The Association between Breast Cup Size and Breast Cancer Incidence: Insights from a Global Dataset

Mehdi Faraz (PhD)[1], Samaneh Nematollahi (PhD)[2], Sedigheh Tahmasebi (MD)[3], James S Welsh (MD, PhD)[4,5], Joseph John Bevelacqua (PhD)[6], Seyed Mohammad Javad Mortazavi (PhD)[7,8], Seyed Alireza Mortazavi (MD)[9]*

[1]Department of Computing, University of Turku, 20500, Turku, Finland
[2]Noncommunicable Diseases Research Center, Bam University of Medical Sciences, Bam, Iran
[3]Breast Cancer Research Center, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran
[4]Department of Radiation Oncology, Edward Hines Jr VA Hospital, Hines, IL, United States
[5]Department of Radiation Oncology, Loyola University Stritch School of Medicine, Chicago, United States
[6]Bevelacqua Resources, Richland, WA, United States
[7]Department of Medical Physics and Engineering, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[8]Ionizing and Non-Ionizing Radiation Protection Research Center (IINIRPRC), Shiraz University of Medical Sciences, Shiraz, Iran
[9]MVLS College, The University of Glasgow, Glasgow, Scotland, UK

ABSTRACT

The relationship between breast size and breast cancer risk is complex and not fully understood. This study investigates how breast size, categorized by cup size, correlates with age-standardized rates (ASR) of breast cancer incidence.

Data were collected from two sources: breast cancer incidence rates from the Global Cancer Observatory (GCO) and breast size data from "Data Pandas," an open-access database. This allowed for a cross-country analysis of breast cancer incidence and breast size characteristics. Descriptive statistics indicated that ASR increased with larger cup sizes, ranging from 34.72 (AA) to 90.17 (C). An ANOVA test revealed significant differences in mean ASR among cup size groups ($F=14.416$, $P<0.001$), with Bonferroni comparisons showing distinct clusters: smaller sizes (AA, AA-A, A) differed significantly from larger sizes (A-B, B, B-C, C).The largest mean ASR difference was between groups A and C (-42.93, $P=0.001$), highlighting higher ASR in larger cup sizes. This suggests a significant association between breast cup size and breast cancer ASR, potentially linked to physiological or hormonal factors.Despite limitations, these findings prompt further investigation. The next phase will focus on breast cancer patients, addressing relevant risk factors for a more comprehensive understanding of the associations observed.

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Keywords

Breast Cancer Risk; Breast Size; Machine Learning; Breast Neoplasms; Carcinoma, Ductal; Peto's Paradox; Physiological Predictors

Introduction

Globally, it is estimated that there were 19.3 million new cancer cases (18.1 million if nonmelanoma skin cancer is excluded) and nearly 10.0 million cancer-related deaths (9.9 million excluding nonmelanoma skin cancer) in 2020 [1]. Female breast cancer has overtaken lung cancer as the most frequently diagnosed cancer, with around 2.3 million new cases (11.7%), followed by lung cancer (11.4%), colorectal cancer (10.0%), prostate cancer (7.3%), and stomach cancer (5.6%) [1]. It is projected that the global number of new cancer cases will reach around 28.4 million by 2040, marking a 47% increase compared to 2020 numbers. This expected growth highlights the critical necessity for enhanced healthcare systems and preventive strategies, particularly in areas anticipated to experience the most significant rises in

*Corresponding author:
Seyed Alireza Mortazavi
MVLS College, The University of Glasgow, Glasgow, Scotland, UK
E-mail: 2921617m@student.gla.ac.uk

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incidence [2].

The high incidence and mortality rates underscore the critical importance of understanding its risk factors, as breast cancer not only impacts individual health but also poses significant challenges for public health systems globally. The rising incidence in low- and middle-income countries, where access to early detection and treatment may be limited, further emphasizes the need for targeted research and interventions [3]. Insights into novel risk factors, such as physiological characteristics, could pave the way for more personalized approaches to prevention and early diagnosis, thereby reducing the global burden of this disease.

The relationship between physiological characteristics and breast cancer risk has garnered significant interest in recent years, particularly in the context of complex biological paradoxes such as Peto's paradox. This paradox highlights the lack of a straightforward correlation between body size or lifespan and cancer incidence across species. Our previous work on Peto's paradox [4] has shaped our current investigation into the relationship between breast size and breast cancer risk. Peto's paradox, first articulated by Sir Richard Peto in the 1970s, challenges the intuitive expectation that larger animals, which have more cells and presumably a greater risk of mutations, would exhibit higher cancer rates. Instead, across species, cancer incidence does not correlate directly with body size or lifespan. This paradox has driven research into evolutionary adaptations [5-9], including genetic mechanisms that mitigate cancer risk in larger animals like elephants and whales, which possess multiple copies of tumor-suppressor genes such as TP53. We explored similar adaptive mechanisms in humans living in high background radiation areas, such as Ramsar, Iran [10-13]. Despite exposure to annual radiation doses exceeding occupational safety limits, residents exhibited no significant increase in cancer rates. This finding suggests potential evolutionary adaptations, such as enhanced DNA repair mechanisms, that reduce cancer risk despite high environmental stressors.

Building on these findings, we turned our attention to apparent paradoxes in human cancer risk related to physiological characteristics. While body size generally correlates with increased cancer risk due to a larger number of cells, our analysis of breast size and breast cancer risk reveals a more nuanced picture. Breast size is predominantly determined by adipose tissue, which does not directly influence the number of epithelial cells lining milk ducts—the primary origin of ductal carcinoma, the most common type of breast cancer. This complexity echoes Peto's paradox in its exploration of factors beyond simple cell count in cancer susceptibility. By applying statistical and machine learning methodologies, our current research seeks to untangle the interplay between breast size, physiological factors, and breast cancer risk, extending our exploration of Peto's paradox within the human context.

Breast cancer remains one of the most prevalent and impactful malignancies affecting women globally, making it critical to identify risk factors beyond genetic predisposition and lifestyle influences. While an increase in body size, such as height, correlates with a higher overall cancer risk due to a greater number of cells, this relationship is not linear when applied to breast cancer. Specifically, breast size is largely determined by adipose (fat) tissue, which does not directly contribute to cancer-prone epithelial cells lining milk ducts. These epithelial cells are the primary origin of ductal carcinoma, the most common type of breast cancer.

In 1996 Thurfjell et al. found a negative correlation between breast size and the risk of breast cancer, which vanished after accounting for parenchymal patterns, as smaller breasts were more likely to exhibit high-risk parenchymal patterns [14]. Moreover, a research by Tavani and colleagues indicated no significant association between breast size and breast

cancer risk after adjusting for known risk factors, suggesting that breast size alone may not be a reliable predictor of risk [15]. Jansen et al. in their systematic review reported that there is both direct and indirect evidence suggesting that breast size plays a significant role in the likelihood of developing breast cancer [16].

A prospective study by Kusano et al. in 2006 reported that larger bra cup size at a young age is associated with a higher incidence of premenopausal breast cancer, particularly among leaner women [17]. Goodwin and Boyd in 2006 reported that after accounting for methodological variations across the studies, a slight prognostic influence of body size was observed [18]. This influence seemed to be most significant in postmenopausal women, in individuals with minimal or no axillary node involvement, and appeared to be independent of other prognostic variables [18].

This study narrows its focus to examine whether breast size, in conjunction with other physiological and demographic factors, influences breast cancer risk. By utilizing advanced statistical and machine learning methodologies, including linear regression, decision trees, chi-square analysis, and ordinal logistic regression, the research aims to disentangle the potential links and provide a deeper understanding of these variables. Such insights could inform tailored risk assessment and preventive strategies in breast cancer care.

Material and Methods

Study Design and Data Sources

This study examined the relationship between breast size, categorized by cup size, and the age-standardized rate (ASR) of breast cancer incidence. Data were compiled from two primary sources. Breast cancer incidence rates were obtained from the Global Cancer Observatory (GCO), which provides standardized global cancer statistics, including ASR per 100,000 women. Breast size data were sourced from "Data Pandas," an open-access database ranking countries by average breast cup size. The combined dataset facilitated a cross-country analysis of breast cancer incidence and physiological characteristics.

Cup Size Categorization

Breast sizes were categorized into seven distinct groups: AA, AA-A, A, A-B, B, B-C, and C. Each group's ASR was analyzed for variations in breast cancer incidence. Descriptive statistics, including mean, standard deviation, minimum, and maximum values, were calculated for each group.

Statistical Analysis

The statistical analysis was conducted using the following methods:

1. Descriptive Statistics: Descriptive statistics were calculated to summarize ASR data for each cup size group. This included measures of central tendency (mean) and variability (standard deviation), as well as minimum and maximum ASR values to highlight distributional characteristics.

2. Analysis of Variance (ANOVA): A one-way ANOVA was performed to assess whether there were statistically significant differences in mean ASR among the seven cup size groups. The ANOVA tested the null hypothesis that the mean ASR was equal across all groups. A significance level of $P<0.05$ was used.

3. Post Hoc Pairwise Comparisons: Bonferroni correction was applied for multiple comparisons to identify specific differences between cup size groups. The method provided adjusted P-values to ensure the robustness of pairwise comparisons, reducing the risk of Type I errors.

4. Correlation Analysis: Pearson's correlation coefficient was calculated to evaluate the linear relationship between cup size and ASR. This complemented ANOVA results by quantifying the degree of linear association.

5. Software and Tools: All statistical analyses were performed using SPSS (Statistical

Package for the Social Sciences), version 27. Visualization of results, including bar charts and scatter plots, was created using Python (Matplotlib and Seaborn libraries).

Results

The statistical analysis conducted to explore the relationship between breast cup size and breast cancer incidence rates revealed significant and insightful findings. The study examined seven cup size groups (AA, AA-A, A, A-B, B, B-C, C), analyzing age-standardized rates (ASR) of breast cancer for each group. Descriptive statistics indicated that larger breast cup sizes were associated with higher mean ASR. The smallest cup size group (AA) had a mean ASR of 34.72, while the largest group (C) exhibited a mean ASR of 90.17. Standard deviations ranged from 12.96 (C) to 21.63 (A), reflecting varying levels of variability within groups. Minimum ASR values ranged from 12.12 (AA) to 71.06 (C), while maximum values spanned 78.74 (AA) to 105.42 (A-B). Figures 1-3 show the

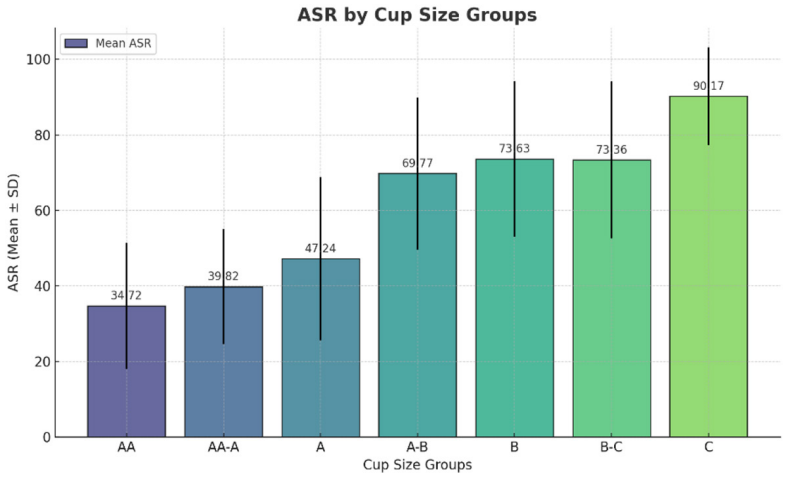

Figure 1: The mean ASR values for each cup size group with error bars representing the standard deviations. (ASR: Age-Standardized Rate)

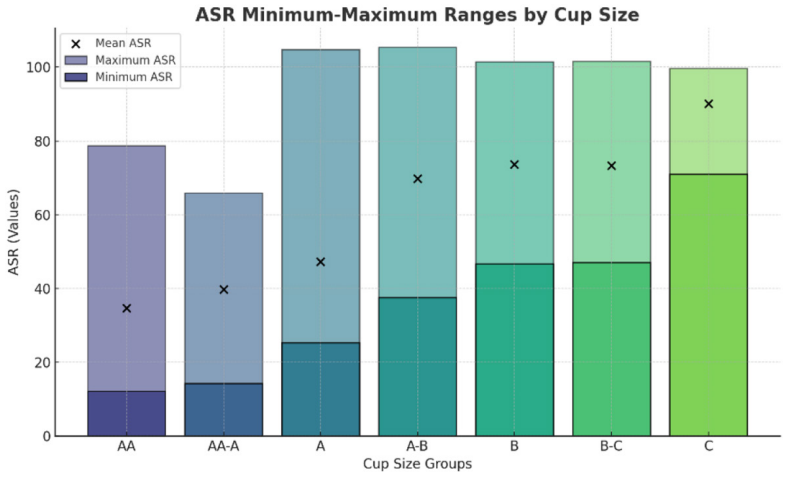

Figure 2: The range of ASR values for each cup size group, with bars representing minimum and maximum values. Black dots indicate the mean ASR for context. (ASR: Age-Standardized Rate)

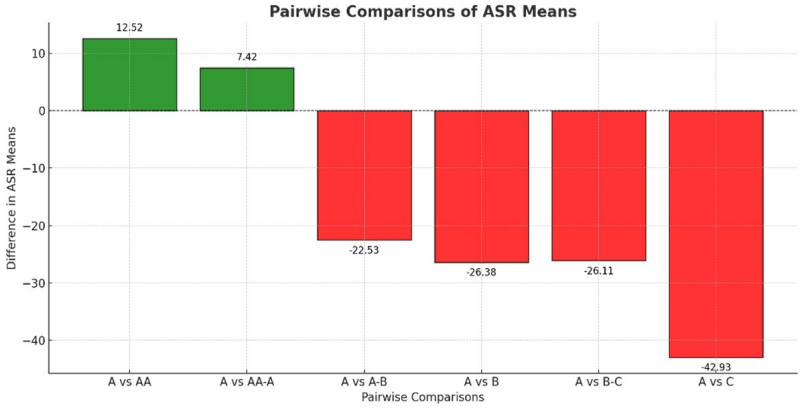

Figure 3: The differences in ASR means between specific cup size groups. Positive differences are marked in green, and negative differences are in red. (ASR: Age-Standardized Rate)

relationship between breast cup size and breast cancer incidence rates.

An Analysis of Variance (ANOVA) test was employed to examine differences in mean ASR across the cup size groups. The results showed a statistically significant difference between groups (F=14.416, P<0.001), indicating that breast cup size is associated with variations in breast cancer ASR. This finding prompted further pairwise comparisons using the Bonferroni correction method.

The pairwise comparisons revealed significant differences in mean ASR between smaller cup sizes (AA, AA-A, A) and larger cup sizes (A-B, B, B-C, C). Notably, group A differed significantly from group C, with a mean difference of -42.93 (P=0.001). Similar patterns were observed between other smaller and larger cup size groups, emphasizing a trend of increasing ASR with larger cup sizes. These results highlight distinct clustering of cup size groups based on their ASR, underscoring the potential influence of physiological factors related to breast size.

Overall, the analysis confirms a strong association between breast cup size and breast cancer incidence rates. Larger cup sizes are consistently linked to higher ASR, suggesting potential hormonal or other biological mechanisms at play. These findings underscore the need for further research to account for possible confounders, such as genetic or lifestyle factors, and to deepen our understanding of this complex relationship.

Discussion

The findings of this study provide compelling evidence of a significant association between breast cup size and age-standardized rates (ASR) of breast cancer incidence. The results indicate that larger cup sizes are linked to higher breast cancer ASR, emphasizing the potential role of physiological traits in influencing cancer risk. While these findings offer valuable insights, they also raise important questions and highlight the need for further research.

Physiological Implications

Breast size is predominantly determined by adipose tissue, which constitutes the majority of breast mass. Larger breast size is often associated with increased levels of estrogen exposure due to the hormone's storage and activity in fat cells. Estrogen is a well-established factor in breast cancer development, as it promotes the proliferation of breast epithelial cells, where most breast cancers originate. The observed trend of increasing ASR with larger cup sizes may partly reflect the hormonal and physiological dynamics linked to adipose tissue. However, it is essential to note that breast

adipose tissue itself is not directly cancerous, and the relationship may be mediated through systemic hormonal effects.

Potential Confounders

While the association between cup size and ASR is statistically significant, the results must be interpreted cautiously. This study did not account for several confounding factors that could influence breast cancer risk. For instance, genetic predispositions, such as BRCA1 and BRCA2 mutations, are critical determinants of breast cancer risk and may not correlate with breast size. Similarly, lifestyle factors, including diet, physical activity, alcohol consumption, and reproductive history (e.g., age at first childbirth and breastfeeding), can significantly impact breast cancer incidence. Future studies should aim to control for these variables to isolate the independent effect of breast size on cancer risk.

Comparisons with Existing Literature

The results of this study align with prior research suggesting a link between body size and breast cancer risk. However, most previous studies have focused on overall body mass index (BMI) rather than specific physiological traits like breast size. The current study's focus on cup size provides a more granular perspective, emphasizing the need to explore localized adipose tissue characteristics in breast cancer risk assessments. Additionally, the findings contribute to the growing body of literature exploring how physiological traits beyond genetic markers can influence cancer susceptibility.

Clinical and Public Health Implications

The observed association between breast size and breast cancer ASR has potential implications for personalized risk assessment and prevention strategies. Integrating physiological traits like breast size into existing risk models could enhance their predictive accuracy, particularly in populations where genetic testing is not readily available. Moreover, these findings underscore the importance of public health campaigns aimed at addressing modifiable risk factors such as obesity, which is closely linked to both larger breast size and increased breast cancer risk.

Strengths and Limitations of Our Study

A key strength of this study is its use of global datasets, enabling cross-country comparisons and generalizability of findings. The combination of cancer incidence data from the Global Cancer Observatory and physiological data from "Data Pandas" provides a unique platform to investigate breast cancer epidemiology. However, the study is not without limitations. The inability to adjust for confounding variables is a notable drawback, as is the reliance on aggregated country-level data rather than individual patient data. Furthermore, cup size measurements from the "Data Pandas" dataset may not fully capture individual variability or represent population subgroups.

Future Directions

The preliminary findings of this study have prompted the initiation of a second phase focused on breast cancer patients. This phase will employ a case-control design, incorporating individual-level data and addressing key confounders such as genetic predisposition, hormonal profiles, and lifestyle factors. Advanced statistical and machine learning methodologies will be utilized to model complex interactions and identify causal relationships. Additionally, the role of breast tissue composition, including the ratio of adipose to glandular tissue, warrants further exploration.

Conclusion

This study highlights a significant association between breast cup size and breast cancer incidence rates, contributing to the broader

understanding of how physiological traits influence cancer risk. While the findings are preliminary, they underscore the importance of incorporating diverse factors into breast cancer research and risk assessment frameworks. Future studies should aim to build on these results by addressing limitations and exploring underlying mechanisms, ultimately contributing to more effective and personalized strategies for breast cancer prevention and early detection.

Authors' Contribution

SMJ. Mortazavi and SAR. Mortazavi conceptualized the study, while S. Tahmasebi, JS. Welsh and JJ. Bevelacqua acted as senior consultants. M. Faraz and S. Nematollahi contributed to data analysis. SAR. Mortazavi prepared the initial manuscript draft, and all authors reviewed and approved the final version. M. Faraz and S. Nematollahi are co-first authors, having contributed equally to the work.

Ethical Approval

This study solely relies on globally gathered data.

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None

Conflict of Interest

SMJ. Mortazavi and JS. Welsh, as the Editorial Board Members, were not involved in the peer-review and decision-making processes for this manuscript.

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