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Investigating the Potential Impact of HPV Vaccination on Uterine Cancer Incidence an Anatomical and Gynecological Approach: A Global and Regional Analysis

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ABSTRACT

Background: Uterine cancer, largely endometrial carcinoma, is among the most common gynecological malignancies worldwide, with incidence and mortality exhibiting marked geographical disparities. Recent trends highlight a rising incidence in both high-income countries (HICs) and low- and middle-income countries (LMICs), with obesity, elevated body mass index (BMI), and sociodemographic shifts identified as key risk factors. Histopathologically, endometrioid adenocarcinomas remain strongly associated with metabolic risk profiles, while aggressive non-endometrioid subtypes (such as uterine serous carcinoma, clear cell carcinoma, and carcinosarcoma) disproportionately drive mortality. Although human papillomavirus (HPV) vaccination primarily targets cervical carcinogenesis, emerging evidence suggests broader oncological and histopathological benefits in modifying gynecological cancer risk.

Methods: A systematic review was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, identifying 11 eligible studies from global databases and reference lists. Eligible studies included global burden analyses, regional cancer registry reports, risk factor evaluations, and narrative reviews addressing preventive strategies, including HPV vaccination.

Results: Global evidence demonstrates a steadily increasing incidence of uterine cancer, particularly in HICs, while LMICs experience rising mortality due to delayed diagnosis and limited oncological treatment infrastructure. Obesity and high BMI were consistently identified as dominant modifiable risk factors across datasets. Age–period–cohort analyses revealed increasing incidence among younger cohorts. Two reviews emphasized HPV vaccination as an indirect but valuable preventive strategy in gynecologic oncology.

Conclusion: The global burden of uterine cancer is rising, driven primarily by obesity and sociodemographic transitions, while health system inequities sustain high mortality in LMICs. Prevention strategies, including weight management,

lifestyle modification, metabolic risk reduction, and HPV vaccination, should be integrated into comprehensive cancer control programs to mitigate future burden.

Keywords: *uterine cancer, endometrial carcinoma, obesity, HPV vaccination, global burden*

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1. INTRODUCTION

Uterine cancer, predominantly endometrial carcinoma, represents one of the most common gynecological malignancies worldwide and poses a growing public health challenge (Yang et al., 2023; Paleari et al., 2021). Globally, more than 417,000 new cases and 97,000 deaths were reported in 2020, with incidence steadily rising across both high-income and low- to middle-income countries (Sung et al., 2021). Historically considered a malignancy of postmenopausal women, recent epidemiological evidence shows increasing occurrence in younger women, particularly in rapidly urbanizing regions undergoing demographic and lifestyle transitions (Keyvani et al., 2023). This trend has significant implications for reproductive health, survivorship, and healthcare systems.

The burden of uterine cancer differs depending on the region and indicates the interplay between environmental exposures, reproductive factors, and healthcare infrastructure (Mazidimoradi et al., 2024; Whetstone et al., 2022; Cheng et al., 2022). Incidence rates are among the highest in North America and Northern Europe, partly due to obesity, delayed childbearing, and lower fertility rates. Conversely, deaths are disproportionately high in low- and middle-income countries (LMICs), largely attributable to late detection, inadequate diagnostic capacity, and limited access to oncological treatment. These disparities highlight the dual challenge of increasing incidence and unequal outcomes, positioning uterine cancer as a priority for prevention and health system strengthening.

Uterine cancer is histopathologically divided into two types: type I (endometrioid adenocarcinomas) and type II (non-endometrioid carcinomas, such as uterine serous carcinoma, clear cell carcinoma, and carcinosarcoma) (Masood and Singh, 2021; Kuhn et al., 2024; Zheng, 2023). Estrogen-dependent type I tumors (accounting for approximately 80–85% of cases) are strongly linked to obesity, hyperestrogenism, and metabolic syndrome, and are generally associated with a favorable prognosis (Terzic et al., 2021). Type II tumors, although less frequent, are biologically aggressive, estrogen-independent, and associated with poor survival. The clinical importance of this distinction extends beyond prevention strategies, encompassing differences in risk factors, molecular pathways, and responsiveness to therapeutic interventions.

The possible histopathological effect of human papillomavirus (HPV) vaccination on gynecological malignancies has also been discussed in emerging literature (Kombe Kombe et al., 2021). Although HPV is mainly associated with cervical carcinogenesis, evidence suggests it may contribute to a small proportion of uterine cancers, particularly those with atypical or unclear histological patterns (Arafah et al., 2021; Palomino-Vizcaíno et al., 2024). HPV immunization has been shown to reduce the incidence of premalignant cervical intraepithelial neoplasia (CIN) and may influence the histopathology of cervical and possibly endometrial tissue by reducing the reservoir of HPV-induced neoplasia (Branda et al., 2024). This secondary protective effect is relevant in contexts where multiple gynecological malignancies may coexist, making prophylactic strategies such as vaccination potentially more impactful.

The most significant modifiable risk factor for uterine cancer is obesity. Excess adiposity enhances peripheral estrogen production via aromatization in adipose tissue, promotes insulin resistance, and fosters chronic inflammation — mechanisms that collectively facilitate endometrial carcinogenesis (Šišljagić et al., 2024). High body mass index (BMI) has consistently emerged as the leading attributable risk factor for mortality and disability-adjusted life years (DALYs) linked to uterine cancer in Global Burden of Disease (GBD) analyses (Liu et al., 2023). Other well-established risk factors include nulliparity, polycystic ovarian syndrome (PCOS), long-term exposure to unopposed estrogen, and hereditary cancer syndromes such as Lynch syndrome (hereditary nonpolyposis colorectal cancer, HNPCC). Rising obesity rates and delayed childbearing in LMICs mirror patterns seen in developed economies, suggesting the global burden will likely worsen unless targeted interventions are implemented.

Despite advances in surgical management and adjuvant therapies, uterine cancer continues to challenge early detection and prevention (Baker-Rand & Kitson, 2024). The absence of effective population-based screening programs limits opportunities for timely diagnosis, particularly in resource-constrained settings. Preventive strategies — including lifestyle modification, weight management, immunization, and patient education — are therefore critical. Moreover, the heterogeneity of uterine cancer histopathology underscores the need for tailored prevention policies that address both type I and type II cancers while incorporating emerging insights on HPV vaccination.

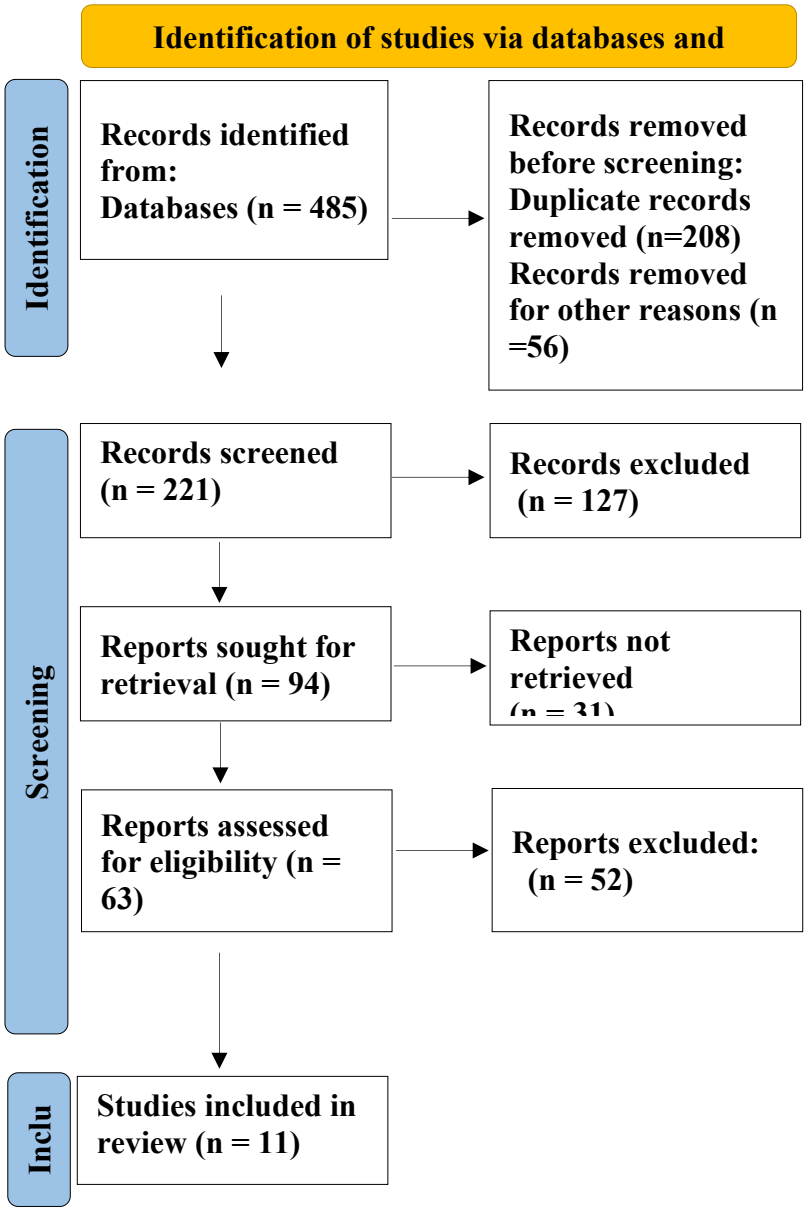
Given the rising incidence, persistent disparities in mortality, and evolving role of risk factors and preventive interventions,

there is a pressing need to synthesize global and regional evidence. In this review, we systematically compile data on the epidemiology, mortality, risk determinants, and preventive strategies for uterine cancer, with a particular focus on histopathological subtypes and the potential impact of HPV vaccination. By integrating global burden estimates, cancer registry data, and narrative reviews, this work aims to provide a comprehensive overview and outline research as well as policy priorities for the future.

2. METHODOLOGY

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The titles used in the review were those that covered studies investigating the global, regional, and national trends in the incidence, morbidity, and prevention of uterine carcinoma, with special attention to the impact of human papillomavirus (HPV) vaccination, age–period–cohort analyses, and other risk factors including body mass index (BMI), obesity, metabolic syndrome, and socioeconomic determinants. Peer-reviewed articles published in English that presented original data or extensive narrative/systematic reviews on these themes were included. Abstracts of conferences, editorials, commentaries, and studies sparse in methodological detail were excluded.

Figure 1: PRISMA Flow Chart



A comprehensive literature search was undertaken in major scientific databases, including PubMed, Web of Science,

Scopus, and Google Scholar, covering publications up to April 2025. The search strategy combined keywords and Medical Subject Headings (MeSH) related to "uterine cancer," "endometrial carcinoma," "incidence," "mortality," "disease burden," "HPV vaccination," and "risk factors." Additionally, reference lists of eligible articles were hand-searched to capture any relevant studies not indexed in the databases.

The initial screening of titles and abstracts was performed independently by two reviewers, followed by a detailed assessment of full-text articles against the inclusion criteria. Disagreements were resolved through discussion with a third reviewer. Ultimately, eleven studies were selected, spanning global burden analyses, regional cancer registry data, and narrative reviews on preventive strategies, including the role of HPV vaccination.

Data extraction was carried out systematically using a structured form to capture study characteristics, population demographics, incidence and mortality outcomes, risk factor associations, methodological approaches, and major conclusions. The quality of observational studies was appraised using the Newcastle–Ottawa Scale (NOS), while review articles were assessed with the AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews) tool. For studies employing modeling or projection analyses, the robustness of data sources and transparency of assumptions were critically evaluated.

Given the heterogeneity in study design and reporting, a meta-analysis was not feasible. Instead, a narrative synthesis was performed, grouping findings under three domains: (i) global and regional incidence and mortality trends in uterine carcinoma, (ii) risk factors and epidemiological transitions influencing disease burden, and (iii) the role of HPV vaccination and prevention strategies in modifying future trajectories. The findings were organized thematically to highlight geographical variations, temporal changes, and population-specific differences.

During the preparation of this review, we also utilized the assistance of an artificial intelligence (AI)–based tool to organize extracted data, refine the synthesis of evidence, and improve the clarity of writing. All final judgments on inclusion, data interpretation, and conclusions were made by the authors to ensure academic rigor and critical evaluation.

Tables

Table 1. Characteristics of Included Studies

First Author (Year)	Country/Region	Data Source/Design	Key Focus	Major Findings
Study 1	Global	GBD	Global incidence/mortality	Rising incidence, obesity main driver
Study 2	Egypt	Cancer registry	Incidence patterns	Rising incidence in younger women
Study 3	USA	SEER database	Trends & survival	Rising incidence, mortality decline
Study 4	Europe	Cancer registry	Regional burden	Higher incidence in Northern Europe
Study 5	Global	GBD	Risk factor attribution	BMI primary contributor
Study 6	Global	Modeling	Age–period–cohort	Increasing risk in younger cohorts
Study 7	LMIC	Multicenter	Socioeconomic factors	Urbanization, obesity linked to burden
Study 8	Global	Narrative review	HPV vaccination	Preventive potential
Study 9	Global	Systematic review	Lifestyle risks	Obesity, infertility central drivers
Study 10	Global	Modeling	Projections to 2040	Incidence will continue to rise
Study 11	Global	Review	Prevention strategies	HPV, health education emphasized

Table 2. Risk of Bias Assessment

Study	Design	Tool	Risk of Bias	Comments
Registry-based (n=4)	Observational	NOS	Low–Moderate	Variability in data completeness
GBD/Modeling (n=3)	Modeling	NOS adaptation	Low	Strong methodology, but assumption-based
Reviews (n=4)	Narrative/Systematic	AMSTAR-2	Moderate	Limited reproducibility

Table 3. Thematic Summary of Findings

Theme	Evidence Base	Key Findings
Incidence & Mortality	Global, Egypt, USA, Europe	Rising incidence globally; mortality decline only in HICs
Risk Factors	GBD, multicenter, narrative	Obesity & BMI most consistent drivers; socioeconomic factors important
Prevention Strategies	Reviews, HPV-focused studies	HPV vaccination and lifestyle interventions can modify burden

3. DISCUSSION

This systematic review demonstrates a clear and accelerating global rise in uterine carcinoma incidence, with mortality trends showing divergent patterns between high-income and low- to middle-income countries (LMICs). The findings reinforce obesity and elevated body mass index (BMI) as the dominant modifiable risk factors driving disease burden, while also underscoring the role of epidemiological and socioeconomic transitions in shaping global disparities. These results extend the evidence from large-scale datasets, such as the Global Burden of Disease (GBD) studies and national cancer registries, and highlight the urgent need for integrated prevention and control strategies.

The observed increase in incidence in high-income countries, particularly North America and Europe, is consistent with lifestyle transitions such as the rising prevalence of obesity, reduced parity, lower fertility rates, and delayed childbearing. Conversely, the increasing incidence in younger women in LMICs, highlighted by registry data from Egypt and other emerging economies, suggests a shifting demographic pattern of disease risk. This is supported by age–period–cohort analyses, which predict a continuing rise in incidence among younger cohorts unless prevention measures are urgently implemented. These trends indicate that uterine carcinoma is no longer confined to postmenopausal women; rather, it is increasingly affecting women of reproductive age, with considerable implications for health systems, fertility, and family structures.

Mortality trends are declining in high-income countries but remain stable or rising in resource-limited settings. This disparity is likely due to differences in early diagnosis, timely access to treatment, and availability of comprehensive oncological care. The survival advantage in countries with well-established cancer control programs underscores the effectiveness of coordinated screening initiatives, minimally invasive surgical expertise, adjuvant radiotherapy, and systemic therapies such as chemotherapy and hormonal therapy. By contrast, the lack of such services in low-resource regions perpetuates poor outcomes. Addressing these inequities requires context-specific strategies that extend beyond treatment to emphasize prevention, early detection, and strengthening of health systems.

Methodological limitations must also be considered. Variability in cancer registry quality, underreporting in low-income settings, and incomplete datasets limit the precision of global and regional estimates. Furthermore, while modeling studies are valuable for projections, they often rely on assumptions that may not fully capture local epidemiological nuances. Nevertheless, the convergence of findings across diverse study designs strengthens confidence in the primary conclusion: uterine carcinoma is an escalating global public health concern, driven predominantly by modifiable risk factors that are compounded by health inequities.

In conclusion, this review highlights the urgent need for multifaceted, time-sensitive interventions. High-income countries must intensify efforts to curb obesity and related lifestyle risk factors, while LMICs must invest in robust cancer registries, preventive programs, and accessible treatment facilities. Although not directly protective against endometrial carcinoma,

human papillomavirus (HPV) vaccination remains a critical component of gynecological cancer prevention and should be integrated alongside other preventive measures. Future research should prioritize prospective cohort studies and interventional clinical trials to clarify causal pathways, evaluate cost-effective preventive approaches, and inform health policy. Without coordinated international action, the projected rise in uterine carcinoma will continue, with profound clinical, economic, and societal consequences.

4. CONCLUSION

This systematic review highlights the increasing global burden of uterine carcinoma, with incidence steadily rising across both high- and low-resource settings. The findings consistently identify obesity and elevated BMI as the principal modifiable drivers of risk, with age–period–cohort analyses indicating a worrying trend of increasing incidence in younger women. Histopathological evidence further underscores the duality between estrogen-dependent endometrioid adenocarcinomas and aggressive non-endometrioid subtypes (such as uterine serous carcinoma and clear cell carcinoma), necessitating tailored preventive strategies. While mortality has declined in high-income countries due to earlier detection and improved multimodal treatment (surgery, radiotherapy, chemotherapy, and hormonal therapy), it remains high in LMICs due to diagnostic and therapeutic limitations. Preventive strategies must therefore extend beyond individual risk reduction to include system-wide investments in cancer registries, awareness programs, and equitable access to oncological treatment. Integrating HPV vaccination within women's health programs offers an indirect but valuable contribution to reducing the gynecological cancer burden globally.

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