent years, multiple hospital-based studies have shed more light on feasibility of grade- and subtype-directed treatment approaches in SSA, eg, on AIDS-related DLBCL,[30] aggressive B- and T-cell lymphoma,[20] BL,[18] and HIV-associated aggressive NHL.[31] We suggest that in case of further amendment of NCCN Harmonized Guidelines, recommendations for treatment of

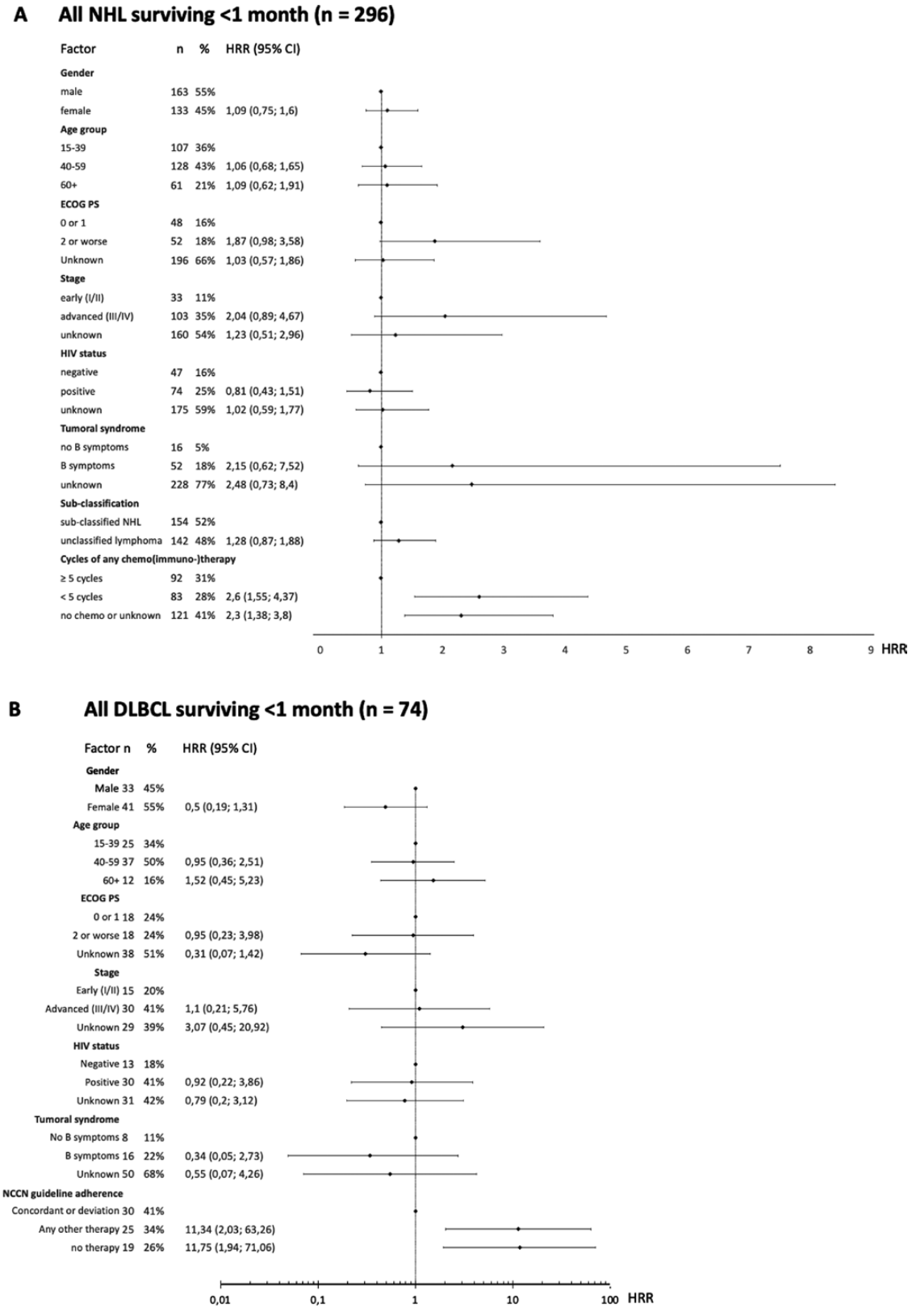


Figure 6. Results of multivariable Cox regression analysis for risk of early death. **A:** All NHL in the population-based cohort with at least 1 month of survival (n = 296). **B:** All DLBCL in the population-based cohort with at least 1 month of survival (n = 74). HRR, hazard rate ratio.

high- and low-grade lymphoma may be considered when further subtyping is not feasible.Another reason may be the lack of certain treatments even when sub-classification of NHL is available. Almost all patients in our cohort received CHOP- (73.0%) or COP-based (12.6%) regimens. An important factor contributing to absence of differentiated treatment may be cost and availability of chemotherapy agents (eg, highly effective bendamustine for MZL and CLL/

SLL[11]). In high-income countries, the introduction of rituximab has led to unprecedented rates of long-term cure and control of B-cell lymphoma.[32,33] CD20 antibodies are included in NCCN Harmonized Guidelines for several B-cell lymphoma subtypes,[11] and cost of biosimilars tends to be lower than rituximab.[7] However, they seemed hardly available in most SSA settings at the time[7,22] though recently proven safe, efficient,[17] and cost-effective for Malawi.[34] In our cohort, the majority of the 20 patients receiving rituximab came from Namibia, a middle-income country where public health insurance started covering the drug in 2013. To improve evidence-based treatment for predominantly aggressive lymphoma of B-cell lineage in SSA, health systems across SSA should increase efforts to procure and provide a wider range of systemic therapy agents at low cost, first and foremost rituximab or its biosimilars. Inclusion of not least CD20 antibodies in universal health coverage could leverage provision of adequate care for patients in the region. A fourth reason for low proportion of guideline-concordant care is the lack of NCCN Harmonized Guidelines for T-cell NHL and other rare entities such as plasmablastic and mantle cell lymphoma (17.1% of all sub-classified NHL).[11] More importantly, fifth, no treatment was documented in 114 of 297 patients traced (39.4%), and despite thorough investigation, another 217 of the 516 patients could not be traced (42.1%). In a worst-case scenario, where all untraced patients received no therapy, the share of patients without any lymphoma-directed treatment would amount to 62.2%.

(2) Overall survival in our study was poor (61.2% one-year survival), but slightly higher than outcomes reported by hospital-based and single-centered studies.[10,20,21,31] We believe that this difference is mostly explained by the high proportion of patients with poor health status and without any treatment documented who were lost to follow up early and therefore censored in analysis.Initiation of guideline-concordant treatment was associated with improved survival for sub-classified NHL. For DLBCL, the most frequent NHL subtype in our cohort, the largest impact on survival of all variables studied was found for administration of at least 5 cycles of (R-)CHOP. In our study, DLBCL patients receiving CD20 antibodies in addition to CHOP appeared to have improved survival, but due to low patient numbers these findings were not statistically significant in our population-based setting. Findings from Malawi indicate that treatment including rituximab is feasible and cost-effective even in settings with high HIV prevalence (2-year OS: 55.5%).[17,34] Similarly, the strongest impact for all NHL was administration of at least 5 cycles of any chemotherapy. These results have to be interpreted with caution since poor clinical status and subsequent early death were more likely found in the group with few cycles or no therapy. Nevertheless, our findings underline the necessity of subtype-directed and guideline-recommended treatment initiation and thorough administration of chemotherapy. Widely spread out-of-pocket expenditure inhibits both the continuation of chemotherapy as well as the adequate management of therapy side effects.[7,34,35] Other reasons impeding completion of care include stigma of cancer disease[36,37] and fear of therapy,[38] travel distances to oncological centers,[39] frequent stock out of chemotherapy,[40] and supportive drugs.[22]

The association between guideline-concordant approaches and improved survival is an encouraging result of our cohort study, but the effect of treatment of any kind was small compared to patients without any therapy documented. An observation from Uganda did not find benefit of treatment on survival.[22] Though we were unable to find detailed data on side effects, we believe that infections and other toxicity-related side effects of chemo(immuno-)therapy overall reduce treatment benefits. Results of single-center NHL cohort studies show death from treatment-related complications in 9%-34% of patients.[18,20-22] Therefore, there may be a need for patient stratification including dose reduction management and supportive care to offer tailored approaches in low-resource settings and eventually improve survival. To inform data-driven policy change regarding patient-centered provision of care, eg, further investigating the benefit of rituximab on survival, multicentre studies across the region should be conducted to address these global oncology challenges in SSA.[41] In this context, it is important to note that our study confirms recent findings from SSA not showing the difference in survival between HIV-positive and -negative patients.[16-19] Further, neither stage, ECOG PS, initiation of any treatment nor completion of at least 5 cycles of chemotherapy were influenced by HIV status in our cohort (Chi square test).

(3) Quality of care varied considerably within and between sites in terms of guideline-concordance and outcome. Addis Ababa, Nairobi, and Namibia had highest 1-year OS amounting up to 76.3%, whereas for Eldoret and Bulawayo it was as low as 37.5%. Proportion of patients diagnosed with NHL subtype ranged from 94.1% in Namibia to 8.3% in Maputo.[24] Further, proportion of patients treated (any therapy) ranged from 71.6% (Nairobi) to 12.8% (Brazzaville), median number of cycles applied ranged from 6 to 1, and initiation of guideline-concordant treatment (including deviations) was found in some 30% of patients from Namibia, but in no patients from Maputo and Bamako. Radiotherapy was found in only 6.6% of all patients originating from 4 of 10 participating registries, matching availability of radiation at the time. This is in contrast to the actual need for radiotherapy that has been estimated up to 64% of NHL patients in low-and-middle income countries.[42]NHL survival trends in Western countries have tremendously improved in the last decades. For example, the 5-year-relative survival for US patients has continuously risen, from 56.3% in the period of 1990-1994[43] to 73.2% in 2011-2017.[6] Reasons include better understanding of lymphoma behavior, improved pathological and molecular diagnostics, a less harmful and more individualized therapy arsenal involving adapted polychemotherapy, monoclonal antibodies, targeted agents, bone marrow transplant, and, importantly, improved supportive care.

Our data explore varying levels of the provision of adequate care in 11 oncological centers on population level and may serve as a baseline for targeting site-specific gaps. Generally, concerted efforts for long-lasting improvement of NHL survival in SSA should address enhancing diagnostic capacity,[12,24] sustainable provision of guideline-recommended chemotherapy and elevation of oncological healthcare workforce,[44] supportive,[45] and palliative care.[46] Prospective studies should examine the applicability of NCCN Harmonized Guidelines and focus on local shortcomings currently impeding significant advances in NHL care in the region.[7]

Limitations and Strengths

The retrospective design of the study resulted in some limitations. First, imprecise staging, poor documentation, and early

loss to follow up were frequent and have been reported from centers elsewhere.[10,22,47] In 43.3% of patients it was not possible to acquire any additional information on diagnosis, treatment, or survival, limiting our report to registry baseline data. This might make some findings, eg, on clinical presentation, less precise than those from prospective, single-institution studies.[18-20,29] It remains a subject of speculation whether patients not traceable have been facing particularly inadequate care, or even no treatment at all—or, quite the opposite, they left the registration area, eg, to seek more appropriate treatment. However, we assume that these patients are few since all of our study areas were major cities, usually providing the best cancer care in the country. We did include both public and private hospitals, and we estimate the proportion of affluent patients able to afford treatment is abroad rather small. Another possible reason for the high loss of follow-up is the problematic archiving system. Many study centers do not have well-established systems to document, trace and archive cases, and lack electronic databases. Nevertheless, it seems more likely that for a large share of the untraced cases, no therapy and therefore no medical records were initiated. In patients traced with incomplete therapy, we presume that a majority discontinued treatment due to a variety of reasons discussed above. In this sense, we consider the high share of loss to follow-up and the constricted diagnostic and therapeutic data not only a limiting factor of this study but also an important finding disclosing the concerning situation of NHL care in SSA.

Second, our survival data may reflect some selection bias. Overestimation of treatment effects is likely: (1) Reverse Kaplan-Meier analysis displayed that treatment was not selected at random, as patients with poor health status may not have been eligible for standard therapy, and some of these patients were censored early. (2) Patients with early deaths did not receive therapy, and (3) degree of guideline-concordance was only assessed during survival time and not before survival time started (immortal time bias, also known as survival bias).[48] To reduce the overestimation of treatment effects and early deaths, we excluded patients surviving less than 1 month.[48] For completion of eg, 6 cycles of CHOP, patients would have had to survive and remain in care for 4 months compared to our median follow-up of 6 months. However, follow-up data of our cohort was too poor to define a longer cutoff, and other cutoffs studied showed little differences in survival analysis. (4) Additionally, the random assignment of treatment could not be realized due to the observational design of the study.

Third, due to the shortage in diagnostic workup, subclassification of almost 6 in 10 NHL was missing. Therefore, analysis of subtype-specific survival beyond OS was limited due to small patient numbers. We decided to hence limit in-depth calculations to the most frequent subtype, DLBCL.

There are important strengths to our study. First, we included a large population-based random sample of all NHL patients from 11 study centers involving both public and private institutions, not just those referred to specialist centers, and patients both with and without treatment. Second, the study involved a variety of countries in SSA, reflecting on a wide range of socioeconomic conditions and different health services in the region. Third, we were able to evaluate the impact of different treatment approaches—from guideline-concordant optimal therapy to none at all—on survival. This study is the first to create a link between NCCN Harmonized Guidelines and therapy actually received on the ground. It is, to our knowledge, the first population-based overview of cross-sectional and longitudinal data on therapy and outcome of NHL patients in real-world SSA.

Conclusion

Advanced disease and considerable share of unclassified NHL reflect the lack of lymphoma awareness among healthcare personnel, poor referral systems, low pathological capacity, and high expenses of diagnosis that are hardly affordable for patients in low- and middle-income countries. Only a small proportion of patients from our cohort received NCCN guideline-concordant therapy, and these had better outcomes. Our results confirmed previous findings from SSA settings with high HIV prevalence that HIV in NHL appears to not be associated with worsened survival. For policymakers as well as institutions in SSA, our results can be an important baseline to plan, implement and measure targeted investments for improved outcomes of NHL patients. Cost-effective step-wise implementation of programs to allow guideline-concordant care should include: capacity-building for NHL subtyping, provision of therapeutic agents, supportive care and oncological workforce, fulfilling nursing requirements, and careful patient-centered care. Population-based cancer registries will facilitate monitoring these services over time.

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Conflict of Interest

The authors indicated no conflict of interest.

Author Contributions

Conception/design: N.C.S.M., E.J.K. Provision of study material or patients: A.Z., J.F.P., F.T., N.G.B., H.W., M.N., E.C., M.K., G.N., C.F.L., M.-T.A.-A. Collection and/or assembly of data: A.Z., J.F.P., F.T., N.G.B., H.W., M.N., E.C., M.K., G.N., C.F.L., M.-T.A.-A. Data analysis and interpretation: N.C.S.M., E.J.K., L.H., M.G., T.P.S., Y.W.J.-F., J.F., J.M., M.B., B.L., M.B., O.H., A.J. Manuscript writing: N.C.S.M., E.J.K., L.H., M.G., T.P.S., Y.W.J.-F., J.F., J.M., M.B., B.L., M.B., O.H., A.J. Final approval of manuscript: All authors.

Data Availability

Data supporting the findings in our study are available upon request. Requests will be evaluated by the AFCRN research committee. The data application process is outlined on the AFCRN website at http://afcrn.org/index.php/research/how-to-apply/76-research-collaborations.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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bjh research paper

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

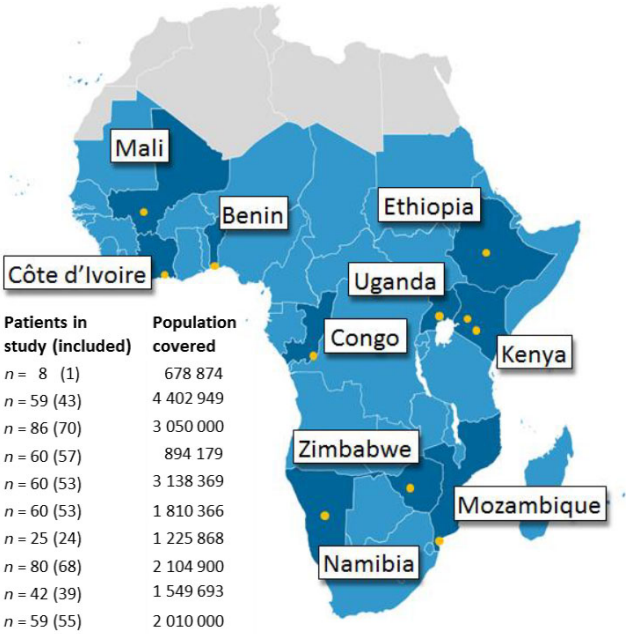
registries due to lack of patients. In total, 1068 patients were available in the registry databases. We assessed prevalence of adequate care from medical records among a random sample that could be assessed within feasible time and efforts in the given setting. We intended to draw conclusions for an 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)

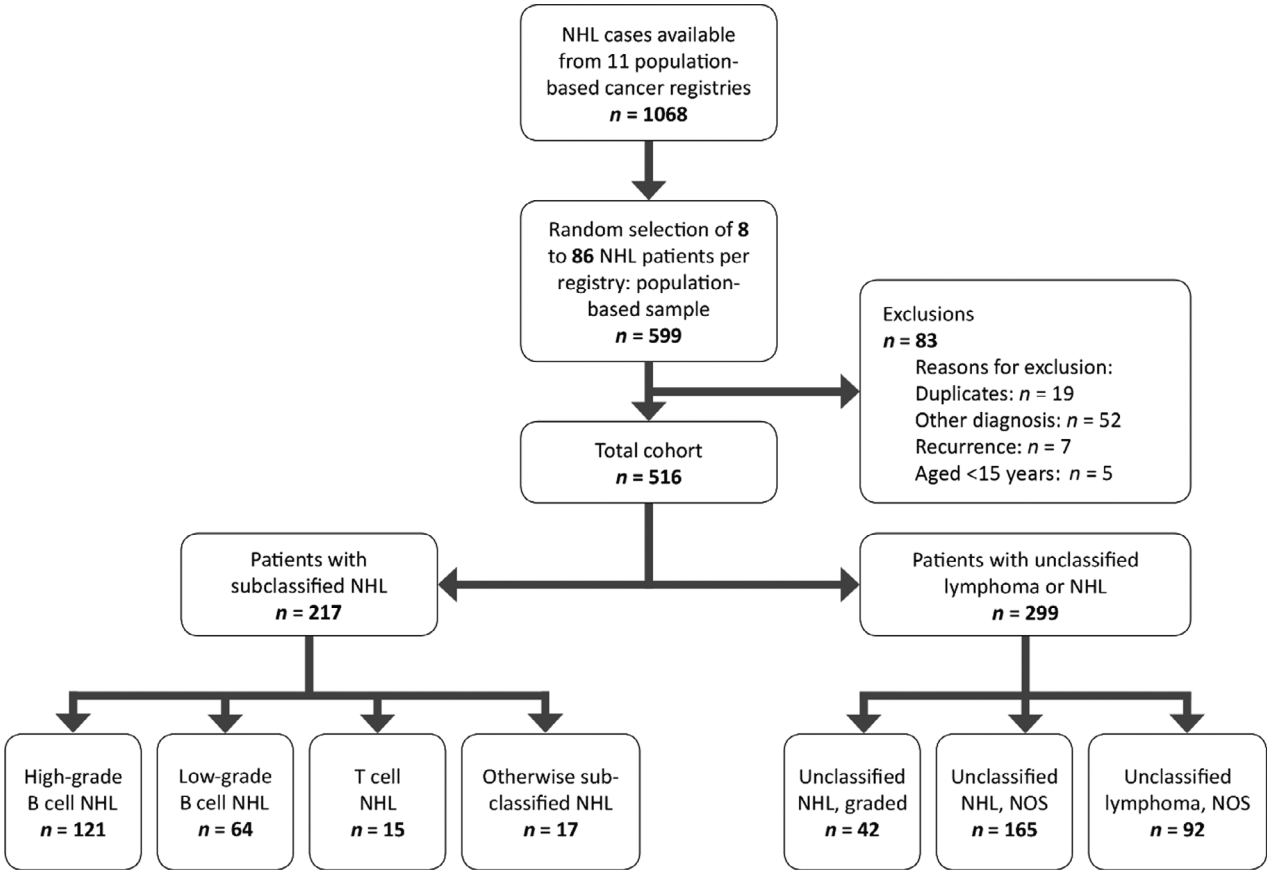


Fig. 2. Flowchart of study population. Stratified by non-Hodgkin lymphoma groups. NHL, non-Hodgkin lymphoma; NOS, not otherwise specified.

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,

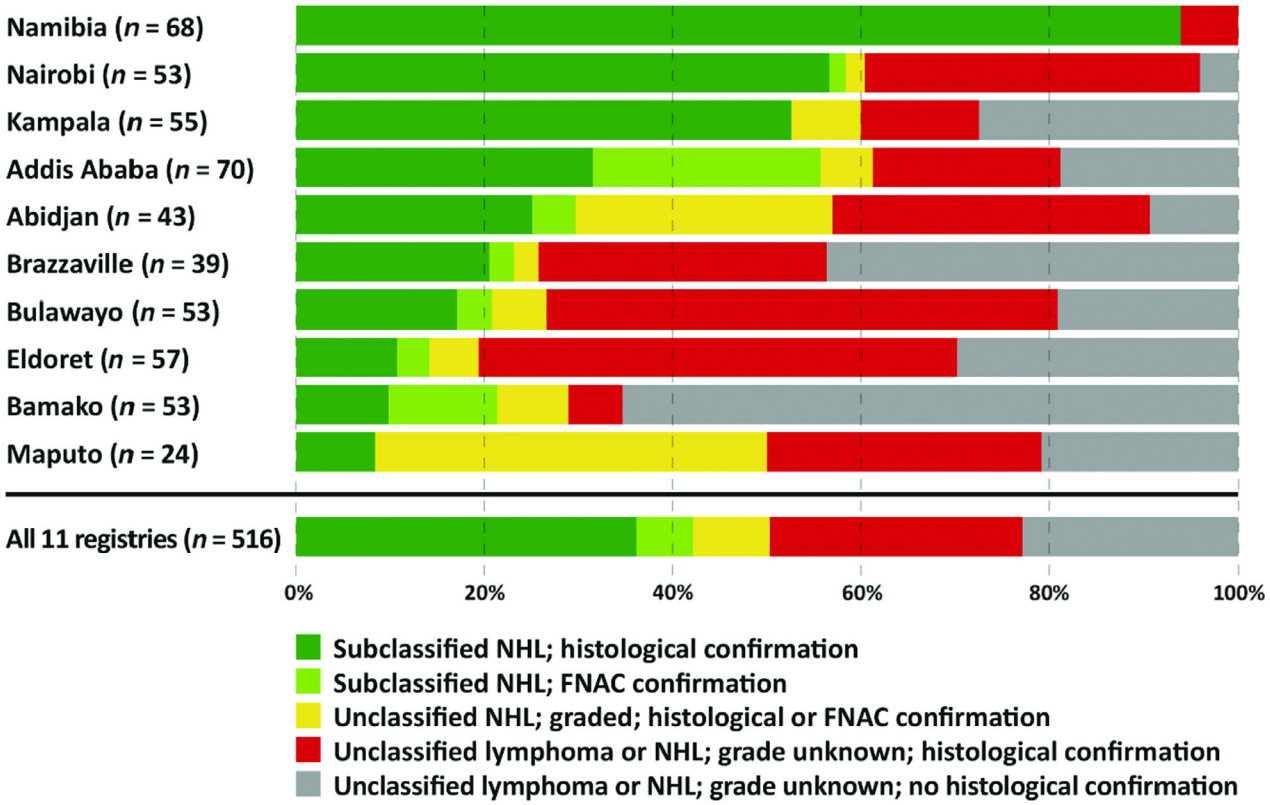


Fig. 3. Quality of pathological diagnosis. Stratified by population-based cancer registries, in order of quality of pathological diagnosis. With respect to non-Hodgkin lymphoma (NHL) subclassification, grade and diagnostic modality [according to National Comprehensive Cancer Network guidelines harmonised 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

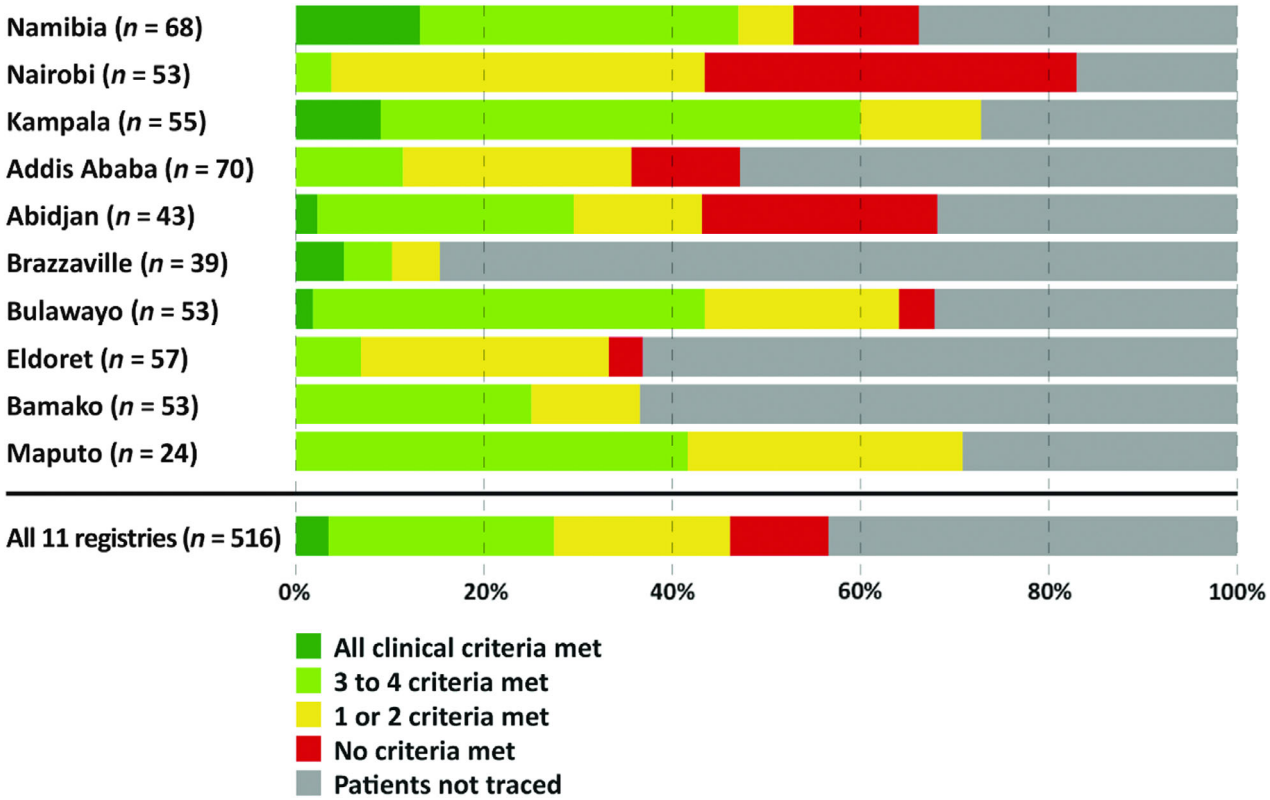


Fig. 4. Completeness of clinical diagnostic criteria. Stratified by population-based cancer registries, in order of Figure 3. With respect to information on Eastern Cooperative Oncology Group Performance Status, B symptoms, human immunodeficiency virus status, stage and any imaging [according to National 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.

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Cancer in Africa 2018: The role of infections

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We estimate the fractions of cancer attributed to infections in Africa in 2018. The number of new cancer cases occurring was taken from Globocan2018 with some additional estimations based on data from African population-based registries. Population attributable fractions were calculated using prevalence of infection and relative risk in exposed *vs*. nonexposed. The greatest share of infection-associated cancers is due to the human papillomaviruses (12.1% of all cancers in Africa and 15.4% in sub-Saharan Africa [SSA]); of these, cervical cancer is by far the most common. Kaposi sarcoma-associated herpesvirus is responsible for 3.1% of all cancers in Africa, the hepatitis viruses (B and C) for 2.9% and *Helicobacter pylori* for 2.7% (non-Cardia Gastric cancer and primary gastric lymphomas). Two percent of cancers are attributable to the Epstein–Barr virus, *Schistosoma haematobium* increases the risk of bladder cancer resulting in 1.0% of all cancers. HIV-related NHL and squamous cell carcinoma of the conjunctiva account for 0.6% of cancers. Altogether 24.5% of cancers in Africa and 28.7% in SSA are due to infectious agents. Infections are by far the most common cancer risk factor for cancer in Africa—the traditional risk factors (smoking, alcohol and unhealthy diet) probably cause only one in eight cancers in Africa. Prevention should focus on those infectious diseases preventable through vaccination (HPV and hepatitis B) which could reduce two-thirds of the burden. *Helicobacter pylori* and schistosomiasis are treatable with antibiotics and praziquantel, with a potential reduction of one in eight infection-associated cancers.

Introduction

Cancer is the second most important cause of mortality globally (after ischemic heart disease). Many cancers are known to be caused by infectious agents, and over the past 20 years estimates have been made of the proportion of cancers caused by infections worldwide.[1–4]

For the year 2012, the global burden of cancers caused by infections was estimated to be 15.4%, while for sub-Saharan Africa (SSA) the share was more than 30%. This would make infections by far the most important cause of cancer in Africa. Despite this, infections do not figure among the risk factors for disease (including cancer) for which the Global Burden of Diseases group[5] publishes quantified estimates.

In this publication, we take advantage of a new set of national estimates of new cancer cases (by age group and sex) occurring in 2018 recently published by IARC in their "Globocan" series[6] to present estimates of the fraction of different cancers, and of all malignant neoplasms, attributable to infectious agents in Africa in the year 2018.

Methods

Geographic divisions

Estimates for the number of incident cancer cases as well as attributable fractions for the different causative infectious agents are calculated for the five regions of Africa, as defined by the UN Population Division:[7] Eastern, Middle, Southern,

Key words: cancer, Africa, infections, population-based

Abbreviations: AFCRN: African Cancer Registry Network; ASR: aged standardized rates; ATLL: adult T-cell leukemia/lymphoma; BL: Burkitt lymphoma; DCO: death certificate only; EBV: Epstein–Barr virus; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HHV: human herpesvirus; HIV/AIDS: human immunodeficiency virus/acquired immune deficiency syndrome; HL: Hodgkin lymphoma; HPV: human papillomavirus; HTLV: human T-cell lymphotropic virus; IARC: International Agency for Research on Cancer; ICD-O: International Classification of Diseases for Oncology; KS: Kaposi's sarcoma; KSHV: Kaposi's sarcoma-associated herpesvirus; NA: Northern Africa; NCD: noncommunicable disease; NCGC: noncardia gastric cancer; NHL: non-Hodgkin lymphoma; NPC: nasopharyngeal carcinoma; PAF: population attributable fraction; PGL: primary gastric lymphomas; SCCC: squamous cell carcinoma of conjunctiva; SSA: sub-Saharan Africa

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What's new?

Infectious agents are a significant cause of cancer in Africa. In the present study, the authors took advantage of new national cancer estimates published in Globocan2018 to determine the current burden of infection-associated cancers in Africa. Analyses show that most infection-associated cancers are due to human papillomaviruses. Herpes virus, hepatitis B and C viruses, *Helicobacter pylori*, and Epstein-Barr virus were other important infectious causes of cancer. In total, nearly 30 percent of cancers in sub-Saharan Africa were related to infection, a finding that is of major significance for cancer control efforts, particularly vaccination and other strategies to prevent infection.

Western Africa (Comprising SSA) and Northern Africa (NA; see Appendix 1 for a list of countries in each region).

Cancer cases and source of incidence date

The estimated numbers of new cases of the following cancers were available from Globocan 2018: Oral cavity (ICD-10 codes C00–06), Oropharynx (C09–10), Stomach (C16), Anus (C21), Liver (C22), Larynx (C32), Kaposi sarcoma (KS; C46), Vulva (C51), Vagina (C52), Cervix uteri (C53), Penis (C60), Bladder (C67), Hodgkin lymphoma (HL; C81) and Non-Hodgkin lymphoma (NHL; C82–86, C96).

For four cancer subsites or histological subtypes causally linked with infectious agents, incidence estimates were not available in Globocan 2018, and separate estimates were made. We used data from the African cancer registries contributing to Globocan, and the same methods[8] to make national and regional estimates for squamous cell carcinoma of conjunctiva (SCCC), Burkitt lymphoma (BL), primary gastric lymphomas (PGL) and noncardia gastric cancers (NCGC). The methods used to estimate the former two cancers will be published elsewhere.[9,10] In summary, they are based on the age-/sex-specific proportions of cancers of the eye that were squamous cell carcinomas, or unspecified cancers of the conjunctiva, and of NHL that were BL (ICD-O M9687/3). PGL was estimated for each contributing registry as the proportion (by age and sex) of NHL located in stomach (C16.x) plus 1/3 of NHL cases recorded as being in the "Abdomen" (C76.2). NCGC was estimated for each registry using the (age-/sex-specific) proportions of noncardia cancers (C16.1–C16.9) of all gastric cancers,[11] ignoring cases with no histology (thereby excluding most cases recorded as C16.9 + ICD-O M8000/3 such as DCO cases).

We also used the same cancer registries to examine, by region, the proportions of liver cancers of known histology (C22.0–C22.7) that were hepatocellular carcinomas (HCCs; C22.0), of anal cancers (C21) that were squamous cell carcinomas (ICD-O M codes 8085–8076, 8083–8084, 8123–8124), and of HLs (C81) that were of the nodular lymphocyte predominant subtype (C81.0).

Attributable fractions

The objective is to estimate the "Population Attributable Fraction" (PAF), that is, the proportion (or number) of cancer cases occurring in 2018 that would have not occurred if the respective carcinogenic agent entirely had been absent. The inputs to the analysis are *(i)* the etiological effect of the infectious agents on cancer-specific risk, *(ii)* the population prevalence of infection (by sex and region).[12]

Selection of cancer-causing infections. We included only infectious agents identified as group 1 carcinogens in the most recent IARC monograph,[13] namely, Hepatitis B and C viruses (HBV, HCV), human papillomaviruses (HPVs), Epstein–Barr virus (EBV), KS herpesvirus (KSHV, also known as HHV-8), human immunodeficiency virus (HIV-1), human T-cell lymphotropic virus (HTLV-1), as well as the bacterium *Helicobacter pylori* and *Schistosoma haematobium*. The occurrence of infection with liver flukes (*Opisthorchis viverrini* and *Clonorchis sinensis*), also identified as group 1 carcinogens is confined to parts of Asia and they are not considered in the present paper.

Calculation of population attributable fractions. For most infectious agents, we estimated PAFs using the formula described by Levin[12]:

$$\mathrm{PAF} = \frac{p(\mathrm{RR}-1)}{p(\mathrm{RR}-1)+1}$$

where p is the prevalence of the infection, and RR is the relative risk in the exposed *vs.* the nonexposed.

For cancers caused by more than one of the infectious agents considered, the PAF for the combined effect cannot be estimated through the simple addition of the PAFs for the individual risk factors. In the absence of information of data on cooccurrence of the risk factors, and the relationship between them, the joint effect is estimated assuming that the risk factors are independent of each other, with the PAF for multiple risk factors can be estimated as[12]:

$$\mathrm{PAF_T} = 1 - \prod_{n=1}^{\mathrm{total}} (1 - \mathrm{PAF_n}).$$

Selection of relative risks and exposure prevalence of cancer-causing infections. These are summarized in Table 1. The justification and sources of data, for the relative risks and prevalence estimate, are provided in Appendix 2. The relative risks are generally based on meta-analyses of cohort and/or case–control studies.

Table 1. Relative risks, prevalence of exposure, and PAFs used in the calculations (selection criteria and references in Appendix 2)

Agent (attributable cancer)	Relative risk	Population prevalence (%)	PAF (%)
HPV			
Cervix cancer			100
Anal cancer			80 (M) 90 (F)
Vulvar cancer			40[a]
Vaginal cancer			72
Penile cancer			40
Oropharyngeal cancer			30
Larynx cancer			4
Oral cavity			4
Helicobacter pylori		70 (SSA); 51 (NA)	
Noncardia gastric cancer	17		92 (SSA) 89 (NA)
Primary gastric lymphoma	7.2		81 (SSA) 76 (NA)
Hepatitis B		1.3–10.1 (Table 4)	
Liver cancer (HCC)	23.4		64 (SSA) 23 (NA)
Hepatitis C		0.5–2.1 (Table 4)	
Liver cancer (HCC)	27.6		23 (SSA) 49 (NA)
NHL	2		0.9 (SSA) 3.5 (NA)
KSHV			
Kaposi sarcoma			100
EBV			
Hodgkin lymphoma			75
Nasopharynx cancer			80 (SSA) 100 (NA)
Burkitt lymphoma			87 (SSA) 32 (NA)
Gastric carcinoma			11 (M) 5 (F)
HIV		EA and SA: 5.2 (M) 8.4 (F)	
NHL	5 (SSA) 50 (NA)		13 (SSA) 0 (NA)
SCCC	10	WA and MA: 1.6(M) 2.3 (F) NA: ‹0.01	29 (M)-38 (F) (SSA)
S. haematobium		EA & MA: 28; SA: 11;	
Bladder cancer	5	WA: 33; NA 8	51 (SSA) 25 (NA)
HTLV I		EA: 1.2; MA: 3.2;	
Adult T-cell leukemia/lymphoma	M: 40×10^{-5}[b]	SA: 1.6; WA: 3.2;	
	F: 25×10^{-5}[b]	NA: 0	

[a]Varies by age.
[b]Annual incidence rate (in carriers age 40+).
Abbreviations: EA, East Africa; HCC, Hepatocellular carcinoma; MA, Middle Africa; NA, North Africa; NHL, Non Hodgkin lymphoma; SA, Southern Africa; SSA, sub-Saharan Africa; SCCC, Squamous cell carcinoma of conjunctiva; WA, West Africa.

Data availability

The data that support the findings of our study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Results

HPV

The PAFs for the cancers associated with HPV, and the numbers attributable to these viruses, are shown in Table 2.

Cervical cancer. Cancer of the cervix is the second most common cancer of women in Africa (after breast cancer). All the estimated 111,630 cases occurring in SSA in 2018 are assumed to be caused by HPV, accounting for 24.3% of cancers in women. In NA, the share is smaller, with 7,650 new cases, comprising 5.1% of cancers in women. The total is 119,280 (19.6% of cancers in women in Africa).

Anal cancer. Almost all anal cancers are squamous cell carcinomas or adenocarcinomas,[14] although some of the latter may represent downward spread of rectal cancers. In the cancer registries of SSA, some 40% of anal cancers in males and 60% in females were SCC; in NA, the proportions were 60% SCC in males and 70% in females. With an estimated PAF of 90%

Table 2. Estimated cancers attributable to Human Papillomaviruses in Africa in 2018

	Sub-Saharan Africa				All Africa					
Cancer (PAF %)	Male	(% total cancer)	Female	(% total cancer)	Male	(% total cancer)	Female	(% total cancer)	Both	(% total cancer)
Cervix (100%)			111,630	24.3%			119,280	19.6%	119,280	11.3%
Anus - SCC only (80–90%)[1]	620	0.20%	1,490	0.32%	840	0.19%	1,750	0.29%	2,590	0.3%
Vulva (40%)[2]			2040	0.44%			2,210	0.36%	2,210	0.2%
Vagina (72%)			1,230	0.27%			1,420	0.23%	1,420	0.1%
Penis (40%)	890	0.29%			910	0.20%			910	0.1%
Oro-pharynx (30%)	430	0.14%	210	0.05%	510	0.11%	250	0.04%	760	0.1%
Oral cavity (4%)	230	0.07%	190	0.04%	300	0.07%	250	0.04%	550	0.1%
Larynx (4%)	200	0.06%	50	0.01%	340	0.08%	70	0.01%	410	0.0%
(Head & Neck)	(860	0.27%)	(450	0.10%)	(1,150	0.26%)	(570	0.09%)	(1,720	0.2%)
All HPV related	2,370	0.76%	116,840	25.4%	2,900	0.65%	125,230	20.6%	128,130	12.1%

[1]SCC cases: 40% (Males)–60% (Females) of anal cancers in SSA; 60% (M) and 70% (F) of anal cancers in NA.
[2]PAF is age related (15–54: 48%; 55–64: 28%; 65+: 15%).

in females and 80% in males, the numbers of anal cancer cases attributable to HPV are 2,590 (840 in males, 1,750 in females), 81% of which are in SSA.

Vulvar cancer. Applying the PAFs shown in Table 2 to the new cancer cases in 2018, 170 of all new vulvar cancer cases in NA and 2,040 of all new cases in SSA are attributable to HPV.

Vaginal cancer. A PAF of 72% implies about 190 vaginal cancer cases in NA and 1,230 in SSA attributable to HPV (Table 2).

Penile cancer. A PAF of 72% gives an estimated 890 penile cancer cases attributable to HPV in SSA and a negligible number of 20 cases in NA (Table 2).

Head and neck squamous cell cancer. We estimate about 1,300 HPV-associated head and neck cancer cases in SSA and 400 in NA, with about two-thirds of the cases occurring in males (Table 2).

Helicobacter pylori

Gastric cancer. With a relative risk of 17, the estimated PAF for NCGC is 92% for SSA and 89% for NA, so that an estimated 20,390 gastric cancer cases in SSA and 6,240 in NA are attributable to *H. pylori*, accounting for 2.6 and 2.2% of all cancer cases in SSA and NA, respectively (Table 3).

Gastric lymphoma. The incidence of PGL was estimated as described in the Methods; it accounts for 4.2% of NHL in Africa (5.9% in NA, 3.3% in SSA). With a PAF of 81% in SSA and 76% in NA, we estimate 850 gastric lymphoma cases attributable to *H. pylori* in SSA and 750 in NA, accounting for <1% of all newly diagnosed cancer cases in 2018 (Table 3).

HBV and HCV

The IARC monograph on carcinogenic agents in humans[13] considers that there is sufficient evidence the HBV causes HCC, as does HCV. HCV is also a cause of NHL.

To obtain the estimated numbers of cases of HCC (by region and sex) we used data from African cancer registries to obtain the proportion of liver cancers (with histological diagnosis) that were HCC (see Methods). Overall, some 77% of liver cancers in SSA are HCCs (varying from 67% to 88% by region) and 52% of cases in NA (Table 4).

For SSA, 50% of all liver cancers are attributable to HBV and 17% to HCV, and, assuming independence of the distribution of the two infections, 55% of liver cancer cases are related to one or the other (or both; Table 4). For NA, 12% of liver cancers are attributable to HBV and 26% to HCV. Thus, in total, some 18,300 cases of liver cancer in SSA are attributable to HBV and 6,400 to HCV. In NA, 3,300 cases are attributable to HBV and 7,100 to HCV. In Africa as a whole, 45% of liver cancers (20,740 cases in males, 8,500 in females) is caused by one of these two viruses (Table 4).

With respect to HCV infection and NHL (a causal association, according to IARC[15]), a PAF of 0.9% for SSA and 3.5% for NA, yields and estimated 880 cases of NHL as caused by HCV two-thirds of them in NA (Table 4).

KSHV (HHV-8)

KS, one of the major AIDS-defining malignancies, is caused by the Kaposi sarcoma-associated herpesvirus (KSHV), with a synergism between this virus and HIV. In Africa, KS represents one of the most common cancers in HIV-infected individuals. The ASR in males is estimated to be as high as 36 per 100,000 population in Malawi and 35.7 per 10,000 in Mozambique.[6] All cases of KS are attributed to infection with HHV-8/KSHV; the estimated numbers in 2018 are 400 in NA and 32,000 in SSA.

Table 3. Estimated cancers attributable to *Helicobacter pylori* in Africa in 2018

	Gastric cancer			Primary gastric lymphoma	
Region	**Cases 2018**	**NCGC cases**	**HP related**	**Cases 2018**	**HP related**
Males					
East Africa	4,570	4,220	3,880	320	260
Middle Africa	2,210	2,150	1,980	80	60
South Africa	1,180	1,010	930	60	50
West Africa	4,550	4,410	4,060	100	80
Sub-Saharan Africa	12,510	11,790	10,850	560	450
North Africa	4,520	4,080	3,630	560	430
Africa	17,030	15,870	14,480	1,120	880
Females					
East Africa	4,640	4,330	3,980	250	200
Middle Africa	1,930	1,880	1,730	50	40
South Africa	830	730	670	90	70
West Africa	3,530	3,430	3,160	110	90
Sub-Saharan Africa	10,930	10,370	9,540	500	400
North Africa	3,180	2,930	2,610	420	320
Africa	14,110	13,300	12,150	920	730
Both sexes					
East Africa	9,210	8,550	7,860	570	460
Middle Africa	4,140	4,030	3,710	130	100
South Africa	2,010	1,740	1,600	150	120
West Africa	8,080	7,840	7,220	210	170
Sub-Saharan Africa	23440	22,160	20,390	1,060	850
North Africa	7,700	7,010	6,240	980	750
Africa	31140	29,170	26,630	2040	1,600

Epstein–Barr virus

IARC[15] considers that there is sufficient evidence for the carcinogenicity of EBV in BL, HL, nasopharyngeal cancers (NPCs), immunosuppression-related NHL and the extranodal NK-T cell lymphoma (nasal type). The latter must be exceedingly rare in Africa, while the fraction of NHL cases related to immunosuppression caused by HIV is considered later. Although based on mechanistic (rather than epidemiological) data, it also considered that "EBV might cause a proportion of gastric cancer".

Nasopharyngeal carcinoma. NPC is not common in Africa, although NA is considered an area of intermediate incidence. The estimated numbers of cases due to EBV infection are 4,810 in SSA and 3,480 in NA.

Hodgkin lymphoma. Assuming that 75% of HL is EBV-related (Methods) implies some 7,500 EBV-related HL cases in 2018.

Burkitt lymphoma. BL was first described in the late 19th century by Sir Albert Cook, who had described children in Uganda with tumors of the jaw. Fifty years later, Denis Burkitt provided the first comprehensive description of the lymphoma, identified clinical features and mapped the occurrence of the tumor all over SSA with the simplest implements, which remains largely valid today.[15] We estimate that EBV is a causative factor in 3170 cases of BL in Africa (81% of the continental total).

Gastric carcinoma. In multinational studies, EBV DNA is present in some 11% of cases in males, 5% in females. This implies that EBV is causative for 2,590 gastric cancers (72% in males, 75% in SSA).

Summary: EBV. In total, for the four cancers considered, EBV was responsible for some 21,570 cases in Africa in 2018, that is some 2.0% of all cancer cases.

Human immunodeficiency virus

Three cancers are considered "AIDS-defining", that is, when a person infected with HIV develops one of them, they are considered to have AIDS. AIDS-defining cancers include KS, HLs and cervical cancer. In addition, IARC[13] considers that there is sufficient evidence for the carcinogenicity of HIV in cancers of the anus, conjunctiva and Hodgkin lymphoma. For most of these, immunosuppression by HIV is simply making manifest the carcinogenic effects of other viruses (KSHV, HPV and EBV) and the fraction of cancers attributable to these

Table 4. Estimated cancers attributable to Hepatitis viruses in Africa in 2018

Region	Liver cancer												NHL	
	Cases 2018		HCC cases			HBV			HCV			Either or both				
							Attributed cases			Attributed cases		Attributed cases				
	Male	Female	Male	Female	Prevalence (%)	Male	Female	Prevalence (%)	Male	Female	Male	Female	% Liver	All cases (2018)	HCV related
East Africa	7,010	4,540	5,190	2,730	5.1	2,760	1,460	0.5	610	320	3,050	1,600	40%	15,350	80
Middle Africa	4,140	1870	2,990	1,040	10.1	2080	720	2.1	1,070	370	2,400	840	54%	3,460	70
South Africa	1,690	1,020	1,240	670	8.5	810	440	0.7	200	100	880	480	50%	4,030	30
West Africa	10,780	5,800	9,620	4,970	9.8	6,610	3,410	1.3	2,470	1,280	7,380	3,810	67%	9,420	120
Sub-Saharan Africa	23,620	13,230	19,040	9,410		12,260	6,030		4,350	2070	13,710	6,730	55%	32,260	300
North Africa	19,910	8,020	11,540	2,910	1.3	2,630	660	3.7	5,700	1,440	7,030	1,770	32%	16,430	580
Africa	43,530	21,250	30,580	12,320		14,890	6,690		10,050	3,510	20,740	8,500	45%	48,690	880

causative agents has already been quantified. The exceptions are NHL and conjunctival carcinomas.

Given the prevalence of HIV-AIDS in adults age 15–19 in the countries of Africa in 2017 published by UNAIDS (Table 1), the PAF for NHL is about 8.4% in Africa (~12.7% in sub Saharan Africa)—resulting in an estimated 4,100 cases (55% in males)—all in SSA.

As described in Methods, a special analysis was carried out to estimate the numbers of new cases of SCCC in Africa in 2018. Assuming a relative risk of 10[13] and the regional prevalence of HIV noted above, we estimate that about one-third (2,060 cases) of the cases of SCCC occurring in Africa in 2018 (6,170) were caused by HIV.

Schistosomiasis

For bladder cancer, the estimated relative risk in persons infected with *S. haematobium* is assumed to be 5, and with the regional prevalences of Schistosomiasis from Steinmann *et al*,[16] the PAF for NA is 25%, for SSA 51% and the number of bladder cancer cases to Schistosomiasis can be estimated as 6,300 and 4,200, respectively.

Human T-cell lymphotropic virus

In the early 1980s, HTLV-1 was the first human retrovirus to be recognized as a carcinogenic agent and able to cause adult T-cell leukemia/lymphoma (ATLL).[13]

Based on the regional prevalences of HTLV in adults from Fox *et al.*[17] and assuming an annual incidence of ATLL among adult (40+) carriers of HTLV-1 in Africa of 40 per 10^5 in males and 25 per 10^5 in females, about 1,400 cases of ATLL (all in SSA) would be caused by HTLV-1 in Africa in 2018. ATLL has been rarely identified in Africa, probably due to lack of diagnostic facilities, although when series of lymphoma cases are reviewed, some 10–20% have characteristics of ATLL (with positivity for HTLV-1[18,19]).

Overall results

Table 5 summarizes the above results for the infectious agents discussed above.

Overall, almost one-quarter of cancers in Africa (258,500 cases in 2018) were caused by infectious agents. The percentage is higher for SSA (28.7%), and, for females of SSA, for whom we estimate that more than one-third of all cancers (34.1%) are infection-related.

The most important cancer-causing infectious agents are the human papillomaviruses, responsible for 12.1% of cancers in Africa (15.4% in SSA), with most of these cases in females (because of the association with cancer of the cervix). HPV is the cause of 25.4% of all cancer in woman of SSA.

KSHV (HHV-8) is the second most common cancer-causing agent—4.1% of cancers in SSA (with almost twice as many cases in men as in women). Hepatitis B & C cause 2.9% of cancers in Africa (2.7% SSA), and *H. pylori* about the same number in SSA (2.7%) and for Africa (2.7%).

Table 5. Cancers caused by infections: Africa and Sub-Saharan Africa

	Sub-Saharan Africa						Africa					
	Male		Female		Both		Male		Female		Both	
	No. cases	% all cancer	No. cases	% all cancer	No. cases	% all cancer	No. cases	% all cancer	No. cases	% all cancer	No. cases	% all cancer
HPV	2,370	0.8%	116,840	25.4%	119,210	15.4%	2,900	0.6%	125,230	20.6%	128,130	12.1%
KSHV	20,410	6.5%	11,640	2.5%	32,050	4.2%	20,710	4.6%	11,740	1.9%	32,450	3.1%
Hepatitis viruses (B & C)	13,880	4.4%	6,860	1.5%	20,740	2.7%	21,230	4.8%	8,890	1.5%	30,120	2.9%
H pylori	11,300	3.6%	9,940	2.2%	21,240	2.7%	15,360	3.4%	12,870	2.1%	28,230	2.7%
EBV	9,350	3.0%	5,090	1.1%	14,440	1.9%	13,930	3.1%	7,640	1.3%	21,570	2.0%
Schistosomes	3,550	1.1%	2,750	0.6%	6,300	0.8%	6,900	1.5%	3,600	0.6%	10,500	1.0%
HIV[1]	3,030	1.0%	3,120	0.7%	6,150	0.8%	3,030	0.7%	3,120	0.5%	6,150	0.6%
HTLV-I	850	0.3%	550	0.1%	1,400	0.2%	850	0.2%	550	0.1%	1,400	0.1%
Total	64,740	20.7%	156,790	34.1%	221,530	28.7%	84,910	19.0%	173,640	28.5%	258,550	24.5%

[1]Cancers related to HIV and not to other infections in this table (NHL and squamous cell carcinomas of conjunctiva).

Figure 1 shows the 16 cancers that are related to infections in Africa, indicating the total numbers of cases (by sex) and the number and proportion of each that is caused by infectious agents. Cancer of the cervix 119,300 cases dominates, with all of the cases ascribed to infection with HPV. Liver cancer is second in frequency, with a PAF due to hepatitis viruses of 45% (48% in males, 40% in females). Four infections are related to NHL (ATLL—cancer caused by HTLV-I—has been allocated to the leukemias)—they are HIV, EBV (Burkitt lymphoma), HCV and *H. pylori*. The combined PAF for these four is 20% for males, 17% for females—9,090 cases in total. All of the cases of KS are related to infection with KSHV, while *H. pylori* and EBV are responsible for about 87% of stomach cancers.

Discussion

For Africa as a whole, we estimate that, in 2018, about 258,500 cases of cancer (24.5% of all cancers) were due to infectious agents, the estimate for SSA is 221,500 (28.7% of the total). Most of this burden was related to viral infections, with just 2.7% related to infection with *Helicobacter pylori* and 1.0% to schistosomiasis.

The results are, of course, "best estimates" and depend not only on the accuracy of estimation of the numbers of cancer cases in Africa (by cancer type, age, sex and region) but also on the choice of relative risk, and the availability and accuracy of data on prevalence of infection in the general population. Where we have used regional estimates of prevalence of infection (for the hepatitis viruses, *H. pylori*, HIV and Schistosomiasis), they derive from samples of subjects in a limited number of countries, and the subjects may not be entirely representative of the population from which the cancer cases are derived. For this reason, some estimates of attributable fractions have chosen to use prevalence of infection among cases of cancer,[20] from published studies, in the belief that the study subjects would be more representative of prevalence of exposure in the populations. For example, Maucort-Boulch *et al.*[21] based their estimates of PAF of hepatitis viruses on prevalence of viral markers in cases of HCC, since they believed that the liver cancer cases in the various studies considered (rather more than 1,000 cancer cases from SSA), would be representative (with respect to positivity for virus infection) of cancer cases from the region as a whole. Since there is no evidence on this point, either way, we chose to use the general approach of population prevalence. In any case, the PAFs for HBV appear to be very similar using the two approaches. However, the estimate of Maucort Boulch *et al.*[21] that 79% of liver cancers in NA are attributable to HCV (rather than our much more modest estimate of 25%) is almost certainly due to their calculation being based largely on HCV prevalence in liver cancer cases from Egypt,[22] an area of notoriously high HCV prevalence, particularly at the period when the studies concerned were carried out (1990–2011), and also to the assumption that "the vast majority of liver cancers are HCC" (and hence potentially HCV-related), which appears to be far from the case (Table 4).

With respect to relative risk, the values chosen are generally from large meta-analyses, although generally not from studies

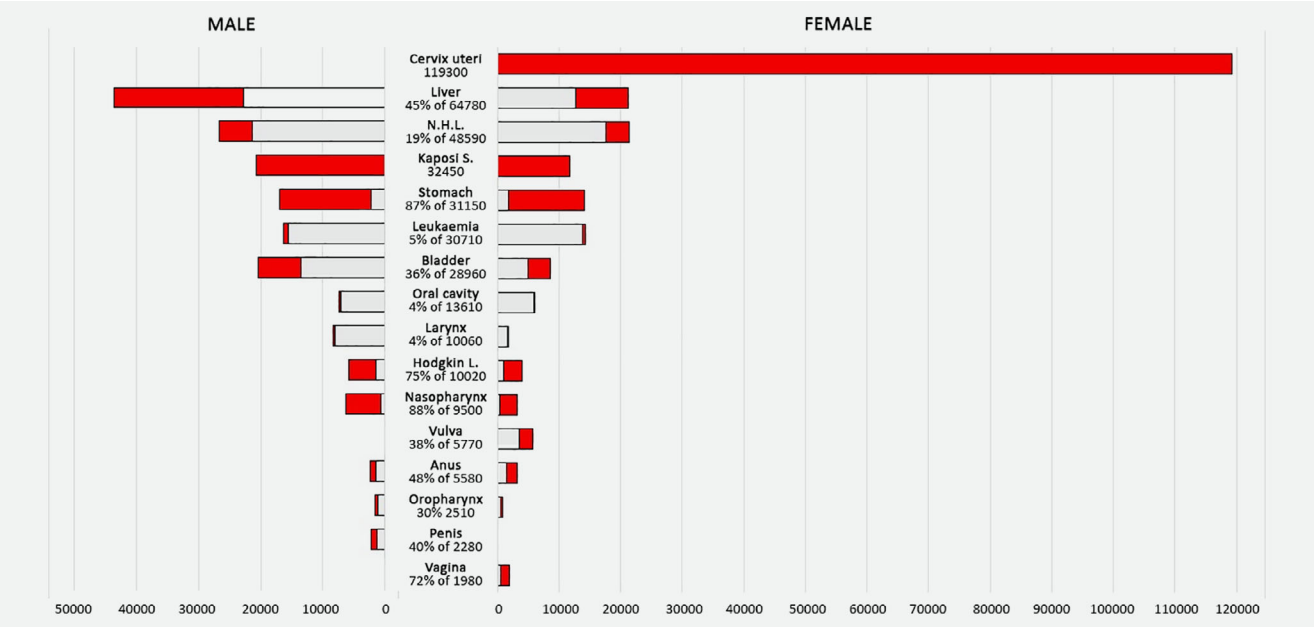

Figure 1. Numbers of cases of the 16 infection-related cancers in Africa, showing (in red) the proportions of each due to infectious agents. The central legend shows the total number of cases in Africa in 2018, and the percentage caused by infectious agents. [Color figure can be viewed at wileyonlinelibrary.com]

uniquely in Africa, under the assumption that a given infectious agent will impose the same relative risk on infected individuals worldwide (ignoring possible differences in the virulence of different strains, cofactors and genetic susceptibility).

For some of the associations, especially in relation to HPV and anogenital cancers, the estimate of PAF was based upon the proportion of tumors in which the virus (as viral DNA) could be detected. The reason is mainly that prevalence of infection in the same tissues of normal individuals is usually unknown. This may overestimate AFs by including some cancer cases in which the presence of the virus was coincidental, without, for example, expressing viral oncoproteins. The estimate of HPV attributable cancers of the oral cavity and pharynx, on the other hand, makes use of data from studies of prevalence of viral oncoproteins E6 and E7 mRNA (or other markers of viral oncogenesis) in cancer cases, so that resulting AFs (4% for oral cancer, 30% for oropharynx) are rather lower than the percentage of tumors with detectable HPV DNA.

The estimated PAF of 28.7% for SSA in 2018 is a little lower than the estimate of 31.3% by Plummer *et al.*[4] for 2012, or 32.7% by de Martel *et al.*[3] for 2008. Some of the discrepancy may be the result of methodological differences, although it is just as likely to be due to a decrease in the estimated numbers of some important infection-related cancers between 2012 and 2018 (KS and liver cancer), and, just as important, a decline in the proportion of cancers that are infection-related due to the rapidly increasing numbers (and resulting proportions) of breast and prostate cancers in Africa. Some 20,000 nonmelanoma skin cancers (2.6% of the total number) are also included in the "all cancer" total for 2018. Thus, although the numbers (and rates) of cervix cancer have increased since 2012,[23] its proportionate share of the cancer total in SSA has declined (from 14.9% to 14.5% of all cancers). The actual number of infection-related cancers in SSA is showing a progressive increase (180,000 in 2008,[3] 200,000 in 2012,[4] 221,000 in 2018).

Our estimate of infection-attributable cancer is probably a conservative one. We included only infections for which the evidence of carcinogenicity is deemed to be sufficient by IARC.[13] Several other associations between infections and human cancers, for which there is evidence for causality, have not been taken into account. For example, EBV has been associated with cancers of the head and neck other than NPC,[24] and a link between infection with HBV and B-cell NHL has also been observed in many studies.[25]

In any case, no case of cancer has been attributed to more than one infectious agent, so that where more than one agent is involved, the cancer cases are attributed to only one of them. This particularly concerns HIV, infection with which is known to increase the risk of many cancer types; the IARC monograph[13] states that "HIV causes cancer of the cervix, anus and conjunctiva, and Kaposi sarcoma non-Hodgkin lymphoma and Hodgkin lymphoma. Also, a positive association has been observed between infection with HIV-1 and cancer of the vulva and vagina, penis, and hepatocellular carcinoma, and non-melanoma skin cancer". The increased risk is, however, indirect, through enhancing the effect other infectious agents *via* immunosuppression. Accordingly, where the infectious agent is known, the infection-attributable component of these cancers has been allocated to it (HPV, HBV/HCV/EBV and KSHV). Only cancers for which there is lack of certainty

about the responsible infection (SCC of conjunctiva, some NHL cases) have been allocated to HIV.

The PAF is a measure that provides an indication of the proportion of a particular cancer that would be avoided if the responsible agent were eliminated (or the human organism was no longer susceptible to it). Effective vaccines are now available for Hepatitis B, and for the major oncogenic papillomaviruses.

Vaccination against HBV has been available since the 1980s, and its effectiveness in reducing the risk of liver cancer in the generations born since vaccination was introduced (1984) has been demonstrated in Taiwan.[26] WHO estimates that Hepatitis B (HepB3) immunization coverage among 1-year-old in the African region (broadly equivalent to SSA) was 72% in 2017.[27] No vaccine against HCV is currently available, and, although treatment of HCV infection with antiviral agents is effective in preventing sequelae (including cancer)[28] it is very expensive, and not a feasible option for prevention in low and middle-income settings. For the moment, prevention must rely on avoiding infection through blood safety programs and universal precautions in healthcare settings.

Vaccination against oncogenic HPV has been shown to be safe and effective in reducing the prevalence/incidence of vaccine-related HPV types and of precancerous cervical lesions in countries where vaccination has been introduced.[29] Introduction of vaccination is more challenging—leaving aside cost considerations, the introduction of vaccination programs has been restricted by the difficulty of reaching the target population of adolescent girls and cultural challenges.[30] Implementation has so far been gradual, although several African countries are moving ahead with national programs.[31] A reduction in incidence of invasive cancer will only occur many years after the introduction of vaccination, because of the long latency period between chronic infection with HPV and onset of malignancy.[32] A more rapid effect can be achieved through population-based screening for cervix cancer and precursor lesions, which has been highly effective in reducing incidence of the disease in high and middle-income countries, where such programs have been implemented.[33] The oldest approach to screening was the use of cytological screening (the Pap test) which, although effective in greatly reducing occurrence of invasive cancer, requires a complex infrastructure to assure regular testing, high-quality cytology, follow-up pathology and treatment. The difficulties of implementation in low-income settings have led to the introduction of simpler, low technology approaches (visual inspection with acetic acid or Lugol's iodine, and see-and-treat protocols). Although the effectiveness of this approach in demonstration projects (or carefully controlled field trials) has been shown, the methods are difficult to implement (and quality control) in large-scale (e.g., national) programs.[34] Future effective screening is more appropriately based on HPV testing of self-collected samples, followed by diagnosis and treatment of detected precancer in women with established chronic HPV infection.[35]

Prevention programs for HIV have focused on avoiding infection, and on prevention of clinical manifestations of AIDS through treatment of infected individuals with antiretroviral therapies (ART). This has been successful in reducing population prevalence of HIV and deaths from HIV-AIDS in Africa.[36] The incidence of AIDS-defining cancers (KS, and, to a lesser extent, NHL) were greatly reduced among persons infected with HIV in the USA following the introduction of ARTs in the early 1990s while other cancers, whose risk is increased by HIV infection (e.g., anal, liver, prostate and lung cancers and Hodgkin lymphoma), have become more common as the numbers of individuals surviving with HIV infection has increased, due to their prolonged survival on ART.[37] The introduction of ART has resulted in a decline in HIV related cancers (KS, NHL, squamous cell conjunctival cancers) in Africa.[38,39]

Eradication of *H. pylori* is possible by combinations of antibiotic treatment.[40] Meta-analyses of various trials and observational studies have shown that eradication of *H. pylori* can decrease the risk of gastric cancer by more than half.[41,42] However, the cost-effectiveness of implementing an effective program for screening and treatment of *H. pylori*, taking into consideration, the other health priorities in low-income countries seems questionable. The challenge of producing a satisfactory vaccine may provide a more acceptable long-term solution.

The focus of schistosomiasis control has shifted over the years from attempts to control the vector (*Bulinus* spp. snails) to preventive chemotherapy by delivery of praziquantel *via* mass drug administration to those shown to be, or presumed to be, at risk of infection and disease. The wider availability of praziquantel at affordable prices has resulted in progress towards Schistosomiasis control in many countries, although progress is uneven. In some countries, there are real prospects for transition from control into interruption of transmission and ultimately elimination,[43] while some authors predict increasing incidence rates of schistosomiasis for the future due to climate change effects, with rising temperature fostering the spread of the parasites.[44]

Conclusions

Cancer prevention is now increasingly seen within the context of control of noncommunicable disease (NCD) for which, on a global basis, the focus for NCD prevention is on tobacco control, promoting healthy diet, physical activity and reducing the harmful use of alcohol (as well as, more modishly, environmental air pollution).[45] Danaei *et al.*[46] in estimating the contribution of nine behavioral and environmental risk factors to the global cancer burden did not include infections nor, as noted earlier, is infection among the causes of disease (including cancer) for which quantified estimates are published by the Global Burden of Diseases group.[5] This omission may skew perceptions of the relative importance of different preventive interventions in cancer control programs for the countries of Africa. A review of National Cancer Control strategies found that 154 (98%) of 157 countries mention the four major risk factors for NCDs (tobacco, alcohol, physical inactivity and obesity), while cancer prevention through immunization against the HBV and HPV was only mentioned in 90 (57%)

of 157 countries and 106 (67%) of 158 countries, respectively.[47] Although tobacco smoking is undoubtedly the biggest cause of cancer globally,[48] this is surely not the case in Africa, where lung cancer (its principal manifestation) accounted for only 3.7% of new cancer cases in 2018.[6] Ezzati *et al.*[49] estimated that 7.7% of cancer deaths in Africa in 2000 were due to tobacco use, while alcohol consumption was estimated to be responsible for 4.8%[50] and overweight and obesity for 1.2% of cancers in 2012.[51]

Our results confirm that infections with a limited number of agents are by far the most important cause of cancer in Africa, and highlight the relative importance of specific infectious agents, and their contributions to the cancer burden by sex and region within Africa. Seeing the great achievements in global vaccination coverage[52] and thus reduction of childhood diseases and deaths clearly calls for action to prevent infectious-agents related cancers as well. With local information on prevalence of exposure to these infections, similar estimates may be made for individual countries, and allow appropriate recognition of the importance of preventive interventions in cancer control plans.

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APPENDIX 1: THE REGIONS OF AFRICA.

Source: United Nations, Department of Economic and Social Affairs, Population Division. World population prospects: the 2017 revision 2017.7

Sub-Saharan Africa	**Southern Africa**	**Northern Africa**
Eastern Africa	Botswana	Algeria
Burundi	Eswatini	Egypt
Comoros	Lesotho	Libya
Djibouti	Namibia	Morocco
Eritrea	South Africa	Sudan
Ethiopia	**Western Africa**	Tunisia
Kenya	Benin	Western Sahara
Madagascar	Burkina Faso	
Malawi	Cabo Verde	
Mauritius	Côte d'Ivoire	
Mozambique	Gambia	
Réunion	Ghana	
Rwanda	Guinea	
Seychelles	Guinea-Bissau	
Somalia	Liberia	
South Sudan	Mali	
Uganda	Mauritania	
United Republic of Tanzania	Niger	
Zambia	Nigeria	
Zimbabwe	Senegal	
Middle Africa	Sierra Leone	
Angola	Togo	

(Continues)

Continued
Cameroon
Central African Republic
Chad
Congo
Democratic Republic of the Congo
Equatorial Guinea
Gabon
Sao Tome and Principe

APPENDIX 2: SELECTION OF RELATIVE RISKS AND EXPOSURE PREVALENCE OF CANCER-CAUSING INFECTIONS

HPV

HPV is considered to be a "necessary cause" of *cervical cancer*[53] so that all cases of these cancers are attributable to the respective infectious agent (PAF = 100%).

For other sites associated with HPV, RRs were not used. The detection of high-risk HPV DNA in cancer cells is considered to constitute sufficient evidence for causal association between the virus and the arising cancer. Consequently, we used approximate estimates of the proportions of cancer cases infected with HPV, as in previous estimations.[2–4]

Anal cancers

Only squamous cell carcinomas (SCCs) are related to infection with HPV.[13] The proportion of invasive SCCs in which HPVs are detected has been described by many studies. A large meta-analysis by de Vuyst *et al.*[54] found 84% of anal cancers positive for HPV, while in a study of 496 cancers from 24 countries, Alemany *et al.*[55] detected HPV DNA in 88%. More recent studies using sensitive assays and/or wider HPV genotype ranges detected HPV DNA in 90–95% of tumors.[56–58] Prevalence in females is generally higher than in males, sometimes significantly so.[54,57] We assume a PAF of 90% in women, 80% in men (Table 1).

The association between HPV and *cancers of the vulva* is age dependent; carcinomas of the basaloid and warty subtypes, found in younger patients are more often HPV positive than keratinizing squamous carcinomas typically found in older patients.[59] For the age group 15–54, we applied a PAF of 48%, for the age group 55–64, 28% and in patients older than 65 years old, 15%.[4,60]

For *vaginal cancer*, as for several other anogenital cancer sites, HPV 16 is by far the most frequent subtype found in cancer tissue. De Vuyst *et al.*[54] reviewed the seropositivity of HPV in a large meta-analysis of case series (none from Africa) and documented 70% positivity in vaginal carcinomas. Alemany *et al.*[61] found HPV DNA in 74% of 408 vaginal cancer specimens (19 from Africa). Based on these two studies, we assume a PAF of 72%.

Backes *et al.*[62] reviewed prevalence of HPV in invasive *penile cancer* in 30 studies including more than 1,200 SCC cases, but none from the African continent. They observed pooled HP prevalence of almost 47.9%. Another multinational meta-analysis with more than 1,400 penile carcinomas found a similar global prevalence in cases of 47%.[63] On the other hand, Alemany *et al.*[64] detected HPV DNA in 33% of 1,010 penile cancer specimens from around the world (just 19 from Africa). Based on those figures, we assume a PAF of 40%.

Three subtypes of *cancers of the head and neck* have been related to HPV: oropharyngeal and laryngeal squamous cell cancer and squamous cell carcinoma of the oral cavity. The generally accepted method to attribute head and neck squamous cell cancer case to HPV is the combined detection of HPV DNA and viral oncoproteins E6 and E7 mRNA in cancer tissue.

Geographic differences in HPV prevalence is evident in multinational analyses. Studying 800 patients in the USA, Europe and Brazil, HPV-16-positivity varied between 60% (USA) and 4% (Brazil) in OPC, and the range of prevalence was similarly diverse for other head and neck cancers.[65] Ndiaye *et al.*[66] in a meta-analysis of 148 studies, contributing data for 12,163 cases of head and neck squamous cell carcinoma from 44 countries estimated attributable fractions, based on the presence of E6/E7 mRNA and HPV DNA positivity of sixteen·3% for oral cavity, thirty-nine·8% for oropharynx and eight·6% for larynx. Castellsague *et al.*[67] examining DNA presence in 3,680 specimens of these three cancers (202 from Africa) estimated HPV attributable fractions based on positivity for HPV-DNA, and for either HPV E6*I mRNA or p16(INK4a), of 22.4, 4.4 and 3.5% for cancers of the oropharynx, oral cavity and larynx, respectively, but again with considerable geographic variability.

In keeping with previous estimations of infection-associated cancer burden and in view of shortage of African-specific data, we assumed the PAF of 30% for oropharyngeal cancer and 4% for laryngeal cancer and carcinoma of the oral cavity.[4,66]

Helicobacter pylori

Two cancers are related to infection with HP: gastric carcinoma and primary gastric lymphoma (PGL). In Africa, only non-Cardia Gastric cancer (NCGC) shows a causal relation

with *Helicobacter pylori* infection, whereas, in Asia, where incidence rates for gastric cancer, in general, are very high, HP-associated malignancies are also described in the cardia.

Reliable estimates of HP prevalence in the general population are relatively scarce for Africa. Two large multinational systematic reviews observed the geographic distribution of HP in settings that are reflective of the general population and included more than 10 African studies in each.[68,69] We extracted the published national data and calculated pooled prevalences for SSA and NA; the average of the two studies was 70% for SSA 51% for NA.

One crucial problem about estimating the risk of *NCGC* with HP infection is the fact that bacterium tends to disappear during the cancer progression process. Studying prevalence of HP in cancer cases, therefore, leads to a severe underestimation of the carcinogenicity of the bacterium; it is necessary to use prospective studies, where the presence of HP can be assessed by sensitive methods, before the onset of the process (gastric atrophy) terminating in invasive cancer. Early detection methods used for HP infection, for example, determination of Anti-HP-antibodies *via* ELISA, are of low sensitivity and lead to underestimation of relative risks. The gold standard is an assessment of HP *via* immunoblot. In recent studies and meta-analyses that consider immunoblot-based data *vs*. ELISA-based data, higher HP prevalence in cases can be observed and the increase in risk is estimated to be 17-fold (95% CI: 11.6–25.0).[70]

Numerous studies have found increased antibody titers to HP in *gastric lymphoma* tissue, both in low-grade Mucosa-associated lymphoid tissue (MALT) and, to a lesser extent, in high-grade diffuse large B-cell lymphoma (DLBCL). In a complex interplay of genetic and endocrine factors, *Helicobacter pylori* strains appear competent to transform normal B-cells into malignant clones, leading to gastric lymphoma.[71] With a RR of 7.2[4] and estimated HP prevalence as above, the PAF is 81% in SSA and 76% in NA.

Hepatitis B and C

A large number of meta-analyses have been published over the last decades based on published case–control and cohort studies that examined the effect of HBV and HCV mono-infection and coinfection on the development of HCC. We use the relative risks from the meta-analysis of Cho *et al.*[72] that included around 60 case–control studies from many countries, examining HBsAg/HBeAg/HBV DNA and anti-HCV/HCV RNA serological markers in both HCC cases and healthy controls. RR for HBV was estimated at 23.4 (95% CI 17.2–31.7) and for HCV at 27.6 (95% CI 19.8–38.4).[21,72]

Recently, the Polaris Observatory Collaborators published data on prevalence of HBsAg on the basis of literature reviews, modeled with a Delphi process including experts interviews, in order to take in consideration dynamics and changes over time as well as differences at a country-level.[73] The same working group published HCV prevalence data using a similar model. They addressed changes in population due to aging, treatment and outcome. Data from more than 100 countries were considered and regional prevalence rates were applied to countries with lack of sufficient data.[74]

We used these modeled prevalence estimates for HBV and HCV to obtain regional estimates of infection prevalence (Table 3). With the aforementioned relative risks, the PAFs for HCC are 64% for HBV in SSA and 23% for HCV. For NA, the PAFs of HCC are 23% for HBV and 49% for HCV.

The IARC[13] review evaluated the association between HCV infection and risk of NHL as causal. In an analysis of seven studies from the International Lymphoma Epidemiology Consortium (InterLymph) based in Europe, North America and Australia, de Sanjose *et al.*[75] observed a relative risk of 1.78 (1.40–2.25) for all NHL. In a review of available studies and meta-analyses published up to 2015, Fiorino *et al.*[76] confirmed the association between HCV infection and B-lymphocyte NHLs with odds ratios ranging between 2 and 3 on average. Assuming a modest RR of 2, and the regional prevalences of HCV infection reported by Blach *et al.*[74] (Table 3), the PAF is 0.9% for SSA and 3.5% for NA.

EBV

EBV is causally related to NPCs, Hodgkin lymphoma and Burkitt lymphoma. IARC[13] notes that "in the case of gastric carcinoma, there is insufficient epidemiological evidence for the involvement of EBV. However, the fact that the EBV genome is present in the tumor cell in monoclonal form, and that the transforming EBV proteins are expressed in the tumor cell provides a mechanistic explanation of how EBV might cause a proportion of gastric cancer".

NPC can be subdivided into three histological types: keratinizing squamous cell carcinoma (Type I); and non-keratinizing carcinoma, that is classified either as differentiated (Type II) or undifferentiated (Type III). In low-incidence areas, Type I NPC is predominant, whereas Type III NPC comprises over 95% of NPC in high-incidence areas, and Type II NPC represents almost the whole of the remaining 5%.[77] The link with EBV is closest for undifferentiated NPC.[78] We estimated the PAF 100% for NA as an area of intermediate incidence and 80% for SSA as an area of low incidence.[4]

The presence of EBV genome in specimens of *Hodgkin lymphoma* has been shown to vary according to cell type, age, sex and geographic region[79–81] with higher prevalences in children, males, and tumors of mixed cellularity subtype. Previous estimates of PAFs have therefore attempted to allow for age (and region), manoeuvres that result in PAFs for Africa of 50–74%.[2,4] However, a large meta-analysis of 119 studies (seven from Africa) by Lee *et al.*[82] found that "the prevalence of EBV-positive classic HL was more than 70% in pediatric patients from Africa, …, and in adult patients from Africa". The "classical" subtypes of HL exclude cases of the nodular lymphocyte-predominant subtype (NLPHL). Although NLPHL may account for 10% of HL internationally,[83] in the African cancer registries contributing to Globocan 2018, NLPHL accounted for only 1% of HL in SSA and 3% in NA. For

the purposes of estimation, therefore, we simply assume a PAF of 75% for HL.

We assume that childhood *BL* in tropical Africa (Western, Middle, Eastern Africa) is of the endemic type (e-BL) with 100% EBV positivity, while elsewhere, and among adolescents and adults, cases are of the sporadic type, with some 30% EBV associated.[13]

Although there are few (if any) studies from Africa, large international studies identify EBV DNA in some 8–10% of *gastric carcinomas*; the virus is monoclonal and absent from normal epithelium.[84] It appears that prevalence is higher in males than in females;[85,86] we assume PAFs of 11% in males, 5% in females.

HIV

We estimate the fraction of two cancers attributable to infection with HIV, which have not been attributed to infection with any of the infectious agents above (HPV, KSHV, EBV and HBV/HCV). They are non-Hodgkin lymphomas (NHL) and squamous cell carcinomas of conjunctiva (SCCC).

Before the availability of HAART, studies in developed countries, such as the USA, showed relative risks NHL of 10- to 160-fold in HIV positive, compared to negative subjects.[87,88] In Africa the relative risk of NHL associated with HIV tends to be an order of magnitude lower, and ranges from 3.8 in Uganda[89] to 12.9 in Rwanda[90] but lack of diagnostic resources and competitive risks from other AIDS-associated diseases may be responsible for the diverging findings.[91–95] For the purpose of estimation, relative risks of 5 for SSA and 50 for NA were used to calculate the PAFs for NHL.

There is consistent and significant evidence of increased occurrence of conjunctival squamous-cell carcinoma in HIV-1 infection, with relative risks in studies conducted in SSA in the range 4–15.[13,96,97] We assume a relative risk of 10.[13]

Data on the prevalence of HIV-AIDS in adults age 15–19 in the countries of Africa in 2017 were obtained from UNAIDS[98] as Eastern and Southern Africa: 5.2% in males, 8.4% in females; Western and Middle Africa: 1.6% in males, 2.3% in females; NA <0.01%).

Schistosomiasis

The IARC monograph on human carcinogens classifies the parasite *S. haematobium* as group 1 carcinogen, referring to eight case–control studies, of which seven showed strong association between the infection with *S. haematobium* and the risk of urinary bladder cancer.[13] With quite varied definitions of exposure, the relative risks ranged from 2 to 15;[99] we assume a relative risk of 5.

Accurate and up-to-date data on country-specific prevalence of infection with *S. haematobium*, especially from SSA, are scarce. The most recently published are for 2003,[16] suggesting prevalences between 33% in West Africa and 11% in Southern Africa—with rather little change since the estimates 10 years earlier.[100]

HTLV-I

Epidemiological studies show clustering of Adult T-cell leukemia/lymphoma and HTLV-I prevalence in southern Japan, but it occurs also rather frequently in other regions of the world, among them West and Central Africa and the Caribbean.[101–104] A systematic review of studies in 25 African countries found the average seroprevalence of HTLV-1 in NA to be 0%, 1.2% in Eastern and Southern Africa and 3.2% in Western and Central Africa.[17]

ATLL occurs in older adults in Japan, and is very rare under the age of 40, but seems to be more common among younger individual elsewhere. In a review of the incidence of ATLL among carriers of HTLV-1 in Japan, Iwanaga *et al.*[105] found the rate to be about 60 per 100,000, 1.35 times higher in males than females. In the Caribbean, where most of the cases present as lymphomas, incidence in carriers is lower: Cleghorn *et al.*[106] estimated it as 15 per 100,000 adults aged 40+ and Murphy *et al.*[107] as 35 per 10^5 in men and 15 per 10^5 in women (aged 40+). We assume an annual incidence of ATLL among adult (40+) carriers of HTLV-1 in Africa of 40 per 10^5 in males and 25 per 10^5 in females.

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The burden of squamous cell carcinoma of the conjunctiva in Africa

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ABSTRACT

Squamous cell carcinoma of the conjunctiva (SCCC) is a relatively common cancer in Africa, although its precise incidence and geographic distribution have not been previously systematically studied.

Methods: Using the methods employed to produce national estimates of cancer incidence for the "Globocan" series of the International Agency for Research on Cancer, along with detailed information on cancer incidence by histological subtype from cancer registries in Africa, we estimate the numbers and rates of incidence by sex, age group, country and region of Africa.

Results: We estimate that the number of new cases occurring in 2018 to be about 6 200, with all but about 50 in sub Saharan Africa, and 55% in females.

On a national basis, the geographic distribution of incidence rates resembles that of the prevalence of infection with HIV, with a strong correlation between them, especially in males.

Conclusions: We estimate that about one third of the total cases of SCCC occurring in Africa are HIV-related.

1. Background

Squamous cell carcinoma of the conjunctiva (SCCC) is relatively common in populations in sub-Saharan Africa [1]. The observation of relatively high incidence rates in tropical Africa was made 50 years ago [2] and led to investigation of possible aetiological factors. With the high occurrence in equatorial regions, an association with exposure to UV irradiation was suspected and has been confirmed at ecological [3,4] and (less certainly) individual level [5]. More striking, however, is the clear association with infection with HIV-AIDS. The evidence has been reviewed by the International Agency for Research on Cancer (IARC), who note the consistent marked increase in risk in persons infected with HIV-1, with a relative risk of about 10 [6]. The onset of the epidemic of HIV-AIDS was accompanied by a marked increase in incidence of this cancer [7,8].

In this report, we estimate the incidence (number of cases, and rates) of SCCC occurring in Africa in 2018, and the likely fraction attributable to HIV-AIDS.

2. Methods

We used the sources of information and methods employed to make national estimates of incidence for Globocan 2018 [9]. Since cancers of the eye, let alone subtypes such as SCCC are not reported in Globocan, we used the original sources used in the estimations to abstract information on SCCC. The sources were the cancer registries of Africa, listed in Annex A of Ferlay et al (Cancer incidence and mortality data: sources and methods by country GLOBOCAN2018_Annex_A.xlsx available at http://gco.iarc.fr).

From these datasets, we abstracted information on cases SCCC, by age and sex, defined by the codes of the International Classification for Oncology (3rd revision [10]) as follows:

Topography 69.0 (conjunctiva) plus Morphology 8000 – 8084

Topography 69.9 (Eye, unspecified) plus Morphology 8050 – 8084

In other words, including conjunctival cancers of unspecified cell type (cancer, carcinoma), and all squamous cell carcinomas of the eye. Malignant tumours of the eyelid are excluded.

Incidence rates were calculated for recent periods, for males and females, for 5 broad age groups (0–14,15-34,35–54,55-74,75+), and the age standardised incidence rates obtained (using the world standard

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Table 1
Estimated age standardised incidence sates and numbers of SCCC cases in 2018, by sex and region.

REGION	Males			Females		
	ASR (per 10^5)	Number	HIV-related	ASR (per 10^5)	Number	HIV-related
Middle Africa	0.35	162	20	0.58	270	46
Eastern Africa	1.25	1928	615	1.31	2225	958
Southern Africa	1.16	349	111	1.37	477	205
Western Africa	0.22	306	39	0.27	395	68
Sub-Saharan Africa	0.73	2745	785	0.83	3367	1277
Northern Africa	0.04	42	0	0.01	9	0
Africa	0.57	2787	785	0.64	3376	1277

population [11]. The national estimates were based on data from one or more cancer registries in the same country, as for Globocan 2018 [9]. Registry data collected by the African Cancer Registry Network (AFCRN) were available for 26 of the 48 countries of sub-Saharan Africa, and 5 of the 6 countries of Northern Africa (countries with populations < 150 000 were excluded from the analysis). For those countries for which no data were available, average incidence rates from selected neighbouring countries in the same region were used (*method 9*, [9]).

Data on the prevalence of HIV-AIDS in adults age 15–19 in the countries of Africa in 2017 were obtained from UNAIDS (http://www.unaids.org/en/regionscountries/countries)

3. Results

Table 1 shows the estimated incidence rates and numbers of cases by region of Africa. There was a total 6 163 cases, all but 51 in sub-Saharan Africa, and 55% in females. The highest rates are observed in Eastern and Southern Africa, while the incidence in North Africa is extremely low. In sub-Saharan Africa, incidence is slightly higher in females than in males.

Fig. 1a shows the incidence rates, per 100 000, by broad age group in sub-Saharan Africa, and North Africa, and Fig. 1b, the estimated numbers of cases, by age group, in SSA. In sub- Saharan Africa, the maximum incidence rate and number of cases is in age group 35-54. There is a female predominance of cases in all age groups (except childhood – 0–14).

Fig. 2 shows a map of Africa, with the estimated incidence rates by country for both sexes combined. The highest incidence rates are in Botswana (ASR 3.4 per 10^5 in males, 3.9 per 10^5 in females), Namibia (4.0 & 2.9), Malawi (2.4 & 4.2), Mozambique (3.0 & 3.6), Zambia (2.7 & 2.5) Zimbabwe (2.6 & 2.5) and e-Swatini (3.2 & 0.9).

These are all countries with a high prevalence of HIV-AIDS. Fig. 3 shows the incidence of SCCC in those countries (26) of sub-Saharan Africa for which the national estimate was based on local data from one or more cancer registries, in relation to prevalence of HIV in adults, in males and females. There is a remarkably good correlation in males (Pearson's r = 0.83), less strong in females (r = 0.60), the latter due to some very high HIV prevalence figures for small countries, for which the estimates of incidence of SCCC are relatively uncertain.

Assuming a relative risk of 10 [6] and the prevalence of HIV among adults published by UNAIDS (Eastern & Southern Africa: 5.2% in males, 8.4% in females; Western and Middle Africa: 1.6% in males, 2.3% in females; Northern Africa < 0.01%), we may estimate that about 2 000 cases of SCCC (about one third of the total) were caused by HIV infection in 2018 (Table 1).

4. Discussion

We used cancer registry data from Africa to derive estimates of the numbers of cases of SCCC occurring in 2018, using the methods developed for 36 other cancer types in Globocan 2018. Although population based cancer registration has been slowly expanding in extent and quality in recent years, with some 30 registries in sub-Saharan Africa meeting criteria rendering them suitable to contribute to the national estimates of Globocan (http://afcrn.org/index.php/membership/membership-list), the data they produce are not perfect. Most score between 4 and 7 on the quality ("q") factor used to produce uncertainty estimates in Globocan, and only 6 of the countries of Africa have registries that aim to cover the entire population – usually only a

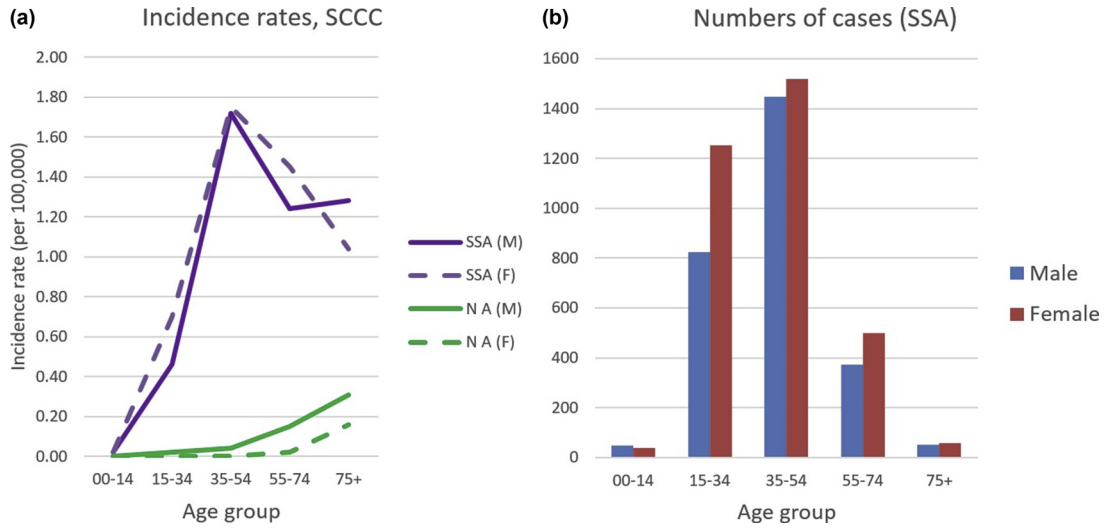

Fig. 1. (a) Incidence rates of SCCC, by age group and sex in sub Saharan Africa (SSA) and North Africa (NA). (b) Numbers of cases of SCCC, by age group and sex, in sub Saharan Africa.

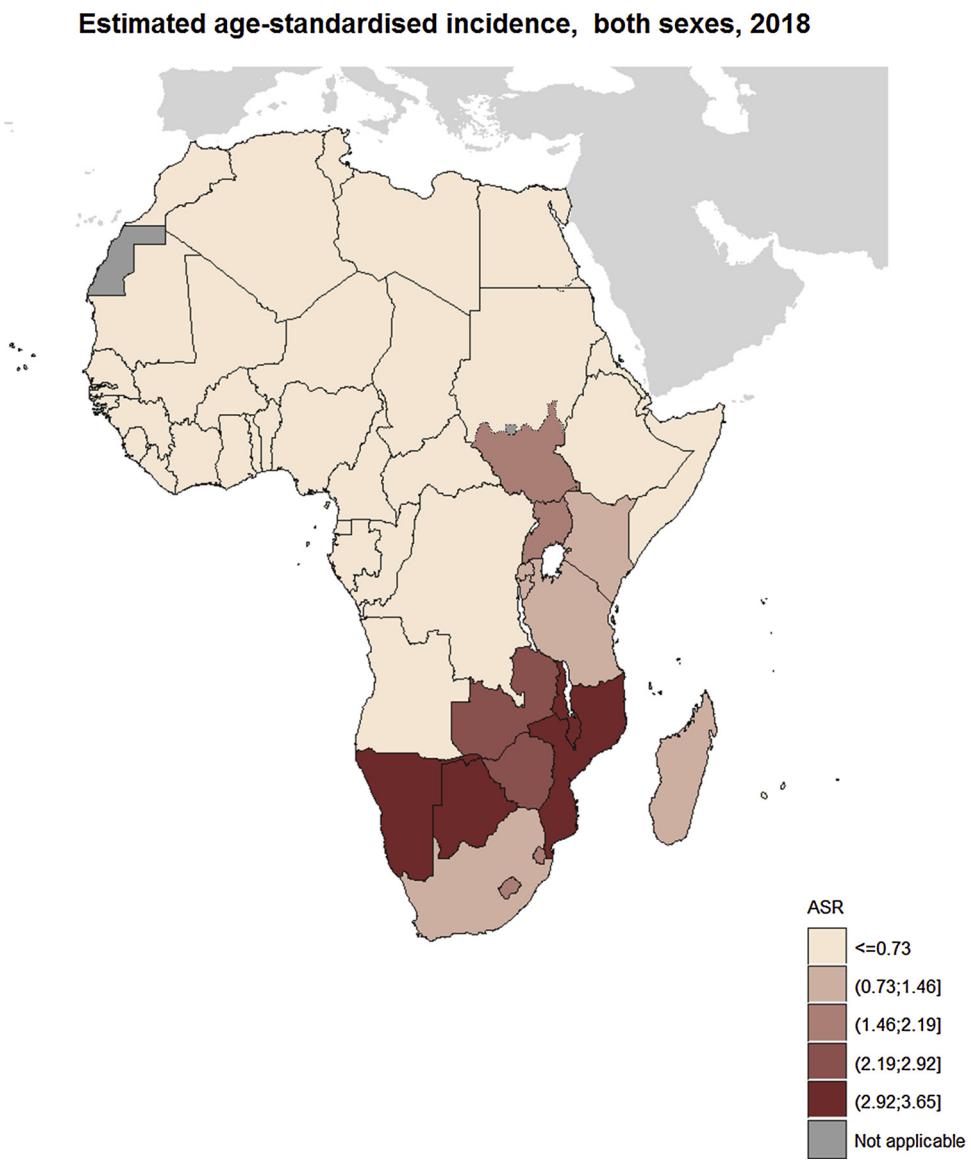

Fig. 2. Age standardised incidence rates, squamous cell carcinoma of conjunctiva – both sexes; by country.

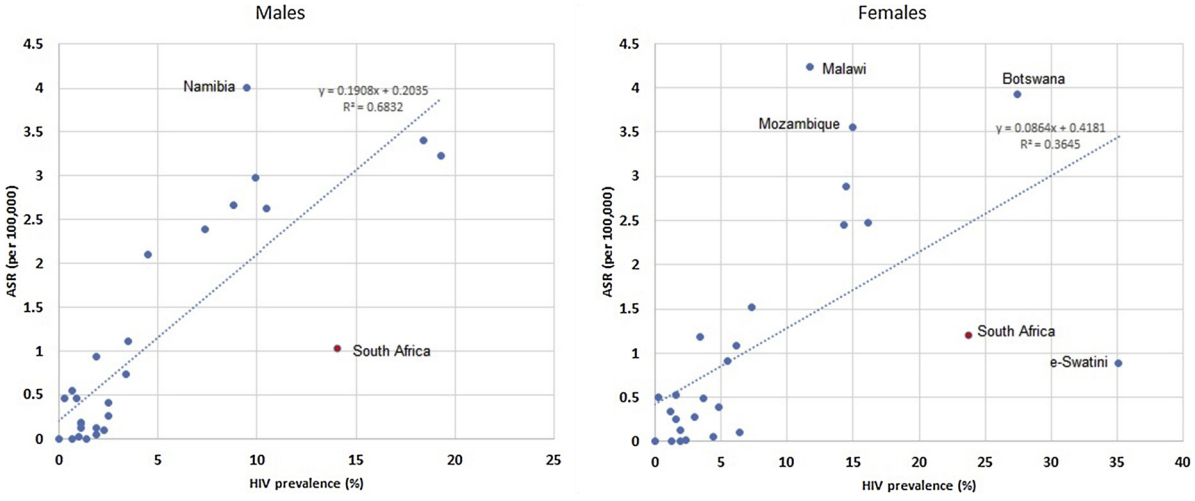

Fig. 3. Estimated incidence of SCCC in relation to prevalence of HIV in adults in 2017.

sample of 5–10% is involved. On the positive side, SCCC is not a difficult cancer to diagnose, being visible and simple to biopsy, and case ascertainment is likely to be much better than for internal tumours. We believe the estimates in this report are the best that can be made, with data currently available.

The observations confirm what has long been suspected concerning the geographic distribution of SCCC, and illustrate how this is largely mediated by the local prevalence of HIV-AIDS. Suspicion has fallen upon the human papilloma viruses (HPV) as the carcinogenic agents whose action is enhanced by immunosuppression (by HIV), primarily because HPV has been identified in tumour specimens from several case series, and also in case control studies [12,13]. In a meta-analysis Carreira et al [14] concluded that only the cutaneous subtypes of HPV seem to be a risk factor (with a relative risk of ˜3); they also confirmed the increase in risk due to HIV (relative risk ˜ 8).

In the present study, we did not examine the relationship between incidence and UV exposure, partly because it would be very difficult to adjust adequately for HIV, and partly because of the limited range of latitude in Africa (if this is to be used as a proxy for UV exposure). As noted above, UV exposure (including occupational exposures) has been identified as a risk factor for SCCC both on an ecological and individual level. Other risk factors include ocular pigmentation (pterygia and pingueculae) and smoking [1,15].

Availability of data and materials

The analysed data were abstracted from the AFCRN Database, which is hosted by the International Agency for Research on Cancer (IARC), under the terms of an agreement by which the confidentiality of data will be maintained.

Funding

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Authors’ contributions

Lucia Hämmerl: played an important role in interpreting the results and responsible for the preparation of the first draft of the article.

Jacques Ferlay: responsible for the analysis of data.

Margaret Borok: has contributed to the discussion of the results.

Carla Carrilho: has contributed to the discussion of the results.

Donald Maxwell Parkin: has designed the study and helped drafting of the article for publication in a scientific journal.

Ethical approval

The study used data from the African Cancer Registry Network database which included no personal identifiers; permission for access was granted by the Research Committee of AFCRN, and approval obtained from the registries whose data were used. The research was performed in accordance with the Declaration of Helsinki.

Data availability statement

The data that support the findings of this study are available from the African Cancer Registry Network (AFCRN). Restrictions apply to the availability of these data, which were used with permission for this study. Data, hosted by the International Agency for Reserach on Cancer (IARC), are available from AFCRN www.afcrn.org with the permission of the Research Committee of AFCRN, and approval obtained from the registries whose data were used.

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Infectious Agents and Cancer

RESEARCH ARTICLE Open Access

The burden of Burkitt lymphoma in Africa

Lucia Hämmerl[1], Murielle Colombet[2], Rosemary Rochford[3], David Martin Ogwang[4] and Donald Maxwell Parkin[5,6*]

Abstract

Background: Burkitt lymphoma (BL) is a relatively common cancer of childhood in tropical Africa, although its precise incidence and continent-wide geographic distribution have not been previously systematically studied.

Methods: Using the methods employed to produce national estimates of cancer incidence for the "Globocan" series of the International Agency for Research on Cancer, along with detailed information on cancer incidence by histological subtype from cancer registries in Africa, we estimate the numbers and rates of incidence by sex, age group, country and region of Africa.

Results: We estimate that the number of new cases that occurred in 2018 to be about 3900, two thirds in males, and 81% in children aged 0–14. On a national basis, the geographic distribution of incidence rates among children in sub-Saharan Africa resembles that of the prevalence of infection with Falciparum malaria. An estimated 81% of cases are associated with infection with Epstein Barr virus (EBV).

Conclusions: BL comprises almost 50% of childhood of non-Hodgkin lymphoma in Africa, almost all of which are associated with EBV, with the geographic distribution – at least in sub Saharan Africa - mediated by infection with malaria.

Keywords: Burkitt lymphoma, Africa, Epstein Barr virus, Epidemiology, Incidence

Background

Burkitt lymphoma (BL), an aggressive B cell lymphoma first recognized as a tumour of African children, occurs throughout the world, but has a markedly different incidence in different world regions, and even within regions [1]. By far the highest incidence rates of BL are found in tropical African countries, where it may account for up to half of all childhood cancers [2], and the tumour in these regions is consequently referred to as "endemic BL." Other African countries outside the equatorial belt have much lower incidence rates, which are similar to those in high income countries. BL in these regions is consequently referred to as "sporadic BL". Immunodeficiency-associated Burkitt lymphoma is primarily associated with HIV infection [3]. Unlike endemic BL, sporadic and HIV-associated BL occur in all age groups. Although there are differences in clinical features and prognosis of the endemic, sporadic and HIV-associated BL [3, 4], the unifying characteristic in all patients with BL is the unique morphology and the chromosomal translocation involving MYC oncogene, which is present in BL irrespective of geographical location, and immunodeficiency status [5]. Another distinguishing feature of BL is the association with Epstein-Barr virus (EBV) infection. The endemic form is almost always EBV-positive while the sporadic BL tumours are less than 30% EBV-positive.

There have been no recent systematic attempt to estimate the actual magnitude of the burden of BL where it is known to occur at a relatively high rate, in Africa. In this report, we estimate the incidence (number of cases, and rates) of BL that occurred in Africa in 2018, and the likely fraction attributable to EB.

Methods

Data sources

We used the sources of information and methods employed to make national estimates of incidence for Globocan 2018 [6]. Since the subtypes of non-Hodgkin lymphoma are not reported in Globocan, we used the original sources used in the estimations, to abstract information on BL. The sources were the cancer registries of Africa, listed in Annex A of

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Table 1 Numbers and incidence rates (per 100,000 population) of Burkitt lymphoma by region and sex

REGION	MALES					FEMALES				
	Numbers		Incidence rate per 100,000			Numbers		Incidence rate per 100,000		
	0–14	TOTAL	0–14	CRUDE	ASR	0–14	TOTAL	0–14	CRUDE	ASR
Eastern Africa	1009	1191	1.09	0.51	0.38	401	487	0.44	0.22	0.19
Middle Africa	350	452	0.91	0.54	0.46	172	217	0.45	0.26	0.20
Southern Africa	13	56	0.13	0.17	0.18	5	46	0.05	0.14	0.14
Western Africa	568	719	0.67	0.37	0.29	350	451	0.43	0.24	0.21
Sub-Saharan Africa	*1940*	*2320*	*0.86*	*0.44*	*0.35*	*928*	*1201*	*0.42*	*0.23*	*0.20*
Northern Africa	233	292	0.59	0.24	0.23	74	87	0.20	0.07	0.07
Africa	2173	2612	0.82	0.41	0.33	1002	1288	0.39	0.20	0.17

Ferlay et al. (Cancer incidence and mortality data: sources and methods by country GLOBOCAN2018_Annex_A.xlsx (available at http://gco.iarc.fr)). From these datasets, we abstracted information on cases BL (ICD-O M9687/3). In addition to these registry data, we used information on the proportions of non-Hodgkin lymphomas that were Burkitt lymphoma in unpublished registry data from Yaoundé (Cameroon)[1] and Gabon,[2] from newly established national paediatric registries in Burkina Faso, Republic of Congo, and Cote d'Ivoire[3], and in published data from the Democratic Republic of Congo [7] and northern Cameroon [8].

Method of estimation

Within the NHL catgory of Globocan 2018 (C82–86, C96 - Non-Hodgkin lymphoma) we take the proportion of BL within 5 broad age group and for each sex. These proportions were applied to the estimated number of NHL cases (by sex and age) in GLOBOCAN 2018. When the Globocan estimate derived from several cancer registries, the mean of the proportions (within age-sex groups) was used.

Incidence rates were calculated for recent periods, for males and females, for 5 broad age groups, and the age standardized incidence rates obtained (using the world standard population [9]. Registry data were available for 26 of the 48 countries of sub-Saharan Africa, and 5 of the 6 countries of Northern Africa (countries with populations < 150,000 were excluded from the analysis). For those countries for which no data were available, average incidence rates from selected neighbouring countries in the same region were used to derive national incidence within the country (*method 9*, [6]).

[1]Courtesy of Prof Georges Enow-Orok
[2]Couretsy of Prof Ernest Belembaogo
[3]http://afcrn.org/index.php/activities/activities-in-2018

Results

Table 1 shows, for the 5 regions of Africa, the estimated numbers of cases and incidence rates per 100,000 population (age specific rate in children age 0–14, and crude and age standardized rate (ASR) at all ages).

The estimate is for a total of 3900 new cases of BL in Africa in 2018, with almost exactly two thirds in males (67%), and 81.4% of cases (3175) occurring in children age 0–14. This is almost half of all the estimated number (6474) of childhood cases of non-Hodgkin lymphoma. At all ages, incidence rates in sub-Saharan Africa do not show much variation by region (ASR's between 0.18 and 0.46 per 100,000 in males, 0.14–0.26 per 100,000 in females), although in North Africa, the apparent rarity of BL in adult females results in a very low estimated ASR (0.07 per 100,000). In children, the highest incidence in boys is in East and Middle (Central) Africa, and in girls, the same two regions, plus West Africa. Estimated rates of childhood BL are lowest in Southern Africa.

Figure 1 shows the incidence rates, by 5-year age group, in children and young adults (ages 0–24), pooling the data from the 35 registries contributing to the national estimates for sub Saharan Africa (857 cases in males, 538 cases in females). Incidence rates peak in the 5–9 year age group, and – in children – are higher in boys that in girls.

Figure 2 shows the distribution of estimated incidence rates of childhood BL at national level, as a map of Africa. The highest incidence rates are observed in Malawi (6.2 per 100,000), Cameroon (2.1), Uganda (1.4), Zambia (1.3) and Cote d'Ivoire (1.1). All of the countries of Southern Africa (as well as Ethiopia) have estimated rates of ≤0.17 per 100,000.

In the zone of high incidence of childhood BL in central Africa, almost all cases of endemic childhood BL are associated with EBV, as demonstrated by the presence of either EBV nuclear antigen (EBNA) or EBV DNA in the tumour cells [3]. This proportion is less in cases of sporadic and immunodeficiency associated

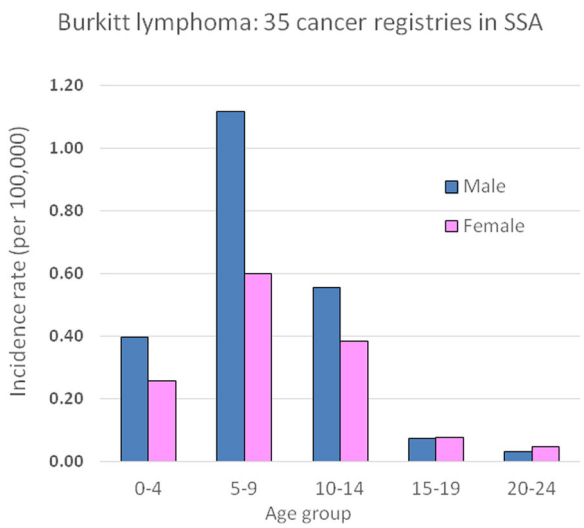

Fig. 1 Age specific incidence rates of Burkitt lymphoma (1395 cases aged 0–24 from 35 cancer registries in sub Saharan Africa)

Burkitt lymphoma [10, 11]. The peculiar distribution in sub Saharan Africa is not related to EBV exposure – which is ubiquitous, but has long been linked to the geographic occurrence on malaria, particularly where it is hyper- or holo-endemic [12]. Even today, the geographic occurrence of childhood BL bears a striking resemblance to that of endemicity of malaria due to *P. falciparum* (Fig. 3).

Assuming that childhood BL in tropical Africa (Western, Middle, Eastern Africa) is of the endemic type (e-BL) with 100% EBV, while elsewhere, and among adolescents and adults, cases are of the sporadic type, with some 30% EBV associated [14], we can estimate that EBV is a causative factor in 3165 cases of BL in Africa (81% of the continental total).

Discussion

We have used cancer registry data from Africa to derive estimates of the numbers of cases of BL occurring on the continent in 2018, using the methods developed for 36 other cancer types in Globocan 2018. Although

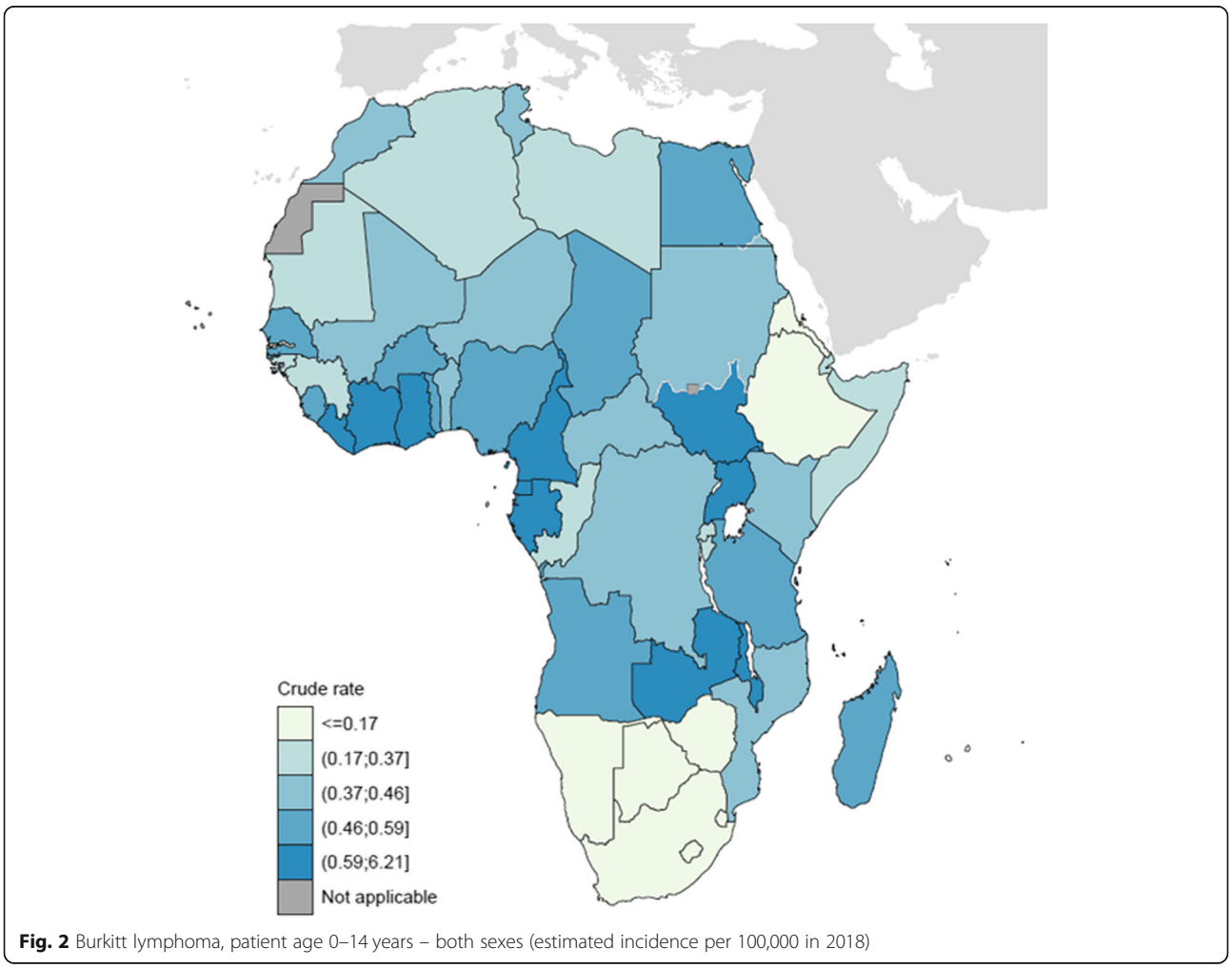

Fig. 2 Burkitt lymphoma, patient age 0–14 years – both sexes (estimated incidence per 100,000 in 2018)

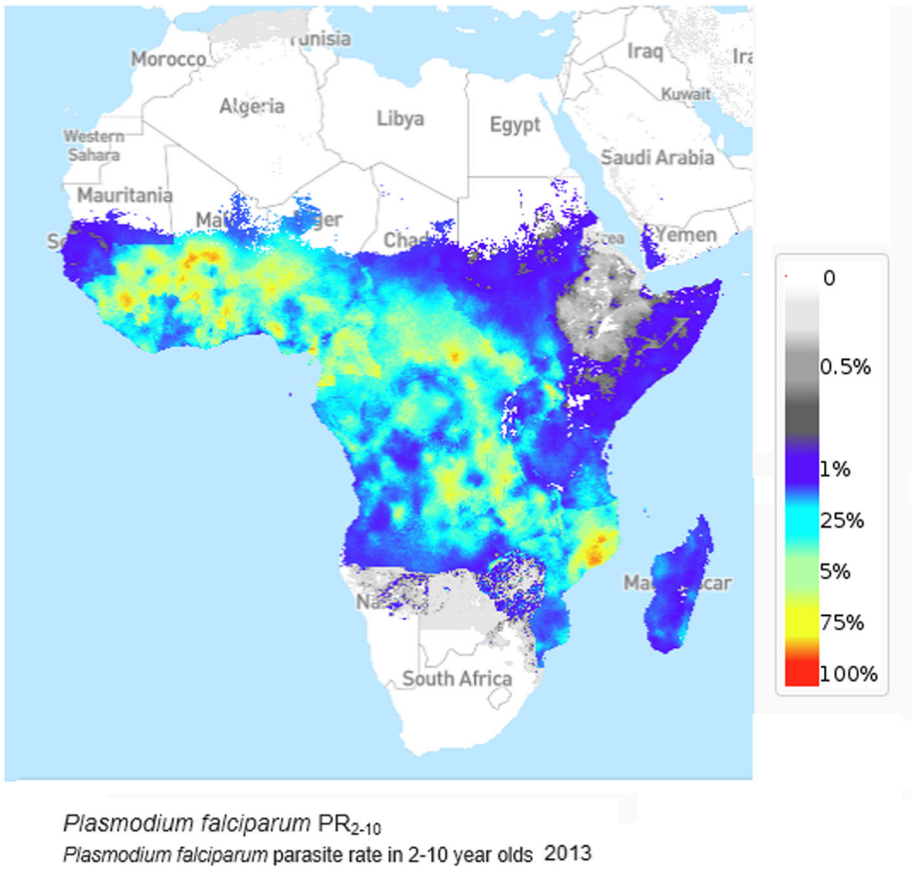

Fig. 3 *Plasmodium falciparum* parasite rate in 2–10 year olds, Africa, 2013 [13]

population based cancer registration has been slowly expanding in extent and quality in recent years, with some 30 registries in sub Saharan Africa meeting criteria rendering them suitable to contribute to the national estimates of Globocan (http://afcrn.org/index.php/membership/membership-list), the data they produce are not perfect. Most score between 4 and 7 on the quality ("q") factor used to produce uncertainty estimates in Globocan, and only 6 of the countries of Africa have registries that aim to cover the entire national population – usually only a sample of 5–10% is involved. On the positive side, BL is relatively easy to diagnose – at least in childhood - because they present as rapidly growing tumours which may affect the face with specific histological characteristics, so that case ascertainment is likely to be much better than for other tumours. Indeed, by making our estimates based on the proportions of NHL cases that are BL, we assume that relatively few of the cancers allocated to the "Lymphoma not specified" codes in ICD-O (9590/9591) will actually have been cases of BL. Most cases of BL in the registry data had been diagnosed based on histology or pathology, indeed, for most registries, all BL registrations were based on morphological verification (MV) of diagnosis. There were some important exceptions – the percentage of MV cases in the series from Ibadan (Nigeria) was 87, 71% in Blantyre (Malawi), and 65% in Kampala (Uganda).

The observations provide more extensive data to confirm earlier studies on BL incidence, indicating an excess of cases in males v females and a peak incidence of childhood BL in the 5–9 year age group. They also confirm what has long been suspected concerning the geographic distribution, and illustrates how the geography is largely mediated by the endemicity of falciparum malaria; indeed, the importance of malarial infection as a co-factor in the occurrence of BL has been demonstrated at the individual level also [15]. Previous reports have shown high rates of incidence in Malawi, Uganda, and Ibadan (Nigeria) [4, 15], Cameroon [8], northern Tanzania [16] and western Kenya [1], while the incidence rates reported from Zimbabwe and South Africa have consistently been low [17], as was the frequency of BL among NHL cases in a large clinical series (487 cases) from South Africa and Zimbabwe [18].

Our estimates of incidence are based on data actually available from Africa, almost all of which are from population based cancer registries. Most of these cover urban populations, although malaria transmission intensity is

highest in rural areas. It is therefore likely that incidence of BL is higher in rural that urban areas, and there is limited data to suggest that this is so [19]. It is thus possible that the calculated numbers of BL cases in Africa are an underestimate of the true burden of BL on the continent, although they are the best that can be made with data currently available.

It is rather surprising to note that the estimated incidence of childhood is moderately elevated in some North African countries, particularly in boys. Burkitt lymphoma has reported to be a common form of childhood NHL – especially in boys - in Egypt [20] and Algeria [21], with most cases being EBV positive, and BL was found to be a moderately common form of childhood cancer in case series from Tunisia, Sudan and Morocco [22]. The absence of holoendemic malaria suggests other pathogens or environmental factors are interacting with EBV to increase the risk for BL.

A recent study by Grande et al. [23] where both EBV+ and – BL tumours were sequenced, identified EBV infection as the BL driving phenotype not the geographic origin. However, because detection of EBV in tumours is not a diagnostic criterion, we were limited in this analysis of population based cancer registries to rely on geography and age to identify the EBV+ tumours. Importantly, in the Grande study, the majority of the EBV+ tumours sequenced were from childhood BL in tropical Africa.

Conclusions

In summary, using population based cancer registry data, we show that the burden of BL remains high in those parts of sub Saharan Africa where Falciparum malaria remains common. EBV is an etiological factor in more than 80% of cases (about 3200 in 2018).

Abbreviation

ASR: Aged Standardlised Rate; BL: Burkitt lymphoma; eBL: Endemic type BL; EBNA: EBV nuclear antigen; EBV: Epstein Barr virus; HIV: Human immunodeficiency virus; IARC: International Agency for Research on Cancer; ICD-O : International Classification of Diseases for Oncology; NHL: Non Hodgkin lymphoma; SSA: Sub-Saharan Africa

Acknowledgements

We would like to thank all of the registries, members of the African Cancer Registry Network, for permission to access the AFCRN database to abstract the information on Burkitt Lymphoma presented in this paper. We also acknowledge the support of the Volkswagen Stiftung for financial support (Grant number: 94631) for the symposium " Cancer Epidemiology meets Infectiology in Africa" held in Entebbe, Uganda, in October 2018, which provided a forum to bring together the researchers involved in this study. Our thanks are due to Jacques Ferlay (IARC) for help in the analysis of the data and Ms. Biying Liu (AFRCN) for administrative support.

Authors' contributions

LH analyzed the registry data regarding incidence of BL. MC abstracted the data on NHL and BL from the registry datasets contributing to Globocan 2018, RR and MO contributed to the Discussion of diagnosis of BL and EBV-related factors, DMP oversaw the analysis and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the AFCRN database. Requests for access should be made via the AFCRN secretariat (https://afcrn.org/index.php/research/researches-and-collaborations).

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

No conflicts of interest.

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