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Corresponding author:
Ting-Yuan David Cheng

ting-yuan.cheng@osumc.edu

Author Affiliation:
The Ohio State University.

Body Size and Body Composition in Relation to the PI3K/AKT/MTOR Pathway Informing Cancer Risk and Outcomes: A Systematic Review

Akasheh, RT; Mahenge, CM; Kalam, F; Adib, A; Schulte S; Cheng, TYD.

ADMINISTRATIVE INFORMATION

Support - NIH/NCI R37CA248371.

Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202450036

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 May 2024 and was last updated on 08 May 2024.

INTRODUCTION

Review question / Objective The main objective is to systematically review the associations between body fatness and body composition with the PI3K/AKT/MTOR pathway in cancer populations and identify research gaps for future studies.
Research questions:
1) Do molecular markers of the PI3K/AKT/MTOR pathway in tumor, adipose, or muscle tissue correlate with body size and/or body composition?

2) What is the current evidence of how these molecular markers, together with body fatness and/or body composition, predict cancer risk and clinical outcomes (recurrence, metastasis, death)?

3) Which molecular markers directly or indirectly involved in the PI3K/AKT/MTOR pathway in tumor, adipose, or muscle tissue have been investigated in relation to body fatness and/or body composition in human populations with cancer or with high risk of cancer?

Rationale Overactivation of the mechanistic target of rapamycin (MTOR) pathway is associated with tumor growth, but the extent to which body size and fatness are associated with mTOR pathway activities in cancer is yet to be summarized. The MTOR pathway is activated by energy influx, amino acids, and insulin-like growth factors (IGFs), and activation of the pathway promotes several cancer hallmarks, such as cell proliferation and angiogenesis. The pathway activation entails a cascade of protein phosphorylation, a post-translational process. Phosphorylated MTOR and its upstream, including PI3K and AKT, and downstream proteins, such as P70S6 Kinase (P70S6K), are highly expressed in solid tumors related to obesity.
Obesity is often characterized by body size measured as body mass index (BMI), waist circumference, and other anthropometry measurements. Recent advancements utilize clinical images, including DXA, CT, and MRI scans for body composition measurements. The individual components of body composition, such

as visceral adipose tissue and skeletal muscle tissue, may be related to the MTOR pathway signaling. Muscle may be affected by up- or down-regulation of the MTOR pathway as the pathway is a key factor of muscle synthesis. The knowledge on the extent to which how energy imbalance variables, such as obesity or sarcopenic obesity, are associated with MTOR-related pathways in individuals with cancer has not been integrated. The integration of such knowledge by systematic review would advance our understanding of the mechanism of energy imbalance that affects cancer prognosis and shed light on the potential for promoting energy balance and MTOR inhibition as strategies to improve clinical outcomes.

Condition being studied Obesity (BMI>= 30) is a negative prognostic factor in cancer. On the other hand, low body weight (BMI <18.5) - also related to low muscle mass - is also associated with poor cancer prognosis and increased mortality. Body composition includes a wider spectrum of phenotypes, such as high adiposity with low muscle, i.e., sarcopenic obesity, high muscle with low adiposity, etc. Thus, measures of body composition may better predict disease prognosis.
Dysregulated cellular energetics is a hallmark of cancer. Pathways that control energy metabolism, cell growth, and proliferation are often altered in cancer favoring tumor survival and growth. The PI3K-AKT-MTOR signaling pathway is a key sensor of cellular energy status and a growth promoter. Upregulation in upstream or downstream components of the MTOR signaling pathway is common in many cancers, owing to germline or somatic mutations or due to post-transcriptional mechanisms entailing altered RNA and/or protein expression. Importantly, MTOR is upregulated in obesity but downregulated in cachectic muscle. Thus, understanding how these conditions relate to MTOR signaling in cancer and its outcomes may provide insights to support precision cancer treatment.

METHODS

Search strategy Pubmed search:
((body mass index[tw] OR waist circumference[tw] OR waist to hip ratio[tw] OR fat[tw] OR adipose[tw] OR adiposity[tw] OR weight[tw] OR obesity[tw] OR overweight[tw]) OR (body composition[tw] OR fatness[tw] OR bmi[tw] OR waist size[tw] OR waist hip ratio[tw] OR hip to waist ratio[tw] OR hip waist ratio[tw] OR waist hip ratio[tw] OR waist-hip ratio[tw] OR waist to height ratio[tw] OR waist height ratio[tw] OR waist-height ratio[tw] OR fat tissue[tw] OR fatty tissue[tw]) OR (fat mass[tw] OR body composition[tw] OR body fat[tw] OR body fat mass[tw] OR percentage fat[tw] OR intra-abdominal fat[tw] OR adipose tissue[tw] OR subcutaneous fat[tw] OR sarcopenia[tw] OR lean soft tissue[tw] OR lean body weight[tw] OR skeletal muscle[tw] OR lean mass[tw] OR fat free mass[tw] OR muscle mass[tw] OR dual energy X ray absorptiometry[tw] OR bioelectric impedance analysis[tw] OR air displacement plethysmography[tw] OR BodPod[tw]))

AND (mammalian target of rapamycin[tw] OR mtor kinase[tw] OR mtor protein[tw] OR mtor protein kinase[tw] OR mechanistic target of rapamycin[tw] OR protein kinase b[tw] OR akt kinase[tw] OR akt protein[tw] OR c akt protein[tw] OR proto oncogene protein c akt[tw] OR pi3k/akt/mtor pathway[tw] OR B Raf kinase[tw] OR initiation factor 4B[tw] OR initiation factor 4E[tw] OR initiation factor 4G[tw] OR insulin like growth factor[tw] OR target of rapamycin complex subunit LST8[tw] OR phosphoinositide dependent protein kinase 1[tw] OR prostaglandin F[tw] OR phosphatidylinositol 3 kinase[tw] OR phosphatidylinositol 3,4,5 trisphosphate 3 phosphatase[tw] OR rapamycin-insensitive companion of mTOR[tw] OR regulatory associated protein of mTOR[tw] OR protein kinase LKB1[tw] OR hamartin[tw] OR tuberin[tw] OR AKT1 OR AKT2 OR AKT3 OR BRAF OR CAB39 OR CAB39L OR DDIT4 OR EEF2K OR EIF4B OR EIF4E OR EIF4E1B OR EIF4E2 OR EIF4EBP1 OR EIF4G1 OR FIGF OR HIF1A OR IGF1 OR INS OR MAPK1 OR MAPK3 OR MLST8 OR MTOR OR PDPK1 OR PGF OR PIK3CA OR PIK3CB OR PIK3CD OR PIK3CG OR PIK3R1 OR PIK3R2 OR PIK3R3 OR PIK3R5 OR PPM1A OR PRKAA1 OR PRKAA2 OR PRKAB1 OR PRKAB2 OR PRKAG1 OR PRKAG2 OR PRKAG3 OR PTEN OR RHEB OR RICTOR OR RPS6 OR RPS6KA OR RPS6KA2 OR RPS6KA3 OR RPS6KA6 OR RPS6KB1 OR RPS6KB2 OR RPTOR OR STK11 OR STRADA OR STRADB OR TSC1 OR TSC2 OR ULK1 OR ULK2 OR ULK3 OR VEGFA OR VEGFB OR VEGFC)

AND (“cancer” OR "neoplasm" OR "neoplasia" OR "neoplasms" OR "neoplasms by histologic type" OR "neoplasms, cystic, mucinous, and serous" OR "neoplasms, embryonal and mixed" OR "neoplasms, germ cell and embryonal" OR "neoplasms, glandular and epithelial" OR "neoplasms, hormone-dependent" OR "neoplasms, post-traumatic" OR "neoplastic disease" OR "tumor" OR "tumour")

AND ((risk*[Title/Abstract] OR risk*[MeSH:noexp] OR (risk adjustment[MeSH:noexp] OR risk assessment[MeSH:noexp] OR risk factors[MeSH:noexp] OR risk

management[MeSH:noexp] OR risk taking[MeSH:noexp]) OR cohort studies[MeSH Terms] OR group[Text Word] OR groups[Text Word] OR grouped [Text Word]) OR (incidence[MeSH:noexp] OR mortality[MeSH Terms] OR follow up studies[MeSH:noexp] OR prognos*[Text Word] OR predict*[Text Word] OR course*[Text Word]))

AND (alladult[Filter] OR adult[Filter] OR middleagedaged[Filter] OR middleaged[Filter] OR aged[Filter] OR 80andover[Filter] OR youngadult[Filter]).

Participant or population Individuals with cancer, cancer survivors, individuals with pre-cancer lesions, high-risk populations, and populations with average risk for studying cancer risk.

Intervention Obesity, abdominal obesity, high body fatness, low muscle mass, high adipose tissue mass.

Comparator Normal weight, low body fatness, high muscle mass, low adipose tissue mass.

Study designs to be included RCT, single-arm trial, intervention study, cohort study, case-control study, cross-sectional study, case series.

Eligibility criteria Inclusion criteria are studies with PI3K/AKT/MTOR measurement (IHC, gene expression. methylation, and mutations) in tumors in cancer-related populations.
Exclusion criteria are studies with blood/serum/plasma markers only; germline SNPs only; not cancer-related populations; no BMI, weight, or body composition measurements; analyses that did not correlate BMI/body weight/body composition with MTOR markers or can't be assessed by manual calculation; or drug trials with the goal of weight reduction or change in metabolism. Non-English articles are also excluded.

Information sources Web of Science, Embase, Pubmed.

Main outcome(s) Mutations, gene and protein expression of PI3K-AKT-mTOR pathway components. cancer-specific survival, overall survival.

Data management We used Covidence – an online systematic review management application – to review abstracts, review full text articles, and extract data from full text articles.

Quality assessment / Risk of bias analysis During the full text data extraction phase, we used a set of 6 criteria to evaluate the quality of each study included in this review:
1. Representativeness of the participants
2. Ascertainment of exposure (body fatness and body composition)
3. Assessment of outcome (laboratory assay)
4. Temporality
5. Sample size
6. Quality of result reporting.

Strategy of data synthesis A Prisma flow diagram will be constructed for the number of articles excluded and included. Extracted data will be tabulated for key variables, including, author, year, population, exposure, laboratory assay, biomarker outcomes, and survival outcomes. Tables will be prepared according to cancer types. Evidence will be synthesized for the main proteins in the pathway as well as proteins in other pathways cross-talking with mTOR or influenced by mTOR. Meta-analyses will be considered if multiple studies reported a comparable body size/composition measurement in association with a tumor marker.

Subgroup analysis Subgroup analyses will be conducted for data involving patients with cancer cachexia and individuals with pre-cancerous lesions.

Sensitivity analysis Sensitivity analysis will be considered if a meta-analysis is performed for a specific biomarker and body size measurement.

Language restriction English.

Country(ies) involved United States (The Ohio State University).

Keywords PI3K/AKT/MTOR pathway, cancer, anthropometry, obesity, body composition, muscle.

Dissemination plans We will submit a manuscript to a peer-review journal for publication.

Contributions of each author
Author 1 - Rand Akasheh - Study design, search term construction, title and abstract screening, data extraction, manuscript drafting.
Email: rand.akasheh@osumc.edu
Author 2 - Mahenge Cuthbert - Study design, title and abstract screening, data extraction.
Email: cuthbert.mahenge@osumc.edu
Author 3 - Faiza Kalam - Title and abstract screening, data extraction, search term construction.

Email: faiza.kalam@osum.edu
Author 4 - Anita Adib - Article search, title and abstract screening.
Email: anita.adib@osumc.edu
Author 5 - Stephanie Schulte - Search criteria construction.
Email: stephanie.schulte@osumc.edu
Author 6 - Ting-Yuan David Cheng - Study design, title and abstract screening, data extraction, manuscript draft, funding.
Email: ting-yuan.cheng@osumc.edu