



Novel Topical Metformin Protects Skin From Radiation Damage By Blocking Fibrosis-related Signatures And Promoting Regeneration While Maintaining Oncologic Safety

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INTRODUCTION

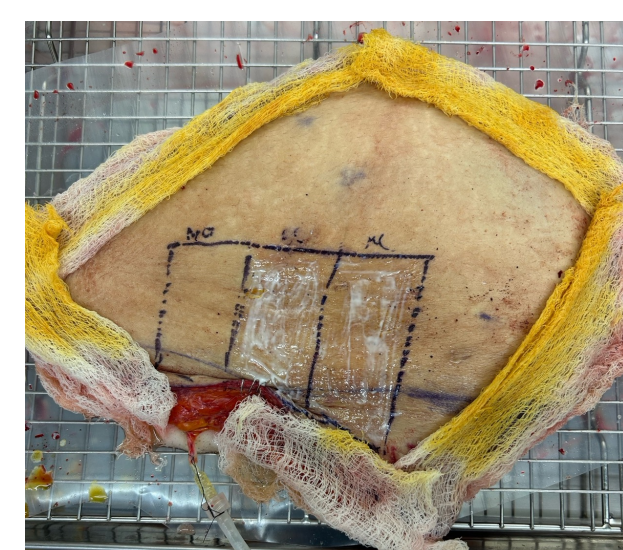
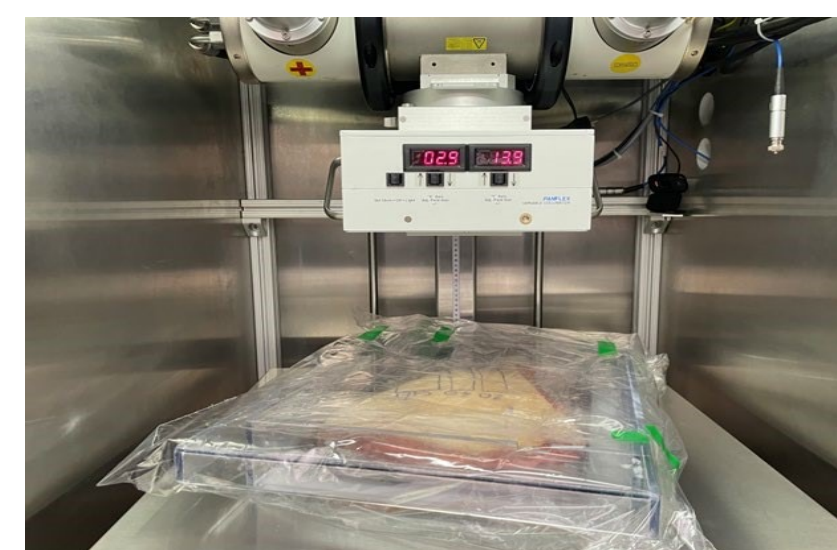
Radiation therapy (RT) is pivotal in breast cancer treatment, however **radiodermatitis** causes functional and cosmetic impairments. Radiation drives fibrosis via oxidative stress, TGF- β , and mTOR signaling. **Metformin** is known to activate **AMPK** and suppress **TGF- β /mTOR** pathways, but its radiation mitigation efficacy and oncologic safety in humans is **unknown**.

OBJECTIVE

To evaluate metformin's **efficacy and oncologic safety** using our first-of-its-kind **human full-thickness skin perfusion model** alongside human **breast cancer cell lines**.

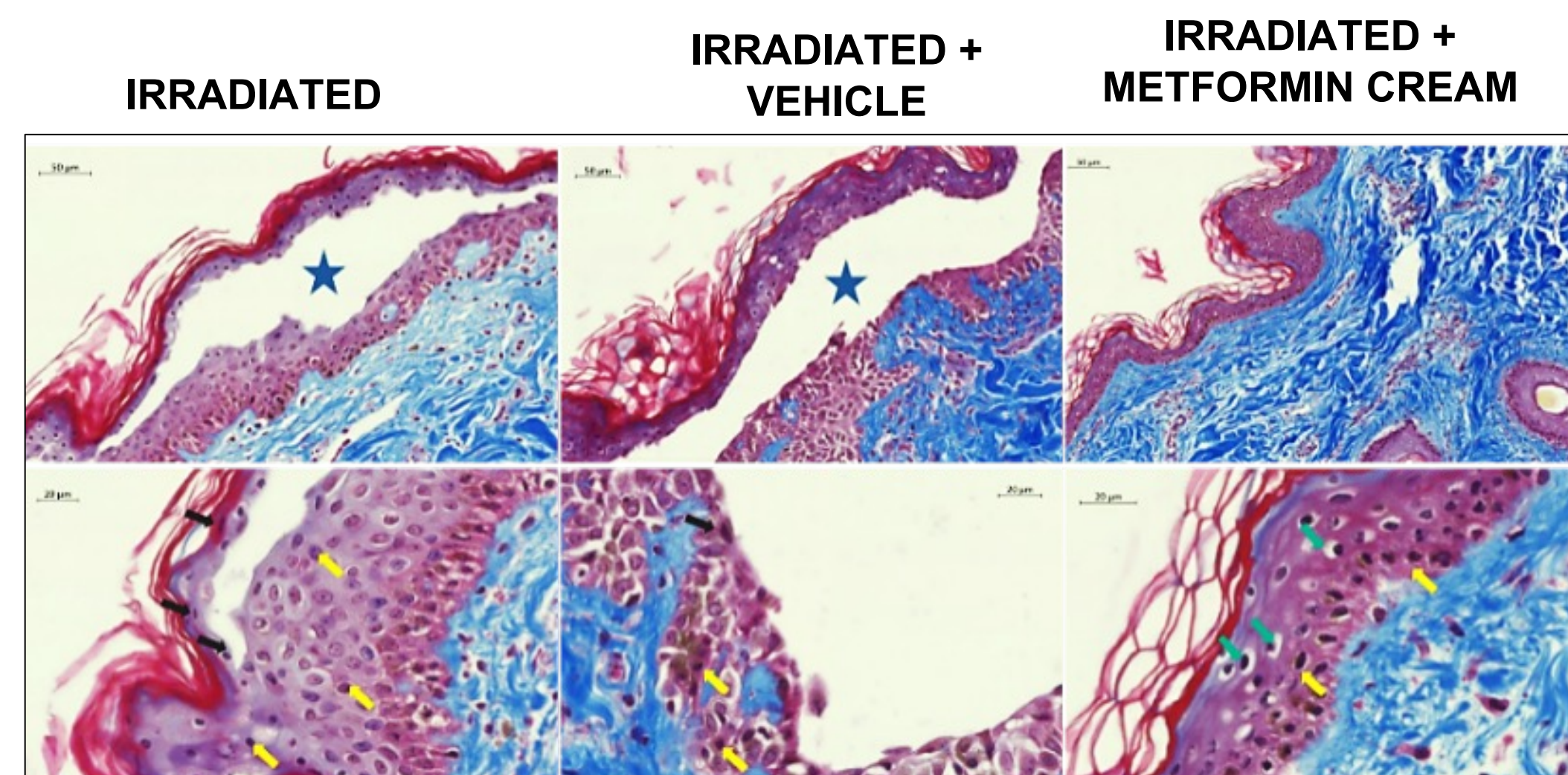
MATERIALS & METHODS

We devised a controlled experimental protocol using our ex vivo human skin perfusion system, where a **human tissue** was subjected to radiation-induced damage at a dosage of **15 Gy**. The experimental intervention involved the topical application of **metformin cream, control cream and no intervention**.

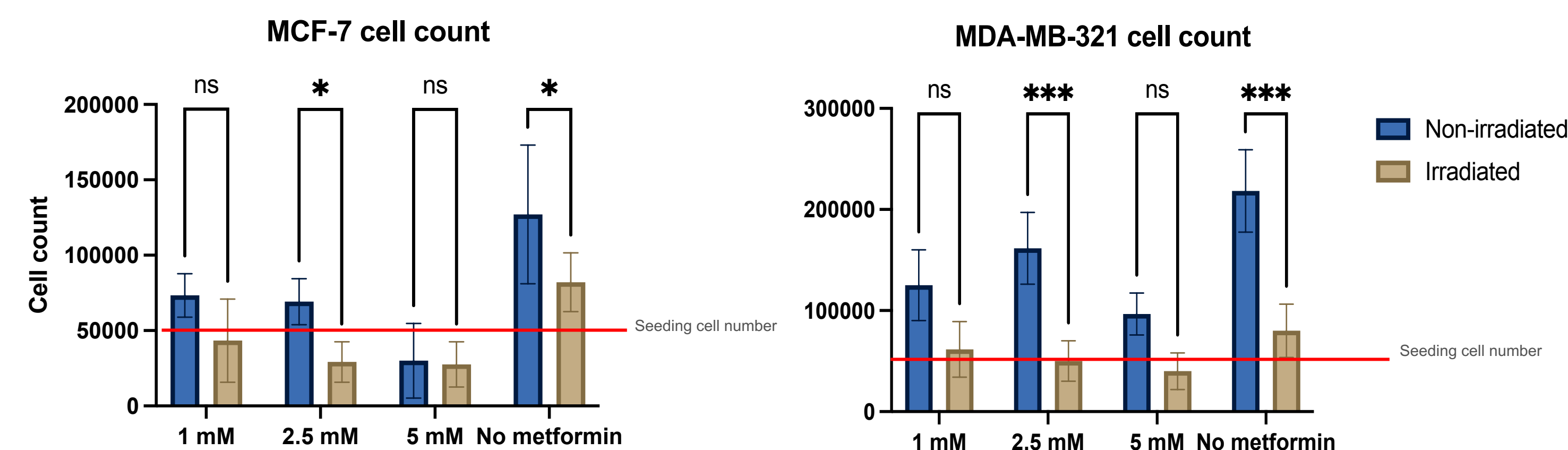


Irradiated and control **human breast cancer cell lines (MCF-7 and MDA-MB-321)** were treated with metformin to study effects on cell proliferation, viability, cytotoxicity, and DNA damage/apoptosis markers.

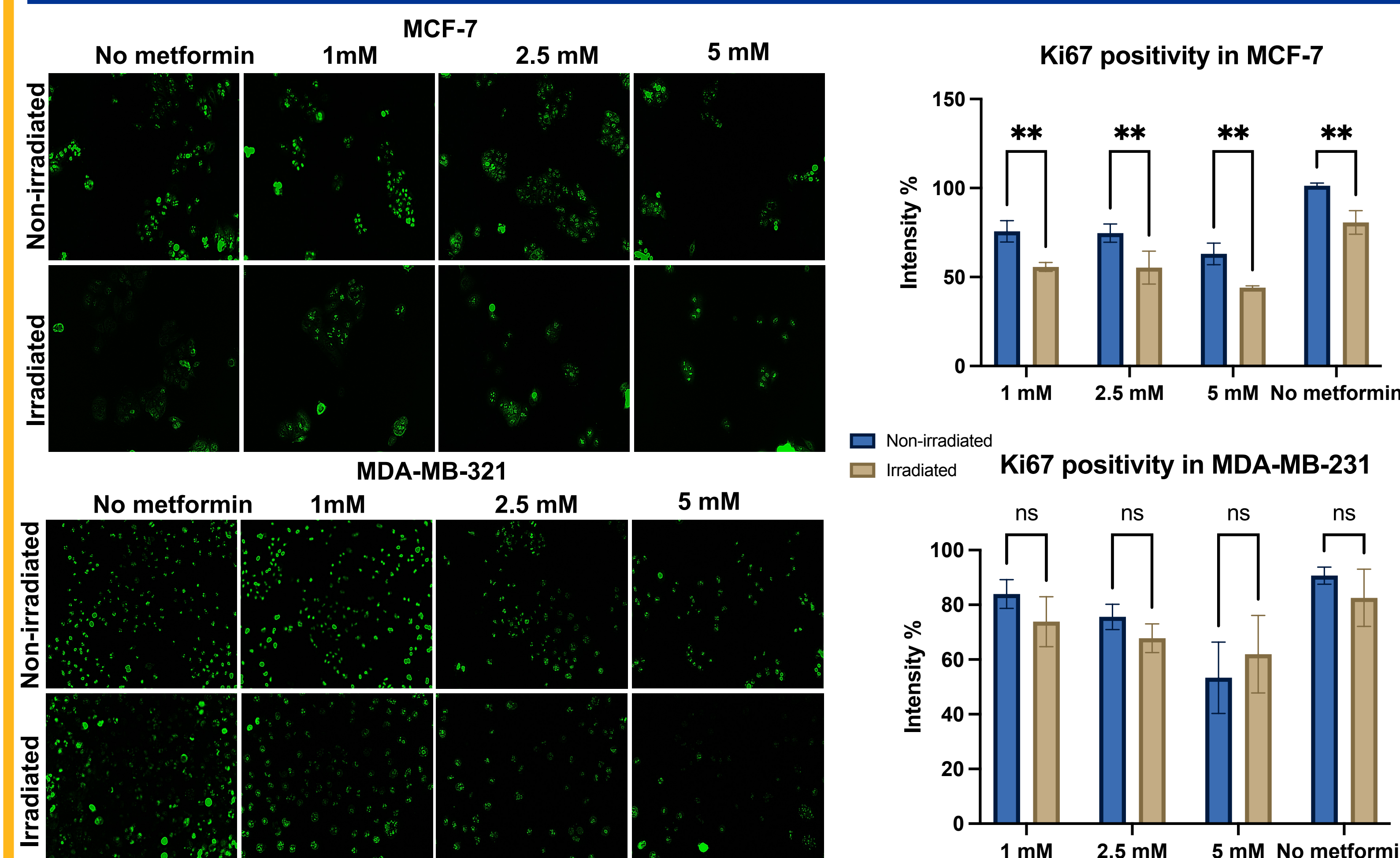
RESULTS



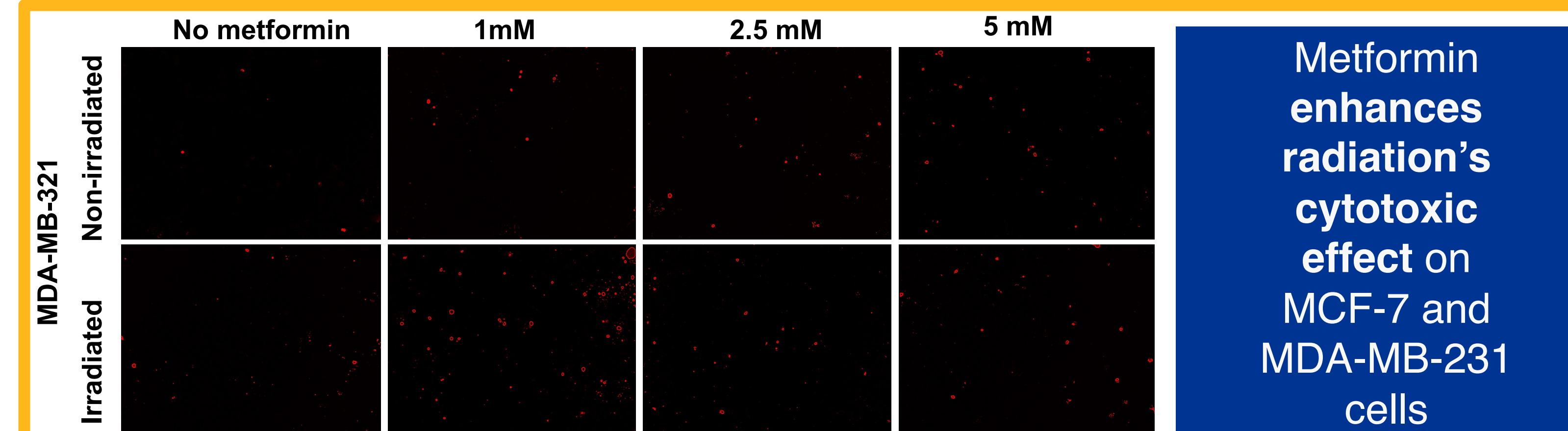
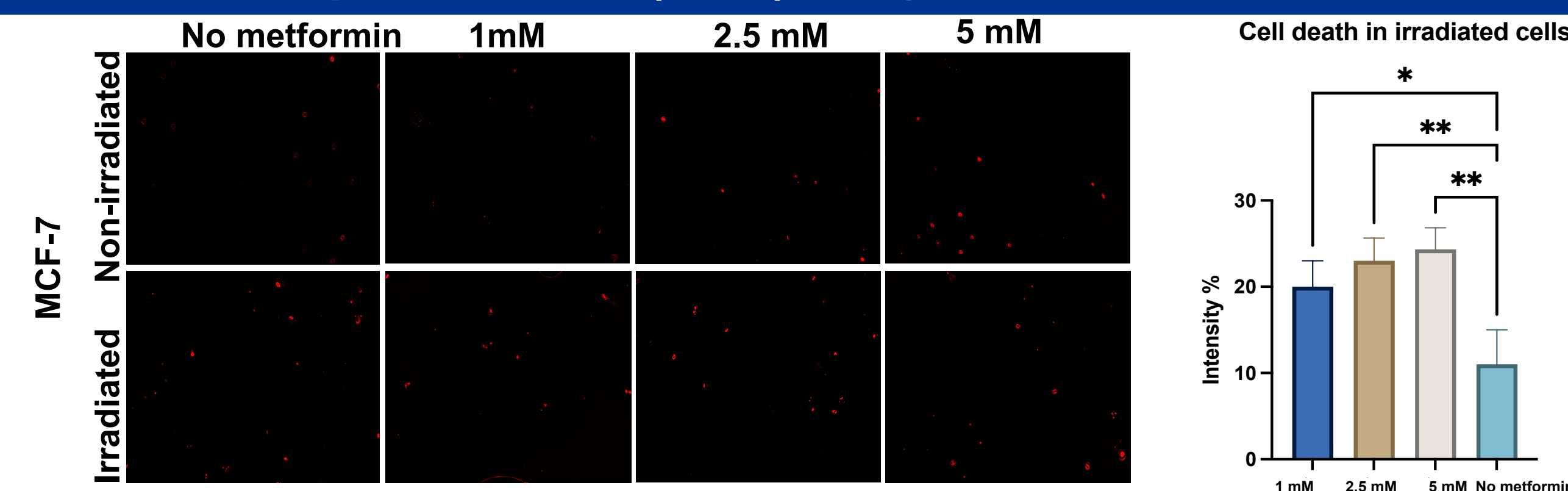
Irradiated control skin and control cream showed **more stressed cells and dermal-epidermal separation** compared to **metformin treated skin**



In both cell lines, cells receiving **no metformin** showed a **significant increase in cell count** when compared to cells treated with metformin.

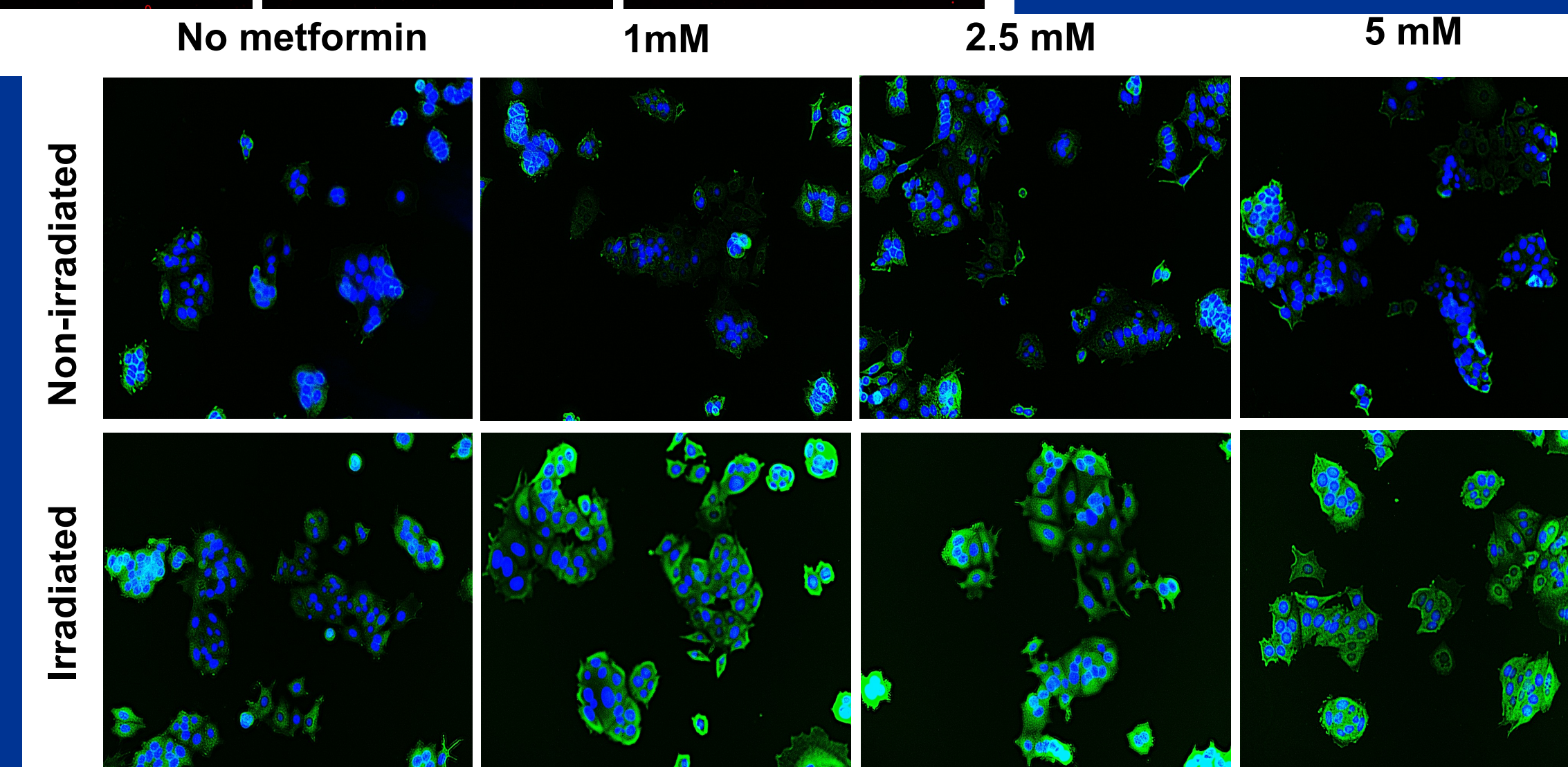


When combined with metformin, irradiated cells show a **further decrease in proliferation (Ki67)** compared to irradiation alone



Metformin enhances radiation's cytotoxic effect on MCF-7 and MDA-MB-231 cells

Metformin enhances apoptosis of breast cancer cells as demonstrated by **Caspase 3** expression



CONCLUSIONS

Metformin **does not interfere** with radiation-induced cytotoxicity in cancer cells

- Metformin-treated cells showed a **significant decrease in proliferation** and viability post-irradiation
- LIVE/DEAD assay confirmed **increased cell death** in metformin-treated groups
- Metformin alone **induces cytotoxicity** in cancer cells
- Non-irradiated** cells treated with metformin also exhibited **reduced proliferation and increased cell death**
- Cytotoxic effects were **dose-dependent**, with higher concentrations (5 mM) showing the strongest effect

Given that metformin does not compromise radiation efficacy in cancer cells, it may serve as a protective agent for healthy tissue and has potential as a mitigator for RISF in breast cancer radiotherapy.