

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



# Research and Therapeutic Innovation: Tissue Resonance InterferoMeter Probe in Early Detection-Screening for Rectal Cancer

Alberto Vannelli and Luigi Battaglia  
Fondazione IRCCS "Istituto Nazionale Tumori", Milan,  
Italy

## 1. Introduction

Clarke's Second Law is: "The only way of discovering the limits of the possible is to venture a little way past them into the impossible" (Clarke, 1962). Tissue Resonance InterferoMeter Probe (trimprob) issues this challenge.

Cancer is a major health problem in developed countries, in many of which it is the second most common cause of death for all ages combined. At the beginning of the 21st century 10 million people in the world develop cancer each year (Blackledge, 2003).

In the Globocan 2002 database of the International Agency for Research on Cancer (IARC), the worldwide burden of colorectal cancer (CRC) is estimated as 550,000 incident new cases and 278,000 deaths for men, and 473,000 incident new cases and 255,000 deaths for women. In 2002, CRC comprised 9.4% of the global cancer burden in both sexes and was most frequent in North America, Australia, New Zealand, and parts of Europe. This has led to colorectal cancer being considered as a disease of the Western lifestyle (Winawer, 2007). The advent of molecularly targeted drugs promised to change survival. Within 20 years CRC will be considered a chronic disease, joining conditions such as diabetes, heart disease and asthma. Although very successfully used in combination, chemotherapy results in metastatic CRC have been disappointing with little more than palliative benefit. For example chemotherapy for advanced CRC cured with a low complete response and most patients relapsed with resistant disease (Vincenzi et al., 2004). These conditions impact on the way people live but will not inexorably lead to death. Individual cancer risk assessment will lead to tailored prevention messages and a specific screening programme to pick up early cancer and have far reaching public health consequences. Therefore, improving screening shows the challenges that need to be addressed in order to deliver most health benefit. But cancer prevention absorbs only 2 per cent of the total funding of cancer care and research in the world. Information regarding resources allocated to cancer is particularly scarce, even more so for CRC (Kanavos et al., 2008). CRC is rapidly increasing in Asia, but screening guidelines are lacking (Sung et al., 2005). Data regarding resources allocated to CRC in Latin America or Africa are absent. CRC expenditure adjusted for cancer population burden in the few countries collecting cancer expenditure, found large variations between countries (high of €85,116 per total cancer death in Sweden to a low of €9,528 in Russia). This continued with CRC expenditure, where the range was from €10,288 per CRC mortality

(Hungary) to €122,828 (France). Approximately half of surveyed countries had formal resource allocation mechanisms; fewer had disease-specific resource allocation, and only Australia reported cancer-specific resource allocation. The majority of countries perceived insufficient resources were allocated to cancer care and CRC care. Eastern European countries reported significant problems with cancer-specific funds, with persistent shortcomings and insufficient funding. Many of the countries that have formal screening activities, be it for CRC or other cancers, have formal screening resource allocation. Australia, some European countries and the USA all have governmental funding for their CRC screening programmes, ranging from €8-25 million. These values are half of what these countries allocate to their breast cancer screening programmes. It appears that cancer spending displays significant variation between countries, along with the majority of countries not accounting for cancer in its resource allocation mechanisms. As cancer accounts for significant morbidity and mortality after cardiovascular disease, this seems to be an important omission. Cancer care is a significant part of health care expenditure, and should be accounted and planned for appropriately.

All these data reinforce the opinion on which the CRC is one of the most important problems in Healthcare. What's the solution? The current opinion suggests to spread screening programmes.

But what is a screening? Screening programmes would be developed on a national basis if they are simple, robust and cheap. Patients would expect the screening to take place at a convenient venue for them – in shopping malls and not be painful or overly time-consuming. Health professionals would demand that any programme is accurate and does not give misleading results, and governments would demand that its costs would lead to more effective use of other resources. Novel providers of risk assessment services are likely to emerge. (Sikora, 2007). According to Mayo Clinic staff: "Colon cancer is cancer of the large intestine (colon), the lower part of your digestive system. Rectal cancer is cancer of the last several inches of the colon. Together, they're often referred to as colorectal cancers. Most cases of colon cancer begin as small, noncancerous (benign) clumps of cells called adenomatous polyps. Over time some of these polyps become colon cancers. Polyps may be small and produce few, if any, symptoms". For this reason, doctors recommend regular screening tests to help prevent colon cancer by identifying polyps before they become colon cancer.

Therefore it's correct to assume that most CRCs arise from sporadic adenomas, and a few from genetic polyposis syndromes or inflammatory bowel disease (IBD). Because of high prevalence, as well as a long asymptomatic phase and treatability of precancerous lesions, colorectal cancer is an ideal target for screening. But these axioms cast doubts about the efficacy of CRC screening.

The term "polyp" refers to a discrete mass that protrudes into the intestinal lumen, but the reported prevalence of adenomatous polyps, on the basis of screening colonoscopy data, is only in the range of 18–36%. Moreover the risk for CRC varies from country to country and even within countries. The risk also varies among individual people based on diet, lifestyle, and hereditary factors. Current guidelines are directed to test asymptomatic men and women who are likely to have adenomatous polyps or cancer but current CRC screening efficacy only on symptomatic population. This screening always needs to be applied within the framework of a program that includes: primary prevention (diet, lifestyle), timely diagnostic work-up with colonoscopy (where available and consistent with the cascade)

overall in those screened positive, and timely treatment (polypectomy, surgery). CRC screening is particularly challenging, as reflected in current low screening rates in most countries where there is a high risk for CRC. CRC screening is complex, as there are multiple options, it requires considerable patient effort (fecal occult blood test slides, colonoscopy preparation, etc.), and it requires sedation and a health-care partner for some tests (colonoscopy). For a screening program to be successful, multiple events have to occur, beginning with awareness and recommendation from the primary-care physician, patient acceptance, financial coverage, risk stratification, screening test, timely diagnosis, timely treatment, and appropriate follow-up. If any one of these steps is faulty or is not of high quality, the screening will fail.

Previous studies have investigated the cost-effectiveness of colonoscopy, flexible sigmoidoscopy, and fecal occult blood testing as screening alternatives (Sonnenberg et al, 2000). Flexible sigmoidoscopy was less cost-effective than fecal occult blood testing and colonoscopy. Fecal occult blood testing is a simple, low-cost screening method, but colonoscopy was more effective in saving lives. All standard options for CRC screening are not convincing because are cost-effective only in average-risk individuals. They are more cost-effective than other forms of medical screening: cholesterol in hypertension.

Screening tests	Evidence		
	Sensitivity	Specificity	
Occult blood tests	50-60%	95.2%	Fecal occult blood testing using the guaiac smear is currently being replaced in many countries by fecal immunochemical tests.
Fecal DNA tests	52%	94.4%	the optimal set of molecular markers remains to be determined, and the feasibility of such tests when applied to the general population is as yet unknown.
Flexible sigmoidoscopy	35-70%,	98-100%	the sensitivity is low due to the significant number of right-sided adenomas that occur in the absence of distal tumors and are therefore missed on flexible sigmoidoscopy.
Colonoscopy	at least 95% for large polyps	at least 95% for large polyps	There are no prospective randomized studies that have examined the impact of colonoscopy on incidence or mortality.
Double-contrast barium enema	48%	50%	It's more likely than colonoscopy to yield false-positives.
Computed-tomographic colonography	93% for polyps 10 mm or larger	97% for polyps 10 mm or larger	When polyps of all sizes were included, the studies were too heterogeneous in sensitivity (range 45-97%) and specificity (range 26-97%).

Table 1. Screening tests and evidence.

Systematic screening colonoscopy in first-degree relatives of patients with CRC, starting at the age of 40, demonstrates an economic benefit only in comparison with multiple-drug intensive chemotherapy for advanced cancer, screening is cost-saving (Table 1). However, high costs and low compliance rates for colonoscopy have encouraged a search for different methods. It has been proposed that cancer exposed to a low level of electromagnetic incident waves may behave differently than healthy tissue. The phenomenon of “nonlinear resonance interaction,” which is produced when the oscillations of an electromagnetic probe are coupled with those from biological tissue, can be used to test for differences between healthy and cancerous tissues (Vedruccio et al., 2004).

## **2. Electro-medical device for non invasive diagnostics**

### **2.1.1 Historical background**

Diagnosis of cancer in humans is mainly based on microscopic observation of morphological changes in cells and irregularities in tissues through the use of cytological and histological methods (Bibbo, 1997). All these processes are the manifestation of hidden processes of biochemical as well as physical nature. One of the most important as well as misleading effect is the Mitochondrial Warburg Effect. For a long time, disturbances in physical processes in cancer development were not adequately taken into consideration. To understand what does it mean, it's necessary to start by the end of this process. Therapeutic selectivity, or preferential killing of cancer cells without significant toxicity to normal cells, is one of the most important considerations in cancer chemotherapy (Pelicano et al., 2006). Understanding the biological differences between normal and cancer cells is essential for the design and development of anticancer drugs with selective anticancer activity. Cancer is a family of diseases that involve uncontrolled cell division and tissue invasiveness (metastasis). In the recent years, tremendous progress has been made in our understanding of the molecular mechanisms of cancer, in identification of specific genes and signalling pathways involved in carcinogenesis and cancer progression, and in developing chemical compounds or specific antibodies that specifically target the oncogenic molecules.

Cancers result from a series (progression) of gene mutations that typically involve two categories of function: promotion of cell division and inactivation of cell cycle suppression. Proto-oncogenes are normal genes that promote cell growth and mitosis, whereas tumor suppressor genes discourage cell growth. Proto-oncogenes can be mutated by carcinogenic agents to become oncogenes. Oncogenes produce excessive levels of growth promoting proteins. Tumor suppressor gene products typified by p53 are frequently transcription factors that suppress mitosis and cell growth to allow for DNA repair. Nearly half of all cancers involve altered p53 genes. Other suppressor genes include Rb (retinoblastoma family), APC (adenomatous polyposis coli), SMAD4, TP53, p16/CDKN2A and BRCA (breast cancer susceptibility protein) types 1 and 2. Cancer results from cumulative mutations of proto-oncogenes and suppressor genes which together allow the unregulated growth of cells. Oncogenes are typically dominant because they provide gain-of-function, whereas suppressor genes are recessive. They contain loss-of function mutations. Both copies of a suppressor gene need to mutate to cause loss-of-suppressor function. Only one copy of a proto-oncogene needs to mutate for gain-of-function. Mutations of tumor suppressor genes can be inherited. Over time malignant cells can self-select for characteristics that make them more malignant: ability to avoid apoptosis; immortalization



due to over expression of telomerase; growth-factor self-sufficiency and resistance to anti-growth factors; increased cell division; altered differentiation; loss of contact inhibition, become metastatic; and able to promote angiogenesis. The target-specific agents have major advantages over the traditional chemotherapeutic compounds in that the targeting agents specifically interact with the key molecular players in cancer cells and have low toxicity to the normal cells. In the past researchers assumed that cancer cells and normal cells had much in common in terms of the internal machinery that allows them to carryout the many activities necessary to stay alive. Chemotherapy drugs effectively target processes that cancer cells need to grow and divide, such as the ability of the cancer cells to replicate their DNA. However, many normal cells, like the cells that line the digestive tract, also need to replicate. In short, though chemotherapy drugs are particularly toxic to cancer cells, they also damage healthy cells. The use of standard chemotherapy therefore produces many, and often severe, side effects. Furthermore, these side effects sometimes prevent patients from being able to take high enough doses to fight the cancer most effectively. While chemotherapy drugs are quite effective treatments for many forms of cancer, researchers have been working diligently to produce drugs that target the processes of cancer cells specifically so as to leave healthy cells unharmed. The accumulation of knowledge about the specific differences between normal and cancerous cells has allowed for the development of treatments targeted at cancer-specific activities.

One of the most fundamental changes found in cancer cells is the presence of mutations in the genes that are responsible for causing cell growth (oncogenes). The defective proteins produced by these altered genes are prime candidates for targeted therapy. As an example, some cancers are caused in part by mutant proteins that send constant signals into the cell causing cell division. Drugs that block only the mutant form of the protein but do not interfere with the activity of the normal version would only affect cancer cells, and would leave healthy cells untouched. Alternatively, many cancers result when genes that normally prevent cell growth (tumor suppressors) are inactivated or turned off. Drugs that "fix" the activity of these proteins would repair the damaged cancer cells, but theoretically have no effect on normal cells.

New agents with a high degree of target specificity and clinical therapeutic activity, exemplified by Gleevec (imatinib), Iressa (gefitinib), herceptin (trastuzumab), and rituximab, represent an exciting direction for cancer drug development. However, the mechanisms underlying cancer development and the disease progression are extremely complex, and it is now recognized that in many types of cancers there are multiple genetic and epigenetic alterations. Even within a specific cancer type, the malignant cell populations are heterogeneous and contain diverse genetic changes, which further alter over time because of genetic instability as the disease progresses. As such, it would be difficult to specifically kill these cancer cells by targeting a single gene. Proper combination of multiple target-specific agents may be required to effectively eliminate the entire cancer cell population.

An alternative strategy to achieve both therapeutic selectivity and efficiency is to take advantage of the fundamental difference between cancer cells and normal cells in their biochemical metabolism. Cell proliferation requires the conversion of nutrients into biomass. One of the first differences noted between cancer cells and normal cells was a difference in metabolism (Vander Heiden et al., 2009). One of the most prominent metabolic alterations in cancer cells is the increase in aerobic glycolysis and the dependency on glycolytic pathway for ATP generation as showed in Figure 1 (Erickson & Cerione , 2010).

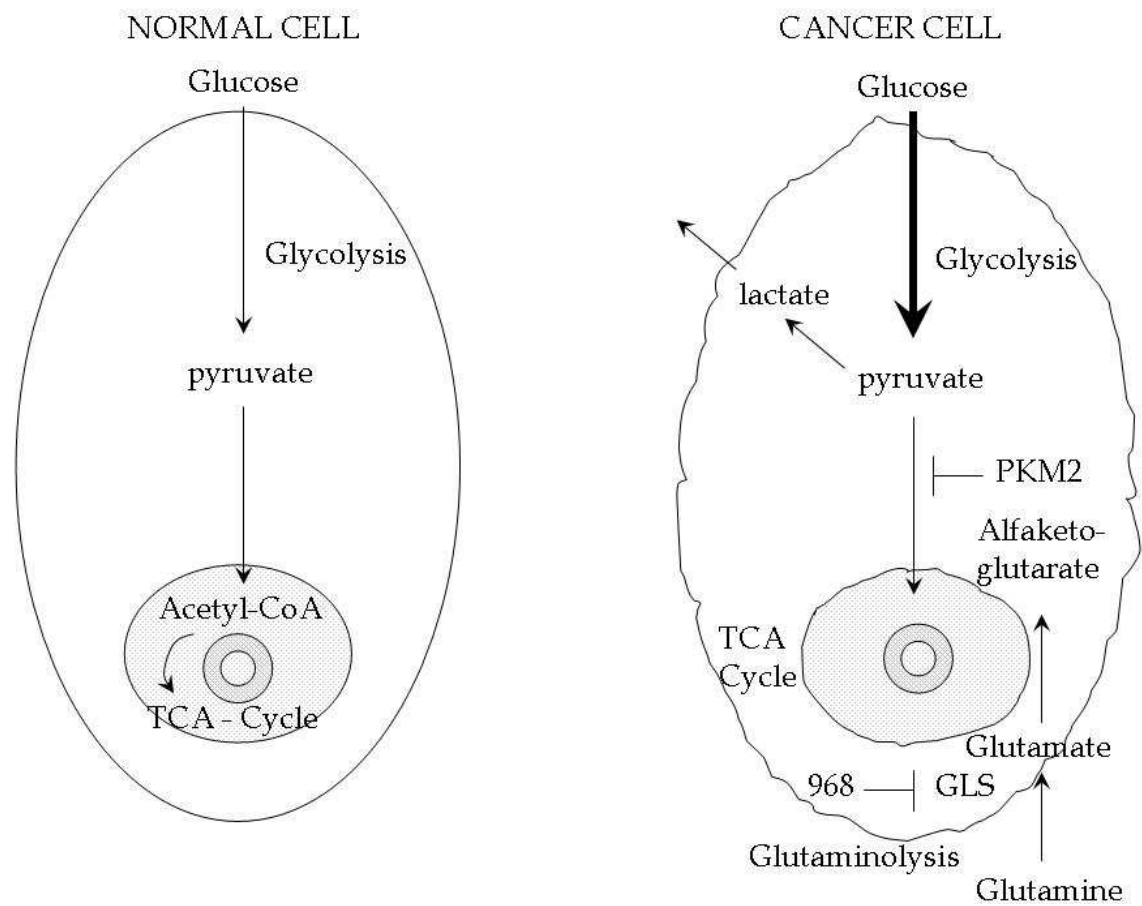


Fig. 1. Different metabolic pathway

This is the Warburg effect (Warburg et al., 1924; Warburg, 1930, 1956). As this metabolic alteration is frequently seen in cancer cells of various tissue origins, targeting the glycolytic pathway may preferentially kill the malignant cells and therefore have broad therapeutic implications. Although cancer cell energy generation is mainly dependent on reactive anaerobic glycolysis, most malignant tumors still breathe, in part by an uncoupling protein-mediated mitochondrial pathway. Uncoupling proteins help import fatty acids and are over expressed in various types of chemo-resistant cancer cells (Mayevsky, 2009). New technologies will help accomplish this systematic work.

2.1.2 Warburg effect

Otto Heinrich Warburg (October 8th, 1883, Freiburg im Breisgau – August 1st, 1970, Berlin), was a German physiologist, medical doctor and Nobel laureate. "Warburg effect" is used for two unrelated observations in biochemical, one in plant physiology and the other in oncology, As early as 1924 he demonstrated that tumor cells exhibit an altered sugar metabolism as they are metabolizing up to 20 times more glucose compared to healthy cells (Warburg et al., 1924). These cancer cells produce lactate in large amounts not only under anaerobic conditions (like their healthy counterparts) but also in the presence of oxygen. This so called "Warburg effect" or "aerobic glycolysis". This is remarkable, since glucose metabolism under aerobic conditions via Embden-Meyerhof pathway (EMP), citrate cycle and respiratory chain yields 38 ATP per molecule glucose, while glycolysis to lactate leads to only 2 ATP. In the presence of oxygen and glucose, healthy cells generate a vast majority

of energy in form of ATP by complete combustion of glucose to CO<sub>2</sub>, while tumor cells metabolize the majority of glucose via pentose phosphate pathway (PPP) to lactate. According to standard textbooks the PPP provides cells with reduction equivalents in form of NADPH and moreover with ribose- 5-P, a key metabolite for DNA/RNA biosynthesis. The non-oxidative part of PPP is controlled by transketolase. Ever since the pioneering observation that aerobic glycolysis in cancer is preferred over oxidative phosphorylation as a mechanism to generate ATP from glucose, numerous experiments have supported and extended the significant role that metabolisms have on transformation, proliferation, angiogenesis and metastasis in cancer. Thus, scanning human tumors with positron emission tomography (PET) has verified that a high uptake rate of glucose constitutes a hallmark in cancer cells, presumably required to confer adaptive advantages when facing acidic and hypoxic environments.

Normal cells use glycolysis prior to respiration in the mitochondria and complete breakdown of glucose by the tricarboxylic acid (TCA) cycle (Figure 1). In cancer cells, glycolysis becomes the primary mode of glucose metabolism resulting in lactate and its secretion. The M2 isoform of pyruvate kinase (PKM2) becomes tyrosine phosphorylated and attenuates pyruvate acetyl-CoA conversion while glutaminolysis provides the cancer cell with an alternate source of biosynthetic precursors, fueling the TCA cycle with glutamine-derived  $\alpha$ -keto-glutarate. The anti-tumor drug 968 inhibits glutamine metabolism by inhibiting the enzyme glutaminase (GLS).

Cancer cells have a high glycolysis rate even in the presence of oxygen (Figure 1). Otto Warburg, assumed that because of mitochondrial malfunction, cancer cells had to depend on anaerobic glycolysis to generate ATP (Warburg, 1956). This hypothesis was later disproved. It was demonstrated, however, that cancer cells with intact mitochondria also showed evidence of the Warburg effect. This effect provides a marker for detecting tumor cells. With positron emission tomography using a glucose radioisotope (18fluorodeoxyglucose), cancer cells can be visualized owing to their significantly higher than normal glucose uptake.

Thus, an alternative explanation was proposed: the Warburg effect helps cancer cells harness additional ATP to meet the high energy demand required for their extraordinary growth while providing a basic building block of metabolites for their proliferation. A third view suggests that the Warburg effect is a defense mechanism, protecting cancer cells from the higher than usual oxidative environment in which they survive. Interestingly, the latter view does not conflict with the high-energy production view, as increased glucose metabolism enables cancer cells to produce larger amounts of both antioxidants to fight oxidative stress and ATP and metabolites for growth. It may be related to the surprising fact that although aerobic respiration produces 18 times the ATP per mole of glucose compared with anaerobic glycolysis, the rate of anaerobic glycolysis is 100 times that of aerobic respiration. According to a population biology model developed at the Max Delbrück Center for Molecular Medicine in Germany, ATP production at a higher rate but lower yield may confer a selective advantage in competing for shared energy resources. Lactate, also a product of glycolysis, induces several oncogenes. In addition, lactate surrounds cancer cells, providing an acidic environment that protects cancer cells from the immune system. A key enzyme of the pentose phosphate pathway, transketolase, was shown to play an important role in cancer proliferation and malignancy. Among colon and uroepithelial cancer patients, the expression level of transketolase-like gene 1 (one of the transketolase genes) was strongly related to the patients' survival rate. Autopsy results confirmed the correlation



between increased expression of transketolase-like gene 1 and a higher mortality rate (Langbein et al, 2006). Several factors contribute to cellular oxidative stress, which occurs when the balance between oxidants and antioxidants is disrupted, resulting in an overall increase in reactive oxygen species (ROS). ROS are produced as a result of various metabolic events; for example, in the formation of water molecules during mitochondrial respiration. Molecular oxygen ( $O_2$ ) is the terminal electron acceptor in the electron transport system of mitochondria and is converted to water ( $H_2O$ ). In some cases,  $O_2$  receives just one electron, becoming a superoxide anion. It is estimated that 4-5% of  $O_2$  molecules are normally converted to superoxide anions (Spitz et al, 2000). Superoxides are then converted to peroxides by an enzyme called superoxide dismutase. Subsequent, pyruvate scavenges the peroxides and converts them into water. Thus, an increased glycolysis rate that leads to increased pyruvate production may reduce oxidative stress.

There are two more ways in which the Warburg effect may reduce oxidative stress. Mitochondrial dysfunction may result in reduced oxidative stress, given that mitochondria are a main source of ROS generation (Orrenius, 2007). Alternatively, the antioxidant production associated with the Warburg effect may protect cancer cells from the negative effects of their explosive glycolysis.

Network modeling of the interconnections among the crucial factors involved in metabolic flow and signaling pathways is a necessary future undertaking. In addition, the mitochondrial uncoupling effect should not be overlooked. Although cancer cell energy generation is mainly dependent on reactive anaerobic glycolysis, most malignant tumors still breathe, in part by an uncoupling protein-mediated mitochondrial pathway (Samudio et al., 2007). Uncoupling proteins help import fatty acids and are over expressed in various types of chemo-resistant cancer cells. This may increase an apoptotic threshold level. On the one hand a better understanding of metabolism in cancer cells may lead to the development of novel therapeutic strategies exploiting their uniqueness.

On the other current technologies may help accomplish this systematic work. In addition to PET and magnetic resonance, the next-generation scans is needed to precisely study cancer cell biochemical. As evidenced by current proteomics and biomarker studies, detection limits should be less than femto- to atto- mole levels, considering that significant proteins or small peptides secreted from a tiny tumor cell may represent only 1% of the total protein and are extensively diluted throughout the human body.

### 2.1.3 Metabolomics

After the pioneered study of Warburg, current research findings confirm that a major difference between healthy and malignant cells is the supply of energy within the cell by oxidative phosphorylation in the mitochondria and glycolysis in the cytoplasm. This biochemical assumption led to develop another innovative consideration in oncology. Traditional Chinese Medicine, Ayurvedic Medicine and the Ancient Greek and Roman Doctors all incorporated 'types' into their healing methods the idea that biological fluids reflect the health of an individual; with the introduction of Warburg effect it has been possible to think a further step: metabolic effect. During the 1940's and 50's Dr. Roger Williams developed the concept of 'biochemical individuality' and determined that "metabolic profiles" were needed to effectively evaluate and treat patients with nutrition. First time was born the concept that individuals might have a "metabolic profile" that could be reflected in the makeup of their biological fluids. The work of Williams and his group, however, was apparently not duplicated by others, to whom his task must have seem rather

herculean, with but few promises of tangible results. Hence, his ideas about the utility of metabolic pattern analysis remained essentially dormant until the late 1960s, when gas chromatography and liquid chromatography was advanced sufficiently to permit such studies to be carried out with considerably less effort. In this way it became feasible to quantitatively (as opposed to qualitatively) measure metabolic profiles. The term “metabolic profile” was introduced at the beginning 1970s after they demonstrated that gas chromatography, especially when interfaced with mass spectrometry could be used to measure compounds present in human urine and tissue extracts, defining the patterns of biochemically related metabolites (Horning, et. al. 1971). Moreover it demonstrated the utility of using nuclear magnetic resonance spectroscopy to detect metabolites in unmodified biological samples.

In general terms the systematic study of the unique chemical fingerprints that specific cellular processes leave behind - specifically, the study of their small-molecule metabolite profiles is metabolomics. Such approach has found applications in many topics: for example oncology. Metabolomics have led to several successes in the field of cancer biology, such as the identification of new tumour subtypes, as well as transcriptional and protein biomarkers for certain types of cancer. Metabolic activity can also be quantified, as various analytical tools have been developed to measure concentrations of low-molecular-weight metabolites. This is a particularly challenging task as low-molecular-weight metabolites represent a diverse range of chemicals.

Metabolomics has also been used to differentiate between different cancer cell lines and to monitor metabolic processes that occur in cancer cells during events such as apoptosis. Despite the successful use of metabolomics to investigate phenotypes of transgenic animals and plants, and its use in the pharmaceutical industry, most functional genomic studies of cancer have focused on transcriptomics and proteomics. Global metabolic profiling analysis holds the promise to permit simultaneous monitoring of precursors, intermediates and products of metabolic pathways. It is a research tool that can detect and monitor unidentified compounds as well as identified metabolites that play important roles in metabolism and physiology (Kaplan et al., 2004). For example metabolite profiling was used to characterize stress responses of potato tissue subjected to reversible electroporation, providing insights on how potato tissue responds to a physical stimulus such as pulsed electric fields (PEF), which is an artificial stress (Galindo et al, 2009).

#### **2.1.4 Vedruccio theory**

Today the study of biochemical interactions becomes the prevailing paradigm used to explain cellular functions and disease progression in oncology. Yet many biological questions cannot be answered with biochemical explanations alone such as the role of endogenously created electromagnetic fields and electrical currents in the body. In the past century, a great number of researchers have given their contribution to the study of the interactions between biological matter and electromagnetic fields. Electromagnetic fields are waves that transport energy through space. They are characterized by wavelength and frequency, the two of which are inversely correlated. Electromagnetic fields include the following (in order of decreasing wavelength and increasing frequency): electromagnetic fields of extremely low frequency (from electric sources), electromagnetic fields of low frequency, electromagnetic fields of radiofrequency and microwaves (from mobile telephones, television antennas etc), ultrasounds, infrared rays, ultraviolet rays, X rays and gamma rays. Since the 1970s the non thermal effects of electromagnetic fields on living

organisms have been well known and also the non thermal mechanisms have been investigated. In the case of a biochemical system we assume that each molecule can be labelled with a mean velocity energy which, in turn, defines an average energy associated with each degree of freedom of the molecule itself. In such a picture a perturbation is termed "thermal" if it is able to change the average kinetic energy associated to each degree of freedom, in such a way that the average of the energies on the ensemble is changed. The rotating motion of water molecules induced by microwaves is the most evident achievement of such a thermal effect. Electromagnetic fields and life identified several significant effects of the interaction of electromagnetic fields with living organisms. If living organisms possess the ability to utilize electromagnetic fields and electricity there must exist physical structures within the cells that facilitate the sensing, transducing, storing and transmitting of this form of energy.

Normal cells possess the ability to communicate information inside themselves and between other cells. The coordination of information by the cells of the body is involved in the regulation and integration of cellular functions and cell growth. When cancer arises cancer cells are no longer regulated by the normal control mechanisms. Measurements on biological materials were based on resistivity or impedance and instruments such as the Wheatstone bridge (Presman, 1970). After the second world conflict, investigations on biological materials were extended into the microwave bands (Messen, 2000). In the 1920s Some authors discovered that both proliferating cells and cancer cells had cell membrane potentials that have been lower than the cell membrane potential of healthy adult cells (Fricke, 1926). They reported that "malignant tumors have a greater polarizability than normal breast tissues or benign tumors". They carried out their experiments at low frequencies around 20 kHz. In cancerous tissue the electrical potential of cell membranes is maintained at a lower level than that of healthy cells and electrical connections are disrupted (Cone, 1975).

Electric fields induce or cause alignment in dipole movements. Most of the molecules in the body are electrical dipoles (Beal, 1996). These dipoles electronically function like transducers in that they are able to turn acoustic waves into electrical waves and electrical waves into acoustic waves. The natural properties of biomolecular structures enables cell components and whole cells to oscillate and interact resonantly with other cells. According to Smith and Best, the cells of the body and cellular components possess the ability to function as electrical resonators. A dipole movement is a function of polarization processes and the strength of the electric field. When biological tissue is exposed to an electric field in the right frequency and amplitude windows a preferential alignment of dipoles becomes established. Since the cell membrane contains many dipole molecules, an electric field will cause preferential alignment of the dipoles. This may be one mechanism that electrical fields alter membrane permeability and membrane functions.

Theoretically we assume two type of electric capacity, the first is the "static capacity" that is independent to the frequency of the alternating current, the second is the "polarization" type that depends upon the interphases in the tissues and suggest that capacity might have a considerable biologic significance. The "polarization" capacity is related to the alternating current applied or irradiated to the tissue under test. Activation of cell membrane receptors that act as antennas for certain windows of frequency and amplitude leading to the concepts of electromagnetic reception, transduction. Biological organisms use weak electromagnetic fields (electric and photonic) to communicate with all parts of themselves. The major charge carriers of biological organisms are negatively charged electrons, positively charged

hydrogen protons, positively charged sodium, potassium, calcium and magnesium ions and negatively charged anions particularly phosphate ions.

For a long time, disturbances in physical processes in cancer development were not adequately taken into consideration despite Warburg's experimental discovery of deteriorated oxygen metabolism. Renewed interest in the Warburg effect has led to research on physical mechanisms in living cells. The role of mitochondrial dysfunction and cytoskeleton disintegration in cancer diagnostics has been recently restyling with the metabolic effect in metabolomics.

There is no doubt that the pathological physical alterations express essential changes in cancer development. Any diagnostic method has to detect important parameters disturbed by cancer process. A new diagnostic method developed by Vedruccio utilizes frequency selective (resonant) absorption of electromagnetic waves in malignant tumors (Bellorofonte et al. 2005). In malignant tumors, therefore, we should expect to find structures oscillating at the frequencies of the emitted signals, whose dissipation is different from that of healthy tissue. As the measurement results do not depend on the tumor size, the electromagnetic resonant interactions might be assumed to take place in cancer cells. The damping of oscillations is significantly It has been proposed that cancer exposed to a low level of electromagnetic incident waves may behave differently than healthy tissue (Vedruccio et al., 2004). The phenomenon of "nonlinear resonance interaction," which is produced when the oscillations of an electromagnetic probe are coupled with those from biological tissue, can be used to test for differences between healthy and cancerous tissues. increased during cancer development.

## 2.2 Tissue resonance interferoMeter probe

In the 1920s the pioneers in the field of radio frequency reported that "malignant tumours have a greater polarizability than normal breast tissues or benign tumours". The authors moreover declared that "It seems probable that the measurement of the capacity may provide a very practical method for diagnosing the malignancy of a tumor". In the 1930s, some authors extended the frequency range of the dielectric properties of biological materials up to 600 MHz, by exploring the propagation of the electromagnetic waves on Lecher wires of variable length and which were terminated by a wire surrounding the biological material. The technological advances in electronic engineering following the second world war made possible the first work on complex permittivity measurements on blood cells and other biological tissues up to 30 GHz. Several years after a method which allowed dielectric measurements on living tissue ('in vivo' measurements) has been presented. The real time determination of complex permittivity is possible over a large frequency band (100 MHz - 10 GHz) by a rapid and continuous frequency scan. One such method is based on an antenna modeling theorem and on the application of microprocessor controlled microwave measurement instrumentation. A short monopole antenna is used as the in vivo probe. A network analyzer combined with error-correction routines and a semi-automated data acquisition/processing system (microcomputer) is used to determine the real part aof the permittivity and the conductivity s of the biological tissue being analyzed. A non-destructive method for measuring the dielectric properties of materials by means of an open transmission line resonator was developed in last 1970s. In the 1980s an open-ended coaxial probe used to measure and compare the fractional power absorption for malignant tumors relative to normal adjacent tissue in rats between 30 MHz and 2 GHz. It found that "tumors have a greater absorption, with a broad peak, centered in the 300 - 400 MHz region".



The majority of the studies cited herein refer to measurements and assessments of passive biophysical parameters of the tissues investigated. Measurements were of capacitance, resistance, complex dielectric constant.

In 1992, while conducting research on the back coupling effects of the damping of the near zone electromagnetic fields on transmitter-tuned circuits, Vedruccio discovered the possibility of noninvasive cancer detection. The author analyzed the perturbation of the electromagnetic field at the open end of a transmission line due to the dielectric material of unknown properties.

In the practical application of this effect, the author first constructed some prototype pieces of apparatus then, proceeded to the international patent application n. WO 01/07909A1 and the licensing of this technology to Galileo Avionica<sup>1</sup>. The final stage is an apparatus devoted to medical diagnostic analysis which is CE certified with the commercial name of Trimprob . This method is fast and accurate up to 4 GHz. The open end of the coaxial line must be in direct contact with the surface of the dielectric material being investigated which has to be smooth and flat.

To avoid any air gap effect, and it is necessary to apply a pressure to the material under test. Measurements on the human skin were given as an example because of the low penetration depth but, the aim was primarily therapeutic.

Preliminary results confirmed that it was possible to observe a stimulated response in altered agglomerates of cells (Vedruccio, 2004). Furthermore, it offered the possibility of detecting responses from biological tissues. When stimulated by the particular pattern of electromagnetic oscillations these tissues responded in a very selective way and quite distinct from the previously investigated Debye and Maxwell-Wagner resonances which extend over decades of frequency. The principle of detection lies in the resonance between the coupled active nonlinear oscillator (the probe) and the passive oscillator (the tissue) in the radiofrequency range of the electromagnetic spectrum. The fundamental frequency of emitted waves is about 465 MHz. The first (930 MHz) and the second (1,395 MHz) harmonics are transmitted too. The probe consists of a linear oscillator fed from the nonlinear element T (Figure 2), together forming a nonlinear active oscillator.

In the equivalent circuit, the oscillator is capacitively coupled to the passive one, the tissue, via the near field of the antenna. The tumor tissue represents a dissipative medium for the energy stored in the field near to source. The near field energy periodically flows out of the probe (the source) and returns to it.

The frequency of the emitted signal is adjusted and locked at the point of the highest absorption. The receiver antenna is located beyond the immediate neighborhood of the source (Figure 3). In comparison with electromagnetic wave propagation without interaction with a tumor, the received signal at the fundamental frequency decreases about fivefold due to damping effects of the cancerous tissue.

The transmitter probe with a resonant cavity incorporates a transmission line tuned to the frequency of oscillation, which is in the 65 cm wavelength band (465 MHz). At the open end

---

<sup>1</sup> Galileo Avionica S.p.A., a Finmeccanica Company, is the Italian avionics leader. It focuses on the design, development and production of avionics and electro-optical equipment, space equipment for platform and payloads. through its Company FIAR it is a national leader in airborne radars, with METEOR company in tactical and training UAVs, training simulator. Galileo Avionica offers cooperative programs (Eurofighter, NH-90, EH-101). in 2001 Galileo Avionica had registred a revenue of more than Euro millions 452.





Fig. 2. Hand-held, battery-operated detection probe.

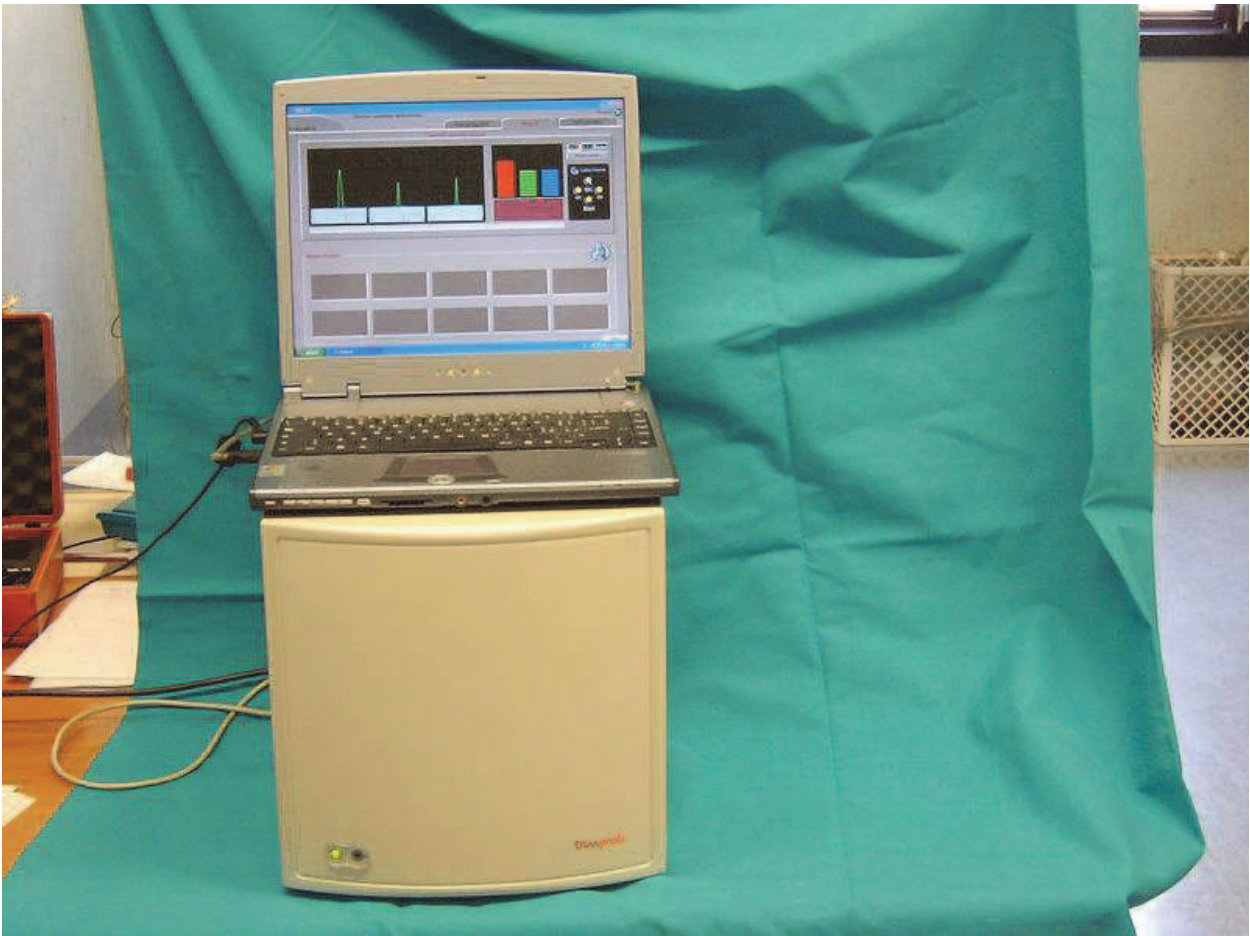


Fig. 3. Receiver, and computer display.

of this line, there is a semiconductor element with nonlinear characteristics that is activated by a nanosecond electromagnetic pulse.

This transient provides an injection of electromagnetic energy into the tuned line, which performs a damped oscillation. This particular tunable amplifier-oscillator represents the core of the Bioscanner trimprob diagnostic device.

It possesses lock-in or synchronization characteristics, and because of its particular construction, it produces a harmonically related group of coherent electromagnetic waves. These oscillations are radiated as a beam through the beam window of the oscillator dome at the end of the probe. After geometrical focusing, the beam is used to irradiate the investigated tissues. The probe is brought close to the investigated region. Nonlinear resonance interaction between the nonlinear oscillator and the tissue reduces the energy of the emitted wave at distinct frequencies depending on the pathological state of the tested tissue. This energy is measured by the spectrum analyzer, which is fed by an antenna situated about 2 m away from the probe.

2.3 Clinical application

The device is user friendly and analyses the patient fully dressed and with no discomfort. Diagnostic accuracy of the Bioscanner was evaluated in several clinical studies. (Bellorofonte et al., 2005; Da Pozzo et al., 2007; Tubaro et al., 2008; and Gokce et al., 2009) performed studies focused on the diagnosis of prostate cancer at 465 MHz. Trimprob diagnostic findings were compared to those resulting from the standard prostate cancer diagnostic methods including digital rectal examination, biopsy, and prostate-specific antigen (PSA) level. Resulting values are shown in Table 2. Data presented are consistent across studies. Diagnostic methods are classified by the proportion of positives and negatives correctly identified, i.e., by sensitivity and specificity, respectively. Prostate cancer diagnosis using trimprob is characterized by high sensitivity; however, the specificity is rather low. Bellorofonte moreover reported a significant difference between patients with benign

Organ	Sensibility	Specificity	V.P.P.	V.P.N.	Accuracy
Prostate					
Tubaro (2008) Trimp	86	63	60	88	72
Tubaro (2008) Trimp+DRE	96	57	59	95	72
Bellorofonte (2005)	95	43	94	90	--
Bladder					
Leucci (2007)	87,5	90,5	83,3	91,1	89,5
Breast					
Paganelli-De Cicco (2006)	84	75	--	80	72
Thyroid					
Sacco (2007)	100	100	--	--	100
Stomach-duodenum					
Mascia (2005)	93	93	95	92	--
Sacco (2007)	100	100	--	--	--

Table 2. Clinical application

prostatic hyperplasia and patients with prostate cancer (Bellorofonte et al., 2005). Trimprob was also tested for detection of breast cancer (De Cicco et al. 2006), bladder cancer (Gervino et al. 2007), rectal malignant lesions (Vannelli et al. 2009), carcinomas in patients with multinodular goiter (Sacco et al. 2007a), and gastric cancer (Sacco et al. 2007b). According to the clinical experience, the trimprob seems to be a simple and reliable investigation method with good diagnostic results.

The first experiments, carried out by the author in the early days of the Bioscanner invention and development, as well as several clinical trials during the last years, have scientifically validated the efficacy of the described low level e.m.f. cancer detector in several body organs like breast, prostate, bladder, stomach-duodenum, thyroid (Vedruccio, 2010).

### **3. TRIMprob and rectal cancer**

#### **3.1 Test principle**

The device is made of a thin probe about 30 cm long, powered by batteries and of a receiver. A specific software entirely elaborated by Galileo Avionica acquires, reads and manages the diagnostic data. The TRIMprob emits a beam of coherent electromagnetic waves at very low power which tunes on the specific frequencies of the examined structures. When the electromagnetic field hits a biologically altered tissue, a phenomenon of interference with the analysed structure takes place. The trimprob system (Galileo Avionica, Turin, Italy), also called a Tissue Resonance InterferoMeter Probe, consists of a hand-held, battery-operated detection probe, a receiver, and a computer display. The probe, which is about 30 cm long, contains a nonlinear oscillator that generates a complex electromagnetic wave of low intensity with three frequency components (465, 930, and 1395 MHz) and a high degree of spatial and temporal coherence. Malignant and normal tissues may differ in the way they interact with such electromagnetic waves because proteins acquire more surface charges in malignant tumours, and the attraction of these charges for water molecules results in the presence of more “bound water” (Bellerofonte et al., 2005) Furthermore, dramatic changes in metabolism, intercellular communication, and adhesion properties of cancer cells result in modification of the number and nature of membrane proteins. The dipolar parts of the membrane proteins, which protrude from the membrane, can be reoriented by an oscillating electric field. The electromagnetic field produced by the nonlinear oscillator of the trimprob stimulates oscillations inside the tissue. When these oscillations begin to resonate, an energy transfer can be detected in the wave emitted by the probe. The receiver situated a short distance from the probe detects the change and acts as a spectrum analyzer. When the probe is brought near cancerous tissue, interaction with the oscillating electric field causes a negative amplitude change in one or more of the spectral lines. The reduction in signal amplitude indicates the presence of abnormal tissues and structures. The frequencies 465, 930, and 1395 MHz were previously determined to be optimal because they appeared to respond in the appropriate way to the resonances of the system.

#### **3.2 Test procedure**

The test was performed for each individual patient according to the procedure shown in Figure 4. The patient stood between the operator and the receiver, at a distance of 120 cm from the receiver. There was a single operator, who was not blinded to the results of the colonoscopy, because the endpoint was the feasibility of this device. The patient was dressed normally, but no metallic objects were allowed on his or her person, and no

electronic devices were admitted in the test area. The pelvic area was scanned by moving the detector at close contact over the pelvic surface through six planes, first in three directions (axial, left, and right) with the patient facing the receiver and then repeating the process with the patient turned to face the operator. The test was performed for each individual patient according to the procedure. The detector was kept in close contact with the pelvic surface and was moved through six planes: A1, posterior right lateral; A2, posterior median; A3, posterior left lateral; B1, anterior right lateral; B2, anterior median; B3, anterior left lateral. There was a single operator, who was not blinded to the results of the colonoscopy, because the endpoint was the feasibility of this device. The patient was dressed normally, but no metallic objects were allowed on his or her person, and no electronic devices were admitted in the test area. In this way, a scan of the whole pelvis volume was obtained with signal acquisition at six positions: posterior median, left lateral, and right lateral; and anterior median, left lateral, and right lateral. Each change in amplitude of the emitted signals at the established frequencies was recorded and stored in an electronic file as a value of the corresponding spectral line expressed in arbitrary units between 255 and 0. Thus, three numeric values, corresponding to the signal amplitude of the spectral lines for the frequencies 465, 930, and 1395 MHz, were obtained for each position.

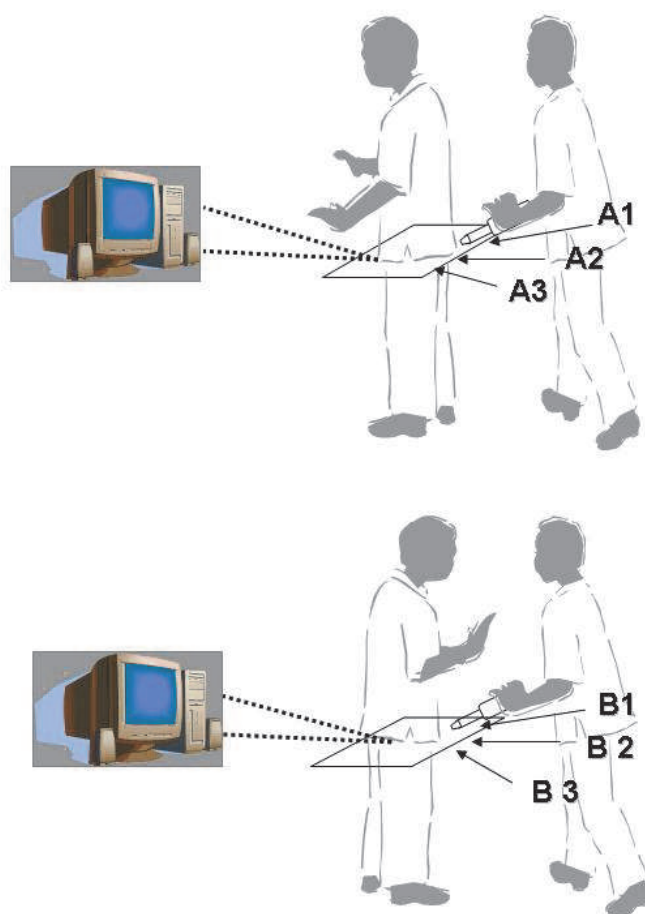


Fig. 4. Trimprob procedures. The detector was kept in close contact with the pelvic surface and was moved through six planes: A1, posterior right lateral; A2, posterior median; A3, posterior left lateral; B1, anterior right lateral; B2, anterior median; B3, anterior left lateral.



The test was performed for each individual patient according to the procedure. The detector was kept in close contact with the pelvic surface and was moved through six planes: A1, posterior right lateral; A2, posterior median; A3, posterior left lateral; B1, anterior right lateral; B2, anterior median; B3, anterior left lateral. The patient stood between the operator and the receiver, at a distance of 120 cm from the receiver. There was a single operator, who was not blinded to the results of the colonoscopy, because the endpoint was the feasibility of this device.

The patient was dressed normally, but no metallic objects were allowed on his or her person, and no electronic devices were admitted in the test area.

## **4. Remarkable experiments**

### **4.1 Introduction**

Population screening programs for the early diagnosis of CRC have the potential to reduce the incidence and mortality from this disease. Most of these programs are based on stool tests or structural exams (Vannelli et al., 2010). The main purpose of the screening should be to detect 90% of the sporadic cases of CRC. In a health care system with unlimited financial resources the choice of the type of screening and the suitable population for this examination does not represent a problem. Everywhere, even though there are different health care systems, financial resources are limited and the rectal screening with the current methods could be applied only to a selected population. On the other hand, the majority of adults are not receiving regular age- and risk-appropriate screenings or have never been screened at all (Zampino et al., 2009). Despite the fact that the primary barriers to screening are lack of health insurance, lack of physician recommendation, and lack of awareness of the importance of RC screening, the historical evidence shows that adults have different preferences and patterns of use among the available CRC screening tests. Thus, a less expensive, faster, and less invasive RC screening procedure with a similar or better efficacy, as compared to available methods, would provide a significant advantage for RC prevention in the general population. We recently carried out a pilot study for the identification of RC by electromagnetic detection, a method that is rapid, non-invasive, and inexpensive. As compared to the results of colonoscopy, electromagnetic detection of rectal cancer was highly specific (85%) and highly sensitive (94%) (Vannelli et al., 2009). Herein, by a prospective study we evaluated the prediction accuracy of CRC by electromagnetic detection. A pilot study has been carried out for the identification of CRC by electromagnetic detection, a method that is rapid, non-invasive, and inexpensive (Vannelli et al., 2009). A subsequent study protocol was approved by the Institutional Review Board and Ethics Committee of the Fondazione IRCCS "Istituto Nazionale Tumori" Milano. The ClinicalTrials.gov ID of the study is: NCT00963794. This study was carried out using a blind and a prospective design, with patients undergoing electromagnetic detection followed by colonoscopy.

### **4.2 Preliminary results**

We hypothesized to adapt trimprobe in early detection-screening for rectal cancer. Of 1,792 patients admitted to our outpatient clinic from March to September 2006 because of gastrointestinal disease, 756 patients underwent colonoscopy and were evaluated for possible participation in the Trimprob study. Exclusion criteria consisted of age younger than 18 years, history of psychiatric illness, and preoperative radiotherapy. To rule out



possible interference with the electromagnetic field, we also excluded patients with active phlogistic processes, such as inflammatory bowel disease, anal abscess, or fistulas. To rule out possible interference from other types of altered tissues, we included only the rectum, with a cut-off 15 centimetres from the anal verge. A total of 228 patients (113 females and 115 males) were selected for participation in the study: 114 patients with negative colonoscopy results and 114 patients with colonoscopy positive for rectal cancer. Written informed consent was obtained from all subjects. The study protocol was approved by the Institutional Review Board of the Fondazione IRCCS "Istituto Nazionale dei Tumori" Milano.

#### 4.3 Clinical trials

After the encouraging results we decide to prepare a prospective randomized clinical trial. 442 patients have been admitted to our outpatient's Department from January to August 2008 because of gastrointestinal disease or clinical symptoms related to colorectal risk. Exclusion criteria consisted of age younger than 18 years, history of psychiatric illness, and preoperative radiotherapy: 27 patients. Under written informed consent, 415 subjects were recruited consecutively (10 patients refused the protocol). All subjects underwent electromagnetic detection of RC, followed by colonoscopy. The patients completed the examination with computed tomography (positive colonoscopy) or abdominal sonography (negative colonoscopy). The device lets the examination limited to the pelvis and we regarded the rectum cutoff within 15 cm from the anal verge. Biopsy of suspected neoplastic lesions and histopathological exam of the eventual lesions were performed (209 patients), showing that 108 patients carried a rectal cancer whereas 101 patients carried a cancer in the upper gastrointestinal tract (right or left colon); these latter patients were excluded from this study (Table 1). The study protocol was approved by the Institutional Review Board and Ethics Committee of the Fondazione IRCCS "Istituto Nazionale dei Tumori" Milano. The ClinicalTrials.gov ID of the study is: NCT00963794.

### 5. Phenomenon interpretation

No adverse effects of the Trimprob procedure were observed in the two trials. The procedure was performed in a short time (approximately 10 minutes) and was well accepted by all patients. In first trial, only the first spectral line, at the 465-MHz frequency, differentiated the group with positive colonoscopy from that with negative colonoscopy in all six probe positions ( $P < 0.001$ ). At 930 MHz, the two groups differed significantly only in the posterior right, posterior median, posterior left, and anterior left positions; no significant differences were seen at 1395 MHz. To evaluate the applicability of trimprob electromagnetic signal as a marker for distinguishing between CRC and non-CRC disease groups, we performed Receiver Operating Characteristic (ROC) curve analysis. Figure 5 shows the curves ROC calculated for each frequency. Only the 465-MHz frequency had an AUC-ROC value close to 1 (0.94), indicating good discrimination between positive and negative colonoscopy at this frequency. In contrast, 930 MHz and 1395 MHz had AUC-ROC values close to 0.5, indicating poor discrimination. ROC curve showed the diagnostic ability of trimprob electromagnetic signal in the differentiation of RC patients versus non-cancer subjects (AUC = 0.96, 95% confidence interval (CI) 0.94 - 0.98;  $P < 2.2e-16$ ). In our cohort, the sensitivity of the trimprob device for RC was 0.94, specificity was 0.84, negative predictive value was 0.88, positive predictive value was 0.92, and accuracy was 0.90 for the electromagnetic signal cut-off value of 50 U. Indeed, an electromagnetic signal  $< 50$  arbitrary

units (U) was significantly associated with detection of RC by colonoscopy ( $p < 2.2e-16$ ). Analysis of accuracy by cut-off value indicated that  $\sim 50$ -55 U represent the best cut-off values for detection of RC. Second trial of 442 subjects enrolled at our Institute due to signs of CRC risk was carried out using a blind and a prospective design, with patients undergoing electromagnetic detection followed by colonoscopy. Histopathologic analysis of biopsies revealed that all CRC cases were of the adenocarcinoma histotype. Data from 196 patients with negative colonoscopy results and 108 patients with rectal cancer by colonoscopy were available for analysis. The median patient age was 65 (range, 24-84) years for the negative colonoscopy group and 65 (range, 22-85) years for the positive colonoscopy group. All patients with a CRC diagnosis have been subjected to computed tomography, which revealed 9 liver metastasis and no other primitive cancer types. All patients with positive colonoscopy were admitted to the hospital with a diagnosis of rectal adenocarcinoma and submitted to surgery. Patients not carrying a CRC, (exception of 13 subjects), have been subjected to abdominal sonography, which revealed no cancer pathology. However, 10 patients revealed active phlogistic processes: 6 inflammatory bowel disease, 1 anal abscess and 3 fistulas. Since PSA levels were not measured as a screening for prostate cancer, this may be a possible limitation to the study results.

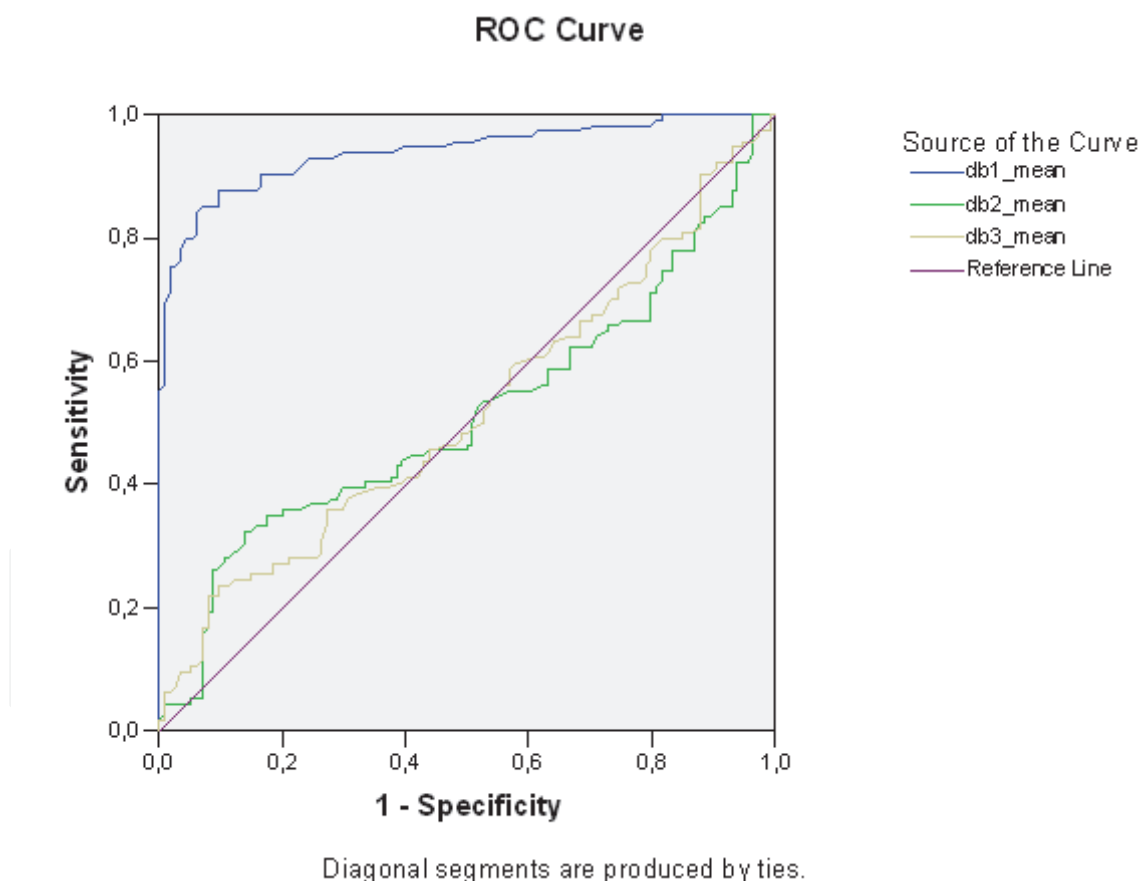


Fig. 5. ROC curve

CRC patients classified by colonoscopy showed a significantly lower electromagnetic signal than did non-CRC subjects, i.e.,  $40.9 \pm 0.9$  U (mean  $\pm$  S.E.) versus  $79.2 \pm 1.4$  U (Figure 6). To evaluate the applicability of Trimprob electromagnetic signal as a marker for distinguishing between RC and non-RC disease groups, we performed ROC (Receiver Operating

Characteristic) curve analysis. ROC curve showed the diagnostic ability of trimprob electromagnetic signal in the differentiation of RC patients versus non-cancer subjects (AUC = 0.96, 95% confidence interval (CI) 0.94 - 0.98;  $P < 2.2e-16$ ). In our cohort, the sensitivity of the trimprob device for RC was 0.94, specificity was 0.84, negative predictive value was 0.88, positive predictive value was 0.92, and accuracy was 0.90 for the electromagnetic signal cut-off value of 50 U. Indeed, an electromagnetic signal  $< 50$  U was significantly associated with detection of RC by colonoscopy ( $p < 2.2e-16$ , Table 3). Analysis of accuracy by cut-off value

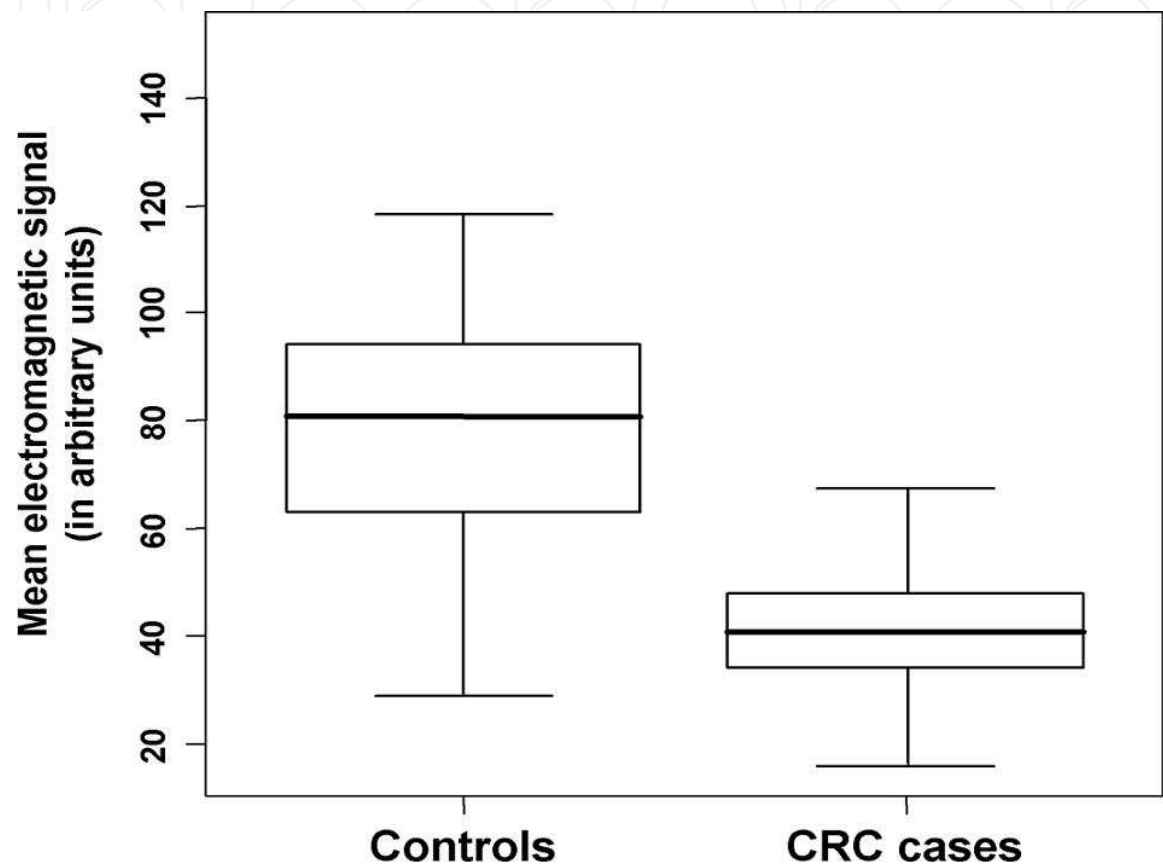


Fig. 6. Lower electromagnetic signal associated with rectal cancer carrier status.  $P < 2.2e-16$ , Kruskal-Wallis test.

Electromagnetic signal score	Number of subjects with		$P^b$
	Non-CRC <sup>a</sup>	CRC <sup>a</sup>	
$\geq 50$	184	17	
$< 50$	12	91	$< 1.0e-16$
$\geq 70$	134	0	
$< 70$	62	108	$< 1.0e-16$
<sup>a</sup> By colonoscopy analysis. <sup>b</sup> Fisher's exact test.			

Table 3. Association between electromagnetic score settled out at different thresholds and the CRC disease status defined by colonoscopy.

indicated that 50-55 U represent the best cut-off values for detection of RC. Since a major goal in screening tests is the minimization of false-negative rates, we identified an electromagnetic threshold, i.e.,  $< 70$  U, at which no RC was missed (Table 3). However, at this threshold, 62 (31.6%) of the non-RC subjects were false-positive (Table 3), whose disease or healthy status would have required clarification by colonoscopy. No association between nodal involvement (N0 versus  $N \geq 1$ ) and the value of the electromagnetic signal was observed. A significant inverse correlation was observed between the size of the neoplastic lesions and the value of the electromagnetic signal (Spearman's  $\rho = -0.290$ ,  $P = 0.002$ ), whereas a significant positive correlation was found between increasing distance from anal verge and the value of the electromagnetic signal (Spearman's  $\rho = 0.362$ ,  $P = 0.0001$ ).

## 6. Discussion

Since up to 10% of the general population might carry a RC, depending on the age of the population undergoing screening, new easy and non-expensive methods for population screening for RC may be helpful for early detection of such disease. The most frequently used screening methods for RC include two general categories: stool tests (tests for occult blood or exfoliated DNA) and structural exams [endoscopy, double-contrast barium enema and computed tomographic colonography (CTC)]. The popular occult blood test is characterized by simplicity, non-invasiveness, and demonstrated mortality benefit but suffers from poor sensitivity, low population compliance, and high costs of follow-up for false-positives. Indeed, in a large study of asymptomatic patients who underwent occult blood testing followed by endoscopy, the sensitivity of the occult blood test for identifying advanced neoplasia was only 24%. Compared to the occult blood test, CTC is much more expensive, whereas this technique has some clear advantages when compared to endoscopy since it is non-invasive, less time-intensive and is associated with a lower risk of complications. However, CTC requires the use of ionizing radiations, a high level of expertise in reading, and has shown wide variations in sensitivity in the various clinical trials (Vannelli et al., 2010). Endoscopy is an invasive, lengthy and expensive procedure requiring adequate clinical infrastructure and medical expertise, and is not without complications. Thus, it represents even a relatively "poor screening" method for RC at the general population level, especially as compared with screening methods, such as the PAP test, for other types of cancer. The ageing of the general population in the Western world, with the consequent increase of people at risk of RC, further makes large screening programs based on colonoscopy unfeasible. Still, early detection of RC can save lives and can also decrease the cost of the patient's clinical management, since patients with early neoplastic lesions require simpler surgical resections and treatments than those with advanced disease. Although endoscopy is generally safe, it is still an invasive procedure with several-fold higher rates of serious complications than for any other commonly used cancer screening test. Repeated examinations over time may incur a substantial cumulative rate of complications. In addition, a relatively small risk (2 to 6%) of RC remains 6 to 36 months after negative colonoscopy, especially when internists and family practice physicians rather than gastroenterologists perform endoscopies. However, in the near term, even greater incidence and mortality reductions could be achieved if a greater proportion of adults received regular screening. Although prospective randomized trials and observational studies have demonstrated mortality reductions associated with early

detection of invasive disease, as well as removal of adenomatous polyps, a majority of adults are not receiving regular age and risk-appropriate screening or have never been screened at all. Recent interest has focused on use of trimprob for diagnosis of disease as new screening strategy. This technique is characterized by simplicity, efficacy, and good patient compliance. In the present prospective study, patients with CRC diagnosed by colonoscopy and histopathologic analysis showed significantly lower values of the electromagnetic signal as compared to non-CRC patients. At a signal threshold of 50 U, defined by our previous study as the optimal threshold in discriminating CRC from non-CRC patients, the electromagnetic detection showed a highly significant association with the CRC status, thus confirming in an independent cohort our previous findings. This technology has also been investigated on other cancers, in particular prostate cancers with favourable outcomes. The observed inverse correlation between the size of the neoplastic lesions and the value of the electromagnetic signal is consistent with the association between low electromagnetic signal values and high probability of CRC, and raises the possibility that CRC size represents a factor affecting the sensitivity of CRC electromagnetic detection. The positive correlation observed between increasing distance from anal verge and the value of the electromagnetic signal may reflect a decreasing detection power of the device with distance of the lesion or, alternatively, with interference of anatomical structures in the anal region. Further studies are needed to clarify the existence of a dimensional threshold or of a minimal distance from anal verge of CRC to be detected by electromagnetic signal. Notwithstanding the highly significant association between electromagnetic detection and CRC status observed using the 50 U signal threshold, the frequency of false-negative results at this threshold was relatively high (15.7%,) and, although much less than the frequency of missing CRCs by the fecal occult blood test, too high for population-based CRC screening. By increasing the signal threshold value to 70 U, we can avoid all false-negative findings in our cohort, thus we can correctly identified all CRC cases but increased the frequency of false-positives to about 30% of the non-CRC subjects. Thus, follow-up colonoscopy in real- and false positive subjects would be necessary to characterize the subject's disease status. We are aware of the limitations of our study, since the relatively small size of our series and the consequent low detection power. Also, trimprob was never tested in a multicentric study for the detection of CRC and control subjects from general population, without any gastrointestinal symptoms related to CRC risk, have not been tested. Other possible limitations that have not been addressed in the present study include operator dependence and the effects of other gastrointestinal diseases.

## 7. Conclusion

Our present findings point to the promise of electromagnetic detection as a simple, accurate, and inexpensive tool for early detection of CRC in cancer prevention programs at the general population level. However, the present results represent only a first step and studies in large cohorts and in different populations are needed to further compare the usefulness of this method with other CRC screening methods, especially colonoscopy. In addition, the description of benefits is complicated by different performance characteristics of the variants tests. Moreover, test performances in research settings and in clinical practice may vary. Therefore, we can imagine in the future the possibility to support the common screening tests with electromagnetic detection.



## 8. Acknowledgments

The authors thank Mrs. Roberta Aceto for her assistance with data collection and MD. Patrizia Gasparini for scientific consulting.

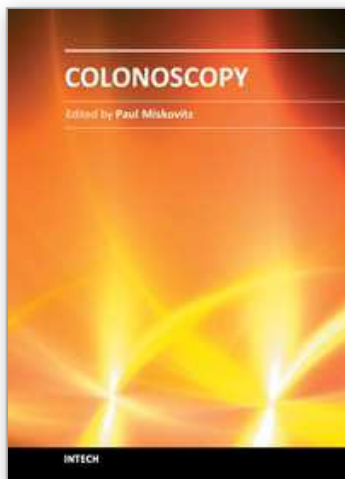
## 9. References

- Beal, JB. (1996). Biosystems liquid crystals & potential effects of natural & artificial electromagnetic fields (EMFs), In: *Second Annual Advanced Water Sciences Symposium*, March 4 2011, Available from <<http://frontpage.simnet.is/vgv/jim1.htm>>
- Bellorofonte, C.; Vedruccio, C.; Tombolini, P.; Ruoppolo, M. & Tubaro, A. (2005). Non-invasive detection of prostate cancer by electromagnetic interaction. *Eur Urol*, Vol. 47, No. 1, (January 2005), pp. 29-37. ISSN 1569-9056.
- Bibbo, M. (1997). *Comprehensive cytopathology* (2<sup>nd</sup> edition) WB Saunders, ISBN 1-56238-380-9, Philadelphia
- Blackledge, G. (2003) Cancer Drugs: The next ten years. *European Journal of Cancer*, Vol. 39, No. 3, (February 2003), pp. 273, ISSN: 0959-8049
- Clarke, AC.; (1962) *Hazards of prophecy :The failure of imagination* in Profiles of the Future, Harper & Row, ISBN 0-445-04061-0, New York
- Cone, C.D. (1975). The role of surface electrical transmembrane potential in normal and malignant mitogenesis. *Ann NY Acad Sci*. Vol. 238, (1975), pp. 420-35 ISSN: 1749-6632
- Da Pozzo, L.; Scattoni, V.; Mazzoccoli, B.; Rigatti, P.; Manferrari, F.; Martorana. G.; Pietropaolo, F.; Belgrano, E.; Prezioso, D.; Lotti, T.; Villari, D. & Nicita, G. (2007). Tissue-resonance interaction method for the noninvasive diagnosis of prostate cancer: analysis of a multicentre clinical evaluation. *BJU Int*, Vol. 100, No. 5, (November 2007), pp. 1055-9. ISSN: 1464-410X.
- De Cicco, C.; Mariani, L.; Vedruccio, C.; Ricci, C.; Balma, M.; Rotmensz, N.; Ferrari, M.E.; Autino, E.; Trifirò, G.; Sacchini, V.; Viale, G. & Paganelli, G. Clinical application of spectral electromagnetic interaction in breast cancer: diagnostic results of a pilot study. *Tumori*, Vol. 92, No 3, (May-June 2006), pp. 207-12. ISSN: 0300-8916.
- Di Viccaro, D.; Perugia, G.; Cerulli, C.; Olivieri, V.; Bova, J.; Zanza, C.; Teodonio, S. & Liberti, M. (2009).The accuracy of tissue resonance interaction method probe (Trimprob tm) in non-invasive diagnosis of prostatic cancer. Analysis of the results of 782 patient. *Urologia*, Vol. 76, Suppl. 15, (2009), pp. 1-3. ISSN: 0004-0614
- Erickson, J.W. & Cerione, R.A. (2010). Glutaminase: a hot spot for regulation of cancer cell metabolism? *Oncotarget* Vol.1, No. 8, (December 2010), pp. 734-40. ISSN: 1949-2553
- Fricke, H. & Morse, A. (1926). The electric capacity of tumors of the breast. *J Cancer Res*. Vol. 10, (1926), pp. 340-76. ISSN: 1538-7445
- Galindo, F.G.; Dejmek, P.; Lundgren, K.; Rasmusson, A.G.; Vicente, A. & Moritz, T. (2009). Metabolomic evaluation of pulsed electric field-induced stress on potato tissue. *Planta*. Vol. 230, No. 3, (august 2009), pp. 469-479. ISSN: 1432-2048
- Gervino, G.; Autino, E.; Kolomoets, E.; Leucci, G. & Balma, M. Diagnosis of bladder cancer at 465 MHz. *Electromagn Biol Med*, Vol. 26, No. 2, (2007), pp. 119-34. ISSN: 1536-8386.

- Gokce, O.; Sanli, O.; Salmaslioglu, A.; Tunaci, A.; Ozsoy, C. & Ozcan, F. (2009). Tissue Resonance Interaction Method (TRIMprob) has the potential to be used alongside the recognized tests in the screening protocols for prostate cancer. *Int J Urol*, Vol. 16, No. 6, (June 2009), pp. 580-3. ISSN: 1573-2584
- Horning, E.C. & Horning, M.G. (1971). Metabolic profiles: gas-phase methods for analysis of metabolites. *Clin Chem*. Vol. 17, No. 8, (August 1971), pp. 802-9. ISSN:0009-9147
- Kanavos, P.; Schurer, W.; Owusuapenten, C. & Sullivan, R. (2008) Colorectal cancer in Europe and Australia: challenges and opportunities for the future, In: *LSE Health*, date of access 2011, available in:  
<<http://www2.lse.ac.uk/LSEHealthAndSocialCare/LSEHealth/pdf/colorectal/ColorectalCancerReport%2025JUNE2008.pdf>>
- Kaplan, F.; Kopka, J.; Haskell, D.W.; Zhao, W.; Schiller, K.C.; Gatzke, N.; Sung, D.Y. & Guy, C.L. (2004). Exploring the temperature-stress metabolome of Arabidopsis. *Plant Physiol*. Vol. 136, No. 4 (December 2004), pp. 4159-4168. ISSN: 1532-2548
- Kurzweil, R. & Grossman, T. (2004). *Fantastic Voyage: Live Long Enough to Live Forever*, Rodale Books (eds.) ISBN 1-57954-954-3. USA.
- Lance, P. (2008). Colorectal cancer screening: confusion reigns. *Cancer Epidemiol Biomarkers Prev*, Vol 17, (September 2008), pp. 2205-7. ISSN 1538-7755
- Langbein, S.; Zerilli, M.; Zur Hausen, A.; Staiger, W.; Rensch-Boschert, K.; Lukan, N.; Popa, J.; Ternullo, M.P.; Steidler, A. & Weiss, C. (2006). Expression of transketolase TKTL1 predicts colon and urothelial cancer patient survival: Warburg effect reinterpreted. *Br J Cancer*. Vol. 94, No. 4, (Februar 2006), pp. 578-585. ISSN 0007-0920
- Mayevsky, A. (2009). Mitochondrial function and energy metabolism in cancer cells: past overview and future perspectives. *Mitochondrion* Vol. 9, No. 3, (Jun 2009), pp. 165-179. ISSN: 1567-7249
- Meessen, A. (2000). Institut de Physique, Université Catholique de Louvain, Louvain-la-Neuvre, In: *Working Principle of an EM Cancer Detector*, March 2 2011, Available from<<http://www.meessnen.net/AMeessnen/EMcancerDet2.pdf>> 2000
- Orrenius, S. (2007). Reactive oxygen species in mitochondria-mediated cell death. *Drug Metab Rev*. Vol. 39, No. 2-3, (2000), pp. 443-455. ISSN 1097-9883
- Pelicano, H.; Martin, DS.; Xu, R.H. & Huang, P. (2006) Glycolysis inhibition for anticancer treatment. *Oncogene*. Vol. 7, No. 25, (Aug 2006), pp. 4633-46. ISSN: 0950-9232
- Pokorný, J.; Vedruccio, C.; Cifra, M. & Kučera, O. (2011) Cancer physics: diagnostics based on damped cellular elastoelectrical vibrations in microtubules. *Eur Biophys J*. 2011 Mar 11. [Epub ahead of print] ISSN 0175-7571
- Presman, A.S. (1970). *Electromagnetic Fields and Life* (1<sup>st</sup> edition), NY: Plenum Press, ISBN 0-688-00123-8, New York
- Sacco R, Sammarco G, De Vinci R, Vescio G, Scarpelli A, Lucisano AM, Pata F, Mascia E, Martines V. (2007). Relief of gastric cancer with an electromagnetic interaction system (TRIMprob) in outpatients. *Chir Ital*, Vol. 59, No. 6, (Nov-Dec 2007), pp. 823-8. ISSN: 0009 - 4773
- Sacco, R.; Innaro, N.; Pata, F.; Lucisano, A.M.; Talarico, C. & Aversa, S. (2007). Preoperative diagnosis of incidental carcinoma in multinodular goitre by means of electromagnetic interactions. *Chir Ital*, Vol. 59, No.2, (Mar-Apr 2007) pp. 247-51. ISSN: 0009 - 4773

- Samudio, I.; Fiegl, M. & Andreeff, M. (2009). Mitochondrial uncoupling and the Warburg effect: molecular basis for the reprogramming of cancer cell metabolism. *Cancer Res.* Vol. 69, No. 6, (March 2009), pp. 2163-2166. ISSN: 1538-7445
- Sikora, K. (2007). Personalized medicine for cancer: from molecular signature to therapeutic choice, In: *Adv Cancer Res*, Vande & Woude, pp. 345-69, Elsevier, Retrieved from <[http://www.sciencedirect.com/science?\\_ob=ArticleURL&\\_udi=B7CT1-4MHNPP7-F&\\_user=5422747&\\_coverDate=12%2F31%2F2006&\\_rdoc=1&\\_fmt=high&\\_orig=gateway&\\_origin=gateway&\\_sort=d&\\_docanchor=&view=c&\\_acct=C000067215&\\_version=1&\\_urlVersion=0&\\_userid=5422747&md5=62364b5c4a356341fcc62806bb8149dd&searchtype=a](http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B7CT1-4MHNPP7-F&_user=5422747&_coverDate=12%2F31%2F2006&_rdoc=1&_fmt=high&_orig=gateway&_origin=gateway&_sort=d&_docanchor=&view=c&_acct=C000067215&_version=1&_urlVersion=0&_userid=5422747&md5=62364b5c4a356341fcc62806bb8149dd&searchtype=a)>
- Sonnenberg, A.; Delco, F. & Inadomi, J.M. (2000). Cost-effectiveness of colonoscopy in screening for colorectal cancer. *Ann Intern Med*, Vol. 133, No. 8, (October 2000), pp. 573-84. ISSN: 1539-3704
- Spitz, D.R.; Sim, J.E.; Ridnour, L.A.; Galoforo, S.S. & Lee, Y.J. (2000). Glucose deprivation-induced oxidative stress in human tumor cells. A fundamental defect in metabolism? *Ann N Y Acad Sci.* Vol. 899, (2000), pp. 349-362. ISSN: 1749-6632
- Sung, J.J.; Lau, J.Y.; Goh, K.L. & Leung, W.K. (2005). Asia Pacific Working Group on Colorectal Cancer. Increasing incidence of colorectal cancer in Asia: implications for screening. *Lancet Oncol*, Vol. 6, No. 11, (November 2005), pp. 871-6. ISSN: 1470-2045
- Tubaro, A.; De Nunzio, C.; Trucchi, A.; Stoppacciaro, A. & Miano, L. (2008) The electromagnetic detection of prostatic cancer: evaluation of diagnostic accuracy. *Urology*, Vol. 72, No. 2, (August 2008), pp. 340-4. ISSN: 1747-8049
- Vander Heiden, M.G., Cantley, L.C., Thompson, C.B. (2009) Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation. *Science* Vol. 324, No. 324, (May 2009), 1029-1033. ISSN 1095-9203
- Vannelli, A.; Battaglia, L.; Poiasina, E. & Leo, E. (2010). Diagnosis of rectal cancer by Tissue Resonance Interaction Method. *BMC Gastroenterol*, Vol. 10, No. 45, (May 2010), pp. 1-6. ISSN 1471-230X
- Vannelli, A.; Leo, E.; Battaglia, L. & Poiasina, E. (2009). Diagnosis of rectal cancer by electromagnetic interactions: preliminary results. *Dis Colon Rectum*, Vol 52, 2009, pp.162-166. ISSN, 0012-3706
- Vedruccio, C. & Meessen, A. (2004). EM cancer detection by means of nonlinear resonance interaction. In: Research Symposium, Pisa Italy March 28-31 2004. *Extended Paper Book of PIERS2004- Progress in Electromagnetics*, pp. 909-12, Pisa, Italy
- Vedruccio, C. (2010). Polarizability of normal and cancerous tissues, a Radiofrequency Nonlinear Resonance Interaction non invasive diagnostic Bioscanner Trimprob detector. *Eur J Oncol - Library*, Vol. 5, (2010), pp. 177-86 ISBN 978-88-6261-166-4
- Vincenzi, B.; Cesa, A.L.; Santini, D.; Schiavon, G.; Grilli, C.; Graziano, F. & Tonini, G. (2004). Predictive factors for response to chemotherapy in colorectal cancer patients. *Crit Rev Oncol Hematol*, Vol. 52, No. 1, (October 2004), pp. 45-60, ISSN: 1040-8428
- Warburg, O. (1956) On the origin of cancer cells. *Science*. Vol. 123, No. 3191 (February 1956), pp. 309-314. ISSN 1095-9203
- Warburg, O.; Posener, K. & Negelein, E. (1924). U<sup>ber</sup> den Stoffwechsel der Carcinomzelle. *Biochem Z*, Vol. 152, (1924), pp. 309-344

- Winawer, S. (2007) Colorectal cancer screening, In: *World Gastroenterology Organisation/International Digestive Cancer Alliance Practice Guidelines*, date of access 2011, available in:  
<[http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/06\\_colorectal\\_cancer\\_screening.pdf](http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/06_colorectal_cancer_screening.pdf)>
- Zampino, M.G.; Labianca, R.; Beretta, G.D.; Magni, E.; Gatta, G.; Leonardi, M.C.; Chiappa, A.; Biffi, R.; de Braud, F. & Wils, J. (2009). Rectal cancer. *Crit Rev Oncol Hematol*, Vol. 70, No. 2, (May 2009), pp.160-182. ISSN: 1040-8428



## **Colonoscopy**

Edited by Prof. Paul Miskovitz

ISBN 978-953-307-568-6

Hard cover, 326 pages

**Publisher** InTech

**Published online** 29, August, 2011

**Published in print edition** August, 2011

To publish a book on colonoscopy suitable for an international medical audience, drawing upon the expertise and talents of many outstanding world-wide clinicians, is a daunting task. New developments in videocolonoscopy instruments, procedural technique, patient selection and preparation, and moderate sedation and monitoring are being made and reported daily in both the medical and the lay press. Just as over the last several decades colonoscopy has largely supplanted the use of barium enema x-ray study of the colon, new developments in gastrointestinal imaging such as computerized tomographic colonography and video transmitted capsule study of the colonic lumen and new discoveries in cellular and molecular biology that may facilitate the early detection of colon cancer, colon polyps and other gastrointestinal pathology threaten to relegate the role of screening colonoscopy to the side lines of medical practice. This book draws on the talents of renowned physicians who convey a sense of the history, the present state-of-the art and ongoing confronting issues, and the predicted future of this discipline.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Alberto Vannelli and Luigi Battaglia (2011). Research and Therapeutic Innovation: Tissue Resonance Interferometer Probe in Early Detection-Screening for Rectal Cancer, Colonoscopy, Prof. Paul Miskovitz (Ed.), ISBN: 978-953-307-568-6, InTech, Available from: <http://www.intechopen.com/books/colonoscopy/research-and-therapeutic-innovation-tissue-resonance-interferometer-probe-in-early-detection-screeni>

**INTech**  
open science | open minds

### **InTech Europe**

University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
[www.intechopen.com](http://www.intechopen.com)

### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821



© 2011 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike-3.0 License](https://creativecommons.org/licenses/by-nc-sa/3.0/), which permits use, distribution and reproduction for non-commercial purposes, provided the original is properly cited and derivative works building on this content are distributed under the same license.

IntechOpen

IntechOpen