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# Developing Scientific Research Proposals (Grant Writing)

2003 Epidemiology and Biostatistics Summer Session



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## Session 2

# Specific Aims

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## Specific Aims

- Developing a research hypothesis
- Crafting your Specific Aims
- Examples of Specific Aims
- Critique of students' draft Specific Aims
- A few words on Passive Voice

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### Developing a Research Hypothesis

- What is the general research question?
- What specific hypotheses will you address?
- Is it important?
- Is it new, exciting, or creative?
- How does it fit into the existing literature?
- What work have you already done that is relevant?
- How can you operationalize the question?

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### Developing a Research Hypothesis

- What is the design?
- What are the independent and dependent variables?
- Are the measures valid and reliable?
- Can you collect the data?
- What analyses will you use?
- Do you have enough power?

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### Specific Aims

1. A general, global or overall statement about what your proposal will address.
2. A set of specific hypotheses you will test.
3. Motivation for your research.

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### Guidelines for Specific Aims

#### **NO AMBIGUITY!!!!**

Be specific and straightforward.

#### **KEEP IT SIMPLE AND FOCUSED!**

Don't confuse your readers.

#### **DELIVER A REASONABLE AMOUNT OF SCIENCE!**

No more, no less.

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### Specific Aims: Introduction

Prevention of cancer through use of vitamin or mineral supplements is a promising modality. However, the results of recent chemoprevention randomized trials have been disappointing, perhaps because the agents tested were selected in part based in studies of diet and cancer, and not on studies designed to assess the effects of supplements per se on the risk of human cancer.

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### Specific Aims: Primary Aims

The specific aims of this five-year proposal are:

1. To recruit a cohort of 75,000 subjects (35,000 men and 40,000 women), recruited in a manner such that 75% have used some type of dietary supplement in the last 10 years, and to collect at baseline information on supplement use over the prior 10 years.
2. To investigate, by follow-up of this cohort for a mean of 2.25 years, the associations of intake of supplemental vitamin C, vitamin E, calcium, and multivitamins with total incidence of cancer.

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### Specific Aims: Secondary Aims

The secondary aim of this five-year proposal is:

1. To investigate the associations of intake of total (dietary plus supplemental) vitamin C, vitamin E, and calcium with total incidence of cancer. While primary aim 2 above addresses supplements as chemopreventive agents, this aim takes advantage of the large nutrient intake variance in this cohort to address the etiologic relationships of these nutrients to cancer risk.

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### Specific Aims: Methods

To meet these aims, a cohort will be recruited by mail within the 13 counties of western Washington State and endpoints will be ascertained by periodic linkage to the western Washington SEER cancer registry. Care will be taken to collect information on and control for potential confounding factors and effect modifiers.

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### Specific Aims: Long Term Goals

If successful, we will propose future follow-up of this cohort (such that mean follow-up will be 6 years). Thus, one aim of this study is to assemble a cohort that will allow us to propose these longer-term aims:

1. To investigate the associations of intake of supplemental vitamin C, vitamin E, calcium, and multivitamins with incidence of cancer of the lung, prostate, breast, and large bowel and with total mortality and mortality from specific causes.

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**Specific Aims: Long Term Goals**

2. To investigate effect modification by genetic markers of the supplement-cancer associations. To meet this future aim, we propose here the collection and storage of DNA samples (by self-collected buccal brushings), to help answer, for example, whether supplements may be particularly beneficial to those with one or more genetic polymorphisms that may alter cancer susceptibility.

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**Specific Aims: Motivation and Importance**

Longer-term follow-up would offer additional scientific opportunities. The association of less common supplements, such as beta carotene, fiber supplements, iron, and melatonin, could be studied in relation to the major cancers, and the association of the common supplements (multivitamins, C, E and calcium) could be studied in relation to less common cancers, including cancers of the bladder, corpus uteri, oral cavity, and pancreas, non-Hodgkin's lymphoma and melanoma.

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**Specific Aims: Introduction**

The incidence of adenocarcinoma of the esophagus and gastric cardia is increasing more rapidly than any other cancer in the United States. In the U.S., approximately 2 million persons have a precursor condition to this adenocarcinoma called Barrett's esophagus, a condition in which the squamous epithelium of the lower esophagus has been replaced by a metaplastic columnar epithelium. Persons with Barrett's esophagus are at a 30 to 40 fold increased risk of developing adenocarcinoma.

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### Specific Aims: Introduction

Neoplastic progression of Barrett's esophagus is a multistep process in which metaplasia progresses to high-grade dysplasia and then adenocarcinoma, with concurrent development of cell cycle abnormalities, somatic genomic instability, aneuploidy and other genetic abnormalities. This process can be monitored in part by following a set of well-characterized markers than include traditional histological assessments (metaplasia, high-grade dysplasia), cell cycle intervals (G0, G1, S and G2 fractions), and measures of genomic instability (aneuploidy).

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### Specific Aims: The Goal and Primary Aims

The overall goal of this proposal is to determine, in a randomized clinical trial, whether a medically prudent diet (designed to reduce intake of dietary fat to 20% of energy, increase intake of antioxidant-rich fruits and vegetables to six or more servings daily, and reduce weight) can reverse or stabilize intermediate markers of neoplastic progression in Barrett's esophagus. The specific aims are:

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### Specific Aims: The Goal and Primary Aims

Specific Aim 1: To determine, in a randomized clinical trial, whether a dietary intervention designed to reduce the intake of fat, increase the intake of fruits and vegetables, and reduce weight will decrease G1 and S phase fractions in Barrett's metaplastic epithelium.

Specific Aim 2: To determine whether the dietary intervention can lead to partial regression of metaplasia in Barrett's esophagus, assessed by the development of islands of normal squamous epithelium in the metaplastic epithelium, decreased length of the Barrett's segment, or both.

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### Specific Aims: Secondary Aims

There are two secondary aims, designed to further elucidate both the impact and mechanisms of dietary modification on neoplastic progression in Barrett's esophagus:

Secondary Aim 1: To determine whether diet intervention reduces the incidence of markers associated with more advanced neoplastic progression, including aneuploidy and accumulation of cells at the G2 cell cycle checkpoint.

Secondary Aim 2: To determine whether the dietary intervention reduces symptoms of gastroesophageal reflux (e.g., heartburn and regurgitation) and whether this association is related to weight loss.

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### Specific Aims: Motivation and Importance

Results of this study, if positive, would be among the first experimental studies in humans to provide evidence of an association of dietary change with cancer prevention.

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### Specific Aims: Introduction

This proposal is for a comprehensive investigation into the associations between dietary intake and the incidence of lung and prostate cancer. This project takes advantage of data already collected from 18,314 man and women enrolled in the Beta-Carotene and Retinol Efficacy Trial (CARET). CARET is a placebo-controlled, double-blind chemoprevention trial to test whether supplementation with retinol and beta-carotene would decrease the risk of lung cancer in a high-risk population, namely heavy smokers and individuals exposed to asbestos.

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### Specific Aims: Introduction

The CARET intervention was stopped in January 1996 when interim analyses found evidence that the supplements increased the risk of lung cancer in this high-risk population. CARET continues to follow participants and, after an average of 4.5 years of follow-up, has endpoint data on approximately 600 cases of lung cancer and 400 cases of prostate cancer. Active follow-up will continue until August, 2000.

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### Specific Aims

#### Lung Cancer

A. To examine the associations of intake of fruits and vegetables, grouped by their phytochemical content, with the risk of lung cancer.

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### Specific Aims

B. To investigate the associations between dietary intake of fruits, vegetables, and their affiliated micronutrients with the risk of lung cancer among smokers grouped by their genetic risk (i.e., genotype of carcinogen metabolizing enzymes: P450, GST, EH, and NAT).

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### Specific Aims

- C. To investigate the associations between serum carotenoids and a-tocopherol with the risk of lung cancer among smokers grouped by their genetic risk (i.e., genotype of carcinogen metabolizing enzymes: P450, GST, EH, and NAT).

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### Specific Aims

#### Prostate Cancer

- A. To investigate the associations between the intake of fat, red meat, and lycopene with the risk of prostate cancer.
- B. To examine the associations the associations of a biomarker of total fat intake and plasma fatty acids (particularly a-linolenic acid and linoleic acid) with the risk of prostate cancer.

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### Specific Aims

- C. To investigate the associations between dietary intake of fruits, vegetables, and their associated micronutrients with the risk of prostate cancer among smokers grouped by their genetic risk (i.e., genotype of carcinogen metabolizing enzymes: P450, GST, EH, and NAT).

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### Specific Aims

D. To investigate the associations between serum carotenoids and a-tocopherol with the risk of prostate cancer among smokers grouped by their genetic risk (i.e., genotype of carcinogen metabolizing enzymes: P450, GST, EH, and NAT).

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### Specific Aims

E. To examine the joint associations between dietary fat intake, obesity, and physical activity in relation to risk of prostate cancer.

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### Specific Aims

#### Lung Cancer

1. To better understand the association of fruits and vegetable intake with the reduced risk of lung cancer. We will measure fruit and vegetable intake as:

- (a) servings per day (total and grouped by phytochemical content),

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### Specific Aims

- (b) micronutrients associated with fruits and vegetables, including vitamins C and E, folate, and carotenoids ( $\alpha$ -carotene,  $\beta$ -carotene, lycopene, lutein, cryptoxanthin, zeaxanthin),
- (c) serum carotenoids ( $\alpha$ - and  $\beta$ -carotene, lycopene, lutein, cryptoxanthin, zeaxanthin) and  $\alpha$ - and  $\gamma$ -tocopherols.

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### Specific Aims

- 2. To examine whether the associations between the of fruit and vegetable intake (as measured above) with lung cancer risk differs among participants grouped by their genetic risk (i.e., genotype of carcinogen metabolizing enzymes: CYP2D6, CYP2E1, CYP1A1; GSTM1, GSTT1; and EH).

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### Specific Aims

#### Prostate Cancer

- 1. To better understand the observed associations between fat intake and the increased risk of prostate cancer. We will measure fat intake as:
  - (a) grams per day of total and saturated dietary fat,

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### Specific Aims

- (b) servings per day of high-fat foods (particularly red meats),
- (c) plasma fatty acids levels (particularly  $\alpha$ -linolenic acid and linoleic acid).

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### Specific Aims

- 2. To examine the association of fruit and vegetable intake with the reduced risk of prostate cancer. We will measure fruit and vegetable intake as:
  - (a) servings per day (total and grouped by phytochemical content),

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### Specific Aims

- (b) nutrients associated with fruits and vegetables, including fiber, vitamins C and E, folate, and carotenoids ( $\alpha$ -carotene,  $\beta$ -carotene, lycopene, lutein, cryptoxanthin, zeaxanthin),
- (c) serum carotenoids ( $\alpha$ - and  $\beta$ -carotene, lycopene, lutein, cryptoxanthin, zeaxanthin) and  $\alpha$ - and  $\gamma$ -tocopherols.

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### Specific Aims

3. To examine whether the associations between fat and fruit and vegetable intake (as measured above) with prostate cancer risk differs among participants grouped by their genetic risk (i.e., genotype of carcinogen metabolizing enzymes: CYP2D6, CYP2E1, CYP1A1; GSTM1, GSTT1; and EH).

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### Passive Voice

**The blood samples were stored at -20 degrees Celsius and analyzed using the protocol developed by Smith.**

Appropriate, because the disposition of blood samples is the focus of the sentence.

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### Passive Voice

**Dr. Smith was selected to represent his department at the University Senate.**

Appropriate, if the focus of the sentence is Dr. Smith. Consider this alternative:

***The faculty selected Dr. Smith as their representative in the University Senate.***

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### Passive Voice

Based on a complete review of the literature, it was determined that there was no evidence that high intakes of alpha-linolenic acid increased the risk of prostate cancer.

Awkward, simplify to make a strong, clear statement

***There is no evidence in the published literature that high intakes of alpha-linolenic acid increases prostate cancer risk.***

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### Passive Voice

The usual frequency of consumption over the past year was asked of each study participant.

Awkward, transpose to active voice.

***Study participants reported their usual frequency of consumption over the past year.***

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### Passive Voice

It has been suggested that passive exposure to cigarette smoke is a risk factor for lung cancer.

Awkward, simplify to clear statement.

***Passive exposure to cigarette smoke may be a risk factor for lung cancer.***

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