The Ecology of Breast Cancer

The Promise of Prevention and the Hope for Healing

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Chapter 6

The electromagnetic spectrum and breast cancer: Sunlight and vitamin D; shift work, artificial light, and sleep; electromagnetic fields

Electromagnetic radiation is a form of energy emitted and absorbed by charged particles. It has wave-like characteristics as it moves through space. The electromagnetic spectrum is the range of wave-lengths and frequencies of electromagnetic radiation (see figure 6.1). Visible light occupies a small portion of this spectrum, bounded on the lower frequency side by infrared and above by ultraviolet. X-rays and gamma rays lie beyond ultraviolet at much higher frequencies. Microwaves, radio frequency (RF) and extremely low frequency (ELF) radiation lie below infrared. The entire spectrum frequency distribution covers many orders of magnitude.

Sunlight includes ultraviolet light, which is responsible for initiating the conversion of vitamin D precursors into the active hormone in most animals and some plants. ELF electromagnetic fields are generated by electrical and electronic appliances and power lines. Radiation in the RF spectrum is generated by wireless devices such as cell phones and cordless phones, cellular antennas and towers, and broadcast transmission towers. This chapter discusses the relationship of these diverse frequencies of electromagnetic radiation to breast cancer.

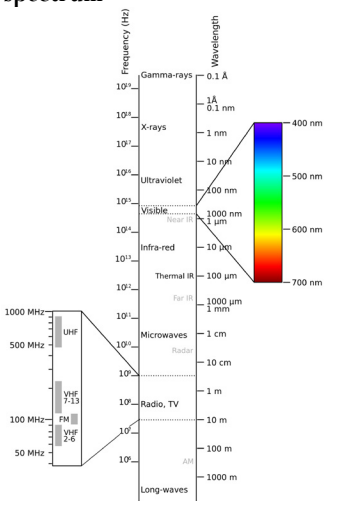
6.1 Vitamin D and breast cancer

Summary

Studies addressing the relationship between dietary vitamin D, vitamin D serum levels, and breast cancer are somewhat inconsistent, but most find higher vitamin D levels associated with lower risk. Insufficient levels of vitamin D are exceedingly common in the U.S. population. Vitamin D insufficiency may be particularly important during fetal development, childhood, and adolescence when cells are rapidly proliferating, tissues are developing, and their hormone responsiveness is established.

Based on estimated current vitamin D intake levels, measured serum levels, the benefits and safety of higher levels, and the available evidence that points toward lower breast cancer risk with higher levels of vitamin D, achieving and maintaining serum levels of 25(OH)D in the range of 30-40 ng/mL is supportable and highly unlikely to be associated with adverse consequences. This serum level is entirely consistent with conclusions of the IOM and the Endocrine Society. For most people, achieving this serum level will probably require some vitamin D supplementation, beginning in pregnancy and continuing in infancy and throughout life, as necessary.[1,2] It is important to recognize, however, that at some point, more is not better. Excessive vitamin D intake carries its own risks. Nonetheless, the margin of safety between current intake levels and safe upper limits is sufficiently large to justify supplementation, guided by laboratory testing of serum levels of 25(OH)D.

Figure 6.1: The electromagnetic spectrum*



* From Wikipedia http://en.wikipedia.org/wiki/File:Electromagnetic-Spectrum.svg

Vitamin D: Biologic activity and breast cancer risk

Vitamin D is an ancient hormone. It is not a vitamin in the sense that it must be supplied from dietary sources. Plants and animals have produced vitamin D as far back in evolutionary time as is traceable.[3] Phytoplankton, zooplankton, almost all animals, and some fungi

and plants exposed to ultraviolet rays from sunlight make forms of vitamin D from existing precursors.* It has diverse, essential biologic functions.[4]

Vitamin D deficiency causing abnormal calcium metabolism and rickets became a major public health problem at the beginning of the industrial revolution when children began to spend increasing amounts of time in sunless environments. The importance of sunlight and consequences of its absence was confirmed. A search for food that would help prevent rickets identified cod liver oil, the flesh of some fatty fish, and to a lesser extent, some mushrooms and eggs that contain naturally-occurring vitamin D. In the United States many dairy products and cereals are now fortified with vitamin D. It is also available as a dietary supplement.

Vitamin D obtained from sun exposure, food, and supplements is biologically inert and must undergo metabolic transformation to the active form. The liver converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. A second step yields the physiologically active 1,25-dihydroxyvitamin D [1,25(OH)2D], known as calcitriol. This conversion occurs primarily in the kidney and to a lesser extent in other tissues, including the breast. Calcitriol binds to vitamin D receptors (VDRs) and initiates biologic effects. Some VDRs are present in the cell nucleus and, when occupied by vitamin D, interact with DNA to modulate gene expression. Other VDRs are present in cell membranes and when activated, initiate a different cascade of events. Vitamin D receptors are present in most body cells, including the small intestine, colon, brain, heart, skin, prostate, gonads, breast, lymphocytes, osteoblasts, and β-islet pancreatic cells.

Historically, the role of vitamin D in calcium metabolism and bone health has received most attention, but in recent years it has become clear that vitamin D has multiple functions in the regulation of cellular growth and differentiation more generally. Inadequate vitamin D levels have been linked to a range of acute and chronic illnesses, including some cancers, immune disorders, infectious diseases, diabetes, neurocognitive disorders, and overall mortality.[5]

In support of the idea that inadequate levels of vitamin D might be linked to cancer, the authors of a paper published in 1980 proposed that lower levels of vitamin D at higher lat-

* Here the term vitamin D refers to vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) Both are produced by photolysis from naturally occurring precursors with light in the UVB spectrum (280–320 nm). Vitamin D2 is produced from ergosterol, a compound found only in plants and fungi. Vitamin D3 is produced from 7-dehydrocholesterol (7-DHC), found in high concentration in the skin of animals, including humans, and some plants.

itudes, where sun exposure is significantly less than at lower latitudes, might help explain geographic differences in colon cancer patterns.[6] More recent ecologic studies also show higher breast cancer incidence or mortality at higher latitudes.[7,8,9]

In vitro laboratory studies show that 1,25(OH)2D can inhibit cellular proliferation and promote programmed cell death (apoptosis) and cellular differentiation in breast tissue.[10,11] The mammary glands of laboratory rodents lacking the vitamin D receptor show altered mammary gland development with enhanced ductal proliferation and responsiveness to estrogen and progesterone stimulation.[12]

A prospective study of 242 pre-puberal girls in Bogota, Columbia also found that lower levels of plasma 25(OH)D were associated with earlier onset menarche.[13]

Laboratory studies show that rodents fed low levels of dietary vitamin D develop more mammary tumors when exposed to a carcinogen than animals fed adequate amounts of vitamin D.[14] The effect is most marked in animals that were also fed a high fat diet, showing that the combination of high fat diet and low levels of vitamin D created increased susceptibility to tumor development after exposure to a carcinogen. Animal studies also show that vitamin D can inhibit both early and later events in mammary tumor development.[15] *In vitro* studies of breast cancer cells show that vitamin D reduces aromatase levels.[16,17] Aromatase is an enzyme that aids in the conversion of androgens to estrogens, and aromatase inhibitors are among the pharmaceutical agents used to treat ER+ breast cancer. Thus, based on extensive laboratory data, a role for vitamin D in breast cancer prevention and treatment is plausible.

A number of epidemiologic studies have examined vitamin D status as a risk factor for breast cancer. Challenges in study design include determining the optimal time for measuring vitamin D status, using food frequency questionnaires to estimate dietary levels, accounting for correlations between calcium and vitamin D status (each may influence breast cancer risk independently), and estimating the primary source of vitamin D from exposure to sunlight.

Prospective observational studies

Some prospective observational studies attempt to examine breast cancer risk related to estimates of vitamin D intake from food or supplements.

The Nurses' Health Study included 88,691 pre- and post-menopausal women and estimated vitamin D intake from repeated food frequency questionnaires and assessment of supplement use.[18] After 16 years of follow-up, the highest vs. lowest estimated total vitamin D intake was associated with 28 percent lower risk of premenopausal breast cancer. There was no association with post-menopausal breast cancer risk and no effect of supplemental calcium. Among premenopausal women, high intake of low fat dairy foods was associated

with about 30 percent decreased risk of breast cancer. But, vitamin D appeared to have a protective effect independent of the "milk effect." This effect was apparent when vitamin D intake of > 500 IU daily was compared to <150 IU daily.

A recent analysis of data from the Nurses' Health Study II (NHS) reports that women with the highest levels of vitamin D intake during adolescence had a 21 percent reduced risk of developing proliferative benign breast disease.[19] This condition is associated with an increased risk of breast cancer subsequently.[20]

The NHANES I epidemiologic 1971-1975 to 1992 follow-up study[21] involved 4,747 white women including 179 breast cancer cases. Non-white women were excluded because there were too few breast cancer cases for a separate analysis. Participants were 25-74 yrs old and baseline vitamin D levels were estimated from sunlight exposure, diet, and dietary supplements. Sunlight vitamin D was classified as considerable, moderate, or low by dermatological skin exam and self-report of time spent in the sun. Several measures of sunlight exposure were associated with an approximately 30 percent decreased risk of breast cancer when comparing highest to lowest. Intake of at least 200 IU vitamin D was associated with 20 percent decreased risk of breast cancer. Higher sun exposure and higher dietary vitamin D intake in women who lived in an area of high solar radiation was associated with 64 percent risk reduction.

The Cancer Prevention Study II nutrition cohort followed 68,567 post-menopausal, mostly white women, using a baseline food frequency questionnaire and information about vitamin D supplement use for past year.[22] Over 9 years of follow-up there were 2855 incident cases of breast cancer. Women with highest level of dietary calcium intake had 20 percent lower risk of breast cancer. There was no association with supplemental calcium or vitamin D intake. Two or more dairy servings a day was associated with 20 percent decreased risk. For estrogen receptor positive tumors, higher levels of dietary calcium, vitamin D, and dairy were each associated with 20-30 percent decreased risk of breast cancer. This study did not inquire about sun exposure or measure serum levels of vitamin D.

Serum levels of 25(OH)D and breast cancer risk

Some studies have examined the relationship between vitamin D status and breast cancer risk by actually measuring serum levels of 25(OH)D rather than estimates of dietary sources or sun exposure. A pooled analysis from the NHS and a British case-control study concluded that women with 25(OH)D serum concentrations* of >52 ng/mL had a 50 percent lower

* Serum levels of 25(OH)D can be expressed as ng/mL or nmol/L. Multiply levels expressed as ng/mL by 2.5 to convert to equivalent levels expressed as nmol/L. For example, 20 ng 25(OH)D/mL is equivalent to 50 nmol 25(OH)D/L.

risk of breast cancer than those with levels < 13 ng/mL.[23] The authors estimated that a serum level of 50 ng/mL can be achieved by consuming about 4000 IU vitamin D daily or alternatively, consuming 2000 IU vitamin D daily and spending about 12 minutes/day in the noon time sun with 50 percent of skin exposed.

A recent meta-analysis of 9 studies (5 case-control; 4 nested case-control) reported that seven of the nine studies showed a lower incidence of breast cancer with higher serum levels of vitamin D.[24] This association was significant in five studies. This association was stronger in case-control (serum 25(OH)D levels measured after diagnosis; higher levels were associated with 40 percent decreased risk) than nested case-control studies (serum levels measured prior to diagnosis; higher levels were associated with 8 percent decreased risk). Thus, the findings are ambiguous.

Recognizing that differences in study populations, including menopausal status and a wide range of circulating levels of 25(OH)D, might explain these inconsistencies, the authors of a recent meta-analysis examined prospective studies using a non-linear dose-response evaluation and looking at pre-and post-menopausal breast cancer risk separately.[25] They found steadily decreasing risk of post-menopausal breast cancer associated with serum levels of 25 (OH)D beginning at 27 ng/mL and continuing up to 35 ng/mL, where the risk decline leveled off. There was no apparent association with risk of pre-menopausal breast cancer. This finding supports the hypothesis that there is a threshold effect of vitamin D on breast cancer risk and that intervention trials should be designed to use enough vitamin D to raise serum levels at least into the 30-35 ng/mL range.

Another meta-analysis examined the impact of individually estimated vitamin D intake, serum 25(OH)D levels, and calcium intake on breast cancer risk.[26] The authors also found decreased risk associated with higher levels of 25(OH)D, as well as with higher intake of vitamin D and calcium.

A more recent nested case-control study in France found that higher levels of serum 25(OH) D at baseline were associated with a 27 percent lower risk of breast cancer during 10 years of follow up.[27] In this study, the decreased risk was more pronounced in premenopausal women.

A case–control study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort and consisting of 1,391 breast cancer cases and 1,391 controls did not find a significant association between serum 25(OH)D levels and the risk of breast cancer.[28] However, higher levels of 25(OH)D were associated with lower risk in women who had taken hormone replacement therapy.

A case-control study found that African Americans were at much higher risk of vitamin D deficiency than European Americans. Low levels of vitamin D coupled with genetic variations in vitamin D metabolism were associated with much higher risk of ER- breast cancer in African Americans, whereas those same genetic variations did not affect the risk of breast cancer in European Americans.[29,30] This suggests that baseline low levels of vitamin D in African American women may increase the risk of aggressive breast cancer, particularly in a subset of women who metabolize vitamin D in a certain way, and adds support to the call for more vigorous vitamin D biomonitoring and supplementation when indicated.

Randomized controlled trials

The Women's Health Initiative included 36,282 post-menopausal women aged 59-70 years in a randomized, double blind study.[31] Half were given vitamin D (400 IU daily) and calcium (1000 mg daily) supplements; half were given a placebo. After an average follow up of 7 years, there was no difference in breast cancer incidence in the two groups. However, further analysis of data showed that women who were not taking vitamin D or calcium supplements at the time the study began and who were assigned to the vitamin D-calcium supplement intervention group had 14-20 percent decreased risk of all cancer, breast cancer, and invasive breast cancer over seven years of follow up.[32]

Another population based, double blind, randomized controlled trial in 1179 postmenopausal women followed for four years compared outcomes using vitamin D (1100 IU daily) plus calcium (1400-1500 mg. daily), calcium alone, or placebo.[33] The study was primarily designed to study bone fracture incidence but the data were secondarily analyzed for cancer incidence. Compared to women taking placebo, the risk of any cancer was 60 percent lower in the vitamin D plus calcium group and 47 percent lower in the calcium-only group. Both treatment and serum 25(OH)D concentrations were significant predictors of cancer risk, including breast cancer.

Studies that assess relationship of time outdoors with breast cancer risk

The Ontario Women's Diet and Health Study is a population based case control study of 3,101 women with breast cancer and 3,420 controls, ages 25-74 with an average age of 56 years.[34] Sixty-eight percent were post-menopausal and most Caucasian. Detailed information was collected about the amount of time spent out of doors at various ages. A decreased risk of breast cancer was associated with increasing time spent outdoors (>21 vs < 6 hrs/ week) during the teenage years (29 percent lower risk), 20s-30s (36 percent lower risk), 40s-50s (26 percent lower risk), and 60s-75 years (50 percent lower risk), all statistically significant. In this same study, vitamin D supplement use of 400 IU or more daily was associated with a decreased risk of breast cancer.[35]

Another population based case-control study in Ontario found a sharply reduced risk of breast cancer in women who had spent more time outdoors during adolescence, but weaker evidence of reduced risk with time spent outdoors from ages 20-29, and no evidence for ages 45-54.[36] Reduced risk was also associated with adolescent cod liver oil use and increasing milk consumption. Cod liver oil is a rich source of vitamin D and milk a source of both vitamin D and calcium.

Vitamin D post-diagnosis and recurrence

A study of 12,019 breast cancer survivors from four different cohorts in the U.S. and China found that vitamin D supplement use after initial diagnosis and treatment was associated with a 36 percent lower risk of recurrence in women with ER+ tumors but not ER- tumors.[37] This finding could be explained at least in part by reductions in levels of aromatase.

Vitamin D status of people in the United States: What level is healthy?

In 2011 an Institute of Medicine (IOM) expert panel concluded that most Americans had adequate levels of vitamin D, based on their assessment that a serum level of 25(OH)D of 20 ng/mL (50 nmol/L) or greater was sufficient.[38] A 2001-2004 NHANES survey had reported the average 25(OH)D level was over 20 ng/mL in the study population. However, people of color, particularly African-Americans, and older people are among those with significantly lower levels.[39] Children who are overweight or obese are also much more likely to have serum 25OH-D levels less than 20 ng/mL.[40]

In contrast, the Endocrine Society Clinical Practice Guidelines recommend a target level of serum 25(OH)D of at least 30 ng/mL, based on their assessment that levels at 20 ng/mL are not adequate.[41] Using the Endocrine Society guideline, over 50 percent of the U.S. population has insufficient levels of vitamin D.

The IOM committee had been charged with determining whether dietary reference intakes (DRIs) for calcium and vitamin D should be changed, based on new scientific information. Dietary reference intakes are intended to improve public health in the general population and provide recommendations for adequate and safe daily intakes of nutrients consumed over many years, possibly a lifetime. Thus, the committee said, the need for sound, causal evidence to make recommendations is essential. The IOM committee prioritized randomized clinical trials (RCTs) as providing the most persuasive evidence, although they supplemented their analysis with observational epidemiologic evidence but gave it lower standing.

After reviewing the available data addressing breast cancer, the IOM report says: "In summary, although experimental studies are suggestive of a role for vitamin D in breast biology, a review of the available evidence from both randomized controlled trials and observational

studies of associations between vitamin D and calcium and risk of breast cancer shows a lack of consistency between study outcomes and insufficiently strong evidence to support DRI development. Both retrospective and prospective studies do not show consistent associations between estimated vitamin D intake or 25 (OH)D status and breast cancer risk. A paucity of RCTs of vitamin D, calcium, or both with breast cancer as a primary outcome further limited the strength of the evidence."

The IOM committee found similar incomplete or inconsistent data for most other health endpoints and based their final recommendations on the relationship between vitamin D, calcium, and bone health alone, for which the data met their criteria for sufficiency.

The IOM report estimates that the average vitamin D intake for males in the U.S. is 300-400 IU daily; for females 200-400 IU daily. The estimates vary with age and do not account for vitamin D from sun exposure. Thus, on average, vitamin D intake in the U.S. is below the recommended daily intake (RDA) of 600 IU vitamin D daily and well below the estimated safe upper limit.

The committee affirmed a RDA of 600 IU daily, except 800 IU daily for men and women > 70 yrs of age, based only on requirements for bone health. But the committee acknowledged a safe upper limit of 1000-1500 IU in infants, 2500-3000 IU in children, and 4000 IU in adolescents and adults

Vitamin D status during pregnancy

The American College of Obstetricians and Gynecologists (ACOG) recommends testing only pregnant women who are at increased risk of vitamin D deficiency (e.g., women with limited sun exposure, women with darker skin that limits absorption of vitamin D). If a woman's vitamin D levels are 20 ng/mL (50 nmol/ L) or less, ACOG recommends vitamin D supplementation in a dosage of 1,000 to 2,000 IU daily.[42]

Vitamin D status in infancy

The American Academy of Pediatrics recommends that all infants, whether breast fed or formula fed, receive a vitamin D supplement, based on widespread inadequate serum levels.[43]

6.2 Shift work and breast cancer

In 2010, the International Agency for Research on Cancer (IARC) concluded that shift work that involves circadian rhythm disruption is "probably carcinogenic to humans."[44] Exposure to light at night may help explain the relationship between shift work and cancer risk.

The major hypothesized mechanism by which shift work and disrupted circadian rhythm might influence breast cancer risk is through alteration in melatonin levels. Melatonin is a hormone secreted by the pineal gland, located in the middle of the brain. Circulating melatonin levels are lowest in daytime light and highest at night. Light at night depresses melatonin levels and disrupts its rhythmic cycle.

Melatonin is a powerful anti-oxidant. It exerts this effect not only by scavenging DNA-damaging free radicals but also by up-regulating antioxidant enzymes.[45] Melatonin also regulates the activity of other hormones and growth factors. It suppresses cell proliferation by delaying the progression of the cell cycle.[46] In breast cancer cells, this is most marked in those that are ER+.[47] Melatonin modulates gene transcription activity of the estrogen receptor and other nuclear receptors. It reduces aromatase activity, thereby reducing estrogen levels, promotes apoptosis in breast cancer cells, and may enhance DNA repair.[48] Laboratory animal studies show that melatonin significantly reduces the incidence and tumor size of rat mammary cancers induced by DMBA or N-nitrosomethylurea (NMU).[49]

Additional evidence supporting the influence of melatonin comes from the observation that blind women have a significantly lower breast cancer risk than women who are not, even after controlling for known risk factors.[50] The risk is more sharply reduced in women who have no light perception at all. People who are blind tend to have reduced spikes of melatonin, but higher baseline levels that vary considerably among individuals. It is unclear, however, whether this fully explains their reduced risk.[51,52]

Other factors at play in shift work may also influence breast cancer risk. People who work at night may spend less time outdoors in sunlight during the day and thereby have lower vitamin D levels. One study in the UK found that women working at night had an average 8 percent lower vitamin D level than others after controlling for social class, BMI, and season.[53] Surprisingly few studies have examined this relationship, however.

Most studies have examined breast cancer risk as it relates to shift work although some have also investigated prostate, colon, and uterine cancer risks. The IARC identified eight studies that examined the relationship between breast cancer and shift work that involved working at night. Six of those studies, including two prospective cohort studies in nurses, showed a modestly increased risk of breast cancer in long-term employees who worked night shifts. The two studies not showing an increased risk had limitations in study design, according to IARC.

A more recent systematic review and meta-analysis identified 12 case-control and four cohort studies examining night shift work as a risk factor for breast cancer.[54] Many of the studies analyzed focused on nurses and most were comprised of relatively high-income, white participants. This analysis excluded studies of airline crews because of other potentially com-

plicating exposures such as cosmic radiation and time-zone changes. The authors reported a nine percent increased risk per five years of night-shift work in case control studies but no increased risk in cohort studies.

6.3 Sleep and breast cancer

In addition to shift work and light at night, epidemiologic studies have also investigated links between sleep and breast cancer risk. Of six studies that have investigated sleep duration and breast cancer, three found no association,[55,56,57] one reported an increased risk with increased sleep duration[58], one found an increased risk with short sleep duration (<6 hrs/day),[59] and one reported a decreased risk with increasing sleep duration and no association with sleep quality.[60]

The metrics associated with the epidemiology of sleep are not yet standardized and this may help explain disparate findings.[61] Sleep duration, quality, and disturbance may be collectively or independently related to disease risk. Erren proposed a "sleep-years" index to assess cumulative sleep over decades as a possible approach.[62]

6.4 Radiation, electromagnetic fields and breast cancer

In general, electromagnetic radiation with frequencies higher than the visible spectrum has sufficient energy to break chemical bonds, creating charged particles (ions) that can cause DNA mutations, various other kinds of cellular damage, and cell death.[63] This is ionizing radiation. Lower-frequency radiation from ELF-EMFs and RF-EMFs does not have sufficient energy to break chemical bonds and create highly reactive ions. Thus, it is called non-ionizing.

In the 20th century it became clear that ionizing radiation could cause mammary gland tumors in laboratory animals and breast cancer in women who had undergone chest fluoroscopy for tuberculosis or X-irradiation for mastitis and in survivors of the atomic bombing in Japan.[64,65,66,67] According to the 2008-2009 Annual Report of the President's Cancer Panel, while ionizing radiation exposures from radon, occupational, and other sources have remained essentially stable over the past 30 years, Americans now are estimated to receive nearly half of their total radiation exposure from medical imaging and other medical sources, compared with only 15 percent in the early 1980s.[68] This panel and others have concluded that reducing exposure to ionizing radiation, including from unnecessary medical procedures, is an obvious and important way to reduce breast cancer risk.[69]

Two kinds of non-ionizing radiation from EMFs are 1) extremely low frequency electromagnetic fields (ELF) from electrical and electronic appliances and power lines and 2) radiofrequency radiation (RF) from wireless devices such as cell phones and cordless phones, cellular antennas and towers, and broadcast transmission towers.[70]

Regulation of the non-ionizing electromagnetic spectrum is muddled. No agency routinely monitors and responds to health concerns arising from exposure to ELF-EMF. The Food and Drug Administration (FDA) has the regulatory authority to take action if a cell phone is found to emit RF-EMFs of sufficient energy to pose a risk of harm. However, to a large extent the FDA allows the Federal Communications Commission (FCC) to set regulatory guidelines for emissions from cell phones, transmission antennas, and towers. The FCC certifies wireless devices, and all phones that are sold in the United States must comply with FCC guidelines on RF exposure.

Some people believe that current regulations, promulgated in 1996 with minor updates in 2003, are out-of-date and not based on more current information that looks beyond thermal effects of exposure.[71] Indeed, there is evidence that the FCC has even failed to enforce certain existing standards.[72] After urging by the Government Accounting Office, the FCC has recently agreed to undertake a review of cell phone exposure standards and the way the phones are tested for compliance with that limit.[73]

Historically, scientists and concerned citizens have considered health effects associated with exposure to EMFs against a backdrop of a commonly-held belief that non-ionizing EMFs that do not generate heat could not plausibly have any adverse biologic effects. The field abounds with skeptics convinced that radiation of insufficient energy to break chemical bonds, ionize atoms, and at least produce heat cannot possibly be harmful. Data tell a different story. They support often-ignored concerns that this is an important public health issue, particularly since virtually everyone in today's world is exposed to ELF-EMFs and RF-EMFs. This means that even relatively small increases in disease risks can have large public health consequences.

This topic is mired in controversy. The BioInitiative 2012 report extensively reviews mechanisms by which ELF- and RF-EMFs can have diverse non-thermal adverse biologic effects and a range of health effects linked to these exposures, including cancer.[74] Potential mechanisms for which there are varying levels of support include genotoxic effects, alterations in gene expression, oxidative stress, up-regulation of stress responses, changes in permeability of membranes and the blood brain barrier, reduced melatonin levels, and altered immune function, among others. Another summary of "expert group reports" finds no "demonstrated health risk" from RF-EMF exposure from cell phones or other wireless technologies.[75] This is a long-standing debate that is unlikely to be resolved anytime soon.

With regard specifically to cancer, in 2001 the International Agency for Research on Cancer (IARC) classified ELF-EMF as possibly carcinogenic to humans, based on an association between higher levels of exposure to EMFs from proximity to high voltage power lines and increased risk of childhood leukemia. In 2011, IARC classified RF-EMFs (cell phones and related technology) as possibly carcinogenic to humans, based on an increased risk of glioma, a malignant brain tumor, associated with wireless phone use.[76] Investigators have also examined the possibility that exposure to ELF-EMF might be associated with an increased risk of breast cancer.

Studying the health impacts of ELF-EMF exposure is challenging. Most importantly, exposure assessments are difficult. At a basic level, it is not always obvious which aspect of the EMF is most biologically important. ELF-EMF exposures have both electric field and magnetic field components. Most epidemiologic studies of ELF and breast cancer have focused on associated magnetic fields. But it may be that electric field exposures also matter.[77] Moreover, investigators often use estimates of average exposures, but peak exposures or even rate of change may be equally or more important. And, since ELF-EMFs are not perceptible and vary substantially with everyday circumstances, they must either be directly measured or estimated using proxies based on conditions that influence exposure—e.g. occupation or electric blanket use. Thus, epidemiologic studies are often limited by imprecise exposure assessments, subject to exposure misclassification, and are likely to be biased toward finding no association, even if one truly exists.

Decreased melatonin production associated with higher exposures is one proposed mechanism by which ELF-EMF could influence breast cancer risk. As previously noted melatonin is a powerful anti-oxidant and has various other properties that are likely to reduce breast cancer risk. Laboratory studies show that melatonin can inhibit proliferation of ER+ breast cancer cells. Studies in cell cultures show that ELF-EMFs can interfere with this effect.[78,79] Other cell culture studies show that the magnetic field associated with ELF-EMF at typical environmental levels can not only interfere with the suppressive action of melatonin but also tamoxifen, a pharmaceutical estrogen antagonist commonly used in the treatment of ER+ breast cancer.[80,81] Thus, ELF-EMFs could plausibly promote ER+ breast cancer.

Results from melatonin studies in various laboratory animal species and humans are inconsistent. Some show that ELF-EMFs reduce melatonin production and activity while others do not.[82] The reasons for these inconsistencies are not entirely clear but differences in study design, including variable exposure patterns and timing of melatonin measurements, are likely to be at least partly responsible.

A 2001 meta-analysis of 15 case-control and 21 cohort studies found a 12 percent increased risk of breast cancer associated with higher ELF-EMF exposures in women [relative risk 1.12 (95 percent CI: 1.09, 1.15)] and a 37 percent increased risk in men [relative risk of

1.37 (95 percent CI: 1.11, 1.71)].[83] The findings in men may be particularly instructive since men do not have many other known risk factors and breast cancer in men is much less common than in women. In the 19 studies of men included in this meta-analysis (5 case-control; 14 cohort), nine used job title or job-exposure matrix to estimate ELF-EMF exposure while the remainder used job title and various other estimates of exposure. Some degree of exposure misclassification is almost inevitable, potentially biasing the results toward finding no association, even if one exists. Thus, the 37 percent increase in relative risk may actually be an under-estimate.

A more recent meta-analysis of 15 studies published between 2000 and 2009 found no significant association between ELF-EMF exposure and female breast cancer risk (OR =0.988, 95 percent CI: 0.898–1.088), including subgroup analyses by exposure modes, menopausal status, or estrogen receptor status.[84] Subgroup exposure modes included occupational vs. residential exposures and electric blanket exposures specifically.

No studies of RF-EMF and breast cancer have been published. However, IARC's recognition of the possible link of RF-EMF to brain cancer has raised concerns about other cancer risks associated with widespread cell phone use and its accompanying infrastructure. Even though RF-EMF is not ionizing radiation, some studies show evidence of genotoxicity associated with experimental RF exposures similar to those from cell phones while others do not.[85,86,87] This has sparked considerable debate inasmuch as exposure to RF-EMF is widespread. According to a UN report, about six billion people throughout the world now have access to cell phones.[88,89]

Anecdotal reports of breast cancer in young women who carried their cell phones in their bras have helped to reveal just how widespread the practice is today.[90] Inasmuch as solid tumors like breast and brain cancer have long latency periods, it will be many years before definitive studies resolve uncertainties about the safety of cell phones and related technologies. To the extent that RF-EMF exposures raise cancer risks even modestly, the public health consequences will be large because of such widespread exposures.

The best ways to reduce RF-EMF exposures from cell phones include:

- keep conversations on cell phones as short and infrequent as possible; use a land line or send texts instead;
- do not put it against your body. Put it in your purse, your backpack, or your case;
- do not keep your cell phone in your bra or pocket;
- always try to keep it a few inches away from your body. The strength of the antenna signal decreases quickly with increasing distance from the source;
- do not call in vehicles (car, bus, train). If your mobile does not have an external antenna, the radiation levels go up in moving vehicles. This is because each time the

cell phone connects to a new tower (the "handshake") an increase in power follows until an optimal level is established;

- avoid placing mobile calls in places with poor reception such as cellars or elevators. The cell phone will increase its power (and thus the radiation) in such situations;
- use the speaker phone feature;
- plug in earphones while talking;
- use the hands-free device;
- keep the phone away from your head;
- do not sleep with it under your pillow;
- put your cell phone in airplane mode.

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