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EDITORIAL

El futuro de la financiación de la investigación del cáncer en países de bajos y medianos ingresos

The future of funding for cancer research in low- and middle-income countries

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Los recientes acontecimientos en todo el mundo, y en particular en EE.UU., han generado una enorme preocupación sobre el futuro de la salud global y planetaria. La retirada de EE.UU. de la Organización Mundial de la Salud (OMS), junto con la suspensión de numerosos paneles de revisión de los Institutos Nacionales de Salud (NIH) y la retirada de la financiación de USAID, representan un desafío para la investigación en salud global en diversas enfermedades, incluyendo el cáncer y la salud pública.

Sin embargo, la importancia de estas políticas para los investigadores de América Latina y otras regiones del mundo con recursos limitados es incierta. Después de todo, la mayoría de las subvenciones otorgadas por instituciones ubicadas en países de altos ingresos, como el Instituto Fogarty, el Wellcome Trust e incluso USAID, se destinan a investigadores, fundaciones e instituciones de dichos países, y muy pocas se otorgan directamente a investigadores de países de bajos y medianos ingresos[1]. Si bien las subvenciones otorgadas a investigadores de países de altos ingresos pueden generar conocimiento y colaboraciones significativas, estas también pueden promover la investigación parasitaria y tienen menos posibilidades de conducir al desarrollo de capacidades y la creación de un grupo de investigadores en los países de bajos y medianos ingresos. Además, estas prácticas, en muchos casos, se derivan de la creencia errónea y discriminatoria de los financiadores de que los investigadores de los países de bajos y medianos ingresos carecen de la capacidad o la formación necesarias para realizar una investigación adecuada[2].

Mejorar este panorama y ayudar a financiar el trabajo de los investigadores de los países de bajos y medianos ingresos requiere la participación de numerosos actores y la creación de verdaderas redes globales de financiación y cooperación, incluyendo colaboraciones sur-sur. Un buen ejemplo de este tipo de fondo es el Fondo Mundial de Lucha contra el SIDA, la Tuberculosis y la Malaria, que canalizó 70,000 millones de dólares a los países de bajos y medianos ingresos para brindar servicios de atención médica para estas enfermedades, que son sumamente relevantes en entornos con recursos limitados, pero no tanto en los países de altos ingresos[3]. Una visión propuesta por investigadores en salud global es la creación de un fondo de este tipo, pero con énfasis en la investigación, con prioridades de investigación establecidas por las partes interesadas en los países de bajos y medianos ingresos, en lugar de por los paneles de revisión en los países de altos ingresos[4].

Las convocatorias de financiación deben tener en cuenta el contexto, la geografía local, la infraestructura de apoyo, la estructura institucional y de gobernanza, y las preferencias de los participantes[5]. Asimismo, los organismos de financiación en los países de bajos y medianos ingresos deberían evitar copiar la estructura y las prioridades de financiación de los países con altos ingresos y considerar priorizar la investigación destinada a mejorar el acceso a terapias estándar o la

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implementación de modelos de atención, sin olvidar que la innovación también puede provenir de las regiones en desarrollo del mundo.

Organizaciones como la Sociedad Mexicana de Oncología (SMEO) podrían desempeñar un papel relevante en la financiación de este tipo de investigación, en particular al centrarse en investigadores jóvenes que, de otro modo, tendrían dificultades para encontrar financiación. Existe la oportunidad de financiar y apoyar ideas que, si bien pueden representar inversiones arriesgadas, ofrecen grandes beneficios, incluyendo impulsar las carreras de los futuros líderes en investigación del cáncer en el país y la región. El Programa de Apoyo a la Investigación del Cáncer en México, recientemente desarrollado por SMEO, es un buen ejemplo de este tipo de iniciativa, que otorga subvenciones de hasta 150,000 pesos mexicanos a investigadores mexicanos que trabajan en proyectos básicos, clínicos o epidemiológicos[6]. Esto sin duda representa una buena inversión y una forma de apoyar proyectos que, de otro modo, tendrían dificultades para obtener financiamiento.

En resumen, la situación mundial actual requiere respuestas contundentes de las organizaciones en los países de bajos y medianos ingresos, incluido México. La investigación local dirigida a reducir la carga del cáncer y mejorar los resultados de los pacientes es esencial y, lamentablemente, la financiación externa será cada vez más difícil de obtener. Por lo tanto, alentamos a las organizaciones y organismos gubernamentales a continuar desarrollando programas destinados a apoyar proyectos innovadores en todas las áreas de la atención oncológica, con especial atención a los jóvenes investigadores.

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ARTÍCULO ORIGINAL

Creencias sobre la prueba de sangre oculta en heces en población con riesgo promedio

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Resumen

Antecedentes: *México tiene el 3.er lugar de la región latinoamericana en prevalencia de cáncer colorrectal (CCR). Uno de los métodos de detección para el CCR es la prueba de sangre oculta en heces (PSOH) para las personas con riesgo promedio. Las creencias sobre el CCR y los métodos de detección pueden influir sobre la adopción de los métodos de detección.* **Objetivo:** *Analizar la asociación entre los conocimientos, las variables sociodemográficas y las dimensiones de modelo de creencias de salud de acuerdo con las etapas de adopción de la PSOH en personas de 40 años o más.* **Método:** *Participaron 352 personas que respondieron la escala del modelo de creencias de salud para el CCR y la PSOH.* **Resultados:** *Se encontró una asociación significativa entre las etapas de adopción de la PSOH y el conocimiento de métodos diagnósticos para CCR (χ^2: 56.6 [3]; $p = 0.000$), se obtuvieron diferencias significativas para las dimensiones del modelo de creencias excepto en la severidad percibida ($p = 0.055$).* **Conclusiones:** *Las creencias susceptibilidad, beneficios, las barreras, la autoeficacia percibida y la motivación para la salud son las que hacen la diferencia entre las etapas iniciales y avanzadas de adopción de la PSOH.*

Palabras clave: *Cáncer colorrectal. Prueba de sangre oculta en heces. Modelo de creencias de salud. Etapas de adopción.*

Health beliefs about fecal occult blood test in an average-risk population

Abstract

Background: *Mexico has the 3rd place in the Latin American region in prevalence of colorectal cancer (CRC). Among the screening methods for CRC is the fecal occult blood test (FOBT) for people at average risk. Beliefs about CRC and screening methods may influence the adoption of screening methods.* **Objective:** *To analyze the association between knowledge, sociodemographic variables and health belief model dimensions according to the stages of adoption of FOBT in people aged 40 years or older.* **Method:** *Thirty-five hundred and fifty-two respondents to the health belief model scale for CRC and FOBT participated.* **Results:** *A significant association was found between the stages of FOBT adoption and knowledge of diagnostic methods for CRC (χ^2: 56.6 [3]; $p = 0.000$), significant differences were obtained for the dimensions of the belief model except for perceived severity ($p = 0.055$).* **Conclusions:** *The realization of FOBT is associated with knowledge of screening methods, being affiliated to a health service and advanced stages of change. Susceptibility beliefs, benefits, barriers, perceived self-efficacy and health motivation are what make the difference between initial and advanced stages of FOBT adoption.*

Keywords: *Colorectal cancer. Fecal occult blood test. Health belief model. Transtheoretical model.*

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Introducción

El cáncer colorrectal (CCR) representa un problema de salud pública creciente y cada año afecta más a los países menos desarrollados[1]. En 2020 se reportaron 1,931,590 casos nuevos de CCR a nivel mundial, ocupando la 3.ª posición[2]. América Latina y la región del Caribe representan el 4.° lugar de prevalencia de CCR a nivel mundial y el 3.er lugar en México. El CCR en hombres mexicanos representó el 2.° tipo de cáncer más común y el 4.° en mujeres en 2020[3].

El CCR figura entre los cinco tipos de cáncer con mayor número de muertes en ambos sexos a nivel nacional y en 2019 encabezó la lista como la principal causa de defunción debido a cáncer en hombres de 30 a 59 años[4].

De acuerdo con la Organización Panamericana de Salud[5], alrededor de un tercio de todos los casos de cáncer se pueden prevenir educando a la población para evitar los principales factores de riesgo, como el tabaquismo, el consumo excesivo de alcohol, una dieta poco saludable y el sedentarismo. Los programas de tamizaje y vacunación han demostrado ser operaciones efectivas para aminorar la carga de ciertos tipos de cáncer. Se prevé que la carga del cáncer irá en aumento, tentativamente en un 60% durante los próximos 20 años[6], lo que se traduce en la afectación de los sistemas de salud, la salud de las personas y de las comunidades.

Los programas de cribado para la detección oportuna de algún tipo de cáncer inician delimitando los tipos de población de riesgo, los cuales son riesgo promedio, elevado y alto. Pacientes mayores de 50 años sin afecciones como poliposis adenomatosa familiar, enfermedad inflamatoria intestinal, CCR hereditario no polipósico o antecedentes familiares positivos de tumoraciones colorrectales se consideran de riesgo promedio[7]; para estos, la Sociedad Americana Contra el Cáncer recomienda que inicien los exámenes de detección regular a los 45 años de edad, la prueba de detección recomendada para esta población es la prueba de sangre oculta en heces (PSOH)[8].

México se encuentra en el 3.er lugar de la región latinoamericana en prevalencia de CCR[2] y se ha reportado un aumento de la mortalidad por este tipo de cáncer, siendo las tasas más altas en el norte del país[9]. A pesar de que se ha reportado que cuenta con capacidad diagnóstica para la PSOH y colonoscopia, aún no cuenta con programas para detectar este tipo de cáncer[10,11], a diferencia de otros tipos de cáncer que tienen mayor difusión en cuanto a métodos de prevención y detección temprana. Además de contar con capacidad, es importante conocer si la población está preparada para adoptar el comportamiento de detección recomendado y los factores psicosociales que influyen en que una persona lleve a cabo dicho comportamiento.

Con relación a esto, el Modelo transteórico del cambio asume que no todos los individuos se encuentran en la misma disposición para adoptar un cambio de comportamiento, por lo que ofrece la oportunidad para planear y ejecutar intervenciones tomando en cuenta las características específicas de cada población o grupo al que irán dirigidas las acciones[12,13]. Propone que el comportamiento saludable es un desarrollo que consta del desplazamiento entre las etapas, desde la negativa a cambiar de comportamiento, hasta el mantenimiento de dicho cambio[14].

En el proceso, las personas tienen la capacidad de decidir si adoptan un comportamiento de salud preventivo en particular[15]. Las principales etapas que considera son: precontemplación, contemplación, preparación, acción, mantenimiento y recaída[16]. En estas etapas influyen las valoraciones cognitivas que realizan las personas acerca del comportamiento de salud, por lo que el modelo de creencias de salud (MCS) podría complementar la información acerca de las creencias del cáncer y sus prácticas de detección[17].

De acuerdo con el MCS, es posible pronosticar la aparición de una conducta de salud cuando el individuo en estudio califica como grave un problema de salud que le amenaza, se percibe susceptible a dicho problema y piensa que la acción necesaria para evitar su aparición será beneficiosa y poco costosa[18]. Las dimensiones del MCS son[19,20]: 1) susceptibilidad percibida, en donde la persona valora la propia vulnerabilidad a enfermar; 2) severidad percibida, se refiere a las creencias vigentes sobre la importancia de contraer una enfermedad debido a su gravedad o a no recibir tratamiento después de contraerla; 3) beneficios percibidos, representan la creencia de que un comportamiento es útil para reducir la probabilidad de contraer alguna enfermedad; 4) barreras percibidas, son la valorización de los costos y dificultades para ejecutar la conducta; 5) autoeficacia percibida, es la apreciación propia de la capacidad para controlar, organizar y ejecutar adecuadamente las conductas[21], y 6) motivación para la salud.

Ambos modelos se han utilizado para explicar los determinantes de comportamientos de detección en diferentes tipos de cáncer, incluido el colorrectal[17,22].

El objetivo de este estudio es identificar los conocimientos sobre los signos, síntomas y factores de riesgo del CCR, las etapas de adopción de la PSOH, analizar la asociación entre los conocimientos, las variables sociodemográficas y las etapas de cambio y comparar las dimensiones de MCS de acuerdo con las etapas de adopción en personas de 40 años o más con riesgo promedio.

Método

Participantes

Se realizó un estudio con diseño transversal descriptivo con una muestra no probabilística por conveniencia. Los criterios de inclusión fueron hombres y mujeres de 40 años a 75 años, sin síntomas de CCR. Los criterios de exclusión fueron contar con antecedente personal patológico y/o familiar de cáncer del tracto digestivo, antecedente personal patológico de lesión colorrectal benigna. El estudio fue aprobado por el comité de ética de la Universidad con el número CE 1/2022-14, los datos fueron recolectados de octubre de 2022 a abril de 2023. Se siguieron las recomendaciones de la declaración STROBE (*Strengthening the Reporting of Observational Studies in Epidemiology*) para artículos observacionales.

Instrumentos de evaluación

CÉDULA DE DATOS SOCIODEMOGRÁFICOS

- Conocimiento sobre signos y síntomas del CCR. Consta de 18 afirmaciones para detectar el nivel de conocimientos sobre síntomas (sí, no, no sé), factores de riesgo (aumenta, disminuye, no afecta) y pruebas de detección de CCR, basado en la información de la Sociedad Americana contra el Cáncer[23]. Cada respuesta correcta tiene el valor de un punto, con un rango de puntaje entre 0 y 18.
- Etapas de cambio. Se evaluó con seis afirmaciones que indicaban cada una de las etapas de adopción, la persona debía seleccionar la afirmación que más refleje su experiencia con la PSOH.
  - Precontemplación. Nunca me he realizado una PSOH y no tengo la intención de realizarme una.
  - Contemplación. Nunca me he realizado una PSOH, pero planeo realizarme una el próximo año.
  - Preparación. Nunca me he realizado una PSOH, pero planeo realizarme en los próximos seis meses y ya cuento con una cita para realizarla.
  - Acción. Recientemente tuve mi primera PSOH y tengo la intención de realizarme una cada año.
  - Mantenimiento. He tenido PSOH durante varios años de forma rutinaria, una vez al año.
  - Recaída. He tenido algunas pruebas de sangre oculta en heces hace varios años, pero no lo hago de forma rutinaria cada año, ni planeo tener una el siguiente año.
- Escala de creencias de salud para el CCR y la PSOH. Se utilizó la versión en español adaptada por los autores Juárez et al. (En prensa). Cuenta con 39 ítems divididos en seis dimensiones: susceptibilidad percibida, severidad percibida, beneficios percibidos, barreras percibidas, autoeficacia percibida y motivación para la salud, las opciones de respuesta van de 1 (no) a 4 (sí), en donde mayor puntaje indica mayor presencia de la dimensión. El alfa de Cronbach para las dimensiones de la escala se encuentra en un rango de 0.68 a 0.86.

Procedimiento

La recolección de los datos se realizó en la sala de espera de un hospital de tercer nivel de atención, se invitaba a participar a las personas que cumplían los criterios de inclusión, los que aceptaban firmaban el consentimiento informado y se aplicaba el cuestionario en forma de entrevista. Antes de comenzar con las preguntas se explicaba a los participantes qué era la sangre oculta en heces para asegurar que conocieran el procedimiento y lo relacionaran con las preguntas.

Análisis estadístico

Para el análisis estadístico se utilizó el programa SPSS versión 22. Se realizó el cálculo de tamaño de muestra con una precisión del 5% y un nivel de confianza del 95%, se realizaron cálculos de muestras la proporción de la hipótesis y tomando en cuenta la muestra sujeta a pérdidas, se obtuvo n = 310. Para identificar los niveles del conocimiento, se obtuvo la frecuencia y porcentaje de cada categoría. Se realizó la prueba de chi cuadrada para la asociación entre el conocimiento y variables sociodemográficas, la t de Student para comparar las creencias entre las personas que se han realizado una PSOH y las que no, y la prueba de ANOVA unidireccional con Games-Howell para el análisis *post hoc* para comparar las creencias entre las etapas de adopción.

Resultados

Descripción de la muestra

Se identificaron 464 personas candidatas para participar, de las cuales 89 no aceptaron y 23 no cumplían los criterios de inclusión, por lo que el total de muestra fue de 352 participantes. La mayoría era del sexo femenino, como estado civil casada, con escolaridad de preparatoria, la edad media fue de 51.38 ± 8.5 años. El 75% de los participantes contaba con un seguro médico. El 65.9% se ha realizado algún estudio de tamizaje para detección de cáncer, respecto a las pruebas de detección del CCR, un 15% se ha realizado la PSOH y un 2% colonoscopia (Tabla 1).

Conocimiento sobre los signos, síntomas y factores de riesgo de cáncer colorrectal

En la tabla 2 se observa que los síntomas principalmente identificados son el sangrado anal o en heces, pérdida inexplicable de peso y cansancio. La mayoría cree que el dolor anal es un signo de CCR. En cuanto a los factores de riesgo, la mayoría de los participantes identifica que el consumo de carnes procesadas, rojas y alcohol aumenta el riesgo de CCR. Respecto al conocimiento de los métodos de detección de CCR, el más conocido fue la colonoscopia, seguido de la PSOH. La mayoría de los participantes se encuentra en la etapa de contemplación y precontemplación.

Análisis de asociación

Entre las variables sociodemográficas y la realización de la PSOH únicamente se encontró asociación entre estar afiliado a algún servicio de salud (χ^2 = 3.7 (1); p = 0.045). Las etapas de adopción de la PSOH y el nivel de conocimiento de signos, síntomas y factores de riesgo no fueron significativas (χ^2: 3.24 [1]; p = 0.072). Sin embargo, sí se encontró una asociación significativa entre las etapas de adopción de la PSOH y el conocimiento de métodos diagnósticos para CCR (χ^2: 56.6 [3]; p = 0.000).

Análisis de comparación

Se compararon las creencias entre las personas que se han realizado PSOH y las que no y se obtuvieron diferencias significativas en la susceptibilidad percibida [t(82.9): 2.72; p < 0.01; d = 0.39], barreras percibidas [t(91.5): –4.91; p < 0.001; d = 0.65] y la autoeficacia percibida [t(82.2): 4.11; p < 0.001; d = 0.56] (Tabla 3).

Tabla 1. Características sociodemográficas y clínicas

	Frecuencia (%)
Sexo	
Femenino	227 (64.5)
Estado civil	
Soltero/a	41 (11.6)
Casado/a	183 (52)
Unión libre	68 (19.3)
Divorciado/a	40 (11.4)
Viudo/a	50 (5.7)
Número de hijos	
0-2	158 (44.9)
3-5	184 (52.3)
6-8	10 (5.6)
Ingreso mensual aproximado	
Menos de 4,000	23 (6.5)
De 5,000 a 10,000	219 (62.2)
De 11,000 a 50,000	108 (30.7)
De 51,000 a 100,000	2 (0.6)
Más de 100,000	0
Escolaridad	
Sin educación formal	5 (1.4)
Primaria	63 (17.9)
Secundaria	101 (28.7)
Preparatoria y/o técnica	121 (34.4)
Licenciatura	57 (16.2)
Posgrado	5 (1.4)
Económicamente activo	
Sí	209 (59.4)
Servicio médico	
Sí	263 (74.7)
Tipo de servicio médico	
Ninguno	89 (25.3)
Público	238 (67.6)
Privado	25 (7.5)
Tamizaje para cáncer	
Citología cervical	160 (45.5%)
Mamografía	118 (33.5%)
Antígeno prostático	44 (12.5%)
PSOH	54 (15.3%)
Colonoscopia	7 (2%)
Otros estudios	21 (5.9%)
Conocimiento de prueba de tamizaje de CCR	
PSOH	150 (42.6)
Colonoscopia	223 (63.7)
Sigmoidoscopia flexible	75 (21.3)
Recomendación médica para tamizaje de CCR	
No	324 (92.0)

CCR: cáncer colorrectal; PSOH: prueba de sangre oculta en heces.

Análisis de comparación entre las etapas de adopción y las creencias de salud

Se realizó el análisis de comparación entre las etapas de adopción de la PSOH, se obtuvieron diferencias

Tabla 2. Conocimiento sobre signos, síntomas y factores de riesgo del cáncer colorrectal

Los siguientes son síntomas/signos sugerentes de CCR	Sí	No	
Masa abdominal	212 (60.2%)	140 (39.8%)	
Cambios en hábitos de evacuación	232 (65.9%)	120 (34.1%)	
Dolor anal	216 (61.4%)	136 (38.6%)	
Tenesmo fecal	181 (51.4%)	171 (48.6%)	
Cólicos o dolor abdominal	216 (61.4%)	136 (38.6%)	
Rectorragia	299 (84.9%)	53 (15.1%)	
Hematoquecia	312 (88.6%)	40 (11.4%)	
Debilidad/cansancio	238 (67.6%)	114 (32.4%)	
Pérdida inexplicable de peso	274 (77.8%)	78 (22.2%)	
Los siguientes factores, ¿aumentan, disminuyen o no afectan el riesgo de padecer CCR?	**Aumenta**	**Disminuye**	**No afecta**
Obesidad	209 (59.4%)	4 (1.1%)	139 (39.5%)
Actividad física moderada/alta	18 (5.1%)	197 (56%)	137 (38.9%)
Alto consumo de carnes rojas	262 (74.4%)	23 (6.6%)	67 (19%)
Comer frutas y verduras	3 (0.9%)	243 (69%)	106 (30.1%)
Comer alimentos integrales y con fibra	11 (3.1%)	229 (65.1%)	112 (31.8%)
Consumo de alcohol	248 (70.5%)	6 (1.7%)	98 (27.8%)
Alto consumo de carnes procesadas	283 (80.4%)	10 (2.8%)	59 (16.8%)
Inactividad física	139 (39.5%)	23 (6.5%)	190 (54%)
Consumo de tabaco	197 (56%)	5 (1.4%)	150 (42.6%)

CCR: cáncer colorrectal.

significativas para las diferentes dimensiones del modelo de creencias excepto en la severidad percibida, que estuvo al límite de la significancia ($p = 0.055$).

En el análisis *post hoc* se encontraron diferencias significativas entre las etapas de precontemplación-contemplación y precontemplación-recaída ($p < 0.01$) para la dimensión de susceptibilidad percibida (Tabla 4). Entre las etapas de precontemplación-preparación ($p < 0.001$), precontemplación- mantenimiento ($p < 0.05$) y entre recaída-preparación ($p < 0.05$) para la dimensión de beneficios.

En la dimensión de barreras entre las etapas mantenimiento-precontemplación ($p < 0.001$), mantenimiento-contemplación ($p < 0.05$), preparación-precontemplación ($p < 0.001$) y recaída y precontemplación ($p < 0.001$). En la dimensión de autoeficacia entre precontemplación-preparación ($p < 0.001$), precontemplación-mantenimiento ($p < 0.001$), precontemplación-acción ($p < 0.05$); también entre contemplación-preparación ($p < 0.05$) y contemplación-mantenimiento ($p < 0.05$) y entre precontemplación-mantenimiento ($p < 0.05$) para la dimensión de motivación para la salud.

Tabla 3. Análisis de comparación

Dimensión MCS	Prueba de sangre oculta en heces	
	Sí (n = 54) m (DE)	No (n = 298)
Susceptibilidad	12.3 (2.6)	11.2 (3.1)
Severidad	18.6 (2.5)	18.7 (3.0)
Beneficios	17.4 (1.9)	17.1 (2.4)
Barreras	12.4 (3.6)	15.2 (4.8)
Autoeficacia	39.5 (4.1)	37.0 (4.8)
Motivación	15.9 (2.8)	15.0 (3.2)

MCS: Modelo de creencias de salud; m: media; DE: desviación estándar.

Tabla 4. Diferencias entre las etapas de adopción de la PSOH y las dimensiones del modelo de creencias de salud

Creencias/ etapas de adopción	Precontemplación^{1} (n = 106) Media (DE)	Contemplación^{2} (n = 166) Media (DE)	Preparación^{3} (n = 26) Media (DE)	Acción^{4} (n = 3) Media (DE)	Mantenimiento^{5} (n = 12) Media (DE)	Recaída^{6} (n = 39) Media (DE)	Comparación múltiple
Susceptibilidad	10.4 (3.2)	11.6 (3.0)	11.6 (3.6)	11.0 (1.7)	12.7 (3.7)	12.3 (2.3)	1 vs. 2, 6*
Severidad	18.1 (3.0)	19.1 (2.9)	18.9 (3.2)	18.0 (1.0)	18.4 (4.3)	18.7 (1.8)	
Beneficios	16.4 (2.8)	17.4 (2.0)	18.7 (1.3)	18.6 (1.5)	18.3 (1.6)	17.0 (1.9)	1 vs. 3, 5† 3 vs. 6†
Barreras	16.5 (5.4)	14.8 (4.4)	12.6 (3.5)	11.3 (2.8)	10.5 (2.7)	13.1 (3.7)	1 vs. 3, 5, 6* 2 vs. 5†
Autoeficacia	35.9 (5.5)	37.2 (4.2)	40.0 (4.1)	44.0 (0.0)	42.3 (2.1)	38.4 (4.1)	1 vs. 3, 5, 6† 2 vs. 3, 5†
Motivación para la salud	10.9 (3.3)	11.6 (2.8)	12.5 (3.1)	12.3 (3.0)	13.6 (2.2)	11.6 (2.6)	1 vs. 5†

*p ≤ 0.0.
†p ≤ 0.05.
PSOH: prueba de sangre oculta en heces.

Discusión

Respecto a la identificación de los conocimientos, al igual que en otros estudios[24,25] el sangrado anal y en heces son los principales síntomas relacionados con el CCR. Sin embargo, un porcentaje alto aún se confunde con algunas condiciones como el dolor en el ano, la inactividad física y consumo de tabaco. Por lo que en general la población muestra un bajo conocimiento sobre los síntomas y factores de riesgo del CCR. El conocimiento es menor a lo reportado en un estudio de Noruega, en el que un 60% identificó los factores de riesgo para el CCR[26]. Esto muestra la importancia de continuar educando a la población respecto a los factores de riesgo modificables.

Respecto al conocimiento de las pruebas de tamizaje para el CCR, se identificó principalmente la colonoscopia, seguida por la PSOH. El 57.4% de los participantes desconocía la PSOH, que es la prueba recomendada de acuerdo con su edad, similar a lo reportado por Rodríguez Hernández et al.[27], donde un 88.9% desconocía la PSOH como método diagnóstico para CCR; otro estudio reportó que el 98% había escuchado sobre la PSOH y un 17% se había realizado la prueba[28], porcentaje mayor al obtenido en este estudio, donde un 15% se ha realizado la PSOH.

En cuanto a la etapa de adopción de la PSOH, la mayoría se encuentra en las etapas en las que aún no se realiza la prueba (precontemplación), los resultados son diferentes a lo reportado en este mismo país en cuanto a la mamografía, en donde las mujeres se encuentran en las etapas de adopción de mantenimiento y recaída[29]. Por otra parte, en Corea el 36% se encuentra en las etapas de acción y mantenimiento[30]. Es importante resaltar que un porcentaje alto se encuentra en etapa de contemplación y preparación, por lo que tienen la intención de realizarse la PSOH. Es en estas etapas donde la promoción o la recomendación de realizar la prueba podría ayudar a que den el paso para realizarla.

La realización de la PSOH se asoció con el conocimiento sobre los métodos de detección y estar afiliado a un servicio de salud; el conocimiento de los métodos diagnósticos también se asoció a etapas de cambio más avanzadas. Estos resultados son parcialmente similares al de Huang et al.[31], que encontraron asociación entre un mayor nivel de conocimiento de los síntomas, factores de riesgo, métodos de cribado y la participación en pruebas de detección para CCR. Al igual que en el estudio de Samuel et al.[32], no encontraron factores sociodemográficos asociados a los métodos de detección de CCR, por lo que es importante que además de dar a conocer los signos y síntomas del CCR se resalten los métodos de detección de este en las campañas de promoción de salud y las realizadas en los servicios de salud a los que acuden los participantes.

De las creencias que hacen la diferencia entre las etapas iniciales de adopción y las avanzadas se encuentra la susceptibilidad percibida, beneficios, las barreras, la autoeficacia percibida y la motivación para la salud. Esto es similar a lo reportado en otros estudios donde las personas en etapa de precontemplación, las cuales no tienen intención de realizarse la prueba, muestran menos beneficios y más barreras percibidas a diferencia de las personas en precontemplación (han pensado en realizarse la prueba) y acción (se han realizado la prueba)[33,34]. Las barreras, beneficios y autoeficacia también predicen la etapa más avanzada, en ambos estudios la etapa más avanzada era preparación. En este estudio también se observa como estas mismas creencias son más altas en personas que están en las etapas de acción, mantenimiento y recaída.

Esto se confirma con los datos obtenidos en la comparación entre las personas que se han realizado la PSOH y las que no, en donde se observa que las personas que se han realizado la PSOH se sienten más susceptibles al CCR, tienen menos barreras percibidas respecto a la PSOH y sienten mayor confianza en realizar los procedimientos que se requieren para realizar la PSOH. Sin embargo, no se encontraron diferencias en la dimensión de beneficios percibidos, lo que nos indica un área de oportunidad para destacar los beneficios de realizarse la PSOH al cumplir la edad recomendada en personas asintomáticas. También es importante dar una explicación adecuada de cómo se realiza para fomentar la autoeficacia e identificar las principales barreras para realizar la PSOH para lograr que las personas que están en las etapas de precontemplación y contemplación del paso a la acción y mantenimiento de la PSOH mediante el desarrollo de programas de intervención que puedan inducir al cambio en la percepción y el comportamiento de los sujetos en la detección del CCR[35].

Limitaciones

Este estudio fue realizado en población que acudía a atención médica, por lo que los valores de conocimiento en cuanto a los métodos de detección pueden ser mayores que en población general entrevistada en otros contextos. Asimismo, los datos de etapa de cambio fueron obtenidos por medio de autorreporte y no fueron verificados en los expedientes médicos. Sin embargo, este estudio nos muestra el panorama psicosocial de la población mexicana en cuanto al CCR.

Conclusiones

La población evaluada con riesgo promedio muestra un bajo conocimiento sobre los síntomas y factores de riesgo del CCR, el 57% desconoce la PSOH y solo el 15% se la ha realizado. La realización de la PSOH se asocia al conocimiento de los métodos de detección, estar afiliado a un servicio de salud y etapas de cambio avanzadas. Las personas que se han realizado la PSOH presentan más susceptibilidad y autoeficacia percibida que las que no.

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Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Consideraciones éticas

Protección de personas y animales. Los autores declaran que los procedimientos seguidos se conformaron a las normas éticas del comité de experimentación humana responsable y de acuerdo con la Asociación Médica Mundial y la Declaración de Helsinki. Los procedimientos fueron autorizados por el Comité de Ética de la institución.

Confidencialidad, consentimiento informado y aprobación ética. Los autores han seguido los protocolos de confidencialidad de su institución, han obtenido el consentimiento informado de los pacientes, y cuentan con la aprobación del Comité de Ética. Se han seguido las recomendaciones de las guías SAGER, según la naturaleza del estudio.

Declaración sobre el uso de inteligencia artificial. Los autores declaran que no utilizaron ningún tipo de inteligencia artificial generativa para la redacción de este manuscrito.

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ORIGINAL ARTICLE

Barriers and facilitators of early lung cancer care in Mexico

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Abstract

Background: *Timely diagnosis and prompt initiation of treatment are crucial for improving outcomes in lung cancer patients in Mexico. However, barriers hinder the achievement of this goal, leading to delayed diagnosis and suboptimal treatment trajectories.* **Objective:** *To explore barriers and facilitators contributing to late diagnosis and treatment.* **Methods:** *In-depth interviews were conducted in spring 2023 among a purposive sample of lung cancer patients, relatives, and health-care professionals in Mexico. Grounded theory was used to identify recurring themes and gain a comprehensive understanding of the challenges faced. Codes included: barriers and facilitators; and origin: individual, family/community, doctor, or health system. The interpretation of the data was guided by the proximal and distal determinants of care and cross-checked by a second researcher.* **Results:** *The study identifies multiple barriers to lung cancer diagnosis and care, including poor symptom recognition, lack of medical training, and family or caregiver burden. However, facilitators such as family perseverance, non-profit organization support, and participation in research protocols can help overcome these obstacles.* **Conclusion:** *Addressing barriers while leveraging the facilitators is essential for improving lung cancer outcomes.*

Keywords: *Barriers. Early cancer care. Diagnosis. Treatment. Mexico. Lung cancer.*

Barreras y facilitadores de la atención temprana del cáncer de pulmón en México

Resumen

Antecedentes: *El diagnóstico oportuno y el inicio rápido del tratamiento son cruciales para mejorar los resultados en pacientes con cáncer de pulmón en México. Sin embargo, diversas barreras dificultan el logro de este objetivo, lo que conduce a diagnósticos tardíos y trayectorias de tratamiento subóptimas.* **Objetivo:** *Explorar las barreras y facilitadores que contribuyen al diagnóstico y tratamiento tardíos.* **Métodos:** *Se realizaron entrevistas en profundidad en la primavera de 2023 entre los componentes de una muestra intencionada de pacientes con cáncer de pulmón, familiares y profesionales de la salud en México. Se utilizó la teoría fundamentada para identificar temas recurrentes y obtener una comprensión completa de los desafíos enfrentados. Los códigos incluyeron barreras y facilitadores, y origen (individual, familiar/comunitario, médico o sistema de salud).* **Resultados:** *El estudio identifica múltiples barreras para el diagnóstico y cuidado del cáncer de pulmón, incluyendo el pobre reconocimiento de los síntomas, la falta de formación médica y la carga para la familia o los cuidadores. Sin embargo, facilitadores como la perseverancia de la familia, el apoyo de organizaciones sin fines de lucro y la participación en protocolos de investigación pueden ayudar a superar estos obstáculos.* **Conclusión:** *Abordar las barreras y apoyar los facilitadores es esencial para mejorar los resultados en cáncer de pulmón.*

Palabras clave: *Barreras. Facilitadores. Cáncer de pulmón. México. Diagnóstico. Tratamiento.*

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Background

Lung cancer is the leading cause of cancer-related mortality in Mexico, with the majority of cases being identified in symptomatic individuals at a late stage of the disease and less eligible for potential curative therapy[1,2].

This is reflected in high mortality-to-incidence ratios[2-4]. At present, Mexico lacks a national public lung cancer screening program[2]. There are large disparities in access to well-equipped diagnostic resources[1]. The absence of a referral protocol further complicates matters, potentially resulting in lost patient follow-ups and difficulties navigating the health system[2]. Moreover, health-care centralization results in unequal distribution of services[5], with specialized oncology care more prevalent in the central region near Mexico City[6]. First and second-level care facilities often lack infrastructure and human resources for diagnosis, whereas third-level hospitals cater only to confirme disease cases[7], potentially contributing to barriers in early diagnosis and timely treatment[3]. Hence, there is a critical need to intensify efforts directed at understanding the barriers lung cancer patients face in Mexico to achieve diagnosis or treatment[2,8].

Krok-Schoen et al. developed a framework of patient-identified barriers[9]. However, because barriers have never been assessed in this population more research should be done to identify them. Thus, qualitative research becomes an indispensable tool for comprehending the experiences of individuals[10-14], lung cancer patients included. Such studies delve into the multifaceted representations held by both patients and their caregivers, shedding light on critical junctures within the patient journey, such as suspicion, diagnosis, and treatment[10-13,15,16]. Furthermore, by triangulating the narratives of primary actors (patients) with those of secondary actors (caregivers), a relational analysis is facilitated, allowing for a comprehensive exploration of the intricacies of the lung cancer journey. Similar research integrating patients and other stakeholders in the identification of barriers has been done in other countries[15,17]. Other studies have also compared barriers to facilitators[13]. Among patients, barriers such as poor relationships with health-care providers, low levels of trust in the health-care system, lack of access, feeling unworthy of treatment, financial toxicity, disconnected interpretations of bodily changes, and lack of awareness of cancer symptoms were among the most frequently found[13,18-20]. Whereas illness management, coping with stress and major life changes were described as negative experiences by caregivers[16]. Instead, patient self-advocacy, provider advocacy, care coordination, and good communication were facilitators of lung cancer care[13].

This research endeavors to bridge a critical knowledge gap concerning the challenges and the potential facilitating roles faced by lung cancer patients, caregivers, and health-care professionals in Mexico, particularly with respect to early diagnosis and treatment. The aim is to generate evidence to allow policymakers and patient organizations to guide decision-making and identify potential areas for intervention.

Methods

Semi-structured interviews were conducted through analog telephone calls of a purposive sample of n = 22 participants. Patients from diverse age groups and backgrounds were invited to contrast healthcare-care journeys. Health professionals from different regions and working in different levels of care were invited to participate. Family members or carers of patients selected for interviews were also invited. The rationale behind the selection of patients, family members or caregivers, and healthcare workers for analysis was grounded in the pursuit of a comprehensive understanding of barriers and facilitators of care from multiple perspectives[15,17]. By including them, we aimed to capture the diverse experiences, perspectives, and insights pertinent to the subject matter.

The reliability and validity of telephone interviews have been extensively studied in the literature and can yield high-quality data that are comparable to face-to-face interviews, particularly when the research involves sensitive topics or when participants are geographically dispersed[21].

The non-governmental organization “Respirando con Valor (RCV)” recruited patients with a lung cancer diagnosis and family or caregivers who had previously requested support from them as a patient-oriented organization. All participants were contacted by RCV and asked to participate in the study in spring 2023. Those who voluntarily decided to participate were interviewed: patients (n = 12), family members or caregivers (n = 5), and health-care workers (n = 5). Ethical approval was granted by an internal committee of RCV.

The interview guide was designed following a thorough literature review on barriers to early cancer care and delays in lung cancer care[9,12,13,15,20,22-25]. Guided by a meticulously designed semi-structured framework[26], the interviews delved into three overarching domains: (1) suspicion and diagnosis, (2) seeking care, diagnosis, and treatment, and (3) the socio-familial milieu. Each of the domains, meticulously delineated, comprised four subcategories, thus affording a comprehensive exploration of the phenomena under investigation.

The domain of suspicion and diagnosis interrogated multifaceted aspects including cultural representations of health and illness, the onset of initial symptoms, markers of suspicion, pivotal moments of diagnosis confirmation, and the subsequent emotional reckoning inherent in confronting such diagnoses. Conversely, the domain pertaining to seeking care and treatment delved into the intricate landscape of health-care access and utilization, encompassing challenges encountered in accessing biomedical treatments, navigating hospital systems, negotiating medical pluralism, and the participants' perceptions of biomedical treatment modalities. Finally, the domain elucidates the social and familial environment probed into interpersonal challenges within familial dynamics, work-related difficulties, and the landscape of mental health and adaptive coping mechanisms amid adversity. Before each interview, the purpose and objectives were explained to participants, and a consent form was signed. Recorded data were anonymized according to the Helsinki Declaration's guidelines and securely stored with complete confidentiality.

The data analysis was rooted in the grounded theory framework[27]. It employed an inductive approach, leveraging empirical data derived from semi-structured interviews, facilitating the exploration of the multifaceted dimensions inherent in the journeys of lung cancer patients and the authentic realities experienced by the main actors involved in the illness trajectory. Key themes, patterns, and commonalities across interviews were identified by one researcher and cross-checked by a second researcher. Codes identified included: Barriers and facilitators; and origin: Individual, family/community, doctor, or health system.

Theoretical saturation was assessed through continuous analysis of the data during the interview process. The evaluation of theoretical saturation involved both inductive and deductive analysis. Initially, data were coded and themes were identified inductively. As new interviews were conducted, these themes were continually compared and refined. Deductively, the predefined categories based on the interview guide were also used to ensure all anticipated areas were covered. The evaluation was conducted in line with the constant comparative method, as described by Glaser and Strauss[27].

The interpretation of the data was guided by the proximal and distal determinants of care from existing literature[9,15,17,28,29]. The study was guided by the standards for reporting and conducting qualitative research[30]. Finally, from the patient narrative, data were used to calculate the time to diagnosis.

Results

Patients varied in gender, age, duration of diagnosis, and location of residence and health-care institution. From the n = 12 patients, seven were women, and five were men, with nine residing in different Mexican states and three in the Metropolitan Area of Mexico City. Most patients received treatment at third-level institutions in Mexico City: The National Cancer Institute (INCAN) and the National Institute of Respiratory Diseases (INER). Family members or carers were all women. Health-care workers were from both rural and urban areas and from different levels of expertise: Oncologist (n = 1), pulmonologist (n = 1), and general practitioners (n = 3) (Table 1**).**

This study identified key barriers and facilitators that lung cancer patients encounter throughout their journey. We were able to attain theoretical saturation, signifying a depth of understanding characterized by robust consistency in our findings. This was facilitated by the identification of discursive regularities among the various actors involved, further enriching our insights and enhancing the overall rigor of our study. Table 2 summarizes the barriers and facilitators that arose from the data, and fits into different dimensions: individual, doctor, system, or family in the Mexican context. Finally, table 3 shows the examples of verbalizations stakeholders made with a brief description of each category.

Discussion

The patient

Early diagnosis and timely treatment are pivotal in improving outcomes, yet various barriers hinder the achievement of these goals. This article explores the complex web of factors contributing to delayed diagnosis and treatment of lung cancer, highlighting the perspectives of patients, their families, health-care providers, and health professionals. The voices and experiences of patients and their families should be continually

Table 1. Joint display of patient sociodemographic characteristics and time to diagnosis

Patient	Age	Sex	Time to diagnosis	Institution	Origin
1	50	Man	1 year	INER	Puebla
2	42	Man	1 year	INCAN	Oaxaca
3	64	Woman	6 months	INER	Tabasco
4	67	Woman	4 years	INCAN	State of Mexico
5	71	Woman	3 years	INER	Mexico City
6	47	Woman	9 years	INCAN	Guerrero
7	63	Woman	2 years	ISSEMYM	State of Mexico
8	73	Woman	4 years	INCAN	State of Mexico
9	52	Woman	1 year	INCAN	Oaxaca
10	38	Man	1 year	INCAN	Puebla
11	44	Man	3 years	INCAN	Puebla
12	63	Woman	4 years	INCAN	Nuevo León

INCAN: National Cancer Institute; INER: National Institute of Respiratory Diseases.

prioritized in future research, as their insights are invaluable in shaping patient-centered care strategies.

As shown in other studies, social constructions of risk[31,32] and prevailing beliefs about illness contribute to the underestimation of symptoms and the prioritization of other life aspects[5,33,34]. Similarly, the lack of knowledge about lung cancer symptoms and its association solely with smoking hindered early recognition and appropriate health-care seeking. Thus, our study emphasizes the importance of raising awareness and promoting effective communication campaigns for lung cancer risk among the population. These campaigns must educate individuals about the most common symptoms and risk factors, including factors not solely related to tobacco smoke exposure.

In our sample, the notion that cancer is a punishment for smoking can lead to reduced adherence to treatment among patients. This negative discourse of guilt has been found to not only be reinforced by family and friends but also within the health-care community[35]. Although smoking is a major causal factor in most cases, it is not the sole cause of lung cancer in Mexico[2,8]. Hence, it is vital to highlight other potential causes when delivering prevention campaigns, such as family history and exposure to various toxic substances like radon, chlorine, asbestos, or wood smoke. These campaigns must prioritize destigmatizing lung cancer patients as people who smoke tobacco. This may result in increased knowledge and reduction of poor symptom recognition, the usage of alternative remedies, and delayed self-appraisal.

Results from this study also suggest campaigns directly targeting rural communities should raise awareness about lung cancer risk factors and promote the importance of regular health check-ups. This approach helps ensure that individuals in remote areas have equal opportunities to participate in screenings and receive timely medical attention if abnormalities are detected[3,36].

Moreover, campaigns targeted at health-care professionals should aim to dispel common misconceptions about lung cancer and challenge prevailing stigmas[5]. This will foster a more compassionate and empathetic approach toward patients, helping to mitigate any resistance or reluctance in seeking treatment due to fear or negative perceptions associated with the disease[37,38].

Previously, studies have described lung cancer patients facing depression, anxiety, distress, and fatigue[39-41], severely disrupting patients' lives, and affecting their self-perception, values, and overall well-being[35]. Although this study did not capture mental health outcomes, fear can be a potential barrier both for the patient and the carer. This is clinically relevant as the emotional and psychological well-being significantly impacts the patient's ability to cope with the disease and adhere to treatment regimens and physical activity[39-41]. Hence, it is also essential to integrate mental health

Table 2. Barriers or facilitators identified in the Mexican population in the context of lung cancer care across different dimensions

Barriers	Facilitators
Individual	
Poor symptom recognition and interpretation Alternative self-care practices and remedies Lack of knowledge about lung cancer Fear of diagnosis Prioritization of functional health Biographical disruption and role adjustments Stigmatization and fear of compassion/pity Limited mental health support Misconception of improvement leading to patient dropouts Treatment's secondary effects	
Doctor	
Lack of medical training for lung cancer identification Time constraints for thorough patient examination Underreporting and misdiagnosis challenges Doctor's lack of empathy	
Family	
Family or caregiver burden Family discord and divergent beliefs	Family or caregiver's perseverance and advocacy
Health system	
Catastrophic expenditures Reduced workforce High patient demand and insufficient diagnostic infrastructure Bureaucratization Disruptive patient journey	Non-profit organizations support Participation in research protocols Facilitators/navigators

support as part of lung cancer care. Implementing proactive mental health services from the outset of the diagnosis will help address the emotional challenges faced by patients and their families, ensuring a comprehensive approach to lung cancer management[5].

Health-care professionals

Our results show there is insufficient training and knowledge among general practitioners. In fact, misdiagnosis is pointed out to be a reason for longer diagnostic intervals. Thus, it is crucial to invest in comprehensive training, awareness, and sensitization campaigns for primary care physicians in both urban and rural settings[3]. These health-care professionals serve as the frontline in patient care and are often the first point of contact for individuals seeking medical attention. By equipping primary care physicians with the necessary knowledge and skills to identify potential cancer cases promptly, the likelihood of early diagnosis and intervention significantly improves[3]. Training programs should focus on enhancing physicians' clinical acumen in recognizing early warning signs and symptoms of cancer[3], especially among individuals with a history of smoking or exposure to environmental risk factors. In addition, it should emphasize the importance of thorough medical histories and appropriate diagnostic evaluations to minimize delays in diagnosis.

Oncologists play a crucial role in ensuring that patients fully comprehend the impact of their treatment on their lives, including potential side effects and how to manage them. Our results show a barrier for continuous lung cancer care is ineffective communication. It is important for oncologists to clearly communicate the possible secondary effects of treatment and provide guidance on how to address them if they occur. Patients need to understand that improvement in their condition does not necessarily signal the end of treatment, and oncologists should explain this aspect thoroughly.

Family and carers as barriers and facilitators

Results point to family members being both a barrier and a facilitator. On one hand, the family environment can significantly impact a patient's health-care decision

Table 3. Barriers and facilitators identified in the Mexican population in the context of lung cancer care, description of each category, and quotes that exemplify the theme

Barriers	Description	Verbalizations/quotes example
Poor symptom Recognition and interpretation	Patients may normalize or attribute symptoms to other causes, such as injuries or falls, further delaying medical help and early diagnosis. Patients may have explanatory models for their symptoms that do not align with biomedical explanations like smoking or exposure to toxins. They may attribute symptoms to other factors, such as injuries, distress, or other non-related causes. These explanatory models can contribute to delayed diagnosis and may lead to feelings of frustration and guilt after receiving the diagnosis.	"I did smoke three cigarettes a day, but honestly, I think, as I mentioned before, that it was the fall from the scaffolding that caused it." (Patient, February 2023).
		"Throughout my lifetime, I have inhaled many things, I maintained elevators, fumigated, used a lot of chemicals, and toxic substances. In these jobs, they provided helmets, but never face masks or gloves, so I think it could be that way I developed cancer". (Patient, March 2023).
		"Sometimes I regret how I faced the problem initially. We must not underestimate cancer, I thought it was gastritis at first, I only had slight intercostal pain but my advice to other people is prevention, pay attention to your own body, do not be afraid or underestimate it." (Patient, March 2023).
Alternative self-care practices and remedies	Patients may adopt self-care practices as the first strategy, relying on knowledge shared within their social circle. Self-care includes self-medication and a combination of allopathic and traditional or alternative practices. This approach may delay seeking biomedical care, especially if the symptoms are not perceived as severe.	"Now I'm following a protocol, and they tell you not to take certain things, but before going to the INCAN, I took syrups and chlorine dioxide for lung problems, my dad would tell me to drink herbal remedies with lemon and honey, I even consumed capsules made from rattlesnake and skunk." (Patient, February 2023).
Lack of knowledge about lung cancer	Patients and their family members often have limited knowledge about lung cancer and its symptoms before diagnosis. Awareness campaigns primarily focus on other types of cancer, leading non-smoking patients to dismiss the possibility of lung cancer. Lack of awareness and understanding among the general population and healthcare professionals at the primary care level contributes to delayed diagnosis of lung cancer.	"I hadn't heard anything about lung cancer until it happened to me. I only knew that, due to smoking, that was our belief, that smokers get cancer. But now we know that there are other factors like asbestos or wood smoke." (Patient, February 2023).
		"I actually thought that it could only happen to smokers, then they explained to me that it can happen to anyone due to several other reasons. In fact, at first, I thought that perhaps it was tuberculosis." (Patient, March 2023).
Fear of diagnosis	Fear of having a more serious illness, including cancer, can also discourage patients from seeking care.	"Honestly, I suspected that something was wrong, but as an adult, I was afraid of having something serious, especially for the sake of my child. One tends to deny it and time goes by." (Patient, February 2023).
Prioritisation of functional health	Patients may prioritize functional health, including work productivity and caregiving for vulnerable individuals, over their own health concerns. The social construction of risk leads to the underestimation of symptoms, particularly if they do not significantly impact daily activities. This delay in recognizing symptoms and seeking care can lead to advanced disease stages at the time of diagnosis.	"In rural areas, preventive care doesn't reach them, and there are insufficient services available. Since these people have a certain mindset, they don't go to the doctor until they feel sick and are unable to work. I've had patients who tell me, 'My animals, my crops are a priority,' and they are more dedicated to that than to their own health." (Health-care professional, March 2023).
		"We visit the doctor only when we are very sick. We take things for granted, and we never say to ourselves, I am partly to blame, I did this, and I did that. We also normalize a cough because we must deal with everyday life and it's tough. It is hard for us to admit that we do not take care of ourselves because we prioritize other things such as our job or our family". (Patient, March 2023).
		"When I started having symptoms, my mother got sick, and even though I knew something was happening to me, I didn't seek help because I thought it would be less serious and my main priority was to look after her." (Patient, March 2023).

(Continues)

Table 3. Barriers and facilitators identified in the Mexican population in the context of lung cancer care, description of each category, and quotes that exemplify the theme *(continued)*

Barriers	Description	Verbalizations/quotes example
Family discord and divergent beliefs	Complex dynamics and differing perspectives within the patient's family regarding the management of the patient's health condition can arise. It reflects the divergence of opinions and support levels among family members, which can significantly impact the patient's healthcare decisions and emotional well-being. Support from family and friends initially fosters encouragement, but negative comments over time may lead to abandonment or resistance to treatment. The concept of family as a source of support is challenged when some family members show disinterest or indifference, becoming an additional barrier to continuing treatment.	"My family has not been able to fully understand my situation. They even say it is better not to take her to the hospital, they are only going to torture her without major benefits. We are 8 siblings and most of them believe the effort is worthless, and to be honest I only receive support from my niece. I often say to myself, 'if we don't try, we'll never know'. At first, some relatives gave me some support, but as time went by, they flew away, they wanted a normal life and we feel alone because the road is very long." (Patient, March 2023).
Time constraints and thorough patient examination	Limited time for conducting thorough medical histories at the primary care level hinders early diagnosis of lung cancer. General practitioners may overlook or misdiagnose lung cancer symptoms due to time constraints, resulting in delays in seeking appropriate specialized care.	"To be absolutely honest, we don't have enough time to examine our patients thoroughly. Most of the time, we only have roughly 15 min to perform the check-up because we have another patient waiting outside; pregnant woman, injuries, etc. Therefore, we do sometimes fail to explore more and send patients to a second level, we must be more suspicious from the very beginning". (Health-care professional, February 2023).
Lack of medical training	Insufficient training and knowledge among general practitioners lead to delayed or missed diagnoses. General practitioners may not consider lung cancer as a possibility and may treat symptoms as unrelated conditions (flu or musculoskeletal injuries).	"Look, there is not so much dissemination about lung cancer because it is not one of the main types of cancer. But I also think that many general practitioners delay diagnosis because we don't have the proper knowledge or training. I try to be up-to-date, and if I have any doubts, I consult a pulmonologist, not underestimate the case, and try to refer the patient to the specialist." (Health-care professional, March 2023).
		"I went to the health center for my cough, this was in January 2020. They told me it was just the flu and gave me cough syrup. Then in March, they even tested me for COVID-19, but it came back negative. Months went by, but I kept losing a lot of weight, and I couldn't work anymore. I reached a weight of 50 kg and was very weak when the pneumologist saw me." (Patient, March 2023).
		"At both, the primary and secondary levels of care, biopsies are not performed, and there are not enough trained doctors who can differentiate lung cancer because they lack the knowledge. There are only a few bronchoscopies being conducted due to the insufficient number of specialists." (Health-care professional, March 2023).
		"Doctors told me it was a throat infection, so I took antibiotics. At first, I felt better, but then the symptoms returned, and they would prescribe something else, but it wouldn't go away. I also started experiencing back pain and extreme fatigue until 1 day I felt like I was suffocating, and they rushed me to the emergency room." (Patient, February 2023).
Disruptive patient journey	Patients may resort to seeking both public and private healthcare, to expedite diagnosis and treatment due to the chronicity of symptoms and worsening condition. Seeking private specialists for diagnosis or explanations not received from general practitioners in public health centers or private clinics is a common approach.	"I went to three private doctors, first I went to my general practitioner whom I trusted because he had seen my children, but he told me that the cough might be asthma, but never mentioned anything about cancer. Then I went to the SIMI clinics, where they told me it was allergies until I was finally taken to a pneumologist." (Patient, February 2023).

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Table 3. Barriers and facilitators identified in the Mexican population in the context of lung cancer care, description of each category, and quotes that exemplify the theme *(continued)*

Barriers	Description	Verbalizations/quotes example
		"INER has been amazing, I am very grateful to God and the doctors and nurses, but one has to take action because sometimes, if you wait for public healthcare, 3 or 4 months pass and your cancer grows. I don't feel that the attention is bad, but at INER, for example, the PET scan was not available, so I had to get it done privately. In my life, every minute counts, and I have always tried to find an alternative." (Patient).
Reduced workforce	A critical shortage of adequately trained medical professionals leads to delayed lung cancer diagnoses and limited access to essential procedures like biopsies and bronchoscopies.	"At both, the primary and secondary levels of care, biopsies are not performed, and there are not enough trained doctors who can differentiate lung cancer because they lack the knowledge. There are only a few bronchoscopies being conducted due to the insufficient number of specialists." (Health-care professional, March 2023).
High patient demand and insufficient diagnostic infrastructure	The high number of patients seeking services at tertiary-level institutions leads to increased waiting times for appointments and diagnostic studies. This influx of patients can overwhelm the healthcare system, affecting the quality and timeliness of care provided to cancer patients. Health settings often lack the necessary infrastructure for comprehensive diagnostic tests and examinations, such as X-rays and ultrasounds. The absence of essential diagnostic tools delays the identification of lung cancer. Patients may need to seek external services or invest their own resources to access specific tests, leading to additional financial burdens.	"INER has been amazing, I am very grateful to God and the doctors and nurses, but one has to take action because sometimes, if you wait for public health care, 3 or 4 months pass and your cancer grows. I do not feel that the attention is bad, but at INER, for example, the PET scan was not available, so I had to get it done privately. In my life, every minute counts, and I have always tried to find an alternative." (Patient).
		"When he arrived at INER his health had worsened already, he was not eating, he was not walking, and they told us that he was in a terminal phase. They only prescribed him tramadol with paracetamol due to the severe pain. They told him that cancer had already metastasized to the colon and kidneys. I think that what delayed us the most was the biopsy because we had to wait for it to be performed. Nowadays I think that maybe we could have sold something, anything really to speed up the process and maybe my husband would be better off." (Family-caregiver, March 2023).
		"They delayed some studies like the PET scan, they told me it would take up to 3 months at INCAN, and it's because there are few machines for a lot of people who need support. I'll be honest, most of my studies I did privately, outside the institution, and that helped me a lot. But I think many people get lost due to the waiting times because they don't have the resources to do certain studies privately." (Patient).
Catastrophic expenditures	Patients from rural areas face significant economic burdens in accessing treatment at centralized urban hospital institutions. The costs of external tests, medications, transportation, accommodation, and meals in Mexico City contribute to barriers in treatment continuity. Some patients can only afford one meal a day due to financial constraints. Transportation under specific conditions and precautions, such as taking flights instead of buses, further increases costs. The economic impact creates imbalances within the family, and some patients and their families may resist continuing treatment due to financial strain.	"Sometimes we spend 3 h going and another 2 h returning. I cannot use the underground, so we take a taxi to INCAN, and it charges us $600 round trip, and that is because he is a neighbor. But sometimes I do not just go for the consultation; I also go to the laboratory, the pneumology, and the dermatology consultation. They say the treatment is comprehensive, so in 1 month, I have several trips to the hospital, 4 or 5 times, not all on the same day." (Patient, February 2023).
		"We do not have enough information about what to do, where to go. Treatments are very expensive, and in my town, people do not really know what to do or where to go. Those of us who have the possibility to go to the city have some hope, but those who do not, they die. Money gives you the opportunity to be cured. If you do not die from cancer, you die from not having the correct treatment or access to the right drugs". (Patient, February 2023).

(Continues)

Table 3. Barriers and facilitators identified in the Mexican population in the context of lung cancer care, description of each category, and quotes that exemplify the theme *(continued)*

Barriers	Description	Verbalizations/quotes example
		"I was lucky enough, because a doctor from Oaxaca who is very humanist, helped me, he moved quickly and thanks to him that's how I entered the protocol. In my community people sell their lands, cattle, or other belongings to pay for the treatment, and if they run out of money, they are already presumed dead, because it is difficult to pay for the treatment. I think that doctors are available, but it is a reality, if you don't have money, you cannot ask for help". (Patient, March 2023).
		"My backbone really hurts, so I cannot travel by bus, I must fly to Mexico City and this implies elevated costs as you may imagine. One of my brothers helped me, but the last time he was there for 10 days, and we barely ate, when I came back, I was all swollen and very tired". (Patient, March 2023).
Bureaucratization	The bureaucratic processes in the healthcare system can be time-consuming and frustrating for patients seeking treatment. Administrative hurdles may delay access to essential tests and therapies, causing unnecessary anxiety and stress for patients and their families.	"There are people who arrive with luggage and sleep at INER, we all understand the high demand for services, and that is something that impacts me a lot and saddens me even more than my own treatment because the waiting hours are terrible at INCAN. Sometimes you spend the whole morning for a consultation and don't leave until 3 in the afternoon." (Patient).
Underreporting and misdiagnosis challenges	Lack of regionalized care and awareness campaigns contributes to the underreporting and delayed diagnosis of lung cancer.	"According to our knowledge, the incidence of lung cancer appears to be less frequent in the country, but there is underreporting because, for example, a general physician who doesn't know what lung cancer is, might think that the patient died from a chronic obstructive pulmonary disease, pneumonia, or another respiratory disease. This situation leads to inadequate registration." (Healthcare professional, March 2023).
Biographical disruption and role adjustments	The illness and its treatment disrupt the lives of both patients and their family environment. Changes in roles and dynamics within the family occur, and introspection leads to adjustments in life goals and attitudes toward others. Family caregivers take on new roles and responsibilities to support the patient's treatment journey. Some patients find a renewed focus on family and attempt to make up for lost time with loved ones.	"Many things have changed. Now my wife is the one who goes to work, and I stay at home taking care of the children. I play board games with them, watch movies, and review their homework. I am more present for them; I want to make up for lost time." (Patient, February 2023).
		"Sometimes I ask my patients: How come you stopped coming here for your treatment, then they tell me, 'I don't have anyone to leave the children with' or 'my husband is working', it is tricky because a disease changes your routine and you have to adjust in many different ways". (Healthcare professional March 2023).
Limited mental health support	Patients and family caregivers may face barriers in accessing professional mental health support due to time, money, and energy constraints. Many choose to address mental health through religious beliefs and support from religious institutions, considering them helpful in navigating difficulties during cancer treatment.	"Actually, I wouldn't seek support for mental health, to be honest. What I need is treatment, that's all. I feel supported by my family and the church I attend." (Patient, February 2023).
		"Some of us may say that we don't need help, but that's not entirely true. I would love to talk about some of my problems, but to be honest, once I leave the hospital, I just want to get home and rest. I would say I'm not against receiving therapy but sometimes I don't have time or stamina to focus on other stuff." (Patient, March 2023).

(Continues)

Table 3. Barriers and facilitators identified in the Mexican population in the context of lung cancer care, description of each category, and quotes that exemplify the theme *(continued)*

Barriers	Description	Verbalizations/quotes example
Family or caregiver's burden	Family caregivers, often female relatives, assume a significant role in accompanying and supporting patients throughout their treatment journey. They act as a "guardian" and are responsible for organizing appointments, providing emotional support, and acting as communicators between the patient and healthcare professionals. The role of family caregivers can be emotionally and physically taxing, leading to stress and anxiety.	"One day I started feeling unwell, I began to feel dizzy, and my blood pressure skyrocketed. The doctors told me that it was probably due to stress and advised me to see a psychologist. But I asked them: 'When? And with what money?'. I used to tell people that nobody knows what I'm going through. If they asked me, I had already touched a part of hell because I couldn't sleep, due to the travels, taking him to his appointments. I couldn't detach myself from him because I saw him writhing in pain. We decided that our child would go to live with my parents because we didn't want him to see us like that. Then I thought, it's not just my mental health anymore, it's my blood pressure. I thought, 'what if we both die, who will take care of my child?'" (Family caregiver, February 2023).
Doctor-patient relationship	Some patients reported encountering doctors who lacked effective communication skills and appeared cold and distant when delivering diagnoses. This lack of empathy can make patients feel abandoned and affect their emotional well-being. A positive doctor-patient relationship is crucial for providing the necessary support and guidance throughout the cancer journey.	"Sometimes the doctors give you the basics, they give you the diagnosis, but they don't provide any further information. It feels cold and insensitive. The journey of treatment begins, and you don't know what to expect, you feel alone." (Patient, March 2023). "Usually, doctors don't listen to us, or for example, they talk to our relatives in private, so we feel anxious and dumb. I think maybe they could be a little bit more straight-forward with their explanations and tell us things in an honest and easier way so we can understand what's going on". (Patient, February, 2023).
Treatment's secondary effects	Weariness associated with the treatment itself, such as radiotherapy or chemotherapy, may also lead to resistance in continuing with the treatment.	"Chemotherapy sessions do knock you down. Sometimes you already want to throw in the towel and quit, but you must not let yourself down, depression is an important obstacle, and you must stay active as much as possible. I do my own things, I get up and try to do my own daily routines, I don't limit myself, I try to live my life normally". (Patient, February 2023).
Misguided improvement and patient drop-outs	Some patients may feel overly confident in the initial success of the treatment, leading to a false sense of improvement and abandonment of treatment.	"We have seen patients who arrive in a very critical condition, start feeling better with the treatment, and then abandon it, thinking they are much better. That is dangerous and something we need to emphasize." (Health-care professional, March 2023).
Stigmatization and fear of compassion/pity	Patients may use synonyms or avoid naming their condition as cancer when discussing it with others to avoid stigmatization and pity. The fear of being perceived as weak or helpless may lead to selective disclosure of the diagnosis only to trusted individuals.	"Now I dare to share my problem with more people, but to this day, I haven't told some family members and friends about my problem. I don't like them seeing me like this and then feeling sorry for me." (Patient, February 2023).
Facilitators	**Description**	**Verbalizations/quotes example**
Facilitators/ Navigators	The presence of a "navigator or facilitator" assists patients in accessing specific tests and confirms the suspicion of lung cancer, guiding them through the process. Facilitators or navigators act as referral agents and help patients access specific hospital institutions more quickly. They also suggest patient participation in research protocols and enable institutional connections for those with limited resources from rural contexts. The support from facilitators is particularly beneficial for patients facing socioeconomic problems and non-smoking lung cancer patients.	"A doctor told me about the organization called 'RCV,' they responded quickly, I told them my story, and they said they could get Erlotinib at a lower price, 10,000 pesos when it's much more expensive outside, like 30,000 or even 40,000 pesos." (Patient, March 2023).
		"Firstly, the attention should be more regionalized as we lack more centers of excellence in the east, northeast, center, and south of the country, that is why so many patients are currently channeled to Mexico City. I wish there were more possibilities to refer patients. Some doctors only treat in private medicine, but for example, those of us who work in both (the public and private sectors), sometimes we try to support patients who don't have a strong financial capacity. It would be much better if these patients wouldn't depend upon a facilitator, but

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Table 3. Barriers and facilitators identified in the Mexican population in the context of lung cancer care, description of each category, and quotes that exemplify the theme *(continued)*

Facilitators	Description	Verbalizations/quotes example
		instead, receive proper help from a fair and efficient system. It is indeed great to be able to support patients when we can, but I genuinely believe that if a general practitioner could have the tools to know how to attend to suspect and channel cancer patients, it would be far easier." (Health personnel, March 2023).
Participation in research protocols	Participation in research protocols provides an alternative for patients to receive treatment, especially due to the high costs of medications like oral chemotherapy pills. The funding from pharmaceutical companies covers treatment costs, but patients need to cover other expenses like transportation and accommodation. Despite the challenges, patients view research protocols as an essential option for accessing treatment and extending their life expectancy.	"I am in a protocol that finances the entire treatment thanks to the pharmaceutical company Janssen because the pills cost 130,000 pesos, or so I've been told. Imagine if one had to pay for them out of pocket, I wouldn't be here anymore." (Patient, March 2023).
		"When I entered INCAN, I couldn't even lift up a pen. I was very skinny back then, nowadays, I greet the police at the entrance and tell them, 'don't you recognize me? I'm still here, and if I'm still alive, it's because of the protocol'. They literally gave me a life expectancy of 5 more years, so I stick to the protocol and everything they tell me to do, because I trust them." (Patient, March 2023).
Non-profit organizations support	Facilitators or navigators recommend seeking support through non-profit organizations like "RCV." These organizations provide assistance through donation or sale of oncology medications at a reduced cost, support with transportation expenses to Mexico City, and in some cases, food supplies. These organizations play a crucial role in helping patients access affordable care and resources during their cancer journey.	"A doctor told me about RCV, they responded quickly, I told them my story, and they said they could get Erlotinib at a lower price, 10,000 pesos when it's much more expensive outside, like 30,000." (Patient, March 2023).
		"There are moments of need for the patient that are crucial to continue with the treatment, and there is where foundations and associations have a meaningful role, managing resources to absorb some of these costs." (Health professional, March 2023).
Family or caregiver's perseverance and advocacy	This entails unwavering commitment, advocacy for medical attention, emotional support, and resourcefulness. Caregivers persistently motivate loved ones, navigate the healthcare system, and overcome resistance, playing a pivotal role in the well-being and healthcare journeys of their family members facing health challenges. The catalyst, a friend or family member, maybe the one who motivates and supports the patient in seeking medical attention when needed.	"Then he told me, 'I don't want to live anymore, whatever has to happen will happen, so better save money for the burial'. Then, I replied, 'I know it's tiring, but you have to face a disease like this, we won't ever let you down'. I said to him, 'you're going to have to put up with it'. As a family member, it's extremely important to constantly motivate them. At that time, he had 10 radiotherapy sessions and couldn't eat." (Family caregiver, March 2023).
		"He was always healthy and in good shape, he did not get sick easily, and that is why he never really paid attention to us when we told him that we saw him deteriorating. We constantly reminded him to visit a doctor, but it was only until a nephew decided to take him involuntarily that he attended. He was in fact deceived because they told him that the consultation was for his mother and not for him." (Family-caregiver, March 2023).
		"My granddaughter was the one who told me, 'I see you more tired, grandma. Have you been to the doctor? That's strange.' And they took me to a specialist who already suspected my condition." (Patient, February 2023).
		"He was always healthy, and rarely got sick, and that's why he dismissed our concerns when we told him he didn't look well and should see a doctor. It was actually a nephew who took him, deceiving him by saying they were going to his mother's appointment." (Family caregiver, March 2023).

RCV: Respirando con Valor; INCAN: National Cancer Institute; INER: National Institute of Respiratory Diseases.

and emotional well-being positively. However, complex dynamics and differing perspectives within the patient's family can arise, leading to varying levels of support and even abandonment or resistance to treatment. Thus, creating awareness of the disease and supporting the patient by mediating with the family might prove useful to reduce negative outcomes.

Although family members can also act as facilitators, this can be emotionally and physically taxing. Family caregivers, often female relatives, assume significant roles in supporting patients throughout their treatment journey. Support for family members is advised in addition to supporting the patient's mental health.

Health system barriers and facilitators

Results show the health-care system itself is a barrier to lung cancer care. For instance, limited time for conducting thorough medical histories at the primary care level can result in overlooked or misdiagnosed symptoms. In addition, high patient demand and insufficient diagnostic infrastructure were called out, as well as a reduced workforce to provide care to lung cancer patients. Thus, the health system necessitates a robust enhancement of diagnostic infrastructure at the primary and secondary levels of health care[3]. In addition, public policies must be formulated to decentralize health-care services[3,5], ensuring equitable access to quality care for all patients. Initiatives such as telemedicine[42] can be leveraged to bridge the gap and provide specialist consultations and support to primary care physicians in underserved regions. This approach is likely to result in better patient survival rates and alleviate the financial burden that families often face in accessing health-care services[1].

Establishing seamless communication channels between primary care centers and specialized oncology institutions can expedite the referral process, thereby reducing the time between symptom presentation and definitive diagnosis[43]. Such coordination is particularly crucial in rural areas where access to tertiary health-care facilities may require additional logistical arrangements[3].

Results from our study show it is essential to urgently address the ethical, economic, and emotional conflicts arising from the need for institutional exclusivity for patients with social insurance who want to receive lung cancer treatment at specialized third-level institutions from the Ministry of Health. By encouraging patients to relinquish their social security benefits to access free treatment at these institutions, additional barriers to oncological treatment adherence are created, causing emotional and financial stress. Thus, policies aiming to reduce catastrophic expenditures should be put in place for all population groups.

Patients often view research protocols as essential alternatives for accessing treatment. However, pharmaceutical companies and research institutions must adopt a comprehensive approach to patients by covering expenses such as transportation, lodging, and meals for both patients and their family caregivers during research protocols. This will help overcome socioeconomic barriers, leading to improved greater coverage and equity.

Patients navigated logistical and administrative issues in the health system that hindered their care. Similar to the literature, bureaucratic processes within the health-care system became time-consuming and frustrating for patients, causing unnecessary stress[5].

A critical finding of this study is the role of medical navigators or facilitators in guiding patients through the health-care system and facilitating access to timely diagnosis and treatment. Their involvement becomes crucial, especially for patients from rural or semi-urban areas. These individuals act as referral agents, helping patient's access specific hospital institutions more quickly and suggesting participation in research protocols.

Patient navigation programs can also help in reducing delays in lung cancer care[44]. These can help make the patient journey less disruptive in the context of a fragmented health system. They can also have a history of helping patients to have access to mental health services or peer groups that might mitigate the fear of diagnosis, treatment, and death. Hence, the navigator or facilitator role can significantly improve patient outcomes[45-50].

It is imperative to recognize the need for ongoing research in this field. Continuous investigation into the barriers and facilitators faced by lung cancer patients in Mexico will not only deepen our understanding but also inform the development of targeted interventions and policies. Engaging with health-care professionals at various levels of the health-care system will also be essential to inform policy changes and improve the overall quality of care for lung cancer patients.

Limitations

While this study has made significant strides in understanding the barriers and facilitators faced by lung cancer patients in Mexico, it is important to acknowledge that it may not capture all possible factors influencing this complex phenomenon. Factors such as geographical variations, socioeconomic disparities, and differences in health-care accessibility might contribute to variations in the barriers and facilitators experienced by different individuals and communities.

Although interviews conducted through telephone may have limitations, the quality of the data that emerged depends on the expertise of the interviewer[51-53]. This was chosen as the preferred data collection method and as a pragmatic choice necessitated by logistical challenges surrounding patient transportation and the limited access to Internet connectivity among participants. This approach has been previously used in complex settings[21,52-54].

Conclusion

Lung cancer patients interviewed in Mexico face barriers to care such as: feeling unworthy of treatment, financial toxicity, lack of awareness of cancer symptoms, and poor symptom recognition and interpretation. Barriers such as poor relationships with health-care providers, and low levels of trust in the health-care system were not found.

Caregivers feel burdened, while also continuing to advocate and persevere in reaching access to diagnosis or treatment. However, doctors do not appear to have an advocating role. Similarly, non-for-profit and patient navigation programs seem to facilitate the patient's journey, and participation in research protocols seems to be an alternative that increases access to treatment.

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Conflicts of interest

Elysse Bautista-González declares no conflicts of interest. However, it is noted that she was granted the MSD Oncology Policy grant during the time the study was conducted.

Author contributions

Elysse Bautista-González: conceptualization, methodology design, formal analysis, translation, writing-original draft, review, and editing. Gunther Adolfo Hasselkus-Sánchez: methodology design, data collection, formal analysis, writing-original draft, review, and editing.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ARTÍCULO ORIGINAL

Gasto indirecto en pacientes con cáncer de cuello uterino sometidas a radioterapia en el centro del Perú, 2020-2021

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Resumen

Antecedentes: *Toda persona sin trabajo a causa del cáncer constituye una pérdida económica para la sociedad. Las medidas más notables para cuantificar es el costo de productividad.* **Objetivo:** *Conocer los gastos indirectos por el tratamiento de irradiación en cáncer de cuello uterino y si estos están asociados o relacionados con factores clínicos, sociales y económicos.* **Método:** *Se recolectaron de manera prospectiva datos clínicos, sociales y económicos. Se usaron pruebas de asociación y correlación, como las pruebas U de Mann-Whitney/Kruskal-Wallis y rho de Spearman.* **Resultado:** *Participaron 149 pacientes, con mediana de distribución del gasto indirecto semanal en dólares americanos para paciente y familiar de $74.47 y $61.05, respectivamente. Está correlacionado negativamente el gasto indirecto semanal acumulado con la edad del paciente y la edad del acompañante, asociado con el sexo varón del acompañante. El estadio clínico se asocia cuando se calcula el gasto por las horas empleadas en el cuidado del acompañante en casa.* **Conclusiones:** *El gasto indirecto por el tratamiento es alto y considerable al comparar con el ingreso promedio mensual. Este gasto semanal se incrementa cuando el acompañante es varón, la edad del paciente o del acompañante es menor a 65 y 45 años, respectivamente.*

Palabras clave: *Neoplasias del cuello uterino. Ayuda financiera. Financiación de la atención de la salud. Costos y análisis de costo.*

Indirect expenditure in patients with cervical cancer who underwent radiotherapy in the center of Peru, 2020-2021

Abstract

Background: *Every person without work due to cancer constitutes an economic loss for society. The most notable measures to quantify is the cost of productivity.* **Objective:** *To know the indirect expenses for irradiation treatment in cervical cancer and whether these are associated or related to clinical, social and economic factors.* **Method:** *Clinical, social and economic data were collected prospectively. Association and correlation tests were used, such as the Mann-Whitney U/Kruskal-Wallis tests and Spearman's rho.* **Result:** *One hundred forty-nine patients were collected, with the median distribution of weekly indirect spending in US dollars for patient and family of $74.47 and $61.05, respectively. The accumulated weekly indirect expenditure is negatively correlated with the age of the patient and the age of the companion, associated with the male sex of the companion. The clinical stage is associated when the expense is calculated for the hours involved in the companion's care at home.* **Conclusions:** *The indirect expense for treatment is high and considerable when compared with the average monthly income. This weekly expense increases when the companion is male, the age of the patient or companion is less than 65 and 45 years, respectively.*

Keywords: *Cervical neoplasms. Financial support. Healthcare financing. Costs and cost analysis.*

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Introducción

El índice de desarrollo humano (IDH) correlaciona negativamente con la incidencia y mortalidad de cáncer de cuello uterino (CACU), que alcanza los primeros lugares en países en vías de desarrollo como Perú e Indonesia, entre otros[1-3]. El cáncer ocurre en el 70% de las personas de ingresos bajos y medios[2]. Además, existe el creciente reconocimiento por parte de los oncólogos de la «toxicidad financiera», un término integral para el daño del paciente debido a los costos directos e indirectos del tratamiento oncológico[4,5].

Debido a la incidencia del CACU (15.2 por 100,000) en América del Sur, la carga económica asociada resultante es significativa tanto para la sociedad como para el individuo. Sin embargo, hay escasez de estudios que hayan analizado el costo del CACU especialmente en América del Sur, que tiene una tasa de mortalidad promedio de 7.1 por 100,000 habitantes[6].

Toda persona que no puede trabajar a causa del cáncer, ya sea de manera temporal o permanente, constituye una pérdida económica para la sociedad. La medida más notable para cuantificar la carga es el costo de productividad, que proporciona una estimación de la pérdida del país debido a la ausencia laboral y la mortalidad relacionada con el cáncer[7,8]. Sin embargo, dichos datos para Latinoamérica son escasos. Los estudios disponibles que evalúan el impacto económico del CACU solo lo han descrito desde la perspectiva de los proveedores de atención médica y concluyen que el CACU tiene un impacto económico sustancial[9,10]. Las políticas de salud de los países se centran en controlar y reducir la carga económica total del cáncer[11]; por lo tanto, el estudio actual se realizó con el objetivo de examinar los gastos indirectos en dólares americanos por el tratamiento de irradiación en CACU y si estos están asociados o relacionados con factores clínicos, sociales y económicos.

Método

Durante el periodo 2020 a 2021, se atendieron 211 pacientes de CACU con indicación de teleterapia seguida o no por braquiterapia de alta tasa de dosis (BATD) en el instituto, ubicado en la región Junín de la Macrorregión Centro de Perú. Al calcular la muestra con margen de error del 5% y un nivel de confianza de 97.5%, resultó en una muestra de 149 casos, siendo escogidas mediante el método aleatorio simple. Se registraron sus datos de manera prospectiva. Características clínicas: edad, sesiones de teleterapia, BATD y estadio clínico. Condiciones sociales: tipo de seguro, acompañante, sexo del acompañante y edad del acompañante. Gasto indirecto: gasto indirecto semanal o por esquema de irradiación.

Los criterios de inclusión fueron los siguientes: pacientes mayores de 18 años, con diagnóstico de neoplasia maligna de cuello uterino por histología, que recibieron la primera teleterapia en 2020 o 2021, más del 70% del total de teleterapias se recibieron en las instalaciones y que mostraron adherencia al esquema planteado. Los criterios de exclusión fueron: esquema de tratamiento para enfermedad en estado de progresión, nunca iniciaron la teleterapia por motivo médico, reirradiación y más del 20% de las sesiones de teleterapia recibidas fueron en condición de hospitalizado.

Características propias del paciente

Respecto a la condición de seguro, tenía dos opciones: si el paciente era atendido bajo el Seguro Integral de Salud (SIS) o bajo la modalidad de Seguro Social de Salud (ESSALUD). La asignación de estadio clínico se realizó según la clasificación de la Federación Internacional de Ginecología y Obstetricia (FIGO)[12]. Los estadios clínicos IB y IIA, IIB al IIIC1, IIIC2, IVA y IVB por metástasis inguinal recibieron cirugía con teleterapia durante cinco semanas, teleterapia más BATD durante ocho semanas, teleterapia a la pelvis más BATD continuando con teleterapia a retroperitoneo durante 13 semanas[3], teleterapia durante siete semanas aproximadamente, y teleterapia más BATD durante nueve semanas aproximadamente[13,14], respectivamente.

Gasto indirecto

El gasto indirecto de la paciente se calculó a partir de la encuesta, en donde mencionaba la cantidad de su remuneración mensual antes del diagnóstico oncológico. El gasto indirecto del acompañante fue a partir de la encuesta, en donde mencionaba cuánto era su sueldo mensual antes de dedicarse a cuidar a la paciente, adicionalmente detalló cuantas horas del día estaba involucrado durante el tratamiento y en casa. El gasto indirecto acumulado era la sumatoria del gasto indirecto del acompañante y paciente en un intervalo de tiempo establecido ya sea semanal o por esquema. Así mismo, se realizó el cálculo paralelo del acompañante acumulado a partir del valor monetario de la hora que pierde por no trabajar.

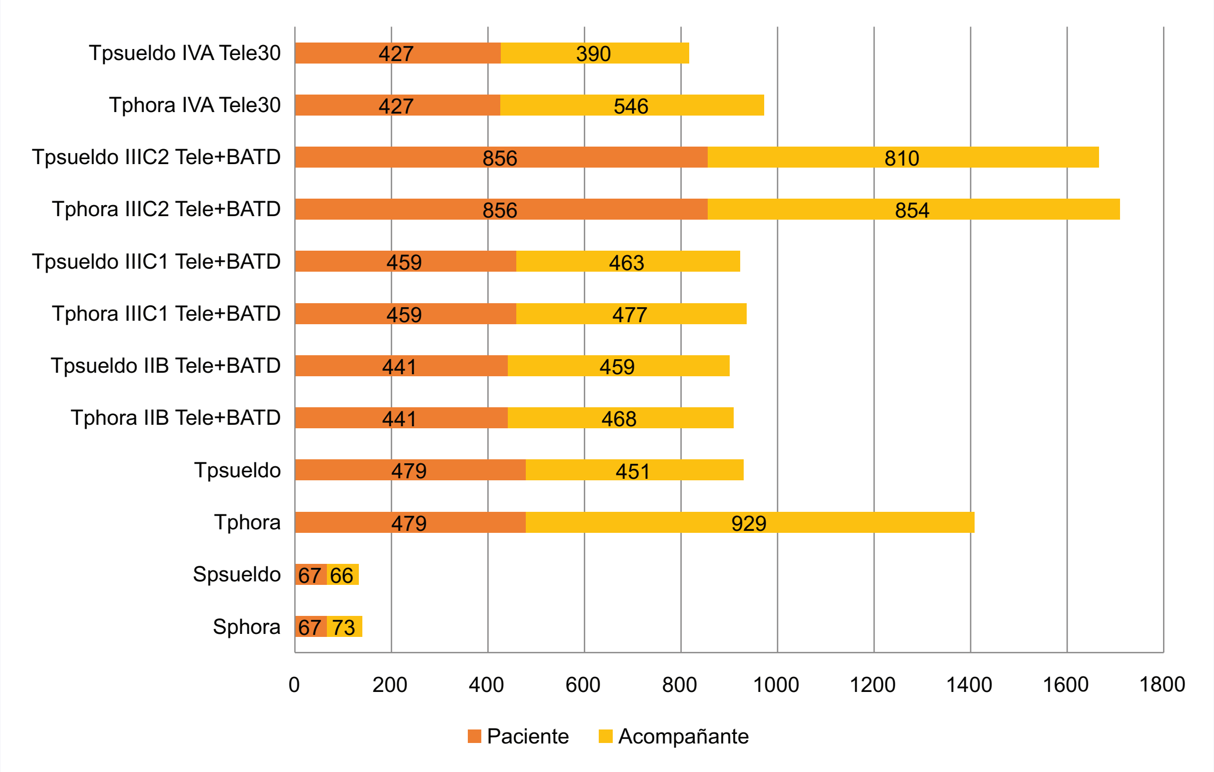

Figura 1. Distribución del gasto indirecto por la radioterapia*.
*Los cálculos están basados en dólares americanos.
Spsueldo: gasto indirecto calculado por equivalente a semana perdida según salario; Sphora: gasto indirecto calculado por equivalente a hora desaprovechada en trabajar; Tpsueldo: gasto indirecto total del esquema según el sueldo promedio mensual; Tphora: gasto indirecto total calculado por equivalente a hora desaprovechada en trabajar; Tele: teleterapia y braquiterapia de alta tasa de dosis.

Análisis estadístico

Todos los datos y el análisis estadístico se realizaron con SPSS (versión 29.0, Chicago, IL, EE.UU.). La descripción se realizó con medias o proporciones. Se analizaron las variables mediante la prueba de normalidad de Kolmogorov-Smirnov, y en caso de que no siguieran distribución normal, se utilizó estadística no paramétrica. Si el caso no contaba con acompañante, se excluía para el análisis de gastos indirectos acumulado o familiar.

Se realizó la presentación del informe de acuerdo con las normas STROBE (*Strengthening the reporting of observational studies in epidemiology*).

Resultados

Se incluyeron 149 pacientes, todas con trabajo antes del diagnóstico. Las características de las pacientes se presentan en la tabla 1, de las cuales solo 119 continuaron con BATD luego de la teleterapia; la distribución por estadio clínico predominante fue IIB y IIIC1, con 22.82 y 32.21%, respectivamente. La presencia de acompañantes predominó, el 70.47% de casos. Las medianas del gasto indirecto semanal en dólares americanos para paciente y familiar fueron de $74.47 y $61.05, respectivamente. El esquema de radioterapia que resultó con mayor costo indirecto fue para el estadio clínico IIIC2 con teleterapia más BATD, siendo siempre mayor cuando se calculaba el gasto indirecto del familiar a partir del sueldo/hora (Fig. 1).

Se analizaron las variables mediante la prueba de normalidad de Kolmogorov-Smirnov, resultando que todas las variables carecen de una distribución normal, lo que forzó a utilizar pruebas no paramétricas para asociación y correlación, como la prueba U de Mann-Whitney/Kruskal-Wallis y la rho de Spearman, respectivamente.

Al evaluar los gastos indirectos semanales, resultó estadísticamente significativo que el gasto indirecto

Tabla 1. Características clínicas, sociales y económicas de las pacientes

Variable		n	Media	Mediana	%	DE
Paciente	Edad	149	54.1	53		12.2
	≤ 40 años	20			13.4	
	41 a 60 años	78			52.3	
	61 a 70 años	37			24.8	
	≥ 71 años	14			9.4	
	Tipo de seguro					
	SIS	121			81.21	
	ESSALUD/particular	28			18.79	
	Tratamiento					
	Teleterapia	149	29.8	28		9
	BATD* Sí	119			79.9	
	BATD* No	30			20.1	
	Estadio					
	IB	12			8.1	
	IIA	3			2.0	
	IIB	34			22.9	
	IIIB	16			10.7	
	IIIC1	48			32.2	
	IIIC2	16			10.7	
	IVA	16			10.7	
	IVB	4			2.7	
	Sueldo mensual	149	261.9[†] (995.6)	276.3[†] (1050.0)		53.64[†] (203.8)
Acompañante	Presencia					
	Sí	105			70.5	
	No	44			29.5	
	Edad	105	34.97	34	7.61	
	≤ 40 años	80			76.2	
	≥ 41 años	25			23.8	
	Sueldo mensual	105	268.2[†] (1019.3)	250.0[†] (950.0)		48.7[†] (184.9)
	Tiempo por tratamiento[§]	105	3.5	3		0.5
	Tiempo por hogar[§]	105	5.3	5		0.9
Gasto indirecto	Semanal[‡]					
	Paciente	149	66.6[†] (252.9)	74.5[†] (283.0)		14.0[†] (53.2)
	Acompañante	105	65.5[†] (249.0)	61.1[†] (232.0)		11.9[†] (45.1)
	Total del esquema[‡]					
	Paciente	149	478.9[†] (1820.0)	483.0[†] (1838.0)		154.4[†] (586.8)
	Acompañante	105	451.0[†] (1714.0)	421.6[†] (1602.0)		121.2[†] (460.7)

*Braquiterapia de alta tasa de dosis.

[†] Valor en dólares americanos (1 dólar es igual a 3.80 soles).

[‡] Calculado a partir del sueldo ganado por semana.

[§] Horas empleadas por día.

BATD: braquiterapia de alta tasa de dosis; DE: desviación estándar; ESSALUD: Seguro Social de Salud; SIS: Seguro Integral de Salud.

semanal acumulado está correlacionado negativamente con la edad del paciente y la edad del acompañante; así mismo, este gasto indirecto es mayor y está asociado con el sexo varón del acompañante. El estadio clínico se asocia cuando se calcula el gasto por las horas involucradas del acompañante en el cuidado en casa (Tabla 2, Fig. 2A y B, Fig. 3A y B).

En la evaluación por gasto indirecto por esquema acumulado resultó estadísticamente significativa la correlación positiva del número de sesiones de teleterapia con la presencia de BATD. El estadio clínico se asocia al gasto indirecto por esquema del paciente, especialmente el III (Tabla 3, Figs. 2C y 3C).

Discusión

Los pacientes con cáncer pueden estar expuestos a la toxicidad financiera de manera diferente según el

Tabla 2. Análisis de la relación entre las variables y el gasto indirecto semanal. El gasto acumulado es la sumatoria del GIS paciente más el GIS acompañante

Variables	Coeficiente	p
Edad del paciente*		
GIS acumulado§	–0.50	0.000
GIS acompañante§	–0.07	0.460
GIS paciente	–0.41	0.000
Tipo de seguro†		
GIS acumulado§	684.50	0.269
GIS acompañante§	812.00	0.966
GIS paciente	576.00	0.520
Sesiones*		
GIS acumulado§	0.099	0.313
GIS acompañante§	0.009	0.930
GIS paciente	0.082	0.320
BATD†		
GIS acumulado§	907.50	0.622
GIS acompañante§	814.50	0.220
GIS paciente	1418.50	0.800
Estadio‡		
GIS acumulado§	2.66	0.448
GIS acompañante§	5.61	0.132
GIS paciente	5.82	0.121
GIS horas acompañante§	41.24	0.000
GIS horas acompañante en radioterapia§	3.75	0.290
GIS horas acompañante en casa§	62.79	0.000
Acompañante†		
GIS acumulado	0.00	0.00
GIS paciente	2211.50	0.679
Sexo acompañante†		
GIS acumulado§	347.00	0.000
GIS acompañante§	195.00	0.000
GIS paciente§	773.00	0.377
Edad acompañante*		
GIS acumulado§	–0.29	0.003
GIS acompañante§	–0.20	0.041

*Prueba de correlación de rho de Spearman, estadísticamente significativa si $p \leq 0.05$.
†Prueba U de Mann-Whitney, estadísticamente significativa si $p \leq 0.05$.
‡Prueba de Kruskal-Wallis, estadísticamente significativa si $p \leq 0.05$.
§Se analizaron 109 casos con acompañante, estadísticamente significativo si $p \leq 0.05$.
BATD: braquiterapia de alta tasa de dosis; GIS: gasto indirecto semanal.

Tabla 3. Análisis de la relación entre las variables y el gasto indirecto total por esquema. El gasto acumulado es la sumatoria del GIS paciente más el GIS acompañante

Variable	Coeficiente	p
Teleterapia*		
GIE Acumulado§	0.31	0.001
GIE Acompañante§	0.21	0.033
GIE Paciente	0.08	0.321
BATD†		
GIE Acumulado§	361.00	0.000
GIE Acompañante§	159.00	0.000
GIE Paciente	752.00	0.000
Estadio		
Acumulado§,‡	4.26	0.235
GIE Acompañante§,‡	5.61	0.132
GIE Paciente ≤	15.45	0.001
I vs. II†	202.00	0.641
I vs. IV†	115.00	0.845
I vs. III†	269.50	0.014
II vs. III†	986.00	0.004
II vs. IV†	337.00	0.581
III vs. IV†	485.50	0.007

*Prueba de correlación de rho de Spearman, estadísticamente significativa si $p \leq 0.05$.
†Prueba U de Mann-Whitney, estadísticamente significativo si $p \leq 0.05$.
‡Prueba de Kruskal-Wallis, estadísticamente significativa si $p \leq 0,05$.
§Se analizaron 109 casos que presentaba acompañante, estadísticamente significativo si $p \leq 0.05$.
BATD: braquiterapia de alta tasa de dosis; GIE: gasto indirecto por esquema; GIS: gasto indirecto semanal.

país en el que reciben atención, ya que los sistemas de atención médica son diversos[15,16]. En nuestro país, el costo directo médico está subvencionado mayoritariamente por el SIS o el ESSALUD, si la persona es trabajadora informal/desempleada o goza de trabajo formal, respectivamente. Existe la posibilidad de atención en forma particular, en la cual el usuario externo asume todos los costos[17,18]. Esto se refleja en los resultados con el predominio del SIS sobre ESSALUD, ya que el instituto a nivel de la Macrorregión Centro es el único servicio que ofrece radioterapia, perteneciendo al Ministerio de Salud (MINSA). El CACU es un problema de salud pública que ocurre típicamente en mujeres sexualmente activas de 30 a 45 años[19], coincidiendo con nuestros resultados de atendidas con predominio en mayores de 40 años. La BATD se recomienda para todas las mujeres que han recibido teleterapia definitiva, sin embargo en las pacientes en estadio clínico IB-IIA que han sido sometidas a histerectomía con bordes libres no es necesario complementar con BATD a pesar de que tengan la indicación de teleterapia[13,20]. Por este motivo en nuestra muestra no todas las pacientes recibieron BATD, ya sea por ser estadio temprano o tener compromiso de vejiga y recto, en este último escenario se difiere la BATD en la institución por no contar con los aplicadores adecuados de irradiación, por lo que se debe completar el esquema con sesiones adicionales de teleterapia.

Cuando se evalúa la pérdida de productividad por semanas del acompañante, suele ser menor el equivalente económico al evaluar por horas de productividad (Fig. 1), ya que implica que el acompañante destine más de ocho horas al día al cuidado cuando recibe

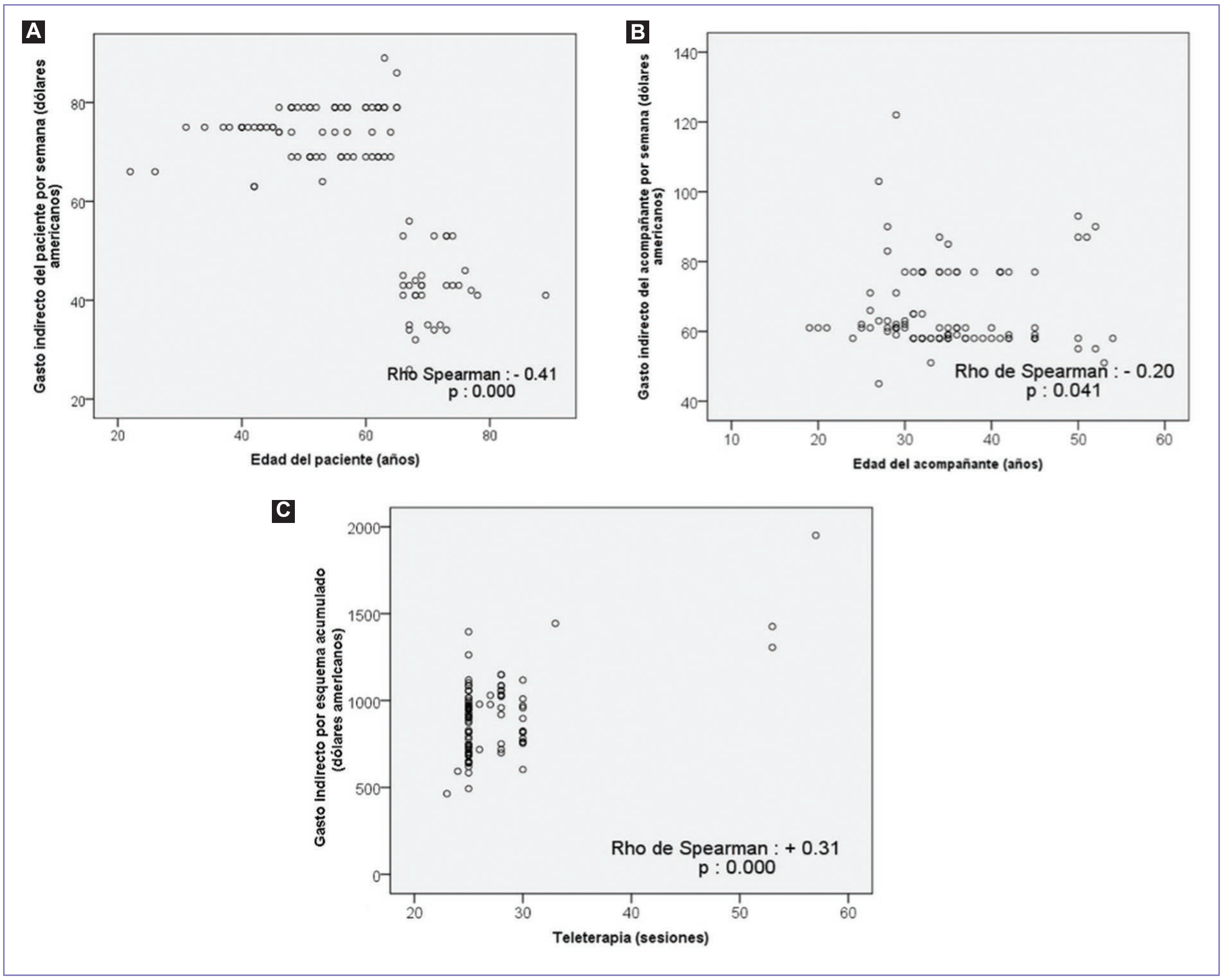

Figura 2. Análisis de correlación entre variables clínicas del paciente y del acompañante con el gasto indirecto. **A:** correlación negativa entre gasto indirecto paciente semanal y edad del paciente. **B:** correlación negativa entre gasto indirecto acompañante semanal y edad del acompañante. **C:** correlación positiva entre gasto indirecto total por esquema y teleterapia.

teleterapia y más de cinco horas durante los fines de semana.

Los cálculos de costos indirectos debido a la pérdida de producción generalmente separan tres tipos de fuentes de estos costos: ausentismo a corto plazo, discapacidad a largo plazo y prematura mortalidad[21]. Nuestro estudio encontró que todas las pacientes se ausentaron de sus trabajos y la mayoría necesitó un cuidador (Tabla 1), esto se debe todavía a las barreras geográficas, sociales y de implementación compatibles con un país con IDH alto con limitada capacidad de prevención y detección de CACU en estadio temprano en zonas rurales[22-24].

Los gastos sanitarios no son los únicos recursos utilizados para la atención de los pacientes con cáncer. El cuidado de los pacientes por parte de familiares, parientes y amigos, lo que a menudo se conoce como cuidador informal, también debe incluirse, y parte del aumento de los costos con el tiempo puede deberse a una transferencia del cuidado informal al cuidado formal. Si bien la magnitud de ese cuidado puede medirse en número de horas, existe el problema adicional de que no hay pagos y, por lo tanto, no existe la oportunidad de observar el costo por hora[21]. Esto se refleja en nuestros resultados, en donde el acompañante se compromete más de ocho horas diarias a predominio del cuidado en casa, expresándose en una pérdida de productividad por encima del 10% cuando se calcula por hora que por el proporcional a sueldo semanal (Tabla 1 y Fig. 1).

La edad del paciente se correlaciona negativamente con el gasto semanal acumulado, siendo marcado a

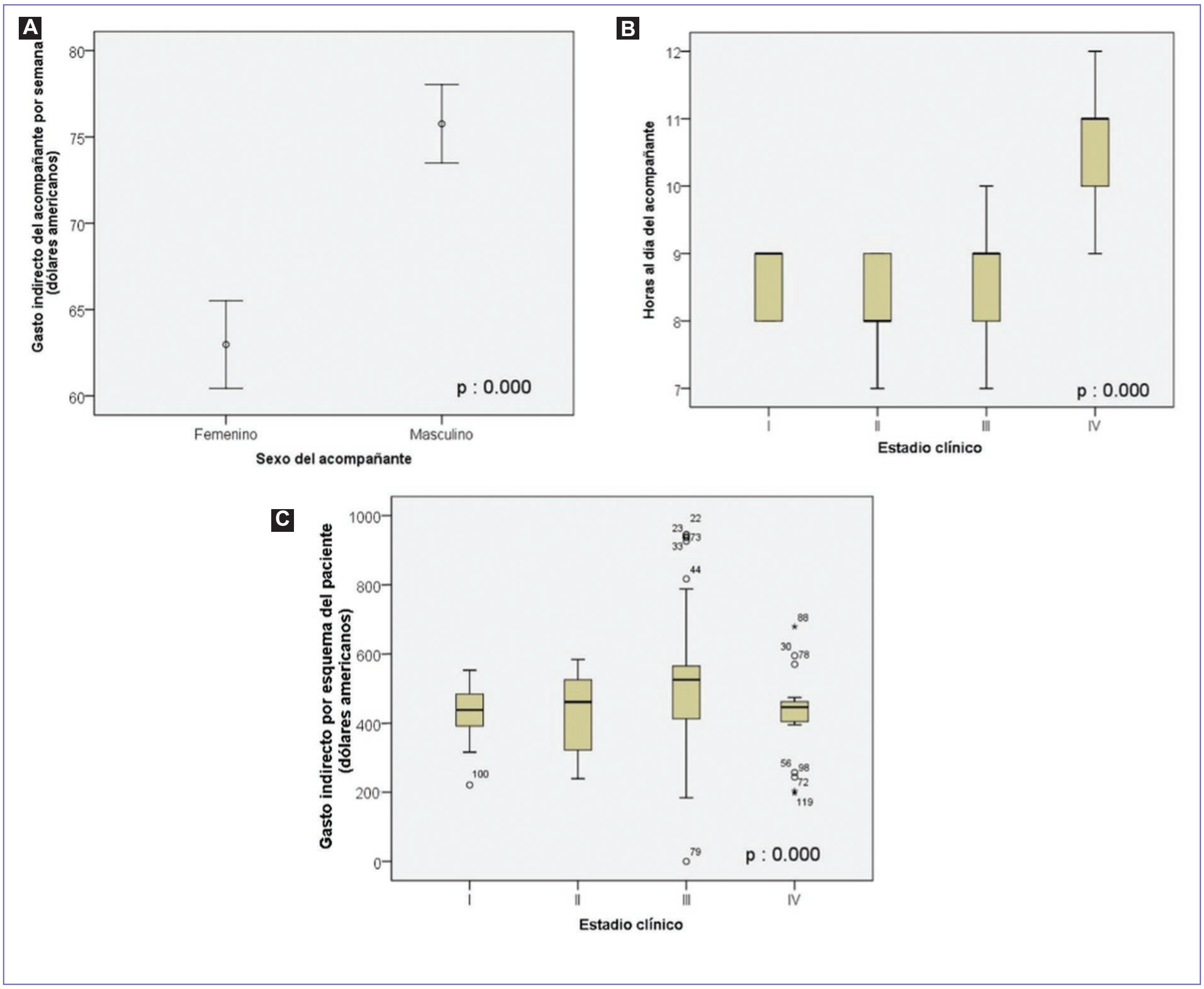

Figura 3. Análisis de asociación entre variable clínica y del acompañante con el gasto indirecto. **A:** asociación entre gasto indirecto del acompañante y sexo del acompañante. **B:** asociación entre horas del acompañante y estadio clínico. **C:** asociación entre gasto indirecto del paciente por esquema y estadio clínico.

partir de los 65 años (Fig. 2) y la presencia del acompañante, siendo este varón y con edad entre 30 y 50 años implica un mayor gasto semanal (Tabla 2, Figs. 2 y 3). Esto se debe a la disparidad de empleo formal e informal por género acentuado en países de ingresos bajo y mediano[25], siendo respaldado por el informe anual de empleo del Perú del 2021[26], en donde el promedio mensual de los trabajadores informales sobre formales está en $244 y $647, respectivamente. Predomina el empleo informal entre la población de sexo femenino (78.8%), en la selva (88.3%), en la ruralidad (95.3%), joven (83.2%) y que solamente llegó a alcanzar el grado educativo de primaria (94.8%)[26].

El estadio clínico más avanzado se asocia con un mayor gasto indirecto semanal de horas acompañante, siendo la fracción de horas de cuidado en casa la de mayor contribución (Tabla 2 y Fig. 3). Este hallazgo se explica porque la atención se vuelve más compleja conforme va progresando el cáncer, lo que implica mayor carga para el cuidador, y si este carece de capacitación para hacerlo, va a tener consecuencias no solo económicas, agregándose: disminución de la autoeficiencia, disminución de la calidad de vida, aumento de la ansiedad y aumento de depresión[27].

Al evaluar por esquema de tratamiento va a depender del estadio clínico, ya que el gasto indirecto por esquema acumulado se correlaciona con el mayor número de sesiones, y se asocia a la presencia de BATD (Tabla 3 y Fig. 3). La BATD es un componente fundamental del tratamiento definitivo del cáncer de CACU y permite la administración segura de aproximadamente la mitad de la dosis de radiación efectiva total necesaria para obtener resultados óptimos[28], pero se debe seleccionar a las pacientes posthisterectomías si va a tener beneficio la braquiterapia a nivel de cúpula vaginal[13]. Resalta el estadio clínico III como causante del mayor gasto indirecto del paciente por esquema (Fig. 3), esto se debe al escenario IIIC2, en donde se brinda casi el doble de sesiones al irradiar la zona pélvica y retroperitoneal de manera secuencial (Fig. 1); para disminuir ese costo indirecto se deben usar técnicas especiales de irradiación que permitan irradiar ambas regiones de manera simultánea como arcoterapia volumétrica modulada[3].

La mejora en el manejo del cáncer tanto de la quimioterapia como de la irradiación, con menos efectos secundarios del tratamiento[29], facilitará a las pacientes a seguir trabajando durante el tratamiento y así reducir el número de días de ausentismo en el trabajo; por lo tanto, esperamos que este costo disminuya con el tiempo. Cuando mejora la supervivencia puede aumentar la discapacidad a largo plazo y, por lo tanto, la pérdida de producción[22]. Sin embargo, el adecuado y moderno tratamiento también puede aumentar la capacidad de trabajo, y esto reducirá el número de personas con jubilación anticipada parcial o total. El CACU es una causa común de muerte entre la población activa[22], con mejoras en la prevención y el tratamiento[22,30] se reducirá el número de años de vida perdidos antes de la edad de jubilación y, por tanto, también los costes por mortalidad prematura.

Esta investigación es pionera a nivel nacional, ya que no se cuenta con reportes sobre los gastos indirectos en el tratamiento del CACU. A nivel latinoamericano existe escasa información. Sin embargo, a nivel internacional se encuentran reportes de pérdida de productividad debido al tratamiento oncológico. Por lo que es necesario en el futuro realizar estudios que correlacionen el gasto indirecto y los desenlaces clínicos de los pacientes. Así mismo, el impacto del gasto indirecto con la adherencia al tratamiento o la calidad de vida de los pacientes o acompañantes.

Nuestro análisis tiene limitaciones por el pequeño número de pacientes que recibieron radioterapia; sus resultados no serán generalizables a Latinoamérica y puede limitar la validez externa. Sin embargo, el muestreo ha sido probabilístico, por lo que puede ser útil extrapolar sus resultados a una población más amplia. Otra posible limitación es que se realizó en un solo centro, pero a nivel nacional solo existen cuatro institutos públicos con las mismas características que ofrecen el servicio de radioterapia, y este instituto desde su apertura tiene un promedio de atendidas en CACU de 130 pacientes al año hasta la fecha, con un incremento progresivo.

Nuestros resultados demuestran que el gasto indirecto por el tratamiento contra el CACU es alto y considerable al comparar con el ingreso promedio mensual de la paciente o acompañante. Este gasto semanal se incrementa cuando está presente el acompañante varón, y la edad del paciente o del acompañante es menor a 65 y 45 años, respectivamente. Se suman otros factores, como el mayor número de sesiones, el estadio clínico III y la presencia de BATD para incrementar el gasto por esquema.

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Conflicto de intereses

El autor declara no tener conflicto de intereses.

Consideraciones éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad, consentimiento informado y aprobación ética. Los autores han obtenido la aprobación del Comité de Ética para el análisis de datos clínicos obtenidos de forma rutinaria y anonimizados, por lo que no fue necesario el consentimiento informado. Se han seguido las recomendaciones pertinentes.

Declaración sobre el uso de inteligencia artificial. Los autores declaran que no utilizaron ningún tipo de inteligencia artificial generativa para la redacción de este manuscrito.

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REVIEW ARTICLE

Prevalence and burden of oral complications in breast cancer: systematic literature review

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Abstract

Clinical management of breast cancer (BC) survivorship rarely involves evidence-based oral care. This review aimed to provide data on the prevalence and burden of oral complications (OC) among BC patients and to provide recommendations for optimal management of OCs in this population. The review was conducted using systematic searches in electronic databases up to July 2023 following a predefined protocol (CRD42021272130). The occurrence of at least one OC, beyond the well-known mucositis or stomatitis, was reported by 14% of close to 8,000 BC patients with an average age of 54 years. The most prevalent were periodontitis, gingivitis, ulcers, pain, tooth loss, or xerostomia. When evaluated, OCs were more prevalent in BC patients compared to controls and were mostly reported temporarily during treatment. A higher prevalence was observed from real-world data compared to interventional data. Although scarce and heterogeneous, burden data suggested that OCs negatively impact patients' quality of life and overall costs of treatment. OCs are scarcely studied but their occurrence impacts negatively patient's everyday lives. Standardized well-designed oral health research focusing on region-specific cost-effective management approaches is crucial for optimizing care delivery for BC survivors.

Keywords: *Oral health. Breast neoplasm. Adverse events. Epidemiology. Quality of life. Economics.*

Prevalencia y carga de complicaciones orales en cáncer de mama: revisión sistemática de la literatura

Resumen

El cuidado oral de supervivientes de cáncer de mama (CM) es un tema poco considerado en la práctica clínica. El objetivo de esta revisión es obtener evidencia médica sobre la prevalencia de las complicaciones orales (CO) y la carga humana y económica que estas generan en pacientes y sistemas de salud, además de presentar recomendaciones para el óptimo manejo de las CO en esta población. La revisión se realizó usando búsquedas sistemáticas en bases de datos electrónicas hasta julio de 2023, siguiendo un protocolo predefinido (CRD42021272130). La ocurrencia de al menos una CO, además de las comúnmente conocidas mucositis y estomatitis, se reportó por el 14% de cerca de 8,000 pacientes de CM con una edad media de 54 años. Las más prevalentes fueron periodontitis, gingivitis, úlceras, dolor, pérdida dental o xerostomía. Esta prevalencia se identificó más comúnmente en estudios de la vida real que en ensayos clínicos. La evidencia de carga humana y económica fue escasa y heterogénea, pero sugiere que las CO impactan negativamente en la calidad de vida y costos generales del tratamiento del CM. A pesar de que no son comúnmente estudiadas, las CO en pacientes con CM son numerosas e impactan negativamente en el tratamiento. La falta de investigación en salud oral estandarizada en la población oncológica representa un reto para el desarrollo de protocolos de atención oral personalizada de las sobrevivientes de CM.

Palabras clave: *Salud oral. Cáncer de mama. Eventos adversos. Epidemiología. Calidad de vida. Economía.*

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Introduction

Breast cancer (BC) is the most prevalent neoplasm among women worldwide. According to the latest estimate from the World Health Organization (WHO), approximately 1.8 million women were living with the disease by the end of 2020, with an annual incidence of 58.5 new cases per 100,000 women[1]. Due to the extensive research, availability of early diagnosis, and effective treatment, most patients can expect a favorable prognosis with long-term BC survivorship care appearing to require region-specific multiple public healthcare interventions[2].

Unfortunately, the sequelae of pharmacological interventions include several adverse effects which can have long-lasting impact on patients, among them, oral complications (OCs). The most commonly OCs experienced by patients undergoing anticancer treatment in clinical trials are oral mucositis and stomatitis with a risk of serious events occurring in up to 46% of oncology patients[3]. In the case of BC specifically, our recent systematic review estimated that mucositis and stomatitis were reported accumulatively by 13 and 15%, respectively, among a cohort of 46,154 women with BC enrolled in 89 randomized controlled trials[4]. Our review also highlighted how all types of anticancer therapy increased the risk of developing mild-to-severe stomatitis or mucositis[5].

In addition to mucositis or stomatitis, recent systematic reviews have shown that cancer patients have a higher prevalence of less studied OC such as higher plaque index, gingival index, or post-extraction complications compared to healthy individuals ranging from 3 to 40%[6,7]. Unfortunately, these less studied OCs often go unnoticed or untreated in clinical practice due to lack of recognition or awareness[8]. To date, there has been no comprehensive review on their prevalence or their impact on the quality of life and economic burden for BC survivors. In addition, current aftercare guidelines for BC often overlook protocols for managing OC, which poses challenges for both research and clinical practice. This issue is particularly prominent in Latin American countries where dental procedures are often performed without considering the specific needs of special populations. In fact, dental treatment is often considered distinctly post-treatment away from their oncologic care.

By conducting an updated analysis on the epidemiology, burden, and treatment patterns of OC in BC survivors – with a focus on Latin American populations – we aim to provide a foundation for developing oral health management protocols tailored specifically for this group. In this article, we present more findings from our systematic literature review which includes the prevalence of less studied OC as well as the economic and humanistic burden associated with all types of OC experienced by BC patients undergoing pharmacological treatment.

Methods

Literature search

A systematic literature search was conducted following the registered protocol with the PROSPERO registration number CRD42021272130[5]. In brief, the systematic review followed the guidelines from the Cochrane Handbook[9] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[10] statement. Six electronic databases (Embase, Medline, Cochrane Database of Systematic Reviews, CENTRAL, Econlit, and LILACS) and complementary sources were searched for publications indexed up to July 2023. Key inclusion criteria included studies published in English or Spanish reporting on epidemiology, management, or burden of OC in adult women (≥ 18 years old) with any stage of BC who have received antineoplastic treatment. Search terms used to identify studies from databases are presented in supplementary table 1. The flow diagram depicting how the studies described here is presented in figure 1.

Descriptive analysis and quality assessment

Each included study was fully reviewed in duplicate. Main study and patient characteristics were tabulated alongside the outcomes of interest which included occurrence rate of OC or adverse effects.

The authors independently assessed the risk of bias and methodological quality of all included studies using best-practice instruments according to each study design.

Statistical method

Studies were categorized based on their design into observational and interventional data. The combined point prevalence of OC was estimated by the addition of the total number of BC patients reporting occurrence divided by the total sample size of all the studies reporting each OC.

Results

Prevalence of OC

At least one of eight OC including periodontitis, tooth loss, xerostomia, overall poor oral health, mouth ulcers,

Table 1. Prevalence of oral complications in breast cancer patients during treatment*

Oral complication (number of studies)	Sample size		All studies
	Real-world data	Interventional studies	Median prevalence [%] (range)
Periodontitis (n = 9)	267	116	55.0 (2.9-98.0)
Tooth loss (n = 7)	468	125	48.1 (23.0-100)
Xerostomia (n = 21)	1,997	3,357	44.8 (1.7-70.7)
Poor oral health (n = 7)	542	100	34.0 (21.9-95.1)
Mouth ulcers (n = 9)	583	862	26.1 (6.5-92.8)
Gingivitis (n = 12)	253	1383	25.0 (2.0-66.0)
Oral pain (n = 14)	422	3,833	17.3 (3.6-55.9)
Bleeding on probing (n = 4)	895	882	11.4 (3.2-50.0)

*The definitions, criteria, and the time related to treatment to capture the occurrence of OCs varied greatly in the included studies. The prevalence presented in the table refers to the occurrence of the complication of any grade or severity at any point from initiation to discontinuation of treatment.

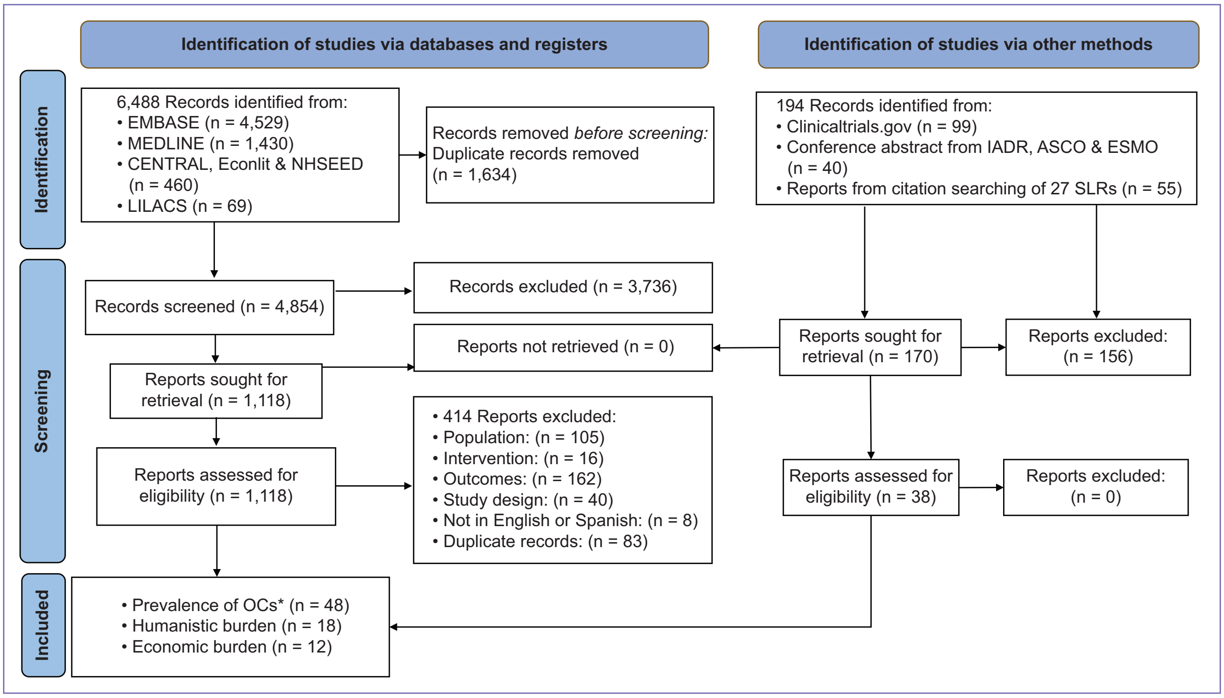
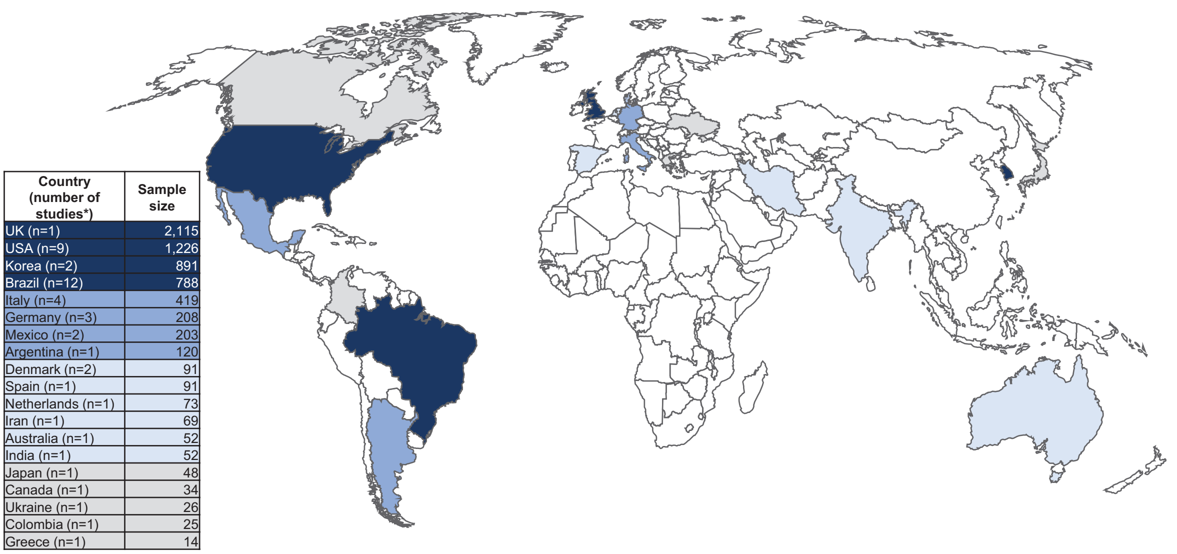


Figure 1. PRISMA flow chart summarizing the process of identification of the eligible and included studies summarized in this review. ASCO: American Society of Clinical Oncology; ESMO: European Society of Medical Oncology; IADR: International Association for Dental Research; LILACS: Literatura Latino-Americana e do Caribe em Ciências da Saúde; NHSEED: National health service economic evaluation database; OC: oral complications (*other than mucositis or stomatitis); SLR: systematic literature review.

gingivitis, oral pain, or bleeding on probing were prevalent in 7996 patients with an average age of 54 years old who received BC antineoplastic treatment based on data spanning from 1999 to 2022 from 48 studies carried out in 19 countries worldwide (Fig. 2). The study and patients' characteristics are outlined in supplementary tables 2 and 3. Most of the studies were observational of real-world data (n = 32) with moderate-to-high



Country (number of studies*)	Sample size
UK (n=1)	2,115
USA (n=9)	1,226
Korea (n=2)	891
Brazil (n=12)	788
Italy (n=4)	419
Germany (n=3)	208
Mexico (n=2)	203
Argentina (n=1)	120
Denmark (n=2)	91
Spain (n=1)	91
Netherlands (n=1)	73
Iran (n=1)	69
Australia (n=1)	52
India (n=1)	52
Japan (n=1)	48
Canada (n=1)	34
Ukraine (n=1)	26
Colombia (n=1)	25
Greece (n=1)	14

* Total number of studies does not add up to 48. There were two studies that were carried out in multiple countries (sample size:1,451) and were not included in this figure.

Figure 2. Geographic distribution of studies reporting on the prevalence of oral complications (OC) following breast cancer (BC) treatment. Darker shades indicate a bigger number of patients evaluated. The included studies reported the occurrence of at least one OC mostly from patients in Europe (n = 14) with data from 3037 patients, followed by North America (n = 12, 1,463 patients), East Asia (n = 3939 patients), and South America (n = 14,933 patients). *The total number of studies does not add up to 48 since there were two studies that were carried out in multiple countries (sample size: 1451) and were not included in this figure.

risk of bias primarily due to small sample sizes (under 100 patients, n = 22), a single-point data collection (cross-sectional studies, n = 14), or the self-reported OC occurrence (n = 14). Patients from observational studies predominantly had undefined BC stages (n = 23) or received undefined chemotherapy (n = 16). Conversely, the remaining studies evaluated BC interventions in highly selected patient groups (n = 16) with low-to-moderate risk of bias. Twelve studies used validated criteria or clinical expertise to identify OCs occurrence, and seven studies were randomized controlled trials. Most studies assessed the prevalence of OCs only once during (n = 30) or after (n = 7) BC treatment while nine studies captured OC occurrence before, during, and after treatment.

Table 1 presents the combined data of each OC's prevalence across all studies, and figure 3 shows the differences noted between observational and interventional studies. The median percentages for all eight OCs occurrence rates ranged from 11 to 55% with periodontitis figuring as the most frequently reported; however, the prevalence ranges were broad for all complications. Xerostomia was the most reported OC (n = 21) with close to half of BC patients (44%) recording its occurrence.

Real-world data indicated higher occurrences compared to interventional studies for six out of eight identified OCs (Table 1). For instance, real-world occurrence rate of periodontitis was threefold higher compared to interventional data. Conversely, oral pain and tooth loss exhibited similar occurrence rates across both study designs.

All the studies that compared OC prevalence to controls or overtime (n = 14) reported higher prevalence in BC patients that increased during treatment and decreased after treatment ceased. For instance, xerostomia was rarely reported before the initiation of chemotherapy but this symptom became a significantly prominent feature as treatment progressed, but this was reduced at follow-up. Furthermore, the likelihood of developing other OC increased with the occurrence of some OCs. For example, in adjusted analysis, BC patients had greater odds of developing melanotic macule, ulcers, or plaque when they have more than 13 missing teeth or xerostomia (2.39-fold (95% confidence interval [CI], 1.06-5.40) and 2.71-fold (95% CI, 1.14-6.42, respectively)[11].

Humanistic burden

There appears to be a lack of published studies specifically focused on BC treatment and their impact of

Table 2. Oral complications and QoL in breast cancer treatment assessed with oral-specific instruments

Author, year Study design Time of data collection Country	Population sample size Average age Cancer therapy	Oral complications/ oral adverse effects	Oral-health-related quality of life (OHRQoL) findings
Oral health-related quality of life (OHIP-14)			
Willershausen et al., 2019[12] Case-control NR 2004 - NR 2014 Germany	Early BC n = 80 Mean age: 60.5 years Chemotherapy	Median index for caries frequency (DMFT index): 19 (IQR 16–22)	Compared to control OR (95%CI) OHIP-German14: 3.14 (0.57; 17.19), p = 0.01 Depression score: 2.8 (0.9; 4.7) p = 0.0002-on average 0.5 points worse per missing tooth
Jardim et al., 2020[11] Cross-sectional Jan - Aug 2017 Brazil	BC (ICD-10, C50) n = 151 Mean age: 55 years Chemotherapy (not specified), radiotherapy and tamoxifen	Dental pain in the previous 12 months: 17.3% Xerostomia: 56.3% Lost at least one tooth: 87.4% Poor oral perception: 21.9%	OHIP-14 scores with a negative impact on QoL Functional limitation: 17.9% Physical pain: 18.5% Psychological discomfort: 26.5% Physical disability: 13.2% Psychological disability: 27.8% Social disability: 39.1% Social handicap: 20.5% Total score: 58.9%
Taichman et al., 2016[13] Prospective, longitudinal Apr 2009 - Sep 2010 USA	HR+BC n = 29 Mean age: 59.3 years Aromatase inhibitors (AI)	Xerostomia and periodontal disease Gum disease (swollen gums, receding gums, infected gums, or loose teeth): 38% Bleeding from your gums: 21% Gingival swelling: 13% Loose teeth: 17%	Mean OHIP-14 scores were poorest at baseline, improved at 6 and 12 months, and slightly worsened again at 18 months. OHRQoL scores at the four points in time showed a significant difference compared to controls (p = 0.005) Significant results ($p < 0.05$) compared to healthy controls Problems with teeth or mouth have cause more regular: Tension Worsened sense of taste Being self-conscious Difficulty relaxing Being irritable with other people Being embarrassed. Difficulty doing usual tasks.
Oral health-related quality of life (OHRQoL)			
Souza, 2022[14] Cross-sectional Oct 2019 - Aug 2021 Brazil	BC (not specified) n = 40 Mean: 56 years Aromatase inhibitors (AI)	Periodontitis Moderate/severe: 72.5%	OHRQoL mean scores compared to non-AI users Better OHRQoL (p = 0.005) Physical (p = 0.001) Social (p = 0.042) Psychological (p = 0.020)

BC: breast cancer; CI: confidence interval; DMFT: decayed, missing, and filled permanent teeth; HR+: hormonal receptor positive; IQR: interquartile range; OR: odds ratio; QoL: quality of life; NR: not reported; USA: United States of America.

their oral health complications. However, the evidence from 18 studies suggests that the occurrence of OCs negatively impacts the quality of life and everyday functionality of at least 7738 BC survivors who underwent treatment between 1999 and 2021. The studies were carried out around the world, mostly in the Americas (USA [n = 5] and Brazil [n = 4]) but also in Japan and UK (n = 2 each) and with one study each, Germany, Iran, the Netherlands, Saudi Arabia, and Spain. Most studies presented cross-sectional data (n = 10) of medium-to-low quality, while only three studies offered data from prospective cohorts and, despite OCs such as mucositis and stomatitis being a common occurrence in clinical trials, only two studies evaluated how these adverse events affected BC patients' quality of life. The outcomes reported are heterogenous, and the magnitude of different OC's impact in the quality of life of BC patients varies according to the type of instrument utilized, as follows:

Table 3. Oral complications and QoL in breast cancer treatment according to patients' perception questionnaires

Author, year Study design Time of data collection Country	Population Sample size Average age Cancer therapy	Relevant instrument (s)	Oral complications/ oral adverse effects	Oral-health-related quality of life (OHRQoL) findings
Alaqeel et al., 2019[16] Cross-sectional NR Saudi Arabia	Early BC (stages I to III) n = 59 Mean age: 48 years Chemotherapy (not specified)	Importance scores questionnaire of 12 pairs of hypothetical treatment side effects	Mucositis/stomatitis: 27%	Importance score for choosing treatment compared to other side effects: 2nd highest
Fall-Dickson et al., 2008[18] Cross-sectional NR USA	BC (not specified) n = 32 Mean age: 49 years Chemotherapy (not specified)	Oral Assessment Guide, the Oral Mucositis Index, the Painometer, the State-Trait Anxiety Inventory, the Beck Depression Inventory	Stomatitis and oral mucositis: 100%	Stomatitis-related Oral Pain: 47% Swallowing mean VAS score > 3 = 22% Sensory words chosen most frequently to describe the oral pain with swallowing Score: 86.7% Burning: 26.5% Aching or pressing: 26.7% Affective words chosen most frequently to describe oral pain with swallowing Annoying: 73.3% Nagging and miserable: 33.3% Troublesome: 26.7% Some degree of depression (mean = 10.2; SD=9.3; range=1-50): 100% Severity Minimal: 61% Mild: 29% State anxiety scores (mean = 34.2; SD=11.5; range of 20-60) Low: 64% Moderate: 32% High: 3%
Taichman et al., 2015[22] Cross-sectional Apr 2009-Sep 2010 USA	ER+BC n = 58 Mean: 61 years Aromatase inhibitors (AI)	Participant's self-perceived oral health, level of saliva and importance of dental health	Periodontitis Moderate/severe: 79%	How would you describe the health of your teeth (on a scale of 1 [poor/not important] to 5 [excellent/very])? 3.14 ± 1.18 p = 0.05 How would you describe the health of your gums? 2.97 ± 1.29 How important is your dental health? 4.72 ± 0.75 p = 0.09
Taichman et al., 2015[21] Cross-sectional NR 1999 - NR 2004 USA	BC (not specified) n = 177 Mean: 69.2 years Any	Perceived oral health	Gingivitis: 48.1% Periodontitis-moderate/severe: 20.1% Gingival bleeding: 4.1%	Perception of oral health compared to no BC Overall health (Fair/Poor): 28.9% p = 0.04 Limited foods due to teeth/mouth (often/sometimes): 13.9%
Taichman et al., 2018[15] Cross-sectional Jun 2014 - Jun 2015 USA	Early BC (stages I-III) n = 140 Mean age: 59.4 years Any	Perceived oral health	Xerostomia: 24% Mucositis: 2%	Oral concern-related responses: % Yes Problems with teeth or gums since diagnosis: 22% Do you believe your oral health problem is related to your cancer treatment? 27% Are you aware that cancer treatment may affect oral health? 68% Was there a time when you wanted to visit your dentist but could not due to your BC treatment? 25%

(Continues)

Table 3. Oral complications and QoL in breast cancer treatment according to patients' perception questionnaires *(continued)*

Author, year Study design Time of data collection Country	Population Sample size Average age Cancer therapy	Relevant instrument (s)	Oral complications/ oral adverse effects	Oral-health-related quality of life (OHRQoL) findings
Lo-Fo-Wong et al., 2016[19] Prospective cohort Mar 2011- Mar 2013 The Netherlands	BC (not specified) n = 746 Median age: 59 years Any	Psychosocial distress assessed with the validated Dutch version of the Distress Thermometer	Contact with a dentist to prevent or treat dental problems not specified	Odds ratio of having had contact with a dentist for patients with clinical distress 6 months post-diagnosis: 2.53 times higher (95%CI, 1.70-3.79) $p < 0.05$ 15 months post-diagnosis: 1.98 times higher (95%CI, 1.322.98) $p < 0.05$
Nazari et al., 2021[20] Discrete choice experiment NR Iran	Metastatic HR+/ HER2- BC n = 78 Mean age: 51.4 years Hormonal and targeted treatments (1st line)	Relative attribute importance (RAI)	Stomatitis: NR	RAI: 12.3% (Rank 4 of 16 scenarios to rate the most important attribute of treatment)
Cameron et al., 2017[17] RCT Dec 2005 - Dec 2008 UK	BC (not specified) n = 1,238 Mean age: 59.2 years Epirubicin followed by Classical/Bonadonna CMF or oral capecitabine	Patient-reported toxicities questionnaire	Sore mouth: 58.3% Mouth ulcers: 43.3% Stomatitis (Stomatitis, Dry mouth, Oral candidiasis, Oral herpes): 67.0%	At the end of cycle 8 Distress caused by toxicity Sore mouth $p < 0.0001$ A little: 27.5% Quite a bit: 9.5% Very much: 6.8% Mouth ulcers $p < 0.0001$ A little: 17.9% Quite a bit: 5.6% Very much: 5.0% Daily interference caused by toxicity Sore mouth $p < 0.0001$ A little: 17.1% Quite a bit: 5.7% Very much: 4.8% Mouth ulcers $p < 0.0001$ A little: 13.1% Quite a bit: 3.9% Very much: 4.0%

BC: breast cancer; CI: confidence interval; CMF: cyclophosphamide methotrexate 5-fluorouracil; ER: estrogen receptor; HER2: Human epidermal growth factor receptor 2; HR: hormonal receptor; NR: not reported; QoL: quality of life; RCT: randomized controlled trial; SD: standard deviation; USA: United States of America; UK United Kingdom; VAS: visual analog scale.

ORAL-SPECIFIC INSTRUMENTS TO MEASURE QUALITY OF LIFE

Of the 18 identified studies, only four[11-14] used one of two validated oral-specific instruments to assess quality of life: the Oral Health Impact Profile (OHIP-14) or the oral health-related quality of life (OHRQoL) questionnaire. Further details on their dimensions and scoring system can be found in supplementary table 4.

Table 2 summarizes the outcomes from studies that utilized OHIP-14 or OHRQoL. Overall, BC patients who received chemotherapy or aromatase inhibitors showed significant results indicating poorer oral and periodontal health along with higher numbers of missing or restored teeth compared to either a control group[12,13] or overtime[13]. These findings were associated with poorer physical and psychological well-being and a diminished oral-health-related quality of life. For instance, multivariate analysis of BC survivors' oral health data showed that they were significantly more likely of having a negative impact on OHRQoL compared to patients without them (Odds ratio: xerostomia 2.9 (95% CI 1.2-7.1); number of restored teeth: 1.9 (95%CI 1.0-3.9) $p = 0.01$ for both)[11].

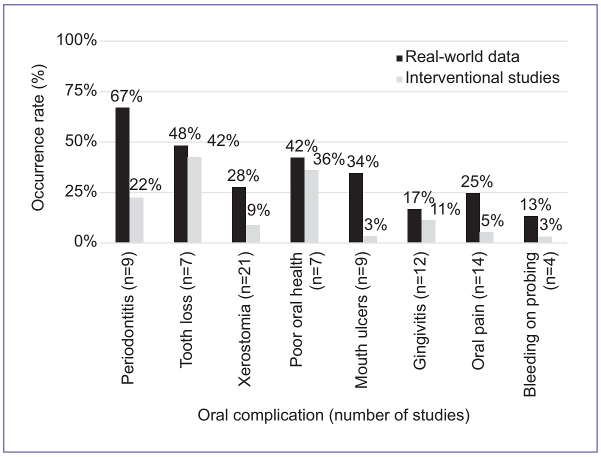


Figure 3. Prevalence of oral complications in breast cancer patients following treatment by study design.

Patient perception questionnaires and self-reported OHRQoL

Eight studies used different patient perception questionnaires to evaluate how the occurrence of OC impacts the quality of life of BC patients at all stages of the disease receiving various types of antineoplastic treatment[15-22]. Table 3 outlines the evidence gathered from patients concerning their BC treatment and the occurrence of OC. The evidence suggests that BC patients usually express lower self-perceived oral health compared to control groups. Oral pain, stomatitis, mucositis, and alterations in tasting or swallowing are highly scored among BC patients as bothersome or the source of distress and even depression. Conversely, other OCs such as dental problems were perceived as less detrimental to daily quality of life. For this population, receiving information from reliable sources and being involved in the choice of cancer therapy regime based on their preferences regarding different oral side effects would be crucial. However, this personalized approach is not common practice for most patients.

Generic instruments reporting OHRQoL

Six studies employed four generic instruments to assess the impact of OCs occurrence in BC patients with the EuroQoL-5D most commonly used (Table 4)[23-28]. These six studies measured the size effect on quality of life associated to mucositis, stomatitis, and oral pain at all severities (grades 1-4). The utility value (worse QoL) of these OCs decreased significantly after BC treatment in general. Results based on VAS scores suggested a bigger influence of oral adverse events on patients' QoL than those derived from EQ5D.

Economic burden

The evidence on the economic burden of OC associated with BC treatment was limited with only 12 studies were identified.

Seven of the 12 studies reported costs of managing stomatitis or mucositis (Table 5)[29-35]: four economic analyses of BC treatments and three retrospective cohort studies of moderate-to-high-quality data. The costs per stomatitis/mucositis episode of any severity were found to be approximately under $1,000 in BC patients in Spain[29] and the USA[35] during 2015 and 2016. However, for more serious events, requiring hospital care could cost escalate significantly to over $70,000[34].

Furthermore, six observational studies with very heterogenous outcomes reported moderate quality data on healthcare resource use due to different OC from BC (Table 5)[15,18,19,21,36,37]. Notably, chemotherapy was the most likely type of BC treatment that can significantly increase the use of dental care services and products to manage OCs compared to other treatments like aromatase inhibitors.

Discussion

This review follows the results of our recently published systematic literature review[5] and reports the prevalence of OC beyond the very well-studied mucositis and stomatitis. BC patients also experienced mostly xerostomia, periodontitis, gingivitis, or oral pain but also tooth loss, mouth ulcers or bleeding on probing, or poor oral health generally following treatment. The high occurrence of xerostomia and periodontitis was expected since they are common among the general population. This greater occurrence in BC survivors compared with controls may be associated with different factors. For example, we previously reported that older BC patients are at higher risk of developing mucositis, gingivitis, and poorer oral health overall[5] compared to controls without BC. In addition, patients' lifestyle behaviors such as alcohol consumption or smoking can increase the odds of developing OCs[38]. In the case of xerostomia, occurrence may be associated with a reduction in salivary flow stemming from hormonal changes the use of medications, exposure to antitumor treatments, and physiological or psychogenic causes, such as depression[39]. However, most data in this

Table 4. Oral complications and QoL in breast cancer treatment assessed with generic instruments

Author, year Study design Time of data collection Country	Population Sample size Average age Cancer therapy	Relevant instrument (s)	Oral complications/ oral adverse effects	Oral-health-related quality of life (OHRQoL) findings
Barbosa-Lima et al., 2020[24] Retrospective cohort Feb 2014-Feb2015 Brazil	BC (not specified) n = 196 Mean age: 59.2 years Chemotherapy (not specified)	CTCAE version 4	Mucositis (n = 97) Any grade: 49.5% Grade 1: 20.4 Grade 2: 23.0% Grade 3: 6.1% Grade 4: 0%	Symptoms following incidence of mucositis Fatigue: 94.8% (p = 0.01 compared with no mucositis) Pain: 41.8% Anxiety: 34.7% Depression: 26% Changes in self-image: 14.8% Changes in self-esteem: 10.2%
Marinho, 2020[26] Prospective cohort Mar 2017 - Feb 2019 Brazil	BC (not specified) n = 140 Mean age: 50.4 years Chemotherapy (Adriamycin, cyclophosphamide and paclitaxel)	EORTC QLQ-C30	Oral mucositis: 85.7%	Multiple linear regression model (β association) EORTC QLQ - C30 and oral mucositis Overall quality of life: –13.4 $p < 0.05$ Body image: –1.8 Perspective of future: –12.5 $p < 0.05$
Diernberger et al., 2022[25] Cross- sectional NR UK	BC (not specified) n = 4,135 Mean age: NR (> 18 years) Epirubicin followed by Classical/Bonadonna CMF or oral capecitabine	EQ-VAS and EuroQol-5D	Stomatitis (Stomatitis, Dry mouth, Oral candidiasis, Oral herpes): 53.2% Dysgeusia: 16.8% Mucosal inflammation: 45.3%	Decrease in quality of life connected to all grades of toxicity EQ5D Stomatitis: 0.0125 Dysgeusia: –0.0113 Mucosal inflammation: 0.0107 VAS: Stomatitis: 1.114 Dysgeusia: –0.892 Mucosal inflammation: –0.560
Prieto-Callejero et al., 2020[27] Cross-sectional May 2012 - Aug 2014 Spain	BC (not specified) n = 110 Mean age: 49.6 years Chemotherapy (docetaxel, epirubicin, and cyclophosphamide)	EuroQol-5D	Mucositis: 41.8%	Size effect on quality of life (Cohen d): 0.46 (significant when > 0.3) Patients with mucositis report having: Some problems performing my daily activities: 50.0% Moderate pain or discomfort: 63.0% A lot of pain or discomfort: 6.5% Moderate anxiety or depression: 28.9% Severe anxiety or depression: 11.1% Worse health status: 71.0%
Tachi et al., 2015[28] Cross-sectional Dec 2012 - Nov 2013 Japan	BC (not specified) n = 48 Mean: 59.6 years Chemotherapy (1st line)	EuroQoL-5D utility value, QOL-ACD	Oral mucositis (grade 1-3): 25% Oral pain (grade 1-3): 10.4%	After chemotherapy Oral mucositis EQ-5D utility value: –0.16 QoL-ACD %deteriorated Mobility: 33.3% Usual activities: 33.3% Pain/discomfort: 50% Anxiety/depression: 33.3% Oral pain EQ-5D utility value: –0.12 QoL-ACD %deteriorated Mobility: 20% Usual activities: 60% Pain/discomfort: 40% Anxiety/depression: 40%

(Continues)

Table 4. Oral complications and QoL in breast cancer treatment assessed with generic instruments *(continued)*

Author, year Study design Time of data collection Country	Population Sample size Average age Cancer therapy	Relevant instrument (s)	Oral complications/ oral adverse effects	Oral-health-related quality of life (OHRQoL) findings
Hagiwara et al., 2018[23] RCT NR Japan	Metastatic BC n = 380 Median age: 58 years Oral S-1 was compared with taxane (paclitaxel or docetaxel)	Health utility EuroQoL-5D-3L and the global health status in the EORTC QLQ-C30 at 3, 6, and 12 months	Oral mucositis Grade 1-2: 8.4% Grade 3-4: 0%	Oral mucositis impact on scores (95%CI) EORTC QLQ-C30 Grade 1 versus 0: –9.3 (–17.9, –0.6) p = 0.036 Grade 2 versus 0: –0.2 (–6.3, 6.0) p = 0.960 EQ-5D-3L based on societal preferences in Japan Grade 1 versus 0: –0.072 (–0.116, –0.028) p = 0.001 Grade 2 versus 0: –0.093 (–0.134, –0.053) p < 0.001 EQ-5D-3L based on societal preferences in the UK and the US. Grade 1 versus 0: UK: –0.083 (–0.148, –0.018) p = 0.012 USA: –0.067 (–0.111, –0.022) p = 0.004 Grade 2 versus 0 UK: –0.040 (–0.153, 0.074) p = 0.492 USA:–0.044 (–0.115, 0.028) p = 0.229 Disutility Grade 1: –9.3 (–18.3, –0.4) p = 0.04 Grade 2: –0.7 (–6.7, 5.4) p = 0.8

ACD: anticancer drug; BC: breast cancer; CTAE: common terminology criteria for adverse events; CI: confidence interval; CMF: cyclophosphamide methotrexate 5-fluorouracil; EORTC: European organization for research and treatment; QLQ: quality of life questionnaire; QoL: quality of life; NR: not reported; QoL: quality of life; RCT: randomized controlled trial; SD: standard deviation; USA: United States of America; UK United Kingdom; VAS: visual analog scale.

review were obtained cross-sectionally without controls making it challenging to associate them with BC treatment without longitudinal comparative research. It was also expected to find great variability in the occurrence rates of OCs between studies since there were noticeable differences in their methodology. Notably, most studies were observational and reported higher numbers of OCs compared to interventional studies. This finding might be explained by the observation of a similar systematic review of interventional studies which highlighted that most trials do not specifically address oral toxicities or include an oral clinical examination, which may lead to underreported and under-investigated oral toxicities[6]. Furthermore, when reported, most RCTs present only the occurrence of serious OCs (grades 3-4), and the prevalence of professionally reported OCs usually varies from self-reported OC. However, OCs can become serious or chronic overtime. Patients with “mild” OCs during treatment are not accounted for nor given adequate follow-up of their oral health leaving a gap in research and representing an unmet need for this population.

The humanistic and economic burden of OCs on BC patients undergoing treatment was also described. The evidence suggests that the occurrence of any OCs has a negative impact on BC patients with the number of events, the severity, and the exposure to chemotherapy associated with worse quality of life either perceived or measured and greater increased costs and resources use compared to those without OCs. These results align with similar studies across several types of cancer. For example, experiencing any chemotherapy-related AEs increased monthly healthcare costs with increasing costs associated to the greater number of

Table 5. Costs and health-care resource utilization associated with oral complications in breast cancer treatment

Author, year Study design Time of data collection Country	Population Treatment	Oral complications/oral adverse effects	Cost perspective Year/Currency Cost related to OCs
Frias et al., 2010[31] Cost-effectiveness model 2009 Spain	Metastatic BC Docetaxel versus Paclitaxel	Stomatitis grade 3/4 Docetaxel: 1.9% Paclitaxel: 0.2%	Societal perspective; 2009 EUR€ Costs of management per cycle: 475.49
Bermejo de Las Heras et al., 2018[29] Cost-of-illness model 2016 Spain	BC (not specified) Active treatment (any line) not specified	Stomatitis and mucositis (grade or prevalence NR)	Societal perspective 2016; EUR€ Costs of management per event: 968.0
Dranitsaris et al., 2015[30] Cost-utility analysis 2014 China	Metastatic BC Nab-paclitaxel, Docetaxel, or solvent-based paclitaxel	Stomatitis grade 3/4 Paclitaxel: 1% Docetaxel: 6.7% Nab-paclitaxel: < 1%	Societal perspective 2014; USD$ Cost of supportive care of symptoms and hydration per event: 5.0-5.65
Mittmann et al., 2010[33] Cost-effectiveness model 2006 Canada	Operable, axillary lymph node-positive BC TAC (Docetaxel+Doxorubicin and Cyclophosphamide) versus FAC (5FU, Doxorubicin and Cyclophosphamide)	Stomatitis grade 3/4 TAC: 2.6% FAC: 2.7%	Societal perspective 2006; CAD$ Costs of management in 6 months TAC: 3,151.18 FAC: 3,371.28
Rashid et al., 2016[34] Chart review Jan-Dec 2011 USA	Metastatic BC Capecitabine, Taxane, Cyclophosphamide, Doxorubicin, Gemcitabine, Epirubicin, Vinorelbine, Ixabepilone, or Eribulin.	Stomatitis (ICD code 528.0×) (grade or prevalence NR)	Payer's perspective 2013; USD$ Costs per episode of care (hospital care and treatment including mouthwashes, oral corticosteroids, mouth, and throat antiseptic, and topical oral anesthetics) - Single episode Outpatient: 5,096 Hospital: 27,781 -Multiple episodes ER+hospital: 71,708
Irwin et al., 2016[32] Retrospective cohort Jan 2006 - Dec 2013 USA	Metastatic BC (ICD-9-CM 174.xx) Biologic or chemotherapy	Mucositis/Stomatitis (ICD-9 CM 528.0×, 528.2, 478.11, 538, 616.81): 10.4% Incidence 17.2/100 person years	Payer's perspective, 2013 USD$ Costs per patient per month: 715.0
Wong et al., 2018[35] Retrospective cohort Jan 2006 - Sep 2015 USA	BC (ICD-9-CM 174.xx or 175.xx) Antineoplastic pharmacologic agent not specified	Stomatitis or mucositis Any grade: 0.8% (14% severe)	Payer's perspective 2015; USD$ Costs of management per episode: 961.0
Bozza et al., 2015[36] Retrospective cohort June 2013-Dec 2014 Italy	Early BC outpatients Adjuvant chemotherapy	Mucositis (grade or prevalence NR)	Healthcare resource utilization Unscheduled presentations to hospital: 8.5% (3rd most frequent reason among other adverse events)
Lo-Fo-Wong et al., 2016 Prospective cohort Mar 2011 -Mar 2013 The Netherlands	BC (any stage) Any treatment	At least one contact with a dentist: 31.9%	Healthcare resource utilization Factors associated with dental care use post-diagnosis OR (95% CI) Chemotherapy 6 months: 2.82 (1.76-4.50) highest most likely predictor 15 months: 1.93 (1.21-3.06) 2nd highest most likely predictor
Taichman, 2015 Retrospective cohort 1999-2004 USA	BC (any stage) Treatment NR	Odds ratio of developing moderate-to-severe event [OR (95% CI)] Gingivitis: 1.24 (0.64-2.53) Periodontitis: 1.7 (0.96-3.02)	Healthcare resource utilization Dental visit last 12 months: OR (95% CI) compared to more than 12 months ago Gingivitis: 0.74 (0.53-1.14) Periodontitis: 0.47 (0.44-0.68)

(Continues)

Table 5. Costs and health-care resource utilization associated with oral complications in breast cancer treatment *(continued)*

Author, year Study design Time of data collection Country	Population Treatment	Oral complications/oral adverse effects	Cost perspective Year/Currency Cost related to OCs
Taichman, 2018 Retrospective cohort Jun 2014 - Jun 2015 USA	BC (any stage) Chemotherapy, Tamoxifen, or aromatase inhibitors (AI)	Responses to the question in the past 3 months have you had (1 = "Never", 2 = "Hardly ever", 3 = "On occasion", 4 = "Fairly often" to 5 = "Very often.") Chemotherapy Mouth sores or mucositis: 2.14 ± 1.09 Mouth feels dry: 2.53 ± 1.42 Change in taste: 3.57 ± 1.67 Bleeding gums: 1.50 ± 1.00 Aching in mouth, teeth, or jaw: 1.50 ± 0.96 Tamoxifen Mouth sores or mucositis: 1.65 ± 1.18 Mouth feels dry: 2.31 ± 1.44 Change in taste: 1.84 ± 1.45 AI Mouth sores or mucositis: 1.36 ± 1.18 Mouth feels dry: 2.60 ± 1.48 Change in taste: 1.62 ± 1.20	Healthcare resource utilization Products requested from the dentist for treatment Mucositis Chemotherapy: 4% Tamoxifen: 0% AI: 0% Xerostomia Chemotherapy: 18% Tamoxifen: 20% AI: 29%
de Araujo Sensever, 2022 Cross-sectional study Jan 2007 - Aug 2007 Brazil	BC (any stage) Tamoxifen	Xerostomia: 70.7% Untreated dental caries: ≤ 1: 72.1% > 1: 27.9% Tooth loss: Mean ± SD 12.96 8.88	Healthcare resource utilization Use of dental services in a year is associated with missing more than 12 teeth: OR 3.29 (CI 95% 1.59–6.77)
Fall-Dickson , 2008 Cross-sectional NR USA	BC (not specified) n = 32 Mean age: 49 years Chemotherapy and autoHSCT	Oral pain: 47%	Healthcare resource utilization Topical anesthetics for oral pain Ulcerease: 9% used 2-6 times/day Viscous lidocaine: 6.3% 6 times/day Mouthwash (equal parts: Maalox, viscous lidocaine, nystatin suspension, benylin syrup): 6.3% 2-4 times/day

AI: aromatase inhibitors; BC: breast cancer; CI: confidence interval; NR: not reported; OR: odds ratio; USA: United States of America.

events and hospitalization rates among those experiencing more events[40]. A systematic review of the literature on the economic implications of preventing and managing OCs up to 2017 reported incremental costs of oral mucositis in the immediate term after cancer therapy at approximately $5,000–$30,000 US dollars among patients receiving radiation therapy and $3,700 per cycle among patients receiving chemotherapy with related hospitalizations or long-term medication as the major drivers of costs[41]. The economic impact of OCs could be significant for patients or healthcare systems. For example, this review described xerostomia with a prevalence up to 70% of BC patients and they would have required long-term sialagogues prescriptions at a cost of $40–$200 per month[41]. Important gaps in the knowledge of OCs associated productivity and out-of-pocket costs could further impact patients' economy for which large-scale micro-costing studies are required.

The main limitation of this review is the inability of providing a meta-analysis which is mostly due to the heterogeneity not only of the definitions of the population, their treatment, and the OC but also the instruments applied in their evaluation. In addition, most identified studies were of moderate-to-low quality due to single data-point collection, lack of controls, small

Table 6. Recommendations for future research and management of oral complications in breast cancer patients

Area	Recommendations
Clinical trials and medical research	Better definition and characterization of a broader range of oral complications that are constantly and consistently reported in a standardized way. Involvement of oral medicine specialists to improve the recognition and management of OCs. Multi-center, prospective population-based studies of the incidence, quality of life impact, and costs of OCs according to specific treatment agents are greatly needed to support evidence-based coverage and reimbursement policies.
Clinical practice	Preventive measures of good oral hygiene should be encouraged throughout including appropriate brushing and dental floss use techniques. Before BC treatment begins: – Provision of complete information about the spectrum of oral complications likely to develop during treatment, either acute or chronic oral effects. – Full dental clinical examination, including periodontal chart, and soft- and hard-tissue assessment (including X-rays) to identify and treat odontogenic pathologies to prevent exacerbation or incidence of OC. – Risk identification of gingivitis, and periodontal disease. – Tailored recommendations and treatment for identified oral diseases in hand with the oncology team advice. During BC treatment – Periodic dental assessment based on the risk identification of gingivitis and periodontitis. – Treatment for any identified oral complications provided in agreement with the oncology team. This may include dose reductions or discontinuation of treatment. After BC treatment – Periodic dental assessment and oral hygiene screening integrated in the comprehensive management of survivorship.

sample sizes, as well as bias from patients self-reporting of outcomes. It would be appropriate to further investigate the associations of incidence and severity of OCs overtime per type of treatment.

OCs may further lead to patient morbidity and negatively affect patients' physical and psychological well-being. Standardizing instruments for diagnosing and managing less well-studied OCs could enhance collaborations between dental and medical professionals as we gain better understanding of the linkage between oral and systemic health. Understanding the pathogenesis of OCs from BC therapy may lead to the development of biomarkers for predicting adverse events and new preventive or therapeutic strategies in the future to improve patient care outcomes.

Conclusions and recommendations

Based on the findings of this study, our previous publications, and expert clinical opinion, the recommendations for future research and for the oral evaluation and treatment of BC patients are presented in table 6. This review highlights an important gap of awareness and information of the oral health in BC but could apply to other solid tumor oncology patients.

Several OCs beyond the well-known mucositis or stomatitis are more commonly experienced by BC patients compared to controls including periodontitis, xerostomia, oral pain, taste alterations dental problems, and gingivitis. These negatively impact patients' everyday lives and also represent an economic burden.

By comprehensively understanding the epidemiology and burden of OC, health-care providers can proactively develop and implement survivorship care strategies to significantly enhance BC patient outcomes and quality of life.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

Supplementary data

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