Course syllabus for Biology 552/652: Evolutionary Medicine

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Office hours: Thursday 1:30-3:30; other times by appointment

Course Description:

The course involves in-depth analyses at the interface of evolutionary biology and the health sciences using readings from the primary literature. Format involves oral presentations, discussion, and a literature-based research project. Formal meetings for Biology 552 and 652 are concurrent. Biology 652 students will be exposed to more advanced material and activities through independent study and additional ad-hoc meetings.

Prerequisites:

Biology 552 students should have taken Biol 240-243 or equivalents, and Biol 372 (Evolutionary Ecology of Disease) or Biol 409 (Evolution) or an equivalent.
Biology 652 students should have taken Biol 669 (Advanced Evolution) or an equivalent.
Other courses in immunology, genetics, microbiology, parasitology, or epidemiology will be useful but are not required.

Reading:

Book: No text is required, but those who have not taken Biology 372 should read my book, *Plague Time* (hardcover: 2000. Free Press: NY.; paperback: 2002. Anchor: NY) by the third week of class. I encourage those who have taken Biology 372 to read the chapters that that have not yet read by the third week of the course. The hardcover edition of *Plague Time* can be obtained for an shockingly low price at amazon.com using the "used & new" link for the book's web page. For some reason Amazon has two web pages for the hardcover edition. To make sure you find the lowest price check the box headed "Also available in…"

Articles: Journal articles will be assigned sporadically during the semester. The articles chosen will depend on where discussions take us and what is published during the semester.

Course Requirements:

Attendance: attend each session unless excused

Classroom hours per week: two 1.25 hour sessions per week; students enrolling in Biology 652 will spend an additional hour per week either in small discussion groups or in one-on-one discussion with me.

Reading: read assigned reading prior to time at which the reading will be discussed

Library/On-line Research Project:

Research activity: study a particular hypothesis or topic using information gathered from the literature and/or other informational sources, such as on line data bases

Oral progress report: A 5-10 minute presentation in which you describe your project, what you have done by that time, what you plan to do, and how you plan to do it. This report will be presented to the class during the middle third of the semester, scheduled on a person-by-person basis.

Final oral report: A 10-15 minute presentation in which you tell us what you have found

and any loose ends that you will try to tie up before you write the written report. This report will be presented to the class during the final three weeks of the semester

Final written report: This report, which will be the culmination of your research project, will be due at 5:00pm on April 28th.

Graduate students requirements: I expect that graduate students in the course will be able to complete their projects with a greater depth and breadth than the undergraduates. Graduate students will have an extra meeting per week during which additional readings will be discussed to accommodate the expected scope and depth of the graduate work in the course.

Grading:

Points will be assigned as follows:

Initial Oral Progress Report on Research Project: 25 points
Final Oral Report on Research Project: 75 points
Final Written report 100 points
In class participation: 50 points

Bonus points: Students are encouraged to take initiative to read and evaluate the popular and scientific literature from an evolutionary perspective. As an incentive I will award bonus points for articles that students have read, summarized and critiqued. These points awarded generally range from 1-10 per article, but there is no maximum. The more detailed and thoughtful the summary and critique, the greater the number of bonus points awarded. More concise writing will be worth points more than less concise writing. There is no maximum on the amount of writing per article, but the submissions generally range from a few sentences to about a page.

Final letter grades will be given according to the standard breakdown of points:

A+	**A**	**A-**	**B+**	**B**	**B-**	**C+**	**C**	**C-**	**D**	**F**
96.7-100%	93.3-96.7%	90.0-92.3%	86.7-90.0%	83.3-86.7%	80.0-83.3%	77.6-80.0%	73.3-77.6%	70.0-73.3%	60.0-70.0%	0.0-60.0%

Last day to withdraw: March 7th (set by College of Arts and Sciences)

Student Learning Objectives

- *Integrative thinking:* The projects will be selected to develop insights based on integrating ideas and information from a variety of different within and among disciplines. This process may involve application of knowledge from biology, psychology, anthropology, and/or chemistry to health issues.
- *Critical thinking*: Development of each project will involve formulation and evaluation of alternative hypothesis. The significance of arguments and evidence will be evaluated in this process to arrive at conclusions and the caveats that must accompany conclusions.

Research project topics

The central theme for the Spring of 2014 will be evolutionary perspectives on the causes and nature of cancer. A student's research project, however, may be chosen from any area of the health sciences. The only constraint is that the topic must incorporate an evolutionary perspective. The topic and the approach taken to it will be worked out by one-on-one discussion with me. The following listing provides illustrations of the kinds of topics that could be studied. A student may choose any one of these topics, a variant of the topic, or something entirely different.

Longevity

The U.S. has the greatest per capita expenditure on health care of all economically developed countries but the lowest longevity. Why? The answer isn't well understood but here are some possible factors. Here are three hypotheses that could be tested.

> *Hypothesis 1:* The expenditures involve only inequities in access to health care.
> Test: See if the differences in longevity among countries still exists when comparisons are made within socioeconomic strata.
>
> *Hypothesis 2:* The US may be more driven by a medication mindset. Medications have side effects and may often sabotage defenses, which could exacerbate the treated disease if the disease is caused by infection or could exacerbate other infections of the treated infividual.
> Test: see if use of medications that exacerbate infection is greater in the US and if the causes of decreased longevity have known or suspected infectious causes.
>
> *Hypothesis 3:* The social environment in the US may be more prone to transmission of pathogens, which in turn may cause more life-shortening chronic disease. [Social environment could involve greater transmission of persistent pathogens (e.g., through drug abuse or sexual contact) or increased pressure to compromise health for short-term success (e.g., work week, macho mindset about work) contributing to the transmission of persistent infections, drug abuse).
> Test: see if longevity is reduced and illnesses among people with stressful workplace environments and if the causes of decreased longevity have known or suspected infectious causes

Japan has a high smoking rate but one of the longest longevities.

> Is the greater longevity in Japan associated with lower incidence of diseases suspected of being caused by infection?
> Do comparisons of Japanese Americans with other Americans shed light on this problem?
> Do comparisons among Japanese Americans or among Japanese people in Japan shed light on these different risk factors.

Cancer

Causes of cancer

Quote from Purves et al (2001) *Life: the science of biology, 6th edition.*, page 343: "Worldwide, no more than 15 percent of all cancers may be caused by viruses. What causes the other 85 percent?" They then said that it was genetic predispositions and mutations. What evidence has been used to dismiss infectious causation of cancer from 1980 to the present?

Does it exclude infectious causation or merely support other mutually compatible causes? For example do the data on smoking and lung cancer exclude infectious causation or could smoking exacerbate infectious causes? (How many nonsmokers get the same kind of lung cancer as smokers?) Associations between pipe smoking and lip cancer and chewing tobacco and oral cancer may provide some insight.

What are the relative strengths of the various hypotheses of causation (infectious, genetic inheritance or noninfectious environmental) that have been advanced to explain cancers whose causes are still currently unknown (e.g., breast cancer, ovarian cancer, prostrate cancer, most leukemias and lymphomas, colon cancer, skin cancer)?

The viruses that are known to cause human cancers inhibit four major cellular barriers to cancer: cell cycle arrest, apoptosis, cellular senescence, and cellular adhesion. How fully are these four inhibited by viral interference. Do mutations in the genes responsible for these barriers dismantle the barriers more fully than the viruses do?

Historical: What evidence was used to dismiss infectious causation of cancer after Rous's discovery of infectious causation of muscle cancers in chickens around 1910. Was it based on evidence or just the mindset of the day?

In 2001 I wrote a paper chapter for a book entitled "The Next 50 Years" in which I predicted to the nearest 5 years the dates by which certain chronic diseases would be accepted as being caused at least in part by infection. I suggested that acceptance could be gauged by whether a majority of medical texts mentioned infectious agents as a cause of each particular disease. Are the predictions about acceptance of infectious causation made by yours truly in 2001 holding up?

Practical benefits of determining infectious causation of cancers.

How does the success of controlling cancers known to be caused by infectious agents (e.g., Hepatitis B and C viruses, *Helicobacter pylori*, Kaposi's sarcoma-associated herpes virus, HPV) compare with the success of the best methods for controlling cancer that do not involve inhibition or prevention of infection? Success can be evaluated by measures such as morbidity in the general population, death in the general population, per capita cost of the cancer.

How many lives have been saved by the screening of hepatitis B and hepatitis C viruses for the prevention of cancer? How does this number compare with the number of lives saved by other "breakthroughs" in medicine?

How many lives can we expect to be saved by the vaccination against HPV (or other anti-infection strategies) for the prevention of cancer? How does these numbers compare with the number of lives saved by other "breakthroughs" in medicine?

Immune suppression, coinfection and cancer

The estrogen immune suppression hypothesis suggests that the higher incidence of breast cancer during and shortly after pregnancy results from the immune suppression during pregnancy, which in turn allows infectious agents such as human papillomavirus (HPV),

Epstein Barr Virus (EBV) and Mouse mammary tumor virus (MMTV) to be less controlled. Is HIV or immune therapy more strongly associated with cancer during these times?

How much coinfection of HPV, EBV and MMTV is there in the general public and in cancer tissue?

Breast cancers generally are not exacerbated by HIV infection or immunosuppressive therapy. But HPV seems to be associated with a small portion of breast cancers, particularly those that occur premenopausally in sexually active women. But HPV induced cervical cancer is exacerbated by HIV infection. This raises a paradox. If HPV causes this subset of early breast cancers they should be exacerbated in HIV patients. If one looks only at sexually active HIV patients premenopausally, is HIV associated with an increase in breast cancer?

The failure of HIV to increase breast cancer seems contradictory to estrogen immune suppression hypothesis for the increased during and shortly after pregnancy. Might this paradox result from differences in kind of immune suppression caused by HIV and immunosuppressive therapy on the one hand and estrogen and progesterone on the other.

Head and neck cancers such as tonsillar cancer is often caused by HPV (probably acquired from oral sex). Does HIV exacerbate these cancers?

AIDS patients are now dying of cancer more than they used to. Do these cancers include those that are known to be caused by pathogens? For the remaining cancers of uncertain cause, is there evidence of infectious causation?

Mouse mammary tumor virus and cancer (MMTV)
MMTV or a virus extremely closely related to it causes mammary tissue cancer in the house mouse (*Mus domesticus*) and may be responsible for up to about 1/3 of human breast cancer within M. domesticus's geographic range. What are the routes of transmission of MMTV in mice? Do they involve infrequent opportunities of transmission and thus favor evolution of persistence inside of mice? This would help explain their possible role as a cause of breast cancer in humans.

What is the connection between MMTV in rodents and "MMTV" in humans? Are human infections always obtained from rodents or are they sometimes transmitted from person to person. If so, how?

EBV and cancer
How good is the evidence supporting the dogma that infectious mononucleosis is more severe when EBV is acquired during adolescence as opposed to early childhood? If so, why is it more severe? Increased dosage from juicy kissing (as opposed to sharing of eating utensils)? Reduced symptomatic defenses (e.g., lower fever?) in adolescence relative to early childhood? Is there any evidence that fever or other symptomatic defenses are effective in controlling EBV? Is there any evidence suggesting that EBV has become more common and/or evolved to be more virulent in response to all the kissing around that has occurred since the mid 1960s.

Is infectious mononucleosis (or EBV infection) more severe in places where kissing contact is

greater? If so, does the association still hold up after the lateness of onset is accounted for?

Is infectious mononucleosis (which is caused by EBV) more severe when people get it in teenage years than in pre-teens?

Breast cancer rates
How are changes in cancer death rates and incidence rates over time related to statistical biases as opposed to interventions; e.g. how much of death due to breast cancer is due to increased ability to find tumors early vs chemotherapy? Could the benefits of early detection be offset by more aggressive tumors, which in turn could be a result of more virulent viruses?

Why have breast cancer rates declined little in response to a massive increase in mammography? Is better mammography pushing down the rates but is something else offsetting this benefits? Or is mammography simply not that effective because aggressive cancers have already spread by the time the first positive mammography is obtained? Or, is mammagrophy itself contributing to breast cancer?

Job-related risks of cancer
How does the probability of death from cancer vary for various professions including professions in which people are exposed to sexually transmitted pathogens or kissing transmitted pathogens (actors, rock and roll stars, athlete stars, etc)? E.g., actors do a lot of kissing; are cancers suspected of being caused by EBV (e.g., breast, hodgkin's, nonHodgkins, nasopharyngeal, ovarian) particularly high among actors?
Are cancer rates particularly head and neck cancer, penile cancer, prostate cancer, particularly common among male who may tend to have a lot of unprotected sex ?

Is there an association between prostitution and cancers of uncertain cause?

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Is the incidence of premenopausal breast cancer associated with the potential for sexual transmission? Does this association break down for postmenopausal breast cancer with increasing age?

Epidemiology of cancer and cancer viruses
What do geographic patterns indicate about the causes of cancer?

A research group at UCBerkeley has found bovine leukemia virus (BLV) to be associated with breast cancer. BLV is transmitted to humans in cows' milk. Is the incidence of breast cancer correlated geographically with human consumption of cow's milk. Is it inversely correlated with a vegan diet? In the US most of the dairy cattle are infected with BLV. The United Kingdom, however, has eliminated BLV from their dairy cattle. Has the incidence of breast cancer declined in the UK relative to the US?

Are the breast cancers associated with HPV or EBV more severe or occur at a younger age than those with unknown causes?

What exactly is the route of transmission of EBV during early childhood in poor countries? Shared eating utensils?

Does the prevalence of HPV's oncogenic serotypes vary geographically in accordance with the potential for sexual transmission?

What do the epidemiological patterns of MMTV tell us about their transmission to and among humans?

Senescence and cancer

Is the probability of cancer per lifetime approximately constant across species of different body sizes, as would be expected from evolutionary theory? Or, is the probably of cancer per cell approximately constant as would be expected from a nonevolutionary application of cell biology?

Infectious causation of chronic diseases

Historical/empirical studies: How often have people been wrong when they have attributed diseases to infection, noninfectious environmental causation or genetic causation? It is often said dismissively that the current attention to infectious causation of chronic disease is reminiscent of the early decades of the 20th century and the last couple of decades of the 19th century when "Everything was explained by infection." The key issue, however, is not whether infection was often invoked but whether people were wrong when they did invoke it. Here are some diseases for which the role of infectious causation needs to be evaluated: Hodgkins and nonhodgkins lymphomas, skin cancers, lung cancers, osteoporosis, attention-deficit disorder, bipolar disorder, schizophrenia, major depression, autism. Specific questions about many of these diseases are given above for cancer or below for other chronic diseases.

Human genetics and disease

What are the best "success stories" of human genetics research and how do the practical benefits from these advancements compare with those of the recent success stories associated with discovery of infectious causes of disease? For example how many lives are saved or improved by the "breakthrough" in the treatment of chronic myelogenous leukemia or phenylketonuria?

-Are there any good examples of "complex genetic diseases"? If not what is the best evidence that they exist?

-Are there any genetic causes of common damaging diseases that appear to be unlinked to protection from infectious disease?

-Are there any diseases besides Alzheimer's, atherosclerosis, and multiple sclerosis that are linked to the epsilon 4 allele of the apolipoprotein E gene? If the epsilon 4 allele is having its negative effect by predisposing people to infection with *C. pneumoniae*, then we would expect diseases that are caused by *C. pneumoniae* (e.g., asthma/chronic obstructive pulmonary disease) to be particularly severe in people with the epsilon 4 allele. Similarly, we would expect that diseases caused by the same pathological process as atherosclerosis (e.g., impotence) to be associated with epsilon 4 and with *C. pneumoniae*.

Sexually transmitted pathogens

Theory proposes that pathogens transmitted by kissing or sexual contact should tend to be persistent and hence should tend to cause a disproportionate amount of chronic disease.

-Among diseases for which specific pathogens are suspected but not yet accepted as causes, what proportion of these pathogens are transmitted by kissing or sexual contact?

-What proportion of diseases that have been accepted as caused by infection over the past 30 years are caused by sexually or kissing-transmitted pathogens.

-Hepatitis C virus now infects about 2 million Americans. Is there evidence that hepatitis C prevalence has increased since the time when transfusion transmission of hepatitis C was prevented through the screening of the blood supply? How does the change or lack of change compare with that for Hepatitis B (which is known to be sexually transmitted.)

-How important is sexual transmission for Hepatitis C virus and how important is hepatitis C as a cause of liver cancer and diabetes?

-Do the data from studies of bacterial pathogens support the view that the most nasty sexually transmitted pathogens tend to be occur in areas with a high potential for sexual transmission?

-Are the most severe human papillomaviruses, hepatitis B and C viruses, HIV, HTLV, and herpes simplex II viruses disproportionately more common in geographic areas with a high potential for sexual transmission?

-Are the most severe EBV, cytomegaloviruses, gum bacteria, herpes simplex 1 viruses disproportionately more common in geographic areas with a high potential for kissing transmission?

AIDS-associated diseases

AIDS may provide a window for understanding the spectrum of chronic diseases that are caused by infection, because AIDS involves the suppression of immune responses to infection.

-What proportion of AIDS-associated diseases are now accepted as caused by infection?

-Are there any AIDS-associated diseases that are not associated with an infectious agent?

-Are the life-threatening diseases that arise during prolonged antiretroviral therapy caused mainly by infection or by the damage from antiretroviral drugs?

-Osteoporosis is an AIDS-associated disease. Does the evidence implicate immune-suppression or some other correlate of HIV infection (e.g., antiretroviral treatment)? Periodontitis, which is caused by gum pathogens, particularly *Porphyromonas gingivalis*, is correlated with osteoporosis. Periodontal disease is exacerbated by immunosuppressive therapy and by some immunosuppressive diseases. Are gingivitis and periodontitis exacerbated by AIDS? If so, *P. gingivalis* would be a candidate agent for causing osteoporosis. Osteoporosis diagnoses have increased from 0.5 million to 3.6 million over the past decade, in accordance with a change in some environmental cause. How important is increased reporting as a contributor to this increase?

-In Biology 372 we discussed the prediction that the HIV subtype E that was brought into Japan from Thailand should evolve toward benignity. Has this change occurred?

-Similarly we predicted that HIV-2 would persist in the general population of Senegal more than it has in other West African countries. We also predicted that milder HIV-1 subtypes would predominate in Senegal. Have these predictions held up?

Selective pressure against chronic diseases:

The traditional argument: people didn't live past their late 40s for most of our evolutionary history and therefore natural selection couldn't have disfavored chronic diseases like cancer because they

usually occur in later decades of life.

-How do contributions to evolutionary fitness vary with age in representative populations?

-What are typical percentages of old people in different cultures and at different historical periods.

-What is the frequency distribution of longevity in hunter/gatherer societies and how does it compare with longevity in other modern societies?

-What is the history of the idea that human life in nature was "nasty, brutish, and short"?

-Are there any cultures that are devoid of old people (e.g., over 50 years old)?

Evolution of virulence and antibiotic resistance

-Is there any evidence that some of the classic nasty diarrheal pathogens (*Salmonella typhi*, which causes typhoid fever; or *Shigella dysenteriae*, which causes the worst kind of dysentery) vary in virulence as a function of geographic and/or temporal variations in water quality?

-Does a review of the information on virulence and antibiotic resistance reveal a positive correlation for closely related pathogens that differ in virulence (e.g., the different species of *Shigella*, which cause dysentery; or the different species of *Salmonella*; or the different species of *Bordetella*, which cause whooping cough; or the different biotypes of *Vibrio cholerae*, which cause cholera).

-The standard dogma is that antibiotic resistance results from patients who do not take their complete regimen of antibiotics. Is this a self-serving claim made by health professionals to shift the blame to the patients, or is there some evidence that supports it? The most extensive use of antibiotics occurs in hospitals. How much of the evidence actually implicates hospitals as the site of selection of antibiotic resistance?

-Has HIV begun to evolve resistance to HAART (=Highly Active Antiretroviral Therapy)? Does it appear to be the more virulent variants of HIV that have evolved such resistance?

Hygiene and human health

The hygiene hypothesis proposes that allergies and autoimmune diseases have increased in frequency over the past century because our environments have become too hygienic. That is, our immune system needs exposure to parasites to tune itself. If the environment is too clean our immune systems tend to overreact?.

What is the best evidence for the hygiene hypothesis?

Are there alternative hypotheses that can explain the evidence that is used to support the hygiene hypothesis? Immune manipulation by parasites as opposed to immune tuning? Infectious exacerbation of autoimmune processes?

Is there evidence that can be used to distinguish between the hygiene hypothesis and alternative hypotheses?

People living in urban areas have more autoimmune diseases. The hygiene hypothesis proposes that this increase results from reduced exposure to parasites. But urban populations tend to have more infectious diseases than rural counterparts Poor people in urban areas live in less hygienic environments than wealthy people. Do poor urban people have more or less autoimmune illness than wealthy urban people?

Antibiotics, agricultural productivity and human growth.

-Why do agricultural animals like cows and chickens grow better when they are given antibiotics? Is it that the antibiotics are controlling growth-stunting pathogens?

-Is there any evidence that the growth advantage due to antibiotics decreases as the duration of administration of antibiotics increases?

-Do changes in human stature over the past century correspond to the usage of antibiotics, improvements in nutrition, changes in hygiene? Are any of these factors better correlated than the others?

Disease manifestations

-What data are available bearing on the long-term effects of symptomatic treatment of inflammation and pain (e.g, by aspirin or cold) on sprains or any other noninfectious ailments?

-Does symptomatic treatment of chronic infectious diseases (e.g., atherosclerosis) tend to be helpful more often than symptomatic treatment of acute infectious diseases (e.g., influenza) ? (By definition, chronic infectious diseases persist in spite of host defenses. If symptomatic defenses were effective, one would not chronic infectious diseases to be chronic). It looks as though aspirin tends to ameliorate chronic diseases (such as type II diabetes, atherosclerosis, Alzheimer's and stomach cancer and colon cancer) but exacerbates acute infectious diseases (such as the common cold, influenza, and chicken pox).

-Was the therapeutic value of malaria therapy for neurosyphilis a result of the fever that was generated or some other effect of the malaria?

-When all of the 30 or so studies evaluating the evolutionary basis of fever are considered, how strong is the support for fever being a defense? Are the exceptions consistent with fever being a side effect or a manipulation? Specifically, with regards to malaria, is there any evidence that fever is helpful in controlling the damage from malaria? Could it be a manipulation?

-How feasible is the hypothesis that infection induced infertility is a manipulation to break up a pair bond? In particular, does *Chlamydia*-induced infertility or gonorrhea-induced infertility break up a pair bond soon enough to cause further transmission of the pathogen?

Mental illnesses

-How do the pathological changes and behavioral alterations in the natural life cycle of borna disease virus correspond to its possible causal role in schizophrenia and bipolar disorder?

-What are the relative merits and weaknesses of the psychiatric, biochemical, and evolutionary explanations of disorders such as obsessive compulsive disorder, schizophrenia, bipolar disorder (manic depression), major depression, chronic fatigue syndrome, attention deficit disorder?

-What are the merits and weaknesses of infectious causation of neurodegenerative diseases such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, Lou Gehrig's disease?

-What is the prevalence of mental illness among the greatest artists in different areas of art (e.g., painting, music, novelists, poets)? Is the prevalence higher during later periods characterized by more abstract art as opposed to "scientific" art (e.g., during the 19^{th}- 20^{th} centuries as opposed to the 15^{th}-18^{th} centuries for painters)?

Endocrinology

-*Polycystic ovary syndrome* (PCOS) has characteristics that suggest infectious causation. The fitness costs of PCOS seem far to great for a genetic disease. What can current evidence tell us about the possibilities infectious and noninfectious environmental causes of PCOS?

-*Diabetes*

--What pathogens have been associated with type one and type II diabetes?

--Is there any reasonable hypothesis for explaining this association other than infectious causation?

--Is the evidence correlating rich diets, lack of exercise and diabetes consistent with

infectious causation?
--Is the evidence generated by research focusing on genetic causation of diabetes consistent with infectious causation?

Glossary Of Terms Pertaining to Cancer

Basal breast tumors – (syn: triple negative breast cancer) tumors that lack expression of estrogen, progesterone and ErbB2 receptors (for ErbB2 see HER-2/neu)

bcl-2 – an antiapoptotic protein that protects cells from programmed cell death by preventing activation of proapoptotic caspase proteins. (bcl-xL, bcl-w are also antiapoptotic, but Bax, Bak and Bok are proapoptotic).

BRCA1 - (named for "breast cancer 1") is a human gene located on the long arm of the 17^{th} chromosome (17q21). This gene, called a tumor suppressor gene, encodes a protein whose function is the suppression of tumor formation. Its mechanism of action involves repair of mutations. A mutation in this gene can lead to an increased risk of certain cancers, particularly breast cancer (in both women and men) and ovarian cancer.

BRCA2 - refers to either a gene (BReast-CAncer susceptibility gene 2, located on human chromosome 13, 13q12-13) or the protein coded for by that gene. The BRCA2 protein functions as a tumor suppressor. Like the BRCA1 protein, BRCA2 seems to function in the cell nucleus to repair damaged DNA. Mutations in the genes that code for the BRCA1 and BRCA2 proteins can result in defective repair of damaged DNA, accumulation of mutations, and tumor formation, particularly in the ovaries and the breast.

Caspase - Caspases are enzymes known as proteases, which play essential roles in apoptosis (cell death) and inflammation. As proteases, they are enzymes that cleave (cut) other proteins. Caspases are essential in cells for apoptosis, one of the main types of programmed cell death in development and most other stages of adult life, and have been termed "executioner" proteins for their roles in the cell. Some caspases are also required in the immune system for the maturation of cytokines. Failure of apoptosis is one of the main contributions to tumour development and autoimmune diseases. Caspases are regulated at a post-translational level, ensuring that they can be rapidly activated. They are first synthesized as inactive *pro-caspases*,that consist of a prodomain, a small subunit and a large subunit.

Cathepsin-D (CD) – an aspartyl protease that is active in intracellular protein breakdown.

C-erb B2 – same as HER-2/neu

Epidermal growth factor receptor (EGFR) – (syn: HER-1, ErbB1) Transmembrane receptor that binds EGF via its extracellular domain & transmits growth signals intracellularly via tyrosine kinase, causing the cells to divide. It is found at abnormally high levels on the surface of many types of cancer cells, so these cells may divide excessively in the presence of epidermal growth factor.

HER-1 - Epidermal growth factor receptor. The protein found on the surface of some cells and to which epidermal growth factor binds, causing the cells to divide. It is found at abnormally high levels on the surface of many types of cancer cells, so these cells may divide excessively in the presence of epidermal growth factor.

HER-2/neu – (syn ErbB2) oncogene. It is overexpressed in many tumors. It is a tyrosine kinase receptor, whose activation leads to proliferative signals within the cell. Also called ErbB2, HER-2/neu belongs to the EGFR family and is overexpressed in several solid tumors.

Ki-67 – a nuclear antigen present only in the nuclei of cycling cells. Acts as a cell cycle and tumor growth marker.

LVI – lymphovascular invasion

nm23 – Gene thought to work in cells to suppress the progression of a tumor to metastasis.

p53 – a cell cycle related transcription factor that promotes transcription of genes that induce cell cycle arrest or apoptosis in response to DNA damage or other cell stresses. This tumor suppressor gene is mutated in about half of all human cancers.

PTEN. Phosphatase and tensin homolog (synonyms: MMAC1, MHAM): PTEN is mutated in a variety of advanced cancers. PTEN is linked with regulation of cellular replication and apoptosis

(programmed cell death). Mutations in PTEN occur in cancers of the breast, prostate, endometrium, ovary, colon, melanoma, glioblastoma. and lymphoma. The loss of one copy of the PTEN gene can interrupt cell signalling fostering uncontrolled cell growth. Aberrant transcripts of PTEN have been identified in normal non-cancerous tissues (see Wang NM, Chang JG Are aberrant transcripts of FHIT, TSG101, and PTEN/MMAC1 oncogenesis related? Int J Mol Med 1999; 3(5):491-5) excerpted from http://www.cancerindex.org/geneweb/PTEN.htm#summary

Tyrosine kinase – an enzyme that can transfer a phosphate group to a tyrosine residue in a protein; these enzymes are a subgroup of the larger class of protein kinases. Phosphorylation is an important function in signal transduction to regulate enzyme activity. The hormones that act on tyrosine kinase receptors are generally growth hormones and factors that promote cell division (e.g., insulin, insulin-like growth factor 1, epidermal-derived growth factor).

Telomerase-Telomerase is a reverse transcriptase that carries its own RNA template for DNA synthesis of telomeres during replication. Also called telomere terminal transferase, its role is to elongate chromosomes by adding telomeric sequences to the end of existing chromosomes.