

Review Article

Pulsed Electromagnetic Fields in Cancer Therapy: A Review of Experimental and Clinical Evidence

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Abstract

Pulsed electromagnetic fields (PEMF) are emerging as a non-invasive adjunct in cancer therapy. Initially approved for orthopedic applications such as bone healing and tissue regeneration, PEMF has demonstrated broader biological effects including modulation of inflammation, angiogenesis, cellular metabolism, and signal transduction. Increasing experimental and early clinical evidence suggests that specific electromagnetic field exposures may inhibit tumor cell proliferation, induce apoptosis, disrupt mitotic spindle formation, and impair angiogenesis across multiple cancer types. This review synthesizes findings from studies investigating low- and high-intensity PEMF, intermediate-frequency tumor-treating alternating electric fields, and tumor-specific amplitude-modulated radiofrequency electromagnetic fields (AM-RF EMF) in cancer cell lines, animal models, and preliminary human clinical trials. Across these modalities, therapeutic responses appear highly dependent on field strength, frequency, waveform, exposure duration, and tumor biology. While intermediate-frequency alternating electric fields selectively target dividing cells through mitotic disruption, AM-RF EMF protocols have demonstrated early clinical activity in hepatocellular carcinoma and other malignancies without significant toxicity. Low- and higher-intensity PEMF exposures have also shown antiproliferative and pro-apoptotic effects in diverse tumor models, often enhancing sensitivity to chemotherapy, radiation, and targeted therapies. Despite encouraging results, clinical translation remains limited due to mechanistic heterogeneity and the absence of standardized treatment protocols. To address these challenges, this review proposes a framework integrating cancer genomics, structural biology, and thermodynamic modeling to guide rational design of electromagnetic field therapies. By estimating the electromagnetic field strengths required to perturb protein–ligand interactions or disrupt key oncogenic signaling pathways, PEMF protocols may be tailored to individual tumor molecular profiles. Although current biophysical estimates remain preliminary, they provide a conceptual basis for hypothesis-driven optimization. Rigorous randomized clinical trials, mechanistic validation, and standardized exposure parameters will be essential to establish the role of PEMF as a precision, mechanism-informed component of multimodal cancer therapy.

Keywords

Pulsed Electromagnetic Fields, Oncology, Electromagnetic Therapy, Cell Proliferation, Mitotic Disruption, Structural Biology, Cancer Driver Genes, Non-invasive Therapy

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Received: 18 February 2026; **Accepted:** 28 February 2026; **Published:** 10 March 2026



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1. Introduction

Pulsed Electromagnetic Field (PEMF) therapy is an FDA-approved, non-invasive modality widely used in orthopedics to support bone healing in conditions such as nonunion fractures, spinal fusions, and osteotomies. Devices like Orthofix's Physio-Stim and Biomet's EBI Bone Healing System deliver time-varying electromagnetic fields to stimulate cellular activity and promote osteogenesis and angiogenesis. These effects are mediated through mechanisms including modulation of ion binding, upregulation of growth factors (e.g., BMP-2, TGF- β), and increased expression of osteogenic markers [1, 2].

Beyond orthopedics, PEMF is gaining attention as a complementary therapy for chronic pain, particularly musculoskeletal conditions such as osteoarthritis, fibromyalgia, and chronic low back pain. Although not FDA-approved for general pain relief, over-the-counter devices (e.g., Oska Pulse, BEMER) are marketed under Class I or II wellness exemptions. Studies suggest PEMF may reduce pain and improve function by modulating inflammation, nociceptive signaling, and microcirculation [3, 4].

Emerging evidence now points to a potential role for PEMF in cancer therapy. Preclinical studies demonstrate that specific PEMF exposures can inhibit tumor cell proliferation, induce apoptosis, and impair angiogenesis in models of breast, lung, and brain cancers. Animal studies support these findings [5], and early clinical trials suggest PEMF may improve quality of life and even exert direct antitumor effects in certain contexts [6].

While clinical data are still limited, recent reviews emphasize the need for rigorous trials to optimize treatment protocols and clarify mechanisms [7, 8]. This review examines key findings from cellular and animal studies, as well as preliminary human trials, tracing the evolution of this field from early research on alternating fields and modulated radiofrequencies to current interest in PEMF for cancer treatment.

2. Low and Intermediate Frequency Alternating Electromagnetic Fields

Alternating electric fields in the intermediate frequency range (100–300 kHz) at field strengths of 1–2.5 V/cm (corresponding to magnetic fields of 0.44–1.1 μ T) have been shown to suppress the proliferation of various rodent and human tumor cell lines—including Patricia C, U-118, U-87, H-1299, MDA231, PC3, B16F1, F-98, C-6, RG2, and CT-26—as well as malignant tumors in animal models. This inhibitory effect is both frequency- and intensity-dependent and is selective for actively dividing cells; non-proliferating (quiescent) cells remain unaffected. The mechanism of action of these tumor treating fields (TTFields) involves disruption of mitotic spindle formation, resulting in mitotic arrest and cell death [9]. These findings have been extended to additional cell lines

(e.g., MDA-MB-231 and H1299) and tumor models (e.g., intradermal B16F1 melanoma and intracranial F-98 glioma). In a pilot clinical study of 10 glioblastoma patients, TTFields therapy more than doubled both median progression-free survival and overall survival compared to historical controls [10].

In contrast, exposure of Caco-2 human colon adenocarcinoma cells to low-frequency (50 Hz), higher-intensity (1 mT) magnetic fields promoted cell growth rather than inhibiting it. This stimulation was time-dependent and accompanied by increased protein oxidation and elevated intracellular reactive oxygen species (ROS). These changes coincided with increased intracellular calcium levels and global activation of the 20S proteasome, along with a reduction in the pro-apoptotic protein p27 [11].

Other studies have reported no significant effects of 1 mT, 60 Hz electromagnetic fields on non-cancerous immortalized cell lines such as Jurkat (human T lymphocytes) and NIH3T3 (mouse embryonic fibroblasts). However, under the same conditions, both MCF-7 (human breast cancer) and MCF-10A (non-tumorigenic breast epithelial) cells exhibited significant reductions in cell number, viability, and DNA synthesis. These effects were attributed to cell cycle delay and induction of the pro-apoptotic gene PMAIP in a context-dependent manner [12].

Overall, the biological effects of low- and intermediate-frequency EMFs on cancer cells are complex and highly context-dependent. Responses vary by cell type, proliferative status, field parameters (frequency and intensity), and exposure duration, underscoring the importance of precise characterization in therapeutic and experimental applications.

3. Amplitude Modulated Radiofrequency Electromagnetic Fields

In 2009, Barbault et al. [13] reported that cancer patients exhibited biofeedback responses to tumor-specific frequencies of amplitude-modulated (AM) radiofrequency electromagnetic fields (RF-EMF). These modulation frequencies, ranging from 0.1 Hz to 114 kHz, were specific to the type of tumor, while the carrier frequency was a fixed 27.12 MHz. The RF signal was generated at 100 mW into a 50-ohm load. In a limited compassionate-use clinical trial involving 28 patients with various cancer types, RF-EMF treatment was delivered intrabuccally for 60 minutes, three times daily, and continued until disease progression or death.

No significant side effects were reported. Of the 13 patients eligible for response evaluation, one breast cancer patient achieved a complete response, and another showed a partial response. Four additional patients (with thyroid, lung, pancreatic cancers, and leiomyosarcoma) exhibited stable disease. The authors concluded that the observed clinical responses were more

likely due to systemic physiological effects rather than direct cytotoxic action, given the low field strength and the anatomical distance between the intrabuccal application site and the tumor sites. Estimated field strengths within 1 mm of the emitter were approximately 30 V/cm (electric) and 13 μ T (magnetic).

A subsequent open-label phase I/II clinical trial involving 41 patients with hepatocellular carcinoma (HCC) confirmed the earlier findings. Using the same protocol of tumor-specific AM RF-EMF delivery, 28 patients were evaluable for response: 4 demonstrated partial responses, 16 had stable disease, and 8 showed disease progression. These preliminary outcomes were considered promising and formed the rationale for pursuing larger, randomized clinical trials [14].

Follow-up mechanistic studies investigated the effects of tumor-specific modulation frequencies on HCC (HepG2, Huh7) and breast cancer (MCF-7) cell lines. Direct in vitro exposure resulted in significant growth inhibition of malignant cells, whereas non-malignant counterparts—THLE-2 hepatocytes and MCF-10A breast epithelial cells—were unaffected. Growth suppression in HCC cells was accompanied by downregulation of the chemokine-related genes *XCL2* and *PLP2*, as well as disruption of mitotic spindle architecture. Notably, reduced expression of *XCL2* and *PLP2* has been associated with improved prognosis in cancer patients [6].

4. Low Intensity PEMF

The biological effects of pulsed electromagnetic fields (PEMF) on tumor cell growth have been recognized for over two decades. Early studies demonstrated that PEMF exposure at a magnetic field intensity of 1.5 mT and pulse frequencies of 1 or 25 Hz enhanced the cytotoxicity of chemotherapeutic agents—vincristine, mitomycin, and cisplatin—against multi-drug-resistant HCA-2/1cch human colon adenocarcinoma cells in vitro [15]. At the same field intensity but a higher pulse frequency (75 Hz), PEMF upregulated A3 adenosine receptor (A3AR) expression in neural tumor cell lines, including PC12 (rat adrenal pheochromocytoma) and U87MG (human glioblastoma). This upregulation was associated with inhibition of NF- κ B signaling and induction of p53, ultimately leading to suppressed proliferation, increased lactate dehydrogenase (LDH) release, and elevated caspase-3 activity—markers of cytotoxicity and apoptosis, respectively [16]. Similarly, growth inhibition and apoptotic induction were observed in the SKOV3 human ovarian cancer cell line following PEMF exposure at 1 mT with pulse frequencies ranging from 8 to 64 Hz [17].

More recent studies have extended these findings to other tumor types. In vitro and in vivo experiments involving human breast cancer MCF-7 cells and human lung adenocarcinoma A549 cells revealed that low-intensity PEMF (0.68 and 1.19 mT) applied at higher pulse frequencies (3.846 and 40.85 kHz, respectively) significantly inhibited tumor growth [18]. This effect was attributed to increased apoptotic activity, evidenced by elevated caspase-3/7 expression and greater annexin V

staining, as well as an accumulation of cells in the G₀ phase of the cell cycle. Gene expression analysis further indicated activation of pathways associated with DNA damage, cell cycle arrest, and growth suppression.

Notably, the systemic impact of PEMF has also been demonstrated in humans. In a recent double-blind, randomized clinical trial involving healthy female volunteers, participants were exposed to PEMF at 1 mT intensity and 50 Hz pulse frequency [19]. Sera collected from treated individuals exhibited significant anti-cancer properties up to one month post-exposure, reducing breast cancer cell proliferation, migration, and invasiveness in vitro. These effects correlated with a reduction in epithelial-mesenchymal transition (EMT) markers, suggesting a systemic modulation of anti-tumor signaling pathways.

5. Higher Intensity PEMF Exposure

For the purposes of this review, high-intensity pulsed electromagnetic fields (PEMF) are defined as those with magnetic field strengths ranging from 2 to 400 mT, remaining within the public exposure limits recommended by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) [20]. The specific pulse frequencies and exposure durations varied across the studies discussed below.

Over the past two decades, a growing body of research involving both tumor cell lines and animal models has demonstrated that PEMF—either as a stand-alone treatment or in combination with chemotherapy or gamma irradiation—can exert antiproliferative and antiangiogenic effects. These studies typically used field intensities between 2 and 20 mT, pulse frequencies from 8 to 120 Hz, and diverse exposure regimens. Tumor types studied included breast, bladder, liver, hematopoietic cancers, osteosarcoma, and fibrosarcoma.

Breast cancer cell lines, particularly MCF-7, have shown notable sensitivity to PEMF. Exposure to PEMF at 3 mT and 20 Hz for 60 minutes daily over three days significantly inhibited proliferation [21]. A separate protocol using full-square wave PEMF at 11 mT and 8 Hz, applied for 30 minutes twice daily over five days, yielded similar antiproliferative outcomes in both MCF-7 and MDA-MB-231 breast cancer cells [22]. These effects were mechanistically linked to DNA damage, apoptosis, and the induction of cellular senescence markers. Importantly, these effects appeared to be selective for malignant cells; normal epithelial and fibroblast cells remained unaffected under the same treatment conditions.

The potential for PEMF to enhance chemotherapy has also been explored. In MCF-7 cells, PEMF exposure significantly potentiated the cytotoxic effects of doxorubicin [23] and etoposide [24]. Both agents inhibit cell proliferation through topoisomerase II inhibition and reactive oxygen species (ROS) generation, and these pathways appeared to be further activated in the presence of PEMF.

Findings from in vitro studies have been validated in vivo.

For example, PEMF exposure inhibited the growth and vascularization of 16/C murine mammary adenocarcinoma tumors implanted in syngeneic C3H/HeJ mice. Treatment consisted of 10-minute daily exposures for 12 days using a 120 Hz pulse frequency and field intensities up to 20 mT [25]. Further studies confirmed that tumor inhibition was dependent on increasing magnetic field intensity rather than increased exposure time at a fixed intensity [26]. PEMF also enhanced the effects of gamma irradiation and the chemotherapeutic agent bleomycin in mouse models bearing human MDA-MB-231 breast cancer xenografts [27] and triple-negative breast cancer (TNBC) MX-1 xenografts in SCID mice [28].

Beyond breast cancer, PEMF has demonstrated antitumor activity in models of bladder cancer [29, 30], hematologic malignancies [28, 31], osteosarcoma [32], and fibrosarcoma [33]. Of particular interest is the reported synergy between PEMF and molecularly targeted therapies: in BCR/ABL (+) leukemia-derived TCC-S cells, PEMF enhanced the efficacy of the tyrosine kinase inhibitor imatinib [20].

6. Discussion

The growing body of evidence supports the continued development of pulsed electromagnetic fields (PEMF) as a complementary modality in cancer therapeutics. At present, PEMF

demonstrates its greatest efficacy when combined with conventional treatments, such as cytotoxic chemotherapy or ionizing radiation. Several novel laboratory protocols have yielded promising results and merit translation into large-scale, double-blind clinical trials to evaluate therapeutic utility and safety in a controlled setting. However, current findings also highlight important areas for further refinement and optimization to overcome the clinical translation gap despite more than two decades of preclinical studies.

To date, no PEMF or EMF protocol has consistently achieved irreversible tumor regression as a stand-alone intervention either in preclinical studies or limited human trials [13, 14, 19]. Moreover, the heterogeneity in field parameters—such as frequency, waveform, intensity, and exposure duration—across studies has impeded the establishment of a unified mechanism of action. Inhibition of cancer cell growth by PEMF appears to involve multiple, and potentially interacting, cellular processes, including alterations in membrane potential, disruption of mitochondrial function, interference with mitotic spindle formation, modulation of growth signaling pathways, increased generation of reactive oxygen species (ROS), and induction of apoptosis (Figure 1). While the preferential sensitivity of malignant cells compared to normal cells is encouraging, the underlying basis of this selectivity remains incompletely understood and warrants further mechanistic investigation.

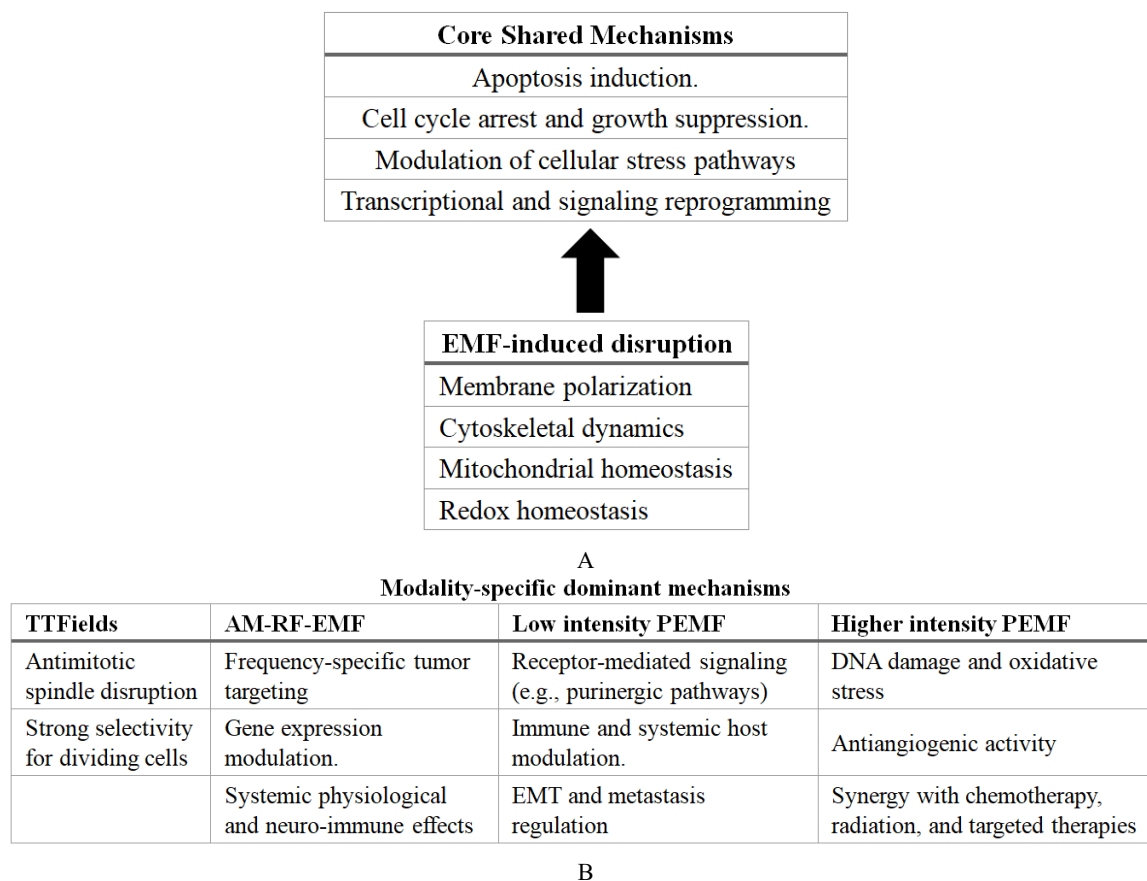


Figure 1. Summary of antitumor mechanisms across treatment modalities.

Reliance on empirical trial-and-error testing may be inefficient and limiting, especially given current advances in cancer genomics and the characterization of key oncogenic driver mutations (34). Moving forward, it would be advantageous to rationally design PEMF protocols that specifically disrupt mo-

lecular pathways activated by such driver genes. This approach could yield targeted, mechanism-informed applications of PEMF with improved therapeutic indices. [Tables 1 through 6](#) summarize major classes of cancer-relevant signaling pathways and representative driver genes identified through high-throughput genome sequencing.

Table 1. Classical Tumor Suppressors & Oncogenes.

Gene	Mutation Frequency	Primary Pathway	Major Cancer Types	Therapeutic Relevance
TP53	>50% all cancers	Cell cycle checkpoint/Apoptosis	Pan-cancer (highest in ovarian, lung)	MDM2 inhibitors, p53 reactivators
KRAS	~30% all cancers	RAS/MAPK signaling	Pancreatic (90%), Colorectal (40%), Lung (25%)	KRAS G12C inhibitors (sotorasib, adagrasib)
PIK3CA	~20% solid tumors	PI3K/AKT/mTOR	Breast (45%), Colorectal (15%), Endometrial	PI3K inhibitors (alpelisib)
APC	80% colorectal	Wnt signaling	Colorectal, Gastric	Wnt pathway modulators (experimental)

Table 2. DNA Repair Pathway Genes.

Gene	Mutation Frequency	Primary Pathway	Major Cancer Types	Therapeutic Relevance
BRCA1/BRCA2	5-10% breast/ovarian	Homologous recombination	Breast, Ovarian, Prostate, Pancreatic	PARP inhibitors (olaparib, niraparib)
ATM	5-15% various	DNA damage response	CLL, Breast, Prostate	ATR inhibitors, PARP inhibitors
MLH1/MSH2/MSH6/PMS2	15% colorectal	Mismatch repair	Colorectal, Endometrial, Lynch syndrome	Immune checkpoint inhibitors

Table 3. Receptor Tyrosine Kinases & Growth Factors.

Gene	Mutation Frequency	Primary Pathway	Major Cancer Types	Therapeutic Relevance
EGFR	15% lung adenocarcinoma	RTK/MAPK signaling	Lung, Glioblastoma, Head/Neck	TKIs (erlotinib, osimertinib)
HER2 (ERBB2)	20% breast cancer	RTK signaling	Breast, Gastric	Trastuzumab, T-DM1, TKIs
ALK	5% lung adenocarcinoma	RTK fusion proteins	Lung, Lymphomas	ALK inhibitors (crizotinib, alectinib)

Table 4. Chromatin Remodeling & Epigenetic Regulators.

Gene	Mutation Frequency	Primary Pathway	Major Cancer Types	Therapeutic Relevance
ARID1A	10-50% various	SWI/SNF chromatin remodeling	Ovarian, Endometrial, Gastric	Synthetic lethal approaches

Gene	Mutation Frequency	Primary Pathway	Major Cancer Types	Therapeutic Relevance
KMT2D	20% lymphomas	Histone methylation	Diffuse large B-cell lymphoma	Histone methyltransferase inhibitors
IDH1/IDH2	70% gliomas, 20% AML	Metabolic/Epigenetic	Glioma, AML, Cholangiocarcinoma	IDH inhibitors (ivosidenib, enasidenib)

Table 5. Cell Cycle Regulation.

Gene	Mutation Frequency	Primary Pathway	Major Cancer Types	Therapeutic Relevance
CDKN2A (p16)	30-50% various	G1/S checkpoint	Melanoma, Pancreatic, Lung	CDK4/6 inhibitors
RB1	90% retinoblastoma	G1/S checkpoint	Retinoblastoma, Small cell lung	CDK4/6 inhibitors, aurora kinase inhibitors
CCND1	15-20% breast	G1/S progression	Breast, Mantle cell lymphoma	CDK4/6 inhibitors (palbociclib)

Table 6. Emerging Drivers (Recent WGS Studies 2024 [34]).

Discovery	Context	Primary Pathway	Cancer Types	Therapeutic Potential
74 New Candidate Genes	Nature Genetics 2024 (10,478 genomes)	RNA processing, protein degradation	Pan-cancer analysis	Under investigation
Non-coding drivers	Regulatory elements, lncRNAs	Gene expression regulation	Multiple cancer types	Epigenetic modulators

Many of the downstream effectors of cancer-associated gene products—such as enzymes, receptors, transcription factors, DNA-binding proteins, and scaffolding proteins—have had their structures experimentally determined and deposited in the Protein Data Bank (RCSB.org) [35], or accurately predicted by AlphaFold (AlphaFold Protein Structure Database) [36]. This structural information provides a powerful foundation for estimating the electromagnetic field (EMF) intensities required to perturb or disrupt their functional interactions. In particular, these insights open the door to the rational design of PEMF protocols targeting specific molecular interactions central to tumor growth and survival.

Functionally disrupting a protein's activity via EMF can be conceptualized as interfering with its interactions with a substrate, ligand, DNA target, or binding partner. This disruption can occur if the energy imparted by the EMF is sufficient to overcome the standard free energy of binding (ΔG^0), or alternatively, the free energy required to partially unfold one or both interacting molecules (ΔG_u).

For binding interference, the minimum energy supplied by the EMF must match or exceed the standard free energy of binding. On a per-molecule basis, this requirement can be

written as:

$$E_{\text{emf}} = (\Delta G^0/N) \tag{1}$$

where N is the Avogadro number ($6.022 \times 10^{23} \text{ mol}^{-1}$) since ΔG^0 values are often given per mole.

The energy provided by an electric field (E) to a dipole or charge depends on the interaction between the field and the molecule dipole moment (μ) or charge (q). For a dipole in an electric field, the potential energy (U) is the vectorial product of the electric field (E) and the dipole moment (μ), and maximum energy occurs when the dipole is aligned with the field and

$$U_m = \mu E \tag{2}$$

where μ is the magnitude of the dipole moment in Debyes or C.m, and E the electric field strength in V/m.

Since the energy required by the field to disrupt binding must at least be equal to the free binding energy,

$$\mu E = \Delta G^0/N \tag{3}$$

Solving for E,

$$E = \Delta G^0 / (N\mu) \quad (4)$$

In practice, ΔG^0 could be derived from the equilibrium binding constant K_{eq} using,

$$\Delta G^0 = -RT \ln K_{eq} \quad (5)$$

where R is the universal gas constant ($\approx 8.314 \text{ J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$) and T the temperature in Kelvin (K).

The corresponding magnetic field strength could be derived from,

$$B = E/c \quad (6)$$

a consequence of Maxwell's equations and where c is the speed of light ($\approx 3 \times 10^8 \text{ m/s}$).

Table 7. Estimated static magnetic field strengths required for disrupting interactions between oncogene products and cognate ligands or substrates.

Target (substrate)	PDB/AlphaFold ID ²	$K_{eq} \text{ (M}^{-1}\text{)}^3$	B (mT) ¹
GTPase switch protein			
Hras (GTP)	PDB 8ELK	9.3×10^{10}	625
Kras (Raf1 Ras BD)	PDB 6XHA	2.8×10^6	130
Protein tyrosine kinase			
c-Abl (ATP)	AF-P00520-F1	8.3×10^4	18
ALK (ATP)	AF-Q9UM73-F1-v4	2.4×10^5	28
BTk (ATP)	AF-Q06187-F1	3.4×10^4	43
EGFR (ATP)	AF-P00533-F1	5.9×10^4	28
HER2 (ATP)	AF-P04626-F1	3.7×10^4	23
c-kit (ATP)	AF-P10721-F1-v4	1.9×10^4	18
SRC (ATP)	AF-P00523-F1-v4	1.2×10^4	102
VEGFR1 (ATP)	AF-P17948-F1	7.7×10^3	6
VEGFR2 (ATP)	AF-P35968-F1	7.7×10^3	10
Protein serine/threonine kinase			
AKT1 (ATP)	AF-P31749-F1	7.6×10^3	36
AKT2 (ATP)	AF-P31751-F1	3.9×10^3	53
ATR (ATP)	AF-Q13535-F1-v4	2.0×10^7	28
Aurora 2 (ATP)	AF-O14965-F1	2.9×10^4	30
Cdk2-PO4/Cyclin A (ATP)	PDB 1JST	4.3×10^4	57
Cdk2/Cyclin E (ATP)	PDB 1W98	2.8×10^5	44
Cdk4/Cyclin D1 (ATP)	PDB 2W96	2.4×10^3	33
Cdk6/vCyclin (ATP)	PDB 1JOW	1.2×10^5	61
Chk1 (ATP)	AF-O14757-F1	7.1×10^5	72
Chk2 (ATP)	AF-O96017-F1	3.0×10^5	30
pERK1 (ATP)	PDB 2ZOQ	3.2×10^5	71
pERK2 (ATP)	PDB 6OPG	5.5×10^5	63
GSK3 β (ATP)	AF-49841-F1	2.0×10^4	44
MEK1 (ATP)	AF-Q02750-F1	1.8×10^5	58
RAF1 (ATP)	AF-P04049-F1	8.6×10^4	36

Target (substrate)	PDB/AlphaFold ID ²	K _{eq} (M ⁻¹) ³	B (mT) ¹
Lipid phosphoinositol kinase			
ATM (ATP)	PDB 7NI6	3.4 x 10 ⁴	19
PIK3CA (ATP)	AF-P42336-F1	5.0 x 10 ⁵	49
MTOR (ATP)	PDB 3JBZ	1.0 x 10 ³	15
Other enzymes			
PARP1 (NAD)	AF-P09874-F1-v4	1.3 x 10 ⁶	29
PARP2 (NAD)	AF-Q9UGN5-F1-v4	5.3 x 10 ⁵	25
IDH1 (Isocitrate)	PDB 3INM	1.5 x 10 ⁴	306
IDH2 (Isocitrate)	PDB 5I95	1.7 x 10 ⁵	230

¹Calculation of B (mT) was based on equations [1-6].

²The dipole moment (μ) of the proteins was calculated from coordinates provided in the corresponding PDB or AlphaFold files shown below, and using the Protein Dipole Moments Server. The server is described in Clifford E. Felder, Jaime Prilusky, Israel Silman, and Joel L. Sussman 2007, "A server and database for dipole moments of proteins", *Nucleic Acids Research*, 35, special Web Servers Issue. https://academic.oup.com/nar/article/35/suppl_2/W512/2922221.

³ The K_{eq} in equation [5] is 1/K_d for simple protein-ligand interaction, or 1/K_m for enzyme substrate interaction. The catalytic K_m is used as a first approximation of substrate affinity. K_d or K_m values were obtained from the following sources: Hras (GTP): John, J., *et al.*, 1993, Kras (Raf1 Ras BD): Tran, T. H., *et al.*, 2021, c-Abl (ATP), BTK (ATP), EGFR (ATP), HER2 (ATP), c-kit (ATP), SRC (ATP), VEGFR1 (ATP), VEGFR2 (ATP), AKT1 (ATP), AKT2 (ATP), Aurora 2 (ATP), Cdk2-PO4/Cyclin A (ATP), Cdk2/Cyclin E (ATP), Cdk4/Cyclin D1 (ATP), Chk1 (ATP), Chk2 (ATP), GSK3 β (ATP), MEK1 (ATP), RAF1 (ATP), ATM (ATP) & MTOR (ATP): Knight, Z. A. & Shokat, K. M., 2005, ALK (ATP): Bossi, R. T., *et al.*, 2010, ATR: data from ReactionBiology and Eurofins, Cdk6/vCyclin (ATP): data from ReactionBiology, pERK1 (ATP) & pERK2 (ATP): Petrosino, M., *et al.*, 2023, PIK3CA (ATP): Maheshwari, S., *et al.* 2017, PARP1 (NAD) & PARP2 (NAD): Thorsell A-G., *et al.*, 2016, IDH1 (Isocitrate): Uniprot O75874, IDH2 (Isocitrate): Uniprot P48735.

Table 7 presents the calculated static magnetic field intensities required to disrupt the functions of selected therapeutic targets in cancer-related pathways. These values calculated using equations [1-6], should be considered preliminary, first-order approximations for several reasons.

First, the estimates are based on simplified dipole moment calculations that assume static electric fields interacting with permanent molecular dipoles. In contrast, pulsed electromagnetic fields (PEMF) are time-varying, and their interactions with biomolecules are considerably more complex. These interactions may involve induced dipole moments, frequency-dependent dielectric properties, shielding by surrounding tissues and water, as well as potential thermal effects. In addition, the calculated field strengths assume direct interactions with isolated proteins in a vacuum, whereas in vivo these proteins exist within highly complex cellular environments characterized by substantial dielectric screening.

Furthermore, electrostatic contributions from bound ligands were not included, although such interactions may significantly influence the net dipole moment of protein-ligand complexes. The application of more advanced computational chemistry approaches would likely improve the accuracy of these field strength estimates.

Despite these limitations, the current calculations provide a useful baseline framework to guide the development of more targeted and effective PEMF protocols. In particular, they may

help inform the selection of key parameters such as field strength, pulse frequency, exposure duration, and considerations related to tissue penetration and attenuation.

As discussed earlier, a complementary approach to estimating the required magnetic field intensity involves the use of the free energy of unfolding (ΔG_u) of the protein or protein-ligand complex. However, accurate ΔG_u values typically require differential scanning calorimetry (DSC) data, which remain sparse in the literature for many of the cancer-associated targets included in this analysis.

Table 7 indicates that most products of cancer driver genes could, in principle, be disrupted within the higher range of magnetic field intensities (2–400 mT) defined earlier. Notably, approximately 82% of the listed cancer driver gene products are predicted to require field strengths greater than 20 mT to interfere with their interactions with cognate substrates or ligands. This suggests that enhanced antitumor effects across multiple cancer types may potentially be achieved by deploying PEMF protocols with maximum field intensities above 20 mT but below 400 mT, which is generally considered the upper acceptable limit for public magnetic field exposure. The only notable outlier is the HRAS–GTP interaction, which is predicted to require field strengths of up to approximately 625 mT.

Importantly, antiproliferative and antiangiogenic effects have already been observed at substantially lower intensities

(2–20 mT) across a broad spectrum of cancers, including breast, bladder, liver, hematopoietic malignancies, osteosarcoma, and fibrosarcoma. These effects have been mechanistically associated with DNA damage, apoptosis, and the induction of cellular senescence markers. However, the extent to which these antitumor responses may also result from direct interference with oncogenic signaling pathways remains to be experimentally validated.

Such validation could be achieved by employing tumor models driven by well-characterized cancer driver genes, enabling systematic assessment of whether PEMF exposure modulates specific oncogenic pathways in a target-dependent manner.

Table 7 further indicates that, in most cases, the magnetic field strengths needed to interfere with key oncogenic pathways fall within the operational range of FDA-approved PEMF devices used for specific clinical indications. Furthermore, some PEMF systems marketed for general wellness are capable of producing high peak magnetic field intensities—up to 100 mT—though often at lower frequencies. Clinical experience in areas such as bone regeneration and pain control suggests that efficacy is not solely determined by maximum field strength. Rather, an optimized combination of intensity, frequency, pulse width, and duty cycle is likely required for therapeutic benefit.

Future advances in PEMF technology—guided by personalized cancer genomic data and supported by rigorous clinical trials—may help establish electromagnetic field modulation as a viable adjunct or alternative in cancer therapy. A rigorous regulatory framework for PEMF devices used in cancer therapy as well as guidelines for safety and contraindications could then be established. Such progress will be essential to gaining broader acceptance within the medical community and among the general public.

7. Conclusion

This review has examined the expanding body of experimental and early clinical evidence supporting the use of pulsed electromagnetic fields (PEMF) and amplitude-modulated radiofrequency electromagnetic fields (AM-RF EMF) as potential adjuncts in cancer therapy. Originally developed and approved for orthopedic indications such as bone healing, PEMF technologies have demonstrated broader biological activity, including modulation of inflammation, angiogenesis, cellular metabolism, and signal transduction. These pleiotropic effects provide a biologically plausible foundation for their investigation in oncology.

Across multiple in vitro and in vivo tumor models, electromagnetic field exposure has been shown to inhibit proliferation, disrupt mitotic spindle formation, induce apoptosis, impair angiogenesis, and enhance sensitivity to chemotherapy and radiation. Notably, intermediate-frequency alternating electric fields (tumor treating fields) selectively target dividing cells through disruption of mitosis, while tumor-specific

AM-RF EMF protocols have demonstrated preliminary clinical activity in hepatocellular carcinoma and other malignancies without significant toxicity. Low- and higher-intensity PEMF exposures have likewise exhibited context-dependent antiproliferative effects across diverse cancer types, with encouraging evidence of synergy with cytotoxic agents and targeted therapies.

A consistent theme emerging from this literature is the marked heterogeneity of biological responses. Therapeutic effects vary according to field strength, frequency, waveform, exposure duration, tumor type, and proliferative state. Importantly, many studies report preferential sensitivity of malignant cells relative to non-transformed counterparts, suggesting a therapeutic window; however, the mechanistic basis for this selectivity remains incompletely defined. At present, no electromagnetic field protocol reliably induces durable tumor regression as a stand-alone intervention, underscoring the need for optimization and rational design.

To move beyond empirical parameter selection, this review proposes a framework grounded in structural biology and thermodynamics. By estimating the electromagnetic field strength required to perturb protein–ligand interactions or overcome binding free energies of key oncogenic targets, it may be possible to tailor PEMF protocols to disrupt specific driver pathways. Integration of cancer genomic data, structural databases, and quantitative biophysical modeling offers a path toward precision electromagnetic oncology. While current calculations are preliminary and subject to biophysical limitations, they provide a conceptual starting point for hypothesis-driven protocol development. Moving forward would include deployment of advanced computational tools to better estimate the required PEMF field strength, testing and optimizing protocols in tumor models with known cancer driver genes, and finally progressing towards human trials.

Ultimately, the clinical integration of PEMF and related electromagnetic modalities will depend on rigorous, adequately powered randomized trials, standardized exposure parameters, and mechanistic validation in well-characterized patient populations. If guided by advances in genomics, structural biology, and device engineering, electromagnetic field modulation may evolve from an empirically applied adjunct into a rationally designed, mechanism-informed component of multimodal cancer therapy.

Abbreviations

PEMF	Pulsed electromagnetic fields
TTFields	Tumor treating fields
ROS	Reactive oxygen species
AM	Amplitude-modulated
RF-EMF	Radiofrequency electromagnetic fields
EMT	Epithelial-mesenchymal transition
LDH	Lactate dehydrogenase

Acknowledgments

The author thanks William T. Windsor for providing some of the literature cited in this review.

Author Contributions

Hung Van Le: Conceptualization, Data curation, Formal Analysis, Investigation, Funding Acquisition, Methodology, Project Administration, Resources, Software, Validation, Visualization, Writing-original draft, Writing – review & editing

Conflicts of Interest

The author declares no conflicts of interest.

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