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Role of EGFR in Breast Cancer Market

TechSci Research Analysts in Conversation with:

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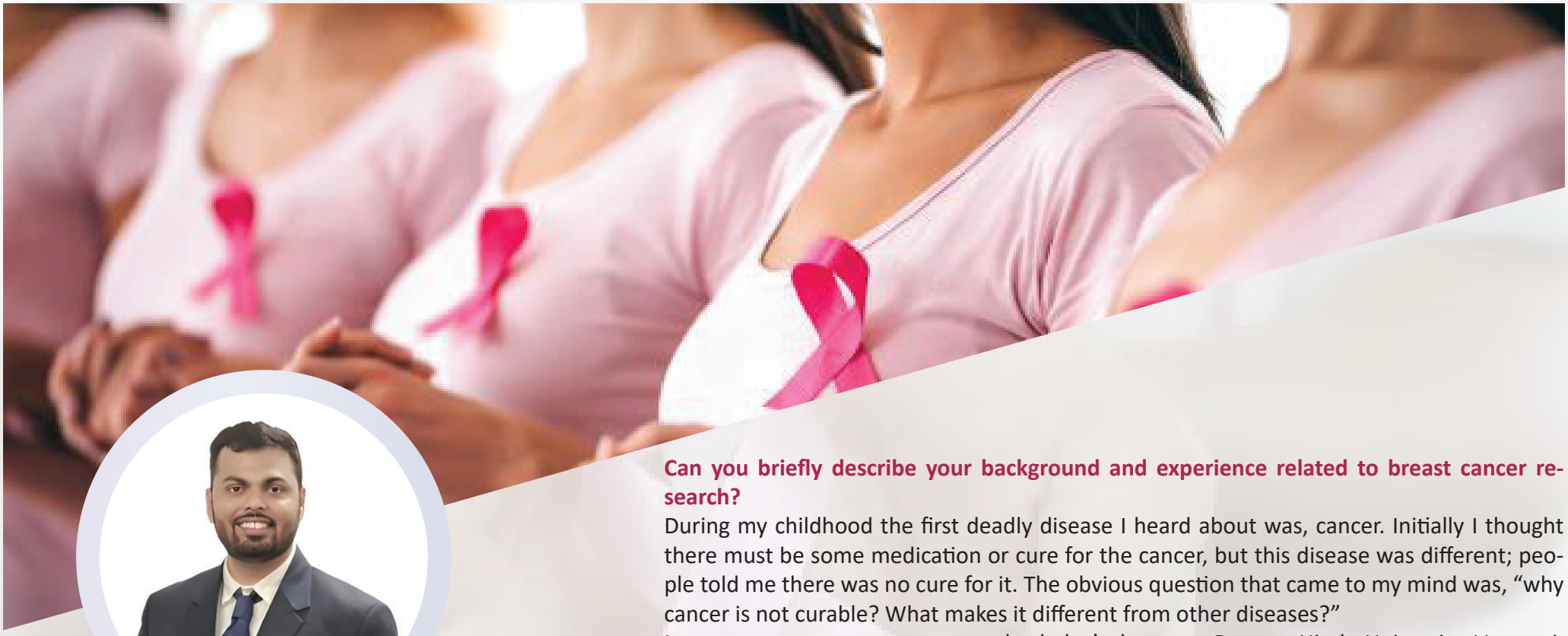
Post-Doc Affiliate at Roswell Park Comprehensive Cancer Center, Buffalo, NY



Satyam Singh, Ph.D.

Post-Doc Affiliate at Roswell Park Comprehensive Cancer Center, Buffalo, NY

Can you briefly describe your background and experience related to breast cancer research?

During my childhood the first deadly disease I heard about was, cancer. Initially I thought there must be some medication or cure for the cancer, but this disease was different; people told me there was no cure for it. The obvious question that came to my mind was, "why cancer is not curable? What makes it different from other diseases?"

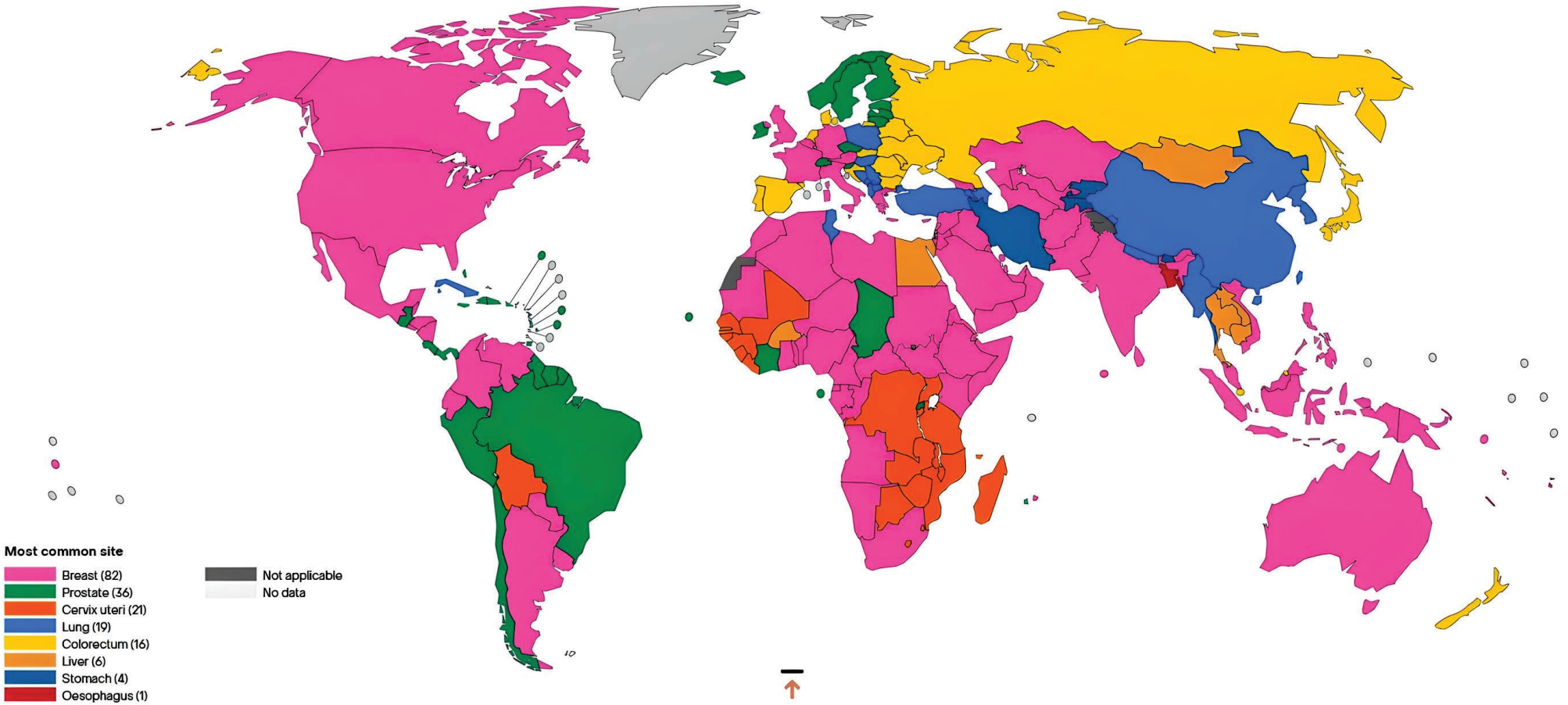
I went on to pursue to pursue my bachelor's degree at Banaras Hindu University, Varanasi. Where I studied and learned that cancer occurs due to mutations and aberrant activation of certain genes, as well as the overexpression or downregulation of specific proteins. Next, I pursued my master's degree at Madurai Kamaraj University, Madurai, where I completed my thesis on cancer metabolomics. Where I first time saw triple-negative breast cancer (TNBC) cell line (MDA-MB-231) under the microscope, which over-expresses Epidermal Growth Factor Receptor (EGFR), it sparked my curiosity to know more about it, and I embarked on a journey to pursue my PhD in Cancer drug discovery at Indian Institute of Technology Indore, India.

During my PhD, I gained knowledge about the detailed mechanism of breast, lung, glioblastoma and skin and cancer progression. I found that one of the main root cause for these cancer is EGFR protein. EGFR is very important for the growth of healthy cells, however upon aberrant activation of this protein, leads to the tumor development. In the breast cancer context, EGFR overexpressed in the TNBC, the most aggressive type of breast cancer.

Hence, targeting EGFR is one of the key strategy to combat the tumor development in EGFR-positive TNBC patient either by EGFR-tyrosine kinase inhibitors or monoclonal antibodies (mAbs). Currently, I am working as a Post-Doc scientist at Roswell Park Comprehensive Cancer Research Center, Buffalo, New York, USA. Here I am trying to understand the role of deubiquitinating enzyme on tumor microenvironment in cancer.

If you see the below attached figure obtained from the World Health Organization (WHO) database, most commonly diagnosed cancer across the globe is Breast cancer (82 countries), including our own country India. Which shows the severity of the Breast cancer in the world which requires immediate attention to completely eradicate this life-threatening disease.

Most common site per country, Absolute numbers, Incidence, Both sexes, în 2022 (excl. NMSC)



Cancer TODAY | IARC
https://gco.iarc.who.int/today
Data version: Globocan 2022 (version 1.1) - 08.02.2024

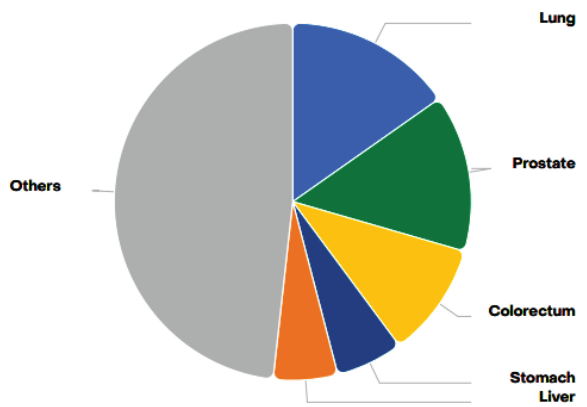
International Agency for Research on Cancer
World Health Organization

What initially drew your interest to the role of EGFR in breast cancer?

If we closely look the below attached data from global cancer observatory, in India, Breast cancer falls number 1 in top 5 most frequently diagnosed cancer in females, as well as if we combine both the sex (male and female).

Top 5 most frequent cancers

Males

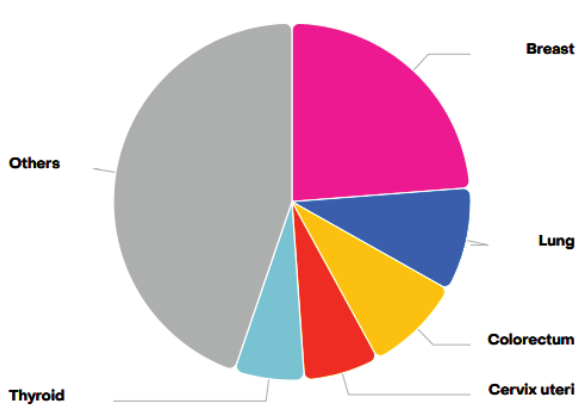


Total: 10 311 610

Rank	Cancer site	Number of cases	Percent
1st	Lung	1 572 045	15.2%
2nd	Prostate	1 467 854	14.2%
3rd	Colorectum	1 069 446	10.4%
4th	Stomach	627 458	6.1%
5th	Liver	600 676	5.8%
-	Others	4 974 131	48.2%

Number of new cases in 2022, males, all ages

Females

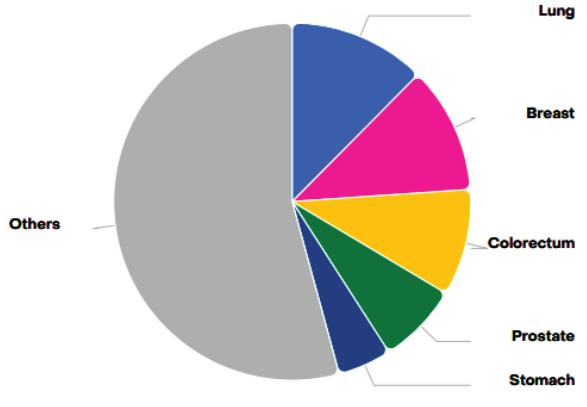


Total: 9 664 889

Rank	Cancer site	Number of cases	Percent
1st	Breast	2 296 840	23.8%
2nd	Lung	908 630	9.4%
3rd	Colorectum	856 979	8.9%
4th	Cervix uteri	662 301	6.9%
5th	Thyroid	614 729	6.4%
-	Others	4 325 410	44.8%

Number of new cases in 2022, females, all ages

Both sexes



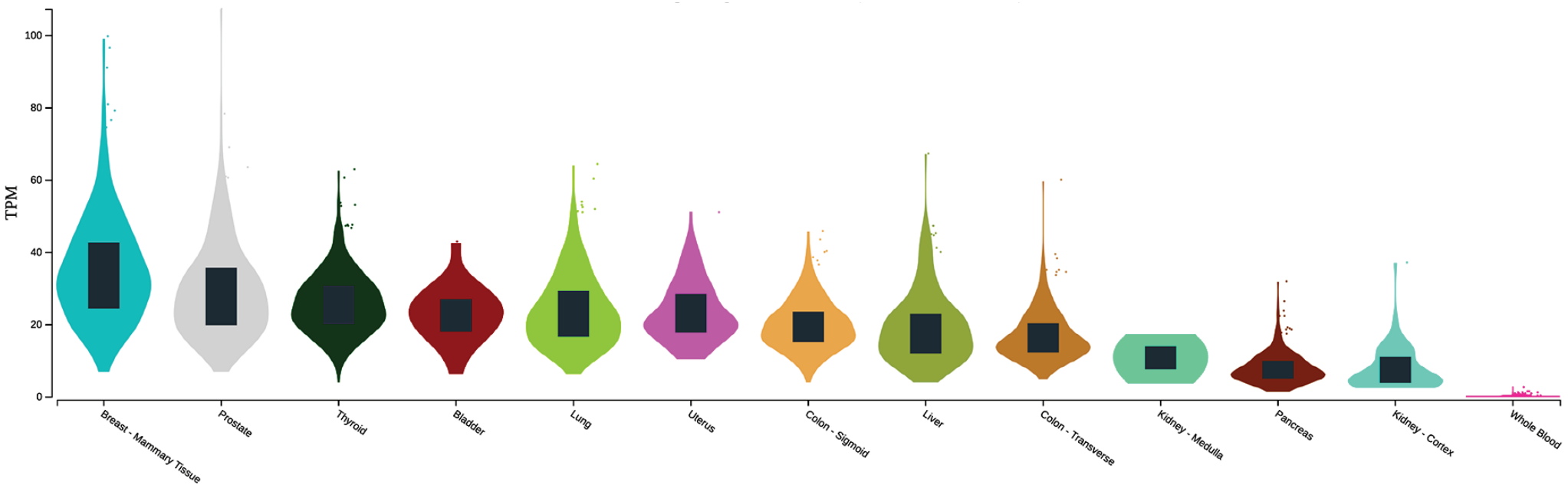
Total: 19 976 499

Rank	Cancer site	Number of cases	Percent
1st	Lung	2 480 675	12.4%
2nd	Breast	2 296 840	11.5%
3rd	Colorectum	1 926 425	9.6%
4th	Prostate	1 467 854	7.3%
5th	Stomach	968 784	4.8%
-	Others	10 835 921	54.2%

Number of new cases in 2022, both sexes, all ages

Next, I performed the GTEx (Genotype-Tissue Expression) analysis (see the figure below) and interestingly observed that EGFR expression is highest in breast cancer tissue compared to other commonly diagnosed cancers, including lung, prostate, liver, and pancreatic cancers, according to the National Cancer Institute (NCI) database. This finding also was one of the key reasons to draw my attention and led me to choose this topic for further study.

Bulk tissue gene expression for EGFR (ENSG00000146648.17)



How do you define the role of EGFR in breast cancer progression?

As I mentioned previously, EGFR is overexpressed in TNBC and inflammatory breast cancer (IBC) cases, which makes it a key target for the treatment EGFR-positive TNBC patients. In TNBC, at least 50% of cases show EGFR overexpression, a rate higher than other breast cancer subtypes.

It has been found that EGFR-targeted therapy could improve the TNBC cells' sensitivity to chemotherapy. Studies have also found that combining erlotinib (an EGFR inhibitor) and doxorubicin (a chemotherapy drug) in time dependent manner led to increased cell death by reducing oncogene activity.

Data obtained from the advanced computational modeling further revealed that this time dependent combination of drugs was most effective in killing aggressive TNBC cells.

For IBC, patients with EGFR-positive tumors have a lower 5-year survival rate and a higher risk of recurrence compared to those with EGFR-negative tumors. Given that traditional chemotherapy is insufficient for IBC treatment, there is a strong need for new therapeutic approaches.

What are the key molecular mechanisms through which EGFR influences breast cancer progression?

One of the most critical pathways activated by EGFR is the MAPK/ERK pathway, which promotes cell division and growth. This pathway drives the expression of genes involved in proliferation, contributing to tumorigenesis.

Additionally, the PI3K/AKT pathway, another major signaling cascade activated by EGFR, enhances cell survival by inhibiting pro-apoptotic factors.

In breast cancer, especially in aggressive subtypes, the activation of the PI3K/AKT pathway leads to resistance against programmed cell death (apoptosis), allowing cancer cells to persist even under treatment.

EGFR also activates the JAK/STAT pathway, particularly STAT3, which regulates genes involved in cell growth and differentiation.Persistent activation of this pathway is associated with more aggressive breast cancers like triple-negative breast cancer (TNBC).

Moreover, EGFR is a key player in promoting epithelial-mesenchymal transition (EMT), a process that transforms cancer cells into a more invasive and mobile form, facilitating metastasis.

What recent findings have emerged regarding EGFR's role in breast cancer that you find particularly significant?

Recent studies have shown that EGFR signaling can promote immune evasion in breast cancer by upregulating immune checkpoint molecules, allowing cancer cells to avoid the identification and killing by the immune system. Completely, understanding how cancer cells are escaping from the immune system plausibly can open the potential avenues for combining EGFR inhibitors with immunotherapy to enhance treatment efficacy.

Research also emphasizes the role of the tumor microenvironment in modulating EGFR signaling, with factors such as stromal cells, extracellular matrix components, and inflammatory cytokines influencing EGFR expression and activity. This interplay impacts the tumor progression and response to therapy, suggesting that targeting the tumor microenvironment alongside EGFR may enhance therapeutic outcomes. Emerging studies have also highlighted the effectiveness of combining EGFR inhibitors with other therapeutic agents, such as chemotherapy, targeted therapies, and immunotherapies.

For example, combining EGFR inhibitors with PARP inhibitors has already shown promise in preclinical model of TNBC, particularly those with BRCA mutations, potentially improving treatment responses and overcoming resistance. Furthermore, recent findings have focused on identifying biomarkers that can predict which breast cancer patients will benefit most from EGFR-targeted therapies. These biomarkers, including specific gene expression profiles and mutations that correlate with EGFR activity, can facilitate more personalized treatment strategies. Additionally, research has elucidated EGFR's role in promoting metastasis in breast cancer, as studies indicate that EGFR signaling can enhance the migratory and invasive capabilities of cancer cells through processes like epithelial-mesenchymal transition (EMT). Targeting EGFR may therefore not only impact tumor growth but also reduce metastatic spread.

Overall, these findings highlight the multifaceted role of EGFR in breast cancer, emphasizing the importance of ongoing research to develop more effective and personalized treatment strategies.

How do these new insights challenge or reinforce existing paradigms about breast cancer biology?

Traditionally, breast cancer research focused on distinct subtypes defined primarily by hormonal receptor status and HER2 expression. However, the recent findings regarding novel EGFR mutations (L858R, T790M, C797S, ex20ins), its role in immune evasion, and the influence of the tumor microenvironment suggest that breast cancer is not merely a collection of static entities but rather a dynamic interplay of molecular mechanisms that can evolve and adapt in response to therapies. This understanding reinforces the need for personalized treatment approaches tailored to individual genetic profiles and tumor characteristics, rather than a one-size-fits-all strategy.

Additionally, the recognition that EGFR signaling contributes to both tumor growth and metastatic potential complicates the existing models of cancer progression, emphasizing the necessity of targeting multiple pathways simultaneously. Overall, these insights underscore the importance of integrating molecular, immunological, and environmental factors into a more comprehensive framework for understanding breast cancer biology, paving the way for more effective therapeutic strategies.

Are there specific subtypes of breast cancer where EGFR plays a more critical role? If so, could you elaborate?

Breast cancer is divided into four main types based on certain characteristics of the cancer cells. These types are luminal A, luminal B, HER2-positive (human epidermal growth factor receptor 2), and TNBC. These categories play a very important role in clinical setting to help the doctors to decide the best treatment plan, as each type of breast cancer are different from each other in terms of protein and gene expression. Among these types, TNBC, which does not express estrogen receptor (ER), progesterone receptor (PR), and HER-2, but it overexpresses EGFR, is the most aggressive subtypes of breast cancer.

If we take a close look in the molecular subtyping of TNBC, Fudan University Shanghai Cancer Center (FUSCC) data revealed the genetic alterations driving each TNBC subtype through an integrative analysis. This approach combined somatic mutations, copy number aberrations (CNAs), and gene expression profiles, classifying TNBC patients into four subtypes: luminal androgen receptor (LAR), immunomodulatory (IM), basal-like immune-suppressed (BLIS), and mesenchymal-like (MES).

Accurately determining the molecular subtype of TNBC based on immunohistochemical staining in the clinic still remains unclear, especially given the limited number of TNBC clinical specimens, and current results are insufficient. As a result, further research is needed to identify specific biomarkers linked to TNBC subtypes and establish their clinical definitions.

In the future, gene chip technology may be used to rapidly determine breast cancer molecular subtypes in patients. Additionally, molecular analysis of protein expression in TNBC clinical specimens could more accurately define the TNBC phenotype and guide the selection of targeted therapies.

In your opinion, how should these insights into EGFR influence current clinical practices in breast cancer treatment?

In my opinion, early detection of EGFR overexpression with precise genotyping would

allow clinicians to tailor treatments more effectively, ensuring that patients receive therapies specifically designed to target their tumour's biology. Another important shift is the more frequent use of EGFR inhibitors in treating breast cancer subtypes with high EGFR expression. Based on pre-clinical study, these targeted therapies, including osimertinib, gefitinib, erlotinib, lapatinib or cetuximab, could be used either as monotherapy or in combination with chemotherapy for patients with EGFR-positive TNBC or IBC. Given that studies have shown the potential for EGFR inhibitors to improve outcomes, especially when combined with other treatments, incorporating them into treatment regimens should be a higher priority. Undoubtedly, the remarkable efficacy of EGFR-TKIs in the treatment of cancer patients is evident. Moreover, the presence of tumor heterogeneity and genomic instability inevitably leads to resistance against EGFR inhibitors. Additionally, combination therapies involving EGFR inhibitors and other agents, such as PARP inhibitors or immunotherapies, may provide more robust responses by tackling multiple cancer pathways simultaneously.

Apart from the EGFR inhibitors, targeted therapies such as monoclonal antibodies and bispecific antibodies, cancer vaccines and nanobodies can be more effective against EGFR C797S mutation. Combinatorial therapy with immunotherapy is also another effective approach to enhance the clinical benefits of EGFR inhibitors.

What are the potential therapeutic strategies targeting EGFR that show promise in clinical trials?

Several FDA approved EGFR inhibitors have been tested in breast cancer treatment, but the results haven't been very promising so far. First FDA approved EGFR inhibitor gefitinib, didn't significantly improve how patients responded to treatment in most studies. Similarly, in a trial involving 69 patients with advanced breast cancer, another drug called erlotinib didn't show a complete response in any patient, and only two patients showed partial improvement.

A plausible reason for these disappointing outcomes might be that the studies didn't focus on patients whose tumors had high levels of EGFR, the protein these drugs target. Instead, they included a broad range of breast cancer patients, many of whom had already undergone several treatments. Analyzing smaller groups of patients from previous trials might help identify who would benefit most from EGFR-targeted therapies.

Two important clinical trials have been tested with EGFR specific monoclonal antibody, cetuximab, either alone or with a type of chemotherapy. Adding cetuximab to the chemotherapy didn't improve patient outcomes. However, in the other clinical trials, cetuximab alone led to a 6% response rate, suggesting that it

might still work for some specific patients. Researchers in that trial also explored how EGFR affects cancer using advanced gene testing, which might provide more clues. In a separate phase II trial with patients who had advanced breast cancer, cetuximab improved response rates, but only for those with triple-negative breast cancer (TNBC). In this group, 38% of patients responded to treatment with irinotecan and carboplatin, while 49% responded when cetuximab was added to the mix.

Overall, the current reported clinical trials suggest that more research on EGFR-targeted treatments in patients with triple-negative breast cancer (TNBC) is need of the hour. However, there is strong hope surrounding this ongoing clinical trial (NCT04395989). This Phase II, open-label, randomized controlled umbrella trial is assessing the efficacy and safety of multiple targeted therapies compared to traditional chemotherapy in patients with unresectable locally advanced or metastatic triple-negative breast cancer. Patient grouping in the trial is determined by results from FUSCC's 500+ gene panel testing and immunohistochemical (IHC) subtype staining, which are performed on rebiopsy tumor specimens.

Can you discuss any challenges or limitations in targeting EGFR in breast cancer treatment?

EGFR-targeted therapy has already shown some promise in terms of improving outcomes in breast cancer patients, but molecular prognostic and predictive factors need to be identified to optimize selection of patients for EGFR-targeted therapies. Mechanistic, hypothesis-oriented clinical trials are needed rather than trials based on the assumption that EGFR-targeted therapy will be effective against EGFR-overexpressing breast cancer. EGFR targeted therapy may be most effective as a chemosensitizer, or therapy designed to prevent metastases. Continuous emergence of mutations, activation of bypass signaling pathways are also playing a very important role in falling the EGFR inhibitors into drug resistance category.

What are the most pressing research questions regarding EGFR in breast cancer that remain unanswered?

Still several questions remain elusive such as, Did EGFR mutations already exist, or did they develop during EGFR-targeted therapies? Are there other important mutations that haven't been studied yet, and what exact role do they play in resistance to treatment? Are fourth-generation EGFR-TKIs the solution to these

challenges, or do we need to explore even newer generations of these therapies? To better understand how resistance to EGFR-TKIs occurs, more research is needed, and the current scientific literature provides a solid foundation for researchers to make exciting progress in this area.

How do you envision the future of EGFR-targeted therapies in breast cancer management?

Researchers are continuously exploring the new types of treatments, including nanobodies (Nbs), which act like a protein that helps cells grow. These treatments are still being tested in labs, but they might be able to temporarily block the main growth signals in certain cancer cells. There's also increasing interest in cancer vaccines for patients with weak immune systems who don't respond well to regular vaccines. Other approaches, like plant-based natural products, peptides, and a new technique called PROTACs, have shown promise in early research. It will be exciting to see how effective they are in real patient trials, whether used alone or combined with other therapies.

What collaborative efforts or initiatives do you believe could accelerate research in this area?

Since many decades, collaborative efforts has already been playing a crucial role in accelerating the research outcome from lab side to bed side. I think, one approach is forming by formation of public-private partnerships are the key avenue that could accelerate the research in this area. Collaboration between academic institutions, basic science labs, translational research labs, pharmaceutical companies, and biotech firms have already been made at several levels and proving promising. Industry involvement is also essential for funding drug development and transitioning from preclinical research to clinical applications, allowing promising therapies to reach patients more quickly.

The creation of patient data-sharing platforms can also be a game-changer for breast cancer research. Similarly, international research consortia could also provide a framework for sharing knowledge, funding, and best practices on a global scale, further advancing to study the role of EGFR in breast cancer research.

Lastly, I would say AI and machine learning collaborations can revolutionize the way researchers analyze genetic and clinical data. By partnering with data scientists, researchers can use these technologies to identify EGFR-related mutations, predict patient responses, and optimize drug discovery. These advanced compu-

tational tools can analyze large datasets far more quickly and effectively than traditional methods, leading to faster breakthroughs. However, there are already several collaborative efforts around the world being made to solve the associated issue with the continuous emerging anti-cancer drug resistance, mutations by keeping the central focus to enhance the overall progression free survival of the patients.

What message would you like to convey to researchers and clinicians regarding the role of EGFR in breast cancer?

The role of EGFR in breast cancer is complex, and further research is crucial. Researchers should focus on better understanding its role in specific subtypes like TNBC, and clinicians should consider targeted therapies in select patients. Collaborative efforts across disciplines and utilizing the advanced technologies like AI/ML will be interesting to see how they can make significant progress in the breast cancer treatment and improved patient survival outcomes.

Are there any additional thoughts or comments you would like to share about this topic?

I believe that the role of EGFR in breast cancer is complex and heterogeneous, with ongoing research highlighting its involvement in tumor growth, metastasis, and immune evasion. Future studies should focus on identifying specific biomarkers for patient selection and explore the combination therapies to enhance treatment efficacy. Continued investigation into resistance mechanisms and the impact of the tumor microenvironment will be crucial for developing personalized treatment strategies.

Lastly, I would like to thank the TECHSCI research team for giving me the opportunity to share my thoughts on this very important topic.

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