

Research Report

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INDOLENT LYMPHOMA

Over the years, significant progress has been made to improve cancer diagnosis, treatment and maintenance, resulting in lymphoma patients living longer, healthier lives. These positive trends could not be achieved without the research being conducted by the scientists and physicians within the cancer research community. The Lymphoma Research Foundation (LRF) has been supporting lymphoma researchers since its inception. To date, LRF has funded \$54.7 million in lymphoma research, ranging from basic laboratory science to clinical studies.

The success of LRF's programming is due to a research strategy that singles out specific lymphomas. This focused approach enables researchers to accomplish their objectives more effectively and efficiently. The first model was implemented to accelerate the pace of research in mantle cell lymphoma (MCL), which began with the establishment of the MCL Initiative in 2003, and was enhanced by the MCL Consortium in 2005. The goal of the MCL Initiative and Consortium is to identify effective and curative treatment strategies for MCL by funding innovative studies.

Based on the success of the MCL Initiative, LRF has started two other programs, one focused on follicular lymphoma (FL) and the other on chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), two forms of indolent (slow-growing) forms of

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The Lymphoma Research Foundation (LRF) is the nation's largest lymphoma-focused voluntary health organization devoted exclusively to funding lymphoma research and providing patients and health care professionals with critical information on the disease. LRF's mission is to eradicate lymphoma and serve those touched by this disease.

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lymphoma. This report highlights the latest developments to come out of LRF's FL and CLL/SLL initiatives.

Lymphoma Research Foundation Grants

In 2006, LRF started an initiative to develop novel therapeutic strategies for the treatment of FL and CLL/SLL. As a result, LRF awarded six 5-year grants to promising researchers in the field totaling more than \$5 million. The following section highlights the research being conducted by these investigators.

Follicular Lymphoma Grantees

Anne J. Novak, Ph.D., (Mayo Clinic College of Medicine) is studying BLyS (B-lymphocyte stimulator) and APRIL (a proliferation-inducing ligand), two factors that influence the growth and survival of both normal and malignant B-cells. Dr. Novak has shown that BLyS is highly expressed in people with non-Hodgkin lymphoma (NHL). She has discovered that an alteration in the BLyS gene correlates with increased BLyS levels in patients with B-cell malignancies. Dr. Novak has set out to determine if genetic variability in BLyS, BLyS receptors (TACI, BCMA, and BAFF-R), or APRIL, are associated with the development of FL and the clinical outcome of patients. In addition, she has proposed to determine the role of APRIL on the biology of FL in B-cells.

Sandra J. Horning, M.D., (Stanford University Medical Center) intends to identify biologic markers that can be used to direct current and future FL therapy. Dr. Horning will identify these markers by examining diagnostic tissue samples from the ECOG 1496 phase III clinical trial of chemotherapy plus maintenance rituximab.

She will utilize a “team science” approach that combines experts in clinical research, molecular diagnostics, pathology and statistics to evaluate genes and proteins that are predictive of outcome in FL treated with state-of-the-art therapy. The knowledge gained can identify new targets for therapy and assist in current treatment selection.

Follicular lymphoma: A type of B-cell non-Hodgkin lymphoma that is usually indolent (slow-growing). The tumor cells grow as groups to form nodules.
National Cancer Institute

Laurence J.N. Cooper, M.D., Ph.D., (M.D. Anderson Cancer Center) has genetically modified T-cells so that they contain a tumor-specific receptor. These modified T-cells are fashioned to recognize a molecule on the surface of B-cells (normal and malignant) called CD19. In the past, LRF supported a trial infusing CD19-specific T-cells at City of Hope in Duarte, CA. Dr. Cooper will now extend these observations at M.D. Anderson Cancer Center to conduct a next-generation clinical trial to determine if lymphoma-specific T-cells can be safely infused into the body following an autologous hematopoietic stem cell transplantation and determine how effective they are at combating FL. In support of this trial he will examine ways to enhance the survival and potency of the tumor-specific T-cells.

Steven H. Bernstein, M.D., (James P. Wilmot Cancer Center) is examining whether rituximab therapy can induce a lymphoma-specific T-cell immune response in patients with FL. According to previous studies, patients who received rituximab continue to experience anti-tumor effects even when rituximab is no longer present in the body. Studies have also shown that a large number of patients that relapse following rituximab

therapy experience a second remission which is often longer than the first. Dr. Bernstein has hypothesized that these two events may result from rituximab's ability to generate an "active" immune response. During an active immune response, the body develops cells that can "remember" the cancer thereby eliciting a strong immune response if the cancer were to come back. The demonstration of such an immune response would have significant implications as to how we treat patients with FL. These results could apply to similar antibody-based therapies of other cancers, leading to novel treatment strategies for cancer in general.

CLL/SLL Grantees

Tracy M. Handel, Ph.D., (University of California, San Diego) is focusing her studies on leukemic cell survival. CLL is characterized by the accumulation of B-cells due to resistance to cell death. However, outside of the body CLL cells die unless they are in contact with support cells (known as "nurselike cells" or NLCs), which are thought to protect cancer cells from chemotherapy-mediated death. One of the factors that is made by support cells and promotes leukemic cell survival is a protein called SDF-1. The goal of Dr. Handel's project is to investigate how SDF-1 causes leukemic cell survival and to investigate modes of interfering with the survival signals in order to identify and validate new therapeutic strategies.

David A. Frank, M.D., Ph.D., (Dana-Farber Cancer Institute) is attempting to identify molecular abnormalities that are unique to malignant B-cells which characterize CLL in hopes of developing a new targeted therapy. To date, Dr. Frank has found that a protein called STAT1, which controls genes responsible for regulating cell survival, is modified abnormally in CLL cells. When STAT1 is activated, CLL cells lose the ability

to survive. To exploit this process, Dr. Frank has identified several drugs that can enhance the activity of STAT1. He intends to determine the activity of these drugs on CLL cells in hopes of developing a clinical trial.

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL): The World Health Organization classifies CLL and SLL as two different stages of the same disease. According to the American Cancer Society, CLL and SLL involve the same type of cell. However in CLL, the cancer is mostly in the blood and bone marrow, and in SLL it is mainly in the lymph nodes.

Indolent Lymphoma Workshop

On October 11, 2007, LRF hosted an Indolent Lymphoma Workshop in Arlington, VA. The meeting brought together some of the most renowned lymphoma experts to discuss the current status of FL and CLL research and to determine its future direction. The following section contains highlights of the meeting.

Indolent Lymphoma Workshop – Directions for Research

Which novel research avenues promise to bring scientists furthest and fastest toward a cure for indolent lymphoma? And how can LRF funding best foster these promising research efforts in CLL and FL to complement the tremendous scientific strides being made across the country and around the world – while avoiding reinvention of the proverbial wheel? LRF's *Indolent Lymphoma Workshop–Directions for Research*, brought together renowned scientific experts to weigh in on these points, as well as the bottom-line question with which LRF president Sue Bliss opened the day of scientific discussion:

“What can we do to avoid duplicating efforts, to get scientific discoveries from the laboratory into clinical studies more quickly, and to make the best use of the money we will have to support this research?”

More than 40 of the most prominent lymphoma experts from the United States and abroad, representing an outstanding group of medical research powerhouses, attended the workshop. They came together in Arlington, VA, to summarize the impressive scientific headway being made in indolent lymphoma research and guide LRF on the crucial question of its funding priorities.

The Scientific Landscape: Chronic Lymphocytic Leukemia

The morning session – which focused on CLL (and the related small lymphocytic lymphoma, or SLL) – was broken down into three sections: *Cooperative Efforts in CLL*; *Relevant Issues for CLL Research Focus*; and *Where Should LRF Place its Resources to Aid CLL Research?*

Cooperative Efforts in CLL

In reviewing what strategies have worked to bring lymphoma researchers closer to a cure, a recurring theme was the synergy achievable when lymphoma researchers share their expertise. Meeting participants were brought up-to-date on the LRF-conceived Mantle Cell Lymphoma (MCL) Consortium and on the research advances of several existing CLL-focused collaborations.

◆ **MCL Consortium.** This 90-member group started by LRF in early 2005 was established to identify effective and curative treatment strategies for MCL, a rare and difficult-to-study form of cancer. The Consortium and its methods for promoting synergy among



Dr. R. Fisher (James P. Wilmot Cancer Center)

MCL investigators to accelerate scientific advances were highlighted at the Workshop to showcase how successful such a cooperative effort can be.

- ◆ **CLL Research Consortium.** This multi-institutional, NIH-funded program brings together clinical sites with varied patient populations and quality basic science laboratories. The Consortium was held up as an excellent example of scientific teamwork toward discovering the next generation of lymphoma therapies. The organizational structure was presented, along with the goals of the Consortium, whose focuses include molecular genetics, biochemistry of apoptosis, immunology, gene therapy, novel pharmacologic agents and clinical trials development.
- ◆ **CLL Global Research Foundation.** This nonprofit partnership of patients, their families, the research community and others interested in finding a cure for CLL focuses on patient-oriented research. Presented as an example of the entrepreneurial model in CLL research, the Foundation stands in contrast with traditional funding because of its low overhead and the research freedom it affords young investigators.
- ◆ **U.S. Cooperative Group.** This collaboration of U.S. and Canadian cancer research groups is investigating the benefits and risks of various single-

agent and combination therapeutic options for CLL. Recently, the group has placed increasing emphasis on risk stratification of CLL and treatments. Also, working together, scientists are rapidly increasing their understanding of active agents in relapsed CLL.

- ◆ **National Cancer Research Institute (NCRI).** This U. K. organization has recently been established to coordinate all cancer research efforts and includes a CLL subgroup. The CLL subgroup has developed a wide portfolio of multi-center clinical trials to establish standard therapy and to develop novel treatment strategies for patients with CLL. In addition, there has been a focus on developing trials in areas of unmet need – for example, those patients with high risk cytogenetic abnormalities and for those older patients with co-morbidities. This clinical trial activity has been matched by initiatives in laboratory-based research and the development of a cell bank.

Relevant Issues for CLL Research Focus

Scientists with expertise in prognostic assessment and cutting-edge treatment strategies for various CLL stages brought the workshop audience up-to-date on these crucial and evolving issues in indolent lymphoma management.



Drs. J. Connors (British Columbia Cancer Agency) and B. Cheson (Georgetown U. Hospital)

Prognostic Factors. Alongside predictors of treatment response, certain gene mutations and other factors used to predict disease outcome are expected to be increasingly valuable as the menu of therapeutic options grows. But predicting the behavior of CLL in a particular patient is difficult. Prognosis currently relies on classical factors such as age and longstanding systems of staging the disease, but scientists are working to identify more accurate CLL markers that are easily obtained and reproducible. However, new prognostic factors under study – such as IgVH gene analysis, the protein ZAP-70, serum markers, cytogenetics or CD38 – can only be useful if standardized. Therefore, for now, classical factors continue in use as prognostic mainstays.

Cell Survival. Scientists have concluded recently that CLL cells proliferate much more rapidly than previously thought, and that this process may not be caused by an intrinsic defect in apoptosis (cell death), but instead survival signals delivered by “bystander” cells, that lead to the accumulation of leukemia cells. Researchers are beginning to understand the molecules involved in CLL cell survival and are eager to learn more about the CLL micro-environment.

Lymphoma experts are taking a closer look at biological differences among CLL patients – whether they express CD38 molecules on the surface of their CLL cells, for example – in the search for potential new therapeutic targets.

CLL a Single Disease? Scientists have recently questioned whether CLL is more than one disease – one in which the leukemia cells’ immunoglobulin genes (Ig) are mutated and another, a much more aggressive form of CLL requiring earlier treatment, in which these genes are not mutated. Recent gene expression profiling studies have shown that CLL patients share a common gene expression signature and that

CLL should be thought of as a single disease with two subtypes. Investigation has also raised the possibility that antigen stimulation may contribute to CLL. A test has been designed that could guide treatment decisions by distinguishing Ig-mutated from -unmutated CLL. Scientists are looking at the in-vivo molecular consequences of CLL treatments such as fludarabine and rituximab to better understand their mechanisms and, in turn, implications for clinical use.

Superior Treatment Strategies. Scientists are rapidly accumulating knowledge about strategies for initial treatment of CLL, as well as approaches for patients with relapsed disease. Clinical and lab studies are being undertaken to shed light on the relative effectiveness of various regimens – fludarabine combined with cyclophosphamide as frontline CLL treatment compared with single-agent fludarabine, for example – and to help clinicians zero in on superior treatment approaches. Scientific focal points in this area include new chemo-immunotherapy agents and combinations; consideration of the need to eradicate minimal residual disease (MRD) after initial therapy; issues of tolerability and access, as well as efficacy, in treatments for elderly patients; the need to rebuild the immune system after treatment; the impact of frontline treatments on salvage therapy; and identification of therapeutic targets.

While the monoclonal antibodies rituximab and alemtuzumab are among the most widely tested immunotherapy agents, many new antibodies are being tested – as single agents and in combinations, as well as frontline treatment and salvage therapy for relapsed CLL. Among the therapies currently in trials: the monoclonal antibodies atumumab and lumiliximab; other agents considered new in the treatment of returned

CLL such as bendamustine, flavopiridol, lenalidomide, and pentostatin; and some agents that target apoptosis. With so many options available and in the pipeline, attention must be given to differentiating agents and combinations using such issues as toxicity and biological differences among patients.

Recommendations for CLL Funding

Given the wide variety of studies relating to CLL management and the various funding models under which scientific advances are being made, LRF requested input on how to best allocate its CLL resources.



Drs. A. Zelenetz (Memorial Sloan-Kettering Cancer Center) and O. Press (Fred Hutchinson Cancer Research Center)

Recommendations from workshop speakers and audience members included such things as: finding ways to eliminate minimal residual disease (MRD), which can lead to a recurrence and is associated with decreased survival; continuing to facilitate patient enrollment in clinical trials – broadening participation at all clinical stages and particularly encouraging participation by groups such as the elderly who are at highest risk; and creating translational pathways to help scientific discoveries go from “bench to bedside” more quickly – by funding trials early, devising ways to move scientific advances through clinical trial phases more

rapidly, and allowing clinical investigators to follow through on their innovative scientific vision with minimal interference.

All of the suggested recommendations will be reviewed, evaluated, and prioritized by LRF's Scientific Advisory Board (SAB) to determine which recommendations are achievable and will have the greatest impact on the indolent lymphoma research community. The SAB, in collaboration with LRF, will set goals and lay out next steps for those recommendations receiving highest priority.

The Scientific Landscape: Follicular Lymphoma

The follicular lymphoma (FL) portion of the discussion was conducted in three parts: *The Molecular Basis of FL*; *State-of-the-Art FL Therapies*; and *What Can LRF Do to Advance FL Research?*

The Molecular Basis of FL

Follicular lymphomas arise from mutations in B lymphocytes and are associated with a molecular rearrangement between chromosomes 14 and 18, also known as a translocation. To understand the evolution of these mutations, the FL workshop began with an examination of the complex events occurring in germinal center B-cells, such as isotype swapping and receptor editing, which ultimately result in B-cells that produce more effective antibodies.

Scientists are investigating oncogenesis, the molecular and cellular changes associated with the development of FL, and other abnormalities originating from the germinal center, to identify precursors of the disease. By identifying molecular and cellular differences among cancer tumors, scientists hope to predict the course of the disease, select the best choice of treatment for an individual patient, and perhaps identify new

therapeutic targets.

State-of-the-Art FL Therapies

While the addition of rituximab or another monoclonal antibody to chemotherapy has increased survival over chemotherapy alone, researchers are constantly striving to improve on conventional FL therapy. Many agents and combinations are under investigation to determine their efficacy as frontline or maintenance treatments and sometimes as a therapy for relapsed disease. Standard treatment approaches include CVP plus rituximab, and CHOP plus rituximab (R-CHOP). Of note, a nationwide, multi-center clinical trial is underway comparing R-CHOP alone to R-CHOP plus Bexxar.

To add to the armamentarium of FL therapies, several monoclonal antibodies are being tested – including several “2nd generation” anti-CD20 antibodies which purportedly have advantages compared to the revolutionary rituximab molecule. Some of these improved CD20 antibodies have better effector functions, including augmented antibody-dependent cytotoxicity and complement fixation, which speed-up apoptosis. Other antibodies that target a variety of alternative molecules on lymphoma cells include CD5, CD23, CD30, CD40, and CD80. Many questions remain about the optimal role for rituximab itself in FL treatment – sometimes in combination with other biological agents. Outstanding questions about monoclonal antibodies include issues of mechanism of action, optimal dosing and scheduling, and optimal combination with chemotherapy or other antibodies.

Vaccine therapy offers another promising avenue for lymphoma research. Despite some initial failures of cancer vaccines, new knowledge provides a reason for optimism that vaccines will be able to strengthen the

body's own defenses against existing diseases. Several comparative trials are ongoing, including phase III trials of idiotype protein vaccines and more preliminary studies of other types, including a potent proteoliposome vaccine formulation that can be produced in a single day – avoiding the time-consuming manufacturing process that limits patient-specific idiotype protein vaccines.

Researchers are pursuing additional biologic agents that may prove useful in FL management – bortezomib and temsirolimus among them – but many questions, including which molecules offer the most promise and how they fit in with other treatments, must be addressed before new small molecules are incorporated into conventional treatment paradigms.

New agents and approaches are also under development to lessen the toxicity associated with stem cell transplants – notable among them, the relatively new non-myeloablative transplantation option, which uses lower doses of conditioning therapy to prepare patients for transplant and relies on the graft vs. lymphoma effect (an anti-tumor response by immune cells present in a donor's transplanted tissue) of the transferred allogeneic cells to eradicate the lymphoma. New evidence is being collected about benefits and risks, including the incidence of graft-versus-host disease, the rejection of therapeutic transplanted tissue.

Recommendations for FL Funding

Workshop participants agreed that fostering collaboration among investigators could maximize research progress. This would allow researchers to share knowledge and ideas; build research resources; help make the case for research support; and speed translation of research from bench to bedside, ultimately prolonging the lives of

those with FL. Based on this recommendation, LRF's Scientific Advisory Board will be responsible for reviewing the information presented on FL and determining next steps to achieve greater collaboration among FL researchers.

Conclusion

Despite consistent and dramatic progress in lymphoma research, CLL and FL are today considered incurable, and myriad questions remain about the best treatment strategies among the numerous approved and experimental therapies. In pursuing its mission of finding a cure for lymphoma, LRF is committed to investing its funds for CLL and FL research to the best advantage of patients. By providing insights into ongoing successes in CLL and FL research and highlighting those promising inroads warranting additional investment, the October workshop informs LRF's investment in research strategies that can benefit patients and ultimately lead to cures for FL and CLL.



Dr. C. Portlock (Memorial Sloan-Kettering Cancer Center)

Recent News From the Field

Lymphoma research is continuously advancing as old therapeutic strategies are improved and new treatment modalities are discovered. Following are some recent findings from the field.

◆ Cephalon, Inc. announced positive results from a Phase III clinical trial of Treanda® (bendamustine HCl) in patients with indolent NHL whose cancer is no longer responsive to treatment with rituximab. Treanda® damages the DNA in cancer cells, which leads to cell death, and stops cancer cells from dividing.¹

◆ Immunomedics, Inc. announced that milatuzumab (an anti-CD74 antibody) showed promising therapeutic activity for B-cell lymphoma in animal models when used by itself, and enhanced activity when combined with anti-CD20 antibodies such as velizumab. Weill Medical College of Cornell University is conducting a phase I study of milatuzumab in patients with recurrent NHL or CLL who have received at least one prior standard treatment.²

◆ Zevalin®, a monoclonal antibody bound to two radioisotopes, was found to improve progression-free survival in patients with advanced follicular lymphoma as a first-line therapy in a late-stage randomized trial. This “consolidation therapy” may extend the drug’s use beyond relapsed or refractory low-grade, follicular, or transformed B-cell NHL.³

◆ In a report published by the Journal of the American Medical Association, long, confusing forms, misinterpretation of HIPAA laws, and increased administrative costs are blamed for poor patient accrual in clinical trials. Only 25% of researchers polled concluded that patient privacy has actually improved while 70% believe HIPAA has made research more cumbersome.⁴

◆ Allos Therapeutics announced that it has started enrolling NHL patients in a multi-center phase I study of its chemotherapy agent RHL. This novel therapy (a small molecule chemotherapeutic agent) is bioactivated by the enzyme DT-diaphorase, commonly over-expressed in advanced solid tumors and NHL.⁵

◆ Lenalidomide (Revlimid®), an oral immunomodulatory derivative similar to thalidomide, was FDA approved in 2005 and is now being investigated in several lymphoma clinical trials. It is currently being tested in combination with bortezomib for mantle cell lymphoma, with dexamethasone for large B-cell NHL, and for refractory indolent NHL. Revlimid induces an immune response and inhibits inflammation, affecting both the cancer cell and its microenvironment.⁶

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CANCER RISK & NUTRITION

The World Cancer Research Fund International (WCRFI) and the American Institute for Cancer Research (AICR) recently developed a report revealing the effects of diet, physical activity, and body composition on cancer risk.

How was the evidence collected?

WCRFI/AICR tasked nine research teams from around the world to collect and review all of the relevant scientific literature linking dietary factors and cancer prevention. Of the nearly half a million studies found, 7,000 met criteria for inclusion in the report. These studies were then forwarded to a 21-member panel to be assessed and judged.

The Panel examined the quality and strength of the research and assigned each potential linkage, or causal relationship, a grade of: convincing, probable, limited, or absence of a causal relation. The causal relationships that were strong enough to meet the criteria for “convincing” and “probable” were used to create public health goals and recommendations.

Why is this report important?

According to the investigators, this report represents the most comprehensive and rigorous effort of its kind. The report developers also indicated that the innovative methods utilized by the investigators allowed them to make reliable recommendations that can be used to create policies that affect change in an effort to prevent cancer worldwide.

What does this mean for lymphoma?

Within the medical community lymphoma is generally recognized as having non-dietary causes. A review of lymphoma was

commissioned by the report and several associations emerged. However, based on the limited evidence, the investigators did not feel that they could “make any judgments regarding the causality of any associations” between dietary factors and the prevention of lymphoma. Therefore, studies involving lymphoma were not included in the development of these recommendations.

Although the evidence was limited and judgments could not be made by report investigators on the causality of any associations, a few studies did suggest a potential linkage between lymphoma and diet. The report stated: consumption of vegetables and fruits were associated with decreased risk; total dietary fat, body fatness, and consumption of meat were associated with increased risk; and consumption of milk/dairy products showed an association with increased risk of NHL.

In order to establish more conclusive evidence linking lymphoma to diet, physical activity, and body composition, report investigators recommended: a more comprehensive and systematic review of studies involving lymphoma and dietary factors; more studies to reveal the underlying biological mechanisms responsible for any identified associations; and separate studies for individual lymphoma sub-types.

To view the ten personal recommendations for cancer prevention turn to page 11 of this report. To view the entire WCRF/AICR Second Expert Report, *Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective* or to order a copy, please visit the following website:

www.dietandcancerreport.org

10 Recommendations for Cancer Prevention (WCRF/AICR)

RECOMMENDATION 1:

Be as lean as possible within the normal range of body weight.

- ◆ Ensure that body weight through childhood and adolescent growth projects towards the lower end of the normal BMI range at age 21.
- ◆ Maintain body weight within the normal range from age 21.
- ◆ Avoid weight gain and increases in waist circumference throughout adulthood.

RECOMMENDATION 2:

Be physically active as part of everyday life.

- ◆ Be moderately physically active, equivalent to brisk walking, for at least 30 minutes every day.
- ◆ As fitness improves, aim for 60 min or more of moderate, or for 30 min or more of vigorous, physical activity every day.
- ◆ Limit sedentary habits such as watching television.

RECOMMENDATION 3:

Limit consumption of energy-dense foods.

Avoid sugary drinks.

- ◆ Consume energy-dense foods sparingly.
- ◆ Avoid sugary drinks.
- ◆ Consume “fast foods” sparingly, if at all.

RECOMMENDATION 4:

Eat mostly foods of plant origin.

- ◆ Eat at least five portions/servings (at least 400 g or 14 oz.) of a variety of nonstarchy vegetables and fruits every day.
- ◆ Eat relatively unprocessed cereals (grains) and/or pulses (legumes) with every meal.
- ◆ Limit refined starchy foods.
- ◆ People who consume starchy roots or tubers as staples also need to ensure intake of sufficient non-starchy vegetables, fruits, and pulses (legumes).

RECOMMENDATION 5:

Limit intake of red meat and avoid processed meat.

- ◆ People who eat red meat should consume less than 500 g (18 oz.) a week, very little if any to be processed.

RECOMMENDATION 6:

Limit alcoholic drinks.

- ◆ If alcoholic drinks are consumed, limit the consumption to no more than two drinks a day for men and one drink a day for women.

RECOMMENDATION 7:

Limit consumption of salt. Avoid moldy cereals (grains) or pulses (legumes).

- ◆ Avoid salt-preserved, salted, or salty foods; preserve foods without using salt.
- ◆ Limit consumption of processed foods with added salt to ensure an intake of less than 6 g (2.4 g sodium) a day.
- ◆ Do not eat moldy cereals (grains) or pulses (legumes). Most problematic in countries with hot, damp climates & poor storage facilities.

RECOMMENDATION 8:

Aim to meet nutritional needs through diet alone.

- ◆ Dietary supplements are not recommended for cancer prevention.

RECOMMENDATION 9:

Mothers to breastfeed; children to be breastfed.

- ◆ Aim to breastfeed infants exclusively up to six months and continue with complementary feeding thereafter.

RECOMMENDATION 10:

Cancer survivors should follow the recommendations for cancer prevention.

- ◆ All cancer survivors should receive nutritional care from an appropriately trained professional.
- ◆ If able to do so, and unless otherwise advised, aim to follow the recommendations for diet, healthy weight, and physical activity.

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