



A.C. Camargo Cancer Center

Centro Integrado de Diagnóstico, Tratamento, Ensino e Pesquisa

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Área de Oncologia

Ingestão de Polifenóis e o Câncer Gástrico: revisão sistemática com metanálise/ estudo caso-controle na região Amazônica do Brasil.

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Orientadora: Dra. Maria Paula Curado
Co-Orientadora: Dra. Gisele Fernandes

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“És senhor do teu destino, e ele tem para ti, como ponto de encontro, o infinito.”

Joanna de Ângelis.

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RESUMO

Fagundes MA. **Ingestão de Polifenóis e o Câncer Gástrico: revisão sistemática com metanálise/ estudo caso-controle na região Amazônica do Brasil.** São Paulo; 2024. [Tese de Doutorado-Fundação Antônio Prudente].

INTRODUÇÃO: Evidências indicam que os polifenóis têm propriedades biológicas importantes, que estão associadas à diminuição do risco de alguns tipos de câncer, incluindo o CG. Contudo, poucos estudos abordam esse tema na população latino-americana. **OBJETIVO:** Analisar a associação entre a ingestão de polifenóis e o adenocarcinoma gástrico na região Amazônica do Brasil. **MATERIAL E MÉTODOS:** Esta tese foi realizada no formato de dois artigos científicos. O manuscrito 1 é um estudo de revisão sistemática com metanálise e o manuscrito 2 trata-se de um estudo caso-controle de base hospitalar, ambos analisaram a associação entre a ingestão de polifenóis e o adenocarcinoma gástrico. Os casos tiveram diagnóstico por histologia de adenocarcinoma gástrico, e os controles hospitalares, pareados por sexo e idade. Questionários de Estilo de Vida e de Frequência Alimentar foram aplicados entre julho de 2017 e fevereiro de 2021. Foram calculados os odds ratios (ORs) e os respectivos Intervalos de Confiança de 95% (ICs) por meio do modelo de regressão logística condicional para analisar a associação entre as principais classes de polifenóis e o adenocarcinoma gástrico. **RESULTADOS:** Artigo 1- Na revisão sistemática e metanálise observou-se que o consumo de polifenóis diminuiu o risco de CG em ambos os sexos, principalmente em mulheres. Além disso, reforçou-se a necessidade de estudos que buscam avaliar a associação entre os polifenóis e o CG na população latino-americana. Artigo 2 - No estudo caso-controle observou-se que o alto consumo de flavan-3-óis (OR 0,41; IC95% 0,18-0,94) e ácidos hidroxibenzóicos (OR 0,24; IC 95% 0,10-0,56) foram associados à redução de chance de GC. O inverso ocorreu em relação à ingestão de flavonas (OR 2,46; IC95% 1,17-5,18) e outros polifenóis (OR 2,54; IC95% 1,16-5,54). O alto consumo de flavonóides totais e flavanonas está associado a menor chance de GC do tipo cardíaca, mas não para GC não cardíaca e GC geral, e o consumo de ácidos hidroxibenzóicos associado a menor chance de não cardíaca e intestinal. **CONCLUSÕES:** Ambos os estudos sugerem que o consumo de polifenóis está associado à redução de risco para câncer gástrico, portanto fortalecer estratégias para encorajar o consumo de alimentos ricos em polifenóis, podem reduzir a incidência de CG.

Palavras-chave: Câncer Gástrico; Polifenóis; Dieta; Caso-controle; Brasil.

ABSTRACT

Fagundes MA. **Polyphenol intake and gastric cancer: systematic review with meta-analysis/case-control study in the Amazon region of Brazil.** São Paulo; 2024. [Tese de Doutorado-Fundação Antônio Prudente].

INTRODUCTION: Evidence indicates that polyphenols have important biological properties, which are associated with a decreased risk of some types of cancer, including GC. However, few studies address this topic in the Latin American population. **OBJECTIVE:** To analyze the association between polyphenol intake and GC in Amazon region of Brazil. **MATERIAL AND METHODS:** This thesis was carried out in the format of two scientific articles. Manuscript 1 is a systematic review study with meta-analysis and manuscript 2 is a hospital-based case-control study, both analyzed the association between polyphenol intake and gastric adenocarcinoma. The cases were diagnosed by histology as gastric adenocarcinoma, and the hospital controls were matched by sex and age. Lifestyle and Food Frequency Questionnaires were applied between July 2017 and February 2021. Odds ratios (ORs) and respective 95% Confidence Intervals (CIs) were calculated using the conditional logistic regression model to analyze the association between the main classes of polyphenols and gastric adenocarcinoma. **RESULTS:** Article 1- In the systematic review and meta-analysis, it was observed that the consumption of polyphenols reduced the risk of GC in both sexes, especially in women. Furthermore, the need for studies seeking to evaluate the association between polyphenols and GC in the Latin American population was reinforced. Article 2 - In the case-control study, it was observed that the high consumption of flavan-3-ols (OR 0.41; 95% CI 0.18-0.94) and hydroxybenzoic acids (OR 0.24; 95% CI 0.10-0.56) were associated with a reduced chance of GC. The opposite occurred in relation to the intake of flavones (OR 2.46; 95% CI 1.17-5.18) and other polyphenols (OR 2.54; 95% CI 1.16-5.54). High consumption of total flavonoids and flavanones is associated with a lower chance of cardia-type GC, but not for non-cardia GC and general GC, and the consumption of hydroxybenzoic acids is associated with a lower chance of non-cardia and intestinal GC. **CONCLUSIONS:** Both studies suggest that the consumption of polyphenols is associated with a reduced risk of gastric cancer, therefore strengthening strategies to encourage the consumption of foods rich in polyphenols may reduce the incidence of GC.

Keywords: Gastric Cancer; Polyphenols; Diet; Case-control; Brazil.

LISTA DE ABREVIATURAS

ACCCC - AC Camargo Cancer Center

CEP - Comitê de Ética em Pesquisa

CG - Câncer gástrico

CID-O - Classificação Internacional de Doenças para Oncologia

FAPESP - Fundação de Amparo à Pesquisa do Estado de São Paulo

HOL - Hospital Ophir Loyola

HUJBB - Hospital Universitário João de Barros Barretos

IC - Intervalo de confiança

IMC - Índice de Massa Corpórea

MSI - Instabilidade de microssatélite

NCC - Nutrition coordinating center

NDSR - Nutrition data system for research

OR - Odds Ratio

QFA - Questionário de frequência alimentar – QFA

RR - Risco Relativo

TBCA - Tabela Brasileira de Composição de Alimentos

TCLE - Termo de Consentimento Livre e Esclarecido

USDA - United States departamento of agriculture

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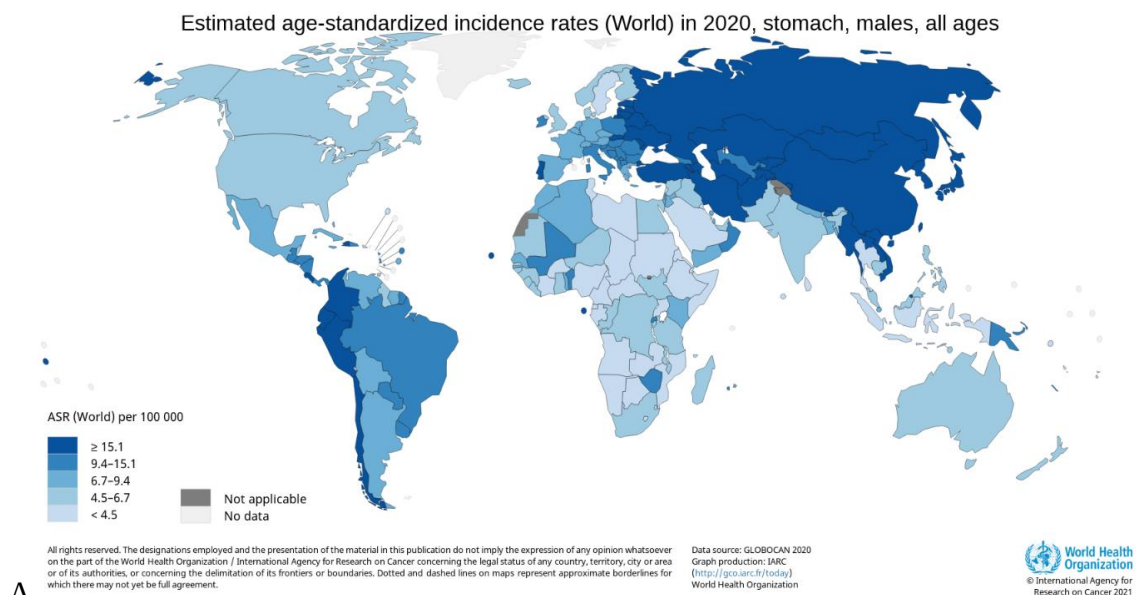
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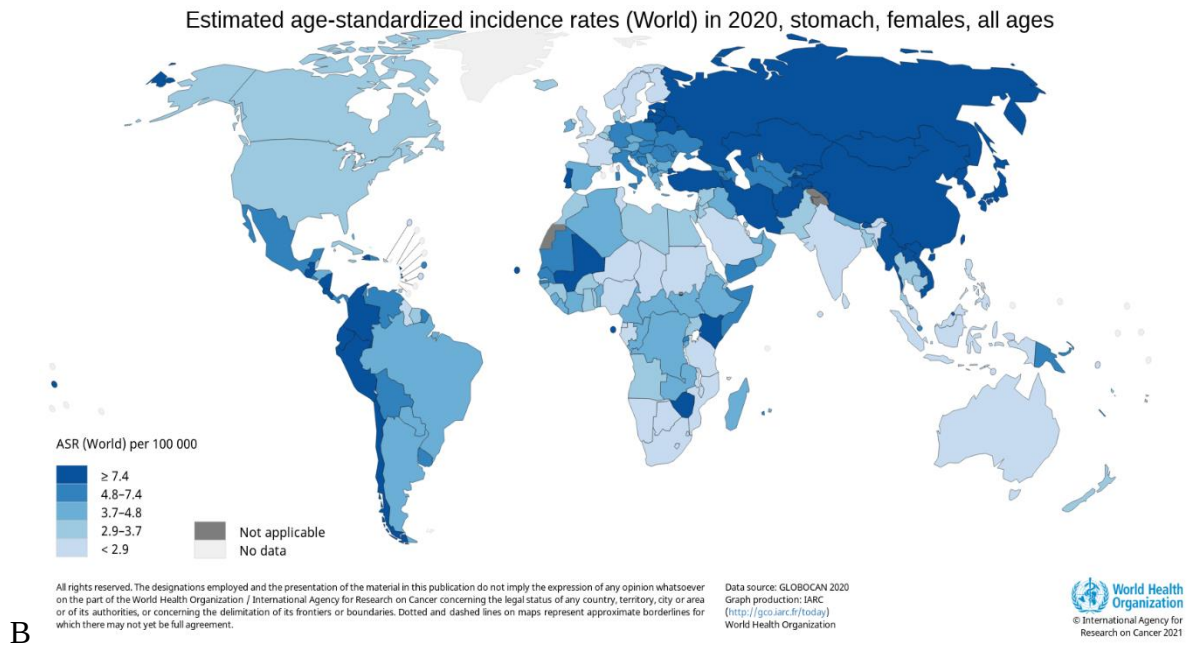
1 INTRODUÇÃO

1.1 INCIDÊNCIA E MORTALIDADE DO CÂNCER GÁSTRICO

No mundo, em 2020, o câncer gástrico foi o quinto mais incidente e o quarto mais letal. Foram estimados mais de um milhão de novos casos, representando 5,6% de todos os cânceres previstos e cerca de 769.000 mortes; sendo o terceiro mais incidente entre homens e o quinto entre as mulheres; as taxas de incidência são o dobro nos homens em comparação às mulheres. As maiores taxas de incidência de câncer gástrico concentram-se na Ásia, no Leste Europeu e na América do Sul, e as menores na América do Norte, Norte da Europa e regiões da África (Figura 1) (SUNG et al. 2021).



Fonte: GLOBOCAN (2020).

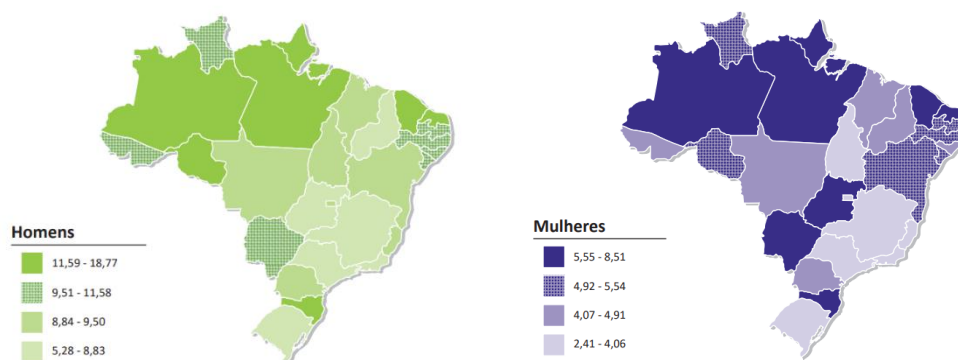


B

Fonte: GLOBOCAN (2020).

Figura 1: A- Distribuição das taxas de incidência padronizadas de câncer de estômago para os homens. **B-** Distribuição das taxas de incidência de câncer de estômago padronizadas para as mulheres.

No Brasil, para o triênio 2023-25, foram estimados 21.480 novos casos de câncer gástrico, sendo o quarto mais incidente em homens, 13.340 casos, e o sexto em mulheres (8.140 casos). As regiões Norte e Nordeste apresentam as maiores taxas de incidência, tanto em homens quanto em mulheres (Figura 2) (Ministério da Saúde 2023).



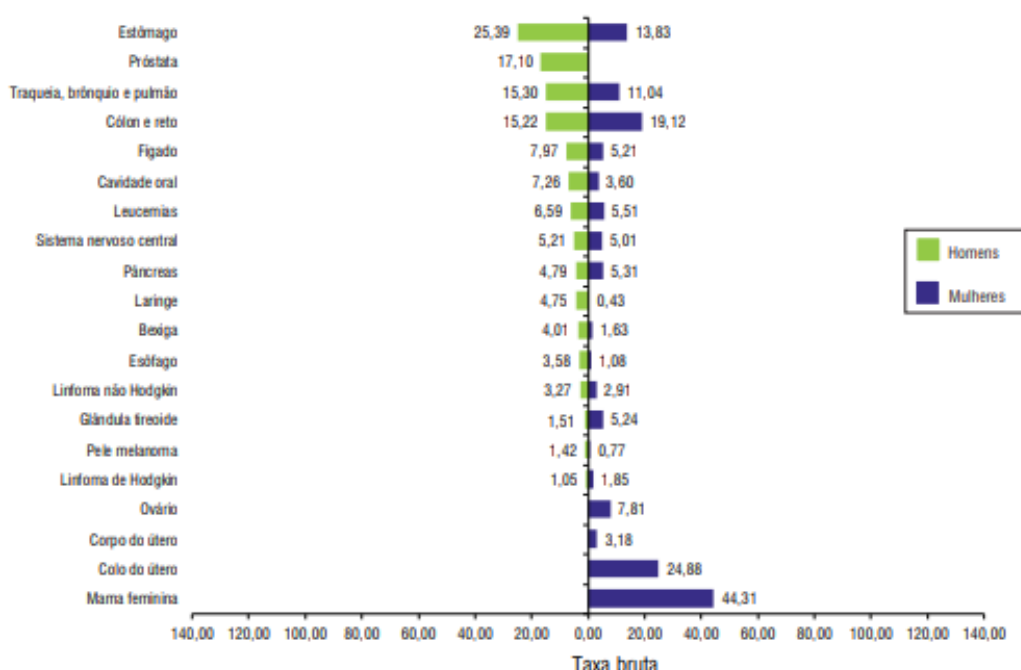
Fonte: Ministério da Saúde (2023).

Figura 2: Representação espacial das taxas ajustadas de incidência de câncer de estômago em homens e mulheres, estimadas para o ano de 2023, por Unidade da Federação.

As regiões do Brasil apresentam disparidades nas taxas de incidência e de mortalidade para o câncer gástrico (CURADO et al. 2019). A incidência do câncer gástrico, em 2023, entre os homens ocupou o 2º lugar no Pará e o 1º na capital Belém; enquanto nas mulheres ocupou o 4º lugar no Pará e em Belém. No estado do Pará, foram estimados 980 casos novos para ambos os sexos, com taxas ajustadas de incidência de 17,20 por 100 mil homens e de 8,11 por 100 mil mulheres. Em Belém, espera-se 320 novos casos para 2023, com taxas brutas de incidência de 25,39 por 100 mil para homens e 13,83 por 100 mil para mulheres (Figura 3) (Ministério da Saúde 2023).

A maioria dos casos de câncer gástrico, independente do subsítio anatômico, ocorre em homens entre 60-70 anos, e pacientes com mais de 50 anos (Ministério da Saúde 2023). Por outro lado, estudos recentes observaram aumento da incidência de câncer gástrico entre adultos jovens (<50 anos) (ARNOLD et al. 2020; HEER et al. 2020).

As maiores taxas de mortalidade foram observadas para o sexo masculino e nos estados da região Norte e no Ceará (GIUSTI et al. 2016; GUERRA et al. 2019).



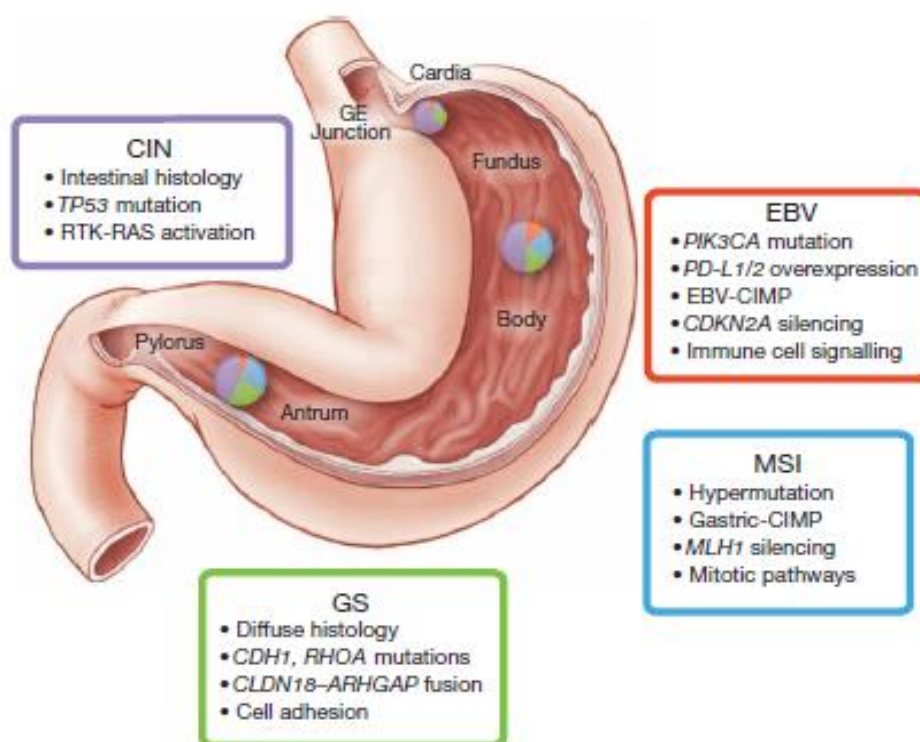
Fonte: Ministério da Saúde (2023).

Figura 3 - Taxas brutas de incidência estimadas para 2023 por sexo, para Belém, capital do estado do Pará.

1.2 CÂNCER GÁSTRICO E FATORES ASSOCIADOS

O adenocarcinoma representa 95% dos tipos histológicos do câncer gástrico. A distribuição de subtipos histológicos dessa neoplasia e as frequências de *H. pylori* e EBV variam no mundo (TCGA 2014; MUKAISHO et al. 2015; Ministério da Saúde 2021).

O TCGA (2014) classificou quatro principais subtipos genômicos de adenocarcinoma gástrico, como EBV, instabilidade de microssatélite (MSI), histológico intestinal (CIN) e difuso (GS) (Figura 4).



Fonte: Cancer Genome Atlas Research Network (2014).

Figura 4: Principais subtipos genômicos do adenocarcinoma gástrico.

O câncer gástrico pode ser classificado em cárdia e não cárdia. Ambos compartilham alguns fatores risco como idade, sexo masculino, tabagismo, consumo de álcool, radiação e história de câncer na família (WCRF/AICR 2018).

Os fatores de riscos modificáveis para o câncer gástrico são o tabagismo e o consumo de bebida alcoólica (MINAMI et al. 2018; PRAUD et al. 2018; POOROLAJAL et al. 2020). É estimado que 11% de todos os casos de câncer gástrico no mundo são atribuídos ao uso de

tabaco, e o risco para essa neoplasia também aumenta naqueles indivíduos que consomem doses de bebida alcoólica acima de 45 mg/dia) (WCRF/AICR 2018).

O histórico familiar de câncer gástrico é considerado um fator de risco importante e é maior na Ásia do que na Europa e América do Norte (MACHLOWSKA et al. 2020).

Os homens têm as maiores taxas de incidência e mortalidade, para ambos os subsítios, mas para o tipo cárdia a proporção é maior em homens (3:1). Essa diferença entre os sexos está relacionada a fatores endógenos, como hormônios reprodutivos, a prevalência de obesidade central ou diferentes níveis de ferro na pré-menopausa (ABDI et al. 2019).

O câncer gástrico do tipo cárdia, na maioria das vezes é identificado em estadiamento avançado e tem pior prognóstico comparado ao não cárdia (ABDI et al. 2019). Evidências sugerem uma etiologia dupla para o câncer de cárdia, algumas associadas à infecção por *H. pylori*, e outras ao excesso de peso corporal e à doença do refluxo gastresofágico (MARTEL e PARSONNET 2018). Porém, os resultados dos estudos apontam uma maior consistência entre a associação da presença da infecção por *H. pylori* e o câncer gástrico não cárdia (YANG et al. 2020; WILD, WEIDERPASS e STEWART, 2020).

Em 2015, a infecção por *H. pylori* foi responsável por 74,7% de todos os casos de câncer gástrico não cárdia no mundo (WANG et al. 2015). Em 2018, foi responsável por 810 mil novos casos (MARTEL et al. 2019). As áreas de alto risco para câncer atribuível a essa bactéria incluem o leste da Ásia, América Latina, Oriente Médio e Europa Oriental. Na América Latina, a prevalência da infecção por *H. pylori* é de 57,57% para todas as idades. No entanto, menos de 5% dos hospedeiros infectados pelo *H. pylori* desenvolvem o câncer, provavelmente devido às diferenças na genética da bactéria e do hospedeiro, idade do indivíduo quando contaminado e fatores ambientais (CURADO; OLIVEIRA; FAGUNDES 2019; MARTEL et al. 2019).

Assim como o baixo nível socioeconômico, cirurgia gástrica prévia e anemia perniciosa, o alto consumo de sal e alimentos ultraprocessados, e baixo consumo de frutas e vegetais também estão associados ao risco de desenvolvimento de câncer gástrico não cárdia (MARTEL e PARSONNET 2018; WCRF/AICR 2018).

1.3 HÁBITOS ALIMENTARES, POLIFENÓIS E O CÂNCER GÁSTRICO

Sabe-se que o padrão alimentar relacionado ao ganho excessivo de peso, à obesidade e às doenças crônicas, como o câncer, é caracterizado, especialmente, pelo baixo consumo de

alimentos in natura e minimamente processados em paralelo ao consumo excessivo de alimentos ultraprocessados (MONTEIRO et al., 2011; SWINBURN et al., 2019).

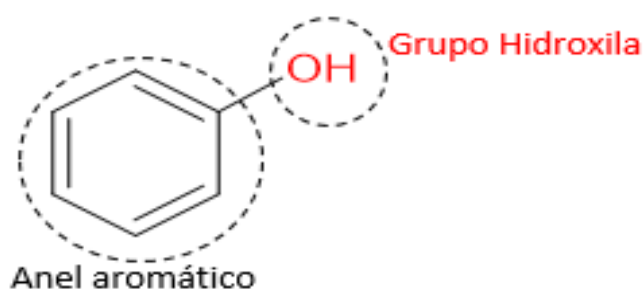
No Brasil, cada região desenvolveu uma cultura alimentar característica, traço que compõe a identidade plural do brasileiro. A região amazônica do Brasil, por exemplo é reconhecida pela sua vasta diversidade e complexa interação entre fatores ambientais e socioculturais (CORRÊA e SILVA 2021). Inserida na região amazônica, a microrregião de Salgado Paraense compreende 11 municípios que compõem um corredor ecológico formado por unidades de conservação de uso sustentável, onde a população depende de recursos naturais locais como a pesca artesanal e a caça ao caranguejo para subsistência (PEREIRA et al., 2009; SANTOS et al. 2022). Por outro lado, nos últimos anos, a alimentação brasileira tradicional vem perdendo espaço para os alimentos ultraprocessados de modo geral (MONTEIRO et al. 2011).

Segundo dados do Sistema de Vigilância de Fatores de Risco de Doenças Crônicas por Inquérito Telefônico (Vigitel) de 2023, a frequência de adultos que consomem regularmente frutas e hortaliças variou bastante entre as capitais, sendo a menor frequência observada em Belém (18,1%) e a maior em Florianópolis (41,2%). Dentre os homens, as maiores frequências foram encontradas em Vitória (38,5%), João Pessoa (38,5%) e Belo Horizonte (35,6%), e as menores em Belém (14,1%), Rio Branco (14,4%) e Salvador (16,0%). Entre as mulheres, as maiores frequências foram encontradas em Curitiba (47,8%), Florianópolis (46,3%) e Belo Horizonte (44,7%), e as menores em Belém (21,4%), Rio Branco (22,8%) e Porto Velho (24,2%).

Enquanto as frutas e vegetais reduzem a chance do câncer gástrico, alimentos grelhados como carnes, preservados com sal e defumados aumentam a chance. Os carcinógenos alimentares têm a capacidade de interagir com as células epiteliais gástricas e provocar mudanças na expressão de seus genes, o que favorece a carcinogênese (WCRF/AICR 2018). A redução da chance é atribuída à ingestão de nutrientes, micronutrientes e outros compostos alimentares, incluindo os antioxidantes como os polifenóis (PETRICK et al. 2015; VITELLI-STORELLI et al. 2020).

Os antioxidantes são substâncias, que em determinadas concentrações, são capazes de retardar ou inibir a oxidação de substratos como lipídios e proteínas. Podem ser classificados em dois grandes grupos, os enzimáticos presentes no organismo, e os não enzimáticos obtidos por meio da alimentação como as Vitaminas (A, C, E e K), minerais (zinco e selênio) e compostos fenólicos (HALLIWELL e GUTTERIDGE 1995; AZAT et al. 2019).

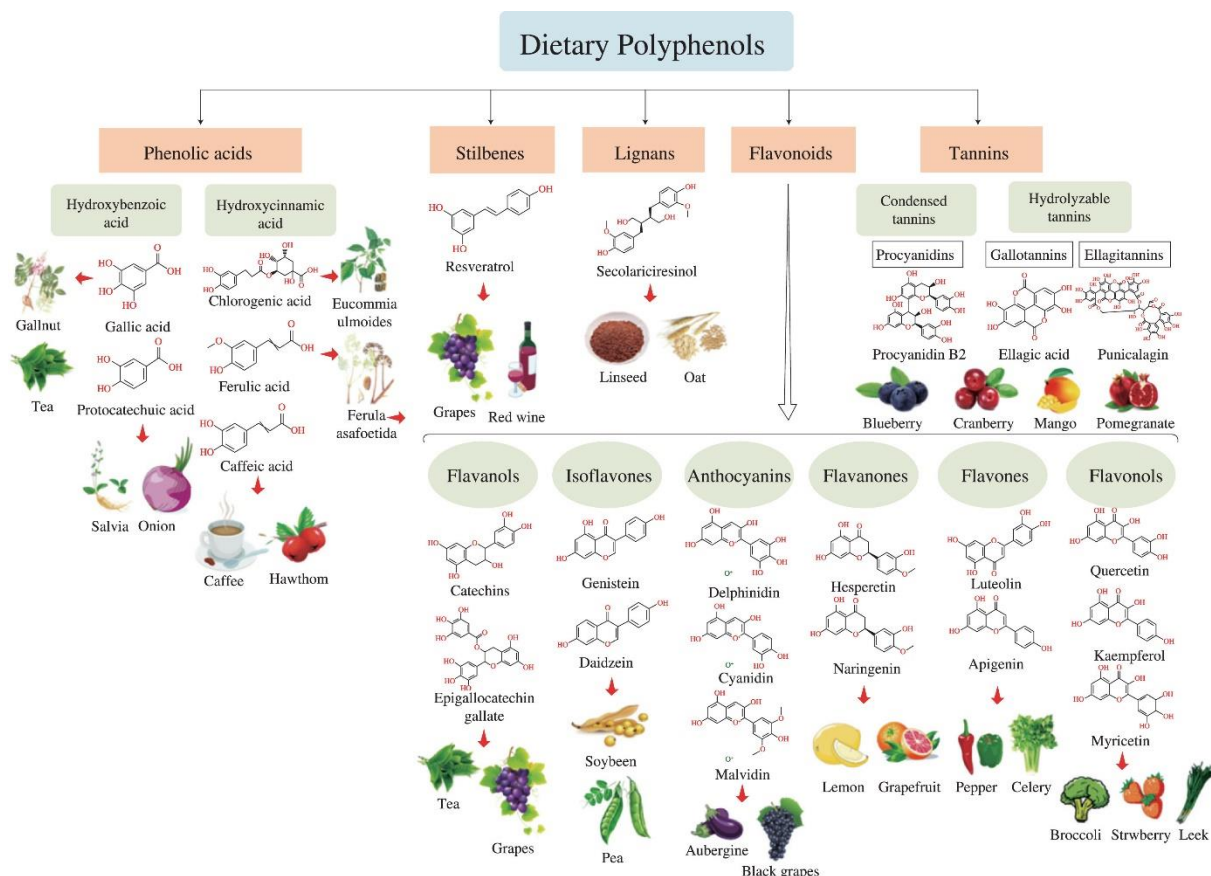
Os compostos fenólicos são os antioxidantes mais abundantes na dieta humana e seu consumo diário pode atingir até 1g (TRESSERRA-RIMBAU; LAMUELA-RAVENTOS; MORENO, 2018; CIONE et al. 2019). Tais compostos possuem anel aromático com um ou mais substituintes hidroxílicos em seus grupos funcionais (Figura 6). Os fenólicos englobam desde moléculas simples até moléculas com alto grau de polimerização, e podem estar presentes nos alimentos na forma livre (aglicona) ou ligados a açúcares (glicosídeos) e proteínas (RIBÉREAU-GAYON 1968; SHAHIDI e NACZK 1995).



Fonte: ÂNGELO e JORGE, 2007.

Figura 5 – Estrutura química de um Fenol.

Existem cerca de oito mil fenóis, entre classes e subclasses (NIEDZWIECKI et al. 2016). Dentre as classes destacam-se os ácidos fenólicos, flavonóides, e não-flavonóides que incluem lignanas, estilbenos, e outros polifenóis. As principais fontes alimentares de polifenóis são as frutas, vegetais, chá, café, cereais, azeitonas e chocolate (CIONE et al. 2019) e vão variar conforme sua subclasse e estrutura química (Figura 6).



Fonte: Li et al. (2023).

Figura 6 – Classificação e principais fontes de Polifenóis.

Os polifenóis possuem propriedades anticarcinogênicas, anti-inflamatórias e antimicrobianas, e atuam nas vias de proliferação celular na inibição do crescimento do *H. Pylori* (GROSSO et al. 2017; CORY et al. 2018). A atividade anticarcinogênica dos fenólicos está relacionada à inibição de cânceres do trato digestivo (NIEDZWIECKI et al. 2016). Estudos apontam um efeito protetor dos flavonóides para o câncer gástrico (GARCIA-CLOSAS et al. 1999; ROSSI et al. 2010; WOO et al. 2014). No entanto, a maioria dos estudos concentra-se na investigação da associação de apenas uma classe de polifenol (GARCIA-CLOSAS et al. 1999; LAGIOU et al. 2004; HARA et al. 2012; SUN et al. 2017).

Os flavonóides são as classes de polifenol mais estudadas. Estudos do tipo caso-controle encontraram associação inversa entre consumo de flavonóides e câncer gástrico na Grécia (LAGIOU et al. 2004), Itália (ROSSI et al. 2010), e Coreia (WOO et al. 2014). O estudo de Rossi et al. (2010) foi o primeiro a sugerir que as proantocianidinas dietéticas reduzem a chance de câncer gástrico.

Estudos de caso-controle multicêntricos, realizados na Europa e Estados Unidos da América, verificaram um menor risco de desenvolver o câncer gástrico quanto maior o consumo

de polifenóis (PETRICK et al. 2015; RUBÍN-GARCÍA et al. 2020). Enquanto estudos realizados na Finlândia (HIRVONEN et al. 2001; KNEKT et al. 2002), Japão (HARA et al. 2012) e Estados Unidos da América (SUN et al. 2017) não encontraram associação entre a ingestão de polifenóis e o câncer gástrico. Observa-se escassez de estudos entre o consumo de polifenóis e o adenocarcinoma gástrico em países da América Latina, como Brasil.

2 JUSTIFICATIVA

Não há um consenso na literatura científica sobre a direção da associação entre o consumo de polifenóis e suas subclasses e o CG (RUBÍN-GARCÍA et al. 2020; HARA et al. 2012; SUN et al. 2017).

Além disso, os estudos de caso-controle e coorte que buscam avaliar essa associação concentram-se em uma só classe (flavonóides), e são escassos na América Latina.

O presente estudo investiga a ingestão de polifenóis em pacientes com adenocarcinoma gástrico em Belém-PA, uma oportunidade singular de avaliar a região que detém as maiores taxas de incidência e mortalidade do câncer gástrico no Brasil (SANTOS et al. 2023).

Sabe-se que a ingestão de frutas e vegetais está inversamente associada ao câncer gástrico (NAEMI et al. 2023; FERRO et al. 2020), devido à composição dos alimentos vegetais, que contém micronutrientes e compostos bioativos, como os polifenóis. Os polifenóis são um grupo amplo e complexo de não nutrientes presentes em alimentos e bebidas, como frutas, vegetais, feijão, café, vinho e chá. Os polifenóis têm propriedades biológicas importantes, como atividades antioxidantes, anti-inflamatórias e antiproliferativas, que estão associadas à diminuição do risco de alguns cânceres, incluindo o gástrico. Devido a ampla variação química e funcional, a maioria dos estudos entre câncer gástrico e polifenóis concentraram-se em algumas classes específicas (CORY et al. 2018; GARCIA-CLOSAS et al. 1999; VITELLI-STORELLI et al. 2020).

Investigar a associação de polifenóis com adenocarcinoma gástrico se torna importante em Belém-PA, na Amazônia, reconhecida pela sua biodiversidade, o que reflete em padrões alimentares peculiares, e a interação entre fatores ambientais, demográficos, sociais, econômicos e culturais (CORRÊA e SILVA 2021). Além disso, não há estudos sobre o consumo de alimentos com polifenóis e a presença de câncer gástrico na região Amazônica do Brasil, portanto, os resultados encontrados poderão servir de subsídios para outros estudos brasileiros além do câncer gástrico.

3 OBJETIVO

Analisar a associação entre a ingestão de polifenóis e o câncer gástrico

3.1 OBJETIVOS ESPECÍFICOS

- Investigar a associação entre o risco de câncer gástrico e a ingestão dietética de polifenóis, para as principais classes e subclasses de polifenóis, por meio uma revisão sistemática com metanálise
- Avaliar a associação entre adenocarcinoma gástrico e o consumo alimentar das principais classes e subclasses de polifenóis na região Amazônica brasileira.

4 MATERIAL E MÉTODOS

Esta tese tem o formato de dois artigos científicos. O artigo 1 “Ingestão de polifenóis e Câncer Gástrico: uma revisão sistemática e metanálise” ; e artigo 2 “Ingestão de polifenóis e Câncer Gástrico: um estudo caso-controle na região Amazônica do Brasil”.

4.1 METODOLOGIA

Artigo 1 - Ingestão de polifenóis e Câncer Gástrico: uma revisão sistemática e metanálise.

Este estudo de revisão sistemática e meta-análise segue as diretrizes PRISMA (MOHER et al. 2009) e foi registrado no PROSPERO (#CRD42022306014).

As bases de dados eletrônicas escolhidas para a busca dos artigos foram PubMed, Scopus, Embase, LILACS, OpenGrey e Web of Science. Foram incluídos estudos publicados até 20 de março de 2022, que avaliaram a associação entre o risco de GC e ingestão dietética de polifenóis. Os termos aplicados foram: polifenol ou fenol ou flavonóide ou flavonol ou “ácidos fenólicos” ou “ácidos hidroxicinâmicos” ou “hidroxibenzóico ácidos” ou “ácidos hidroxifenilacéticos” ou lignanas ou estilbenos ou alquilfenóis ou alquilmetoxifenóis; e “câncer gástrico” ou “tumor gástrico” ou “câncer de estômago” ou “adenocarcinoma gástrico” ou “neoplasia do estômago” ou “neoplasia do estômago”. Incluiu-se estudos observacionais, de coorte e/ou caso-controle, sem restrições de idioma; a ingestão de polifenóis medida por meio de questionário validado. Uma busca manual por citações adicionais foi realizada através da avaliação das listas de referências dos artigos incluídos. Os pesquisadores realizaram seleções cegas dos artigos na plataforma Rayyan e as áreas de discordância ou incerteza foram resolvidas por consenso entre todos os autores.

Dois autores extraíram independentemente as seguintes informações dos estudos elegíveis: (1) sobrenome do primeiro autor; (2) ano de publicação; (3) país; (4) desenho do estudo; (5) período de estudo; (6) número total de participantes, número de casos e controles; (7) método de avaliação de polifenóis; (8) fonte alimentar de polifenóis; (9) polifenóis estudados; (10) risco relativo (RR)/odds ratio (OR) e intervalo de confiança de 95% (IC) indicando as categorias mais altas versus as mais baixas de ingestão de polifenóis na dieta; (11) comparação de consumo; e (12) variáveis de ajuste.

A técnica de metanálise de efeitos aleatórios foi usada para avaliar a associação entre dieta ingestão de polifenóis, incluindo as principais subclasses (exposição) e a chance de GC (desfecho), com ORs calculadas juntamente com seus ICs de 95%.

O teste qui-quadrado de Cochran e o teste I^2 foram utilizados para quantificar a heterogeneidade dos estudos onde, para $p < 0,05$ e/ou $I^2 > 50\%$, a heterogeneidade era considerada alta entre os estudos, quando I^2 igual ou menor que 50% a heterogeneidade moderada/baixa (HIGGINS; THOMPSON 2002; WANG et al. 2021). A escolha das ORs para análise foi feita considerando todas as classes de polifenóis. A ordem de escolha dos ORs foi: polifenóis totais, flavonóides totais, flavanonas, ácidos fenólicos, lignanas e estilbenos.

Foram selecionadas as OR de ambos os sexos. Quando os estudos analisaram o consumo de polifenóis por sexo e localização anatômica separados, as OR do sexo feminino e tipo não-cárdia foram selecionadas. Análises de subgrupos por subclasses (flavonóides e não flavonóides), sexo (masculino ou feminino), desenho do estudo (caso-controle e/ou estudo de coorte), topografia (cárdia ou não cárdia), subtipo histológico (difuso ou intestinal), área geográfica (Europa, Ásia ou América) e as variáveis de ajuste foram histórico familiar de CG; consumo de frutas e/ou vegetais) para identificar potenciais confundidores. Em relação ao desenho de estudo e área geográfica, as estimativas de risco foram para ambos os sexos.

A Escala Newcastle-Ottawa foi usada para avaliar o risco de viés, determinando a qualidade dos estudos observacionais usando duas escalas independentes uma para coorte e estudos de caso-controle). A escala é composta por itens divididos em três domínios: seleção, comparação e exposição (estudos de caso-controle) ou resultado (estudos de coorte). Estudos com uma classificação de 6 ou superior foram consideradas de alta qualidade (YAMADA et al. 2018). O teste de Egger e os gráficos de funil foram realizados para avaliar potencial viés de publicação, onde um valor de $p < 0,05$ foi considerado diferença estatisticamente significativa para todos os testes utilizados. Todas as análises estatísticas foram realizadas utilizando o software STATA, versão 15.0 (Stata Corporation, College Station, TX, EUA).

4.2 METODOLOGIA

Artigo 2 – Ingestão de polifenóis e Câncer Gástrico: um estudo caso-controle na região Amazônica do Brasil.

4.2.1 População, local e período de estudo

Trata-se de um caso-controle de base hospitalar, parte do projeto “Epidemiologia dos Adenocarcinomas Gástricos no Brasil”, onde o Hospital Ophir Loyola (HOL) e Hospital Universitário João de Barros Barreto (HUIBB), centros de referência em oncologia da região Norte situados na cidade de Belém-Pará, foram centros participantes.

Os casos foram pacientes com diagnóstico de adenocarcinoma gástrico confirmado por histologia e codificado conforme a CID-O-3 (C16) (FRITZ et al. 2013) e idade entre 18 e 75 anos, os quais foram recrutados por conveniência durante a internação e a partir do conhecimento da agenda de consultas semanais do ambulatório de abdômen dos hospitais HUIBB e HOL. Os controles hospitalares foram pacientes atendidos no HUIBB, na triagem, clínica médica e nos ambulatórios de fisioterapia, nutrição e abdômen (Hérnia umbilical - CID 10 K42).O recrutamento ocorreu e por meio do pareamento dos casos com controles por sexo e idade em quinquênios.

Foram excluídos indivíduos portadores de outras neoplasias malignas com exceção do carcinoma de pele não melanoma; pacientes com diagnóstico confirmado de CG há mais de dois anos no momento da entrevista; pacientes sem condições físicas e/ou psicológicas de participar da pesquisa.

As entrevistas foram conduzidas no período de julho de 2017 a fevereiro de 2021, e realizadas por pesquisador treinado, em um único momento com duração aproximada de uma hora. As entrevistas foram realizadas nos leitos de internação e na sala de espera da consulta ambulatorial de abdômen dos hospitais HUIBB e HOL, quando livres e disponíveis. Os pacientes foram abordados no momento pré-operatório ou que já tivesse iniciado o tratamento oncológico. Não houve recusa de participação neste estudo.

4.2.2 Instrumentos e Variáveis

Foram aplicados dois questionários, um sobre estilo de vida (Anexo 1) e outro sobre frequência alimentar adaptado de Lameza (2010) (Anexo 2), além de um questionário prévio de identificação pessoal e sócio demográfico (Anexo 3). No Questionário de Frequência Alimentar (QFA) validado por Lameza, foram incluídos os itens alimentares descritos no Quadro 1.

CARNES E PEIXES
Carnes processadas (almôndega, hambúrguer). Churrasco Carne em conserva
PEIXES E FRUTOS DO MAR SALGADOS
Camarão salgado/seco Pirarucu e outros peixes salgados
SOPAS E MASSAS
Macarrão instantâneo (miojo)
VERDURAS E LEGUMES
Cariru Jambu
MOLHOS E TEMPEROS
Cheiro Verde Salsa Pimenta vermelha / de cheiro / pimentinha verde Molho de pimenta industrializado
FRUTAS
Cupuaçu Bacuri Pupunha Graviola
ALIMENTOS (PREPARAÇÃO REGIONAL)
Tacacá Pato no Tucupi Arroz Paraense Maniçoba Vatapá Farinha de Tapioca Açaí Tapioca
BEBIDAS
Suco Natural de Cupuaçu Suco Natural de Graviola Suco Natural de Bacuri

Quadro 1 – Itens alimentares adicionados ao QFA aplicado validado por Lameza (2010).

Os dados obtidos nas entrevistas foram armazenados em um banco de dados informatizado (REDCap™ - ResearchElectronic Data Capture, EPGC Versão 4.1 19-04-2016).

As variáveis escolhidas para análise foram: idade em anos, sexo (feminino, masculino), escolaridade (≤ 8 , 9 a 12 e ≥ 13 anos), estado civil (solteiro(a), casado(a), viúvo(a) e divorciado(a)), etnia (branco, preto/negro e pardo), procedência (região do salgado paraense ou não), consumo de álcool, tabagismo, Índice de Massa Corpórea (IMC), histórico de câncer na família, subtipo anatômico (cárdia e não cárdia), subtipo histológico (intestinal e difuso) de LAUREN (1965), e as variáveis do QFA para análise de polifenol.

A procedência dos indivíduos foi categorizada de acordo com a referência geográfica do estado do Pará: municípios que fazem parte da microrregião do Salgado Paraense e aqueles que não fazem parte, como a própria região metropolitana de Belém.

O Consumo de álcool foi calculado segundo Boffetta e Garfinkel (1990), conforme a equação (1):

$$(1) \text{ Total Álcool} = \frac{\left[\frac{\text{unidade} \times \text{quantidade}}{\text{frequência}} \text{ em dias} \right] \times (\text{teor alcoólico} \times \text{massa}) \times 365 \times (\text{idade final} - \text{idade inicial})}{\text{total de tempo em dias de consumo}} = \text{gramas etanol mililitros/dia.}$$

Após calculado, o consumo de bebidas alcoólicas foi categorizado em consumo baixo se ≤ 12 g/dia e moderado/alto se > 12 g/dia. Quanto ao consumo de tabaco, categorizado segundo o status (sim/não), ≤ 10 maços/ano como consumo baixo de tabaco e > 10 maços/ano como consumo moderado/alto (PARAGOMI et al. 2022).

O IMC foi calculado pela fórmula $\text{IMC} = \text{Peso} / \text{Estatura}^2$. Os valores de referência utilizados foram da Organização Mundial da Saúde e para idosos segundo a Organização Pan-Americana da Saúde, sendo categorizados em: baixo peso, eutrófico, sobrepeso e obeso ($\text{IMC} > 30 \text{ kg/m}^2$) (WHO 2000, OPAS 2001). O histórico de câncer foi categorizado segundo status sim ou não.

Cada questão do QFA foi composta por três categorias: frequência de consumo :1) quantas vezes você comeu o alimento, variando de 1 a 10; 2); a unidade de consumo - diário, semanal, mensal ou anual; e 3) o tamanho da porção ingerida - pequena, média ou grande - nesta questão, cada alimento apresenta o tamanho da porção em gramas e seu equivalente em fatias, colheres e / ou xícaras. O consumo foi calculado em gramas / dia: ((quantidade * porção) / unidade-dia)) x gramas. O QFA faz referência à frequência alimentar no último ano antes do diagnóstico.

Os alimentos do QFA foram avaliados quanto à composição polifenóis. A ingestão alimentar de polifenóis foi estimada usando o Phenol-Explorer (<http://phenol-explorer.eu/>) (ROTHWELL et al. 2013). Essa ingestão é expressa como aglicona separada por cromatografia após métodos analíticos de hidrólise. A estimativa do teor de polifenóis em alimentos incluídos no Phenol-Explorer foi calculada através da seguinte equação (2):

$$(2) P_{\text{aglycone}} \frac{\text{mg}}{100\text{mg}} = \left(\frac{[\text{glucoside}]}{P_{\text{m glucoside}}} \right) \times P_{\text{m aglycone}}$$

Esses valores foram usados para calcular a ingestão de polifenóis em miligramas por dia para cada alimento. Foi realizada a análise de consistência do consumo alimentar para verificar extremos na ingestão de energia, menor que 500kcal ou maior que 5000kcal, conforme WOO et al. (2014), e posteriormente a ingestão de compostos fenólicos foi categorizada em quartis de acordo com a distribuição entre casos e controles.

Os dados de consumo alimentar foram quantificados utilizando o software Nutrition Data System for Research (NDSR), versão 2021, desenvolvido pelo Nutrition Coordinating Center (NCC), University of Minnesota, Minneapolis, MN, que utiliza como base os dados de composição de alimentos disponibilizados pelo United States Department of Agriculture (USDA). Esse software possui cadastrados cerca de 18.000 alimentos e preparações, e mais de 160 nutrientes e outros componentes alimentares (NDSR, 2021). A composição dos alimentos regionais brasileiros e outros ausentes no NDSR, foram extraídos da Tabela Brasileira de Composição de Alimentos – TBCA (TBCA-USP, 2020).

4.2.3 Análise estatística

Como a ingestão de polifenóis aumenta com o maior consumo de alimentos, o consumo de polifenóis foi ajustado pelo consumo energético (mg de polifenóis por 1.000 kcal/d (4.184 kJ/d) de energia total consumida). O polifenol total e suas principais classes e subclasses foram categorizadas por tercís, com base na distribuição dos controles para análise. Os odds ratios (ORs) e os respectivos Intervalos de Confiança de 95% (ICs) para câncer gástrico foram calculados entre os tercís de polifenóis dietéticos usando regressão logística. O tercil mais baixo de consumo de polifenóis em cada subclasse de polifenóis dietéticos foi utilizado como referência. As variáveis de ajuste incluídas no modelo de regressão logística múltipla foram escolaridade, raça/etnia, procedência, IMC, histórico familiar de CG, tabagismo, consumo de bebida alcoólica, uso de aspirina e consumo de frutas e vegetais. O modelo final foi avaliado pelo teste de qualidade de Hosmer e Lemeshow (1985).

Para o processamento e análise dos dados foi usado o programa estatístico SPSS para Windows, Versão 25.0.

4.2.4 Cálculo amostral

O cálculo amostral foi feito baseado na incidência do CG do Brasil. A amostra foi calculada adotando-se um poder do estudo ($1-\beta$) de 80%, erro alfa de 5%, com razão de 1:1 (caso-controle) e resultou em 147 casos e 147 controles para o centro participante de Belém.

4.2.5 Comitê de Ética em Pesquisa

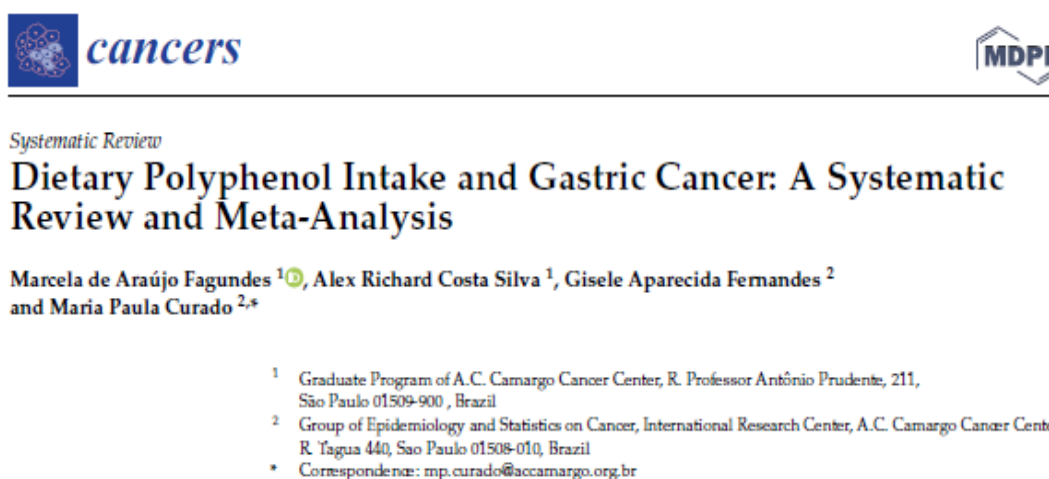
Trata-se de uma pesquisa afiliada ao estudo multicêntrico temático “Epidemiologia dos Adenocarcinomas Gástricos no Brasil”, o qual recebeu financiamento da Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) com bolsa 2014 / 26897-0 e foi aprovado pelo Comitê de Ética em Pesquisa (CEP) do A.C. Camargo Cancer Center – SP (ACCCC), sob número 2169/16J (Anexo 4). Todos os indivíduos entrevistados, assinaram o Termo de Consentimento Livre e Esclarecido (TCLE) (Apêndice 1).

5 RESULTADOS E DISCUSSÃO

5.1 ARTIGO PUBLICADO 1

Artigo de acesso livre publicado na revista Cancers (A1) em novembro de 2022 (na íntegra ao final do trabalho, após as referências).

Fagundes, M.d.A.; Silva, A.R.C.; Fernandes, G.A.; Curado, M.P. Dietary Polyphenol Intake and Gastric Cancer: A Systematic Review and Meta-Analysis. Cancers 2022, 14, 5878. <https://doi.org/10.3390/cancers14235878>



5.2 ARTIGO PUBLICADO 2

Artigo de acesso privado publicado na Cancer Epidemiology (A2) em janeiro de 2024 (versão inicial submetida disponível ao final do trabalho, após as referências).

de Araújo Fagundes M, Alves Carnauba R, Fernandes GA, Pimentel de Assumpção P, Curado MP. Polyphenol intake and gastric cancer: A case-control study in the Brazilian Amazon region. Cancer Epidemiol. 2024 Jan 2;88:102518. doi: 10.1016/j.canep.2023.102518. Epub ahead of print. PMID: 38171205.



Polyphenol intake and gastric cancer: A case-control study in the Brazilian Amazon region

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6 CONSIDERAÇÕES FINAIS

A partir das investigações conduzidas, identificou-se que a incorporação de polifenóis na dieta pode reduzir o risco de CG em ambos os sexos. No estudo caso-controle realizado em Belém, pioneiro no Brasil, certos polifenóis foram associados a diminuição do risco de CG, enquanto outros se associaram a um aumento no risco, sugerindo que alimentos ricos em polifenóis, como o açaí, podem desempenhar um papel crítico nessa relação. Dessa forma, o consumo de açaí merece uma exploração mais aprofundada em investigações futuras sobre o tema. Ademais, considerando as particularidades da região amazônica, torna-se essencial a condução de estudos similares em diferentes regiões do Brasil para uma compreensão abrangente do fenômeno.

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Systematic Review

Dietary Polyphenol Intake and Gastric Cancer: A Systematic Review and Meta-Analysis

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Simple Summary: Phenolic compounds are the most abundant antioxidants in the human diet. There are about eight thousand types of phenols, but the main classes are flavonoids, phenolic acids, stilbenes, lignans, and other polyphenols. These compounds have anticarcinogenic properties and may exert a protective effect against several cancers, including Gastric Cancer (GC). However, previous studies investigating GC have focused on flavonoids and the results are controversial. Our systematic review with meta-analysis is the first to report the association between total polyphenol intake, as well as the consumption of more than two classes of polyphenols concomitantly, and GC risk. Polyphenol consumption decreased the risk of GC in both sexes, but to a greater extent in females. The risk reduction was greater in studies carried out in Europe and Asia, therefore further studies in the Latin American population are warranted. Considering the high incidence rates of GC worldwide and the fact modifiable risk factors, such as diet, are amenable to intervention, the findings from this systematic review and meta-analysis can help strengthen strategies to encourage the consumption of foods rich in polyphenols and reduce the incidence of GC.

Abstract: Background: Phenolic compound consumption may have a protective effect against gastric cancer (GC). Most GC studies focus on the flavonoids class, but results are conflicting and knowledge gaps remain for other classes and total polyphenol intake. This study aimed to assess the association between polyphenol intake (total, flavonoids, and other classes) and GC. Methods: In this systematic review and meta-analysis, the PubMed, Embase, Scopus, LILACS, Web of Science, and OpenGrey databases were searched for studies published up to 20 March 2022. Case-control and cohort studies analyzing the association between polyphenol intake and GC were included. For the meta-analysis, pooled summary estimates were calculated using a random-effects model, and the estimates extracted adjusted for most variables. Subgroup analyses were performed for subclass (e.g., flavonoids and other classes), sex, geographical area, study design, anatomical subtype, histological subtype, family history of GC and fruit and/or vegetable intake. The study was registered with PROSPERO (#CRD42022306014). Findings: The search identified 2752 records, of which 19 studies published during the period 1999–2021 including a total of 1,197,857 subjects were eligible. Polyphenol consumption reduced GC risk by 29% (RR = 0.71; 95% CI: 0.62–0.81; $I^2 = 60.5\%$); while flavonoid intake decreased GC risk by 28% (RR = 0.72; 95% CI: 0.61–0.85; $I^2 = 64.3\%$), similar to the reduction for other classes (RR = 0.65; 95% CI: 0.54–0.79; $I^2 = 72.0\%$). Protective effects against GC were observed in both sexes (male, RR = 0.79; 95% CI: 0.67–0.94, $I^2 = 31.6\%$; female, RR = 0.65; 95% CI: 0.48–0.87, $I^2 = 49.7\%$) and for intestinal subtype (RR = 0.65; 95% CI: 0.52–0.82, $I^2 = 0.0\%$). By continent, polyphenol consumption reduced GC risk in both Europe (RR = 0.67; 95% CI: 0.57–0.79, $I^2 = 44.2\%$) and Asia (RR = 0.67; 95% CI: 0.51–0.89, $I^2 = 60.7\%$). Conclusions: Dietary polyphenol intake decreased GC risk. The reduction was greatest in females. Most previous studies were carried out in Europe and Asia. Further studies investigating polyphenol consumption and GC in Latin American populations are warranted.

Keywords: dietary polyphenol intake; gastric cancer; systematic review; meta-analysis

1. Research in Context

1.1. Evidence before Study

Polyphenols have anticarcinogenic, anti-inflammatory, and antimicrobial properties and act on cellular proliferation pathways to inhibit the growth of *H. pylori*. Therefore, the ingestion of polyphenols might be associated with the inhibition of cancers of the digestive tract. Since 1999, studies have suggested that flavonoids exert a protective effect against gastric cancer, but results are inconsistent. There are about 8000 phenols that can be categorized into various classes and subclasses, with flavonoids, phenolic acids, lignans, stilbenes, coumarins, and tannins being the most common. Despite this complexity, most studies have focused on investigating the association of only one of these polyphenol classes (flavonoids), while comprehensive analyses of the effect of total polyphenol intake, as well as its subclasses, on gastric cancer risk are lacking.

1.2. Added Value of Study

To the best of our knowledge, this systematic review with meta-analysis is the first to report the association between total polyphenol intake, as well as the consumption of more than two classes of polyphenols concomitantly, and gastric cancer risk. We identified inverse associations between dietary polyphenol intake (total, flavonoids, and other classes including lignans, phenolic acids, stilbenes, and other polyphenols) and gastric cancer. Subgroup analyses by sex, study population, study design, and Lauren histological classification were also performed.

1.3. Implications of Available Evidence

Guidelines recommend a high consumption of fruits and vegetables to prevent against cancer. This dietary advice may be related to the presence of polyphenols in these foods, whose ingestion reduces the risk of gastric cancer, regardless of sex. Considering the high incidence rates of gastric cancer worldwide and the fact modifiable risk factors, such as diet, are amenable to intervention, the findings from this systematic review and meta-analysis can help strengthen strategies to encourage the consumption of foods rich in polyphenols and reduce the incidence of gastric cancer.

2. Introduction

Gastric cancer (GC) ranks fifth in incidence and fourth in lethality among all cancers. Estimates suggest there were over one million new cases in 2020, representing 5.6% of all cancer cases and around 769,000 deaths [1]. Among the various factors involved in the carcinogenesis of GC, epidemiological studies have suggested that a high intake of fruit and vegetables is inversely associated with the risk of GC [2,3]. This reduced risk is attributed to the intake of nutrients, micronutrients, and other dietary compounds, including antioxidants such as polyphenols [4,5].

Polyphenols have shown specific and nonspecific anticarcinogenic properties and may exert a protective effect against several cancers, including GC [6]. These compounds have diverse chemical structures, with the most common variations in the chemical skeleton including the degree of oxidation, hydroxylation, methylation, and glycosylation. The main classes of polyphenols are flavonoids, phenolic acids, stilbenes, lignans, and other polyphenols [5]. Stilbenes, lignans, and tannins are classified as nonflavonoids, and some subclasses are shown in Figure 1.

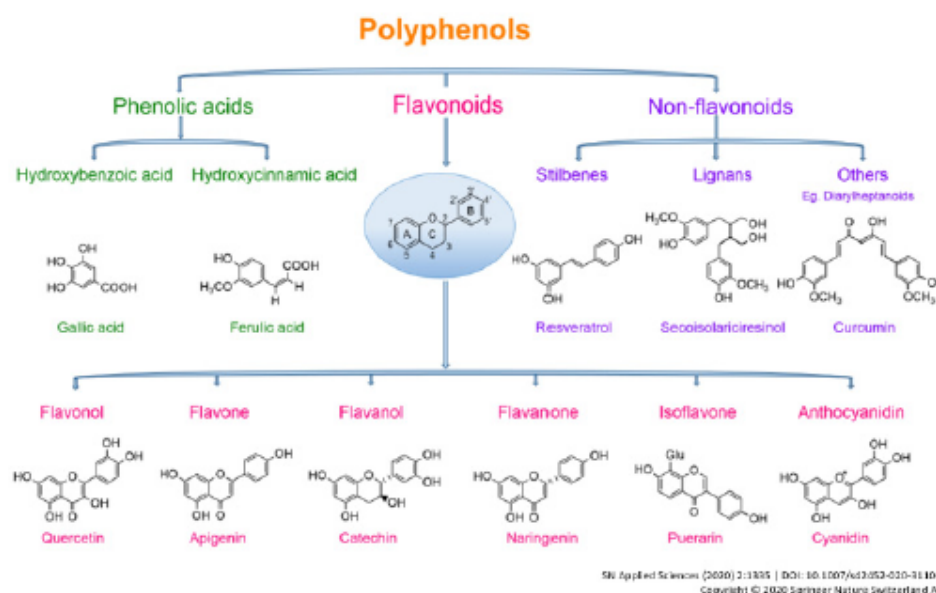


Figure 1. Classification of polyphenols [7].

Previous studies investigating GC have focused on specific polyphenol classes [8–11]. Flavonoids are the most-studied polyphenol class [10–13]. An inverse association between flavonoid consumption and GC has been observed in Greece [9], Italy [14], and Korea [13]. Similarly, multicenter case–control studies carried out in Europe and the USA have found that individuals who consume greater amounts of polyphenols have a lower risk of developing GC [4,5,15]. However, cohort studies conducted in Finland [12,16] and Japan [10] failed to demonstrate an association between polyphenol intake and GC. Moreover, most of the previously published meta-analyses on this topic only analyzed the intake of a single class of polyphenols (flavonoids). In addition, the results of subanalyses proved inconsistent, possibly due to the small number of studies assessing the variables of interest in the subanalysis [17,18]. Therefore, we performed a systematic review and meta-analysis investigating the association between GC risk and dietary polyphenol intake, for the main classes and subclasses of polyphenols.

3. Methods

3.1. Search Strategy and Selection Criteria

This systematic review and meta-analysis followed the PRISMA guidelines for the reporting of meta-analyses [19]. The electronic databases PubMed, Scopus, Embase, LILACS, OpenGrey, and Web of Science were searched for studies published from the date of each database's inception up to 20 March 2022 that assessed the association between GC risk and dietary polyphenol intake, using the following search terms: (polyphenol or prophenols or phenol or flavonoid or flavanol or "phenolic acids" or "hydroxycinnamic acids" or "hydroxybenzoic acids" or "hydroxyphenylacetic acids" or lignans or stilbenes or alkylphenols or alkylmethoxyphenols) and ("gastric cancer" or "gastric tumor" or "stomach cancer" or "gastric adenocarcinoma" or "neoplasm, stomach" or "stomach neoplasm"). The full search strategies used for each database are described in Table S1. A manual search for additional citations was also performed by examining the reference lists of the articles retrieved. Articles were included if they: assessed the association between the intake of di-

etary polyphenols and risk of GC; were observational studies, such as cohort or case–control studies, with no language restrictions; and polyphenol intake was measured by validated questionnaires. Articles in languages other than English were translated if necessary. Two authors (MAF and ARCS) independently screened the title and abstract of potentially eligible articles according to the eligibility criteria, and any duplicates were excluded. The researchers performed blind double-checks, and areas of disagreement or uncertainty were resolved by consensus among all authors. When the eligibility criteria were met based on the title and abstract screening, the full text was retrieved for data extraction. The following types of articles were excluded: (1) cell studies and animal studies; (2) review articles, letters to the editor, case reports, ecological studies, and cross-sectional studies; and (3) studies in which polyphenol levels were measured in blood or urine.

3.2. Data Analysis

Two authors (MAF and ARCS) independently extracted the following information from all eligible studies: (1) last name of the first author; (2) year of publication; (3) country; (4) study design; (5) period of study; (6) total number of participants, numbers of cases and controls; (7) polyphenol assessment method; (8) food source of polyphenols; (9) classes of polyphenols studied; (10) relative risk (RR)/odds ratio (OR) and 95% confidence interval (CI) indicating the highest versus the lowest categories of dietary polyphenol intake where estimates extracted were adjusted for most variables; (11) intake comparison; and (12) adjustment variables (family history of GC and fruit and/or vegetable intake).

The most adjusted OR (highest versus lowest intake of polyphenols) was considered to be an approximation of the RR, and the summary results were reported as RR for simplicity. Random-effects meta-analysis was used to assess the association between dietary polyphenol intake, including the main subclasses (exposure), and GC risk (outcome), with pooled ORs calculated together with their 95% CIs.

Cochran's chi-squared test and the I^2 test were used to quantify the heterogeneity of the studies where, for $p < 0.05$ and/or $I^2 > 50\%$, substantial heterogeneity existed among studies [20,21]. The choice of ORs for analysis was made considering all classes of polyphenols. The order of choice of ORs was: total polyphenols, total flavonoids, flavanones, phenolic acids, lignans and stilbenes. The ORs for both sexes were selected. When studies were analyzed by sex and anatomical type separately, female gender and non-cardia type were selected. Subgroup analyses by subclasses (flavonoids and non-flavonoids), sex (male or female), study design (case–control or cohort study), topography (cardia or noncardia), histological subtype (diffuse or intestinal), geographical area (Europe, Asia or America), and adjustment variable (family history of GC and fruit and/or vegetable intake) were also performed to identify potential confounders/modifiers. Adjusted risk estimates in subgroup analyses were for the specific variables cited. Regarding study design and geographic area, risk estimates were for both sexes and chosen in the order outlined above for general meta-analysis. For studies providing fully adjusted results (multiple variables), ORs were extracted from statistical models that provided adjustment for the variable of interest, in the case of subgroup analyses by adjustment variable, such as family history of gastric cancer or fruit and vegetable intake.

The Newcastle–Ottawa Scale [22] was used to assess the risk of bias by determining the quality of the observational studies selected using two independent scales (for cohort and case–control studies). The scale consists of items divided into three domains: selection, comparison and exposure (case–control studies) or outcome (cohort studies). Studies with a rating of 6 or higher were considered high quality [23]. Egger's test and funnel plots were conducted to assess potential publication bias, where a value of $p < 0.05$ was considered a statistically significant difference for all tests used. All statistical analyses were conducted using the software STATA, version 15.0 (Stata Corporation, College Station, TX, USA). This study was registered with PROSPERO (#CRD42022306014).

4. Results

The literature search led to the retrieval of 2752 records, of which 637 were excluded as duplicates and a further 2096 excluded after initial screening of titles and abstracts. Two additional articles were later identified in the references of the screened articles [16,24]. A total of 21 full-text articles were assessed for eligibility (Figure 2), with subsequent exclusion of two articles because polyphenol content was measured in plasma, giving 19 studies for inclusion in the review. All studies, published during the period 1999–2021 and involving 1,197,857 participants (patients and controls), were included in the meta-analysis. The median Newcastle–Ottawa rating for the 19 studies reviewed was 7 (range: 6–9; Table S2). Quality score ranges were 8–9 for the cohort studies and 6–8 for the case–control studies. Therefore, all studies were considered to be of high quality.

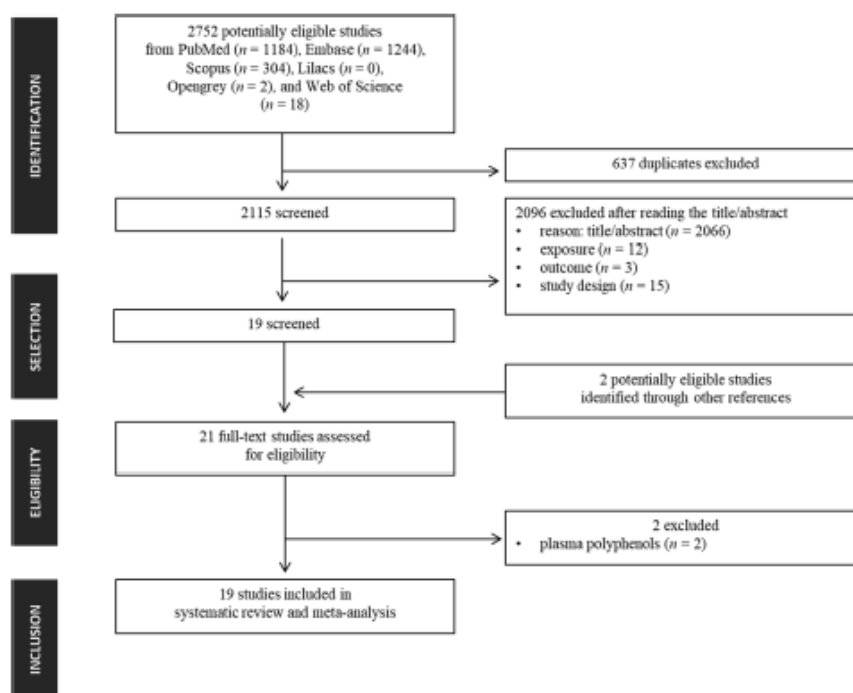


Figure 2. Flow diagram of selection of eligible studies for inclusion in systematic review according to PRISMA guidelines.

The main characteristics of the included studies are summarized in Table 1; seven were cohort studies, and 12 were case–control studies. Eleven studies were conducted in Europe (multiple European countries, n = 2; Italy, n = 1; Greece, n = 1; Sweden, n = 2; Finland, n = 2; and Spain, n = 3), five studies were conducted in Asia (Korea, n = 3; Japan, n = 2), and only 3 studies were conducted in North America (USA, n = 2; Mexico, n = 1). Over half the studies were published after 2010 (n = 12). Twelve studies analyzed the flavonoid class only, whereas two investigated 3 classes of polyphenols. A total of 16 studies used food-frequency questionnaires to measure polyphenol intake. The confounders used by the studies were: age, sex, education, total energy intake, body mass index, physical activity, smoking, alcohol intake, and total fruit and vegetable consumption. All variables for each statistical model are shown in Table 1.

Table 1. Characteristics of studies on dietary polyphenol intake and gastric cancer risk.

Author/Country	Study Type and Period	Sample	Diet Assessment Method	Source of Polyphenols	Classes of Polyphenols	RR/OR (95% CI)	Intake Comparison	Adjustment Variables
García-Closas et al. [8] Spain	Case-control 1987–1989	Cases = 354 Controls = 354	Past year's diet history	Fruit, vegetables, fruit juices, wines and tea infusions	Total Flavonoids Quercetin Kaempferol Myricetin	0.44 (0.25–0.78) 0.62 (0.35–1.10) 0.48 (0.26–0.88) 1.12 (0.67–1.85)	Highest quartile X Lowest quartile	Intake of nitrites, nitrosamines, vitamin C, total energy, total carotenoids, and other specific flavonoids.
Hirvonen et al. [12] Finland	Prospective cohort 1985–1993	27,110 GC = 111	Past year's diet history	Fruit, vegetables, teas, wines and sweets	Flavonoids and Flavones Total Flavonoids Quercetin	1.2 (0.71–1.9) 0.87 (0.44–1.75) 1.03 (0.52–2.07)	Highest quartile X Lowest quartile	Age and supplementation group.
Knekt et al. [16] Finland	Prospective cohort 1966–1972	9865 GC = 74	Past year's diet history	Fruit, vegetables, sweets and beverages (including tea and wines)	Quercetin Kaempferol Myricetin Hesperetin Naringenin	1.14 (0.99–2.22) 1.16 (0.99–2.26) 0.88 (0.43–1.80) 0.94 (0.47–1.88)	Highest quartile X Lowest quartile	Sex, age, geographic area, occupation, smoking, and BMI.
Lagiou et al. [9] Greece	Case-control 1981–1984	Cases = 110 Controls = 100	FFQ last 5 years	Items not described	Flavanones Flavan-3-ols Flavonols Flavones Anthocyanidins Isoflavones	Model 1/2 0.49 (0.32–0.76)/0.55 (0.31–0.96) 1.10 (0.76–1.60)/1.04 (0.68–1.58) 0.40 (0.25–0.64)/0.27 (0.42–1.40) 0.60 (0.40–0.89)/0.70 (0.43–1.14) 0.88 (0.60–1.28)/1.14 (0.72–1.80) 1.27 (0.84–1.93)/1.16 (0.73–1.84)	Per one standard deviation increment: per 19.8 mg/day per 135.1 mg/day per 10.0 mg/day per 0.3 mg/day per 40.4 mg/day per 2.0 mg/day	Model 1: Age, gender, place of birth, BMI, height, years of education, smoking habits and duration of smoking, alcohol consumption, total energy intake. Model 2: Model 1 + fruit and vegetable consumption.
Hernández-Ramírez et al. [25] Mexico	Case control 2004–2005	Cases = 248 Controls = 478	FFQ last 3 years	Fruit, vegetables, noodle soup, hot sauce, beans, orange juice, red wine	Cinnamic Acids Secoisolaricresinol Coumestrol	Model 1/2/3/4 0.52 (0.34–0.81)/0.49 (0.31–0.78)/0.61 (0.38–0.97)/0.80 (0.49–1.31). 0.42 (0.27–0.65)/0.41 (0.26–0.64)/0.47 (0.30–0.74)/0.57 (0.32–0.99). 0.45 (0.29–0.70)/0.45 (0.29–0.71)/0.42 (0.27–0.65)/0.47 (0.32–1.16). Male: 0.66 (0.42–1.04) Female: 0.49 (0.25–0.94) Cardia: 0.76 (0.40–1.44) Noncardia: 0.57 (0.40–0.83) Intestinal: 0.51 (0.32–0.82) Diffuse: 0.54 (0.31–0.92)	Highest tertile X Lowest tertile	Model 1: Energy, age, gender, <i>H. pylori</i> CagA status, schooling and consumption of salt, chili, alcohol. Model 2: Model 1 + vitamins C and E. Model 3: Model 2 + fruits and vegetables. Model 4: Model 3 + polyphenols.
Ekström et al. [26] Sweden	Case control 1989–1995	Cases = 505 Controls = 1116	FFQ last 20 years	Fruit, vegetables, wine, tea, coffee and fruit juices.	Quercetin		Highest quintile X Lowest quintile	Age, gender, socioeconomic status, number of siblings, body mass index, smoking, and energy and salt intake.

Table 1. Cont.

Author/Country	Study Type and Period	Sample	Diet Assessment Method	Source of Polyphenols	Classes of Polyphenols	RR/OR (95% CI)	Intake Comparison	Adjustment Variables
Rossi et al. [14] Italy	Case control 1997–2007	Cases = 230 Controls = 547	FFQ last 2 years	78 items such as fruit, vegetables, soup, tea, wine and chocolate.	Isoflavones Anthocyanidins Flavan-3-ols Flavanones Flavonols Proanthocyanidins	0.88 (0.53–1.46) 0.91 (0.56–1.47) 0.75 (0.45–1.23) 0.91 (0.54–1.51) 0.83 (0.50–1.39) 0.62 (0.38–1.02) 0.34 (0.20–0.58) Model 1/2 Male 0.98 (0.80, 1.20)/1.00 (0.81, 1.24) Female 0.99 (0.71, 1.37)/1.07 (0.77, 1.50)	Highest quintile X Lowest quintile	Sex, age, education, year of interview, body mass index, tobacco smoking, and total energy intake.
Hara et al. [10] Japan	Prospective cohort 1990–2006	84,881 GC = 1249	FFQ past year	Miso soup, food and soy milk	Isoflavones	Model 2 only Cardia: 2.00 (0.97, 4.12) Noncardia: 0.97 (0.74, 1.26) Male: 0.97 (0.67, 1.41) Female: 0.49 (0.30, 0.80) Cardia: 0.84 (0.64, 1.11) Noncardia: 0.85 (0.70, 1.03) Intestinal: 0.70 (0.52, 0.94) Diffuse: 0.94 (0.74, 1.19) Male: 0.98 (0.68, 1.41) Female: 0.71 (0.44, 1.16) Cardia: 0.89 (0.69, 1.15) Noncardia: 0.90 (0.79, 1.04) Intestinal: 0.92 (0.73, 1.16) Diffuse: 0.86 (0.75, 0.99) Male: 0.93 (0.63, 1.37) Female: 0.45 (0.27, 0.75) Cardia: 0.85 (0.60, 1.20) Noncardia: 0.90 (0.71, 1.13) Intestinal: 0.72 (0.49, 1.06) Diffuse: 1.04 (0.78, 1.40) Male: 0.91 (0.64, 1.28) Female: 1.01 (0.68, 1.50) Cardia: 0.92 (0.81, 1.05) Noncardia: 0.99 (0.90, 1.09) Intestinal: 1.10 (0.92, 1.32) Diffuse: 0.96 (0.87, 1.07)	Highest quartile X Lowest quartile	Model 1: Age and public center area. Model 2: BMI, smoking status, ethanol intake, family history of gastric cancer, vegetable intake, fruit intake, fish intake, salt intake, and total energy intake.
Zamora-Ros et al. [27] EPIC study (Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden and UK)	Prospective cohort 1992–2010	477,312 GC = 683	Several validated FFQs	Items not described	Total flavonoids Anthocyanidins Flavonols Flavanones	Male/Female: Highest quartile X Lowest quartile Cardia/Noncardia; Intestinal/Diffuse: log ₂	Male/Female: Highest quartile X Lowest quartile Cardia/Noncardia; Intestinal/Diffuse: log ₂	Age, educational level, physical activity, BMI, alcohol and energy intake, and daily consumption of fruit, vegetables, and red and processed meat.

Table 1. Cont.

Author/Country	Study Type and Period	Sample	Diet Assessment Method	Source of Polyphenols	Classes of Polyphenols	RR/OR (95% CI)	Intake Comparison	Adjustment Variables
Lin et al. [28] Sweden	Prospective cohort 1987–2009	81,670 GC = 128	FFQ	65 unspecified items	Flavones	Male: 0.86 (0.60, 1.23) Female: 0.59 (0.38, 0.93) Cardia: 0.83 (0.65, 1.07) Noncardia: 0.94 (0.82, 1.07) Intestinal: 0.97 (0.76, 1.24) Diffuse: 0.92 (0.78, 1.09)	Highest quartile vs Lowest quartile	Model 1: Sex, age, and energy intake. Model 2: Model 1 + education, BMI, alcohol intake, smoking status, gastric ulcer, duodenal ulcer, and diabetes. PS: For men only, adjustment for sex was not included.
						Male: 0.95 (0.64, 1.34) Female: 0.52 (0.32, 0.83) Cardia: 0.89 (0.70, 1.11) Noncardia: 0.90 (0.78, 1.05) Intestinal: 0.78 (0.65, 0.94) Diffuse: 0.98 (0.81, 1.19)		
					Flavanols	Male: 0.98 (0.68, 1.40) Female: 0.55 (0.34, 0.88) Cardia: 0.91 (0.79, 1.05) Noncardia: 0.93 (0.84, 1.02) Intestinal: 0.83 (0.72, 0.95) Diffuse: 1.01 (0.89, 1.14)		
					Flavan-3-ol monomers	Male: 0.84 (0.55, 1.27) Female: 0.71 (0.44, 1.15) Cardia: 1.05 (0.71, 1.56) Noncardia: 0.92 (0.78, 1.09) Intestinal: 0.86 (0.71, 1.04) Diffuse: 0.98 (0.78, 1.24)		
					Proanthocyanidins	Male: 1.06 (0.73, 1.54) Female: 0.57 (0.36, 0.91) Cardia: 0.98 (0.95, 1.02) Noncardia: 0.99 (0.97, 1.01) Intestinal: 0.95 (0.92, 0.98) Diffuse: 1.02 (0.99, 1.05)		
					Theaflavins	Male: 0.77 (0.50, 1.18) Female: 1.05 (0.61, 1.82) Cardia: 1.13 (0.85, 1.50) Noncardia: 1.00 (0.83, 1.19) Intestinal: 1.08 (0.80, 1.47) Diffuse: 0.90 (0.71, 1.13)		
					Isoflavones	Male: 0.99 (0.63, 1.55) Female: 0.94 (0.54, 1.64) Cardia: 0.61 (0.33, 1.13) Noncardia: 0.85 (0.59, 1.23) Intestinal: 1.17 (0.65, 2.12) Diffuse: 0.79 (0.50, 1.25)		
					Lignans	Model 1/2 0.78 (0.48–1.28)/0.89 (0.52–1.55) Men only 0.81 (0.43–1.55)/0.83 (0.40–1.76)		
					Lignans			
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Table 1. Cont.

Author/Country	Study Type and Period	Sample	Diet Assessment Method	Source of Polyphenols	Classes of Polyphenols	RR/OR (95% CI)	Intake Comparison	Adjustment Variables
Woo et al. [13] Korea	Case-control 2011–2014	Cases = 334 Controls = 334	FFQ past year	144 unspecified items	Total flavonoids	Model 1/2 Total 0.49 (0.31–0.76)/0.62 (0.36–1.09) Male 0.70 (0.39–1.24)/0.80 (0.39–1.63) Female 0.33 (0.15–0.73)/0.68 (0.25–1.86) Total 0.51 (0.32–0.82)/0.69 (0.39–1.20) Male 0.59 (0.32–1.10)/0.65 (0.32–1.35) Female 0.51 (0.24–1.10)/1.22 (0.47–3.16) Total 0.51 (0.31–0.82)/0.72 (0.38–1.35) Male 0.70 (0.38–1.29)/0.84 (0.37–1.89) Female 0.15 (0.06–0.38)/0.22 (0.07–0.67) Total 0.66 (0.43–1.02)/0.92 (0.55–1.52) Male 0.90 (0.52–1.56)/1.12 (0.58–2.17) Female 0.39 (0.18–0.86)/0.64 (0.27–1.52) Total 0.58 (0.38–0.88)/0.73 (0.45–1.18) Male 0.70 (0.41–1.21)/0.78 (0.41–1.49) Female 0.36 (0.17–0.77)/0.65 (0.27–1.57)	Highest tertile X Lowest tertile	Model 1: Total energy intake, <i>H. pylori</i> , age, sex, education, smoking status, alcohol consumption, BMI, physical activity, consumption of pickled vegetables, red and processed meat. Model 2: Model 1 + fruit and vegetable consumption.
					Flavonols			
					Flavones			
					Flavanones			
					Flavan-3-ols			

Table 1. Cont.

Author/Country	Study Type and Period	Sample	Diet Assessment Method	Source of Polyphenols	Classes of Polyphenols	RR/OR (95% CI)	Intake Comparison	Adjustment Variables
Petrick et al. [4] USA	Multi-center Case-control 1993–1995–2000	Cases = 589 Controls = 662	FFQ last 3–5 years	Fruit, vegetables, juices, wine, tea, coffee, pizza, bread, cake, soups, chicken	Anthocyanidins	Total 0.73 (0.46–1.15)/1.06 (0.62–1.80)	Highest quartile X Lowest quartile	Age, sex, race, geographic center, cigarette smoking, and dietary energy intake.
						Male 0.92 (0.51–1.67)/1.16 (0.57–2.34)		
						Female 0.58 (0.27–1.25)/1.22 (0.49–3.07)		
						Total 0.72 (0.46–1.12)/0.85 (0.54–1.35)		
						Male 0.90 (0.52–1.54)/0.98 (0.56–1.73)		
						Female 0.51 (0.24–1.08)/0.67 (0.31–1.47)		
					Total flavonoids	GCA: 1.32 (0.87, 2.00) OGA: 1.08 (0.73, 1.58) GCA: 0.71 (0.46, 1.10) OGA: 0.70 (0.47, 1.03)		
					Anthocyanidins	GCA: 1.17 (0.77, 1.78) OGA: 1.30 (0.88, 1.92)		
					Flavan-3-ols	GCA: 1.23 (0.81, 1.87) OGA: 0.88 (0.60, 1.28)		
					Flavanones	GCA: 1.09 (0.71, 1.67) OGA: 1.01 (0.69, 1.50)		
					Flavones	GCA: 1.42 (0.93, 2.17) OGA: 0.98 (0.67, 1.46)		
					Flavonols	GCA: 1.56 (0.93, 2.60) OGA: 1.50 (0.96, 2.37)		
					Isoflavones	GCA: 1.01 (0.65, 1.58) OGA: 0.73 (0.48, 1.11)		
					Lignans			
Wada et al. [29] Japan	Prospective cohort 1992–2008	30,792 GC = 678	Diet record-12 days and FFQ (past year)	Miso soup, tofu (soy bean curd), deep-fried tofu, fried tofu, freeze-dried tofu, natto, houba-miso, soy milk and boiled soy beans	Isoflavones	Male: 0.81 (0.60–1.09) Female: 0.60 (0.37–0.98)	Highest quartile X Lowest quartile	Age, BMI, physical activity score, smoking status, alcohol consumption, salt intake and education years for men, and menopausal status for women.
Sun et al. [11] USA	Prospective cohort 1995–2011	469,008 GC = 1297	FFQ past year	116 unspecified items	Total flavonoids	Cardia: 1.02 (0.78, 1.34) Noncardia: 1.11 (0.86, 1.44) Cardia: 1.05 (0.80, 1.39) Noncardia: 0.94 (0.72, 1.23)	Highest quintile X Lowest quintile	Age, sex, race, education, smoking status, BMI, alcohol intake, self-reported health, vigorous physical activity of ≥ 20 min and total energy intake.
					Anthocyanidins	Cardia: 1.04 (0.80, 1.36) Noncardia: 1.19 (0.92, 1.54) Cardia: 0.87 (0.68, 1.13) Noncardia: 0.99 (0.76, 1.30)		
					Flavan-3-ols			
					Flavanones			

Table 1. Cont.

Author/Country	Study Type and Period	Sample	Diet Assessment Method	Source of Polyphenols	Classes of Polyphenols	RR/OR (95% CI)	Intake Comparison	Adjustment Variables
Yang et al. [30] Korea	Case-control 2011–2014	Cases = 377 Controls = 754	FFQ past year	Legumes, tofu, soy milk, sprouts, and doenjang (Korean traditional fermented soybean paste and soybeans)	Flavones	Cardia: 0.99 (0.73, 1.34) Noncardia: 1.06 (0.80, 1.40)	Highest tertile X Lowest tertile	Education, alcohol consumption, smoking status, <i>Helicobacter pylori</i> infection, and regular exercise.
					Flavonols	Cardia: 1.08 (0.80, 1.45) Noncardia: 1.25 (0.94, 1.65)		
					Isoflavones	Cardia: 0.99 (0.73, 1.34) Noncardia: 0.73 (0.54, 0.98)		
Vikelli-Storelli et al. [31] Spain	Multi-center Case-control 2008–2013	Cases = 329 Controls = 2700	FFQ	Vegetables and legumes, fruit, cereals, sweets and snacks, and alcoholic and other beverages.	Isoflavones	0.70 (0.49–1.00) Male: 0.63 (0.40–0.99) Female: 0.82 (0.45–1.49)	All cases: log2 Male/Female; Cardia/Noncardia; Intestinal/Diffuse; Highest quartile X Lowest quartile	Age, gender, socioeconomic status, area of residence, GC family history, BMI, smoking, physical activity, energy, sodium, red meat, vegetables and past alcohol intake.
					Total flavonoids	0.76 (0.65, 0.89) Male: 0.51 (0.31–0.82) Female: 0.89 (0.42–1.90) Cardia: 0.67 (0.33, 1.39) Noncardia: 0.55 (0.35, 0.87) Intestinal: 0.74 (0.38, 1.42) Diffuse: 0.38 (0.17, 0.84) 0.88 (0.80, 0.96)		
					Anthocyanidins	Male: 0.47 (0.30–0.74) Female: 1.14 (0.59–2.22) Cardia: 0.62 (0.29, 1.31) Noncardia: 0.67 (0.42, 1.06) Intestinal: 0.61 (0.32, 1.15) Diffuse: 0.92 (0.42, 1.98) 0.89 (0.83, 0.95)		
					Chalcones	Male: 0.48 (0.31–0.74) Female: 0.90 (0.80, 1.03) Cardia: 0.40 (0.2, 0.79) Noncardia: 0.60 (0.37, 0.98) Intestinal: 0.39 (0.19, 0.82) Diffuse: 0.89 (0.4, 1.98) 1.02 (0.95, 1.11)		
					Dihydrochalcones	Male: 1.35 (0.67–2.69) Female: 0.96 (0.45–2.05) Cardia: 1.92 (0.92, 4.02) Noncardia: 1.38 (0.87, 2.2) Intestinal: 1.4 (0.73, 2.67) Diffuse: 1.23 (0.57, 2.67) 0.89 (0.84, 0.95)		
					Dihydroflavonols	Male: 0.38 (0.24–0.59) Female: 0.89 (0.38–2.06) Cardia: 0.60 (0.29, 1.23) Noncardia: 0.47 (0.29, 0.76) Intestinal: 0.54 (0.29, 1.01) Diffuse: 0.49 (0.21, 1.11)		

Table 1. *Cont.*

Author/Country	Study Type and Period	Sample	Diet Assessment Method	Source of Polyphenols	Classes of Polyphenols	RR/OR (95% CI)	Intake Comparison	Adjustment Variables
					Flavan-3-ols	0.82 (0.73, 0.92) Male: 0.49 (0.32–0.77) Female: 0.61 (0.29–1.28) Cardia: 0.65 (0.28, 1.48) Noncardia: 0.59 (0.35, 0.98) Intestinal: 0.57 (0.28, 1.16) Diffuse: 0.42 (0.16, 1.01) 0.92 (0.85, 1.00)		
					Flavanones	Male: 0.66 (0.43–1.00) Female: 0.88 (0.42–1.83) Cardia: 0.60 (0.29, 1.23) Noncardia: 0.79 (0.51, 1.22) Intestinal: 0.89 (0.49, 1.64) Diffuse: 0.64 (0.30, 1.36) 0.99 (0.89, 1.11)		
					Flavones	Male: 0.75 (0.47–1.20) Female: 1.42 (0.65–3.15) Cardia: 0.70 (0.32, 1.5) Noncardia: 1.27 (0.8, 2.02) Intestinal: 1.36 (0.72, 2.56) Diffuse: 1.64 (0.74, 3.62) 0.93 (0.78, 1.10)		
					Flavonols	Male: 0.62 (0.37–1.02) Female: 1.71 (0.74–3.92) Cardia: 0.84 (0.36, 1.98) Noncardia: 1.13 (0.68, 1.88) Intestinal: 1.28 (0.63, 2.56) Diffuse: 1.46 (0.63, 3.4) 1.05 (0.98, 1.12)		
					Isoflavonoids	Male: 1.11 (0.65–1.91) Female: 0.99 (0.89, 1.11) Cardia: 1.27 (0.54, 2.98) Noncardia: 1.36 (0.78, 2.38) Intestinal: 1.81 (0.8, 4.08) Diffuse: 1.22 (0.51, 2.93)		
					Proanthocyanidins	0.82 (0.71, 0.94) Male: 0.57 (0.36–0.93) Female: 1.22 (0.57–2.58) Cardia: 1.1 (0.52, 2.35) Noncardia: 0.84 (0.51, 1.38) Intestinal: 1.01 (0.5, 2.07) Diffuse: 0.87 (0.39, 1.98)		

Table 1. *Cont.*

Author/Country	Study Type and Period	Sample	Diet Assessment Method	Source of Polyphenols	Classes of Polyphenols	RR/OR (95% CI)	Intake Comparison	Adjustment Variables
Vitelli-Storelli et al. [5] Stop Project (Italy, Greece, Spain, Portugal, Mexico, Russia)	10 Case-control studies 1998–2015	Cases = 3471 Controls = 8344	FFQ	Vegetables, fruit, sweets, cereals, alcohol, juices and other drinks.	Total polyphenols Total flavonoids Anthocyanidins Flavanols Flavonols/flavanones Total phenolic acids Hydroxybenzoic acids Hydroxycinnamic acids	0.67 (0.54–0.81) 0.73 (0.55–0.90) 0.74 (0.56–0.92) 0.77 (0.66–0.88) 0.76 (0.51–1.01) 0.57 (0.44–0.69) 0.75 (0.55–0.94) 0.73 (0.57–0.89) 0.82 (0.58–1.06)	Highest quartile X Lowest quartile	Age, sex, social class, alcohol consumption, BMI, family history of gastric cancer, smoking status, and salt consumption.
Rubín-García et al. [15] Spain	Multi-center Case-control 2008–2013	Cases = 329 Controls = 2700	FFQ past year	Legumes, vegetables, fruit, cereals, sweets and snacks, as well as alcoholic beverages and others.	Stilbenes Lignans Hydroxybenzaldehydes Hydroxycoumarin Tyrosols Other polyphenols	0.47 (0.32–0.69) 0.53 (0.36–0.84) 0.41 (0.28–0.61) 0.49 (0.34–0.71) 0.56 (0.39–0.80) 1.49 (1.06–2.10)	Highest quartile X Lowest quartile	Age; sex; socioeconomic status; smoking status; first-degree family history of GC; physical activity; BMI; alcohol consumption; and vegetables, red meat, salt, and total energy intake.
Kim et al. [32] Korea	Case-control 2011–2014	Cases = 415 Controls = 830	FFQ	Mostly fruit and vegetables	Total phenolics	Model 1/2 0.52 (0.37–0.75)/0.57 (0.39–0.83)	Highest tertile X Lowest tertile	Model 1: Age, BMI, education level, income, physical activity, smoking status, first-degree family history of GC, and total energy intake. Model 2: Model 1 + <i>H. pylori</i> infection status.

Note: Abbreviations: BMI—Body Mass Index; CI—Confidence Intervals; FFQ—Food Frequency Questionnaire; GC—Gastric Cancer; GCA—Gastric Cardia Adenocarcinoma; OGA—Other Gastric Adenocarcinoma; ORs—Odds Ratios; RRs—Relative Risks. If there was log and quartile for a single variable, the “quartile” was chosen.

The pooled RRs with 95% CIs (highest versus lowest categories of dietary polyphenol intake) were calculated to assess the association between dietary polyphenol intake and risk of GC. As shown in Figure 3, consumption of polyphenols reduced the risk of GC by 29% (RR = 0.71; 95% CI: 0.62–0.81; $I^2 = 60.5\%$). The analysis of flavonoid consumption and risk of GC showed that the intake of total flavonoids or some types of flavonoids had an inverse association with GC (RR = 0.72; 95% CI: 0.61–0.85; $I^2 = 64.3\%$) (Figure 4). Likewise, there was an association between the consumption of other classes of polyphenols (lignans, phenolic acids, and other polyphenols) and GC. As shown in Figure 5, the consumption of other classes of polyphenols reduced the risk of GC by 35% (RR = 0.65; 95% CI: 0.54–0.79; $I^2 = 72.0\%$). Other data combinations were also made to assess the effects of sex (male or female) and anatomical subtype (cardia or noncardia), and the meta-analysis showed a significant inverse association between polyphenol intake and GC risk (Figures S1, S2 and S3). Heterogeneity was substantial for most of the pooled estimates. The funnel plot shows no evidence of asymmetry (Figures 6, S4 and S5), and Egger's test showed that no publication bias was detected in this meta-analysis ($p = 0.316$).

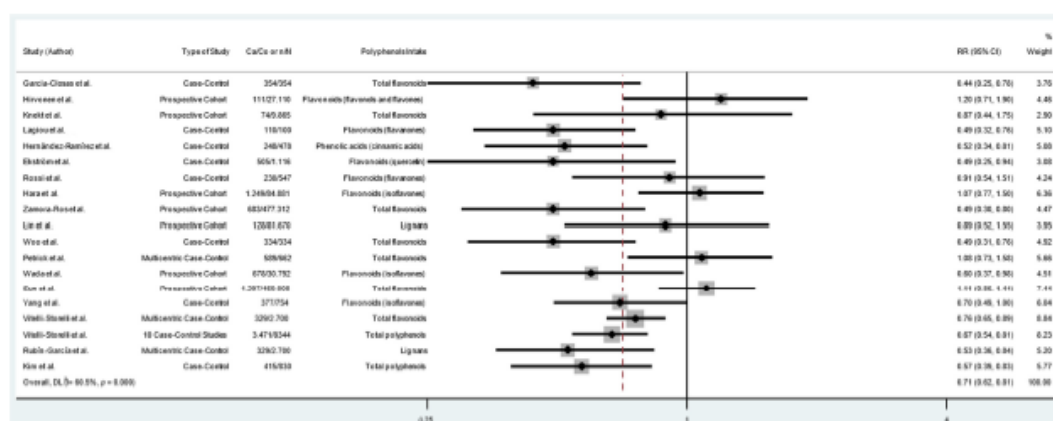


Figure 3. Forest plot of polyphenol consumption and gastric cancer risk. Case-control and cohort studies are presented in chronological order of publication. Square boxes represent study-specific estimates. Markers vary in size according to weight assigned to each study, the size of each box reflects the study's weight in the analysis, and horizontal lines represent 95% confidence intervals. Diamonds show the pooled effect. Abbreviations: RR, relative risk; Ca, number of cases; Co, number of controls; n, number of events; N, number of patients [4,5,8–16,25–32].

On subgroup analyses, the protective effects of polyphenol intake against GC were observed in both sexes (male, RR = 0.79; 95% CI: 0.67–0.94, 8 studies, P for heterogeneity = 0.176, $I^2 = 31.6\%$; female, RR = 0.65; 95% CI: 0.48–0.87, 7 studies, P for heterogeneity = 0.064, $I^2 = 49.7\%$) and intestinal histological type (RR = 0.65; 95% CI: 0.52–0.82, 3 studies, P for heterogeneity = 0.494, $I^2 = 0.0\%$). When the analysis was stratified by geographical area, an inverse association between polyphenol intake and GC was observed in both Europe (RR = 0.67; 95% CI: 0.57–0.79, 11 studies, P for heterogeneity = 0.056, $I^2 = 44.2\%$) and Asia (RR = 0.67; 95% CI: 0.51–0.89, 5 studies, P for heterogeneity = 0.038, $I^2 = 60.7\%$). Regardless of whether the studies were adjusted for a family history of GC or fruit/vegetable intake, the protective effect of polyphenol intake against GC was observed (Table 2).

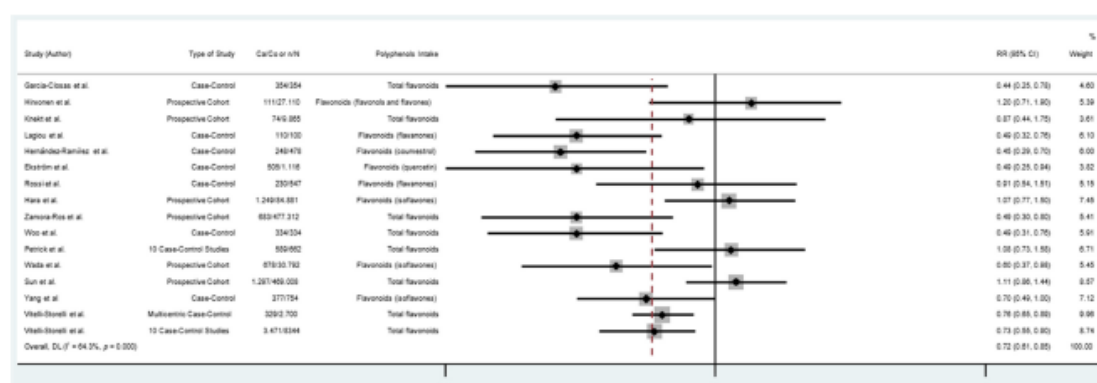


Figure 4. Forest plot of flavonoid consumption and gastric cancer risk. Case-control and cohort studies are presented in chronological order of publication. Square boxes represent study-specific estimates. Markers vary in size according to weight assigned to each study, size of each box reflects the study's weight in the analysis, and horizontal lines represent 95% confidence intervals. Diamonds show the pooled effect. Abbreviations: RR, relative risk; Ca, number of cases; Co, number of controls; n, number of events; N, number of patients [4,5,8–14,16,25–27,29–31].

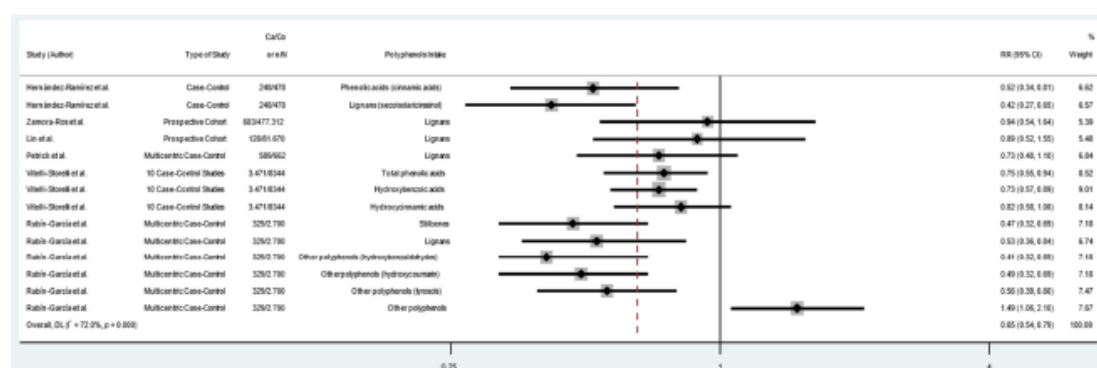


Figure 5. Forest plot of consumption of lignans, phenolic acids, stilbenes, and other polyphenols and gastric cancer risk. Case-control and cohort studies are presented in chronological order of publication. Square boxes represent study-specific estimates. Markers vary in size according to weight assigned to each study, size of each box reflects the study's weight in the analysis, and horizontal lines represent 95% confidence intervals. Diamonds show the pooled effect. Abbreviations: RR, relative risk; Ca, number of cases; Co, number of controls; n, number of events; N, number of patients [1,4,5,15,25,27,28].

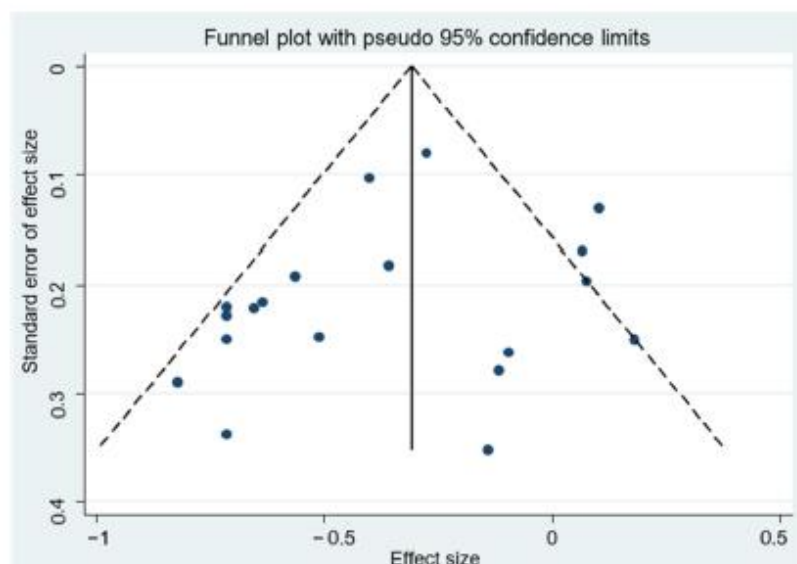


Figure 6. Funnel plot of dietary polyphenol intake and gastric cancer risk.

Table 2. Subgroup analyses of dietary polyphenol intake and gastric cancer risk.

Subgroup	Number of Participants	Number of Studies	RR (95% CI)	Heterogeneity Test	
				I ² (%)	p
All studies	1,197,857	19	0.71 (0.62–0.81) *	60.5	<0.001
Study design					
Cohort	1,171,647	7	0.88 (0.69–1.12)	54.7	0.039
Case-control	26,210	12	0.64 (0.56–0.74) *	44.4	0.049
Sex ¹					
Male	264,991	8	0.79 (0.67–0.94) *	31.6	0.176
Female	399,416	7	0.65 (0.48–0.87) *	49.7	0.064
Anatomical type ¹					
Cardia	1343	6	1.01 (0.79–1.27)	42.3	0.123
Noncardia	2603	6	0.85 (0.69–1.05)	65.2	0.013
Histological type ¹					
Diffuse	476	3	0.63 (0.37–1.09)	71.8	0.029
Intestinal	662	3	0.65 (0.52–0.82) *	0.0	0.494
Geographical area					
Asia	118,717	5	0.67 (0.51–0.89) *	60.7	0.038
America	470,985	3	0.87 (0.56–1.36)	78.3	0.010
Europe	608,155	11	0.67 (0.57–0.79) *	44.2	0.056
Adjustments					
Family history of gastric cancer, Yes	103,999	5	0.71 (0.59–0.86) *	59.3	0.044
No	1,093,858	14	0.70 (0.57–0.86) *	63.5	0.001
Fruit and/or vegetables intake ² , Yes	569,855	7	0.68 (0.55–0.83) *	49.5	0.065
No	638,597	16	0.72 (0.61–0.85) *	61.2	0.001

Note: ¹ the total number of studies that analyzed the specific variable was considered. ² the relative risk of the statistical models that used fruit and/or vegetable intake as an adjustment or otherwise was considered. * exhibited statistical significance.

5. Discussion

This systematic review and meta-analysis showed an inverse association between polyphenol consumption and GC, for the intake of total polyphenols and of the main classes, including flavonoids, lignans, phenolic acids, stilbenes, and other polyphenols. Previous studies report conflicting results regarding the relationship between polyphenol

intake and GC risk. Multicenter case–control studies carried out in Europe and the USA have found that individuals who consume greater amounts of polyphenols have a lower risk of developing GC [4,5,15,31]. However, cohort studies carried out in Finland [12,16], Japan [10] and the USA [11] failed to demonstrate this association. In the present systematic review, there was a dearth of studies analyzing the consumption of polyphenols and GC risk in Latin American countries, with a sole investigation in Mexico [25].

On the current subgroup analysis by geographic location, an inverse association between polyphenol intake and GC was identified in Europe and Asia but not in North America. The results of other meta-analyses also indicate an association in European populations only [17,33], where one of the reasons for this phenomenon may be the diversity of the diets across the different studies. The level of polyphenols contained in vegetables and fruit, for example, depends on the type of cultivation, crop variety and location, as well as the specific morphology of the plant source. In addition, ethnic differences in food structure or cultural differences in the storage and preparation of foods, particularly those of vegetables might also account for this result [34,35]. Other factors which might explain the geographic disparities found, beyond polyphenols, include the fact that the populations surveyed differ for other characteristics, as do the studies reviewed.

Flavonoids are the most-studied polyphenol class included in systematic reviews and meta-analysis studies [6,13,17,30,33,35–39]. In the meta-analysis performed by Bo et al. [37], no association was found between the highest dietary flavonoid intake and the risk of digestive tract cancers, including GC. In contrast, the meta-analyses of GC risk and dietary flavonoids by Xie, Huang, and Su [33], and by Woo and Kim [18], showed an association between flavonols and GC risk based on a limited number of selected studies. In the study by Woo and Kim [18], several subclasses of flavonoids, mostly in case–control studies, showed protective effects against stomach cancer risk, but total dietary flavonoid intake was not associated with a reduced risk of stomach cancer. Likewise, Grosso et al. [38], in a meta-analysis on dietary flavonoid and lignan intake with cancer risk, found no association between lignan intake and GC. This result differs from the findings of the present study, which showed lower risk of GC with increased flavonoid consumption. In addition, intake of lignans, phenolic acids, stilbenes, and other polyphenols was associated with a reduced risk of GC. Within natural compounds, polyphenols (including all classes and subclasses) represent a large diverse group used in the prevention and treatment of cancer [39]. Numerous studies have demonstrated that dietary polyphenol compounds exhibit a variety of bioactivities that can repress carcinogenesis and cancer progression, such as anticarcinogenic, anti-inflammatory, and antimicrobial properties, and act on cell proliferation pathways to inhibit the growth of *H. pylori* [36,38,40–42]. Furthermore, in gastric cancer, the immunological paradigm must also be taken into account, given reports suggesting some foods rich in polyphenols may improve immune function of gastric cells, besides improving the immune functions of lymphocyte proliferation, cellular and humoral immunity responses, thymocyte differentiation, and tumor immunity [38,43,44].

In the present study, subgroup analysis by study design was also conducted, revealing lower GC risk in case–control studies but not for cohort studies. Bo et al. [17] and You et al. [21] found that neither case–control nor cohort studies showed an association between polyphenol intake and GC risk. In the present analysis, heterogeneity was higher among the cohort studies, whereas the presence of greater recall and selection bias in case–control studies may potentially have led to a spurious association.

The analysis of the association between polyphenol intake and GC risk by sex revealed a significant risk reduction for both men and women. This finding differs from the results observed by other meta-analyses, in which either no association was found for males and females [37] or an inverse association was seen for women only [35]. In the present study, the risk reduction was greater for females, which may be partly explained by the fact that polyphenols can regulate female hormones and play a protective role against cancer. Similarly, a large prospective study has demonstrated associations between stomach cancer risk and age at menopause, years of fertility, and years since menopause [45]. However,

to the best of our knowledge, this is the first meta-analysis to identify a lower risk of GC for males, suggesting that a diet rich in polyphenols has preventive effects against GC for both sexes.

However, no association was found between polyphenol intake and reduced risk of noncardia gastric adenocarcinoma or gastric cardia adenocarcinoma. These findings are similar to the results of Yang et al. [24]. In contrast, a study by Xie, Huang, and Su [33] found an association between flavonol intake and reduced risk of noncardia gastric adenocarcinoma only. Regarding histological subtype, the present study showed a reduction in risk for intestinal-type GC but not for the diffuse type. A study published by Ekström et al. [46] found that a high intake of antioxidants, as a consequence of a high consumption of fruit and vegetables, was associated with a decreased risk of cardia and noncardia GC of both the intestinal and diffuse types. Few studies have analyzed the association between polyphenol intake and the histological subtypes of GC [26,27,31], where the present meta-analysis is the first investigation to assess these pooled results. However, the subanalysis by histological type was based on 3 studies and results should therefore be interpreted with caution.

The subgroup analyses also revealed an association between polyphenol intake and GC risk, irrespective of adjustments for family history of cancer or fruit and vegetable intake. Polyphenols are considered mediators of the protective effects of vegetables and fruit against various forms of cancer and chronic diseases. However, as these foods contain other compounds, it is important to identify which compound mediates the preventive potential of fruit and vegetables. To this end, some studies have used fruit and vegetable intake in statistical models to assess whether the association between polyphenol intake and GC remains significant [9,10,15]. Given that 7 out of the 19 studies included in the present review used fruit and vegetable intake as an adjustment factor, this subanalysis was performed, revealing that the risk of GC decreased independently of adjusting for fruit and vegetable intake. The subanalysis also served to determine whether family history of GC was a potential confounder, confirming that the association between polyphenol intake and GC was independent of this adjustment.

The present study has several strengths. First, a large sample drawing on a satisfactory number of studies was analyzed. A total of 19 studies were included, allowing a subgroup analyses to be carried out. Limitations of the meta-analysis included that some studies stratified results by sex and anatomical localization, while most investigations on the topic addressed only one class or subclass of polyphenols, hampering comparison with other studies.

6. Conclusions

In conclusions, the current study provided evidence for an inverse association between dietary polyphenol intake and GC risk, for total polyphenol intake as well as for various polyphenol classes, in a representative sample. Polyphenol consumption decreased the risk of GC in both sexes, but to a greater extent in females. Moreover, the risk reduction was greater in studies carried out in Europe and Asia. Further studies investigating the association of polyphenol consumption with GC in the Latin American population are warranted.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/cancers14235878/s1>, Table S1: Full search terms for each database; Table S2: Risk of bias assessments according to Newcastle-Ottawa Scale; Figure S1: Forest plot of polyphenol consumption and gastric cancer risk with other data combinations; Figure S2: Forest plot of flavonoid consumption and gastric cancer risk with other data combinations; Figure S3: Forest plot of consumption of lignans, phenolic acids, stilbenes, and other polyphenols and gastric cancer risk, with other data combinations; Figure S4: Funnel plot of dietary flavonoid intake and gastric cancer risk; Figure S5: Funnel plot of dietary lignans, phenolic acids, stilbenes, and other polyphenols and gastric cancer risk.

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Polyphenol intake and gastric cancer: a case-control study in the Brazilian Amazon region

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Abstract

Background: Polyphenol intake has been associated with a decreased risk of some types of cancer, including gastric cancer (GC). However, few studies address this topic in the Latin American population. In the present study, we evaluated the association between polyphenol intake and the risk of GC in the Brazilian Amazon region. **Methods:** A case-control study was conducted in Belém (Amazon region) from July 2017 to February 2021. A total of 193 GC cases and 194 controls of both sexes, between 18 and 75 years old, were included in the study. Dietary data were collected using a validated food-frequency questionnaire and polyphenol intake identified using the Phenol-Explorer database. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CI), with adjustment for potential confounders. **Results:** Cases and controls had similar total polyphenol intake (356.4 mg/1000kcal/d and 331.1 mg/1000kcal/d, respectively; $p = 0.086$). After adjusting for potential confounders, high consumption of flavan-3-ols (highest vs. lowest tertile: OR 0.41, 95% CI 0.18-0.94) and hydroxybenzoic acids (highest vs. lowest tertile: OR 0.24, 95% CI 0.10-0.56) was associated with a decreased risk of GC. The opposite was true regarding the intake of flavones (OR 2.46, 95% CI 1.17-5.18) and other polyphenols (OR 2.54, 95% CI 1.16-5.54). When stratifying according to anatomical topography, we observed that the intake of total flavonoids, flavan-3-ols, and flavanones reduced the risk of cardia GC while that of hydroxybenzoic acids reduced the risk of non-cardia GC. In addition, the intake of flavones and other polyphenols was associated with an increased risk of non-cardia GC. According to histologic subtypes, hydroxybenzoic acid intake was associated with a reduced risk of intestinal-type GC (OR 0.21, 95% CI 0.07-0.64), while flavone consumption was associated with an increased risk of diffuse-type GC (OR 2.59, 95% CI 1.05-6.42). **Conclusions:** Our findings suggest that in the Brazilian Amazon region the high intake of total flavonoids, flavan-3-ols, flavanones, and hydroxybenzoic acids is associated with a reduced risk of GC, suggesting a potential beneficial role of these compounds against GC.

Keywords: Gastric cancer, diet, polyphenol intake, case-control study, Brazil.

Background

Gastric cancer (GC) is the fifth most common type of cancer and remains a public health concern worldwide, with the highest incidence rates concentrated in Asia, Eastern Europe, and South America (1). In Brazil, the geographical regions show disparities in the incidence and mortality rates for GC, probably due to a variety of risk factors such as dietary patterns, lifestyle habits, genetics, and exposure to carcinogens (2,3). In Belém, a city in the Brazilian Amazon region, GC is the most common cancer among men, with an incidence rate of 24.43 per 100,000 inhabitants, representing the highest adjusted rate among all capitals in the country (4).

In the context of dietary habits influencing the risk of cancer, the intake of fruits and vegetables is known to be inversely associated to GC (5,6). This may be due to the beneficial composition of plant-based foods, which comprise mainly micronutrients and bioactive compounds, such as polyphenols. Polyphenols are a wide and complex group of non-nutrients usually present in plant-based foods and beverages, such as fruits, vegetables, beans, coffee, wine, and tea. Over 8,000 different molecules have been identified in foods thus far, falling into different classes and subclasses according to their chemical structure. The four main polyphenol classes are phenolic acids, flavonoids, stilbenes, and lignans, occurring either as glycosides, esters or polymers, or in the free form (aglycones) (7).

Accumulating evidence indicates that polyphenols have important biological properties, such as antioxidant, anti-inflammatory, and anti-proliferative activities (8), which are associated with decreased risk of some types of cancer, including GC. Nevertheless, most studies evaluating associations between GC and polyphenols focused on specific classes, mainly flavonoids (9–14). A recent systematic review and meta-analysis study showed an inverse association between the intake of total polyphenols and its classes and the risk of GC in both sexes (14).

To date, data on the relationship between polyphenol intake and the risk of GC in Latin American countries remain scarce. Thus, this pioneering case-control study aimed to evaluate the association between GC and the dietary intake of the main polyphenol classes and subclasses in the Brazilian Amazon region.

Methods

Study population

Cases and controls were recruited from July 2017 to February 2021 in Belém (Pará state, Brazilian Amazon region). Recruitment took place in the Ophir Loyola Hospital and the João de Barros Barreto University Hospital, both of which are reference centers for oncology in the country's northern region. The inclusion criterium for cases was having histologically confirmed stomach adenocarcinoma, classified according to the International Classification of Diseases for Oncology, third edition (ICD-O3). Controls comprised patients with no diagnosis or clinical suspicion of gastric cancer, recruited from outpatient clinics of the João de Barros Barreto

University Hospital. Cases and controls were matched by frequency and according to sex and age (18–75 years, in 5-year groups). Control and case participants were interviewed during the same period. The exclusion criteria were: previous malignancy (except for non-melanoma skin cancer), preneoplastic lesions (such as intestinal metaplasia), and physical, mental, or cognitive conditions that could prevent understanding of the questions posed by the interviewers.

For sample size calculation, we used a study power ($1 - \beta$) of 80%, alpha error rate of 5%, and odds ratio (OR) of 2 for a two-tailed hypothesis, which indicated that a minimum of 133 cases and 133 controls were needed. In the present study, 193 cases and 194 controls were included after excluding participants with missing data and after energy adjustment (Figure 1).

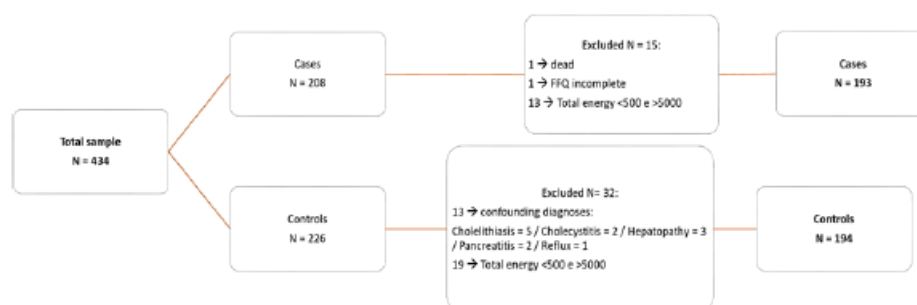


Figure 1. Flowchart of the participants' selection – Belém, Amazon region, Brazil (2017-2021).

All participants signed the informed consent. The study was designed according to the Declaration of Helsinki and approved by the ethics committees of the participating institutions.

Data collection

Cases and controls were interviewed at baseline by trained personnel, who administered questionnaires and conducted face-to-face interviews with the study participants. Information on sociodemographic factors (sex, age, marital status, education level, skin color, and origin), health behaviors (alcohol intake or smoking), weight and height, and family history of cancer were collected. The origin of the individuals was categorized according to the geographic reference of Pará state. The microregion of Salgado Paraense is inserted in the mesoregion of Northeast Paraense, which comprises 11 municipalities that make up an ecological corridor formed by conservation units of sustainable use, where the population relies on local natural resources such as artisanal fishing and crab hunting for subsistence (15). The metropolitan region of Belém is not part of the Salgado Paraense. Alcohol and tobacco consumption were classified as never, low,

and intermediate/high according to the consumption of grams per day and packs per year, respectively (16). Participants were classified according to their body mass index (BMI) as underweight, eutrophic, overweight, and obese (17,18). In addition, we collected clinical information on each gastric tumor case, which included anatomical subtype (cardia and non-cardia) and histological subtype (intestinal and diffuse) (19).

A validated food-frequency questionnaire (FFQ) (20,21) was applied at recruitment. This dietary questionnaire includes questions about the previous year's frequency of consumption of foods grouped under ten categories: rice and tubers; legumes and eggs; meats and fish; soups and pasta; greens and vegetables; sauces and seasonings; fruits; snacks; drinks; sweets and desserts. For each food, the participants indicated the frequency of consumption, that is, the number of times it was consumed (1–10) per day, week, month, or year. The size of the ingested portion was presented as small, medium, or large, represented in slices and spoons, and transformed into grams according to each type of food. Consumption (grams/day) was calculated as follows: $((\text{frequency} \times \text{portion}) / \text{days}) \times \text{grams}$ (e.g., 2 spoons of rice (50 g each), consumed 7 times/week). Total energy intake estimated in < 500 kcal or > 5000 kcal per day were considered implausible (22).

Estimation of polyphenol intake

For the analysis of polyphenol intake, a subset of 42 plant-based foods and beverages was considered, including fruits, vegetables, cereals, wine, and others. The Phenol-Explorer database (<http://phenol-explorer.eu/>) was used to identify the polyphenol content in foods. This database contains data on 501 different polyphenols in more than 450 foods. Individual polyphenol content values included in the Phenol-Explorer database were determined by reversed-phase high-performance liquid chromatography (HPLC), with the exception of proanthocyanins, which were determined by normal-phase HPLC. As for polyphenols that cannot be obtained through normal extraction conditions (e.g., lignans, ellagic acid, and hydroxycinnamic acids), data were obtained by HPLC after basic or acid hydrolysis (23).

In the case of regional foods and beverages (e.g., açai) and other highly prevalent items in the Brazilian diet (e.g., rice, beans, and orange), we used data from foods collected and analyzed in Brazil by HPLC. We have also used data from the Brazilian Food Composition Database (TBCA, available at www.tbca.net.br/), a database on flavonoid content (expressed as aglycone) in regional and other foods commonly consumed in Brazil, analyzed by HPLC (24).

Statistical analysis

Descriptive statistics was used to display characteristics of cases and controls, using the Mann-Whitney test for continuous variables and the chi-square test for categorical variables. A value of $p < 0.05$ was considered statistically significant for all tests used. Since polyphenol intake

increases with higher food consumption, the former was calculated in energy-adjusted terms (mg of polyphenols per 1000 kcal/d (4184 kJ/d) of total energy consumed). Total polyphenol and its main classes and subclasses were categorized by tertiles, based on the control distribution for the analysis. Odds ratios and 95% confidence intervals for gastric cancer were calculated across the tertiles of dietary polyphenols using logistic regression after controlling for known risk factors. The lowest tertile of each dietary polyphenol subclass was used as the reference. The adjustment variables included in the multiple logistic regression model were education, race/ethnicity, origin, BMI, family history of GC, smoking status, alcohol consumption (25–27), aspirin use (28,29), and fruit and vegetable intake. The final model was evaluated by the Hosmer-Lemeshow quality test (30). Summary results were reported as risk rather than probability for simplicity's sake, in line with similar case-control studies (22,31–33). All statistical analyses were conducted using the software SPSS Statistics for Windows, Version 25.0.

Results

This study includes 193 GC cases and 194 controls, whose characteristics are described in Table 1. Most of the case and control individuals were male with a mean age of 58 years. Differences between the two groups were observed regarding race/ethnicity, education level, origin, family history of GC, BMI, tobacco and alcohol consumption, and energy, fruit and vegetable intake. Cases had lower educational level (72.5% of ≤ 8 years), a family history of GC (23.8%), and higher tobacco use (46.9%) and alcohol consumption (42.6%) compared with controls. In addition, cases had a higher energy consumption and greater medians of fruit and vegetable intake.

Table 1. General characteristics of cases and controls – Belém, Amazon region, Brazil (2017-2021).

Variables		Cases N 193 (%)	Controls N 194 (%)	<i>p</i> value*
Sex	Male	116 (60.1)	122 (62.9)	0.574
	Female	77 (39.9)	72 (37.1)	
Age, median (min-max)		58 (27-75)	57.5 (27-75)	0.494
Anatomical type	Cardia	15 (7.8)	-	
	Non-Cardia	166 (86.0)	-	
	Missing	12 (6.2)	-	
Histological type	Intestinal	65 (33.7)	-	
	Diffuse	71 (36.8)	-	
	Mixed	3 (1.6)	-	
	Undetermined	2 (1.0)	-	
	Missing	52 (26.9)	-	
Race/Ethnicity	White	20 (10.4)	39 (20.2)	< 0.001
	Brown (mixed race)	156 (80.8)	120 (62.2)	
	Black	17 (8.8)	34 (17.6)	
	Missing	-	1	
Education (years)	≤ 8	140 (72.5)	45 (23.2)	< 0.001
	9 a 12	47 (24.4)	107 (55.2)	
	≥ 13	6 (3.1)	42 (21.6)	
Marital status	Not married	39 (20.2)	36 (18.6)	0.870
	Married	127 (65.8)	128 (66.0)	
	Other	27 (14.0)	30 (15.4)	
Origin	Microregion of Salgado Paraense	21 (10.9)	4 (2.1)	< 0.001
	Other regions	172 (89.1)	190 (97.9)	
Family history of GC	No	147 (76.2)	192 (99.0)	< 0.001
	Yes	46 (23.8)	2 (1.0)	
Smoking	Never	65 (33.9)	120 (61.9)	< 0.001
	Low	37 (19.2)	26 (13.4)	
	Intermediate/High	90 (46.9)	48 (24.7)	
	Missing	1	-	
Alcohol consumption	Never	75 (39.5)	133 (68.9)	< 0.001
	Low	34 (17.9)	26 (13.5)	
	Intermediate/High	81 (42.6)	34 (17.6)	
	Missing	3	1	
Body Mass Index	Eutrophic	89 (46.1)	105 (54.1)	<0.001
	Low weight	76 (39.4)	36 (18.6)	
	Overweight	16 (8.3)	47 (24.2)	
	Obese	12 (6.2)	6 (3.1)	
Aspirin use	No	190 (98.5)	194 (100.0)	0.081
	Yes	3 (1.5)	0 (0.0)	
Energy (kcal/d), median (25-75 th percentile)		1909 (1345-2504)	1254 (912-1713)	< 0.001
Fruit intake (g/d), median (25-75 th percentile)		226.1 (109.7 – 387.4)	192.8 (107.7 – 305.9)	0.049
Vegetable intake (g/d), median (25-75 th percentile)		47.1 (21.2 – 82.8)	32.6 (17.5 – 66.0)	0.020

* Chi-squared and Mann-Whitney Tests.

The median consumption of polyphenol subclasses for the entire sample is presented in Table 2. Case and control participants consumed, on average, similar amounts of total polyphenol and its subclasses. Hydroxycinnamic acids, flavan-3-ols, and anthocyanins were the main subclasses contributing to total polyphenol intake in both groups. The intake of total flavonoids, flavan-3-ols, and hydroxybenzoic acids was higher among controls compared with cases ($p \leq 0.049$). The three highest food contributors to the intake of total polyphenol and that of its classes and subclasses, for the whole sample, are shown in Table 3. The main individual food contributors to phenolic acid intake were coffee, papaya, and rice, with respective contributions of 83.9%, 4.9%, and 2.8%. As for flavonoids, the main individual food contributors were açai (49.8%), tea (12.7%), and grapes (7.3%); the main contributors to the intake of flavan-3-ols were açai (59.0%), tea (20.1%), and chocolate milk (11.3%); while to that of flavones, bread (51.8%), pasta (45.8%), and pumpkin (1.7%) were the main ones. No differences were found between cases and controls in terms of the most consumed individual polyphenols, as well as the foods contributing to the consumption of total polyphenol and its classes and subclasses (see online Supplementary Table 1).

All the ORs and 95% CIs for GC were analyzed across tertiles of polyphenol intake (Suppl. Table 2). Figure 2 shows the adjusted ORs and 95% CIs for GC, comparing the highest and lowest tertiles of polyphenol intake. Significant associations were observed for flavones, flavan-3-ols, hydroxybenzoic acids, and other polyphenols. Flavan-3-ols and hydroxybenzoic acids were associated with reductions in the total risk of GC by 59% [OR (95% CI): 0.41 (0.18–0.94)] and 76% [OR (95% CI): 0.24 (0.10–0.56)], respectively. Regarding the consumption of flavones and other polyphenols, an increase in the risk of GC was observed (flavones: OR (95% CI) 2.46 (1.17–5.18), other polyphenols: OR (95% CI) 2.54 (1.16–5.54)). Total flavonoids, flavonols, flavanones, anthocyanins, and lignans showed protective tendencies against GC, although no association was detected.

Table 2. Polyphenol intake distribution¹ (mg/ 1000kcal/ day) according to cases and controls. Belém, Amazon region, Brazil (2017-2021).

Polyphenols	Cases (N 193)		Controls (N 194)		<i>p value</i> *
	Median	25-75 th percentile	Median	25-75 th percentile	
Phenolic acids	257.5	152.7 – 409.0	211.5	108.3 – 400.1	0.049
Hydroxybenzoic acids	2.2	0.7 – 5.7	5.3	2.5 – 10.7	<0.001
Hydroxycinnamic acids	248.8	149.2 – 399.7	203.4	96.9 – 394.2	0.031
Flavonoids	81.5	41.1 – 154.3	95.0	59.8 – 142.7	0.049
Flavonols	8.2	5.1 – 12.5	8.2	5.0 – 12.1	0.929
Flavones	6.5	4.2 – 10.8	6.0	3.0 – 9.3	0.034
Flavan-3-ols ²	37.3	12.5 – 85.6	51.5	28.9 – 81.1	0.007
Flavanones	3.6	0.0 – 9.6	3.6	0.0 – 7.7	0.809
Anthocyanins	14.6	4.5 – 39.5	20.1	9.8 – 34.0	0.097
Lignans	1.1	0.7 – 1.8	1.0	0.5 – 1.6	0.031
Other polyphenols ³	3.6	2.3 – 5.7	3.0	1.6 – 5.2	0.010
Total polyphenols	356.4	236.6 – 590.3	331.1	209.5 – 504.4	0.086

¹The consumption of isoflavones and stilbenes was very near zero in this population. ²includes proanthocyanidins. ³including alkylmethoxyphenols, methoxyphenols, hydroxycoumarins, tyrosols, and other minor phenolics. *Mann-Whitney Test.

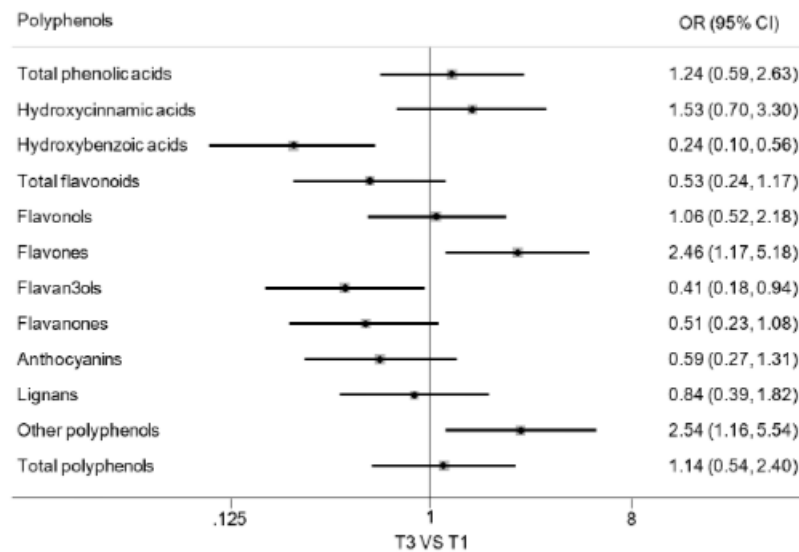


Figure 2. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) comparing the tertiles 3 (T3) and 1 (T1) of polyphenol intake for gastric cancer (GC). Data estimated using multiple logistic regression models adjusted by education, race/ethnicity, origin, BMI, family history of GC, smoking status, alcohol consumption, aspirin, and fruit and vegetable intake. Flavan-3-ols intake includes proanthocyanidins.

When analyzing the association between polyphenol intake and GC taking topography and histological subtypes into account (Table 3), the results were found to be similar to those for the overall risk of GC. The intake of total flavonoids, flavan-3-ols, and flavanones was associated with a decreased risk of cardia GC, while the intake of hydroxybenzoic acids reduced the risk of non-cardia GC. Regarding the major food sources, fruits such as açai, grapes, and oranges, as well as tomatoes and tea, were the main contributors to the intake of the aforementioned subclasses. On the other hand, the intake of flavones and other polyphenols was associated with an increased risk of non-cardia GC, and major contributors to their consumption were bread, pasta, and coffee.

Regarding histological subtypes, we have also found differences between polyphenol groups. While flavone intake was associated with an increased risk of the diffuse GC type [OR (95% CI): 2.59 (1.05–6.42)], hydroxybenzoic acid intake reduced the risk of the intestinal type by 79% [OR (95% CI): 0.21 (0.07–0.64)].

Table 3. Association between polyphenol intake¹ and gastric cancer considering anatomic and histologic subtypes, percentage of daily intake for the top three most consumed individual polyphenols, and most consumed foods considering all subjects of the study. Belém, Amazon region, Brazil (2017-2021).

Polyphenols	Topography		Histologic Type ²		Individual Polyphenols and Foods with Highest Contribution in All Cases and Controls	
	Cardia (N = 15)	Non-Cardia (N = 166)	Diffuse (N = 71)	Intestinal (N = 65)	Top three most consumed individual polyphenols (%)	Top three main food contributors (%)
Phenolic acids	↓	↑	↑	↑	5-Caffeoylquinic acid (31.3), 4-Caffeoylquinic acid (25.0), 3-Caffeoylquinic acid (21.7)	Coffee (83.9), papaya (4.9), rice (2.8)
Hydroxycinnamic acids	↑	↑	↑	↑	5-Caffeoylquinic acid (31.9), 4-Caffeoylquinic acid (25.5), 3-Caffeoylquinic acid (22.1)	Coffee (86.9), papaya (3.6), rice (2.9)
Hydroxybenzoic acids	↓	↓*	↓	↓*	Protocatechuic acid (28.8), 4-Hydroxybenzoic acid (28.3), 5-O-Galloylquinic acid (24.0)	Tea (44.8), papaya (43.1), rice (2.5)
Flavonoids	↓*	↓	↓	↓	Procyanidin trimer C1 (44.9), Cyanidin 3-galactoside (13.5), Cyanidin 3,5-O-diglucoside (8.2)	Açaí ³ (49.8), tea (12.7), grape (7.3)
Flavonols	↑	↓	↓	↑	Quercetin (66.5), Kaempferol (9.2), Isohammetin (5.6)	Kale (21.7), spinach (17.4), tea (13.1)
Flavones	↓	↑*	↑*	↑	Apigenin 6,8-C-galactoside-C-arabinoside (59.6), Apigenin 6,8-C-arabinoside-C-glucoside (39.6), Luteolin (0.8)	Bread (51.8), pasta (45.8), pumpkin (1.7)
Flavan-3-ols ³	↓*	↓	↓	↓	Procyanidin trimer C1 (79.7), Epicatechin (3.6), Catechin (2.7)	Açaí ³ (59.0), tea (20.1), chocolate milk (11.3)
Flavanones	↓*	↓	↓	↓	Naringenin (50.0), Hesperetin (49.7), Naringenin 7-O-glucoside (0.3)	Orange (99.8), tomato (0.2)
Anthocyanins	↓	↓	↓	↓	Cyanidin 3-galactoside (54.3), Cyanidin 3,5-O-diglucoside (32.9), Malvidin 3-O-glucoside (5.4)	Açaí ³ (73.9), grape (26.1)
Lignans	↓	↑	↑	↑	Lariciresinol (59.6), Pinoresinol (33.9), Secoisolariciresinol (4.1)	Orange (41.5), melon (33.8), rice (14.0)
Other polyphenols ⁴	↓	↑*	↑	↑	4-Ethylguaicol (19.6), Pyrogallol (16.6), 4-Vinyguaicol (14.1)	Coffee (75.9), bread (12.2), pasta (10.8)
Total	↓	↑	↑	↓	5-Caffeoylquinic acid (21.4), 4-Caffeoylquinic acid (17.1), 3-Caffeoylquinic acid (14.8)	Coffee (51.5), açaí ⁴ (18.9), tea (5.9)

Note: Association between gastric cancer and polyphenol intake assessed by comparing tertiles 3 and 1. ¹The intake of polyphenol classes and subclasses in mg/1000kcal/day. Data estimated using a multivariable logistic regression model adjusted by education, race/ethnicity, origin, BMI, family history of GC, smoking status, alcohol consumption, aspirin, and fruit and vegetable intake. ²Mixed histological type was not considered in the regression due to the limited number of cases (N = 3). ³Includes proanthocyanidins. ⁴Including alkylmethoxyphenols, methoxyphenols, hydroxycoumarins, tyrosols, and other minor phenolics. ⁵Brazilian fruit grown predominantly in the Amazon region. ↑ increased risk; ↓ decreased risk; * statistically significant.

Discussion

The present study reports on the association between polyphenol intake and the risk of GC in the Brazilian Amazon region. We observed an inverse association between the intake of phenolic acids, hydroxybenzoic acids, flavonoids, flavan-3-ols, and flavanones and the risk of GC. These findings corroborate some previous studies, though not all. An inverse association between polyphenol intake and GC has been observed in Greece (10), Mexico (34), and Italy (35). On the other hand, studies conducted in the United States (12,36), Finland (37), and Japan (11) showed no associations between polyphenol intake and the risk of GC. However, up until now, no study had investigated these associations in Latin American populations, including Brazil (14).

Polyphenols may play a role in reducing the risk of carcinogenesis through diverse mechanisms, such as reducing oxidative processes and cell proliferation, inducing apoptosis, regulating immune responses, and inhibiting the formation of carcinogenic N-nitroso compounds under acidic conditions in the stomach (8,38). Flavonoids are a major polyphenol class, and their intake is associated with antibacterial, antithrombotic, anti-inflammatory, and anticarcinogenic effects (39). Regarding the risk of cancer, GC cell lines were found to be sensitive to epicatechin 3-O-gallate, which induced apoptosis by inhibiting expression downstream of p73 (40). In relation to epidemiologic data, a prospective cohort from 10 European countries showed that women in the highest quartile of flavan-3-ol intake had a 45% lower risk of developing GC compared with those in the reference level (lowest quartile) (41). Other studies have also reported an inverse association between the intake of flavan-3-ols and the risk of GC (13,42).

In this context, açai (*Euterpe oleracea* Mart.) – a berry-like fruit native of the Amazon region, consumed mainly in the North and Northeast Brazilian regions – was found to be the main source of total flavonoids and flavan-3-ols (proanthocyanidins) in our study, accounting for up to 42% of the Amazon community diet. In fact, high levels of numerous polyphenols, such as phenolic acids and flavonoids (proanthocyanidins and anthocyanins), have been reported in açai (43,44).

Regarding other flavonoid subclasses, unlike our results, studies have shown an inverse association between GC and the intake of isoflavone (45) and anthocyanins (42) in men, and that of quercetin (flavonol subclass) in women (46). However, other studies corroborate our findings, with no associations having been found between GC and these compounds (9–11,35–37). In our analysis, the intake of isoflavones approached zero, thus we were unable to analyze its association with GC. Regarding anthocyanins, cases and controls displayed a similar intake level ($p = 0.097$).

Among phenolic acids, we found an inverse association between hydroxybenzoic acid consumption and the risk of GC, corroborating Vitelli-Storelli et al. (13), who reported that a higher intake of hydroxybenzoic acids was associated with a reduction of GC risk, while hydroxycinnamic acids showed no significant association.

We observed that the intake of flavone and other polyphenol subclasses increased the risk of GC, including according to anatomical and histological subtypes. Similar results were found by Rubin-García et al. (31) for other polyphenols, while in Greece a protective effect of flavones regarding the risk of GC was observed (10). In vitro studies indicate considerable differences in the antioxidant potential of different flavonoid subgroups, which depends on their chemical structures, bioavailability, and metabolism (47). Furthermore, the polyphenol content in food varies depending on the food matrix and processing degree.

In our study, the major food sources of flavone and other polyphenol subclasses were bread, pasta, and coffee. Consumption of savory bread and other processed and ultraprocessed foods were found to be independently associated with the probability of having GC in two Brazilian regions – Amazon region and São Paulo (21). Regarding coffee intake, the evidence on it being a potential risk factor for GC remains inconsistent, because their association has been attributed to the residual confounding effect of tobacco (48,49).

We found no association between the intake of total polyphenols and lignans and the risk of GC, contrary to previous studies that observed a reduction in the risk of GC associated with total polyphenol intake (13,50). As for lignans consumption, no association with GC risk has been reported (36,41,51).

Regarding topography, a higher intake of total flavonoids, flavan-3-ols, and flavanones reduced the risk of cardia GC, while that of hydroxybenzoic acids reduced the risk of non-cardia GC. Much like what has been observed for GC in general, the intake of flavones and other polyphenols increased the risk of non-cardia GC, which may be related to the food source that most contributed to the intake of these subclasses (ultraprocessed and processed foods and coffee) and their controversial role. Flavone intake had a direct association with the risk of diffuse GC, while hydroxybenzoic acid intake reduced the risk of intestinal GC. In addition, as pointed out in a recent metaanalysis, the intake of polyphenols reduced the risk of intestinal cancer, although there was no association with the diffuse type (14). Our results may partly explain the association between diet and the risk of GC; for example, the foods that most contributed to the intake of hydroxybenzoic acids in our study population were tea and papaya. Martimiannaki et al. (32) found an inverse association between tea intake and GC.

Our study has strengths. It is the first evaluating the association between total polyphenol and its classes and the risk of GC in Latin America, not to mention that we have reported the results also in terms of histological subtype and anatomical tumor subsite. The present study also has some limitations. Firstly, this is a hospital-based, case-control study; consequently, a recall bias in the dietary assessment could have led to misclassification. Furthermore, the study has a sample size of 193 individuals compared to 194, and it was conducted in a region with high incidence and mortality of gastric cancer. We must also mention that the Phenol-Explorer database used for the epidemiological studies on diet does not include regional foods.

Nevertheless, to minimize this bias, we included information on Brazilian food composition. Another limitation concerns the Amazon region itself: this region is recognized for its vast biodiversity, which is reflected in peculiar dietary patterns and cultural factors (52). Therefore, our results may not be generalizable to the entire Brazilian population.

In conclusion, our results showed that the high intake of total flavonoids, flavan-3-ols, flavanones, and hydroxybenzoic acids is associated with a lower risk of GC in the Brazilian Amazon region, suggesting a beneficial potential of polyphenols against GC. Although the intake of these compounds in Belém is rather high, this city has the highest incidence of GC in Brazil, indicating that other competing factors may be associated. A valid strategy to reduce the risk of gastric cancer is an increase in the consumption of foods rich in polyphenols, such as tea and fruits like açai, papaya, grapes, and oranges. We believe our study paves the way for further research on this topic, especially in Latin American populations.

Authors' contributions: MAF and MPC designed the study. MAF wrote the manuscript. MAF and RAC performed the analysis. RAC, GAF, PPA and MPC were involved in planning, helped write the manuscript and supervised the work. All authors aided in interpreting the results, discussed the results and commented on the manuscript.

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ANEXOS

ANEXO 1 – QUESTIONÁRIO DE ESTILO DE VIDA

História Ocupacional			
Você trabalha ou já trabalhou ?	☐ Yes ☐ No		
* must provide value	Por tempo integral por pelo menos 1 ano		
Qual a sua ocupação por maior tempo?			
* must provide value			
Preencher na versão Online - Anotar			
Quantos anos?			
* must provide value	Anos		
Ainda exerce esta atividade?	☐ Yes ☐ No		
* must provide value			
História de doenças pessoais:			
Possui ou já teve alguma doença listada abaixo, confirmada pelo médico?			
Doença:			
1- Doença reumática (dizer reumatismo).	☐ Yes ☐ No		reset
* must provide value			
2- Angina / infarto / falha cardíaca (problema do coração).	☐ Yes ☐ No		reset
* must provide value			
2. 1 - Insuficiência cardíaca congestiva	☐ Yes ☐ No		reset
* must provide value			
3- Derrame (AVC):	☐ Yes ☐ No		reset
* must provide value			
3.1 - Doença vascular periférica	☐ Yes ☐ No		reset
* must provide value			
4- Hipertensão (pressão alta).	☐ Yes ☐ No		reset
* must provide value			
5- Diabetes:	☐ Yes ☐ No		reset
* must provide value			
5.1 - Diabetes com complicações	☐ Yes ☐ No		reset
* must provide value			
6- COPD (Asma, Bronquite Crônica, Enfisema).	☐ Yes ☐ No		reset
* must provide value			
7- Problemas renais crônicos (problemas nos rins) / insuficiência renal.	☐ Yes ☐ No		reset
* must provide value			
8- Diarreia ou sangue nas fezes (por mais de um mês).	☐ Yes ☐ No		reset
* must provide value			

9- Anemia: * must provide value	☐ Yes ☐ No	reset
10- Doença hepática crônica (doença do fígado). * must provide value	☐ Yes ☐ No	reset
10.1 - Disfunção hepática moderada ou severa * must provide value	☐ Yes ☐ No	reset
11- Tuberculose: * must provide value	☐ Yes ☐ No	reset
12- Malária: * must provide value	☐ Yes ☐ No	reset
13- Dengue: * must provide value	☐ Yes ☐ No	reset
14- HIV Positivo (AIDS). * must provide value	☐ Yes ☐ No	reset
15- Hepatite B,C: * must provide value	☐ Yes ☐ No	reset
16- Doença Psiquiátrica: * must provide value	☐ Yes ☐ No	reset
16.1 - Demência * must provide value	☐ Yes ☐ No	reset
17 - Doença do tecido conjuntivo * must provide value	☐ Yes ☐ No	reset
18 - Úlcera * must provide value	☐ Yes ☐ No	reset
19 - Hemiplegia * must provide value	☐ Yes ☐ No	reset
Já fez alguma cirurgia? * must provide value	☐ Yes ☐ No	reset

História pessoal e familiar sobre câncer:		
Já teve câncer confirmado pelo medico? * must provide value	☐ Yes ☐ No	reset
Em qual local? * must provide value		reset
Qual idade? * must provide value		
Tem histórico de câncer na família? * must provide value	☐ Yes ☐ No	reset
Especifique:		
1- Parente: * must provide value		
1- Em qual local? * must provide value		reset
1- Idade ao diagnóstico: * must provide value		
Outro caso:		
☐ Sim.		

Tabagismo		
Já fumou cigarros regularmente (pelo menos semanalmente por mais de 6 meses)?	☒ Yes ☐ No	reset
* must provide value		
Ainda fuma?	☒ Yes ☐ No	reset
* must provide value		
Listar o consumo de cigarro iniciando quando começou a fumar regularmente.		
1- Da idade de:		
* must provide value		
1- A idade de:		
* must provide value		
1- Tipo:	☐ Fabricado e com filtro ☐ Fabricado sem filtro ☐ Não fabricado (de palha)	reset
* must provide value		
1- Quantidade de cigarro por dia:		
* must provide value		
Outro campo?	☐ Sim.	
Já fumou charuto regularmente? (semanalmente ou por mais de seis meses).	☒ Yes ☐ No	reset
* must provide value		
Ainda fuma?	☒ Yes ☐ No	reset
* must provide value		
1- Idade de início:		
* must provide value		
1- Idade de término:		
* must provide value		
1- Dias por semana:	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7	reset
* must provide value		
Consumo de álcool:		
Já consumiu bebidas alcoólicas regularmente? (por pelo menos uma vez "1x" por semana por mais de 6 meses)	☒ Yes ☐ No	reset
* must provide value		
1- Produto:		
* must provide value		
1- Quantidade média utilizada por dose:		
* must provide value		
1- Qual a quantidade de dose consumida por dia?		
* must provide value		
1- Quantos dias por mês que bebia:		
* must provide value		
1- Idade de início:		
* must provide value		
1- Idade de término:		
* must provide value		
Outro campo?	☐ Sim.	

Histórico de uso de medicamentos		
Já usou medicamentos regularmente (de modo contínuo por mais de 3 meses)?	☐ Yes ☐ No	reset
Uso de Omeprazol, Ranitidina, Pantoprazol ou Nexium (Esomeprazol)?	☐ Yes ☐ No	reset
Uso de antiácidos - Mylanta, Sal de Frutas (Eno), Kolantyl, Etc.	☐ Yes ☐ No	reset
Uso de anti-inflamatórios (Flotac, Toragesic, Ponstan, Ibuprofeno)	☐ Yes ☐ No	reset
Faz uso de AAS (Aspirina)	☐ Yes ☐ No	reset
FAZ USO DE METFORMINA?	☐ Yes ☐ No	reset
Qual a última vez que usou antibióticos?		
Saúde Bucal		
Perdeu algum dente permanente?	☐ Yes ☐ No	reset
Já foi diagnosticado com doença periodontal?	☐ Yes ☐ No	reset
Faz uso de dentaduras parcialmente ou totalmente?	☐ Yes ☐ No	reset
Quantas vezes por dia escova os dentes?		
Faz uso de fio dental?		
☐ Diário ☐ Algumas vezes na semana ☐ Raramente ☐ Não usa		reset
Faz uso regular de enxaguante bucal?		
☐ Diário ☐ Algumas vezes na semana ☐ Raramente ☐ Não usa		reset
Avaliação do entrevistador		
Se a entrevista não estiver completa, forneça as razões para a falta de dados.		
Qualidade da entrevista:	☐ Boa ☐ Mediana ☐ Ruim	reset
Identidade do Entrevistado:		
Form Status		
Complete?	Incomplete	

ANEXO 2 – QUESTIONÁRIO DE FREQUÊNCIA ALIMENTAR

QUESTIONÁRIO QUANTITATIVO DE FREQUÊNCIA ALIMENTAR

Data da entrevista ____/____/____	Nº de identificação: _____
Visita: _____	Entrevistador: _____
Nome: _____	Tel: _____ Sexo: () F () M
Idade atual: _____ anos	Data de nascimento: ____/____/____

1. Você mudou seus hábitos alimentares recentemente ou está fazendo dieta para emagrecer ou por qualquer outro motivo?

- (1) Não
 (2) Sim, para perda de peso
 (3) Sim, por orientação média
 (4) Sim, para dieta vegetariana ou redução do consumo de carne

- (5) Sim, para redução de sal
 (6) Sim, para redução de colesterol
 (7) Sim, para ganho de peso

Outro Motivo: _____

2. Você está tomando algo para suplementar sua dieta (vitaminas, minerais, outros produtos)?

- (1) Não (2) Sim, regularmente (3) Sim, mas não regularmente

3. Se a resposta da pergunta anterior for SIM, favor preencher o quadro abaixo:

Suplemento	Composição	Dose	Frequência

4. As questões seguintes relacionam-se ao seu hábito alimentar usual no PERÍODO DE UM ANO. Para cada quadro responda, por favor, a frequência que melhor descreva QUANTAS VEZES você costuma comer cada item e a respectiva UNIDADE DE TEMPO (se por dia, por semana, por mês ou por ano). Depois responda qual a sua PORÇÃO INDIVIDUAL USUAL (se pequena, média ou grande, conforme o indicado no questionário). ESCOLHA SOMENTE UM CÍRCULO PARA CADA COLUNA.

Se você não come ou raramente come um determinado item, preencha o círculo da primeira coluna (N = nunca come). NÃO DEIXE ITENS EM BRANCO.

GRUPO DE ALIMENTOS	Com que frequência você costuma comer?		Qual é o tamanho da sua porção?
	QUANTAS VEZES VOCÊ COME:	UNIDADE:	SUA PORÇÃO:
Alimentos e Preparações	Número de vezes: 1, 2, 3 etc. (N = nunca ou raramente comeu no último ano)	D = por dia S = por semana M = por mês A = por ano	P = porção pequena M = porção média G = porção grande

LEITE E DERIVADOS	QUANTAS VEZES VOCÊ COME	UNIDADE	PORÇÃO	
Leite - tipo: () Integral () desnatado () semi-desnatado	N 1 2 3 4 5 6 7 8 9 10	D S M A	1/2 xícara pequena (50ml)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 xícara pequena (120ml)	☐ M
			2 xícaras pequenas (240ml)	☐ G
Iogurte Integral - tipo: () natural () com frutas	N 1 2 3 4 5 6 7 8 9 10	D S M A	1/2 pote peq. nat. (85g), 1 pote fruta (110g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 pote peq. nat. ou 1 1/2 potes fruta (165g)	☐ M
			1 1/2 potes peq. nat. ou 2 potes fruta (230g)	☐ G
Queijo mussarela, prato, parmesão, provolone	N 1 2 3 4 5 6 7 8 9 10	D S M A	1 fatia média (20g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 1/2 fatias médias (30g)	☐ M
			2 fatias médias (40g)	☐ G
Queijo minas, ricota	N 1 2 3 4 5 6 7 8 9 10	D S M A	1/2 fatia média (15g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 fatia média (30g)	☐ M
			2 fatias médias (60g)	☐ G
Vitamina de Frutas	N 1 2 3 4 5 6 7 8 9 10	D S M A	< 1/2 copo de requeijão (<120ml)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1/2 copo de requeijão (120ml)	☐ M
			1 copo de requeijão (240ml)	☐ G

PÃES, BISCOITOS e COMPLEMENTOS	QUANTAS VEZES VOCÊ COME	UNIDADE	PORÇÃO	
Pão francês e pão de forma	N 1 2 3 4 5 6 7 8 9 10	D S M A	1/2 unidade ou 1 fatia (25g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 unidade ou 2 fatias (50g)	☐ M
			2 unidade ou 4 fatias (100g)	☐ G
Pão Integral	N 1 2 3 4 5 6 7 8 9 10	D S M A	1 fatia (25g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	2 fatias (50g)	☐ M
			4 fatias (100g)	☐ G
Biscoito sem recheio (doce, salgado)	N 1 2 3 4 5 6 7 8 9 10	D S M A	2 unidades (12g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	4 unidades (24g)	☐ M
			6 unidades (36g)	☐ G
Biscoito recheado, waffle, amanteigado	N 1 2 3 4 5 6 7 8 9 10	D S M A	2 unidades (20g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	4 unidades (40g)	☐ M
			6 unidades (60g)	☐ G
Bolo Simples	N 1 2 3 4 5 6 7 8 9 10	D S M A	1/2 fatia média (30g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 fatia média (60g)	☐ M
			2 fatias médias (12g)	☐ G
Bolo Recheado	N 1 2 3 4 5 6 7 8 9 10	D S M A	1/2 fatia média (50g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 fatia média (100g)	☐ M
			2 fatias médias (200g)	☐ G
Cereal Matinal	N 1 2 3 4 5 6 7 8 9 10	D S M A	3 colheres de sopa cheias (18g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	6 colheres de sopa cheias (36g)	☐ M
			10 colheres de sopa cheias (50g)	☐ G
Aveia	N 1 2 3 4 5 6 7 8 9 10	D S M A	1 1/2 colheres de sopa cheias (22,5g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	2 1/2 colheres de sopa cheias (37,5g)	☐ M
			4 colheres de sopa cheias (60g)	☐ G
Manteiga ou margarina () comum () light	N 1 2 3 4 5 6 7 8 9 10	D S M A	1 ponta de faca (7g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	2 pontas de faca (14g)	☐ M
			3 pontas de faca (21g)	☐ G

CAFÉ, CHÁ e ACHOCOLATADO	QUANTAS VEZES VOCÊ COME	UNIDADE	PORÇÃO	
Café () com açúcar () sem açúcar	N 1 2 3 4 5 6 7 8 9 10	D S M A	1 dedo de copo de requijão (35ml)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	2 dedos de copo de requijão (70ml)	☐ M
			4 dedos de copo de requijão (140ml)	☐ G
Chá () com açúcar () sem açúcar	N 1 2 3 4 5 6 7 8 9 10	D S M A	1/2 xícara de chá (100ml)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 xícara de chá (200ml)	☐ M
			2 xícaras de chá (400ml)	☐ G
Achocolatado	N 1 2 3 4 5 6 7 8 9 10	D S M A	1 colher de sobremesa (12,5g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	2 colheres de sobremesa (25g)	☐ M
			4 colheres de sobremesa (50g)	☐ G

ARROZ E TUBÉRCULOS	QUANTAS VEZES VOCÊ COME	UNIDADE	PORÇÃO	
Arroz branco cozido com óleo e temperos	N 1 2 3 4 5 6 7 8 9 10	D S M A	2 colheres de sopa cheias (82g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	4 colheres de sopa cheias (124g)	☐ M
			8 colheres de sopa cheias (248g)	☐ G
Arroz integral cozido com óleo e temperos	N 1 2 3 4 5 6 7 8 9 10	D S M A	3 colheres de sopa cheias (90g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	5 colheres de sopa cheias (150g)	☐ M
			10 colheres de sopa cheias (300g)	☐ G
Batata, mandioca, inhame (cozida ou assada), purê	N 1 2 3 4 5 6 7 8 9 10	D S M A	1/2 unidade ou 1 colher sopa de purê (45g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 unidade ou 2 colheres sopa de purê (90g)	☐ M
			2 unidades ou 4 colheres sopa purê (180g)	☐ G
Batata frita, mandioca ou polenta frita	N 1 2 3 4 5 6 7 8 9 10	D S M A	2 colheres de sopa cheias (50g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	4 colheres de sopa cheias (100g)	☐ M
			6 colheres de sopa cheias (150g)	☐ G
Farofa, farinha de mandioca, farinha de milho	N 1 2 3 4 5 6 7 8 9 10	D S M A	2 colheres de sobremesa cheias (20g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	4 colheres de sobremesa cheias (40g)	☐ M
			6 colheres de sobremesa cheias (60g)	☐ G
Salada de maionese com legumes	N 1 2 3 4 5 6 7 8 9 10	D S M A	1 1/2 colheres de sopa (45g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	3 colheres de sopa (90g)	☐ M
			6 colheres de sopa (180g)	☐ G

LEGUMINOSAS E OVOS	QUANTAS VEZES VOCÊ COME	UNIDADE	PORÇÃO	
Feijão (carolina, roxo preto, verde)	N 1 2 3 4 5 6 7 8 9 10	D S M A	1/2 concha média (43g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 concha média (86g)	☐ M
			2 conchas médias (172g)	☐ G
Lentilha, ervilha seca, grão de bico	N 1 2 3 4 5 6 7 8 9 10	D S M A	1 1/2 colheres de sopa rasas (34g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	2 1/2 colheres de sopa rasas (40g)	☐ M
			5 colheres de sopa rasas (80g)	☐ G
Feijoada, feijão tropeiro	N 1 2 3 4 5 6 7 8 9 10	D S M A	1/2 concha cheia (100g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 concha cheia (200g)	☐ M
			2 conchas cheias (400g)	☐ G
Ovo Cozido	N 1 2 3 4 5 6 7 8 9 10	D S M A	1/2 unidade (25g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 unidade (50g)	☐ M
			2 unidades (100g)	☐ G
Ovo Frito ou Omelete	N 1 2 3 4 5 6 7 8 9 10	D S M A	1/2 unidade (25g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 unidade (50g)	☐ M
			2 unidades (100g)	☐ G

CARNES E PEIXES	QUANTAS VEZES VOCÊ COME	UNIDADE	PORÇÃO	
Carne assada / cozida ensopada	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 bife médio (50g) 1 bife médio (100g) 2 bifos médios (200g)	☐ P ☐ M ☐ G
Carne Frita	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 bife médio (50g) 1 bife médio (100g) 2 bifos médios (200g)	☐ P ☐ M ☐ G
Carne com Legumes	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1 1/2 colheres de arroz chelao (105g) 3 colheres de arroz chelao (210g) 4 colheres de arroz chelao (280g)	☐ P ☐ M ☐ G
Carne seca, carne de sol	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1 pedaço pequeno (20g) 2 pedaços pequenos (40g) 4 pedaços pequenos (80g)	☐ P ☐ M ☐ G
Bacon	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1 fatia média (15g) 2 fatias médias (30g) 4 fatias médias (60g)	☐ P ☐ M ☐ G
Carne de porco (ombo, bisteca)	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 fatia média ou 1/2 bisteca (50g) 1 fatia média ou 1 bisteca (100g) 2 fatias médias ou 2 bistecas (200g)	☐ P ☐ M ☐ G
Linguiça	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 gomo (30g) 1 gomo (60g) 2 gomos (120g)	☐ P ☐ M ☐ G
Salicha	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 unidade (25g) 1 unidade (50g) 2 unidades (100g)	☐ P ☐ M ☐ G
Frango assado / cozido ensopado	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 sobrecoxa ou 1 coxa pequena (33g) 1 sobrecoxa ou 2 coxas pequenas (66g) 2 sobrecoxas ou 4 coxas pequenas (130g)	☐ P ☐ M ☐ G
Frango Frito	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 filé grande (55g) 1 filé grande (110g) 2 filés grandes (220g)	☐ P ☐ M ☐ G
Míldos (Boi ou Frango)	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 bife de fígado (50g) ou 1/2 colher de servir corações (10g) 1 bife de fígado (100g) ou 1 colher de servir corações (35g) 2 bifos de fígado (200g) ou 2 colheres de servir corações (70g)	☐ P ☐ M ☐ G
Peixe assado / cozido ensopado	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	< 1/2 filé pequeno (<50g) 1/2 filé pequeno (50g) 1 filé pequeno (100g)	☐ P ☐ M ☐ G
Peixe Frito	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 filé pequeno (50g) 1 filé pequeno (100g) 2 filés pequenos (200g)	☐ P ☐ M ☐ G
Embutidos (presunto, mortadela, salame)	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1 fatia média (15g) 2 fatias médias (30g) 3 fatias médias (45g)	☐ P ☐ M ☐ G
Nuggats e almôndega	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1 unidade (26g) 2 unidades (52g) 3 unidades (78g)	☐ P ☐ M ☐ G

SOPAS E MASSAS	QUANTAS VEZES VOCÊ COME	UNIDADE	PORÇÃO	
Sopas Creme	N 1 2 3 4 5 6 7 8 9 10 O O O O O O O O O O	D S M A O O O O	1 concha chela (130g) 3 conchas chelas (390g) 5 conchas chelas (520g)	☐ P ☐ M ☐ G
Sopas de Legumes, Canja	N 1 2 3 4 5 6 7 8 9 10 O O O O O O O O O O	D S M A O O O O	1/2 concha chela (65g) 1 concha chela (130g) 2 conchas chelas (260g)	☐ P ☐ M ☐ G
Macarrão com molho sem carne	N 1 2 3 4 5 6 7 8 9 10 O O O O O O O O O O	D S M A O O O O	1/2 prato raso (100g) 1 prato raso (200g) 2 pratos rasos (400g)	☐ P ☐ M ☐ G
Macarrão com molho com carne, nhoque	N 1 2 3 4 5 6 7 8 9 10 O O O O O O O O O O	D S M A O O O O	1/2 escumadeira (47g) 1 escumadeira (93g) 2 escumadeiras (186g)	☐ P ☐ M ☐ G
Lasanha, Canelone	N 1 2 3 4 5 6 7 8 9 10 O O O O O O O O O O	D S M A O O O O	1/2 pedaço peq., 1 panqueca ou 1 1/2 canelones (85g) 1 pedaço peq., 1 1/2 panquecas ou 3 canelones (130g) 2 pedaços peq., 3 panquecas ou 6 canelones (260g)	☐ P ☐ M ☐ G
Salgados fritos (pastel, cozinha, risólia, bolinho)	N 1 2 3 4 5 6 7 8 9 10 O O O O O O O O O O	D S M A O O O O	1 unidade (50g) 2 unidades (100g) 3 unidades (150g)	☐ P ☐ M ☐ G
Salgados assados (esfiha, bauruzinho, torta)	N 1 2 3 4 5 6 7 8 9 10 O O O O O O O O O O	D S M A O O O O	1 unidade de esfiha (80g) 2 unidades de esfiha (160g) 4 unidades de esfiha (320g)	☐ P ☐ M ☐ G
Pizza	N 1 2 3 4 5 6 7 8 9 10 O O O O O O O O O O	D S M A O O O O	1 fatia média (106g) 2 fatias médias (212g) 4 fatias médias (424g)	☐ P ☐ M ☐ G
VERDURAS E LEGUMES	QUANTAS VEZES VOCÊ COME	UNIDADE	PORÇÃO	
Alface	N 1 2 3 4 5 6 7 8 9 10 O O O O O O O O O O	D S M A O O O O	1 1/2 folhas médias (15g) 3 folhas médias (30g) 5 folhas médias (50g)	☐ P ☐ M ☐ G
Espinafre, Escarola	N 1 2 3 4 5 6 7 8 9 10 O O O O O O O O O O	D S M A O O O O	1 colher de sopa (25g) 1 1/2 colheres de sopa (37g) 3 colheres de sopa (74g)	☐ P ☐ M ☐ G
Agrão, Rúcula	N 1 2 3 4 5 6 7 8 9 10 O O O O O O O O O O	D S M A O O O O	1/2 prato de sobremesa (10g) 1 prato de sobremesa (20g) 1 1/2 pratos de sobremesa (30g)	☐ P ☐ M ☐ G
Couve	N 1 2 3 4 5 6 7 8 9 10 O O O O O O O O O O	D S M A O O O O	1 colher de sopa chela (20g) 2 colheres de sopa chelas (40g) 4 colheres de sopa chelas (80g)	☐ P ☐ M ☐ G
Rapinho	N 1 2 3 4 5 6 7 8 9 10 O O O O O O O O O O	D S M A O O O O	1 1/2 colheres de sopa (18g) 3 colheres de sopa (36g) 6 colheres de sopa (70g)	☐ P ☐ M ☐ G
Couve-Flor, Brócolis	N 1 2 3 4 5 6 7 8 9 10 O O O O O O O O O O	D S M A O O O O	1 1/2 colheres de sopa (15g) 3 colheres de sopa (30g) 6 colheres de sopa (60g)	☐ P ☐ M ☐ G
Tomate	N 1 2 3 4 5 6 7 8 9 10 O O O O O O O O O O	D S M A O O O O	1 1/2 fatias médias (23g) 3 fatias médias (46g) 6 fatias médias (90g)	☐ P ☐ M ☐ G

VERDURAS E LEGUMES	QUANTAS VEZES VOCÊ COME	UNIDADE	PORÇÃO	
Cenoura	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1 colher de sopa cheia (12g)	☐ P
			2 colheres de sopa cheias (24g)	☐ M
			4 colheres de sopa cheias (48g)	☐ G
Berinjela	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1 colher de sopa cheia (25g)	☐ P
			2 colheres de sopa cheias (50g)	☐ M
			4 colheres de sopa cheias (100g)	☐ G
Beterraba	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1 colher de sopa cheia (16g)	☐ P
			2 colheres de sopa cheias (32g)	☐ M
			4 colheres de sopa cheias (64g)	☐ G
Chuchu	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1 1/2 colheres de sopa cheias (30g)	☐ P
			3 colheres de sopa cheias (60g)	☐ M
			5 colheres de sopa cheias (100g)	☐ G
Abóbora	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1 1/2 colheres de sopa (30g)	☐ P
			2 1/2 colheres de sopa (50g)	☐ M
			4 colheres de sopa (100g)	☐ G
Pepino	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	3 fatias médias (10g)	☐ P
			6 fatias médias (20g)	☐ M
			9 fatias médias (30g)	☐ G
Abobrinha	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 colher de sopa rasa (10g)	☐ P
			1 colher de sopa rasa (20g)	☐ M
			2 colheres de sopa rasas (40g)	☐ G
Cebola	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1 fatia média (6g)	☐ P
			2 fatias médias (12g)	☐ M
			4 fatias médias (24g)	☐ G

MOLHOS E TEMPEROS	QUANTAS VEZES VOCÊ COME	UNIDADE	PORÇÃO	
Óleo ou azeite para tempero de salada	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 colher de sobremesa (2,5ml)	☐ P
			1 fio ou 1 colher de sobremesa (5ml)	☐ M
			2 fios ou 2 colheres de sobremesa (10ml)	☐ G
Maionese, molho para salada, patê	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 colher de sobremesa (2,5g)	☐ P
			1 colher de sobremesa (5g)	☐ M
			2 colheres de sobremesa (10g)	☐ G
Shoyu	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	2 colheres de chá (2ml)	☐ P
			4 colheres de chá (4ml)	☐ M
			8 colheres de chá (8ml)	☐ G
Molho Vinagrete	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1 1/2 colheres de sopa cheias (45g)	☐ P
			3 colheres de sopa cheias (90g)	☐ M
			6 colheres de sopa cheias (180g)	☐ G
Catchup, Mostarda	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/4 colher de sobremesa (6,3g)	☐ P
			1/2 colher de sobremesa (12,5g)	☐ M
			1 colher de sobremesa (25g)	☐ G
Sal para tempero de salada	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 pitada (0,2g)	☐ P
			1 pitada (0,4g)	☐ M
			2 pitadas (0,7g)	☐ G

FRUTAS	QUANTAS VEZES VOCÊ COME	UNIDADE	PORÇÃO	
Laranja e mexerica	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 unidade média (90g) 1 unidade média (180g) 2 unidades médias (360g)	☐ P ☐ M ☐ G
Banana	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 unidade média (43g) 1 unidade média (86g) 2 unidades médias (172g)	☐ P ☐ M ☐ G
Maçã e pêra	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 unidade média (80g) 1 unidade média (120g) 2 unidades médias (240g)	☐ P ☐ M ☐ G
Mamão	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/4 unidade ou 1 fatia de mamão (78g) 1/2 unidade ou 1 fatia de mamão (155g) 1 unidade ou 2 fatias de mamão (310g)	☐ P ☐ M ☐ G
Melão e melancia	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 fatia de melão ou melancia (peq) (50g) 1 fatia de melão ou melancia (peq) (100g) 2 fatias de melão ou melancia (peq) (200g)	☐ P ☐ M ☐ G
Abacaxi	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 fatia média (38g) 1 fatia média (75g) 2 fatias médias (150g)	☐ P ☐ M ☐ G
Manga	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 unidade (espada) (70g) 1 unidade (espada) (140g) 2 unidades (espada) (280g)	☐ P ☐ M ☐ G
Abacate	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1 colher de sopa cheia (45g) 2 colheres de sopa cheias (90g) 4 colheres de sopa cheias (180g)	☐ P ☐ M ☐ G
Golaba (na época)	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 unidade média (85g) 1 unidade média (170g) 2 unidades médias (340g)	☐ P ☐ M ☐ G
Caqui (na época)	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 unidade média (55g) 1 unidade média (110g) 2 unidades médias (220g)	☐ P ☐ M ☐ G
Uva (na época)	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 cacho pequeno (85g) 1 cacho pequeno (170g) 2 cachos pequenos (340g)	☐ P ☐ M ☐ G

LANCHES, SNACKS	QUANTAS VEZES VOCÊ COME	UNIDADE	PORÇÃO	
Hot Dog, Sanduíche Hambúrguer	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1 unidade (125g) 2 unidades (250g) 3 unidades (375g)	☐ P ☐ M ☐ G
Salgadinho (Cheiros, Doritos, Torcida)	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 pacote (20 g) 1 pacote (40g) 1 1/2 pacotes (60g)	☐ P ☐ M ☐ G
Pipoca	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1 saco pequeno (15g) 2 sacos pequenos (30g) 3 sacos pequenos (45g)	☐ P ☐ M ☐ G
Amendoim, Castanha Peri, Nozes	N 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	D S M A ☐ ☐ ☐ ☐	1/2 colher de sopa (11g) 1 colher de sopa de amendoim (18g) 2 colheres de sopa de amendoim (37g)	☐ P ☐ M ☐ G

BEBIDAS	QUANTAS VEZES VOCÊ COME	UNIDADE	PORÇÃO	
Suco Industrializado () com açúcar () sem açúcar	N 1 2 3 4 5 6 7 8 9 10	D S M A	1/2 copo de requeijão (120ml)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 copo de requeijão (240ml)	☐ M
			2 copos de requeijão (480ml)	☐ G
Suco Natural () com açúcar () sem açúcar	N 1 2 3 4 5 6 7 8 9 10	D S M A	1/2 copo de requeijão (120ml)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 copo de requeijão (240ml)	☐ M
			2 copos de requeijão (480ml)	☐ G
Refrigerante () comum () diet/light	N 1 2 3 4 5 6 7 8 9 10	D S M A	1/2 copo de requeijão (120ml)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 copo de requeijão (240ml)	☐ M
			2 copos de requeijão (480ml)	☐ G
Bebida a base de soja	N 1 2 3 4 5 6 7 8 9 10	D S M A	1 dedo de copo de requeijão (35ml)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	2 dedos de copo de requeijão (70ml)	☐ M
			1/2 copo de requeijão (120ml)	☐ G
Cerveja	N 1 2 3 4 5 6 7 8 9 10	D S M A	1 lata (350ml)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	2 latas (700ml)	☐ M
			4 latas (1400ml)	☐ G
Vinho	N 1 2 3 4 5 6 7 8 9 10	D S M A	1/2 taça	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 taça	☐ M
			2 taças	☐ G
Calpirinha, destilados	N 1 2 3 4 5 6 7 8 9 10	D S M A	2 dedos de copo de requeijão (70ml)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1/2 copo de requeijão (120ml)	☐ M
			1 copo de requeijão (240ml)	☐ G

DOCES E SOBREMESAS	QUANTAS VEZES VOCÊ COME	UNIDADE	PORÇÃO	
Bala e Pirulito	N 1 2 3 4 5 6 7 8 9 10	D S M A	1 bala ou 1/2 pirulito (5g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	2 balas ou 1 pirulito (10g)	☐ M
			4 balas ou 2 pirulito (20g)	☐ G
Chantilly, Leite de Coco, Leite Condensado	N 1 2 3 4 5 6 7 8 9 10	D S M A	1 colher de sopa (15g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	3 colheres de sopa (45g)	☐ M
			5 colheres de sopa (75g)	☐ G
Chocolata, bombom	N 1 2 3 4 5 6 7 8 9 10	D S M A	1 bombom ou 1/2 unidade pequena (16g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 1/2 bombons ou 1 unidade pequena (32g)	☐ M
			3 bombons ou 2 unidades pequenas (64g)	☐ G
Doce de Frutas	N 1 2 3 4 5 6 7 8 9 10	D S M A	1/2 colher de sopa chela (22g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	1 colher de sopa chela (44g)	☐ M
			2 colheres de sopa chelas (88g)	☐ G
Gelatina	N 1 2 3 4 5 6 7 8 9 10	D S M A	2 colheres de sopa chelas (50g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	3 colheres de sopa chelas (75g)	☐ M
			6 colheres de sopa chelas (150g)	☐ G
Doces de confeitaria (tortas, pudins, mousses)	N 1 2 3 4 5 6 7 8 9 10	D S M A	2 colheres de sopa chelas de mousse ou 1/2 fatia de torta (50g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	4 colheres de sopa chelas de mousse ou 1 fatia de torta (100g)	☐ M
			8 colheres de sopa chelas de mousse ou 2 fatias de torta (200g)	☐ G
Sorvete	N 1 2 3 4 5 6 7 8 9 10	D S M A	1 1/2 colheres de sopa chelas (75g)	☐ P
	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐	3 colheres de sopa chelas (150g)	☐ M
			6 colheres de sopa chelas (300g)	☐ G

Quando você come carne bovina ou suína, você costuma comer a gordura visível?				
(1) Nunca Ou Raramente	(2) Algumas Vezez	(3) Sempre	(9) Não Sabe	__
Quando Você Come Frango Ou Peru, Você Costuma Comer A Pele?				
(1) Nunca Ou Raramente	(2) Algumas Vezez	(3) Sempre	(9) Não Sabe	__

Por favor, liste qualquer outro alimento ou preparação importante que você costuma comer ou beber PELO MENOS UMA VEZ POR SEMANA que não foram citados aqui.

ALIMENTO	FREQUÊNCIA POR SEMANA	QUANTIDADE CONSUMIDA

ANEXO 3 - QUESTIONÁRIO DE IDENTIFICAÇÃO PESSOAL E
SOCIODEMOGRÁFICO

1. Identificação do sujeito da pesquisa

1.1. Número de identificação ACCCC |__||__||__||__||

1.2. Nome completo:.....

1.3. Local da entrevista: |__||__|

(1) AC Camargo (2) Pará (3) Ceará (4) Outro

Data da entrevista: |__||__||__||__||__||

1.4. Endereço pessoal: Rua: No.....Apto.....

Complemento:..... Cidade: CEP.....Estado:

1.5 Telefone fixo: Código de Área:.....

Telefone celular:.....

Outros telefones (qq. membro da família):.....

E-mail:.....@.....

1.7. Nome do chefe da família:.....

1.7. 1Endereço 2 (parente ou amigo):.....

Cidade: Estado: Cidade ou fazenda:.....

Rua: No: CEP:.....

Telefone fixo: Código de área:.....

Telefonecelular:.....

[Note: Em qualquer lugar do questionário, use 9 ou 99 ou 999 ou 9999 quando um campo não for preenchido. No final da entrevista, certifique que não há campo em branco]

9. Sexo: (1) M (2) F |__|

1.10. Data de nascimento |__||__||__||__||__||

1.11. Raça -auto-atribuída |__|

(1) Caucasiano (2) Negro (3) Pardo (4) Japonês (5) Outras

1.12. Estado civil: |__|

(1) Solteiro (2) Casado/ (“Morando junto”) (3) Viúvo (4) Divorciado/separado (5) Outros

1.13. Grau de instrução: |__|

(1) Analfabeto (2) Menor do que 5 anos (3) 6 a 8 anos (4) 9 a12 anos

(5) Ensino Médio (6) Graduação (7) Pós-graduação

ANEXO 4 – Aprovação do projeto de Doutorado pelo Comitê de Ética em Pesquisa do A.C.
Camargo Cancer Center – SP



COMITÊ DE ÉTICA
EM PESQUISA - CEP

São Paulo, 22 de julho de 2020.

À

Dra. Maria Paula Curado

Aluna: Marcela de Araújo Fagundes (Doutorado)

Ref.: Projeto de Pesquisa nº. 2169/16J

**"ESTILO DE VIDA E BIOMARCADORES ASSOCIADOS À SOBREVIVÊNCIA DE
PACIENTES COM ADENOCARCINOMA GÁSTRICO: UM ESTUDO
PROSPECTIVO EM BELÉM, PARÁ, NORTE DO BRASIL. "**

Os membros do Comitê de Ética em Pesquisa da Fundação Antonio Prudente – A.C. Camargo Cancer Center, em sua última reunião de **14/07/2020**, **analisaram e aprovaram** o seguinte documento:

- Solicitação de dispensa da submissão da documentação obrigatória e análise ética do projeto acima mencionado por se tratar de um projeto afiliado ao temático “Epidemiologia dos Adenocarcinomas Gástricos no Brasil”, registrado neste CEP sob nº. 2169/16 O projeto afiliado em referência será Doutorado da aluna Marcela de Araújo Fagundes.

Atenciosamente,

Luciana Facure Moredo

1ª. Vice-Coordenadora do Comitê de Ética em Pesquisa

APÊNDICES

APÊNDICE 1 – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO (TCLE)

RESOLUÇÃO 466/12 CNS/MS

I - DADOS DE IDENTIFICAÇÃO DO PARTICIPANTE DA PESQUISA OU RESPONSÁVEL LEGAL

1. NOME DO PARTICIPANTE:

.....
DOCUMENTO DE IDENTIDADE Nº: SEXO : M F
DATA NASCIMENTO:/...../.....
ENDEREÇO: Nº
..... APTO:
BAIRRO: CIDADE:
CEP: TELEFONE: DDD (.....).....

2. RESPONSÁVEL LEGAL:

.....
NATUREZA (grau de parentesco, tutor, curador etc.):
.....
DOCUMENTO DE IDENTIDADE Nº: SEXO : M F
DATA NASCIMENTO:/...../.....
ENDEREÇO: Nº
..... APTO:
BAIRRO: CIDADE:
CEP: TELEFONE: DDD (.....).....

II-DADOS SOBRE A PESQUISA CIENTÍFICA

1. TÍTULO DO PROTOCOLO DE PESQUISA:

EPIDEMIOLOGIA DOS ADENOCARCINOMAS GÁSTRICOS EM 3 CAPITAIS
BRASILEIRAS

2. PESQUISADOR RESPONSÁVEL:

MARIA PAULA CURADO

3. PESQUISADORES ENVOLVIDOS:

- **Maria Paula Curado – Departamento de Epidemiologia do A.C. Camargo Cancer Center**
- **Marcela de Araújo Fagundes – Pós-graduação (doutorado) do A.C. Camargo Cancer Center**

4. DURAÇÃO DA PESQUISA:

60 meses

III - INFORMAÇÕES A (O) PARTICIPANTE

O (A) senhor (a) está sendo convidado (a) a participar do projeto de pesquisa (“Epidemiologia dos Adenocarcinomas Gástricos no Brasil”), que no estado do Pará, será realizada nos hospitais João de Barros Barreto (HUJBB) e Ophir Loyola (HOL).

O participante será abordado no Departamento de Cirurgia Abdominal e nas enfermarias do HUJBB e HOL.

IV – OBJETIVOS DA PESQUISA

Analisar o estilo de vida e biomarcadores associados à sobrevida de pacientes com adenocarcinoma gástrico em Belém-Pará, Norte do Brasil.

V- JUSTIFICATIVA PARA A PROPOSTA DA PESQUISA

Apesar de sua patogenia bem determinada, o conhecimento atual dos mecanismos moleculares que promovem sua gênese e evolução do câncer gástrico não foi traduzido em um impacto significativo no tratamento ou diagnóstico personalizado e novas modalidades de tratamento ainda não conseguiram alterar o curso natural da doença. Este projeto visa aumentar de modo significativo o conhecimento clínico acerca desta patologia no Brasil, investigando os fatores de risco epidemiológicos e prognósticos em estados brasileiros, como o Pará, em um estudo multicêntrico.

VI – DESENHO DA PESQUISA

Trata-se de uma coorte prospectiva observacional de base hospitalar. A amostra será composta de pacientes com diagnóstico de adenocarcinoma gástrico que tenham idade entre 18 e 75 anos. A coleta será realizada por seis meses, sendo os pacientes incluídos na pesquisa acompanhados por três anos através de dados em prontuários, de registros hospitalares ou por ligação telefônica.

VII – DESCRIÇÃO DOS PROCEDIMENTOS

Se você concordar em participar deste estudo, será solicitado que você participe de uma entrevista sobre o seu estilo de vida e hábitos alimentares. Além disso, nós pediremos sua permissão para coletar informações clínicas relevantes do seu prontuário médico (estadiamento clínico). Se você decidir não responder, seja a uma questão específica ou a todas as informações, não sofrerá nenhuma penalidade. A entrevista por meio dos questionários tem a duração de aproximadamente uma hora e consiste de questões relacionadas a estilo de vida e hábitos alimentares. Um entrevistador aplicará os questionários enquanto você estiver no hospital. Os resultados da pesquisa não são adequados para uso em testes clínicos, como parte de seu atendimento médico. Portanto, os resultados desses estudos não estarão disponíveis para você. Não haverá nenhum custo financeiro para você participar neste estudo. Não há nenhuma compensação ou pagamento pela participação nas entrevistas.

VIII - DESCONFORTOS E RISCOS ESPERADOS DECORRENTES DO PROCEDIMENTO

O(s) questionário(s) poderá (ão) causar um sentimento de desconforto ou ansiedade frente às perguntas realizadas. Os pesquisadores estarão disponíveis para conversar e prestar apoio se necessários, frente a estas situações.

IX - BENEFÍCIOS QUE PODERÃO SER OBTIDOS

Não haverá benefícios diretos para você que não a satisfação de participar desta pesquisa para o possível benefício das gerações futuras. Sua participação é muito importante para o sucesso desta pesquisa científica. Um dos benefícios para a sociedade é conhecimento do perfil, epidemiológico e clínico, dos pacientes com câncer gástrico da região norte, a fim de oferecer ao hospital e aos profissionais da saúde informações que possam subsidiar estratégias de prevenção e diagnóstico precoce, devido a peculiaridade da região.

X - CONFIDENCIALIDADE

A confidencialidade de suas informações será mantida e sua identidade será preservada, sendo que somente os membros da equipe médica e do Comitê de Ética em Pesquisa terão acesso aos registros. A sua participação neste estudo é voluntária, tendo o direito de retirar-se a qualquer momento. A recusa ou desistência da participação nesse estudo não irá prejudicar seu acompanhamento médico e tratamento.

XI - DANOS RELACIONADOS À PESQUISA

Qualquer dano resultante da sua participação no estudo será avaliado e tratado de acordo com os benefícios e cuidados a que você tem direito. Ao assinar este formulário de consentimento você não está abrindo mão de qualquer um dos seus direitos legais.

XII - ACOMPANHAMENTO, ASSISTÊNCIA E RESPONSÁVEIS

O pesquisador e a equipe envolvida na pesquisa se comprometem a dar informação atualizada ao longo do estudo, caso este seja o seu desejo. **TELEFONES PARA CONTATO EM CASO DE INTERCORRÊNCIAS CLÍNICAS, REAÇÕES ADVERSAS OU QUALQUER DÚVIDA SOBRE O ESTUDO:** (011) 2189-5000 – ramais: 2942 entrar em contato com Dra. Maria Paula Curado; (091) 984171112: entrar em contato com Dr. Paulo Assumpção.

XIII. OBSERVAÇÕES COMPLEMENTARES:

Esta pesquisa poderá ser interrompida durante a sua realização e após o aval do CEP da instituição, em casos onde: a) O pesquisador responsável decida que algum motivo ou situação possa pôr em risco a segurança do participante ou; b) O CEP julgue que o estudo esteja sendo conduzido de maneira eticamente inaceitável.

XIII. QUEM DEVO CONTATAR EM CASO DE DÚVIDAS:

Pesquisador Responsável: Dr(a). Maria Paula Curado
Departamento de Epidemiologia do A.C. Camargo Cancer Center - São Paulo.
Telefones para contato: (11) 2189-5000 ramais 2942 / 5178
Endereço: Rua Professor Antônio Prudente, 211 – Liberdade – São Paulo.

Pesquisadores Responsáveis em Belém: Dr. Paulo Assumpção
Núcleo de Pesquisas em Oncologia, ligado à Universidade Federal do Pará
Hospital Universitário João de Barros Barreto, Belém – PA
Telefone para contato: (91) 984171112
Dr. Rommel Burbano
Hospital Ophir Loyola, Belém - PA
Telefone para contato: (91) 988364667

Se o pesquisador responsável não fornecer as informações/ esclarecimentos suficientes, por favor, entre em contato com o Comitê de Ética em Pesquisa em Seres Humanos da Fundação Antônio Prudente – Hospital do Câncer - A.C. Camargo/SP pelo telefone (11) 2189-5000, ramal

5020 de segunda-feira à quinta-feira das 8 horas às 18 horas e sexta-feira das 8 horas às 17 horas.

Este documento será elaborado em 2 (duas) vias. O (a) senhor (a) receberá uma das vias originais e a outra será arquivada pelo pesquisador em seu arquivo de pesquisa.

Eu, _____ declaro ter lido, compreendido e discutido o conteúdo do presente Termo de Consentimento e **concordo em participar desse estudo de forma livre e esclarecida** autorizando os procedimentos acima relacionados:

Assinatura do participante ou responsável
legal

_____/_____/_____
Data

Assinatura do responsável pela pesquisa
(Dra. Maria Paula Curado)

_____/_____/_____
Data