Repatriation Medical Authority

Proceedings of the Consensus Conference on Smoking and Prostate Cancer

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Consensus Statement on Smoking and Prostate Cancer

Does smoking cause malignant Neoplasm of the Prostate?

After careful consideration of this question and the available data, the consensus conference concluded:

1. There is inadequate evidence that smoking is causally related to the occurrence of prostate cancer.

   (a) There is limited evidence that smoking is associated with increased mortality attributed to prostate cancer.

   (b) There is inadequate evidence that smoking is associated with prostate cancer incidence.

2. A plausible inference from these statements is that smoking may be associated with poorer survival.

Additional studies that may help interpret the possible association include those that:

- Quantify misclassification of prostate cancer on death certificates according to smoking status
- quantify misclassification of smoking status in cohort studies
- identify additional existing cohorts that may provide data
- conduct meta-analysis of cohort data and exclude early data from US Veterans
- study case survival for prostate cancer cases by smoking status (by staging at diagnosis)
- more adequately determine screening status and its impact in cohort studies
- through linkages and other approaches, better describe the relation between incidence and mortality from prostate cancer
- in any future case-control studies consider markers for subgroups that may be susceptible to smoking.

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Introduction

In this overview I place the consensus conference in context and outline the issues that will be discussed in the meeting. The primary question to be addressed by the Repatriation Medical Authority consensus conference is "Does smoking cause malignant neoplasm of the prostate?". This question arises because some, but not all, studies have reported a small elevation in risk of mortality from prostate cancer among men who smoke when compared to men who never smoked. If the consensus is reached that smoking causes prostate cancer, then the conference must address the following questions:

- What is the summary level of risk of prostate cancer among smokers?
- What proportion of prostate cancer may be caused by smoking?
- Is there a particular dose level that is associated with risk (how many cigarettes per day must be smoked before risk is increased)?

Following the small group work to construct a summary statement to answer these questions, the overall panel of experts will work to achieve consensus on this issue. The summary of each group and the discussion which followed, leading to the final consensus statement, are reproduced in these proceedings.

Moving from prostate cancer to more general considerations of smoking, the conference will address how best to define risk and how to express the level of smoking. Should this be in terms of pack-years smoked, the average number of cigarettes smoked per day, or some other measure? How do we define minimum dose? Further, how do we characterize risk according to time since quitting smoking? Following these papers, the participants will work in groups to come to consensus on the best approach to use when determining dose for decisions about eligibility for compensation.

Because smoking has also been associated with a number of rarer cancers in some studies but not others, the consensus conference will conclude with a session devoted to smoking and risk of these rarer cancers. These include Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, and leukemia.

Throughout the conference, the participants will identify areas where further research may resolve issues, where additional analysis of existing data may answer some of the uncertainties, and where no additional data are needed.

These proceedings are prepared to capture the issues raised during the consensus conference and to make the background for the consensus statements available to a wide readership. We also report the numerous areas identified that could benefit from further research.

The focus of epidemiology at the close of the 20th century

As modern epidemiology measures risk across a wide range of lifestyle and occupational exposures focusing on the etiology of chronic disease, Susser notes that epidemiology has become somewhat remote from public health issues of the day. Modern epidemiology is more concerned with technique than the issues being addressed. Susser contends that this increasing emphasis on technique is unfortunate and has occurred at the price of social understanding, with the risk that any knowledge brought to bear on prevention will be fragmentary and mechanical[1]. Variables analyzed are multiple and often divorced from the social context, sacrificing breadth of the discipline. Because epidemiology is entangled in our society we must take hold of this locus, and be responsible for our research in its social context. This is clearly in conflict with writings of Rothman who maintains that our focus should be on causation and that as a discipline we should avoid political or policy debates[2].

As epidemiology focuses on the distribution of ill-health as well as the social determinants of disease it is not purely an observational discipline, but an actor as well. Research on passive smoking exemplifies the political rather than the purely scientific audience for research findings. The epidemiologist has a specific responsi-

bility to inform, even outside the scientific community[3]. Regular media coverage of epidemiologic findings published in leading medical journals gives clear evidence of this in the Western world. As this publicity of our work has expanded over the past decade, some argue that by informing outside of the scientific community we do more harm than good.

The public is not capable of interpreting data as it is so often reported in the media. Rather, efforts must be made to place data in a context that the public can understand. Misunderstanding of the risk of breast cancer among educated US women 40 to 50 years of age who consider that "1 in 10" means that the probability of dying in the next ten years is 1 in 10 exemplifies the failure of our efforts to communicate[4]. Further, this sample of women estimated that 1 in 5 women would be diagnosed with breast cancer in the next 10 years, and that mammography offered a 60% reduction in risk of breast cancer. These gross misperceptions of risk among a group of women, determined by the investigators to be at average risk of breast cancer, highlights the limitations of media communication of risk.

Clearly those who translate risk of breast cancer for communication to the public need to provide appropriate explanations to allay fears[5]. Analysis of data from the US indicates that among women basic knowledge about disease risk is very poorly understood. Knowledge that risk of breast cancer increases with age, for example, actually decreases among older women. Among women aged 25-34 who completed the National Health Interview Survey, 35% reported that risk of breast cancer increased with age, but by age 75+ only 16% knew that age was a risk factor for breast cancer[6].

A recurring theme in recent writings is the need for epidemiologists to more closely link with the implementation of their research findings. We must bring public health action and implementation back to the products of our research endeavors. In discussing occupational epidemiology and its contribution to prevention, Wegman notes that the academic discipline has become increasingly divorced from applications of prevention in the workplace[7]. He contends that this slows the transfer of knowledge and thus leads to delay in prevention with consequent damage to health and loss of life.

Wall proposes that to effectively prevent disease, the discipline of epidemiology must bridge the gap between social behavior, political structure and economic power[3]. This notion is consistent with writings of Richmond who defines the forces that interplay to implement prevention policy[8].

Richmond, former Surgeon General of the United States, has proposed a model of prevention policy. The model gives a robust structure to the underlying influences on prevention implementation. He documents the interplay of the scientific knowledge base, the social strategy to implement prevention, and the political will. As we generate the knowledge base through epidemiologic studies, we must do so in the context of the society and the political forces that bear around us.

The knowledge base is the scientific and administrative data base upon which to make decisions. It includes:

1) the magnitude of disease burden,
2) knowledge of effectiveness of prevention strategies,
3) understanding of the underlying biology of disease.

The political will is society's desire and commitment to support or modify old programs or develop new programs. This is the process of gaining the support needed for change. It is achieved by changing norms, building constituency, coalitions with advocacy groups, etc.

The social strategy is the plan by which we apply our knowledge base and political will to improve or initiate programs and includes:

1) preventive services delivered by health providers,
2) structural intervention implemented by government and industry to protect the public from harm,

3) local activities that promote a healthier environment and lifestyle.

Growing focus on biologic issues

Though biologic plausibility is one component of Hill's considerations for assessing causality[9], are we too preoccupied with this aspect of the scientific process in public health? Are we too focused on molecular mechanisms rather than preventive implications of data that are already available to us, if analyzed appropriately? As epidemiologists are we now missing the opportunity to implement prevention?

Diet and lung cancer may serve as a useful example. But, first let us remember the recommendations to stop smoking preceded the clear definition of which specific components of cigarette smoke were responsible for the increase in risk. The strong and consistent relation between smoking and lung cancer supported cessation messages. Nor were public health workers in a position to define the molecular damage caused by cigarette smoke. Elegant work in the past five years has documented the molecular changes induced by components of cigarette smoke. Though potentially important scientific understanding, this work has been completed 30 years after the first report of the US Surgeon General on the adverse health effects of smoking[10]. With time, however, it appears that we have, as a discipline, moved to expect and perhaps even demand this level of understanding prior to suggesting implementation of change in behavior. Does this reflect a maturing of the discipline or a missed opportunity?

Diet and lung cancer

Just under 20% of total mortality in developed countries is attributable to tobacco[11]. More than 30 studies have been conducted to address the contribution of diet to risk of lung cancer. Green and yellow vegetable consumption consistently decreases risk of lung cancer across many studies dating back to the 1970s[12-15]. However, efforts to identify the specific micronutrients responsible for this relation have been less successful. Perhaps this mechanistic preoccupation is a diversion from more direct efforts at prevention through modification of the diet of smokers. Do we need to know which components of green and yellow vegetables are responsible for the reduced risk of lung cancer among smokers with high intake before we recommend improved diets for those who smoke? Some may argue that manufacturing a pill that contains the 'right agent' to prevent lung cancer will be more effective than having smokers change their diets. In following this strategy, we ignore the existing knowledge base and commit the current generation of smokers to greater risk than need be. Further, this strategy presumes that smokers will afford and use the pill when it is available.

In the studies of diet and lung cancer, carrots and greens have shown the most consistent relation, with higher intake leading to lower lung cancer rates among smokers. Diets of smokers differ from those of nonsmokers: men and women who smoke eat fewer fruits and vegetables[16]. Furthermore, cigarette smoking lowers plasma carotenoid levels in a dose-response relation reflecting the number of cigarettes smoked per day, even after controlling for dietary intake of carotenes[16, 17]. While potential exists for numerous different components of green and yellow vegetables to reduce the risk of lung cancer[18], cessation from cigarette smoking clearly represents the greatest single lifestyle change that would reduce risk of cancer among smokers[19]. If our focus was on harm reduction at the population level, then the addition of carrots to the diet of smokers would, in all likelihood, halve the risk of lung cancer among those who continue to smoke. Having taken a step towards reducing risk, some smokers may be empowered to quit. Rather than follow a harm reduction strategy, the National Cancer Institute is pursuing strategies to reduce the burden of lung cancer with the following approaches: randomized trials of retinoids, beta-carotene, vitamin E, selenium, folate, vitamin B12, and niacin; basic research into possible vaccine development; early detection; adjuvant therapy including cisplatin with other agents[20].

A long term increase in carrot consumption among men and women who smoke may halve

their rates of lung cancer. Where in the pathway to carcinogenesis do these dietary components act? Smoking acts both early as a carcinogen, and very late in the process of carcinogenesis as a promoter. Building on the Armitage-Doll model of lung cancer incidence[21], Brown and Chu estimate that the relative magnitude of the carcinogenic effects of cigarettes on the two stages indicate that the largest proportion of the lifetime lung cancer risk among continuing smokers is due to its late stage effect[22].

Have epidemiologists only drawn the biological conclusions of their research rather than the social, economical and political consequences[3]? While the focus on biologic and mechanistic issues of exposure may further our understanding of disease etiology, at times it can also speed us to prevention. Both the molecular biology of colon cancer and morphologic studies support the role of progression from small polyp to large polyp to colon cancer. This increase in understanding of colon cancer biology has allowed us to place specific exposures in the time sequence to disease. From this understanding we can place the action of specific agents in a temporal relation that spans some 30 to 40 years. As a consequence, we can more adequately plan and predict the time course of benefits from specific prevention strategies. Given the value of this understanding, how do we balance knowledge of biologic mechanisms against broader issues that face us?

Likewise, the elegant statistical modeling of lung cancer incidence has clear implications for prevention[23, 24]. In the short run, due to the relative magnitude of the late promoter effect of smoking on lung cancer[22], reducing smoking among current smokers will have the greatest public health impact[25]. In the longer term, reducing or delaying the uptake of smoking among adolescents is an essential component of a prevention program[26].

The combination of epidemiologic data addressing risk and statistical techniques to model incidence and latency together advance our understanding of the temporal relation between exposures and disease. It is this presentation of data, rather than molecular mechanisms, which must be translated into refining etiology and prevention. Unfortunately, to date these applications have been limited in scope to lung[24] and breast cancers[27, 28].

Issues that are raised by the application of epidemiologic data to compensation under the Veterans' Entitlements Act

The Veterans' Entitlements Act 1986 in Australia has evolved to compensate veterans when a causal connection between incapacity or death and service during an eligible period is established. Considerable evidence has documented the commencement or exacerbation of smoking during war service. Cigarettes were provided in ration packs, were available duty free and their use generally was encouraged to relieve both stress and boredom[29].

Given the legislative mandate to determine the presence or absence of causal relations between smoking tobacco and chronic disease, particularly cancer, we are confronted with questions of causation and, if this is present, the duration of risk following cessation from smoking. The legislation indicates that the presence or absence of a causal association should be assessed using the criteria for causation currently applied in the field of epidemiology.

What is the form of the exposure disease relation?

This issue is important for understanding etiology of disease, for prevention research and applications of epidemiologic data to prevention guidelines. The shape or functional form of the relation between an exposure and disease determines the time course over which disease attributable to exposure will occur and the prevention benefits due to changes in exposure will accrue. For the general population, this information is also important. Once lifestyle has been changed (for example, a smoker has successfully quit),

how long does it take for risk to decline? For those who were occupationally-exposed to carcinogens in the past, but who are now no longer exposed, at increased risk of cancer? Should they worry or undergo increased surveillance or screening, or should they be reassured that their risk is no different from the general population? Though issues such as these have been raised[25], and approaches to the analysis of epidemiologic data are described[30], they are often ignored in the analysis that are published[31].

There is ongoing interest in temporal relations between exposure to herbicides and health effects at the US National Academy of Science[32]. Specifically, the Veterans' administration asked the committee to examine "the length of time since first exposure and the possible risk of cancer development"[32]. Focusing on latency for dioxin, the committee notes that data have not been presented in a manner that allows us to look at length of exposure and latency. The National Institute of Occupational Safety and Health (NIOSH) report combining data from occupational cohorts in the United States[33] did not present sufficient data (e.g. a cross classification of age at first exposure, duration of exposure, and time since exposure), in part because of small numbers of cases when results are summarized by cancer site. Given that there are several additional cohorts of occupationally exposed workers, it may be possible to combine these studies and provide a more informed response to this issue. Of course, for rare cancers such as soft tissue sarcoma, even a combined analysis is not likely to be informative.

While the focus of modern epidemiology is on risk factors for chronic disease, often categories used for analysis of exposures are broad. Addressing issues of causal interpretation, epidemiologists examine dose response. The dose response is usually considered from the perspective of a test for trend — is it significant or not? Actual point estimates at extremes of low or high doses (exposure) are rarely individually statistically significant. They may then be omitted from scientific reports under pressure from editors striving to keep manuscripts brief. Though Greenland argues that tests for trend across categories of exposure are not maximally efficient, and he proposes alternative models for data fitting[34], the key point for those using the data is that the form of the relation be presented rather than merely the p-value for a test. How much does the risk of cancer decrease per serving of fruit and vegetables? To inform health care providers who counsel patients, policy analysts who formulate regulations (be they national or local standards), or individuals striving to change behaviors, etc. the quantification of dose response is essential.

How much exercise is required to reduce risk of colon cancer? When does risk of breast cancer rise among women who consume alcohol? Small numbers have precluded informative estimates from individual studies, but combined data can usefully address these issues. For example, in the combined analysis of fat and breast cancer, Hunter and colleagues observed a significant increase in risk of breast cancer below 20% of calories from fat, perhaps due to substituting fat with high carbohydrate diets that stimulate Insulin-like Growth Factor (IGF) and perhaps promote breast cancers. Longnecker, combining data on alcohol and breast cancer, notes that risk increases with increasing alcohol consumption[35].

What then is the role of epidemiology?

Clearly we must move beyond our increasingly molecular and mechanistic focus to translate our findings on risk into useful measures. Failure to do so results in ill-informed policy, or sub-optimal applications of our findings, such as can occur in policy analysis; either formal cost-effectiveness analysis or decision-analysis, or less formal research synthesis to inform policy. One approach to achieve this end is a wider use of statistical methods to define the time relation between exposure and disease.

In the context of compensation, be it for occupational exposures, or for smoking related diseases, a central question is the minimum dose required for a disease to be associated with exposure.

Consider lung cancer. While we know that risk rises rapidly with the number of cigarettes smoked per day, how important is the risk among those who smoke say five to ten cigarettes per day? As these are the most likely to stop smoking, how long after stopping is their risk returned to that of a never smoker? Attempts to quantify the benefits of quitting, well exemplified by the 1990 report of the US Surgeon General, focus on the overall benefit of quitting[19]. The finest stratification of smoking status prior to quitting comes from the American Cancer Society (ACS) study where data were specifically prepared for that report[19]. An alternative approach is to use the mathematical model of lung cancer incidence, as applied by Brown and Chu[22], to estimate the risk after accounting for years of smoking, number of cigarettes smoked and years since stopping. Widespread access to computers should make for more ready use of such equations to estimate risk more precisely.

Changes such as these are urgently required if the product of epidemiologic investigations is to be translated into prevention through regulation, or recommendations for changes in lifestyle that will enhance health. As a profession we must rise to this challenge. A broader application of methods to understand temporal relations may have far greater public health impact than elegant molecular biology incorporated into epidemiologic investigations.

Prostate cancer

Background

By 1991, cancer was the leading cause of premature mortality (defined as death before age 70) in Australia. Of 43,125 deaths in 1991 among people less than 70 years of age, 35% were due to cancer, 19% were due to ischemic heart disease, 5% were due to cerebrovascular disease, and 14% were due to external causes[36].

The incidence of prostate cancer rises rapidly with age. In Australia, over 6,000 new cases of prostate cancer will be diagnosed in 1996 and more than 2,500 men will die from this cancer.

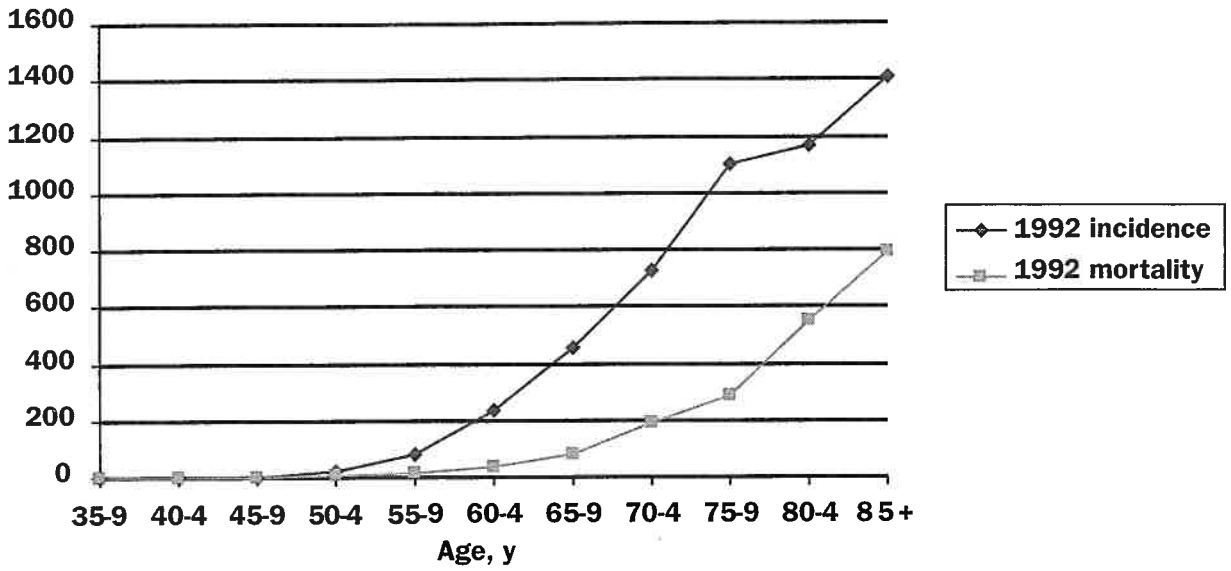
Over the past 20 years mortality from prostate cancer has risen only slightly in Australia: age-standardized mortality rates have risen from 15.2 per 100,000 in 1955–59, to 15.3 in 1980–84, to 16.8 in 1985–89 and 17.8 in 1990–91[37]. Prostate cancer is the most common cancer diagnosed among men over age 65[38].

Internationally, mortality rates vary substantially (perhaps more than 100 fold differences between countries)[39], though this may be inflated by differences in case finding between countries. Rates are highest in the United States and Canada, slightly lower in Australia and New Zealand, lower in the UK, and lowest in Japan. Unlike the frequency of infiltrative or invasive prostate cancer, latent prostate cancer does not vary appreciably among countries[40]. By age 70, 40 percent of men have latent prostate cancer in both the United States and Japan. This suggests that the initiation of this cancer is not related to exogenous factors or that any initiators do not vary substantially across countries. Rather promotion varies from country to country and drives the variation in prostate cancer mortality rates between countries.

It has been postulated that testosterone could be an initiator, if levels do not vary between countries. Support for this comes from observations that diet does not appear to influence testosterone levels among middle-aged men[41]. Levels decrease with age and with increasing obesity.

Lifestyle factors related to progression of prostate cancer and invasion outside the gland may be fundamental to the international differences and may act as late promoters and inhibitors in the carcinogenesis pathway. Support for the role of exogenous factors in the progression of this disease comes from migrant studies. Men who have migrated from low incidence countries, such as Japan and Poland, experience substantial increases in their risk of prostate cancer after living in the United States[42, 43].

Figure 1. Age-specific incidence and mortality rates (per 100,000) — prostate cancer, New South Wales, Australia, 1992



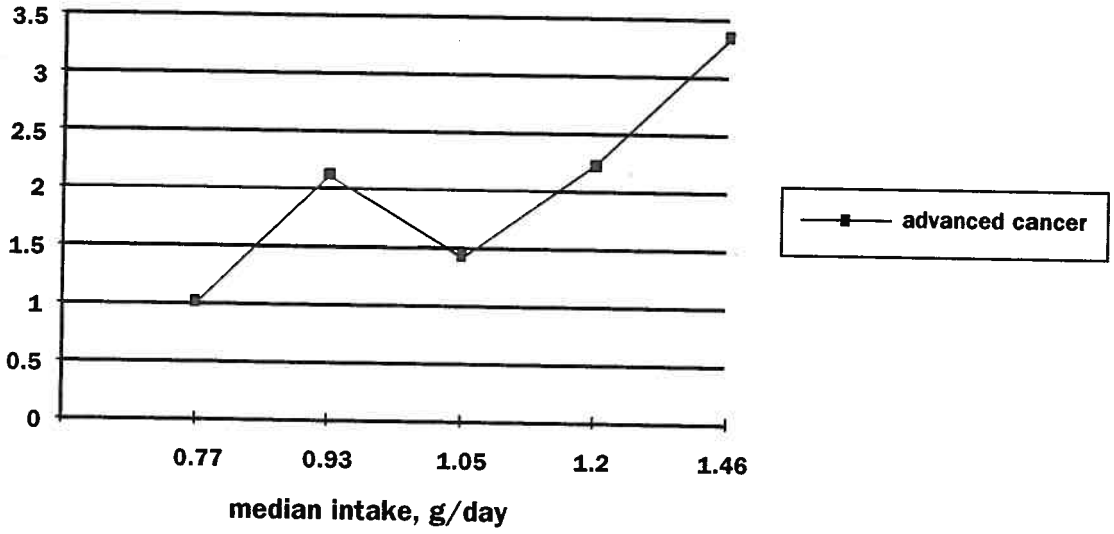
Source: Coates et al. Cancer in New South Wales Incidence and Mortality 1992. NSW central cancer registry. NSW Cancer Council.

Diet

An initial hypothesis was that dietary fat increased the risk of prostate cancer. Armstrong and Doll, comparing dietary data and international incidence rates, proposed this relation in 1975[44]. Despite the relative weakness of this type of international correlation study, the relation initially proposed has held up in the majority of more detailed studies reported to date. Dietary fat and meat consumption are associated with increased risk of prostate cancer, both in the United States and other countries[45].

High intake of fat and low intake of antioxidants have been postulated to increase risk of invasive disease. Total energy intake was not consistently measured in the studies published to date that address fat intake and risk of prostate cancer, so it is impossible to know whether the reported associations reflect an effect of dietary composition or an association with overall crude intake. While the relation between fat intake and prostate cancer remains inconclusive, several prospective studies show that animal fat intake is associated with increased risk[46,47]. Overall, 10 of 13 case-control studies and five of eight prospective studies show a positive relation between meat or animal fat consumption and risk of prostate cancer. Emerging evidence suggests that this relation may be due to the intake of α-linolenic acid. This essential fatty acid comes from both animal and vegetable sources. In the Health Professionals Follow-up Study, a cohort of some 50,000 US men followed since 1986, α-linolenic acid was positively related to the risk of prostate cancer, and remained a significant predictor of advanced prostate cancer when other fatty acids were considered simultaneously[46]. Supporting this diet-based finding, a study of blood levels of α-linolenic acid and subsequent risk of prostate cancer showed that men with low levels had a low risk of prostate cancer[48]. Further, the ratio of α-linolenic to linoleic acid was strongly related to risk of prostate cancer (RR = 8.6 comparing high vs. low). Compatible with this association, rates of prostate cancer are high in North America and Northwestern Europe where either rapeseed oil (Canola) or soybean oil intake is high[49]. These are major sources of α-linolenic acid. In contrast, adipose levels of α-linolenic acid are low in Italy[50] where olive oil is a major source of fatty acids; prostate cancer incidence is low in Italy. Post-industrial oil manufacture has added soy and canola to the food supply, these are now the most common sources of α-linolenic acid in the US diet.

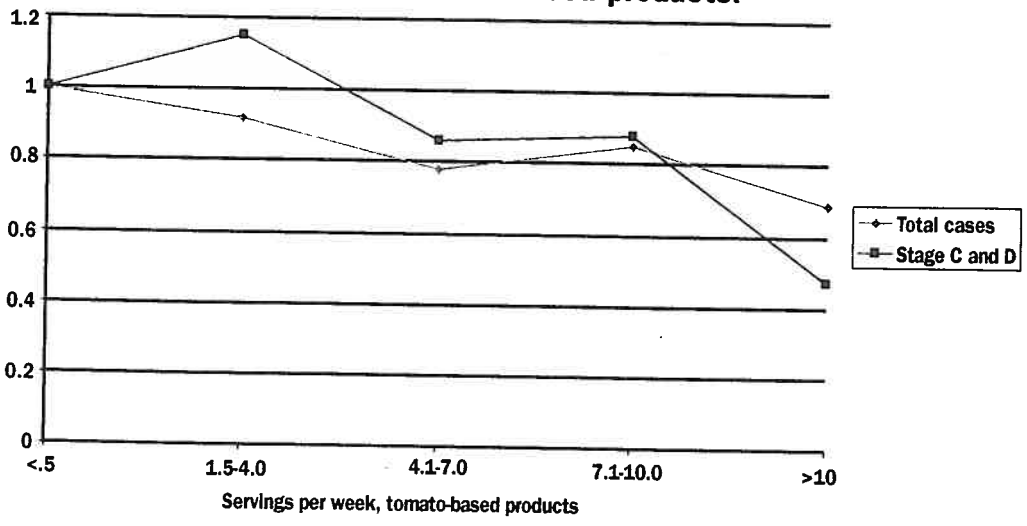
Figure 2. Adjusted relative risk of stage C and D prostate cancer, by level of a-linolenic acid



The precise factors responsible for this relation are not clear. One proposed mechanism is that dietary fat increases sex hormone levels, a possible risk factor for prostate cancer. However, data from a sample of Massachusetts men indicate that dietary fat intake is not related to any of a wide range of hormones[41]. Moreover, there is little evidence that sex hormones are important in the progression to clinical disease. Hormone levels decrease substantially with age, as the incidence of invasive prostate cancer rises. Further, cigarette smoking is associated with significantly higher testosterone levels in some[41, 51] but not all studies[52]. Studies relating smoking to prostate cancer show weak relations, with one summary estimate combining published results from 20 studies giving an overall relative risk of 1.16[53].

Vitamin A has long been postulated as a protective factor against prostate cancer. The most promising evidence supports a specific carotenoid, lycopene, which comes primarily from tomatoes. Several studies show that either tomatoes[54, 55] or prediagnostic blood lycopene levels[56] are inversely related to risk of prostate cancer[57]. For each additional serving of tomato based foods per week (tomato sauce, tomatoes, tomato juice, and pizza), risk of prostate cancer decreases by approximately 3%. Further, the protection against metastatic disease may be greater. In the figure below, data from the Health Professionals Follow-up Study, a cohort of 50,000 US men, is presented to summarize this important relation.

Figure 3. Multivariate-adjusted relative risk of prostate cancer according to servings of tomato based products.



Data from the Health Professionals Follow-up Study. Giovannucci et al, J Natl Cancer Inst 1995.

The mechanism by which lycopene protects against prostate cancer is not clearly defined, but could include anti-oxidant function within the prostate gland, where it is the most abundant carotenoid[58]. It is of note that, within the Health Professionals Follow-up Study, the intake of tomato products was some 38% lower among African-American men than among those of Southern-European origin. Within the US, age-specific incidence rates of prostate cancer are significantly higher among African American men than whites.

Family history

Family history is also a risk factor for prostate cancer. The majority of studies show that men with either a brother or father diagnosed with prostate cancer have a two-fold risk of disease compared to those who do not have a family history. In this disease, as for other cancers, family history may account for up to 10% of prostate cancer[59].

Vasectomy

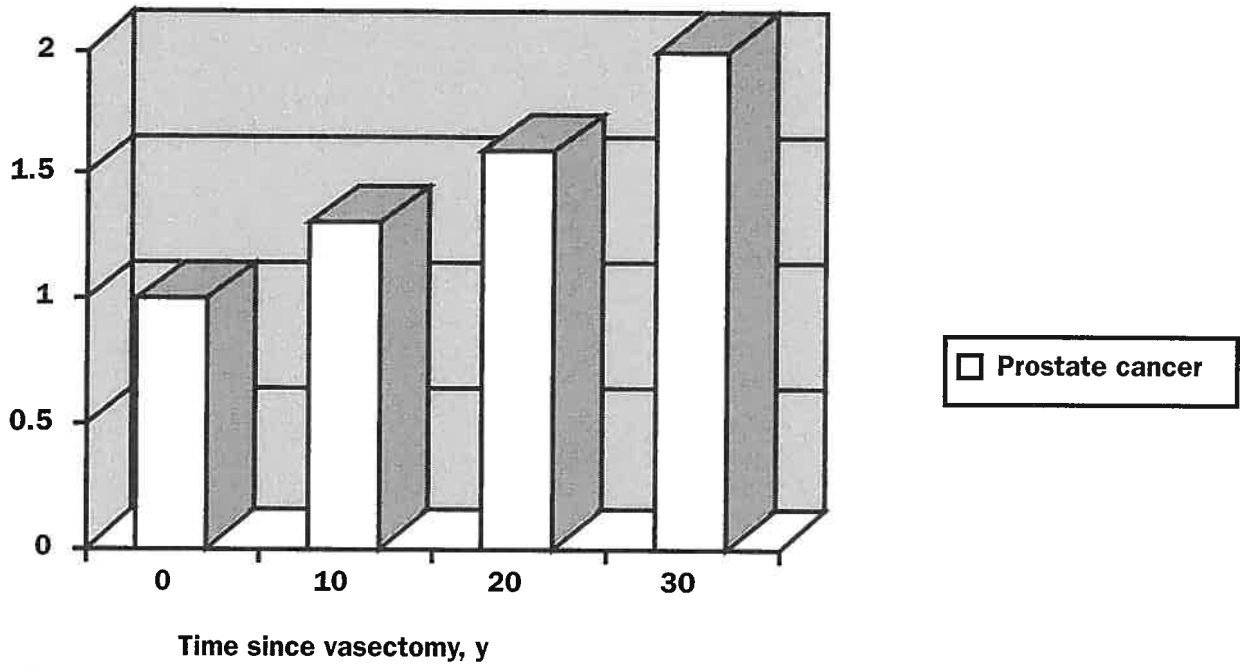
Evidence that vasectomy may increase risk of prostate cancer has been controversial. It may, however, inform us with regard to the time course of this disease. Though the evidence comes from both retrospective case-control studies and prospective cohort studies[60, 61], concern lingers among some in family planning that no biologic mechanism exists. In six of eight studies, a significantly elevated risk of prostate cancer following vasectomy is reported. Regressing time since vasectomy on risk of prostate cancer, Giovannucci and colleagues observed a significant relation with duration from surgery. For 10 years since vasectomy, the relative risk was 1.3 (95% confidence interval [CI], 1.2-1.4), after 20 years the risk was 1.6 (95% CI, 1.4-1.8) and after 30 years the risk was 2.0 (95% CI, 1.7-2.5).

A large, unstated concern, is that vasectomy offers an important approach to family planning world-wide and has lower complication rates than tubal ligation, the other common approach to family size limitation. Abandoning this approach to family planning would have dramatic consequences world wide where the risks and benefits may vary substantially.

Over 15% of men in the US who are 40 years of age and older have had a vasectomy. Thus a causal association would have important implications. The consistent association between vasectomy and risk of prostate cancer 20 or more years after the procedure is unlikely to be due to chance. But, concern lingers that men who have a vasectomy in their 30s are more likely to see a urologist and have prostate cancer diagnosed in their 50s and 60s than are men who have not had a vasectomy. This bias in detection could explain a higher incidence among men who have had a vasectomy. However, Giovannucci et al. showed an elevation in risk for advanced, metastatic disease, as well as for total incidence of prostate cancer. Despite these data, this unlikely scenario persists in the literature as an explanation.

The data from studies published through 1992 are summarized in figure 4. They again illustrate the need to consider time from exposure to actual detectable increase or decrease in risk of cancer.

Figure 4. Relative risk of prostate cancer according to time since vasectomy, among men with vasectomy compared to men who have not had a vasectomy.



Detection of prostate cancer

Among the factors related to detection of prostate cancer is the treatment of benign prostatic hypertrophy, leading to detection of incidental carcinoma on biopsy. Abdominal obesity is a strong predictor of symptoms from benign prostatic hypertrophy (BPH) and also prostatectomy[62]. Thus abdominal obesity may confound the relation between lifestyle and prostate cancer. For example, cigarette smoking is positively related to abdominal obesity in numerous studies[63-65]. If abdominal obesity leads to treatment of BPH, then it may result in a spurious relation between smoking and prostate cancer in countries where treatment for symptoms of benign prostatic hypertrophy are common. Though tenuous as an explanation, this complex relation highlights the interrelations among factors that may distort relations between smoking and prostate cancer.

The advent of PSA (prostate specific antigen) screening for prostate cancer has resulted in dramatic changes in incidence rates in the US and presumably other countries. Incidence rose by three-fold following the introduction of PSA screening resulting in the detection of primarily latent cancers[66]. As PSA will continue to complicate the interpretation of prostate cancer incidence for the foreseeable future, one might gain insight from analyses that focus on mortality.

Mortality

Mortality rates are the product of incidence rates and relative survival among those diagnosed with disease[67]. Thus, in addition to considering the potential of smoking to influence incidence, we might also consider the possible influence on survival, perhaps even in the absence of any relation with incidence of this cancer. Because treatment for advanced prostate cancer has long included suppression of testosterone levels, one might postulate that testosterone levels are associated with poor survival. Evidence based on actual testosterone levels is weak[68]. Several studies suggest that smoking is associated with higher levels of testosterone[41, 51], though not all studies confirm this relation. Thus it is possible that smoking may influence mortality from prostate cancer but have little relation with incidence, particularly in an environment where detection of prostate cancer, and hence incidence rates, are problematic. Alternatively, smokers may have higher probabil-

ity of being classified as dying from prostate cancer than non-smokers, though evidence to support this bias is not currently available. It could easily be ruled out with a study.

The challenge of the consensus conference

Unraveling these possible relations between cigarette smoking and prostate cancer are important challenges ahead of us. The rich collection of data in the papers which follow, includes results from China, the USA, and Australia. The Repatriation Medical Authority must make determinations regarding causation using material that has been published in the medical or scientific literature. Further, in assessing causation, they must determine that the evidence meets the applicable criteria for assessing causation currently applied in the field of epidemiology. Accordingly, the criteria for assessing causation as described by Bradford Hill[9] are summarized below:

- **Strength of association.** A very strong association is more likely to be causal.
- **Consistency.** An association repeatedly observed by different persons, in different places, circumstances and times.
- **Specificity.** An association limited to specific workers and to particular sites and types of disease is a strong argument for causation.
- **Temporality.** Exposure of interest precedes the development of the disease.
- **Biologic gradient.** A gradient or dose-response curve.
- **Plausibility.** It is helpful if the causation that is suspected is biologically plausible.
- **Coherence.** The cause and effect interpretation of data should not conflict with generally known facts of the natural history or biology of the disease.
- **Experiment.** Experimental or semi-experimental evidence offers the strongest support for causation.
- **Analogy.** In some circumstances it is fair to judge by analogy.

Does smoking cause malignant neoplasm of the prostate? If so, what is the summary level of risk? What proportion of prostate cancer may be caused by smoking? Is there a particular dose level that is associated with risk? How do the Bradford Hill criteria apply to this decision making?

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Section I

Smoking and Prostate Cancer

Smoking and Prostate Cancer: A Population-Based Case-Control Study in Shanghai, China

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Abstract

To examine the role of cigarette smoking in prostate cancer, we conducted a population-based case-control study in Shanghai, China. Cases (n=239) were residents of Shanghai newly diagnosed with prostate cancer between December 1992 and April 1995. Controls (n=472) were randomly selected from permanent residents of Shanghai, frequency-matched to cases on age. In addition, 206 patients with benign prostatic hyperplasia (BPH), undergoing prostatic surgery in the same hospital as the index case, were selected as hospital controls (matched by age). An in-person interview was conducted to elicit information on smoking and other risk factors. The prevalence of ever-smoking was 53% for cases, 56% for BPH controls, and 63% for population controls. Risks of prostate cancer associated with ever- and current smoking were 0.79 (95% CI, 0.58-1.09) and 0.70 (95% CI, 0.48-1.02), respectively, when population controls were used as the comparison group. No excess risks were found for intensity, duration of use, or for early age at first use. Adjustment for age, education, marital status, a history of BPH, and use of alcohol and tea did not materially change the risk estimates. Results from this low-risk population (the incidence of prostate cancer in US is 30 to 50 times that in China) suggest that cigarette smoking is not associated with prostate cancer risk. However, when BPH controls were used as the comparison group, smoking was associated with a slightly increased risk. Future studies are needed to confirm these results.

SMOKING AND FATAL PROSTATE CANCER IN A LARGE COHORT OF ADULT MEN

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Abstract

The authors examined the relationship between smoking and risk of fatal prostate cancer in a large prospective mortality study of 450,279 men who were cancer free at enrolment in 1982. During nine years of follow-up, 1,748 deaths occurred from prostate cancer. Cox proportional hazards modeling was used to adjust for other risk factors. Current cigarette smoking was associated with fatal prostate cancer (rate ratio (RR), 1.34; 95 % confidence interval (CI), 1.16-1.56). The RR was greater at younger ages, decreasing from 1.83 (95% CI, 1.04-3.24) among men below age 60, to 1.11 (95% CI, 0.79-1.S8) among men age 80 and above. No trend in risk was observed with number of cigarettes per day nor with duration of smoking among current smokers at baseline, and no increased risk was found among former smokers. Race did not significantly modify the association between cigarette smoking and fatal prostate cancer. Although these data and three other mortality studies show an association between current cigarette smoking and fatal prostate cancer, the lack of a consistent dose-response gradient, and the lack of association with incident prostate cancer in other studies raises the possibility that smoking, or a correlate of current smoking, may adversely affect case survival.

Key words: Cohort study, tobacco, prostate cancer United States

Cigarette Smoking as a Predictor of Death From Prostate Cancer in 348,874 Men Screened for the Multiple Risk Factor Intervention Trial

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Abstract

The association of cigarette smoking and mortality from prostate cancer was evaluated in 348,874 black and white men who were screened as part of the Multiple Risk Factor Intervention Trial (MRFIT). Current smoking status was assessed, serum cholesterol was measured, and demographics were recorded at screening; however, no information was collected on history of smoking, prostate screening, or diet. The vital status of each member of this cohort was ascertained through 1990. Death certificates were obtained from state health departments and coded by a trained nosologist. A total of 826 deaths due to prostate cancer occurred over an average of 16 years of follow-up. The proportional hazards model was used to study the joint association of age, race, income, cigarette smoking, serum cholesterol level, and use of medication for diabetes on risk of death from prostate cancer. Statistically significant associations were observed with age ($p < 0.01$), cigarette smoking status [relative risk (RR) = 1.31, $p < 0.01$], black race (RR = 2.70, $p < 0.01$), and serum cholesterol (RR = 1.02 for 10 mg/dl higher cholesterol level, $p < 0.05$). Similar results were obtained when deaths that occurred during the first 5 years were excluded. Among cigarette smokers, there was some evidence of a dose response relationship ($p = 0.20$). The relative risk for those who reported that they smoked 1-25 cigarettes per day compared with nonsmokers was 1.21 ($p = 0.04$); the relative risk for those who reported smoking (26 cigarettes per day compared with nonsmokers was 1.45 ($p = 0.0003$). These findings add to the limited evidence that cigarette smoking may be a risk factor for prostate cancer.

Key words: blacks; diabetes mellitus; prostate cancer; smoking.

Although prostate cancer has not been traditionally included among the smoking-related malignancies[1, 2], the results of two recently reported cohort studies have drawn attention to the possibility that cigarette smoking may be a preventable cause of mortality from prostate cancer[3, 4]. In a 26-year follow-up of nearly 250,000 US veterans, Hsing et al.[3] found that cigarette smokers had about an 18 percent increase in risk of death from prostate cancer. The risk elevation was most pronounced among veterans who smoked 40 or more cigarettes per day [relative risk (RR) = 1.51, 95 percent confidence interval (CI) 1.20-1.90]. In a further cohort study of 17,633 white male insurance policy holders, Hsing et al. (4) found that cigarette smokers were more likely to die from prostate cancer (RR = 1.8, 95 percent CI 1.1-2.9). These potentially important findings have generated controversy owing to the difficulty in drawing causal inferences from weak associations[5], and because most other cohort studies of prostate cancer have failed to find a positive association with cigarette smoking[6-13]. Many earlier cohort studies have been limited by the relatively small number of prostate cancer deaths, however. The findings of case-control studies that have examined associations with smoking have also been inconsistent[14-23].

In order to further evaluate the relation of cigarette smoking to prostate cancer, we undertook a prospective study of possible predictors of mortality from prostate cancer among 348,874 black and white men who were screened as part of the Multiple Risk Factor Intervention Trial (MRFIT).

Materials and Methods

The methods of this follow-up study have been reported in detail elsewhere[24-27]. MRFIT was a multicenter study of the effect of coronary heart disease risk factor reduction in middle-aged men at high risk of coronary heart disease. Beginning in 1973, 361,662 men aged 35-57 years were screened on a single occasion over a two-year period at 22 clinical centers in 18 US cities in order to identify participants eligible for randomization to the trial. This report is restricted to 348,874 men who described their race as black or white. The screening data included birth date, race, social security number, current cigarette smoking status, and serum cholesterol. A smoking history was not obtained. Thus, never smokers cannot be differ-

entiated from ex-cigarette smokers. Serum cholesterol was measured in one of 14 laboratories under the supervision of the MRFIT Central Laboratory in San Francisco, California, and the Lipid Standardization Laboratory of the Centers for Disease Control in Atlanta, Georgia. A one-page questionnaire was administered to determine demographic characteristics, the number of cigarettes smoked per day, use of medication for diabetes mellitus, and other selected information. Median family income specific for families headed by black and white individuals within zip code areas is used as an ecologic marker of socioeconomic status. Thus, for black men, the median income of families headed by black individuals within their zip code of residence is the income measure, while for white men the median income of families headed by white individuals within their area of zip code of residence is used.

The vital status of each member of this cohort was determined through 1990 using the National Death Index (1979 through 1990) and the Social Security Administration (1973 through 1988). Death certificates were then obtained from state health departments, and underlying cause of death was coded by a nosologist according to the International Classification of Diseases, ninth revision (ICD-9)[28]. Death certificates were obtained for 99 percent of the decedents. Among the 348,874 black and white men, who were followed for an average of 16 years, there was a total of 826 deaths identified with ICD-9 code 185, which corresponds to prostate cancer.

Age-adjusted rates per 10,000 person-years were obtained using the direct method and the age distribution at screening for the 348,874 black and white men screened. The proportional hazards model with stratification by clinical center was used to obtain adjusted estimates of relative risks (strictly speaking, hazard ratios) while taking other screening measurements into account[29]. Age adjustment and regression analyses were performed using both screening age and current age. These analyses yielded results which were essentially identical. Kaplan-Meier estimates of cumulative mortality were also cited[30].

Results

The cohort studied included 23,490 black men and 325,384 white men. The average age at screening was 46 years. Thirty-seven percent of the men reported that they smoked cigarettes at the time of screening. The average number of cigarettes smoked per day was 26. Eight hundred and twenty-six deaths due to prostate cancer occurred over an average of 16 years of follow-up. The cumulative mortality from prostate cancer after 5, 10, and 15 years were 0.01, 0.07, and 0.21 percent. The majority of deaths from prostate cancer (76 percent) occurred among men over 50 years of age at screening. The average age at the time of death was 64 years.

Age-adjusted mortality rates per 10,000 person-years from prostate cancer were approximately three times as high for black as compared with white men (table 1). An inverse association was observed with income. The relation of serum cholesterol and mortality from prostate cancer was not graded, although death rates for each of the upper four quintiles were higher than the lowest quintile. A positive association with reported cigarette smoking was observed although evidence for a graded increase in risk with increasing numbers of cigarettes smoked per day was not strong (table 1).

Table 2 summarizes results from a proportional hazards model that considers the joint influence of each of the factors in table 1 on mortality from prostate cancer. These results are generally consistent with those in table 1. Cigarette smoking was associated with a 31 percent increased risk of death from prostate cancer (95 percent CI for relative risk: 1.13 to 1.52). Because of the small number of deaths in some of the smoking categories in table 1, a separate analysis in which cigarette smokers were categorized into two groups — 1-25 cigarettes per day and ≥26 cigarettes per day — was also performed. The relative risk for death from prostate cancer for these two groups relative to nonsmokers were 1.21 (95 percent CI 1.01 to 1.46; p= .04) and 1.45 (95 percent CI 1.19 to 1.77; p = 0.0003), respectively. A separate analysis for smokers was also carried out in

which the dose-response relation with death from prostate cancer was estimated. In this analysis, the log-linear coefficient for cigarettes per day was 0.0059 (p = 0.20).

Because the presence of prostate cancer could alter smoking habits or cause changes in serum cholesterol, the analysis shown in table 2 was repeated excluding deaths in the first 5 years of follow-up. Essentially identical results were obtained — the relative risk associated with cigarette smoking was 1.31 (p = 0.0005) and the relative risk of death from prostate cancer associated with a 10 mg/dl higher serum cholesterol was 1.02 (p = 0.007).

Smoking-associated relative risks of mortality from prostate cancer by age were also examined (results not shown). No trend with age was evident - the p-value corresponding to the test for interaction was p = 0.88. Risks of death from prostate cancer associated with smoking were very similar for blacks and whites (results not shown).

Discussion

The results of this study are consistent with those of other cohort studies[3, 4] that have suggested that cigarette smoking may be associated with a modest increase in risk of prostate cancer. The results of two additional cohort studies[31, 32] offer qualified support for this hypothesis. Nevertheless, most cohort studies of prostate cancer that have examined this question have not shown an elevated risk due to smoking[6-13]. A weak association could have been masked in some studies, however, owing to the relatively small number of cases or general constraints on the ability of observational studies to detect weak associations such as bias due to the misclassification of exposures and the possibility of residual confounding. The large cohort size of the present study, which is among the largest that have been used to evaluate whether cigarette smoking is associated with prostate cancer, offers the advantage of enhanced statistical power for detecting weak associations. Another strength of the present study is the large number of cases (n = 826) available for analysis, a number exceeded only by the 4,607 deaths from prostate cancer in the cohort study of US veterans by Hsing et al.[3] which also showed a modest increase in risk among smokers. The men screened for MRFIT are also younger on average than the subjects included in most previous studies of smoking and prostate cancer; the risk estimates are therefore less likely to be attenuated by competing risks of mortality.

We cannot rule out the possibility that the associations identified in the present study are explained by uncontrolled confounding due to socioeconomic factors, dietary factors, or other exposures more directly related to risk of fatal prostate cancer. However, the weak association with cigarette smoking persisted after adjustment for age, race, income, diabetes, and serum cholesterol. Nevertheless, data from other studies suggest that smokers may have lower vegetable consumption and higher intake of total fat and meat than nonsmokers[1, 4]. Data on prostate cancer screening were also unavailable in the present study. A further concern is that misclassification of exposures is likely to have occurred to some extent owing to changes in smoking habits over time. Such misclassification of exposures is likely to have been nondifferential, however, which would tend to bias the risk estimates for cigarette smoking toward one. Nevertheless, the lack of information on duration of smoking and changes in smoking status during the follow-up period are important constraints in interpreting the association with smoking including dose-response relations. Although cigarette smoking habits might be altered by the detection and treatment of prostate cancer, the results were unchanged by the exclusion of deaths that occurred during the first 5 years. Because the information collected in the initial screen did not allow for former smokers to be separated from men who never smoked, the risk estimates for cigarette smoking are likely to be conservative.

We also cannot rule out the possibility that the association with cigarette smoking is due to a decreased survival of smokers during treatment for prostate cancer. However, in the study of US veterans by Hsing et al.[3], an increased risk of

prostate cancer mortality was observed among both current and former smokers, suggesting that the associations observed in their study were not due to a survivorship effect. Although the reliance on ICD-9 codes is a further limitation of the present study, studies of the accuracy of death certificates in the United States have shown prostate cancer to be a valid underlying cause of death[33, 34]. For example, Percy et al.[33] found prostate cancer detection and confirmation rates of 94.7 and 96.3 percent, respectively, in comparing underlying cause of death on death certificates from the Third National Cancer Survey with hospital diagnoses.

Although the results of the present study (and the collective results of all studies reported to date) do not implicate cigarette smoking as a casual factor in prostate cancer, the association is biologically plausible. The association could be accounted for by exposure to N-nitroso compounds - which have been shown to induce prostatic cancer in laboratory animals - or by the antiestrogenic effect of cigarette smoking[3, 35, 36]. Male cigarette smokers have been found to have higher levels of circulating androgens[3, 38].

Thus, the results of this study add to the limited evidence suggesting that cigarette smoking is associated with a modest elevation in risk of prostate cancer mortality. Although the results of studies carried out to date have been inconsistent, a weak association with cigarette smoking could have been overlooked in studies with relatively few prostate cancer cases or other design limitations. If smoking is causative and the observed associations are not due to uncontrolled confounding or other biases, even a modest excess risk among smokers would be important from a public health standpoint owing to the high prevalence of cigarette smoking in men.

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TABLE 1.

Age-adjusted rates and relative risks of mortality from prostate cancer among 348,874 black and white men screened for the Multiple Risk Factor Intervention Trial through 1990 (average of 16 years of follow-up).

Characteristic	No. of men	No. of deaths	Age-adjusted rate†	Age-adjusted relative risk‡
Race				
Black	23,490	122	3.93	3.09**
Non-black	325,384	704	1.44	1.00§
Estimated income(s)‖				
<$15,000	17,474	79	3.08	1.00§
$15,000–$24,999	168,428	398	1.55	0.73**
≥25,00	135,007	283	1.45	0.65**
Cigarettes per day				
None	220,229	514	1.46	1.00§
1–15	25,914	79	2.18	1.54**
16–25	43,304	102	1.74	1.27*
26–35	28,212	58	1.71	1.23
36–45	23,047	54	1.93	1.50*
≥46	8,168	16	1.57	1.22
Medication for diabetes mellitus				
Yes	5,381	14	1.23	0.90
No	343,493	812	1.59	1.00§
Serum cholesterol quintiles (mg/dl)				
<182	68,561	119	1.39	1.00§
182–202	70,057	1.48	1.48	1.06
203–220	68,491	196	1.88	1.34**
221–224	70,128	188	1.68	1.20
≥245	71,637	175	1.50	1.07

* $p<0.05$; ** $p<0.01$.

† By direct method per 10,000 person-years.

‡ Obtained from a proportional hazards regression model that included age at screening and the indicated characteristic.

§ Fixed reference category.

‖ Income data were available for 320,909 men with complete data among whom 760 died from prostate cancer.

TABLE 2.

Relative risks of mortality from prostate cancer among black and white men screened for the Multiple Risk Factor Intervention Trial through 1990 (average of 16 years of follow-up)†

Covariate	Relative risk	95% confidence Interval
Age (10 years)	7.88**	6.69–9.27
Black race (1 = yess, 0 = no)	2.70**	2.10–3.47
Income ($5,000)	0.95	0.89–1.01
Cigarette smoking status (1 = smoker, 0 = non-smoker)	1.31**	1.13–1.52
Diabetes Mellitus (1 = yes, 0 = no)	0.77	0.43–1.36
Serum cholesterol (10 mg/dl)	1.02*	1.00–1.04

* $p<0.05$; ** $p<0.01$.

† Relative risk estimates are obtained from a proportional hazards model with stratification by clinical center and with all covariates in the model. Analysis is based on 320,909 men with complete data among whom 760 died from prostate cancer.

Cigarette Smoking and the Risk of Prostate Cancer.

A Review of the Evidence.

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Introduction

After lung cancer, prostate cancer is the second leading cause of cancer death in black and white men in the US. In addition, the incidence of, and mortality from prostate cancer are increasing, with an estimated number of 244,000 newly diagnosed cases and over 40,000 deaths in 1995[1]. Therefore, full attention needs to be given to the etiology and prevention of this type of cancer.

Recognized risk factors for clinically overt prostate cancer include age, a family history of the disease and living in Western and more developed countries. Disease rates are much higher in black compared to white men, and black men in the US have the highest rates in the world [2-5]. Incidence and mortality are low in Asia, but rise significantly among immigrants to Western countries [6]. The low rates in Asia compared to Northern Europe and the US and the findings from immigrant studies suggest that environmental factors such as differences in dietary fat intake could be an important determinant of prostate cancer. Indeed, most retrospective[7-14] and prospective[15-19] epidemiologic studies on dietary factors show a modest (30-50%) increase in risk for subjects with a high, compared to a low level of dietary fat intake. However, differences in fat intake between ethnic groups can explain only part of the differences in prostate cancer rates[20].

With regard to the association between cigarette smoking and prostate cancer, most general reviews do not report an association[2-4,21]. One study[22] does, as do some case-control and cohort studies. Because we are not aware of an extensive review of this topic in the literature and the association between cigarette smoking and prostate cancer may be of intrinsic interest, such a review is provided hereunder.

Methods

From previous reviews[2-4,22] and from a Medline search starting in 1966, we collected all publications which included data on the association between cigarette smoking and prostate cancer. The materials include a variety of epidemiologic designs, such as case-control, cohort and cross-sectional studies.

For case-control studies, the association between prostate cancer and cigarette smoking (current, former and ever vs. never) was compared. We also estimated the magnitude of two potential sources of divergent results among the published studies, namely race (black vs. white men), and the choice of controls (hospital vs. population). Using published tabular data as available, the Mantel-Haenszel summary odds ratio (OR) across studies within these categories, comparing current, former, and ever smokers to never smokers, was then calculated.

In a separate case-control analysis, we examined the relation between five measures of lifetime smoking habits (ever/never/current smoker, age started smoking, number of years smoked, cigarettes smoked per day and the number of years since quitting) using data from our ongoing case-control study[23] of tobacco related illnesses. This latter analysis pertains to patients and their (hospital) controls interviewed between 1969 and 1991.

For cohort studies we examined the relation between the number of cigarettes smoked per day (CPD) and prostate cancer incidence or mortality. For various reasons some cohort studies are discussed in more detail.

Results

We identified 18 case control studies[23-42] from the literature. Some studies were reported on more than once. Black men were included in only four[12,23,24,41]. There was a mix of hospital and population controls, and matching of cases with multiple controls (generally three or less) was common. In only two studies[29,41] were patients with benign prostate hypertrophy (BPH) used as controls. Matching variables typically included age (within 1-5 years), race, and date of diagnosis or a proxy thereof. The proportion of ever smokers among the cases ranged from 48 to 95%. Across the studies, the weighted averages of the odds ratios for current (OR,

0.97; 95% confidence interval (CI), 0.81-1.08), former (OR, 0.99; 95% CI, 0.87-1.12), and ever smokers (OR, 1.04; 95% CI, 0.95-1.14) vs. never smokers, stratified for type of control (hospital vs. population) and race, show no association between cigarette smoking and prostate cancer. Studies with hospital controls tend to show a weak inverse, and studies with population controls a weak positive association for current and former smokers compared to never smokers. The ORs are close to unity and statistically non-significant for both types of study. These patterns hold in both black and white men.

In the American Health Foundation case-control study of tobacco related illnesses, we previously[23] reported no relation between smoking status (current or ever vs. never) and prostate cancer for patients diagnosed between 1969 and 1984. An ad-hoc examination of the relation, using additional and more detailed measures of lifetime smoking habits (ever/never/current smoker, age started smoking, number of years smoked, cigarettes per day smoked and the number of years since quitting) for patients interviewed in the period 1969-1991, shows no association between any of these measures and prostate cancer (Submitted for publication).

We identified 11 cohort studies[16-18,43-57] with a prostate cancer mortality follow-up from the literature and five studies[15,58-62] with a prostate cancer incidence or prevalence follow-up. Some studies were reported on more than once. Generally, smoking status was compared for one to four levels of number of cigarettes smoked per day (CPD) relative to never smokers, and for former smokers compared to never smokers. As best we know, no significant number of black men was studied except in the Kaiser Permanente morbidity follow-up which included 23% black men[59].

Eight of 11 cohort studies showed no association between level of smoking (CPD) and prostate cancer mortality. In the British Doctors' study[49-51], one of the negative studies, mortality was assessed after 10, 20, and 40 years of follow-up using administrative records. In addition, questionnaires were mailed out to study subjects at regular intervals to obtain information regarding current smoking habits. Three studies, the US Veterans study[43], the MRFIT Screening cohort[48], and the Lutheran Brotherhood cohort[16] did report a positive association. Here the study subjects were not contacted during follow-up and cause of death was compared by smoking habits at study entry only. The follow-up period in these studies ranged from 16-26 years and the cause of death was ascertained from insurance records. The risk of prostate cancer mortality in the US Veterans study is marginally elevated, with a risk ratio (RR) of 1.18 for current smokers and 1.13 for former smokers. In the MRFIT study, the reported RRs in two smoking level categories (1-25, 26+ CPD) are 1.2 and 1.5, and no estimates are given for the risk of current or former vs. never smokers. In the Lutheran Brotherhood cohort, the RR was 1.9 for former, and 1.8 for ever smokers.

Discussion

Case-control studies show basically no association between cigarette smoking (current, former, or ever) and prostate cancer. Reports with elevated odds ratios are usually atypical in one or more respects. As an example, controls for the Dutch cancer registry study (OR=2.12 for ever smokers)[29], were selected from patients with benign prostate hypertrophy (BPH). Since there is evidence that BPH is negatively associated with smoking[22], this choice of controls might well overestimate a smoking-prostate cancer association. The odds for ever smoking are also elevated (OR=1.71) in the second study with BPH controls[41].

Contrary to other suggestions[43,59] we found that case-control studies with population controls are quite common. The use of population controls results in slightly increased OR estimates for current (OR, 1.03; 95% CI, 0.87-1.21) and former (OR, 1.10; 95% CI, 0.91-1.33) smokers, but these results are still essentially indistinguishable from unity, both from a clinical and a statistical perspective. None of the case-control studies showed a consistent relation between

amount of smoking (pack years or CPD), duration of smoking, age started smoking, age quit smoking, or any other measure of exposure and prostate cancer.

Most published cohort studies also fail to show a relation between cigarette smoking and prostate cancer incidence or mortality. In the three cohort studies that do report an association[16,43,48], the information on smoking status was only collected at study entry and mortality among the subjects was ascertained after a follow-up period ranging from 16-26 years. This could result in biased outcomes for two reasons. The first being that classification at study entry does not take into account that, in the US and elsewhere, there has been a dramatic decline in the proportion of smokers from 1950 to 1995. There is evidence that in the US Veterans and the Lutheran Brotherhood studies, between 40-50% of the smokers may have quit smoking after study entry[16,43]. The second reason is that there has been a dramatic change in the composition of the cigarettes smoked; from high-tar, high nicotine, non-filter cigarettes smoked in the 1950s to low-tar, low nicotine, filtered cigarettes smoked at present[63]. If quitting smoking is associated with smoking level at study entry, which seems plausible[64], a major source of bias would be introduced.

Comparisons between cohort studies are not easy to make because smokers have been categorized in many different ways, using a variety of cutpoints for CPD. This also leaves an opportunity for ad hoc groupings after data inspection. It is, therefore, difficult to evaluate the reported dose-response relations between number of cigarettes smoked and prostate cancer mortality. The categories used in the MRFIT screening cohort, for instance, are 1-25, and 26 or more cigarettes per day. No data are provided aggregating all levels of smoking. In the Lutheran Brotherhood study, the categories include ever and former smokers, and no dose-response is seen with cigarettes per day, categorized at 1-19, 20-29, and 30 or more.

Conclusions

On the basis of data presently available, a causal association between cigarette smoking and prostate cancer does not seem likely. The positive associations between cigarette smoking and prostate cancer reported by three large cohort studies should not be ignored, however, if only because of study size. At this point they are hard to interpret because smoking status in these studies was only available at study entry and, during the follow-up period, (ranging from 16 to 26 years) dramatic changes in smoking behavior and the composition of cigarettes took place. A re-analysis of some of the cohort studies using uniform categories for cigarettes smoked per day at study entry would be helpful, as would be an attempt to trace and interview a sample of the subjects who are still alive. Among other things, this would allow for a more detailed examination of the association between level of smoking at study entry and subsequent quitting patterns, and for a better interpretation of the nature of the association.

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Smoking and Prostate Cancer: An Interim Analysis of the Australian Collaborative Case-control Study of Risk Factors for Prostate Cancer

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Summary

In 1994 we commenced a 5-year case-control study of 4,000 male residents of Melbourne, Sydney and Perth to test various dietary hypotheses in regard to the risk of clinically significant prostate cancer. Cases and controls were restricted to men who were registered on the Electoral Rolls and who resided within the city boundaries. Cases were excluded if their adenocarcinomas were well differentiated or had Gleason scores less than 5. The men were aged 40 to 74 years at interview when they were asked questions in regard to many other topics including cigarette smoking. An analysis of smoking associations is presented, based on the questionnaire schedules that were available for coding and data entry prior to the beginning of 1996. The numbers comprised 751 cases and 386 controls. Response rates are estimated in cases and controls at about 75% and 65%, respectively. A statistically significant odds ratio of 0.78 was identified for current smokers, but no associations were observed with ever or past smoking, nor was any dose response observed with age at starting to smoke, the number of cigarettes smoked, the number of years smoked or the number of pack years smoked. We conclude that there is no causal association between cigarette smoking and the incidence of clinically significant prostate cancer. As more data come to hand, the analysis will be able to be repeated with an equivalent number of controls and to be adjusted not only for age, but also for other potential confounding factors such as dietary fat.

Background

In Australia, prostate cancer became the leading cancer in males in 1989. In 1995, over 7,000 Australian men were diagnosed with prostate cancer and 2,700 died from it — the incidence and mortality rates standardised to the World population were estimated to be 54 and 20 per 100,000, respectively. Ten years earlier, in 1985, the rates were 42 and 16 per 100,000, respectively. These rates are much lower than those found in North America, but are increasing swiftly due to the large amount of ad hoc screening activity occurring since the advent of the prostate specific antigen (PSA) test. Mortality trends remain fairly flat.

There being no recommended method of early detection nor evidence of successful treatment from randomized controlled trials, it was decided to carry out an epidemiological study to ascertain the extent to which prostate cancer might be prevented. We were guided by Nomura & Kolonel's review[1] to conduct a large population-based case-control study specifically focusing on diet (particularly fat intake) and including alcohol consumption, vasectomy, and ionising radiation. We also collected data on family history and now plan to follow up relevant cases and their families to collect blood and tumour samples for future molecular research. The study was limited to patients with diagnoses before the age of 75, and included men with well differentiated cancers (or Gleason scores less than 5). This was to focus on disease that accounted for significant years of life lost and/or morbidity and to exclude clinically insignificant tumours of low metastatic potential. Additional data on staging and method of detection will be used for further sub-group stratification in future analyses.

Methods

It is planned to recruit around 2,000 cases and 2,000 age frequency-matched controls over a four to five year period. Cases are identified by sampling the pathology notifications to the population-based cancer registries in each city. Permission to approach each case is obtained from the treating doctor. Controls are identified from electronic copies of the Electoral Roll (voting is compulsory in Australia). Cases are also checked for presence on these rolls. Interviews are arranged face to face in the participants' homes or mutually convenient locations, in the absence of other people. Some materials are sent in advance for the man to complete ahead of the interview — a lifetime calendar to aid recall, and a family history/pedigree schedule that requires some preparation. The interview com-

prises three sections. First, is an administered interview using a structured questionnaire with prompt cards. This covers a variety of topics including medical history, previous X-rays to the abdomen, alcohol consumption, smoking, occupation and activity levels at work etc. Next, an optically-scannable food frequency questionnaire (FFQ) is administered. The FFQ was developed for use in Australian populations of this age for a prospective cohort study of 42,000 people in Melbourne[2]. Finally, the man is asked to complete privately a questionnaire concerning urinary symptoms and sexual activity.

Analysis

The available data for analysis comprised 1,137 interviews with almost twice as many cases (751) as controls (386). Analysis was conducted using logistic regression in S-Plus. Age was stratified into five groups: 40-49, 50-59, 60-64, 65-69 and 70-74 years.

Results

Response rates in the cases and controls are estimated at 75% and 65%, respectively. The odds ratios and their 95% confidence limits are given in Table 1. All analyses are adjusted for age.

Conclusions

On the basis of this preliminary analysis, we find no evidence of a causal association between cigarette smoking and the incidence of clinically significant prostate cancer in Australian men aged 40 to 74 years. There is a suggestion that cigarette smoking may be protective.

Table 1:

Associations between indices of smoking and the risk of clinically significant prostate cancer to Australian men aged 40 to 74

	Cases N = 751	Controls N = 386	OR[1]	(95% CI[2])
never smoked	248	122	1.00	
ever smoked	503	264	1.09	(0.83-1.42)
past smoker	439	211	1.09	(0.98-1.20)
current smoker	64	53	0.78	(0.63-0.97)
age started smoking				
≤15	133	84	0.99	(0.83-1.18)
16-20	273	127	1.05	(0.96-1.16)
20+	97	53	1.02	(0.93-1.12)
years smoked				
<10	61	37	0.98	(0.78-1.24)
10-19	93	36	1.13	(0.97-1.32)
20-29	116	64	0.98	(0.89-1.07)
30-39	108	67	0.95	(0.88-1.01)
40+	125	60	1.00	(0.94-1.06)
cigarettes smoked daily				
1-9	79	32	0.96	(0.76-1.21)
10-20	263	142	0.95	(0.83-1.10)
21-39	80	46	1.00	(0.93-1.07)
40+	79	42	1.05	(0.96-1.15)
pack years smoked				
<10	114	57	0.99	(0.82-1.21)
11-20	87	47	0.97	(0.84-1.11)
21-30	87	43	1.01	(0.91-1.11)
31-40	60	32	0.99	(0.90-1.08)
41-50	54	34	0.95	(0.89-1.04)
51-60	25	13	1.00	(0.90-1.10)
>60	74	36	1.01	(0.95-1.06)

[1] OR, Odds Ratio; adjusted for age
[2] CI, Confidence Interval

References

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PROFESSOR SIR RICHARD DOLL

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I would like to begin by associating myself with everybody else that has spoken from outside Australia by thanking you for giving us the privilege of visiting Queensland in this present weather.

I have been asked to make some comments on the papers that have been given which, I take it, means general comments but not conclusions because I don't want to say now what I think I am likely to say at the end of our group discussion after tea. In any case, my conclusion might well be modified by that group discussion.

I have got a number of comments which, I would suggest, might be worth taking into consideration when the groups break up to discuss whether or not there is any causal relationship between cigarette smoking and prostate cancer. Well, the first clear and obvious finding, with which all the papers are in agreement, is that smoking is not closely related to the development of prostate cancer and, indeed, one could not define any group of smokers in whom it would be possible to say that the chances were more than equal that the case was actually contributed to by smoking; where one would say the probability of smoking being the cause was greater than 50 %, ie, a relative risk of more than 2.

So we are dealing with a situation in which we are trying to draw conclusions about the existence of a weak relationship. Now, there is a temptation to say, well, these are unimportant; they are weak relationships; but they are not, of course, always unimportant if the disease is a common one and 20 or 30 per cent excess of a common disease from a common exposure can be very, very much more important than a 95 per cent chance of causation by a rare exposure of a rare disease. It may be very interesting, scientifically, and it is nice to clear up the causation of a disease, but the social importance of it is very much less than the importance of a 20 per cent excess from a common factor of a common disease.

Well, this is a problem which epidemiology is having to deal with and concentrate on more and more in the last few years and will, I believe, have to concentrate on more and more in the next few years. And I think there are some conclusions which we can draw that are applicable to this problem. The first relates to the use of case-control studies. Now, I have long been a proponent of case-control studies. There have been critics that have said that case-control studies are too unreliable and there are a number of critics who have said that case-control studies using hospital controls are unreliable. Well, I do not think that it is true in general.

But when you have an agent which causes as many diseases as smoking does, then the use of hospital controls does become very dubious because if you sit down and try and draw up a list of conditions which you are sure are unrelated to smoking, either positively or, of course, negatively, and there are a few which are negatively related to smoking, and then strike all those out, how many are you left with for your hospital controls in a case-control study? We have just been trying to do this in a study on the effect of radon in causing lung cancer in parts of Britain where there are high radon levels and it has been extremely difficult to agree on patients that are suitable for inclusion.

You end up with a number of eye conditions and a few others. You can have accidents, of course, because accidents are related to the amount you drink and the amount you drink is related to the amount you smoke, so you cannot have accidents in your control group. And it becomes extremely difficult. I am inclined to think myself and suggest that case-control studies using hospital patients should not be regarded as relevant for assessment and that is a great pity, but at any rate it is my conclusion. Now, what about population controls? I hate the term population controls because it sounds as if you have really got a controlled group that you can rely on. Well, of course, population controls, as

so often described in case-control studies nowadays, are even worse than hospital controls very often.

The technique which has been so common in the United States of random digit dialling, goodness knows what this means. Nowadays, when such a high proportion of people have answering machines, they are certainly not going to bother to ring back if you tell them that you are wanting to make some inquiry which is going to take three-quarters of an hour or an hour of their time. And, of course, even leaving aside that extreme situation, the sort of person that is prepared to sit down over a telephone and answer a long questionnaire has personality characteristics which are different from those that will not answer to you. I think that any case-control study based on so-called population controls which are derived from random digit dialling has also got to be abandoned.

So what does that leave us with? That leaves us with Dr Hsing's study in Shanghai pretty well. I was hoping to be able to say it left us with Dr Giles' study also. But we have heard from him that although he set out for his controls to be randomly allocated population sample, he got what, a 60 to 65 per cent response rate. Now, how on earth can we be confident that a 60 to 65 per cent response rate is going to give us such an adequate estimate of the population's smoking habits to enable us to be confident about a 20 per cent excess in the disease we are studying? I am afraid my conclusion is that we cannot, and I think Graham would very likely agree with that, but of course, as he said, his study was not aimed to study the effects of smoking.

We have one study from England which has not yet been reported which I think can be taken into account, and that is one Tim Key has been carrying out in which the controls are drawn from the general practice lists of the doctors who have also got prostate cancer. I am trying to find out, I am not sure of what response rate he's got from those controls, but that is an acceptable means of drawing a control group for a case-control study. And I may say that the results of that study that Dr Key kindly let me have, show that current smokers have a relative risk of 1.06, which is nothing like statistically significant, based on about 200 cases altogether.

So, apart from Dr Hsing's study, the results of which I think are entitled to be described as sound medical evidence, but is it relevant to a situation in the United States when cancer of the prostate has a 30 or 40-fold difference in incidence in the two countries, and it may well be that the aetiological factors are different? Nevertheless, for what it is worth, and I think it is worth a great deal, it may not be entirely applicable to the Australian situation. That study fails to show any relationship with smoking and is important evidence, with the qualification that we can't be absolutely sure that it would apply to a country with a much higher incidence.

So, that brings us to the cohort studies. Now, the cohort — and my own view is that we are going to have to lay much — for this particular problem, lay much more stress on the cohort studies. Well, the first of those cohort studies showed a really big effect of smoking, but of course this was the hypothesis-forming study. The Veterans study, it would be perfectly appropriate to say, "Well, we'll leave that out," because that study was first published in the late 1950s I think, and it must be the basis on which people who have had any interest in the relationship between smoking and prostate cancer, and had gone on to look at it. But I don't think it would be fair to exclude that study altogether, because the first report of that study can be regarded as hypothesis-forming, but there were only 52.

There were only 52 deaths from prostate cancer at that time when the relative risk was shown to be so high, whereas there was something — I forget the number now, is it several thousand — yes, I think it is 4000 deaths from prostate cancer. What I would like to see would be the Veteran study data reported excluding the data initially reported in the Dorn. study. I don't think it would make — it would [not] be very different from what we see now because there were only 52 cases, but technically speaking, I

think we should say the Dorn study was hypothesis-forming and let's include that study after excluding those cases.

Well, we've got three very large cohort studies, and I am leaving the Veterans' one in because I don't think the results will be altered by much by leaving out the first set of data. And they are all in agreement in showing an excess of prostate cancer of the order of 30, 35 per cent. But, of course, there are a lot of other cohort studies, some of them too small to take into account. But it is slightly odd the small studies all put together show no effect, and actually the fourth and fifth biggest studies, ACSI (American Cancer Society, Cancer Prevention Study I), and the British Physician Study, if they are combined they actually have more cases than the ASCII study (American Cancer Society, Cancer Prevention Study II), and those two studies combined show no effect of smoking. The British Physician Study, as has been pointed out, does have the advantage in that the mortalities related to fairly recent smoking habits, as the smoking habits have been updated on a half a dozen occasions over the 40 years. So one does not have complete consistency in the cohort studies, but the weight of the evidence of the cohort studies does suggest an excess risk.

Now, is this risk a causal risk, and here, of course, we can apply all the standard criteria. One of them only shows a biological gradient, the first one the Veteran study, the other two don't show any biological gradient. They don't show a progressive fall off with risk as you give up smoking. They show a drop immediately you give up smoking to near the non-smoker's level. So you have certainly not got data which are the sort that would encourage you to think you had a causal relationship. Two interesting hypotheses have been mentioned in relation to these cohort studies; one an effect of screening taking out some of the non-smokers who are postulated to be more concerned with their health, and to have been screened. I think this may well apply nowadays with the blood test that we have for screening, but I doubt very much if screening by digital-rectal examination will have picked up a sufficient number of cases to account for the result, a sufficient number of cases even postulating that the non-smoker had more digital-rectal examinations than the cigarette smoker.

So it is an interesting explanation for the results. I don't find it a wholly convincing one without some more positive evidence that the type of screening that was common before the onset of the MRFIT (Multiple Risk Factor Intervention Trial) Study, and the ACSII Study was, in fact, substantially more common amongst non-smokers, and did, in fact, result in a substantial increase in recognition of prostate cancers. Another interesting study, suggestion was made that perhaps smoking is speeding up the malignancy of cases, is accounting for a positive relationship when mortality is looked at, whereas there was no positive relationship with incidence. I had forgotten to mention that in relation to the review of the cohort studies. But, of course, all the incidence studies were relatively small, and I did mention that all the mortality cohort studies tended to show no relationship.

Well, personally, I am not terribly attracted by the idea that smoking would increase the rate of progression unless you found a quantitative relationship with the amount smoked. I find it difficult to believe that 20 a day would have no more effect on progression than five a day.

So I don't think we get away from the difficulty of there being no biological gradient by saying that smoking is just acting as a factor causing progression of the cancer, or indeed, promotion of the cancer. I would like to distinguish between these two terms, promotion and progression. I think they're sometimes used rather confusedly in the literature. By promotion, I mean causing a greater incidence of malignant disease to appear by some mechanism other than by initiation, other than by altering the DNA some extra genetic mechanism. I have no reason to believe that such promotion can also occur without a relationship to the intensity exposure to the agent.

So it would, of course, explain the fact, if smoking was acting as a promoting agent here — I'm say "promoting" rather than "progression" here. Progression I take to mean turning a malignant

growth into a highly malignant growth such as you see clinically, occurs very often, for example in leukemias and in all cancers really — but you could expect to see with promotion that stopping exposure would immediately have an effect. We were very surprised when we first found this happened with lung cancer, but it's been confirmed time and time again. You do not undo the damage that has been done, but you do very quickly get an effect from stopping smoking, and I think if smoking was having a small promoting effect it would be perfectly reasonable to find that stopping smoking you lost the effect quite quickly, within 5 years.

So promoting seems to me something we should consider. Whether it makes sense in the light of absence of a biological gradient is perhaps something we can discuss in the groups. Well, that leaves us with one other explanation and that is confounding. Of the cohort studies that have been reported to us none have been able to systematically take confounding into account. We have heard from Professor Colditz that there are several major factors with which smoking is confounded which could play a part in increasing the risk of the disease in smokers, and I think perhaps we ought to place special attention, more attention than we have yet today paid to it, to the possibility of confounding counting for the observations.

Well, as I said, I didn't want to state what my conclusions were, and anyway I shan't come to a conclusion until after we've had our discussions after tea with the rest of the group. I put it to you for your consideration that we should not put much weight on case-control studies apart from Dr Hsing's, that we should concentrate on the cohort studies. We should note that the three bigger studies do show a positive relationship with smoking, though only one with a biological gradient and you can do this after we've excluded the initial hypothesis forming data and the Veteran study, and that if we have to consider the possibility of this being — but whereas all the minor ones, smaller cohort studies put together, don't show such an effect.

One of those, I would suggest to you, does have the advantage — this is the British Physicians study — does have the advantage that it's dealing with a socially homogeneous population. So if there are going to be socio-economic factors playing a part in causing the excess in, for example, the Veteran study or the ACS study, those factors will not be present in the British Physicians Study. Then, we have to consider whether causality, promotion, or confounding is the most likely explanation for the small excesses in the three large cohort studies, or whether we can conclude, despite the absence of a biological gradient, that there is a causal relationship reflected by data.

Questions for Syndicates

Each syndicate is asked to tackle a series of issues and report back.

Question 1

Are cigarette smoking and prostate cancer causally related?

If so,

What is the summary level of risk?

What proportion of prostate cancer may be caused by smoking?

Is there a particular dose level that is associated with risk?

Question 2

How should dose levels of smoking risk be expressed (pack years, average numbers smoked per day etc.)?

Consensus Development

PROF COLDITZ: This morning we have the challenge of integrating the summary statements from the four groups that either struggled or solved the problem very quickly yesterday, depending on which group we may be referring to. The challenge this morning is to have each group, I hope briefly, present their answer. I would ask that the group have someone present it who is prepared to stand up as they would at, shall we say, an epidemiologic meeting to justify the position that is taken.

And after all four groups have presented, we will open the floor to discussion so that we know in fact how far we are from consensus before we start pulling things apart.

Group 2.

DR LEIBOFF: This is fairly brief and straight to the point and it gives no indication of the sort of mental acrobatics we had to go through. So, it does actually represent a reduction from our discussions, but that's what we were asked to do.

Overhead from group 2 (Refer Appendix A).

The group found unanimously, that present evidence is insufficient to suggest the causal association between smoking and prostate cancer. There was a tendency to say that there's no adequate evidence that smoking is associated with an increased incidence of prostate cancer. The wording was chosen carefully. And there is limited evidence that smoking is associated with progression of prostate cancer, progression being determined mostly by the fact that mortality studies, the cohort studies were those that found the association more strongly.

In terms of the strength of association, there's limited evidence for weak association for the progression of prostate cancer. Again based upon the cohort studies of mortality, we found that there's no evidence of an association of prostate cancer incidence and smoking.

We also raise the question of biological plausibility, which had not really been addressed in the conference yesterday, but we thought it was important that we didn't find the evidence was anything but very indirect and weak. Also, we addressed biological gradient and dose-response, and we recognised that there was the dose-response in the US Veterans Study, which certainly raises some questions, but apart from that we really didn't find any evidence, but we certainly noted that study. Then in terms of the debate that followed, we really had to try and determine what factors could establish causality because the evidence that we had as presented before did not indicate to us that there's any strong evidence in favour, and it's those factors presented up on the overhead that we need to replicate in studies addressing incidence and progression, and this can only be done by staging of the disease being incorporated into the studies.

We are very concerned that reliance on prostate cancer deaths significantly under-estimated the incidence of prostate cancer. We are also concerned about assessing ongoing exposure status, smoking status, in the cohort studies and factors concerning the determination of screening status was also raised in the group.

PROF COLDITZ: Any comments from anyone who was in group 2; does anything need to be clarified? As a group, you're all comfortable to stand behind that summary?

DR HOAR ZAHM: I think the main concern for future studies was, first of all, replication, but the other issue was just whatever factors might be related to progression. They are hinted at there by screening status, but it was the idea of the aggressiveness of the malignancies. This whole issue needs to be researched more, along the lines of the comments that Ann Hsing made yesterday. This is really the area where research needs to be directed.

Group 1.

PROF KALDOR: In answer to the first question, we found that there was not evidence of causal association, but we spent a lot of time trying to figure out why we thought there wasn't. We identified the three types of studies — the cohort mortality studies, the cohort incidence studies, and the case-control studies. Of course all the discussion really revolved around what the cohort mortality studies meant. These are the only ones that really lent any support at all to the hypothesis of a causal association between smoking and prostate cancer.

Overhead from group 1 (Refer Appendix B).

Now, within the cohort mortality studies, of course, we couldn't get away from the fact that the Veterans study was not only the biggest, but it actually was bigger than all the rest put together. It was the only one that had a dose-response relationship, and this I guess was a point we kept coming back to again and again. I think we might have been slightly influenced by the presence of some of the investigators of that study in our group in saying that it was probably a very good study. At least that should be said in the negative. We questioned the investigators very hard to find out if there were some weaknesses that we could expose and were unable to do so. But it remains the single study with a dose-response, but interestingly the next two biggest studies, the MRFIT and the ACS, had increased risks of about the same order of magnitude, if not any evidence of a really clear dose-response.

So we asked ourselves: what do we have against the idea of a causal relationship with a small relative risk, and what it came down to was there was only one study that had a dose-response which was the Veterans and, despite the fact that it was the biggest study, it could still have been a chance finding in that one single study. I think if we'd seen two cohort studies with a dose-response, we would have been in quite a different situation. It was something that only emerged in US mortality studies. That is, of course, partly the fact that all the studies have been done in the US. There are not really big mortality studies, apart from British doctors, outside of the US, and we talked a lot about confounding, and none of us could really convince ourselves that known confounders for prostate cancer could account for what was going on.

So, we couldn't come up with an alternative explanation for that increased relative risk, but I think it really came down to the fact that there was only one study, albeit the biggest, that was supporting that dose-response relationship.

And, finally, we did the hypothetical: if it is "yes", if it is an association, well, we said the relative risk was probably about 1.3, and we took a stab and attributed a risk which is the proportion of people whose prostate cancer would be attributable to smoking, and that's 0.18 of the total cases of prostate cancer. That's under the assumption of 75 per cent smoking prevalence in the population under consideration. And, of course, if there is no dose-response shape, then of course we did not identify a so-called safe or risk-free dose. Thanks.

PROF COLDITZ: Everyone in group 1 happy or have anything to add to clarify that, expand? There being no further discussion, Group 3 presented its summary.

Group 3.

DR HICKEY: The majority of the group felt that the sound medical scientific evidence available indicates that a causal link between smoking and prostate cancer is unproven but it is not

ruled out. A minority felt that a causal link is unlikely and participants felt that more analysis of existing cohort studies was required, and this would include, for example, validation studies to exclude bias in the cohort studies and follow-up of maybe the older case-control studies regarding mortality.

PROF COLDITZ: Again, any comments from others in the group to clarify? Everyone is happy from Group 3. Then for the last group, I think Richard Doll is rapporteur.

Group 4.

PROF DOLL: Well, first, I must apologise for us not having any overheads to show. The reason for that is not that we failed to come to a conclusion, but that we had such a long discussion of the data that we were unable to come to a conclusion until 8.50 this morning. Last night we felt thoroughly bemused, and we said, "Let's sleep on it and see if we can come to any clearer conclusion in the morning". Well, we have done so, and we have come to a clearer conclusion, and it is not quite the same as the conclusions that have been put to you.

Firstly, we agreed that the data were not the sort of data that you would expect if cigarette smoking was a cause of cancer of the prostate for the reasons that have been rehearsed many times yesterday and several times already today, and I need not go over them. We were befuddled, as obviously everyone has been, by the really rather sharp difference between the American Veteran Study and other studies.

If the American Veteran Study stood by itself, and one had no other information about it than had been reported yesterday, one would certainly have to think that there was a possibility of a causal relationship. Though I am very worried why the relative risk fell off so rapidly with the course of time and it is difficult to explain it wholly on the grounds of people giving up smoking.

Dr Bordujenko had some more information about that study which had not been reported previously, namely, that in the early days a lot of the veterans came to autopsy and if a cancer was found at that autopsy, this was given preference to any other cause of death, so that all cancers of prostate found at autopsy in the early years would have been put down as the cause of death.

Well, as the mortality in cigarette smokers in that population was very much higher than in non-smokers, there would have been a lot of cancer of the prostate diagnosed in cigarette smokers that would not have been, in the ordinary course of events', if the death certificate was used as the cause. We concluded, therefore, that really one should dismiss the early findings of the Veterans Study. We would like very much to see what the results were in, say, the last 16 years of that study in which this procedure had not been used.

Well, given that, and the absence in other studies of the type of evidence that one would look for before accepting a causal relationship, we tried to think what other explanations there could be for the results, and one was obviously confounding, but we couldn't for the life of us really satisfy ourselves that confounding would produce the same sort of findings as were obtained. Again any lack of any biological gradient. There must be some sort of quantitative relationship between confounding and cigarette smoking which you would expect to show itself in some form of a biological gradient and possibly also a relationship with time since stopping.

So we were unhappy about confounding. One of our colleagues suggested there was one form of confounding which might show the sort of characteristics that were observed, namely confounding with lack of physical exercise, but that didn't seem to be relevant to a cancer of the prostate. So we were unable to attribute it to confounding. We were unable to attribute the relationship to cause and effect, and that left us with chance.

Well, we noted that the case-control studies which we sought had adequate controls to enable one to draw a negative conclusion. Easy enough to draw a strongly positive conclusion from case-control studies, but the controls, as were mentioned yesterday, you have to be confident they are representative of the population

from which the cases are drawn to be sure of a negative relationship. The two case-control studies in which we thought the controls were the most reliable, namely Dr Hsing's and Dr Key's from Oxford, were effectively random population, a very high proportion of whom were interviewed, both were completely negative.

We were conscious that the smaller cohort studies tended to be negative, and we thought that if all the cohort studies were put together in a meta-analysis, which is what we should like to see, excluding the first 10 years of the Veteran Study which, of course, we couldn't do, we guessed that the results could well be compatible with chance. Our conclusion, therefore, Mr Chairman, was that the data we were presented with did not show a causal relationship between smoking and prostate cancer, and the most likely explanation of the findings was chance.

PROF COLDITZ: Are there any comments from the group?

PROF DOBSON: Sorry, I'm not clear. Perhaps if Ann Hsing could just confirm the factual basis because that last thing was based on data outside that was available to the rest of the groups. Could you just confirm the business about post-mortems and the preferential diagnosis for prostate cancer in the US Veteran Study?

DR HSING: I am not aware of autopsy diagnosis in early years, and a greater reporting of prostate cancer death from death certificates, so I think we need to look into that. But from our discussion yesterday with Aaron, and he has also worked with this data, said the assessment of mortality actually is quite uniform so there shouldn't be any differential, but if truly in the earlier years there is greater opportunities of autopsy diagnosis of prostate cancer cases and reported on death certificates, that could be a possibility but if that only occurs in the first 10 years or in the 1950s, I think this issue can be easily addressed, that we could re-analyse the data excluding earlier cases.

PROF MATHEWS: My recollection is from a few years ago in relation to another study of Veterans, and the reason why the autopsy rate was high in Veterans was that some of the Veterans' pension benefits to next of kin were related to whether or not there was an autopsy, and that partly explained the higher autopsy rate. Can anyone confirm that?

DR HOAR ZAHM: I'm not sure I understand the implication of this because wouldn't you have to imply that the autopsy rate varies by smoking status, and that's the only way it can affect the risk estimates here. Is there any evidence of that, and if not what is the implication?

DR BORDUJENKO: I suppose that would be the basic assumption. 84 per cent of the men in the 1954 study were between 50 and 70, so if you're going to make an assumption that there would be some years of life lost in smokers, and particularly heavy smokers, then their mortality rate at that first Dorn paper two and a half years into it may be increased. I think an autopsy had been made in nearly one-third or 31 per cent of deaths for information concerning method of — so we had an autopsy rate in this paper of about one-third.

They provided a mortality ratio for specific causes of death and 117 of the persons who had died had a cancer which was not considered one of the causes of death by the attending physician, and examples of this were clinically quiescent cancer of the prostate and they don't actually divide or give any example as to the number of cases, which at that time was only 52 which were clinically quiescent, nor do they specify whether they were smokers or non-smokers, but we based the concern that there may have been — or quite probably were a higher rate of autopsies in smokers than non-smokers, but that is an assumption.

PROF DOLL: It wouldn't be necessary, I think, to have a higher rate of autopsy in smokers. The mere fact that the smokers had a higher mortality would mean that more cases would come to autopsy.

PROF HAKULINEN: I think this earlier part can be also regarded as a hypothesis-generating study and when you are then summing up the information, you should probably exclude that, or at least part of the study, as Richard was putting it yesterday.

DR THUN: I had a question about chance being the most likely explanation. In the mortality studies that are published, it's not only the US Veteran Studies, but also MRFIT and the Lutheran Brotherhood that show an increased risk, and cancer prevention study 2 isn't published, but I can't quite get it out of the back of my mind. So it seems to me that something other than chance is suggested.

DR BLAIR: In our group, we also tried to look at the case-control studies and I think we took Professor Doll's wisdom about, maybe, the hospital based case-control studies would not be particularly useful, but we did look at the population based case-control studies and even though they might have some difficulties, as a matter of fact most of those also showed an excess. So there is sort of slight other collaborating evidence that leaves — it left our group, I think, with this sort of uncertain feeling. Sort of about where the data lie, we clearly came down on the side saying there wasn't sufficient evidence yet, but speaking for myself, it's sort of an inkling there that there may be a little more to it than just, "No, there's nothing there."

PROF COUGHLIN: In the MRFIT Study, we had no biologic plausibility for an association between serum cholesterol and mortality from prostate cancer and I was very impressed by how close the relative estimate was to one.

PROF DUGGAN: Following up Sir Richard's point about smokers dying at a greater rate than non-smokers, in the 60s, from my observation of the States, there was also a social gradient in those who went to VA hospitals versus those that did not, so it seemed to me, and I had a very clear impression that what in the British we'd called social class 4 and 5 went to VA hospitals and social class 1, 2, and 3 carried insurance and did not, and I wonder at that stage, would there have been, as I expect, a social class gradient in terms of smoking habit? If so, then that would bias the results towards smokers, social class 5, dying in a VA hospital and having prostate cancer recorded.

DR BLAIR: You're talking, John, about the US Veteran Study?

PROF DUGGAN: Yes.

DR BLAIR: Actually, the cohort was established from records of servicemen who had life insurance policies. So it wasn't people who went to the VA hospitals. They may have eventually gone there, but it was sort of established before that. They had records of life insurance policies.

PROF DOBSON: The business about the dose-response in the cohort studies, in the very nice summaries that Dr Lumey had presented for us -which, I must say, was one of the most useful documents in our discussion — in fact, if I'm reading it correctly, the MRFIT Study there is suggestive of a slight dose-response. Now, in your paper, when you presented that, there was a question because the data weren't consistent between the paper that you presented and the abstract and, in fact, in neither case for the age adjusted relative risks did you give us the confidence intervals, but I wonder whether that information is, in fact, available, because I think it could add substantially to the data.

PROF COUGHLIN: The crude and adjusted rates presented in table 1 of the manuscript don't show clear evidence of a dose-response relationship. In a previous preliminary analysis that was based upon a few years of follow-up, it was much more distinct. When we extended the follow-up to 16 years, it was much less, but those strata were decided upon before we looked at the results and they weren't altered in any way to make it appear more distinct.

In the multivariate analysis, where we included several covariates, not just age but also race, income, and so forth, and had two design variables for three categories of smoking and non-smokers at baseline, those who smoked one to 25 cigarettes per day and those who smoked 26 or greater, there was some suggestion of a dose-response relationship. That was in the multi-

variate analysis. Then we did a further analysis where we limited the subjects to those who smoked at all and treated smoking as an ordinal or, approximately, continuous variable was not significant at the 0.05 level, but it was also suggestive of a dose-response relationship.

PROF DWYER: One of the problems we had is in coming to terms with the relationship and having, as Sir Richard said, excluded the Veterans study and thinking about an all-or-nothing effect and that doesn't usually characterise the smoking disease relationships we've observed, except for one for which there's less certainty and that's passive smoking and coronary heart disease, but there are not so many parallel examples and I wondered whether the groups had actually thought about how in terms of causing a cancer this might occur without there being a dose-response relationship.

PROF MATHEWS: I made the point yesterday, if you've got competing causes you can explain the lack of a dose-response, particularly if the competing causes have got a higher dose-response than what you're trying to estimate and what we heard just now from Steven would be consistent with a longer period of follow-up, the evidence for dose-response became less. I mean, that's not to say that's a correct explanation.

DR THUN: It is possible. There are several studies that show a small increase in risk and there is only one study that shows a clear dose-response and that is the reason why we are uncertain. There are lots of things you can speculate about but the state of the published data, I think, is that there is this difference, where one study shows a dose-response and the others, on the whole, do not.

DR HSING: Our feeling yesterday was actually there are many more cohort studies available and probably have not reported a look into this relationship: the Framingham cohort in the US and there are others, and also I was wondering what are the results from the health professional cohort and the physicians cohort in Boston?

PROF COLDITZ: That is a good question. The physicians, I do not know what they saw. They have a very low prevalence of smoking to start with. The health professionals, without anything more than a passing conversation with Ed Giovannucci, the impression that he conveyed to me was that there was nothing for incidence and maybe something for mortality. Given the inconclusive data he wanted more cases to be able to do a more rigorous analysis. Thus he was awaiting the completion of an additional follow-up cycle. But you are right that there are other cohorts. There is probably more data from Kaiser that could be updated and so on.

DR BLAIR: I wonder if there might be a little discussion about use of case-control studies in trying to look at this particular issue. There are clear limitations on drawing of controls, as has been well pointed out, and you worry about whether you are getting the right base population here. But there are clear limitations on the cohort side; all except the British doctors. We know we built in substantial misclassification of exposure because we only have one measure of exposure at some time in the past. And for the mortality studies we also know we have got substantial misclassification of disease because looking at death certificates there is plenty of evidence to indicate it is probably about 30 per cent wrong. Both of those things drive the risk toward the null and, I mean, it seems to me like this is not an insignificant problem in most of the cohort studies except the one Sir Richard is involved with where they go back and reinterview periodically to update the exposure.

For the case-control studies, of course, we have probably a very good definition of disease and at least we have a historical sense of exposure up to the time when the interview took place. So it sort of seemed to me like there is a balance there between the two designs and the case-control design, what it can provide you is a better opportunity maybe to look at the nature of the disease. That is a little harder in the cohort fashion. I just wondered what others thought.

DR HSING: I think it is a great idea to follow up cases in a case-control study to see whether smokers have a higher fatality or a shorter survival. But, given the distribution stage of cases

in the western populations, one-third to maybe 40 per cent of them would be localised prostate cancer and the survival for this is actually quite good. So you may need five to ten years to have enough mortality.

PROF COLDITZ: I think that is why group 3 said to go back to the older case-control studies that may be able to link through to mortality.

DR LUMEY: I was going to make that point, because our first cases were picked up 25 years ago and we could take the 70, 80 years olds from then.

PROF COLDITZ: Okay. It seems to me that we have at one extreme chance and the furthest we get away from that is probably group 1.

PROF DOBSON: It seems to me that, in fact, most of the groups said that the case was unproven at present. There is obviously that feel that causation can not be ruled out and then we seem to have the suggestion for particular focus, I think, on re-analysis, meta-analysis of the cohort studies of mortality with the addition of other cohorts and I wonder, for example, for Australia, if the Busselton study could not add it. They have done all the mortality linkage, I think, and so we might suggest that in any meta-analysis — no? John says no? Sure, it would be very small and would not stand alone, but might contribute to a meta-analysis. But, coming back to my original statements, unproven at present but can not be ruled out, is the suggestion.

PROF COLDITZ: Are people happy with that?

PROF DUGGAN: I wonder whether there is not a role — one of our problems has been the definitional one. We have just heard that a definition of death from carcinoma of the prostate was something that was quite unexpected and it has turned, as I read things, upside down or nearly done so. Is there not a role for this meeting seeking some sort of uniformity on when is a carcinoma of the prostate reported as a carcinoma of the prostate on a death certificate, or is that too ambitious?

PROF MATHEWS: From the point of view of the RMA, that is clearly something to aim for in terms of understanding what is going on which is, I guess, where most of the panel is coming from. One needs to understand the processes that happened between cancer induction, diagnosis and the classification errors that happen at each stage and the problems between diagnosis and death and then whether, in fact, it gets mentioned on the death certificate, and all those parts of the process are subject to biases that none of us can do more than speculate about at the moment.

And I think we need to — if we seriously want to understand what is happening we have to unbundle all those processes and get information about each of them which, as a number of us have suggested, can be piggy-backed on some existing studies to some extent by collecting additional information. But I think to create a definition now might help the RMA but not help the understanding of the process.

PROF COLDITZ: Given this spectrum of opinion from chance through to unproven association, is there some way that we can come to consensus? We may be arguing over minor wording but it has implications for the ultimate interpretation and how strongly one may want additional data collected or analysed.

DR HOAR ZAHM: Yes. We actually were the number 2 group, and we discussed the fact that it was kind of comfortable to use terminology that was similar to what IARC (International Agency for Research and Cancer) used, because those words have accepted definitions. You know, so to use things like "limited" or "sufficient" or "insufficient" had some appeal.

PROF HELLER: I think that there seems to be pretty general agreement around the room as to what we're talking about, but it's very difficult with a group of this size to come up with exact wording. It seems to me there's pretty general agreement. And whether the rapporteurs of the four groups could come together and hammer out a form of wording that we could put up for agreement, because I think the group is too large to do it.

PROF KALDOR: One thing I'm having, I guess, a little bit of trouble with in terms of wording is — and it relates to what Shelia said — is that, without knowing the wordings used in the RMA context, other smoking associations and how their associations are viewed, it's hard to say where this association sits or doesn't sit in that framework. So I guess you've tried to put it into an IARC framework, and I don't know if the IARC framework is what's generally used for, and I know it's probably not what's generally used for looking at the other smoking associated diseases, but is there an existing structure of wordings or principles or ways in which these things are expressed for other smoking-related diseases? Or excluded?

PROF COLDITZ: I don't know that I can answer that perfectly, but given the charge to look at the existing literature with standard epidemiologic approach, I would think that using the IARC language, if you will, is probably closest to a standard way to look at carcinogens and carcinogenesis more than anything else. So I myself would feel comfortable heading in that direction, even if the RMA has not traditionally used the same words as IARC. Because our first charge is to look at this as scientists and for the RMA to then interpret that is a secondary — that's their problem, if you will.

PROF KALDOR: Sure, but I think we can be more useful if we try to put things in language that is — because we are talking about words at this stage. I mean, we're trying to come up with some words that are agreeable to the group as a whole, and that's obviously easier if there's a context for that.

PROF DONALD: I agree with Graham's comment. I don't think this group should try to guess how the RMA might phrase such a finding. That's none of, in a sense, your business, and is our problem. I think you should stick to whatever is the scientific process of standardisation with which you're comfortable and leave us to make whatever interpretation of that has to be done under legislation.

PROF HELLER: I'd agree with that. I think that if we do adopt the suggestion of asking a little sub-group to come up with a form of wording with which we could then maybe agree, maybe the other thing that we need to do is to create some sort of list of other information that we would actually like to obtain, and that's something we could go around the room and do.

PROF COLDITZ: So we should move to that under the assumption that the four groups will be represented in a synthesis of their summaries. Meanwhile we should look at the possible research that would help us interpret the existing results.

PROF KALDOR: I guess we didn't go through that process specifically as a group, so I guess I'd be speaking more for myself than for the group as a whole, because we didn't come up with a set of points. But certainly this issue that's come up, that I've heard for the first time this morning, about the early data being more biased by autopsy would need to be reviewed, and I guess if there are other big cohorts out there that can be looked at. I do have some puzzlement about the case-control studies as to why, if they can document smoking better, or current smoking better at least, and if they have good population-based controls, how do they fit with the cohorts, and the obvious answer to that is it is an effect on mortality, because they're mostly incident studies.

So something about looking at what happens to cases after diagnosis, I suppose, is the question.

PROF DOBSON: I'm keen that we concentrate on mortality. The point I want to make is misclassification of prostate cancer deaths. The possibility of reviewing the cause of death, just doing some checking, if that's possible, might make people a little bit more cheerful. I guess also the key word that's missing there is meta-analysis, meta-analysis of cohorts.

PROF COUGHLIN: It is also true that there may be sub-groups of prostate cancer cases, perhaps sub-groups that could be identified using molecular biology, that are caused by environmental exposure such as smoking. So, the list should probably include a suggestion that future studies look not only at environmental

risk factors but also combine that with molecular techniques.

DR HOAR ZAHM: I just want to clarify a little bit the focus that we had on the mortality studies and the fact that those were where the action was or whatever. I do not think we should limit ourselves in thinking for the future we should only do mortality studies because the idea was that the mortality studies somehow were the serious prostate cancers. Well, if we can figure out some way to tell who those are before people die, there is no reason you cannot do a case-control study and you will have much more numbers and better exposure information, better disease information. You know, we were talking about whether, well what if the PSA level tells you what is more aggressive and what is not, and it did not appear that that was true, but there may be something else and that is where a lot of research needs to go. But if we can get an answer to that, there is no reason why we cannot do case-control studies to look at aggressive tumours. We are not — there are limitations to just mortality studies.

DR HSING: I underscore statements by Shelia and Steve because I have been thinking about this problem for about, I do not know, 10 or 15 years now, and we always think that incidence is superior. But actually for prostate cancer, Iam gradually coming to the conclusion that it may be quite important to study fatal studies because that is probably more important especially in the new studies. I also agree that we need to look at progression if we are interested in aetiology and concession. So, I think there needs to be some balance that we need to continue to do studies to understand what factors are affecting progression, but if we simply just use incidence and never really looked at mortality, we may be missing some important factors.

PROF DWYER: I just want to emphasise that I think of all the things we are looking at, the one about misclassification of prostate cancer deaths, I think, is the most important one and we just have to focus on what it is that produce the results that Dr Hsing told us about yesterday. Have a look at whether smokers are more likely to have autopsies because possibly they die suddenly from coronary heart disease and therefore they are the ones that get them and non-smokers do not and so on. An answer to that would be helpful even in letting us know why mortality is going up from prostate cancer at the moment in Australia. So, I think that is a focus of current research and particularly in relation to this issue.

PROF COLDITZ: I have a question for Michael Thun as to whether it is possible to link ACS-II, at least a sub-set of your participants, against tumour registries to look at some of these issues without having to go too far.

DR THUN: Well, we are doing that — for approximately 180,000 people who live in the 21 states that have better tumour registries, but I have not actually thought through how it might apply to this.

PROF COLDITZ: So, if this list was prioritised to come back to the issue, as Terry emphasised, that we are trying to make each additional piece of information help us interpret the body of data that we have, are we missing something?

PROF HELLER: The other thing it is — I do not think it is one of the priorities, but I think it is something that would be very helpful and it picks up something that Terry mentioned earlier which is analogy with other smoking-related conditions, where we have got — and John mentioned it as well — where we have got a situation with a lowish relative risk and are there other smoking-related conditions where we do not see a dose-response relationship and also are there examples where confounding might have created the problem. So, I guess it is how does this fit in the general experience of other smoking related diseases in that type of low relative risk setting?

PROF DOLL: We shall have some evidence on this when we come to look at other cancers related to smoking, and I have reviewed quite a number of those recently for an issue of the British Medical Bulletin which came out in January. And for nearly all of them, there is a clear biological gradient with amount smoked,

even when one is talking about quite small relative risks of less than two, for example, cancer of the stomach which we shall be discussing here later. There is a — myeloid leukemia is another example where the overall relative risk in cigarette smokers is quite low, but the biological gradient is quite clear.

There is one example where the relative risk in cigarette smokers is about 1.4, 1.3 or 4 but without any biological gradient, and that is cancer of the colon and that provides sets of data which are very similar to those we see for cancer of the prostate. What the meaning of that relationship is, of course, is just about as difficult to decide, but there is a very similar relationship with cancer of the colon, but the great majority of the weakly related ones, you do see nice biological gradients.

PROF COHEN: I am not an epidemiologist, so I put this forward with some reluctance, but it seems one of the easy ways to encompass an understanding of a disease such as AIDS is to make it notifiable. And we cannot obviously notify carcinoma of the prostate, but the medications used in the management of carcinoma of the prostate now, are all subject to release by the Government under very strict regulations. But would it be possible to link the supply of those materials with information about smoking?

DR McCREDIE: Can I just clear up the point that carcinoma of the prostate is notifiable. It is a notifiable disease in Australia, all cancers are notifiable to cancer registries. This is by law.

DR BLAIR: With regard to priority, when you are trying to look at the weight of the evidence and see where things stand, sometimes you are doing it where there are not many studies and so one is simply saying, "Well let's do some more studies like we have". This seems not to be the case here. I mean we should not discourage people from looking at other cohorts, you know, that have not reported and that sort of thing, but my guess is if we do 20 more studies, we will get a spectrum just about like what we have now if we do them in the same way, you know. So, I think that points that there ought to be considerable focus on doing things that are different, such as people have talked about focusing better on a finer definition of what the disease is and things such as that.

DR HSING: So, it seems that out of this group of issues we could in some way focus to understand the existing data. We could get a priority and have some direction to go forward and not replicate another 20 studies so we're still in the dark, but rather understand what may be explaining the relations that are currently observed in the cohort studies in particular. So, I think the only thing left is for the reporters from the four groups to get together and find a common set of words that we can come back to maybe later in the day. That potentially could happen over morning tea I expect.

PROF DONALD: If the four group leaders or four representatives of the groups might like to start getting together and see if we can't get this thing decided; so, could we do that. Could four people from the groups please start the process of agreeing on an IARC-based set of words? It is Michael Thun, and Richard Doll, Steven Coughlin and John Kaldor, on behalf of the four groups.

Consensus Statement on Smoking and Prostate Cancer

Does smoking cause Malignant Neoplasm of the Prostate?

After careful consideration of this question and the available data, the consensus conference concluded:

1. There is inadequate evidence that smoking is causally related to the occurrence of prostate cancer.
   (a) There is limited evidence that smoking is associated with increased mortality attributed to prostate cancer.
   (b) There is inadequate evidence that smoking is associated with prostate cancer incidence.
2. A plausible inference from these statements is that smoking may be associated with poorer survival.

Additional studies that may help interpret the possible association include those that

- quantify misclassification of prostate cancer on death certificates according to smoking status
- quantify misclassification of smoking status in cohort studies
- identify additional existing cohorts that may provide data
- conduct meta-analysis of cohort data and exclude early data from US Veterans
- study case survival for prostate cancer cases by smoking status (by staging at diagnosis)
- more adequately determine screening status and its impact in cohort studies
- through linkages and other approaches, better describe the relation between incidence and mortality from prostate cancer
- in any future case-control studies consider markers for subgroups that may be susceptible to smoking.

Section II

Measures of Smoking and Potential Confounders

Various Measures of Smoking as Predictors of Cancer of Different Types in Two Finnish Cohorts

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Abstract

In 1962, a cohort of 4601 men (labelled here as cohort I) representing urban and rural areas with high, intermediate and low lung cancer risk in Finland was interviewed, among other things, with respect to their smoking habits. Another health survey, including questions on smoking habit, was conducted in 1972 and 1977 in the counties of North Karelia and Kuopio, areas with high cardiovascular disease and lung cancer risk in Finland. Altogether 23,290 persons, both men and women, participated (cohort II). The cancer incidence in these two cohorts has now been followed until the end of 1993 through the nationwide and population-based Finnish Cancer Registry. There was no prospective follow-up for changes in smoking habits.

The results are expressed as standardized incidence ratios, SIR, using the whole country as the reference. The SIR for all cancers was 0.96 in cohort I (1186 cancer cases) and 0.98 and 0.86 in males and females of cohort II, respectively (1819 cases). For lung cancer, the SIR for never-smokers among men in cohort I was 0.07 (6 cases), for ex-smokers it was 0.42 (37) and for current smokers it was 1.56 (267). In cohort II these figures were 0.09 (4), 0.29 (32) and 2.32 (251), respectively, in males, and 0.40 (14), 0.20 (1) and 3.66 (14) in females. Prostatic cancer did not show any relationship with smoking. The SIRs in cohort I were 1.10 (62), 0.93 (48) and 1.11 (99) in never-, ex- and current smokers; and in cohort II, 0.85 (17), 1.07 (56) and 0.82 (36), respectively. No consistent pattern emerged, either, when applying different indices of smoking (cross-sectional or cumulative numbers of cigarettes or tobacco smoked).

For rarer cancers, analyzing the two cohorts together, the rate ratios between current smokers and never-smokers were 1.7 for cancer of the kidney, 1.9 for cancer of the bladder, 2.1 for cancer of the liver and 3.4 for cancer of the cervix uteri (five exposed cases only). Cancers of the nervous system with a rate ratio of 1.0 and non-Hodgkin's lymphomas with a rate ratio of 0.8 did not show elevated rates for smokers.

Even with a reservation of unknown confounding factors and of lack of potential effect due to the lack of follow-up of later smoking habits, it appears that smoking is not related to cancers of the prostate and nervous system or to non-Hodgkin's lymphomas. The result for kidney cancer is valid for carcinoma affecting parenchymal cells as more than 95 % of the tumours are in this category. The corresponding proportion for liver cancer is about two thirds. The classical smoking-related cancers express their effect irrespective of the index used to quantify the smoking habit.

Introduction

There is sufficient evidence that tobacco smoke is carcinogenic to humans (International Agency for Research on Cancer 1986). The evidence supports causality for cancers of the lung, larynx, urinary bladder, kidney, oral cavity, pharynx, oesophagus, lip and pancreas. The role of tobacco smoke is less clear in cancers of the stomach, liver and cervix uteri.

The purpose of the present study is to use two Finnish cohorts to assist in estimating the relationships between smoking and certain forms of cancer by providing different indices of exposure, together with a complete follow-up of the cohorts. In addition to the classical smoking-dependent cancers of the lung, kidney and bladder, a special emphasis was focused on cancers of the liver, nervous system and cervix uteri as well as on non-Hodgkin's lymphomas.

Material and Methods

The first study cohort, here called cohort I, comprised the Finnish part of the Finnish-Norwegian population survey of 1962 (Tenkanen et al. 1985). Three urban and three rural areas with high, intermediate and low lung cancer risk were selected in Finland for the study. The rural areas were situated in western and eastern Finland, the urban areas in Helsinki and in south-western and central Finland. Approximately the same number of people were drawn from each of the birth cohorts born in

1898-1902, 1903-1907 and 1908-1917 by systematic sampling from electoral lists in each area. A total of 4601 men were interviewed about their smoking and sauna habits, occupations, symptoms etc. The non-response rate was 11%, with only slight variation by area or age group.

The second cohort, here called cohort II, consisted of males and females included in the 1972 and 1977 population surveys to assess changes in certain cardiovascular disease risk factors in North Karelia and Kuopio counties, areas with the highest cardiovascular disease risk in Finland (Vartiainen et al. 1994). Independent random samples were drawn from the national population register. The surveys included a questionnaire on socio-demographic data, medical history and health behaviour as well as measurements of height, weight and blood pressure. The participation rates were 94% and 89% in North Karelia in 1972 and 1977, respectively, and 91% in Kuopio county in both surveys. Altogether 23,290 persons participated in the two surveys of cohort II.

The follow-up for death and cancer covered the time from the surveys up to the end of 1993. The follow-up was complete. It was based on the unique personal identification numbers that have been in use in Finland since 1967. For the earlier years, manual identification procedures based on name and address were used. The information on deaths was received from Statistics Finland and that on new incident cancer cases from the population-based and nationwide Finnish Cancer Registry (Hakulinen et al. 1989).

The smoking habits for current smokers were assessed at the time of the survey whereas for ex-smokers the amount smoked at the time of quitting was recorded. The amount of smoking was expressed in grams/day based on both the total tobacco consumption and on cigarette consumption only. Those smoking less than 15 grams a day were considered light smokers; those smoking 15-24 grams a day, moderate smokers and those smoking more, heavy smokers. Daily consumption was multiplied by the number of years smoked in order to obtain a cumulative index of smoking in gram-years. Again, three categories were employed: those with less than 200 gram-years, those with 200-499 gram-years and those who had smoked more. The amount of smoking variables were not available for analysis for the ex-smokers in cohort II. There was no prospective follow-up for changes in smoking habits after the date of interview in cohort I, and, for cohort II, data collected after the survey were not yet available for analysis.

The results were expressed as standardized incidence ratios, SIR, (Breslow and Day 1987) using the rates for the whole country as the reference. Regional reference rates were not used as they may be greatly affected by the different smoking habits in different areas.

Results

About one-half of the males were current smokers at the time of the baseline surveys, whereas more than 70% of the females had never smoked (Table I). In cohort I, most of the persons were 45-59 years of age at the time of the interview, but they had time to age considerably during the long follow-up (Table II). The persons in cohort II had a wider age-range and were, on average, younger, with a shorter follow-up than for Cohort I (Table III). In cohort I, the proportion of smokers, 55% at the baseline, decreased to 44% in person-years lived after a 20-year follow-up.

The majority of current and ex-smokers in cohort I were light smokers, irrespective of whether smoking status was based on total tobacco consumption or cigarettes only (Table IV). In the males of cohort II, the moderate smokers, those smoking 15-24 grams per day, made up almost one-half of all current smokers (Table V) whereas, among females, 70% of the current smokers were light smokers (Table VI). The amount of smoking in gram-years naturally depended strongly on age (Tables VII and VIII). The ex-smokers had smoked, on average, for ten years less than current smokers of the same age (Fig. 1). At ages of 55 years and over, the average daily tobacco consumption of the (surviv-

ing) smokers was lower than that of ex-smokers of the same age.

Lung cancer was a rare disease for the never-smokers in both cohorts (Table IX). The risk of lung cancer depended very strongly on smoking whereas the risk of prostatic cancer did not show an association with smoking. The lung cancer risk was increased for smokers of all ages and for all periods of follow-up (Table X). The results remained unchanged when tobacco exposure was estimated based on cigarettes only (Table XI). The use of a cumulative life-time exposure gave rather similar results (Table XII).

Cancers traditionally linked with tobacco smoking, e.g., those of the kidney and urinary bladder, showed a clearly increasing SIR with smoking (Table XIII). The same was true for cancers of the liver and cervix uteri as far as smoking itself was concerned but, unlike cancers of the kidney and bladder, there was no relationship with tobacco dose (Table XIV). The risks of cancer of the nervous system and non-Hodgkin's lymphoma were not related to smoking.

Discussion

In Finland, as in other populations smoking mainly cigarettes, it did not matter whether the smoking index was based on total tobacco or on cigarette consumption only. Moreover, as the persons in a cohort were all followed for the same length of time and as the starting of smoking takes place during a relatively short period in late childhood or early adulthood, it did not really matter whether cumulative dose or the cross-sectional dose of smoking exposure at the beginning of the follow-up was employed. Differences might have emerged had there been a prospective follow-up of the persons' smoking habits and had the past smoking patterns of the persons been studied in greater detail. The consistent differences in lung cancer risk between the different categories of smokers, however, suggest that smoking habits are rather persistent once they have been adopted. It is likely that persons who were never-smokers at the time of the survey did not start smoking later, whereas many of the current smokers later moved to the category of ex-smokers. In cohort II, by 1987, this proportion was nearly one-half. Therefore, the over 20-fold contrast between current and never-smokers observed in this study is probably smaller than that adjusted for subsequent smoking history would be.

Lung cancer is a very rare disease in never-smokers. Therefore, it was considered more useful to employ an SIR compared to the whole Finnish population rather than a relative risk where the never-smokers were the reference category. The problem with the present selection is that the reference risk depends on the prevalence of the different categories of the factor studied, smoking. The selective general mortality removes smokers more than non-smokers from the population with aging, and the oldest age groups are already much affected by this selection bias. On the other hand, a selection process also takes place among the smokers. The final result of the selection works against a dilution of the effect of smoking.

Smoking did not appear to have any effect on risks of cancer of the prostate, tumours of the nervous system and non-Hodgkin's lymphomas. In theory this does not exclude the possibility that different indices of smoking are needed for different diseases and that the correct indices were not employed in the present study. No relevant confounding factors that could conceal an eventual elevated risk can be readily suggested.

Some confounding factors may either create or conceal real relationships. This is a particular concern for those cancers studied whose relationship with smoking is less clear. Liver cancer risk was increased for smokers, but there appeared to be no dose-response relationship in current smokers. If the doses of smoking and alcohol are not correlated, although the habits of smoking and excessive alcohol use are associated, the current results possibly support the aetiological role of alcohol use. An increased number of sexual partners is related to smoking habit. The present data in women showed an increased risk of cancer of the cervix uteri for smokers but, because there was very little variation in smoking dose in women, no dose-

response could be shown. The current results do not allow distinction of the effect of smoking from that of the more traditional risk factors for cervical cancer.

This study, as many others, had a number of issues that were far from ideal. It would have been better to have individual data on changes in smoking habits during the follow-up. There has been a drastic decrease in the proportion of smokers in the Finnish population. In the early 1960s, the proportion of smokers among males was close to 60%, and it had decreased to almost 30% twenty years later (Teppo 1984). In females, there had been a slight increase in the same time, but the proportion had remained under 20%.

The decrease in males could, to a lesser extent, be seen by comparing the proportions of smokers in males in cohorts I and II, although cohort II had been selected from an area with higher than average smoking rates in the 1960s (Vartiainen et al. 1991). Differences in smoking habits between birth cohorts hardly explain the decreased proportion of smokers in males in Finland (Hakulinen and Pukkala 1981). Thus, the main reason for the decrease was stopping of smoking. It did not appear that the dose of smoking would have had a major effect on a person's successful quitting (Fig. 1).

Lung cancer risk has been used as an indicator of a smoking dose (Peto et al. 1994). In the present study, this indicator worked well, and, as previously in numerous studies, high relative risks of lung cancer were recorded for the different smoking categories. The same was true also for cancers of the kidney and bladder. The result for kidney cancer is valid for carcinoma affecting parenchymal cells as more than 95% of the tumours in Finland are included in this category. The corresponding proportion for liver cancer is about two thirds.

No significance tests were made as the results are intended for a pooled analysis of different studies. A proper Poisson regression analysis (Breslow and Day 1987) might, nevertheless, improve the summarization of the results.

In conclusion, the classical smoking-related cancers express their effect irrespective of the index used to quantify smoking, and this study did not reveal any new cancer types associated with smoking.

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Table I. Number of study persons by cohort, sex and smoking status

Cohort and sex	Smoking status							
	Never		Ex		Current		Total	
	N	%	N	%	N	%	N	%
Cohort I	962	20.9	1130	24.6	2509	54.5	4601	100.0
Cohort II								
Males	2131	18.7	4089	36.0	5153	45.3	11373	100.0
Females	8471	71.1	1937	16.3	1509	12.7	11917	100.0

Table II. Numbers of persons and person-years of follow-up in cohort I, by age and length of follow-up

Age	Persons	Person-years x 1000 Length of follow-up (years)		
		0-9	10-19	20-
30-44	60	0.0	-	-
45-59	3141	17.1	1.7	-
60-74	1400	23.6	19.7	4.4
75-	-	0.0	5.6	9.4
Total	4601	40.7	26.9	13.8

Table III. Numbers of persons and person-years of follow-up in cohort II, by sex, age and length of follow-up

Age	Males			Females		
	Persons	Person-years x 1000 Length of follow up (years)		Persons	Person-years x 1000 Length of follow up (years)	
		0-9	10+		0-9	10+
15-29	1792	5.3	-	1601	4.6	-
30-44	4926	44.8	17.3	4947	43.9	16.2
45-59	4229	44.7	42.1	4795	49.8	44.8
60-74	426	13.6	27.4	574	18.9	38.8
75-	-	-	2.0	-	-	3.8
Total	11373	108.4	88.9	11917	117.3	103.6

Table IV. Number and percentage of light, moderate and heavy smokers among current smokers in cohort I in 1962, by age

Age and type of tobacco	Light 1-14g/day		Moderate 15-25g/day		Heavy >25g/day		Total	
	N	%	N	%	N	%	N	%
30-44								
All tobacco	13	32.5	17	42.5	10	25.0	40	100.0
Cigarettes only	13	32.5	19	47.5	8	20.0	40	100.0
45-59								
All tobacco	910	51.9	554	31.6	289	16.5	1753	100.0
Cigarettes only	927	53.4	559	32.2	251	14.5	1737	100.0
60-74								
All tobacco	440	63.3	183	26.3	72	10.4	695	100.0
Cigarettes only	432	63.7	182	26.8	64	9.4	678	100.0
Total								
All tobacco	1363	54.8	754	30.0	371	14.9	2488	100.0
Cigarettes only	1372	55.9	760	31.0	323	13.2	2455	100.0

Table V. Number and percentage of light, moderate and heavy smokers among current male smokers in Cohort II at the time of survey (1972 or 1977), by age

Age and type of tobacco	Light 1-14g/day		Moderate 15-25g/day		Heavy >25g/day		Total	
	N	%	N	%	N	%	N	%
15-29								
All tobacco	273	29.7	476	51.7	171	18.6	920	100.0
Cigarettes only	216	25.5	468	55.3	162	19.1	846	100.0
30-44								
All tobacco	607	28.2	1041	48.3	508	23.6	2156	100.0
Cigarettes only	465	23.6	1014	51.5	491	24.9	1970	100.0
45-59								
All tobacco	705	36.6	856	44.4	366	19.0	1927	100.0
Cigarettes only	579	33.0	819	46.7	354	20.2	1752	100.0
60-74								
All tobacco	74	58.7	43	34.1	9	7.1	126	100.0
Cigarettes only	66	55.9	43	36.4	9	7.6	118	100.0
Total								
All tobacco	1659	32.3	2416	47.1	1054	20.5	5129	100.0
Cigarettes only	1326	28.3	2344	50.0	1016	21.7	4686	100.0

Table VI. Number and percentage of light, moderate and heavy smokers among current female smokers in Cohort II at the time of survey (1972 or 1977), by age

Age and type of tobacco	Light 1-14g/day		Moderate 15-25g/day		Heavy >25g/day		Total	
	N	%	N	%	N	%	N	%
15-29								
All tobacco	272	71.6	94	24.7	14	3.7	380	100.0
Cigarettes only	267	74.0	81	22.4	13	3.6	361	100.0
30-44								
All tobacco	457	67.2	198	29.1	25	3.7	680	100.0
Cigarettes only	445	67.5	189	28.7	25	3.8	659	100.0
45-59								
All tobacco	303	72.3	105	25.1	11	2.6	419	100.0
Cigarettes only	290	73.0	96	24.2	11	2.8	397	100.0
60-74								
All tobacco	22	88.0	3	12.0	-	-	25	100.0
Cigarettes only	20	87.0	3	13.0	-	-	23	100.0
Total								
All tobacco	1054	70.1	400	26.6	50	3.3	1504	100.0
Cigarettes only	1022	71.0	369	25.6	49	3.4	1440	100.0

Table VII. Number and percentage distribution by amount smoked in gram-years, of ex- and current smokers in cohort I at the time of survey (1962), by age

Smoking group and age	Amount smoked (gram-years) 1–199		200–499		500+		Total	
	N	%	N	%	N	%	N	%
Ex-smokers								
30-44 years	4	36.4	5	45.5	2	18.2	11	100.0
45-59	251	38.1	250	37.9	158	24.0	659	100.0
60-74	95	27.6	112	32.6	137	39.8	344	100.0
Total	350	34.5	367	36.2	297	29.3	1014	100.0
Current smokers								
30-44 years	8	20.0	16	40.0	16	40.0	40	100.0
45-59	266	15.7	737	43.4	694	40.9	1697	100.0
60-74	104	15.6	254	38.2	307	46.2	665	100.0
Total	378	15.7	1007	41.9	1017	42.3	2402	100.0

Table VIII. Number and percentage distribution by amount smoked in gram-years, of current smokers in Cohort II at the time of survey (1972 or 1977), by sex and age

Sex and age	Amount smoked (gram-years) 1–199 N	1–199 %	200–499 N	200–499 %	500+ N	500+ %	Total N	Total %
Males								
15-29 years	519	62.8	296	35.8	12	1.5	827	100.0
30-44	460	24.1	1035	54.3	411	21.6	1906	100.0
45-59	197	11.6	624	36.7	880	51.7	1701	100.0
60-74	20	18.0	39	35.1	52	46.8	111	100.0
Total	1196	26.3	1994	43.9	1355	29.8	4545	100.0
Females								
15-29 years	317	93.2	23	6.8	-	-	340	100.0
30-44	448	73.3	154	25.2	9	1.5	611	100.0
45-59	200	55.4	126	34.9	35	9.7	361	100.0
60-74	13	61.9	6	28.6	2	9.5	21	100.0
Total	978	73.4	309	23.2	46	3.5	1333	100.0

Table IX. Standardized incidence ratios (SIR) and numbers of lung and prostatic cancer cases (N), by cohort, sex and smoking category based on average daily consumption in grams

Smoking category	Lung cancer I SIR	Lung cancer I N	Lung cancer II/Males SIR	Lung cancer II/Males N	Lung cancer II/Females SIR	Lung cancer II/Females N	Prostatic cancer I SIR	Prostatic cancer I N	Prostatic cancer II/Males SIR	Prostatic cancer II/Males N
Never-smokers	0.07	6	0.09	4	0.40	14	1.10	62	0.85	17
Ex-smokers	0.42	37	0.29	32	0.20	1	0.93	48	1.07	56
1-14 grams/day	0.33	15	..	..	..	..	0.83	23	..	..
15-24	0.48	12	..	..	..	..	1.24	18	..	..
25+	0.57	10	..	..	..	..	0.72	7	..	..
Current smokers	1.56	267	2.32	251 *	3.66	14	1.11	99	0.82	36
1-14 grams/day	1.32	125	1.61	67	1.43	4	1.03	52	0.82	15
15-24	1.75	91	2.65	123	10.80	10	1.30	34	0.77	14
25+	2.02	51	3.15	60	0	0	1.04	13	1.00	7

Note : ".." (double dot) indicates unknown.
"*" Includes one person with unknown daily consumption

Table X. Standardized incidence ratios (SIR) and numbers of lung and prostatic cancer cases (N) in current smokers, by cohort, sex, period of follow-up since survey (years) and age

Smoking category	Lung cancer I SIR	Lung cancer I N	Lung cancer II/Males SIR	Lung cancer II/Males N	Lung cancer II/Females SIR	Lung cancer II/Females N	Prostatic cancer I SIR	Prostatic cancer I N	Prostatic cancer II/Males SIR	Prostatic cancer II/Males N
Follow-up										
0-9 years	1.60	113	2.43	114	4.13	5	1.34	19	0.78	8
10-19	1.58	108	2.26	136	3.45	9	0.98	35	0.84	28
20-	1.40	46	..	0	..	0	1.15	45	..	0
Age										
30-44 years	0	0	1.44	3	0	0	0	0	0	0
45-59	1.47	32	2.48	97	2.00	3	1.16	2	0.64	4
60-74	1.61	185	2.27	142	5.68	11	1.17	51	0.85	28
75-	1.42	50	2.52	8	0	0	1.06	46	0.90	4
Total	1.56	267	2.33	250	3.67	14	1.11	99	0.82	36

Note : ".." (double dot) indicates unknown due to zero person-years.

Table XI. Standardized incidence ratios (SIR) for lung and prostatic cancer in ex and current smokers at the time of survey, by cohort, sex smoking category and total tobacco consumption (Total) and cigarette consumption only (Cigs).

Smoking category	Lung cancer I Total	Lung cancer I Cigs	Lung cancer II/Males Total	Lung cancer II/Males Cigs	Lung cancer II/Females Total	Lung cancer II/Females Cigs	Prostatic cancer I Total	Prostatic cancer I Cigs	Prostatic cancer II/Males Total	Prostatic cancer II/Males Cigs
Ex-smokers	0.42	0.43	0.29	..	0.20	..	0.93	0.94	1.07	..
1-14 grams/day	0.33	0.32	..	..	..	..	0.83	0.90	..	..
15-24	0.48	0.54	..	..	..	..	1.24	1.27	..	..
25-	0.57	0.61	..	..	..	..	0.72	0.50	..	..
Current smokers	1.56	1.60	2.32	2.38	3.66	3.60	1.11	1.12	0.82	0.82
1-14 grams/day	1.32	1.30	1.61	1.56	1.43	1.51	1.03	1.03	0.82	0.81
15-24	1.75	1.89	2.65	2.68	10.80	10.54	1.30	1.28	0.77	0.74
25-	2.02	2.22	3.15	3.10	0	0	1.04	1.14	1.00	1.04

Note : ".." (double dot) indicates unknown.

Table XII. Standardized incidence ratios (SIR) and numbers of lung and prostatic cancer cases (N), by cohort, sex and smoking category based on amount smoked in gram-years

Smoking category	Lung cancer I		Lung cancer II/Males		Lung cancer II/Females		Prostatic cancer I		Prostatic cancer II/Males	
	SIR	N	SIR	N	SIR	N	SIR	N	SIR	N
Ex-smokers	0.42	35	0.29	32	0.20	1	0.98	48	1.07	56
1-199 gram-years	0.06	2	..	..	..	..	0.99	19	..	..
200-499	0.46	14	..	..	..	..	0.56	10	..	..
500-	0.87	19	..	..	..	..	1.60	19	..	..
Current smokers	1.59	262	2.39	222	3.94	13	1.12	95	0.80	30
1-199 gram-years	0.43	13	0.73	10	0.98	2	0.82	14	0.56	3
200-499	1.62	109	1.84	68	6.83	7	1.11	38	0.75	11
500-	2.08	140	3.40	144	17.88	4	1.29	43	0.91	16

Note : ".." (double dot) indicates unknown.

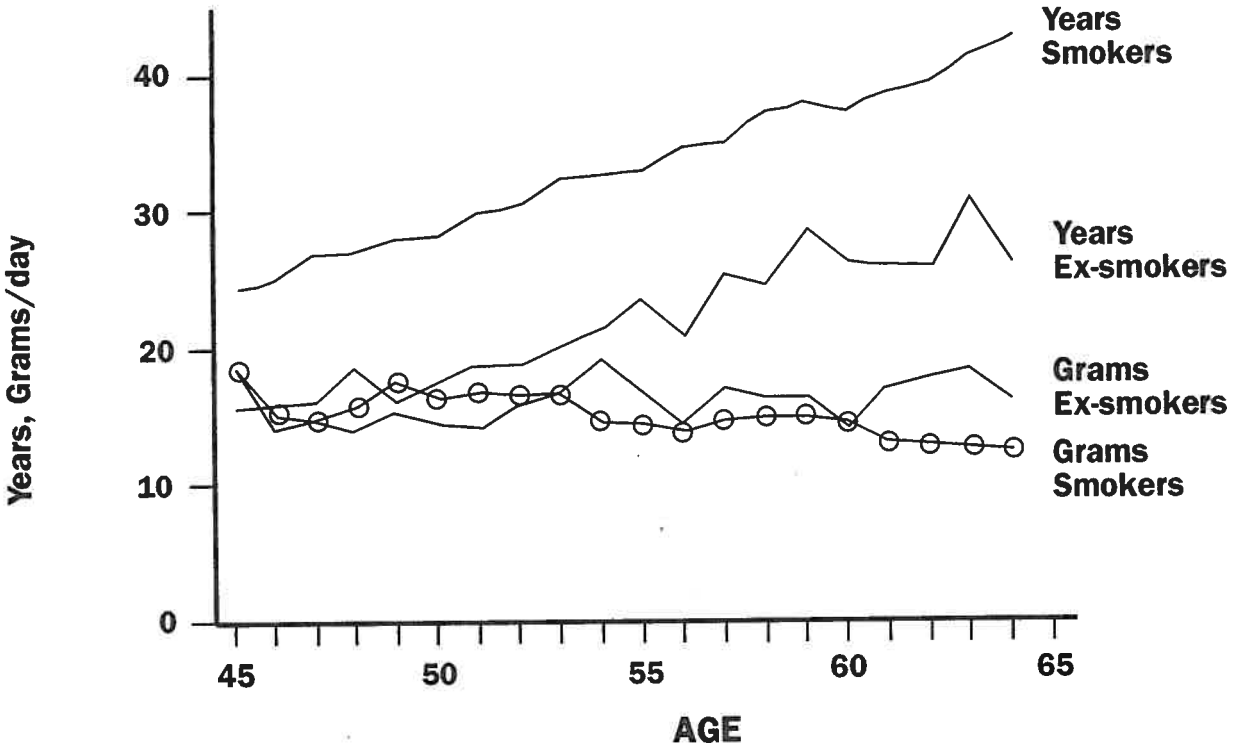
Table XIII. The observed (Obs) and expected (Exp) numbers of cases and the standardized incidence ratios (SIR) for cancers of the kidney, urinary bladder, liver and nervous system, non-Hodgkin's lymphomas and cancer of the cervix uteri, by cohort, sex and smoking category

Cancer, cohort and sex	Never-smokers			Ex-smokers			Current smokers		
	Obs	Exp	SIR	Obs	Exp	SIR	Obs	Exp	SIR
Kidney									
Cohort I	5	7.87		6	7.90		13	14.27	
Cohort II,males	3	7.89		11	17.61		16	17.66	
Cohort II,females	14	24.63		1	3.62		4	2.80	
Total	22	40.39	0.54	18	29.13	0.62	33	34.73	0.95
Urinary bladder									
Cohort I	10	16.92		12	16.85		32	28.74	
Cohort II,males	8	9.48		19	22.95		32	21.43	
Cohort II,females	8	11.84		2	1.61		2	1.23	
Total	26	38.24	0.68	33	41.41	0.80	66	51.40	1.28
Liver									
Cohort I	3	4.28		4	4.27		6	7.54	
Cohort II,males	0	2.48		5	6.14		8	5.73	
Cohort II,females	4	7.66		0	1.04		0	0.79	
Total	7	14.42	0.49	9	11.45	0.79	14	14.06	1.05
Nervous system									
Cohort I	4	3.69	6	3.74	12	7.24			
Cohort II,males	7	6.02	18	12.10	7	13.40			
Cohort II,females	27	32.36	5	6.10	5	4.73			
Total	38	42.07	0.90	29	21.94	1.32	24	25.37	0.95
Non-Hodgkin's lymphomas									
Cohort I	6	6.40	8	6.40	5	11.28			
Cohort II,males	6	6.11	11	13.18	13	13.47			
Cohort II,females	25	24.09	4	3.85	3	2.94			
Total	37	36.60	1.01	23	23.43	0.98	21	27.69	0.76
Cervix uteri									
Cohort II,females	11	18.57	0.59	4	3.17	1.26	5	2.49	2.01

Table XIV. The observed (Obs) and expected (Exp) numbers of cases and the standardized incidence ratios (SIR) of cancers of the kidney, urinary bladder, liver and nervous system, non-Hodgkin's lymphomas and cancer of the cervix uteri, in current smokers at the time of the interview, by cohort, sex and daily tobacco consumption in grams

Cancer, cohort and sex	1–14 g/day			15–24 g/day			25+ g/day		
	Obs	Exp	SIR	Obs	Exp	SIR	Obs	Exp	SIR
Kidney									
Cohort I	7	7.70		3	4.36		3	2.10	
Cohort II,males	4	6.39		6	7.85		6	3.30	
Cohort II,females	1	2.04		3	0.68		0	0.07	
Total	12	16.13	0.74	12	12.90	0.93	9	5.47	1.65
Urinary bladder									
Cohort I	18	15.87		6	8.55		7	4.11	
Cohort II,males	3	8.24		21	9.26		8	3.76	
Cohort II,females	1	0.91		0	0.29		1	0.03	
Total	22	25.02	0.88	27	18.10	1.49	16	7.90	2.03
Liver									
Cohort I	4	4.10		2	2.28		0	1.10	
Cohort II,males	4	2.23		2	2.46		2	0.99	
Cohort II,females	0	0.58		0	0.19		0	0.02	
Total	8	6.91	1.16	4	4.93	0.81	2	2.11	0.95
Nervous system									
Cohort I	7	3.82		5	2.26		0	1.11	
Cohort II,males	2	4.52		1	6.18		4	2.62	
Cohort II,females	3	3.36		2	1.21		0	0.14	
Total	12	11.70	1.03	8	9.65	0.83	4	3.87	1.03
Non-Hodgkin's lymphomas									
Cohort I	2	6.15		2	3.40		1	1.64	
Cohort II,males	5	4.79		5	6.05		3	2.53	
Cohort II,females	1	2.12		1	0.73		1	0.08	
Total	8	13.06	0.61	8	10.18	0.79	5	4.25	1.18
Cervix uteri									
Cohort II,females	4	1.78	2.25	1	0.62	1.61	0	0.07	0

Fig. 1. Daily tobacco consumption in grams and amount of tobacco smoked in gram-years in ex- and current smokers in cohort I, by age. The consumption refers to the time of the interview in 1962 for current smokers, to the time of quitting for ex-smokers.



Factors that Confound Smoking

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Introduction

This paper is a selective review of the literature.

The purpose of this paper is to demonstrate that there are factors which vary with smoking status in such manner as might have significant biological effect.

My aim was to select those factors which other work has suggested may also be of aetiological relevance to human neoplasia, particularly in relation to prostate cancer. It is not possible (and may not be productive) to review all of the factors that are associated with smoking. Coffee, tea, total calories, sugar, starches, illegal drug use, and desire to lose weight are factors which have to be seen to vary with smoking status. Some of these have been suggested as linked to human disease, but I did not address these factors, as I found limited evidence that this could be related to prostate cancer. The factors that I have searched for evidence that they vary with smoking status are dietary fibre, fruit and vegetable consumption, Vitamin C consumption, carotene consumption, tomato consumption, alcohol consumption, meat consumption, fat consumption, physical exercise and fitness and body weight.

I have tried to select the more recent publications of studies with larger group numbers. Only English language titles were selected, and only from journals available in Australia. As this is not a comprehensive review of the literature, there is a danger that I may have exercised a selection bias. My personal selection bias would also need to be considered, as well as publication bias which, I feel intuitively, could be strong in this area.

The initial purpose of conducting such a review is to draw together data on confounders for cigarette smoking and so provide a synthesis of factors to consider when interpreting the relations between smoking and disease.

With respect to prostate cancer, it is my view that the quality of the evidence of at least some of these factors points more towards a true causal link than does the quality of evidence suggesting that smoking itself causes prostate cancer.

Dietary Fibre and Smoking

Dietary fibre is one factor which has been frequently studied in relation to cigarette smoking. Dietary fibre has, in turn, been independently related to a variety of human health effects.

The NHANES II study showed a negative correlation between smoking and dietary fibre, and this difference was significant at the 0.001 level for men, and the 0.01 level for women.[i] When this study, in a separate report, was broken down by gender, race and age group, most of the comparison showed smokers as consuming less fibre than non-smokers.[ii]

The MONICA study in France has also revealed a negative correlation between smoking and dietary fibre.[iii] In this study of 1,126 men, non-smokers consumed 18.3 gms/day, light smokers 17.5 gms/day, moderate smokers 16.0 gms/day and heavy smokers ate 15.9 gms/day of dietary fibre, which was highly significant.[iv]

In the Scottish Heart Health Study, both men and women demonstrated a negative correlation between smoking and dietary fibre.[v] In men, current smokers consumed 20 gms of fibre per day; never smokers consumed 23 gms per day significantly more than the current smokers; ex-smokers were intermediate between these extremes.[vi] In women, current smokers ate 17 gms of fibre per day, whereas never smokers ate 20 gms of fibre per day.

Leigh and Fries studied 1,864 bank retirees and found that cigarette consumption was negatively and significantly associated with the consumption of dietary fibre.[vii] On univariate analysis, a significant correlation of -0.151 was found.[viii] This remained significant on multivariate analysis.

Similarly, an English study has also found that dietary fibre is strongly negatively correlated with smoking status.[ix] This was true for both males and females. In this study former smokers were observed to be intermediate in fibre consumption between never smokers and current smokers.

In a survey of South Australian women, a strong negative association was found between cigarette smoking and dietary fibre. Never smokers ate 22.8 gms of fibre per day, current light smokers ate 19.4 gms, and heavy smokers 18.1 gms per day.x These differences were significant when tested by both smoking status (current, former, never) and by cigarette consumption (none, light, heavy).

This result was similar to a survey of men and women in New England, in that the women who smoked had significant differences in dietary intake compared to non-smokers ($p < 0.01$).[xi] No significant difference in fibre consumption was observed between male smokers and non-smokers.

Larkin *et al* also choose to study a group of women, surveying 1,338 women in America.[xii] Mean daily dietary fibre consumption was significantly higher in the "never smoking" group than in the "current smokers", and significantly higher again in the "quitters" group.

Morabia and Wynder did not measure overall dietary fibre, but several of the food groups that they examined might be markers for fibre.[xiii] They found a strong inverse association between smoking and fruit consumption, breakfast cereal and vegetable consumption in males. In females these inverse relations were less consistent.[xiv]

A study by Strickland, Graves and Lando did not show a negative correlation between dietary fibre and smoking. This study included 3,495 subjects in Midwestern American towns, and found that smokers consumed more fibre than non-smokers (22.0 gms and 18.1 gms respectively), whereas quitters were intermediate.[xv] In this study smokers ate substantially more food. Their consumption of food of nearly all types was greatly elevated. When dietary fibre was examined as grams per kilocalorie, smokers had the lowest level of fibre intake, which was significant.[xvi]

In summary, a wide variety of studies from many different regions, using divergent methodologies and with different researchers, nearly all show the same relation: smoking is strongly inversely correlated with dietary fibre. Further, although the differences vary between the studies, in most these differences are substantial — usually more than 10%, and often closer to 20% lower than intake among smokers. Former smokers tend to be like non-smokers.

A small number of studies have suggested that diets high in dietary fibre may be protective against the development of prostate cancer. A large study of fruit and vegetable consumption in Italy showed a significantly protective effect from fruit and vegetable consumption.[xvii]

Further, in a study by Mills *et al,* a number of foodstuffs which are rich in dietary fibre are negatively associated with prostate cancer risk. Dried-canned beans, lentils and peas were negatively associated with prostate cancer risk, with those eating these foods more than three times per week having a relative risk of 0.53 (95% CI = 0.31–0.90) compared with those who ate less than once per week, with a p for trend of 0.01.[xviii] Fresh citrus fruit and an index of fruit consumption was also negatively associated with prostate cancer risk.[xix]

In contrast, Hsing *et al* found no association with fruit, vegetable or bread consumption.[xx] Similarly, La Vecchia et al found no significant difference between the level of fresh fruit, vegetable and wholemeal bread or pasta in prostate cancer cases, when compared with controls.[xxi] A case-control study in Hawaii did not demonstrate an association between prostate cancer and the consumption of foods high in fibre, such as fresh fruit and vegetables.[xxii]

The evidence of a protective effect of high fibre diets against prostate cancer is weak. However, there is good evidence that fibre intake is lower among smokers and that it may be even lower among those who smoke more heavily.

Dietary Fibre Consumption (gms/day) and Smoking in Men

	SMOKING STATUS (cigs/day)					
Author	Never	Not Current	Former	Current		p
						CvN
Bolton-Smith	23		22-20	20		<0.001
Cade	20.6		19.9	17.5		<0.0001
Fehily		20.9		17.9		<0.001
				1-20	21+	CvH
Hebert	12.9		12.2	10.7	10.9	=0.0001
Knekt		33.3		32.5		=0.02
McPhillips		17.1		16.9		NS
				1-19	20+	
Margetts		26.6		22.5	21.6	<0.001
				1-10	11-20	21+	
Nuttens		18.3		17.5	16.0	15.9	=0.002
Subar	11.1		10.6	10.1		<0.001
						CvN
Troisi	21.54		20.47	16.51		0.0001

Fruit and Vegetables and Smoking

A wide variety of studies have assessed the consumption of dietary fruit and vegetables in relation to cigarette smoking. In some of these studies, a further analysis is undertaken of various vitamins, such as ß-Carotene. The question of the relationship of ß-Carotene and other antioxidant vitamins is addressed later.

In a large study of nearly eight thousand hospital based subjects (all controls for another study), vegetable and fruit consumption varied significantly by smoking status.[xxiii] For males, two different measures of fruit consumption decreased with the number of cigarettes smoked per day, with a *p* for trend less than 0.001.[xxiv] Females had similar changes. Vegetable intake also varied with smoking status, with never smokers consuming a mean of 27.1 servings of vegetables per month, compared with 23.3 for very heavy smokers.[xxv]

A similar strong relationship between smoking and vegetable consumption, and smoking and fruit consumption was observed in a large study in France.[xxvi] Grams per day of vegetable varied with smoking status: non-smokers ate 241.0 gms of vegetables per day compared with 190.2 gms for smokers of the highest level; the *p* value for trend across number of cigarettes smoked is 0.0001. Fruit consumption also varied according to smoking status, with a strong negative correlation (*p* for trend 0.003). Potato consumption did not vary with cigarette status; leguminous vegetable positively correlated with smoking status.

The results of the NHANES II study have also suggested a correlation between cigarette smoking and fruit and vegetable consumption.[xxvii] For different genders, age groups and races, a negative correlation was demonstrated between "all vegetable" and "all fruit" consumption. Most individual vegetable group consumption was also negatively associated with smoking

status.[xxviii] These changes tended to diminish with increasing age.

This result was similar to one obtained from the U.S. Health Interview Survey.[xxix] Fruit consumption was substantially lower in smokers, with never smokers eating 3.2 servings per week, compared with 2.2 servings for smokers.[xxx] Vegetable consumption was similar between smokers and non-smokers. But when potatoes were excluded from the analysis, smokers had lower consumption of vegetables.[xxxi]

In a study of nutrient intake of British adults, although an overall category for "fruit" and "vegetable" is not provided, individual fruits and vegetables are reported.[xxxii] Potato chip consumption did not vary significantly with smoking status for males, but did change greatly for women, with female smokers eating many more chips ($p > 0.001$).[xxxiii] For all other fruit and vegetable types examined, smokers of either gender ate either the same amount, or less, and in some cases significantly less. For example, non-smokers ate 1.65 gms of carrots per week, whereas light smokers (< 20 cigs per day) ate 0.72 gms, and heavy smokers ate even less — 0.53 gms.[xxxiv]

Berger and Wynder found that smoking was associated with a lower consumption of fruits and also of vegetables. For fruit, 18.2% of never smokers ate two or more servings of fruit per day, while for heavy smokers only 7.1% ate two or more servings of fruit per day. For vegetable consumption, 19.9% of never smokers ate fewer than one serve per day, while 28.7% of heavy smokers ate fewer than one serve per day.[xxxv]

Knekt has also found differences in fruit consumption (but not "all vegetables") between smokers and non-smokers.[xxxvi] In a population based study in Finland, non-smokers consumed a mean of 162 gms of fruit and berries; smokers ate 134 gms of the same fruit group, this difference being significant.[xxxvii] Mean vegetable consumption did not vary between the smokers and non-smokers, although potato consumption was higher in smokers, who ate 284 gms, compared with 267 gms in non-smokers, ($p < 0.001$).[xxxviii]

This finding contrasts somewhat with a study of the diets of female smokers and non-smokers by Larkin *et al.*[xxxix] In a study of fourteen hundred American women, they found that both vegetable and fruit consumption was substantially lower in smokers. For fruits, smokers consumed an average of 78 gms per day, whereas never smokers ate 127 gms per day, ($p < 0.001$). For vegetables, never smokers consumed 177 daily grams; smokers ate 151 gms, ($p < 0.001$). Quitters were also significantly different to smokers, eating more fruit and vegetables than either other group.

La Vecchia studied both men and women, and did not find that Italian women who smoked differed significantly to non-smokers. Italian women in this group ate virtually the same amount of fruit, cabbages and total green vegetables, although ex-smokers did eat more vegetables than non-smokers and smokers. Turning to men, however, never smokers ate 7.9 gms of total vegetables per day, light smokers (< 15 cigarettes/day) at 7.7 gms per day, but heavy smokers (> 15/day) fell to 6.5 gms per day.[xl] Fresh fruit consumption varied similarly between smoking status, and there were significant differences between several types of vegetables and fruit (with smokers always lower than non-smokers).[xli]

A reverse gender difference was found in a study of the diet of men and women in New England.[xlii] For "all vegetables", men who were non-smokers consumed slightly (and non-significantly) fewer number of servings of vegetables.[xliii] Fruit consumption was slightly lower in male smokers, but this was not significant. For women, on the other hand, fruit and vegetable consumption was significantly lower in smokers.[xliv]

In summary, several studies suggest a negative correlation between smoking and fruit and vegetables. The exception to this is potato, which seems to be positively correlated with smoking. In general, the larger and better designed studies have more frequently shown an association between smoking and decreased fruit and vegetable consumption. As with fibre, the differences noted are large. As with fibre, quitters become like non-smokers.

A wide variety of studies have found that fruit and vegetable consumption is negatively associated with the risk of prostate cancer. For example, Negri *et al* have shown that prostate cancer risk declines with both fruit and vegetable consumption.[xlv] For vegetable consumption, using those who ate less than seven portions per week as the referent, moderate consumers (seven portions) had a relative risk of 0.8 (Cl = 0.5-1.3), while high consumers had a risk of 0.3 (Cl = 0.1-0.5), with p for trend < 0.01. For fruit consumption (7-13 portions per week) had a risk of 0.8 (Cl = 0.5-1.3), while the highest tertile (fourteen or more) had a risk of 0.4 (CI = 0.3-0.8), $p < 0.01$.

In contrast, the Lutheran Brotherhood Cohort Study did not show any difference in prostate cancer risk according to the level of fruit and vegetable consumption.[xlvi]

Further, in the American Health Professional Follow-Up Study, there was no association found between overall intake of vegetables and fruits and prostate cancer. [xlvii]

In conclusion, although there is some consistency of reports to suggest that smoking status varies fruit and vegetable consumption, there is less evidence that fruit and vegetable consumption alters risk for prostate cancer.

Vegetable Consumption and Smoking in Men

Author	Measure	SMOKING STATUS (c/day) Never	Not Current	Former		Current			p
				1-9	10+	1-10	11-20	21+	
Berger	%<1/day	19.9		18.4	22.9	28.2	27.0	28.7	
Emmons	f&v ser/wk		2.28				2.71		<0.001
						1-19		20+	
Hebert	broccoli times/mth	3.6			3.6	3.4		3.1	NS
						1-14		15+	
La Vecchia	green veg/wk	7.9			8.0	7.7		6.5	<0.05
McPhillips	serves/wk		21.7				22.7		NS
						1-19		20+	
Margetts	gms carrot/wk		1.65			.72		.53	0.018
						1-19	20-39	40+	
Morabia	times/mth	27.1			26.6	23.9	25.2	23.3	0.0006
						1-10	11-20	21+	
Nuttens	g/d		241.0			215.1	201.1	190.2	0.0001
Subar	serving/wk	12.8			13.5		12.9		NS
						1-9	10-19	20+	NvH
Thornton	%< score	53.9				48.1	54.5	60.7	0.001
						1-15		16+	NvH
Whichelow	% frequent green	56.2			61.6	57.5		49.7	0.01
						1-15		16+	
Whichelow	% frequent pulses	57.8			53.2	59.5		56.9	NS
						-15		16+	FvN
Whichelow	% frequent chips	25.1			11.5	28.4		30.3	=0.001

Fruit Consumption and Smoking in Men

		SMOKING STATUS (c/day)						
Author	**Measure**	**Never**	**Not Current**	**Former**		**Current**		*p*
Berger	%fruit>2/day	18.2		11+ 16.4	1-10 12.4	1-10 6.9	11-20 10.2	21+ 7.1
Emmons	servings of f&v		2.28				2.71	0.001
Hebert	fruit sum/mth	19.9			18.4	1-20 10.9	21+ 9.5	NvH 0.001
La Vecchia	fresh fruit/mth	10.4			10.8	1-14 9.3	15+ 8.1	Trend <0.05
McPhillips	all fruit ser/wk		21.8				18.9	NS
Margetts	gms of apples and pears		32.9			1-19 16.6	20 16.0	Trend <0.001
Morabia	times/mth	22.5			21.3	1-19 19.4	20-39 15.9	40+ 13.9 =0.0001
Nuttens	gms/day		180.7			1-10 168.8	11-20 157.4	21+ 145.7 =0.003
Subar	servings/wk	3.2			3.6		2.2	<0.001
Thornton	%<fruit score	35.3%				1-9 39.6%	10-19 53.4%	20+ Trend 65.3% <0.001
Whichelow	fruit summer	72.2%			70.8%	1-15 59.5%	16+ 48.8%	EvN <0.001
Whichelow	fruit winter	52.4%			56.8%	1-15 39.2%	16+ 27.2%	CvN <0.001

Vitamin C and Smoking

Given the relations between smoking and fruit and vegetables one would expect a relation with Vitamin C consumption.

In a study in the United States, Vitamin C was strongly negatively correlated with smoking status.[xlviii] Never smokers ate the highest level of Vitamin C, followed by former smokers and then current smokers. This negative correlation was significant. Non-smokers ate a mean of 30 per cent more Vitamin C in men than did smokers, and 24 per cent more in women who did not smoke compared to current smokers.

In a study of Italian men, La Vecchia *et al* noted that non-smokers consumed the largest amount of Vitamin C, ex-smokers and light smokers consumed equal amounts (less than the never smokers), and heavy smokers the lowest level.[xlix] This trend was significant.

This result was similar to that found by McPhillips *et al* in their study based on two communities in New England, where Vitamin C consumption varied according to smoking status.[l]

Much larger differences in Vitamin C consumption were noted in a study of American women.[li] Using a dietary questionnaire to 1,459 women, the investigators found that smoking women ate an average of 64 mgs of Vitamin C per day, while never-smokers ate 88 mgs/day ($p < 0.001$). Quitters of more than 1 year duration had levels of Vitamin C similar to never smokers.

A relatively small study in Scotland examined both dietary consumption and serum levels of Vitamin C.[lii] Smokers ate significantly lower quantities of Vitamin C (49.4 mgs/day) than non-smokers (61.1 mgs/day). Serum levels of Vitamin C were similarly divergent, with smokers having a mean concentration of 18.4 µM, compared with a mean of 37.0 µM for non-smokers.

In a much larger study in Scotland, involving a dietary questionnaire which was sent to over nine thousand people, the difference in dietary consumption of Vitamin C varied significantly between smokers and non-smokers.[liii] Current smokers ate an average of 49 mgs/day, whereas never-smokers consumed 56 mgs/day.[liv] This difference was significant for both amounts per day and based on nutrient density. An ANOVA analysis for changes across the ex-smoking individuals, grouped by duration of cessation, was not significant.[lv]

These Scottish results were very similar to the results of a study in England, in which the dietary intakes of 2,340 subjects were assessed by use of a questionnaire.[lvi] In both men and women, smokers ate less Vitamin C than non-smokers, with former-smokers close to never smokers in their Vitamin C consumption (men: non, 55.2; ex, 52.3; current 47.7; women: non, 49.3; ex, 47.6; current, 41.7).[lvii] This trend was of borderline significance for men ($p = 0.05$), but was highly significant for women ($p = 0.007$).[lviii]

Similar results were observed by Jarvinen *et al* in Finland.[lix] In a large dietary questionnaire in six different regions of Finland, Vitamin C consumption tended to be lowest in the highest smoking group, although the differences were small.[lx] The overall consumption in all groups was very high, with a mean male consumption of 79.4 mgs/days, and a female mean of 83.7 mgs/day.[lxi] These very high levels of dietary consumption of Vitamin C, with small (but significant) differences between smokers and non-smokers are also responded by Knekt, who studied nearly thirty thousand men in Finland.[lxii]

As noted above, serum levels of Vitamin C tend to be even lower than the differences in dietary intake. The additional loss in serum Vitamin C appears to be as a result of oxidation of Vitamin C by product of cigarette smoke, which has resulted in the suggestion that smokers should eat 16 mgs more Vitamin C per 20 cigarettes a day smoked.[lxiii]

In summary, Vitamin C consumption is lower in the diets of smokers, and serum Vitamin C appears to be even lower and perhaps only half of that of non-smokers. Quitters seem to become like never smokers.

A recent review concludes that there is consistent evidence of a protective effect for Vitamin C consumption, fruit and vegetable consumption, and lung cancer, colorectal cancer and breast cancer.[lxiv] There is very poor evidence which suggests that Vitamin C is related to prostate cancer.

Dietary Vitamin C Consumption (mgs/day) and Smoking in Men

	SMOKING STATUS (cigs/day)				
Author	**Never**	**Former**	**Ever**	**Current**	*p*
Bolton-Smith	61.1			49.4	<0.001
Bolton-Smith	56	56-53		49	<0.001
Cade	55.2	52.3		47.7	0.05
Duthie	61	54		63	NS
Emmons	50		40		0.001
Fehily	57.5			44.7	<0.001
Jarvinen	80.9	80.7		1-14: 78.4; 15+: 77.8	0.04
Knekt	80.9			78.1	0.003
La Vecchia (gms/mth)	3.6	3.5		1-14: 3.5; 15+: 3.2	<0.05
McPhillips	155.8			175.3	<0.1
Margetts	81.7			1-19: 65.9; 20+: 62.5	0.01
Subar	124	111		95	<0.001

Carotene and Smoking

In a major study in America, involving twenty two thousand adults in all 48 contiguous states, carotene intake was negatively correlated with cigarette smoking.[lxv] Current smoking men ate 2,357 µgms of carotene, whereas never smoking men ate 2,441 gms.[lxvi] When smokers were divided into levels of daily consumption, a significant ($p < 0.01$) linear trend could be found for both men and women.[lxvii]

A more pronounced difference was found in a study in the United Kingdom, in which 2,197 subjects undertook a dietary survey.[lxviii] Non-smoking men ate a mean of 2,615 µg of carotene, and this was significantly different ($p < 0.05$) from light smokers (1,986 µg) and heavy smokers (2,233 µg).[lxix] For women, non-smokers ate 2,359 µgs of carotene per day, this was significantly higher than for heavy smokers (1,601) and light smokers (1,766 µgms).[lxx]

Larkin *et al* completed a study of women only, and found that smokers ate less carotene than non-smokers both on a nutrient value and on a nutrient density basis.[lxxi]

In contrast to these results, La Vecchia *et al* did not find a significant relationship between smoking and the consumption of ß-carotene in women; non-smoking women ate 148.2 IU per month — almost exactly the same as both light and heavy current smokers, who ate 151.1 IU and 150.8 IU respectively.[lxxii] Men did show very large variations between the various categories, with 140.7, 131.8, 132.8 and 114.1 for never, former, light and heavy smokers.[lxxiii]

A group of Finish authors also found a lack of an association between cigarette smoking and the consumption of -carotene in women (p = 0.14).[lxxiv] In men, never smokers and ex-smokers ate about the same amount of -carotene, but light smokers ate less, and heavier smokers ate even less (p < 0.01).[lxxv]

A study in South Wales has also shown a significant difference in ß-carotene consumption between smokers and non-smokers.[lxxvi] Non-smoking men ate 2,282 µg of ß-carotene, whereas the smoking group ate 1,703 µg/day; this difference was significant (p < 0.001).[lxxvii]

A study of nine thousand people in Scotland also showed a difference between the carotene consumption of smokers and non-smokers. This was more pronounced in men, where the differences between current smokers and non-smokers was significant on both a gms/day (p < 0.01) and density basis (p < 0.001).[lxxviii] For women, the differences were only significant on a density analysis.

A further study in Scotland has shown that these differences in dietary carotene are reflected in even more pronounced differences in serum levels of ß-carotene.[lxxix] That is, for any given level of dietary consumption of carotene, smokers have, on average, a lower level of serum carotene. Smokers had serum levels of carotene 30% lower than non-smokers.

This study is similar to that of Stryker *et al,* who found that smokers had much lower levels of serum beta-carotene than non-smokers, although their levels of dietary consumption were only marginally lower.[lxxx] In a review of these studies, Rimm and Colditz concluded that smoking and drinking may both decrease serum or plasma carotene levels.[lxxxi]

In summary, a wide variety of studies have shown an inverse correlation between cigarette smoking and dietary consumption of carotene. Those studies in which the association has not been found tend to be in women. There is evidence to suggest that there is even more significant difference in serum levels of carotene.

There is little material on former smokers, but what there is suggests that their -carotene level becomes like that of non-smokers.

The results of studies of carotene consumption and the risk of prostate cancer have been variable.

In a major review of the literature, van Poppel and Goldholun noted that of the five retrospective studies of the consumption of -carotene, three had demonstrated a statistically significant protective effect for prostate cancer, while the remaining two studies showed no effect.[lxxxii] In contrast, none of the prospective studies had demonstrated any significant effect when dietary consumption was assessed, and one small study (n = 32) assessing serum [carotenoids] had found a strong positive association.[lxxxiii]

Since that time a major case-control study and a major cohort study have also reported the absence of any protective effect from -carotene. Whittemore et al have reported that they failed to find any clear or consistent association between carotenes or foods high in carotenoid content.[lxxxiv] In the American Health Professional Follow Up Study, of the carotenoids, no protective association was found between carotenes (other than lycopene) and the risk of prostate cancer.[lxxxv]

Further, the result of a randomised, double-blind, placebo-controlled trial (followed up for five to eight years) demonstrated an increase in prostate cancer in the group that was given 20 mg of beta carotene per day.[lxxxvi]

To conclude, although there is significant evidence that the level of smoking varies with the level of dietary consumption of carotenoids, and that serum concentrations of carotenoids may be further altered by smoking, there is contradictory evidence that -carotene or other carotenoids (other than lycopene — see next section) have a relationship with prostate cancer.

		SMOKING STATUS (cigs/day)				
Author	Measure	Never	Not Current	Former	Current	*p*
Bolton-Smith (a)	µg/d of C		3526		2924	<0.05
Bolton-Smith (b)	µg/d of C	3400		2982-3400	3063	CvN <0.01
Cade	µg/d of ß	1071		909	728	0.002
Duthie	µg/d of C	2489		1867	2498	NS
Fehily	µg/d of C		2282		1703	<0.001
Jarvinen	µg/d of C	1830		1840	1-14: 1730; 15+: 1630	<0.01
Knekt	µg/d o ßf		1778		1617	<0.001
La Vecchia	x10³IU/mo of ß	140.7		131.8	1-14: 132.8; 15+: 114.1	<0.05
Subar	µg/d of C	2441		2557	2357	

Tomato Consumption and Smoking

A variety of human neoplasms have been suggested as related to tomato consumption. For example, Franceschi *et al* have found that tomato consumption is negatively correlated with the incidence of digestive-trait cancers.[lxxxvii] However, tomatoes are rarely reported as an individual food product; they can also be reported as both a fruit and a vegetable. This can confuse reports of their food group. In addition, many dietary assessments do not examine tomato products.

La Vecchia and his colleagues have examined the level of tomato consumption, and found that there existed a difference in tomato consumption between smokers and non-smokers.[lxxxviii] In this study of nearly eighteen hundred hospital patients, they found that male non-smokers ate an average of 3.7 servings of tomato per week; former smokers ate the same amount. Those who smoked less than 15 cigs per day ate 3.0 servings per week, while heavier smokers at 3.2 serves per week. The study is unclear about tomato products, such as tomato pastes and purees. The difference between smoking level and tomato consumption males were significant ($p < 0.05$ for trend), but not for women.

A moderately sized study of American hospital-based subjects has also noted slight and non-significant differences in tomato consumption between smokers and non-smokers.[lxxxix] There were differences of borderline significance between former smokers and smokers.

In a major study of British adults, tomato consumption was not specifically examined; "salad" consumption was examined, and this may be a proxy measure of tomato consumption. In the never smoker group, 51.3 per cent ate salad vegetables 6 or less times per week.[xc] Among the smokers, light smokers (1-9) were not significantly different from non-smokers (49.7 eating 6 or less per week), but moderate smokers were significantly different ($p < 0.001$), with 62.6% not eating 6 or more serves per week, and heavy smokers showing an even higher proportion of individuals eating salads regularly (69.2%, $p < 0.001$).[xci] The p for trend was significant for non-smokers versus smokers ($p < 0.001$), and between the groups of smokers ($p < 0.001$).[xcii]

In summary, very few studies have examined the relationship between smoking and tomato consumption. The few that have suggested that there may be a significant difference in tomato consumption between smokers and non-smokers.

A difficulty with seeing tomato consumption as a true confounder for smoking is that the component of tomato which has been postulated to be of importance in the aetiology of prostate cancer — lycopene — has been unusually demonstrated to not vary according to smoking status. In a small study of 96 individuals, lycopene levels did not vary with smoking status.[xciii] In plasma, buccal cells and skin tissue, the levels of lycopene for smokers and non-smokers were nearly identical. Further, the use of dietary supplements and the dietary consumption of lycopene did not significantly alter concentrations of lycopene. This could be reflected by some forms of lycopene consumption (such as tomato juice) having poor availability, compared with tomato sauce.[xciv]

Although the lack of an association between smoking and levels of lycopene is a serious difficulty with the suggestion that lycopene consumption confounds smoking, it is worthwhile to note that several studies have noted a negative correlation between tomato product consumption and prostate cancer risk. Most notably, the Health Professional Follow-Up, a prospective study of some fifty thousand men, has found a significantly negative association with tomato sauce (p for trend, 0.001), tomatoes (p for trend 0.03) and pizza (p for trend 0.03).[xcv] This result has some similarity with a prospective study of fourteen thousand Adventists, which also found that tomato consumption was negatively correlated with prostate cancer risk.[xcvi]

Interestingly, serum lycopene was also noted by Peng et al to vary significantly ($p = 0.02$) and increasingly with age ($r = -0.312$).[xcvii] This would correlate with the increasing of prostate cancer with increasing age.

This finding was not confirmed by a study in Hawaii, in which prostate cancer risk was not found to vary with tomato consumption.[xcviii] However, this study does not mention tomato products, which may be a dietary source with higher bioavailability.

To conclude, recent studies have suggested a link between dietary lycopenes and prostate cancer. Some reports have indicated smoking may negatively correlate with dietary lycopene, although a study of plasma and tissue concentrations have not suggested an association.

Tomato Consumption and Smoking in Men

		SMOKING STATUS (cigs/day)				
Author	**Measure**	**Never**	**Former**	**Current**		*p*
				1-20	21+	
Hebert	serves/month	17.3	18.0	15.6	15.3	
				1-14	15+	Trend
La Vecchia	portions/week	3.7	3.7	3.0	3.2	<0.05

Alcohol and Smoking

The relationship between alcohol and smoking has been extensively studied. One of the most consistently observed features of smokers is that they drink more alcohol than non-smokers. Further, in practically all studies the amount of alcohol consumed increases with the amount of smoking.

For example, Kato *et al,* in a major study of thirty three thousand Japanese individuals who responded to a dietary questionnaire, found very strong and positive correlations between smoking studies and alcohol consumption.[xcix] In males, using current smokers as the referent category, the relative risk for non-smokers for daily consumption of alcohol was 0.69 (95% CI = 0.65-0.74), $p < 0.01$.[c] For females, the relative risk was 0.29 (95% CI = 0.12-0.47), $p < 0.01$.[ci] In both genders, the consumption of sake and beer was significantly related to smoking status.

Berger and Wynder found that 7.7% of non-smokers drank more than 3.5 oz of alcohol per day.[cii] About 30% of smokers drank the same amount, whereas former smokers had rates that were intermediary — about 20% drank more than 3.5 ozs per day.[ciii]

Bolton-Smith found a mean daily alcohol consumption in current smokers of 27 gms per day, with never smokers consuming an average 16 gms per day, and former smokers having values between these extremes.[civ] An ANOVA analysis for covariance based on data adjusted for age and class, showed that this was significant ($p < 0.001$).[cv]

A much smaller study found non-significant differences in alcohol consumption, with current smokers consuming a mean of 10.8 gms per day, past smokers 9.1 gms per day and lifelong non-smokers drink 7.2 gms of alcohol per day.

A study in South Wales found a non-significant difference in alcohol consumption between smokers and non-smokers.cvi Although smokers consumed 20% more alcohol than non-smokers, this difference was not significant.[cvii]

A study in Holland found a number of clusters of dietary habits.[cviii] One such cluster, the "high in fat/high alcohol" group had a much higher proportion of smokers — 54% smoking, which compared with 42% for the entire study group, and 24% for the "moderate fat/low alcohol" group.[cix]

Larkin *et al,* in a study of 1,338 women, found that women who smoked drank significantly more alcohol and alcoholic beverages than never-smokers.[cx] Smokers drank twice as much ethanol as non-smokers, and this difference in consumption was significant.

Similarly, La Vecchia found that never smoking Italian males drank least, that light smokers drank more, and heavy smokers drank the most (p for trend < 0.05).[cxi] The same trend and significance for the trend was found for women, although they drank much less than did the Italian men.

In a moderately large study of bank retirees, which suffered from a low response rate, the same pattern of a positive correlation between smoking and alcohol consumption, was noted.[cxii] This was significant (p = 0.0001).

McPhillips et al found that non-smoking men drank about half of the level of alcohol as non-smokers (19.4 gms and 10.4 gms respectively), which was a significant difference, $p < 0.01$.[cxiii] For women, there was much less magnitude to the difference in consumption, and it was of borderline significance ($p < 0.01$).[cxiv]

A study of 2,197 subjects in Britain found a positive correlation between alcohol consumption and cigarette smoking.[cxv] Non-smoking men obtained a mean of 6.2% of their energy from alcohol, and this was significantly different to light (< 20/day) smokers (8.4%) and heavy smokers (8.9%).[cxvi] Women drank much less alcohol, and light smokers only were significantly different from non-smokers.

An Australian study of 451 women did show a significant variation in dietary alcohol between different categories of smokers.[cxvii] Never smokers drank an average of 4.6 gms of alcohol per day whereas, former smokers drank 6.1 gms, light smokers drank 8.1 gms/day and heavy smokers drank 10.7 gms per day. This was significant on a never, light, heavy basis ($p = 0.0002$), and on a never, past, current basis ($p = 0.001$).

Morabia and Wynder conducted a study of 7,860 individuals and found a strong and positive correlation between alcohol intake and cigarette smoking status.[cxviii] On both a percentage of non-consumers and an intake basis, male never smokers drank less than past smokers, who drank less than light smokers, who in turn drank less than moderate smokers, who drank less than heavy smokers.cxix The p value for trend (excluding ex-smokers) was 0.0001 for both analyses. Women showed similar correlations between smoking dose and alcohol dose.[cxx]

In France, the MONICA study also found a significant correlation between alcohol consumption and cigarette dose.[cxxi] Non-smokers drank an average of 29.8 gms/day; heavy smokers drank 49.1 gms/day, with light and moderate smokers being intermediate between these extremes. The trend was significant, $p = 0.001$.

Subar and Harlan analysing the National Health Interview Survey, found that for both men and women alcohol consumption was positively correlated with smoking dose.[cxxii] This trend was highly significant for both men and women, $p < 0.001$.[cxxiii]

A major British survey has also demonstrated an association between alcohol consumption and cigarette consumption.[cxxiv] Among never smokers, only 23.3% had moderate or higher alcohol consumption, but 42.0% of heavy smokers had moderate or higher levels of alcohol consumption.[cxxv] There was a significant trend for p ($p < 0.001$) for both all groups and within the various levels of smoking.[cxxvi]

The MRFIT study has also revealed a positive association between alcohol consumption and smoking status. In this study, smokers obtained 7.9% of their total calories from alcohol, while non-smokers obtained only 6.5% of their calories from alcohol.[cxxvii]

In summary, a very large number of studies have found positive correlations, between smoking dose and alcohol dose. A handful have found no significant association. None have found a negative association. From the literature there is little doubt that alcohol consumption covaries with cigarette consumption. The variation in alcohol dose between smoking level is large; it is likely to have biological effects. Quitters are like non-smokers, but seem to drink slightly more than them.

Several studies have examined the effect of alcohol consumption on the risk of prostate cancer. Hiatt *et al* was unable to demonstrate any rela-

tionship between alcohol and prostate cancer.[cxxvi-ii] (Interestingly, this study did show an increased risk among very heavy smokers).[cxxix]

Similarly, a case-control study conducted in Utah failed to note any association between alcohol consumption and risk for prostate cancer.[cxxx]

In the Lutheran Brotherhood Cohort Study, which is one of the studies which does demonstrate an increased risk of developing prostate cancer mortality in smokers, no increased risk was found for most categories of alcohol consumption; smoking adjusted risks for those who currently consume beer were marginally elevated -1.7 (95% CI = 1.0-2.9).[cxxxi]

A large cohort study from the Netherlands, in which some categories of smokers had increased risk, there was no increased risk associated with alcohol consumption.[cxxxii] The Odds Ratio for all drinkers was 1.36 (95% CI = 0-.84-2.22). These authors reviewed nearly twenty other studies of alcohol consumption and prostate cancer, and noted an absence of association in these studies.

As alcohol to consumption is apparently unrelated to prostate cancer, it should not be a factor that would confuse studies of smoking and prostate cancer.

Alcohol and Smoking in Men

		SMOKING STATUS (cigs/day)						
Author	Measure	Never	Not Current	Former	Current			p
Berger	%>3.5g/day	7.7%		1-10 19.0	10+ 20.7	1-10 29.9	11-20 28.3	21+ 33.3	—
Bolton-Smith	gms	16		19-23			27		CvN <0.001
Women Holly	% 3+ 12g		6				19		0.004
Women Holly	% 2+ liquor		5				22		0.001
Women Holly	% 1 glass wine		39				19		0.009
La Vecchia	drinks/day	3.1		3.6		1-14 3.7		15+ 4.5	<0.05
Margetts	gms/day		22.5			1-19 31.4		20+ 31.7	0.001
Morabia	ml/day	21.0		48.0		1-19 63.0	20-39 93.0	40+ 114.0	0.0001
Nuttens	gms/day		29.8			1-10 38.3	11-20 39.0	21+ 49.1	0.0001
Subar	serves/week	1.1		1.5			3.8		<0.001
Thornton	1.1-50/week	23.3				1-9 35.3	10-19 32.5	20+ 42.0	<0.001
Troisi	gms/day	5.53		8.33			11.93		CvN 0.0001
Whichelow	%>10	37.3		34.5		1-15 42.3		16+ 55.4	0.0001

Consumption of Meat and Smoking

A wide variety of studies have found a positive correlation between dietary meat and cigarette consumption. Berger and Wynder, for example, found that only 46.1% of non-smokers ate meat more frequently than once per day. Quitters were intermediate, between smokers and non-smokers, with those who gave up more than 10 years previously having about 50% who ate meat more than once per day; of those who gave up in the last 10 years, 55% ate meat more than once per day. When one turns to the current smokers, light smokers had levels of meat consumption similar to recent quitters, with 55% eating meat at least daily. Moderately heavy smokers ate more meat — about 57.2% eating meat daily. Heavy smokers had the highest level of consumption of meat, with 63% at least having meat daily.[cxxxiii]

La Vecchia *et al* did not measure dietary meat as such, but they did assess the consumption of a number of animal meat products.[cxxxiv] While the consumption of most meat products remained constant across the different smoking categories, the consumption of sausage and salami and canned meat was positively correlated with tobacco consumption in men, and poultry consumption was negatively related.[cxxxv] In women, fish consumption was positively associated with smoking, as was canned meat consumption.

In a study of 1,608 individuals in New England area of America, there was a highly significant increase in red meat consumption in men, but not in women. Men who smoked ate thirty per cent more red meat ($p < 0.01$).[cxxxvi]

A major American study, involving nearly eight thousand subjects, was divided by gender. Although females in this study did not markedly vary their meat consumption by smoking status, the men showed a pronounced and highly significant change in level of meat consumption by level of monthly meat consumption, with a P for trend of 0.001.[cxxxvii]

Margetts and Jackson studied in excess of two thousand subjects collected from England, Wales and Scotland; this group was then further divided into light smokers (less than 20 cigs/day) and heavy smokers (more than 20 cigs/day).[cxxxviii] In women, consumption of overall meat products was substantially less in non-smokers, and heavy smokers ate more meat products.[cxxxix] Male smokers ate significantly more sausages than non-smokers.

When Subar and Harlan reported in 1993, they were able to show that smokers had a higher daily consumption of red meat.[cxl] Looking at red meat intake, smokers consumed a mean of 4.2 servings per day, whilst never smokers ate 3.7 servings, and former smokers were lowest of all, consuming 3.2 serving of red meat per week.[cxli] There was a positive association for trend, which was significant for men ($p < 0.01$) and more as for women ($p < 0.001$).

These findings are similar to a study of 1,126 French men.[cxlii] In this study, on univariate analysis, there was a significant correlation between meat consumption and smoking, with non-smokers eating an average of 183.2 gms per day, whilst those who smoked more than 20 cigs/day ate 209.5 gms per day ($p = 0.0005$).[cxliii]

However, on multivariate analysis, the significance of the correlation between smoking and meat consumption disappeared.[cxliv] These authors noted that other studies have not controlled for the effect of alcohol, which correlates with both smoking and meat consumption.[cxlv]

Further, in a large study involving nine thousand respondents from the Health and Lifestyle Survey, no association was found with meat overall.[cxlvi] This study did not break down diet to constituent parts, but examined food types. Although there were some minor differences in consumption of red meat, these were not significant.[cxlvii] There was some significant differences in the consumption of poultry (the more you smoke, the less you eat) and processed meats (heavy smokers eat more).[cxlviii]

In summary, there have been a wide range of studies, most of which have shown differences in the level of meat consumption and the eating of meat products between smokers and non-smok-

ers. There is some doubt that alcohol has been completely controlled.

There have been several studies which have shown a positive correlation between consumption of meat and risk of prostate cancer. For example, Giovannucci *et al* demonstrated a relative risk of 2.64 (1.21-5.77) for highest quintile to lowest quintile of red meat consumption, with a *p* for trend across the quintiles of 0.02.[cxlix]

Le Marchand *et al* found evidence of significantly increased risks in "high-fat animal products", and some types of meat consumption, such as beef.[cl]

Far more equivocal was the result from Mills *et al,* who found that consumption of high fat animal products is not associated with increased risk, although the authors feel that their results showed a trend that could be compatible with increased risk.[cli]

In contrast to the above generally positive findings, there have been a number of negative studies. For example, in the Lutheran Brotherhood Cohort, none of the meat subtypes was associated with a significant increase in risk.[clii]

A variety of studies have shown a positive association between meat consumption, particularly red meat, and prostate cancer. This is felt by most to be associated with high fat rather than meat as such. However, smokers do eat more meat, and these two factors may confound each other.

Protein, Meat Products or Meat Consumption and Smoking in Men

		SMOKING STATUS (cigs/day)								
Author	**Measure**	**Never**	**Not Current**	**Former**		**Current**				*p*
Berger	%1 day meat	46.1		1-10 50.1	10+ 55.1	1-10 55.0	11-20 57.2	20+ 63.1		
Bolton-Smith	protein gms	85		94-86			90			CvN <0.001
Fehily	protein gms		83.1				82.4			NS
Hebert	meat/mth	19.1		21.6		1-20 19.4		20+ 23.4		NvH =0.003
McPhillips	all red meats/wk		4.7				6.0			<0.01
McPhillips	processed meats		4.1				5.2			<0.05
Margetts	meat product gm/wk		134.0			1-19 141.6		20+ 139.2		NS
Morabia	meat/mth	20.0		22.6		1-19 20.0	20-39 25.7	40+ 24.5		=0.0001
Nuttens	animal protein gm/d		66.5			1-10 64.1	11-20 67.5	20+ 70.2		NS
Subar	protein gm/d	76		67			80			
Subar	red meat/wk	3.7		3.2			4.2			(current only) <0.001
Whichelow	red meat % freqently	44.3		50.4		1-15 47.9		16+ 49.8		NS

Consumption of Fat and Smoking

Strickland *et al* studied dietary fats for 3,495 subjects in midwest American communities. They found "a significant and strong association between two risk factors [smoking and dietary fat] that are considered independent risk factors for a number of disease outcomes".[cliii] In this study, current smokers consumed an average of 95 gms of fat per day, whilst never smokers ate only 72 gms per day.[cliv]

Similarly, the Scottish Heart Health Study, found that current smokers had a mean daily consumption of 92 gms of fat per day, whereas new smokers had a daily average consumption of 85 gms of fat per day, with $p < 0.001$.[clv] The smokers had a slightly higher level of poly-unsaturated fat, with a mean of 11 gms/day compared to non-smokers of 12 gms per day, $p < 0.05$.[clvi]

This result is somewhat similar to a result by Cade and Margetts, who studied the diets of 2,340 English smokers and non-smokers. Although the differences were not statistically significant, the mean consumption of fat was 101.6 gms, with 102.7 gms per day for past smokers, and 104.8 gms/day for current smokers.c[clvii] There was a significant difference in the measure of the ratio of poly-unsaturated fat to total fat, with a mean ratio of 0.34; past smokers had an average ratio of 0.35. Using an ANOVA analysis, these differences were significant, with $p = 0.0004$.[clviii]

This pattern of marginal elevation in total dietary fat is similar to that found in a study of 1,338 women in America.[clix] There was found to be no significant difference in daily fat consumption, although smokers did have a slightly higher mean consumption of fat (68 gms cf 67 gms).[clx]

McPhillips *et al* found that total fat consumption was higher in both men who smoked and in women who smoked, with male smokers consuming about 79 gms of fat per day, whereas male non-smokers consumed an average of 71 gms of fat per day, this being significantly different ($p < 0.01$).[clxi] In some subsequent comparisons adjusting for the effect of age and total energy consumption, these differences lost statistical significance, but the consumption of saturated fat remained significantly different.[clxii]

In terms of total fat consumption, smokers were not dissimilar to non-smokers.[clxiii] Poly-unsaturated fat consumption was significantly higher in non-smokers, and the ratio of poly-unsaturated fat to saturated fat was significantly different between non-smokers and both categories of smoking.[clxiv]

In a study of Australian women, it was found that non-smokers, former smokers and current smokers all consumed a similar level of dietary fat, although the differences (more fat in smokers) approached statistical significance.[clxv] The poly-unsaturated/saturated ratio was markedly different by current smoking status (never, former, current), but did not show a significant dose-response relationship (never, light, heavy).[clxvi]

In the MONICA study in France, on univariate analysis, there was no significant difference in the consumption of fat and the various sub fractions of fat. On multivariate analysis, when multiple other variables where adjusted for, total fat was not significantly correlated, but poly-unsaturated fat was negatively correlated with smoking, although this difference was "trivial", and of "doubtful significance".[clxvii]

In a major study of more than eleven thousand subjects in the United States, little difference was found between the fat consumption of smokers, when they were compared to non-smokers.[clxviii] There were also only minor differences in the consumption of saturated fat. Looking at men only, current smokers consumed an average of 90 gms of total fat and 34 gms saturated fat per day, whereas never smokers consumed 79 gms fat and 30 gms per day of saturated fat.[clxix] Former smokers consumed even less saturated fat and fat than never smokers.[clxx]

A further study in England has found differences in fat consumption between smokers, never smokers and ex-smokers.[clxxi] A sample of

2,700 subjects was selected from Southampton, and in men the total fat consumption varied significantly by smoking status.[clxxii] Looking at total fat, smokers ate an average of 87.5 gms/day, former smokers 80.0 gms/day and never smokers 78.4 gms/day.[clxxiii] Looking at poly-unsaturated fat, smokers ate less than non-smokers, whereas with saturated fat the reverse pattern was found.[clxxiv] The ratio of poly-unsaturated to saturated fat was significantly different for the various smoking groups, with $p < 0.0001$ after adjustment for BMI, alcohol consumption and energy.[clxxv]

A Dutch study investigated the possibility that dietary habits that could be in favourable cluster, and that these clusters may have particular health behaviour.[clxxvi] Smoking discriminated between the clusters, with the "high fat-high alcohol" having 54% as current smokers the "high fat-low alcohol" having 39% smoking, and the "moderate fat-low alcohol" having only 24% as smokers.[clxxvii]

In summary, a wide variety of studies suggest that smokers have different levels of dietary fat although this is not universal. Most commonly, smokers have been found to have higher levels of total fat, although this finding has not been consistently noted. Stronger relationships exist between the quantity of saturated fat and the proportion of total dietary fat that is saturated. No studies have found that smokers have significantly lower levels of dietary fat, or that the quantity or relative amount of saturated fat is lower in smokers. Quitters seem like never-smokers, although possibly that they eat slightly more.

A variety of studies have suggested that variations in dietary fat of the types described above are associated with an increased risk of prostate cancer.

In a review of the published material, Prentice and Sheppard have noted that there is a degree of consistency to the published case-control studies relating to prostate cancer and dietary fat.[clxxviii] Of the seven studies that they note, only two do not show an increased risk, and both of these involve ethnic Japanese.[clxxix]

Since the publication of this review, there have been a small number of additional studies which have been published. These studies have generally been supportive of an association between high fat diet and prostate cancer. For example, in a report of the American Health Professional Follow-Up Study, total fat consumption increased risk, although a breakdown by fat type indicated that the α-linoleic acid component of the fat was the type most strongly associated with increased risk.[clxxx] In greater contrast was the finding of a case-control study in Canada, which found an inverse association saturated fat, and a lack of an association with total and mono-saturated fat, a finding which the authors themselves note runs counter to the results of previous studies, and to conventional thinking on the biological role of saturated fat in carcinogenesis.[clxxxi]

To conclude, there is evidence, albeit with some inconsistency, particularly as to strength of association, of a positive correlation between dietary fat and smoking. With some notable exceptions, dietary fat, and saturated dietary fat, seem to be also related to an increased risk of prostate cancer.

Exercise, Fitness and Cigarette Smoking

A variety of studies have examined the relationship between smoking and physical fitness and undertaking exercise.

For example, McPhillips *et al* in their study of sixteen hundred people in New England found that 60.5% of male non-smokers exercised regularly, whereas 46.4% of male smokers exercised to the same degree.[clxxxii] This difference was significant ($p < 0.01$).[clxxxiii] For women, both the significance and degree of difference between smokers and non-smokers was less ($p < 0.05$).[clxxxiv]

In a study of Norwegian army officers, smokers were found to exercise significantly less frequently than non-smokers.[clxxxv] For example, only 11% of smokers exercised three or more times per week, while 36% of non-smokers exercised at this level ($p < 0.01$, and, adjusted for age, < 0.01).[clxxxvi]

However, when people were asked if they obtained "enough" exercise (this being a self-defined level), smokers were of similar self-opinion to never smokers.[clxxxvii] Quitters thought that they did not get enough exercise when compared with non-smokers.[clxxxviii] Of course, self-reporting of individuals having "sufficient" exercise may not reflect that the level of exercise is actually appropriate.

A small study completed in America, also looked at the differences in the types of physical activity that men undertake.[clxxxix] This study, although small, is one of the few studies to look at the types of physical activity that individuals undertake. Smokers and non-smokers had no significant differences for most forms of physical activity, such as physical activity at work, but did differ significantly for physical activity from "leisure time, aerobics and sport".[cxc]

This finding has now been replicated by a major Australian study.[cxci] Using data from the National Heart Foundation Risk Factor Prevalence Survey involving 9,054 respondents, non-smoking was found to correlate with light-to-moderate physical activity. Using current smokers as referents, never smokers had an adjusted odds ratio for mild physical exercise of 1.32 (95% 1.61-1.51).[cxcii] Former smokers had higher odds ratio of 1.48 (95% CI = 1.28-1.72).[cxciii]

This work is consistent with a study of the US Navy, in which the physical fitness and exercise habits of 3,045 naval personnel were examined.cxciv This study found that while former smokers and never smokers had no significant differences in their levels of physical exercise, smokers expended for less energy per week ($p < 0.0001$), exercised less frequently ($p < 0.0001$) and had periods of exercise of lesser duration ($p < 0.0001$).[cxcv] When measures of actual physical fitness were examined, smokers performed worse on both the 1.5 mile run and the number of push-ups which could be completed in 2 minutes.[cxcvi] These changes in physical fitness remained significant after the effect of physical activity was controlled.

This result is similar to a wide range of results from America. In the Multiple Risk Factor Intervention Trial, for example, cigarette consumption was negatively correlated with total leisure-time physical activity.[cxcvii] This very large study of middle-aged men has an intensive questionnaire examination of physical activity, listing 18 major activity groups and 62 individual physical activities.[cxcviii] After dividing physical activity determinations into tertile, cigarette smoking was found to vary across the tertiles, both on a percentage that were smokers ($p < 0.001$ for trend) and mean number of cigarettes smoked ($p < 0.001$ for trend).[cxcix] Some of the differences were not great — the difference in average number of cigarettes/day was 2.2 or about 10%.[cc]

The finding of a significant difference in both physical activity and physical fitness in the U.S. Navy was replicated in a study in Norway, which found a significant negative association between smoking and fitness in both men and women ($p = 0.0021$ and 0.0384 respectively).[cci]

Finally, a West German study has demonstrated a correlation between serum thiocyanate and the duration of sporting activity.[ccii] Using this as a

measure of cigarette use, both males and females were found to have decreasing levels of thiocyanate with increasing duration of physical activity with a p for trend less than 0.001 in both genders.[cciii] For men, the highest thiocyanate levels were found in those who did no physical exercise (98.86 mgs/dl), which compared with significantly lower ($p < 0.001$) levels for those who performed more than 120 minutes of physical exercise.[cciv] Women had similar but lesser (both in terms of magnitude and significance) changes.

In summary, there is a wide variety of studies of various methodologies which indicate a negative correlation between levels of physical exercise and smoking. There is some evidence which suggests that most of this change relates to aerobic and leisure-time physical activity. It would appear that these changes are large enough to have some biological effects. There is little evidence that quitters have much difference to never smokers.

The biological significance of the observation that smokers have less physical activity (particularly recreational physical activity) is that a variety of workers have found decreasing levels of physical activity associated with increased risk of prostate cancer.

For example, in a large cohort study of 53,000 Norwegian men, Thune and Lund showed a protective effect of borderline significance for physical exercise.[ccv] For those who had an occupation which involved walking, there was a significant trend ($p < 0.03$) for the various grades of recreational activity.[ccvi] For those who had occupations that involved walking and had high levels of physical activity in their recreation, the relative risk was 0.45 (95% 0.20-1.01).[ccvii]

This finding is somewhat at variance to the findings of the Harvard Alumni Health Study. This study, in the first report, showed that a protective effect existed for those who were very active, expending more than 4,000 kcal/week.[ccviii] Although the results needed to be interpreted with some caution, as there was very small numbers in some of the categories, the very active had a rate ratio of 0.12 (95% CI = 0.02-0.89).[ccix] At the further report of this cohort, two different models of physical exercise were used.[ccx] In one model, the very physically active (> 4,000 kcal/week) were shown to have a protective effect, but because of the small number of incident cases, the confidence intervals are wide.ccxi Using an alternative model, moderate levels of physical exercise were found to be not only not protective — it nearly significantly increased risk.[ccxii]

In further contrast is a large case-control study from Hawaii, which demonstrated that prostate cancer risk was positively associated with physical activity, although the authors noted that this risk was "weak and inconsistent".[ccxiii]

In reviewing the literature, all three of these papers have noted the inconsistent nature of the epidemiological literature. Biologically plausible mechanisms have been noted to suggest increases or decreases from prostate cancer.

To conclude, smoking seems to vary with level of physical activity. Physical activity has been inconsistently related with prostate cancer, but is a potential confounder.

		SMOKING STATUS (cigs/day)				
Author	**Measure**	**Never**	**Not Current**	**Former**	**Current**	***p***
Conway	exercise/wk	9.2		8.9	7.4	<0.0001
Conway	mins exercise	25.4		24.4	22.9	<0.0001
Conway	kcals/wk	2311		2296	1764	<0.0001
Conway	situps/5min	56.0		55.0	489	<0.0001
Conway	run time	12.3		12.3	12.9	<0.0001
				10+ 1-9		
Flegal	% mod 5/wk	35.6		43.7 36.4	33.1	
Flegal	% high 3/wk	9.0		9.7 8.8	5.2	
Johnson	OR any physical light/mod activity	1.46 (1.29–1.65)		1.65 (1.44–1.89)	1.00	
Johnson	OR any physical light/mod activity	1.32 (1.16–1.51)		1.48 (1.28–1.72)	1.00	
					Amount of COHb	
Klesges	physical activity z score		2.3		2.0 2.0 2.2 2.4	NS
Klesges (b)	leisure-aerobic z score		-0.56		0.09	<0.005
Klesges (b)	leisure-anaerobic z score		0.23		-0.06	NS
Klesges (b)	work		0.42		-0.10	NS
Klesges (b)	anaerobic at work		0.06		-0.01	NS
Klesges (b)	moderate activity		-0.12		0.04	NS
					1-9 10+	
Simons	% inactive	1.0		0.9 (08-100)	1.2 1.5 (0.9-1.5) (1.3-1.8)	
					1-9 10-19 20+	
Thornton	? do you get enough exercise		46.4		45.9 44.9 46.5	NS
McPhillips	% reg exercise		46.4		62.5	0.01

Weight and Smoking

A wide variety of researchers have noted that weight is influenced by smoking status. A variety of measures of weight have been reported. In this review, I focus on Body Mass Index (BMI), and on males.

Smoking is generally associated with lower body weight, and smoking cessation is associated with increased body weight.[ccxiv] Flegal et al have recently reported that the additional increase in weight that was associated with smoking cessation was 4.4 kg for men and 5.0 kgs for women.

Berger and Wynder had previously shown a similar result, with 26.7% of non-smokers having a BMI > 28.4, compared with 24.5 per cent of those who smoked 1-10 cigs/day, 21.7 per cent of those who smoked 11-20 cigs/day and 26.7 of those who smoked more than 20 per day.[ccxv] Former smokers had about 30% who had a BMI > 28.4.

Similarly, a study of the dietary habits in three English towns found that the BMI of smokers is less than non-smokers, with a ratio of 26.1 for male non-smokers cf 25.6 for male smokers.[ccxvi] Measures for former smokers were similar to non-smokers.

In the Caerphilly Heart Disease Study, both smokers and non-smokers were found to have about the same height.[ccxvii] Smokers tended to have less weight, with the three highest mean measurements all found in the cigarette smoking groups, and the p for trend < 0.01.[ccxviii] There was also a relationship with BMI and smoking, with smokers having a lower BMI than that of non-smokers having a lower BMI than that of non-smokers, and a p for trend that was highly significant (p < 0.001).[ccxix]

In a large survey of Japanese, Kato demonstrated a relationship between BMI and smoking status.[ccxx] Using current smokers as the referent group, non-smokers males had a rate ratio (RR) of 1.22 (95% CI = 1.15-1.28).[ccxxi] In both males and females, former smokers had BMIs that were generally greater than non-smokers.[ccxxii]

A study by Strickland *et al,* using both a smoking questionnaire and serum thiocyanate also noted that smokers have a significantly (p < 0.05) lower BMI than non-smokers.[ccxxiii]

Klesges et al have also found that some categories of former smokers have higher body weights than current smokers.[ccxxiv] In men, there was a U shaped curve for current smokers, with the lowest BMI found in the moderate smokers.[ccxxv]

In an extension of this work, a subset of this population had carboxyheamoglobin (COHg) tested against BMI; COHg has an advantage over self-responded tobacco consumption, in that it is an objective measure of tobacco use.[ccxxvi] This research indicated that smoking in men was associated with a decreasing level of body mass.[ccxxvii]

A large study by Thornton *et al* has examined the percentage of a representative sample who were overweight or underweight.[ccxxviii] There was a significant (p < 0.001) negative correlation in the percentage who were overweight, and an equally significant but a difference of much stronger magnitude in the percentage of smokers who were underweight.[ccxxix]

A study involving several communities in New England also showed a strong correlation between cigarette smoking and BMI.[ccxxx] The association was stronger in men (p for difference < 0.01).[ccxxxi]

Not all studies have found a difference in BMI between smokers and non-smokers. For example, Margetts and Jackson found in a study which spanned England, Wales and Scotland that there were no significant differences in BMI.[ccxxxii] In this study, the difference in BMI did not pass standard tests of significance in either men or women.

In a major review of the literature published in 1990, the US Surgeon-General concluded that there was an average weight gain of about 2 kilograms after cessation from smoking cigarettes.[ccxxxiii] However, this is a mean figure — several of the studies noted that there was far greater weight gain in a sub-population.[ccxxxiv]

In a recent report, it was noted that between 1978 and 1990, there has been a significant

increase in the percentage of Americans who are overweight, and it was noted that the prevalence of smoking had also declined over the same period.[ccxxxv] As found in most other studies, there was a strong association between BMI and smoking; current smokers are thinner than never smokers and former smokers.[ccxxxvi] The authors of this study conclude that smoking cessation accounts for a small part of the increased obesity noted in the American population.[ccxxxvii]

This finding is in contrast to an Australian study over the same period.[ccxxxviii] This analysis found that BMI increased in all smoking groups between 1980 and 1989, and the authors concluded that the evidence did not support the hypothesis "that decreases in smoking rates in Australia have led to increases in overweight and obesity".

Interestingly, a study in Finland has found that at two different points in the 1980s, there was some evidence to suggest that the difference in BMI between smokers and non-smokers was decreasing, with an average BMI difference of 1.76 decreasing to 1.42 between 1982 and 1987.[ccxxxix] This was against a background of a substantial increase in body weight that had occurred in Finish men.ccxl This same trend towards increasing body weight has been noted.

In summary, there is a very large body of literature which points to a relationship between BMI and smoking. Smokers are usually thinner, and cessation results in weight gain. There are a few reports that suggest that this difference in weight may be beginning to diminish, along with a general trend towards increasing weight.

Some studies have also detected an increase risk for prostate cancer with increasing body weight or with BMI.

For example, Hayes et al demonstrated an OR of 1.5 for the highest to lowest quantile of BMI, but this was not significant (95% CI = 0.6-3.6).[ccxli] Weight immediately prior to the cancer developing was significantly associated with an increased risk, with an OR for the highest weight category of 2.6 (95% CI = 1.1-6.4), p for trend < 0.01).[ccxlii]

A retrospective cohort study of nearly thirty thousand men, half of whom had undergone vasectomy found that BMI was not significantly related to prostate cancer.[ccxliii] This finding was based on a relatively small number of cases of prostate cancer (n = 96). A larger study, based in Norway, with more than forty thousand men and 217 cases, did show that BMI increased significantly with age on age-adjusted univariate proportional analysis, with relative risk of 1.25 (95% = 1.05-1.50).[ccxliv]

In a 14-year follow-up of 1,776 men, BMI was found to be weakly associated with increased risk of prostate cancer. When cases alone were considered, no significant association was found, but when this was combined with those who died during the follow-up period, an association of borderline significance emerged.[ccxlv] On univariate analysis, the mean BMI for cases was 26.12 while for controls it was 25.62; this difference was of borderline significance, p = 0.05.ccxlvi On multivariate analysis the relative risk for BMI was 1.2 (90% rate 90% CI = 1.0-1.5), p = 0.06.[ccxlvii]

Le Marchand and his colleagues have noted a lack of an association between BMI and the development of prostate cancer. After following a cohort of twenty thousand Hawaiian men, no association was seen between weight and BMI.[ccxlviii]

Similarly, a cohort (n = 14,000) study of Adventist men followed for six years revealed 180 histologically confirmed prostate cancer cases, but there was no relationship between Quetelets index and prostate cancer.[ccxlix]

Finally, a study of mortality in 336,442 American men followed prospectively thirteen years by the American Cancer Society revealed a thirty per cent increase in mortality in the categories of greatest obesity.

In summary, the evidence that obesity, weight itself or BMI is positively related to prostate cancer is inconsistent and weak. It has tended to be larger studies which have detected risk; when detected, the risk appears small. It appears that the studies have not controlled for other possible confounders.

On the other hand, there is good evidence that smoking significantly affects weight and BMI, particularly in previous years.

BMI and Weight Measures and Smoking in Men

		SMOKING STATUS (cigs/day)								
Author	**Measure**	**Never**	**Not Current**	**Former**		**Current**				*p*
				1-9	10+	1-10	11-20	21+		
Berger	%28.4	26.7		29.8	30.1	24.5	21.7	26.7		—
Bolton-Smith	BMI	26.3		26.4-25.6			25.4			—
				1-9	10+					
Flegal	BMI	26.9		27.9	27.3		25.8			
				1-9	10+					
Flegal	% overweight	36.6		46.5	40.4		27.6			—
				1-9	10+					
Flegal	wgt gain in 10 years	1.49		5.28	2.39		1.82			—
						1-14	15-24	25+		
Fehily	BMI	26.4		26.6		25.8	25.3	25.6		<0.001
						<3	3	4.49	4.5-5.9 >6	
Klesges	BMI		25.5			25.1	24.7	24.4	24.4	—
McPhillips	BMI		27.1				25.5		<0.01	
							1-19	20		
Margetts	BMI		25.0				24.5	24.7		NS
Marti (82)	BMI		26.65				25.82			—
Marti (87)	BMI		26.97				26.45			—
Thompson	BMI	26.1		26.9			25.8			(inc. women) <0.0001
ALL PEOPLE										
						1-9	10-19	20+		
Thornton	% overweight	44.9				39.7	35.6	39.7		<0.001
Triosi	BMI	26.37		26.73			25.60			NS

A Tentative Hypothesis

One interesting feature of several of the studies that have found studied associations between smoking and prostate cancer is that former smokers often have higher risk than current smokers.

For example, in Mills' study of 14,000 Adventist men, current smokers had a relative risk of 0.49, but past smokers had a risk of 1.24.ccl In a larger case-control study in heavy former smokers and heavy current smokers were alone in having a significant elevation of risk, with 1.4 (1.0-1.9) and 1.5 (1.0-2.4) respectively.[ccli]

In the 26-year follow-up of the US veterans, former smokers were higher than non-smokers and light smokers.[ccliii] In the Lutheran Brotherhood Cohort Study, former smokers have significantly increased risk — 1.9 (1.1-3.3), which is higher than any category of current smokers.[ccliii] Ex-users of smokeless tobacco have a higher risk than occasional users, although lower regular users.ccliv

While several studies have shown this pattern, it has not be found consistently. For example, in a study of forty three thousand Californian men, heavy smoking resulted in elevated risk — 1.9 (1.2-3.1), but former smokers, light smokers and never smokers had similar risk.[cclv]

It should further be noted, as Hsing *et al* noted in their discussion, that a considerable portion of those classified as "current" smokers would have become "former" smokers after data collection.[cclvi]

Although the pattern is not entirely consistent, there appears to be a body of data which suggests that giving up smoking, once you have become a smoker, increases your risk of prostate cancer. Whilst this conclusion must be tentative, a logical explanation would be that obesity is truly causal, and the rebound weight gain of former smokers results in increased risk.

Conclusion

There are a very large number of factors that vary with smoking.

These factors themselves can result in increased risk to human disease, such as malignancy. Some factors, such as lower BMI, might be associated with reduced risk to cancer.

Thus, studies in which smoking correlates with increased rates of prostate cancer can be expected, without a true causal relationship existing.

For several postulated causes of prostate cancer, higher relative risks have been found more frequently than the lower relative risks found for smoking.

For some human diseases, such as prostate cancer, there is evidence that factors that covary with smoking may have a true causal role. Among these are dietary fibre, types of dietary fat, exercise, fruit and vegetable consumption, obesity and even lycopene consumption.

It is not until controls are established for these confounders that smoking may be seen as truly causal. However, where no possible confounders exist, it may be possible to establish a causal link with smoking. For example, there appears to be limited evidence that any of the above factors cause leukaemia.

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Cigarette Smoking: Quantity, Quality and Comparison

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Introduction

Differing acute and chronic modes of action have been postulated for the role of cigarette smoking in relation to vascular disease, respiratory disease and cancer. Cardiovascular disease is seen to be mediated through both acute hemodynamic and physiologic effects as well as chronic atherogenesis; while respiratory disease is mediated via irreversible effects on airways and alveoli as well as acute bronchial hyperreactivity. Initiation and/or promotion of cancer may occur due to a range of chemical constituents or their metabolites. Because of the range of modes of action and attendant variables the focus of this paper is confined to smoking and cancer.

The consumption of tobacco products is the most common cause of cancer death in western society and, according to the US Surgeon General, accounts for 30% of all cancer related deaths that occur annually in the United States of America (USDHHS, 1989). Smoking contributes to 45% of cancer deaths in men and 21.5% of cancer deaths in women (Shopland et al, 1991). Cohort studies support a total mortality rate from cancer which is twice as high in smokers and 3-4 times higher in heavy smokers when compared to lifetime nonsmokers.

RMA Requirements

The Australian repatriation system is unique in that there is recognition that the habit of smoking may be linked to eligible war, peacekeeping, hazardous or defence service, and thus compensation for smoking related illness and disease is possible, where a causal connection can be established. The standard of proof required differs from that required in usual civil jurisdictions (dealt with on day one).

The Repatriation Medical Authority (RMA) is required to assess not only the evidence for a causal relationship between smoking and a range of diseases — the minimal dose for such a relationship to occur needs to be specified as well. This is a concept which may seem unusual: for example cigarette smoking is recognized as a cause of bladder cancer and no 'threshold level' has been well documented in the literature. While there is the simplicity of a statement that causal exposure is equivalent to 'ever smoking' it seems rather remote that the consumption of one or two cigarettes at a time in the distant past would cause an individual's bladder cancer. The 1987 US National Health Interview Survey (Shopland et al, 1991) asked the question "have you smoked at least 100 cigarettes in your entire life?" Could or should such a minimal level be applied in the repatriation compensation arena, and if so, should it be entertained for all smoking related disease? If not, which data can provide a sound basis for definitions of minimal dose?

The path chosen to date, has been to consider available data and synthesise a quantitative exposure which is reasonable and practical to establish a minimum dose for causal association.

Cigarette Smoking: Quantity

1. Measurement of dose

How does one best express the evidence distilled from a range of studies so that the information may be applied within the bounds of our, or any, legislative requirements?

Published literature and research studies are of varied use as many describe associations between current/past/never smokers without reference to amount consumed. There are many possible confounders, such as alcohol and dietary consumption, other lifestyle activities and the more general propensity to risk taking behaviour which may impact on results describing an association between the habit of smoking, the number of cigarettes consumed per day and duration of smoking, and disease risk.

Current habit or consumption is often used both as a measure of current exposure and as a surrogate for longterm/lifetime use and those studies which consider overall dose often look at categories of pack-years or cigarette-years as an aggregate of exposure. It seems simplistic to state that smoking impact, particularly at the

margin, is a function of both daily dose and duration, but these two components are pivotal in the assessment of dose.

2. Temporal factors

There is evidence also of the importance of temporal factors, such as cigarette consumption at certain periods within the human timeline of exposure, as well as the recognized beneficial effect of cessation. This has been most researched and best demonstrated for lung cancer (USDHHS, 1990) where age at commencement between 15-20 years confers an increased risk compared to commencement after 25 years of age, while smoking cessation confers a significant decline in risk (IARC, 1990). Effects appear to vary between malignancies, such that early age at commencement is associated with elevated risk of lung cancer but such a strong association is not seen in pancreatic cancer, where the recency of the habit appears more important. In other malignancies, for example colorectal cancer, with historically less clear association with smoking, a long latency period has been supported by recent cohort reports (Giovannucci et al, 1994a, 1994b, Heineman et al, 1995). The mode of action in initiation and/or promotion of cancer at different sites by different chemical constituents within tobacco smoke or their metabolites may explain some of these differences.

3. Cessation

The significant and early decline in risk for most malignancies which is seen after smoking cessation is exemplified by the risk of lung cancer mortality. Table 1, from The Surgeon General's Report on the Health Benefits of Smoking Cessation (USDHHS, 1990) summarizes mortality ratios for lung cancer among former smokers as reported in five cohort studies: British physicians, US veterans, Japanese males, and the American Cancer Society (ACS) Cancer Prevention Studies (CPS) I and II. Compared with current smokers, former smokers abstinent for 15 years or more demonstrated an 80 to 90% reduction in risk in the British, US veteran and CPS-II cohorts. The risk, however, was still elevated in comparison to never smokers. The duration of the smoking history prior to cessation is important in the pattern of risk reduction in ex-smokers, with the decline in risk associated with stopping greater for smokers with shorter smoking histories (Lubin et al, 1984).

Every method of measurement and description has its limitations: is one cigarette per day for twenty years equivalent in biological effect to 20 cigarettes per day for one year? How will temporal factors in the smoking history effect any assessment? Will such variations in consumption produce differing effects in different organs? How will interaction with other exposures such as alcohol, asbestos or ionizing radiation affect these measures?

While the genetic mutation and cellular transformation to neoplasia may be a random event, there is strong evidence of a clear dose-response curve, particularly for lung cancer. It has been suggested that tobacco is a relatively weak carcinogen (Doll et al, 1990) even in lung cancer, as smoking needs to be continued for many years before much effect is observed. As well, the human organism is dynamic with repair mechanisms available against extrinsic and intrinsic assault.

In this paper I wish to explore smoking dose in relation to measures of total quantity, touch on some factors relevant to both quantity and quality of tobacco consumption; and through this process and some examples (and the conference discussion) I hope to arrive at a practical description of consumption which has validity both for the specific disorder and for comparison with other smoking related cancers.

Cigarette Smoking: Quality

There are perhaps obvious differences between the composition and consumption (and the consumers) of cigarettes, cigars and pipe tobacco; but even to narrow smoking to just cigarettes: Are all cigarettes equal? No they are not, but does this matter in practical terms for our assessment of risk?

Australia now produces the world's lightest cigarettes, containing 25-30% less tobacco than cigarettes in other countries (due to the levy of excise tax on tobacco products by weight rather than any perceived benefit to smokers' health). Between 1975 and 1992, a 20% decline in tobacco leaf consumption was reported in Australia, however the numbers of cigarettes sold during the same period increased from 25.8 billion to 33.2 billion. Since 1967, levels of tar and nicotine in popular brands of cigarettes have been monitored and marked diminution in levels of these substances has been noted over time. In 1969, almost 70% of the brands tested had a tar content over 19mg per cigarette and by 1991 85% contained 1-12 mg, with over one third containing 6 mg of tar or less (Winstanley et al, 1995). (Tar is the term used to describe all solid particles in cigarette smoke greater than 0.1 micrometers in size and some of the vapours and gases trapped within the particles. Tar content varies with filter design and composition, porous paper and type of tobacco used.)

There are cultural and temporal factors which affect differences in cigarette production as well as consumption (gender differences, age at commencement and smoking practice, for example, inhalation); use of black versus blond tobacco (Clavel et al, 1989; Malaveille et al, 1989; Vineis, 1991) and filtered versus hand rolled and unfiltered cigarettes. The introduction of low tar and low nicotine cigarettes also contributes to different chemical exposures.

For example, Siemiatycki et. al. (1995) point out some of the variations between Canadian, American and British cigarettes. Canadian cigarettes are predominantly Virginia flue cured tobacco grown in southern Ontario while American cigarettes are made with mixtures of bright, burley and oriental tobaccos. These differences impact on the chemical composition of tobacco smoke and, particularly, on the composition and distribution of several carcinogens in the vapour and particulate phases of tobacco smoke. On average Canadian cigarettes deliver approximately two-thirds less n'-nitrosonornicotine (NNN) and one-quarter less 4-(methylnitrosamino)-1-(3pyridyl)-1-butanone (NNK) than American cigarettes and about one-quarter more of both NNN and NNK than British cigarettes. Most sources describing the content of Australian cigarette smoke use North American base data.

Factors within consumer groups such as differing subgroup preferences, for example the French Canadians and Latinate groups in South America and Europe use more black tobacco (Vineis, 1991), and the differing chemical compositions may explain some of the disparities in the international comparison of relative risks for smoking related mortality (Vineis and Caparoso, 1995). While accepting a myriad of cultural and temporal differences in tobacco production and consumption, there remains a powerful international consistency when examining risk from cigarette consumption and, in light of this, the individual and obvious differences are subsumed into the overall best assessment of risk.

Cigarette smoking: Comparison

In the search for internal and external consistency, one option would be to simply specify doses for cancers with strong, medium, or weak association (based on relative risk) with the consumption of tobacco products.

Alternatively, when sufficient data exist, one might examine the dose and time relationships between smoking and disease incidence for each cancer site. Table 2 provides a simple comparison of the importance of these variables for certain of the malignancies currently recognized as smoking related in the RMA Statements of Principle. How to deal with cancers where insufficient data are available remains an important issue as, once smoking is accepted as causal, a level must be described for the purposes of the Statements of Principle, even in the absence of sufficient epidemiologic data.

Features of Current RMA Statements of Principle

The RMA examines individual diseases and exposures and Table 3 shows the smoking — dose comparison and current RMA minimum dose schedule for malignant neoplasms. The dif-

fering descriptions of dose are evidence of the evolution of this process, where possible, temporal features of the smoking habit have been included in the dose framework.

External consistency and comparison

The following summary table, Table 4, focuses on the malignancies with most data supportive of a causal association with cigarette smoking. The table is amalgamated from several sources, predominantly using the US CPS II mortality results and extrapolating these figures (Peto et al, 1992) to the available data on Australian mortality from these diseases.

There is support for a hierarchy of association between these tumors and cigarette smoking, which is consistent with international cohort studies reporting associations between disease specific mortality and smoking.

The figures in Table 5, confined for simplicity to male gender, are advanced by Perkin et al (1994) and modify those in Table 4 from the ACS CPS-II as they argue that smokers are differentially exposed to other important risk factors, such as alcohol, which have an independent or multiplicative effect on the risk of cancer, so that some of the apparent excess risk in smokers is consequential to alcohol consumption which is higher than in nonsmokers. Relative risk estimates for oral, oesophageal and laryngeal cancer in men were highlighted (Sterling et al, 1993, Perkin et al, 1994) as those most likely to be confounded by alcohol.

Other American studies suggest that the relative risk (RR) of oral cancer due to tobacco smoking, adjusted for alcohol and other confounders, is in the order of four to five in men, and at variance to the CPS figures (Blot, 1988; Marshall et al, 1992). Tuyns et al (1988), considering both alcohol and smoking, a described relative risk for laryngeal cancer of ten in moderate smokers, increasing to 20 in heavy smokers, risks consistent with the CPS findings. Two US studies reporting on the role of alcohol and cigarette smoking in oesophageal cancer (Yu et al, 1988; Wynder and Bross, 1961) suggest a relative risk in smokers of considerably less than ten, even in heavy smokers. This is consistent with RRs observed in non-US high-risk populations and in female and male populations. An estimate of 5.0 for both genders was suggested (Parkin et al, 1994). Table 5 incorporates these findings and provides altered relative risks.

Comparison

The summary tables of relative risk estimates support the following associations between tobacco smoking and certain cancers:

VERY STRONG:	LUNG
STRONG:	LARYNX/ORAL CAVITY/OESOPHAGUS
MEDIUM:	BLADDER/KIDNEY/PANCREAS
WEAK:	STOMACH/AML

where, for this comparison, a very strong association equates to a relative risk in current smokers of 15 or more, while a medium association is in the two-four range and weak implies a relative risk of two or less. It would seem appropriate in this structure that the stated 'minimum dose' required for acceptance of a cancer strongly associated with tobacco smoking should be less than that stated for a malignancy only moderately or weakly associated with smoking. With this hierarchy in place, the minimum dose for particular diseases may be considered, and compared with others in the hierarchy.

While recognizing the many factors relevant to both the quantity and quality of tobacco consumption, how can we arrive at a practical description of consumption which has validity both for the specific disorder and for comparison with other smoking related cancers, such as those outlined above?

An Example: Bladder Cancer

To exemplify this process, bladder cancer has been chosen as a malignancy which has a recognized association with smoking.

Tobacco consumption and bladder cancer

Almost 50% of all deaths from bladder cancer in males are attributable to cigarette smoking. In women the contribution to mortality from bladder cancer is lower, at about 37% (USDHHS, 1989). The incidence of bladder cancer has been increasing since 1950, while mortality from this disease has seen a steady decline in both males and females.

The association between smoking and bladder cancer has been observed in numerous case-control and cohort studies, some of which are included in Table 6. The published data are consistent with the risk of bladder cancer in current smokers being two-three times higher than that of nonsmokers for both male and female smokers (refer also to Tables 4 and 5) and that, while not uniform, (Burch et al, 1989) a detectable, though smaller risk may be conveyed by cigar and pipe smoking (Hartge et al, 1985; Slattery, 1988).

The gradient of risk for smoking and bladder cancer is evident for

number of cigarettes smoked per day

duration: number of years smoking

degree of inhalation (Clavel et al, 1989)

and may be influenced by use of black (air cured) versus blond (flue cured) tobacco (Clavel et al, 1989; Malaveille et al, 1989; Vineis, 1991) and unfitered versus filtered cigarettes (Wynder et al, 1988) (as explanation for international variations).

Specific issues for developing a Statement of Principles for bladder cancer relate to

1. the minimum dose of tobacco
2. effect of cessation of cigarettes

on the development of this malignancy.

A brief summary table, Table 6, has been used in the examination of studies relating to the minimum dose issue on file with the RMA secretariat. These studies represent a broad sample of those published in English which report cigarettes consumed per day in the analysis of cigarette consumption. As many reports do not provide useful data at the lower margin they are a fraction of all those relating to tobacco and bladder cancer.

1. Minimal dose: cigarettes per day (cpd) and total dose

There is reasonably consistent evidence supporting the smoking and bladder cancer link. The dose below which risk is not materially elevated is much less clearly defined (Table 6). Some early case-control studies (Howe, 1980 and Vineis, 1984) reported statistically significant results in those smoking less than 10 cigarettes per day. The results of other early work (Wynder and Goldsmith, 1977) as well as later, larger case-control studies by Augustine (1988) and Sorahan (1994) were not statistically significant at these levels. The recent report on the 26 year follow-up of the US Veteran's cohort (McLaughlin et al, 1995) does not report any significant increase in bladder cancer mortality at consumption below 10 cpd. Certainly, there are marked differences in subject populations and in exposures (inhalation and types of cigarettes smoked, eg the Latinate groups, with high black tobacco consumption, studied by Vineis), as well as methods and consideration of confounders, between several of these works which could affect the findings. Also, the early point ascertainment of smoking history in cohorts may influence findings, for example the US Veteran's study, where those smoking less than ten cigarettes per day (as reported in 1954 or 1957) may be more likely to stop smoking during the 26 year follow up period which would attenuate the associated estimate of risk.

Minimal dose may also be considered as a function of some total dose measure. The categories studied are generally simple and wide (eg 0, 20 pack-years or less and > 20 pack-years) with little interest in the lower spectrum of consumption. Several examinations of total dose required in smokers and ex-smokers have found no statistically significant elevation of risk in those with less than a 20 pack-year history (Augustine,

1988; and Harris et al, 1990) though Hartge (1987) in a large multicentre study conducted by the National Cancer Institute (NCI) found an increased risk with a 1-19 pack-year history (OR, 1.5; 95% CI, 1.2-1.7). This is a very broad range of tobacco consumption, as was that used in the Canadian case control study by Siemiatycki et al, (1995) which reports a risk of 1.6 (95% CI, 1.0-2.6) for those with a history of smoking for 1-500 cigarette/years.

A number of authors propose the involvement of cigarettes in two stages of tumorigenesis, ie initiation and promotion, and explain their findings within these models. This finds support in recent reviews of smoking and cancer (Vineis and Caparoso, 1994). This supports our proposition that a relatively small dose of cigarettes per day in current smokers is associated with increased risk of bladder cancer. This daily dose, however, may differ from the accumulated total dose required in ex-smokers. Cessation diminishes, but does not remove the risk of developing bladder cancer, and the decline in risk is less than that evident in the aerodigestive cancers (USDHHS, 1990).

2. Cessation

Cessation of smoking decreases the risk of bladder cancer compared with continuing smokers (McLaughlin, 1995). While some authors have found a marked decline approximating to that of nonsmokers after 20 years cessation (Wynder and Goldsmith, 1977; Sorahan et al, 1994), others have clearly documented an early sharp decline in risk but a residual risk which continues apparently indefinitely (Hartge, 1987, Vineis et al, 1984, Howe et al, 1980). Unlike the smoking related aerodigestive cancers, bladder cancer risk appears to stabilize after an early and rapid decline post smoking cessation (USDHHS, 1990). While the studies have some conflict in these results, given the potential of cigarette smoking to act in both the initiation and promotion of bladder cancer, no cessation period is seen to remove risk completely. This stance is supported by a number of cohort studies and by the more general findings of the Whitehall study (Ben-Shlomo et al, 1994) where exsmokers with a history of 20 pack-years or more consumption of cigarettes still experienced increased mortality from neoplasms even after 30 years cessation.

Bladder cancer current interpretation of minimal dose

Amalgamation of the findings in the literature suggests that a dose at least in the order of two to five pack-years would be required to convey a material risk for this neoplasm and no cessation period is evident. The factor currently is presented as:

REASONABLE HYPOTHESIS

> SMOKING AT LEAST TEN CIGARETTES PER DAY, OR THE EQUIVALENT THEREOF IN OTHER TOBACCO PRODUCTS, FOR AT LEAST FIVE YEARS BEFORE THE CLINICAL ONSET OF MALIGNANT NEOPLASM OF THE BLADDER

BALANCE OF PROBABILITIES

> SMOKING AT LEAST TEN CIGARETTES PER DAY, OR THE EQUIVALENT THEREOF IN OTHER TOBACCO PRODUCTS, FOR AT LEAST TEN YEARS BEFORE THE CLINICAL ONSET OF MALIGNANT NEOPLASM OF THE BLADDER

These levels are equivalent to two and a half and five pack years of exposure respectively. The above results for a 'medium risk' malignancy may be of use to compare with others of greater and lesser association.

Comparison

The hierarchy described previously as

VERY STRONG:	LUNG
STRONG:	LARYNX/ORAL CAVITY/OROPHARYNX
MEDIUM:	BLADDER/KIDNEY/PANCREAS
WEAK:	STOMACH/AML

would then lend itself to an empiric dose schedule for reasonable hypothesis cases along the following lines:

VERY STRONG:	ONE HALF PACK YEAR (current SOP for MN of the Lung)
STRONG:	
MEDIUM:	TWO AND A HALF TO FIVE PACK YEARS
WEAK:	MORE THAN FIVE PACK YEARS

Is such a schedule appropriate for this purpose and are the doses adequately described?

Accepting that a description of the quantity of smoking is required, and that a description of smoking per se is inadequate (this itself may be a source of fruitful discussion), some level of exposure or dose needs to be delineated. Should this minimum specified exposure level be similar across all malignancies as an absolute minimum, ie "x" cigarettes or regular smoking habit? As described earlier, the RMA deals with each disease individually and amalgamates available epidemiologic evidence to arrive at a factor describing tobacco consumption.

The hierarchy outlined above is one suggestion which has some comparative merit, though it does not consider individual variation in type of tobacco or style of consumption. The hierarchy would exist only to provide focus and other factors, such as recency (in SOP terms the effect of cessation) or latency, would need to be stated separately.

Should the dose be expressed as a total exposure in pack-years or in some other denomination? Certainly the pack itself has evolved from the early equation where one pack contained a standard 20 cigarettes; now in real terms in Australia it may encompass from 15 to 50 cigarettes per pack. Cigarette-years is a term gaining favour in recent publications: equating to the number of cigarettes per day multiplied by the number of years smoking at this level.

Alternately, a minimal daily consumption, ie cigarettes per day over a period of time, may be stated. The major difficulty with this form of description is that fluctuations in smoking habit, which can be accommodated in the total exposure descriptions, are not so easily dealt with in those where daily consumption is specified.

For the purposes of the RMA, and those attempting to use our product, a description of total dose which has both internal and external or comparative consistency would be the ideal. This would be in addition to the data compiled for individual diseases and would merely provide a base for comparison. For smoking related malignancies, Table 7 could be applied (example only).

Conclusion

The purpose of this paper has been to explore some of the variables to be considered in tobacco consumption and the measures of smoking. Very often the published epidemiologic data available support an association between an exposure and disease but the lower margin of exposure is not delineated. Here we attempt to arrive at a practical description of cigarette consumption which has validity both for the specific disorder and for comparison with other smoking related cancers. I hope that this also engenders a strong and healthy debate on smoking and dose, and some resolution to the descriptive difficulties we have experienced in the development of this process. Once this dose measurement has been considered, the issue of passive smoking in this arena needs to be addressed.

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Table 1.

Lung cancer mortality ratios among never, current, and former smokers by number of years since stopped smoking (relative to never smokers), prospective studies (USDHHS, 1990)

Reference	Population	Smoking status and yr since stopped smoking	Mortality ratios (N)	Comments
Doll and Peto (1976)	British male physicians	Never smokers	1.0 (7)	1951–61, 20yr followup: data on former smokers in summary form
		Current smokers	15.8 (123)	
		Former smokers		
		1-4	16.0 (15)	
		5-9	5.9 (12)	
		10-14	5.3 (9)	
		≥15	2.0 (7)	
Rogot and Murray (1980)	US veterans	Current smokers	11.3 (2,609)	1954–69, 16pyr followup
		Former smokers		
		1-4	18.8 (47)	
		5-9	7.7 (86)	
		10-14	4.7 (100)	
		15-19	4.8 (115)	
		≥20	2.1 (123)	
US DHHS (1982)	Japanese males	Current smokers	3.8	
		Former smokers		
		1-4	4.7	
		5-9	2.5	
		≥10	1.4	

Table 1 continued

Reference	Population	Smoking status and yr since stopped smoking	Mortality ratios (N)		Comments
Hammond (1966)	ACS CPS-I males		1-19 cig/day	≥20 cig/day	1959–63, 3.5-yr followup, men aged 50–69
		Never smokers	1.0 (32)	1.0 (32)	
		Current smokers	6.5 (8.0)	13.7 (351)	
		Former smokers			
		<1	7.2 (3)	29.1 (33)	
		1-4	4.6 (5)	12.0 (33)	
		5-9	1.0 (1)	7.2 (22)	
		≥10	0.4 (1)	1.1 (5)	
ACS (unpublished tabulations)	ACS CPS-II males		1-20 cig/day	≥21 cig/day	
		Never smokers	1.0 (81)	1.0 (81)	
		Current smokers	18.8 (608)	26.9 (551)	
		Former smokers			
		<1	26.7 (33)	50.7 (64)	
		1-2	22.4 (71)	33.2 (117)	
		3-5	16.5 (82)	20.9 (96)	
		6-10	8.7 (80)	15.0 (106)	
		11-15	6.0 (69)	12.6 (95)	
		≥16	3.1 (144)	5.5 (112)	

Table 2.

Comparison of importance of smoking variables for certain malignancies currently recognized as smoking related in Statement of Principles (SOPs)

Type of cancer	Age at start	Duration	Number of cigarettes	Recency	Comments
Lung	+++	+++	+++	+++	early commencement, total dose, and marked decline with cessation
Larynx	-	+++	+++	++	total dose and decline with cessation. multiplicative effect with alcohol consumption
Oral cavity or hypopharynx	-	+++	+++	++	total dose and decline with cessation. multiplicative effect with alcohol consumption
Oesophagus	-	+++	+++	++	total dose and decline with cessation. multiplicative effect with alcohol consumption
Bladder	-	+++	+++	++	total dose, less effect of cessation compared with aerodigestive cancers
Pancreas	-	++	++	+++	recent (previous two decades) duration and consumption
Kidney	-	++	++	++	duration, consumption and recency of habit
AML	-	++	++	++	duration, consumption and recency of habit
Rectum	-	++	++	-	consumption of cigarettes in early adulthood, number and duration, long latency 30+ yrs
Colon	-	++	++	-	consumption of cigarettes in early adulthood, number and duration, long latency 30+ yrs

NB. Both Duration and Number of cigarettes in this table relate to potent dose-response effects

Table 3.

SMOKING-DOSE COMPARISON TABLE
Current RMA minimum dose schedule for malignant neoplasms

Cancer Type	Reasonable Hypotehsis Dose	Balance of Probabilities Dose
LUNG	(a) in relation to any of the following kinds of malignant neoplasia of the lung: (i) squamous cell carcinoma of the lung; or (ii) oat cell carcinoma of the lung; or (iii) small cell carcinoma of the lung; or (iv) malignant neoplasm of undetermined histology; or (v) large cell carcinoma of the lung, smoking cigarettes or other tobacco products for at least one half of a pack-year before the clinical onset of malignant neoplasm of the lung; or (b) in relation to adenocarcinoma of the lung, smoking cigarettes or other tobacco products for at least three pack-years before the clinical onset of malignant neoplasm of the lung; or (c) in relation to a malignant neoplasm of the lung other than typical carcinoid tumour of the lung, immersion in an atmosphere with a visible tobacco smoke haze in an enclosed space for at least 20 hours per week for at least five years, at a time or times before the clinical onset of malignant neoplasm of the lung.	(a) in relation to any of the following kinds of malignant neoplasia of the lung: (i) squamous cell carcinoma of the lung; or (ii) oat cell carcinoma of the lung; or (iii) small cell carcinoma of the lung; or (iv) malignant neoplasm of undetermined histology; or (v) large cell carcinoma of the lung, smoking cigarettes or other tobacco products for at least one half of a pack-year before the clinical onset of malignant neoplasm of the lung; or (b) in relation to adenocarcinoma of the lung, smoking cigarettes or other tobacco products for at least three pack-years before the clinical onset of malignant neoplasm of the lung; or (c) in relation to a malignant neoplasm of the lung other than typical carcinoid tumour of the lung, immersion in an atmosphere with a visible tobacco smoke haze in an enclosed space for at least 20 hours per week for at least ten years, at a time or times before the clinical onset of malignant neoplasm of the lung.
ORAL CAVITY OR HYPO-PHARYNX	(a) smoking : (i) between five and ten cigarettes per day or the equivalent thereof in other tobacco products, for at least ten years, before the clinical onset of malignant neoplasm of the oral cavity and where smoking has ceased, the clinical onset has occurred within 15 years of cessation; or (ii) smoking more than ten cigarettes per day or the equivalent thereof in other tobacco products, for at least five years, before the clinical onset of malignant neoplasm of the oral cavity and where smoking has ceased, the clinical onset has occurred within 15 years of cessation; or (b) the regular oral use of smokeless tobacco and similar products for at least five years before the clinical onset of malignant neoplasm of the oral cavity and, where oral use of these products has ceased, the clinical onset has occurred within 15 years of cessation;	(a) smoking ten or more cigarettes per day or the equivalent thereof in other tobacco products, for at least ten years, before the clinical onset of malignant neoplasm of the oral cavity and, where smoking has ceased, the clinical onset has occurred within ten years of cessation; or (b) the regular oral use of smokeless tobacco and similar products for at least ten years before the clinical onset of malignant neoplasm of the oral cavity and, where oral use of these products has ceased, the clinical onset has occurred within ten years of cessation;

Cancer Type	Reasonable Hypotehsis Dose	Balance of Probabilities Dose
LARYNX	(a) smoking three pack years of tobacco products before the clinical onset (b) being exposed to an atmosphere with a visible tobacco smoke haze in an enclosed space for at least 20 hours per week for at least seven years, at a time or times prior to the clinical onset	(a) smoking five pack years of tobacco products, where such smoking had not ceased more than 20 years before the clinical onset (b) being exposed to an atmosphere with a visible tobacco smoke haze in an enclosed space for at least 20 hours per week for at least 12 years, at a time or times prior to the clinical onset
OESOPHAGUS	(a) for squamous cell carcinoma of the oesophagus only: (i) smoking five to ten cigarettes per day or the equivalent thereof in other tobacco products, for at least ten years, before the clinical onset of malignant neoplasm of the oesophagus; or (ii) smoking more than ten cigarettes per day or the equivalent thereof in other tobacco products, for at least five years, before the clinical onset of malignant neoplasm of the oesophagus; or (b) for adenocarcinoma of the oesophagus only: (i) smoking ten to twenty cigarettes per day or the equivalent thereof in other tobacco products, for at least ten years, before the clinical onset of malignant neoplasm of the oesophagus; or (ii) smoking more than twenty cigarettes per day or the equivalent thereof in other tobacco products, for at least five years, before the clinical onset of malignant neoplasm of the oesophagus;	(a) for squamous cell carcinoma of the oesophagus only: (i) smoking ten or more cigarettes per day or the equivalent thereof in other tobacco products, for at least ten years, before the clinical onset of malignant neoplasm of the oesophagus;
MN OF THE BLADDER	smoking at least ten cigarettes per day, or the equivalent thereof in other tobacco products, for at least five years before the clinical onset of malignant neoplasm of the bladder;	smoking at least ten cigarettes per day, or the equivalent thereof in other tobacco products, for at least ten years before the clinical onset of malignant neoplasm of the bladder;
MN OF THE PANCREAS	smoking ten pack-years, all or part of which were smoked within the 20 years before the clinical onset of malignant neoplasm of the pancreas;	NONE
ADENOCARCINOMA OF THE KIDNEY	smoking at least 20 cigarettes per day for at least 15 years before the clinical onset of adenocarcinoma of the kidney and, where smoking has ceased, the clinical onset has occurred within 10 years of cessation;	smoking at least 20 cigarettes per day for at least 20 years before the clinical onset of adenocarcinoma of the kidney and, where smoking has ceased, the clinical onset has occurred within 10 years of cessation;
STOMACH	smoking at least 15 pack-years, more than five years before the clinical onset of malignant neoplasm of the stomach;	NONE

Cancer Type	Reasonable Hypotehsis Dose	Balance of Probabilities Dose
ACUTE MYELOID LEUKAEMIA	smoking 15 pack-years before the clinical onset of acute myeloid leukaemia, and at least some of that smoking being within the ten years before the clinical onset of acute myeloid leukaemia;	NONE
CHRONIC MYELOID LEUKAEMIA	smoking 15 pack years of cigarettes before the clinical onset of chronic myeloid leukaemia, with at least some of that smoking being within the 10 years before the clinical onset of chronic myeloid leukaemia;..	NONE
MN OF THE LIVER	smoking at least five cigarettes per day for at least 20 years before the clinical onset of malignant neoplasm of the liver;	smoking at least ten cigarettes per day for at least 30 years before the clinical onset of malignant neoplasm of the liver;
PENIS	smoking at least 10 cigarettes per day, or the equivalent thereof in other tobacco products, for at least 10 years before the clinical onset of malignant neoplasm of the penis;	smoking at least 20 cigarettes per day, or the equivalent thereof in other tobacco products, for at least 10 years before the clinical onset of malignant neoplasm of the penis;
COLON	smoking cigarettes or other tobacco products for at least 15 pack years, all or part of which were smoked 30 years or more before the clinical onset of malignant neoplasm of the colon;	smoking cigarettes or other tobacco products for at least 30 pack years, all or part of which were smoked 30 years or more before the clinical onset of malignant neoplasm of the colon;
RECTUM	smoking cigarettes or other tobacco products for at least 10 pack years, all or part of which were smoked 25 years or more before the clinical onset of malignant neoplasm of the rectum;	smoking cigarettes or other tobacco products for at least 15 pack years, all or part of which were smoked 30 years or more before the clinical onset of malignant neoplasm of the rectum;

There are some perceived inconsistencies within these factors, particularly when comparison between malignancies is undertaken. For this reason the external consistency of findings needs particular examination.

Table 4.

SUMMARY OF SMOKING AND CANCER MORTALITY

Type of Cancer	Gender	Relative Risk Amongst Current and Former Smokers data from CPS II[a]		Annual Mortality Attributable to Current or Past Smoking in USA		Annual Mortality Attributable to Current or Past Smoking in Australia[d]
		Current	Former	Percent[a]	Number[c]	Number[d]
Lung[a]	M	22.4	9.4	90%	85900	4000
	F	11.9	4.7	79%	49000	1300
Larynx[a]	M	10.5	5.2	81%	2600	200
	F	17.8	11.9	87%	800	20
Oral Cavity[a]	M	27.5	8.8	92%	5000	430
	F	5.6	2.9	61%	1800	110
Oesophagus[a]	M	7.6	5.8	78%	6400	390
	F	10.3	3.2	75%	2000	170
Bladder[a]	M	2.9	1.9	47%	3500	230
	F	2.6	1.9	37%	1400	90
Pancreas[a]	M	2.1	1.1	29%	3800	210
	F	2.3	1.8	34%	4700	220
Kidney[a]	M	3.0	2.0	48%	3400	-
	F	1.4	1.2	12%	600	-
Stomach[b]	M	1.5	?	17%	1500	130
	F	1.5	?	25%	1800	120
AML[b]	M	2.0	?	20%	900	-
	F	2.0	?	20%	800	-

(a) Shopland DR, Eyre HJ and Pachacek TF.(1991) Smoking attributable cancer mortality in 1991 JNCI vol 83 pp 1142-1148

(b) Newcombe & Carbone (1992). Cigarette Smoking and Cancer. Medical Clinics of Nth America, 76:2 pp 305 Ñ 331.

(c) Wingo et al (1995). Cancer Statistics 1995. Ca 45: pp 8-30.

Table 5.

SUMMARY OF SMOKING AND CANCER MORTALITY (2)

Type of Cancer	Relative Risk Amongst Current Male Smokers — data from CPS II[a] corrected after[c]
Lung	22.4
Larynx	**10.5**
Oral Cavity	**4.5**
Oesophagus	**5.0**
Bladder	2.9
Pancreas	2.1
Kidney	3.0
Stomach	1.5
AML[b]	2.0

(a) Shopland DR, Eyre HJ and Pachacek TF.(1991) Smoking attributable cancer mortality in 1991 JNCI vol 83 pp 1142-1148

(b) Newcombe & Carbone (1992). Cigarette Smoking and Cancer. Medical Clinics of Nth America, 76:2 pp 305 — 331.

(c) Parkin DM et al (1994) At least one on seven cases of cancer is caused by smoking. Global estimates for 1985. Int J Cancer 59 pp494-504

TABLE 6

CASE-CONTROL AND COHORT STUDIES REPORTING TOWARD THE LOWER DOSE MARGIN FOR CIGARETTE CONSUMPTION.

Case-Control Studies	Cigarettes per day	RR	95% CI/ No of cases
Wynder and Goldsmith, 1977	0	1.0	—
	1-10	1.4	(0.9-2.2)
	11-20	2.4	(1.7-3.3)
	21-30	2.7	(1.8-4.1)
	31-40	2.3	(1.5-3.4)
	41+	3.3	(2.1-5.3)
Howe et al, 1980	0	1.0	—
	<10	2.6	(1.7-4.4)
	10-20	3.8	(2.6-6.0)
	>20	5.1	(3.5-8.6)
Moller-Jensen et al, 1983	0	1.0	—
	1-14	4.2	82
	15-24	4.9	112
	25+	4.3	54
Vineis et al, 1984	0	1.0	—
	1-14	4.0	(2.4-6.8)
	15-29	5.7	(3.5-9.3)
	30+	10.1	(4.9-20.7)
Morrison et al, 1984			
Boston current smokers	0	1.0	53
	<20	1.4	25
	20-39	3.2	91
	40+	4.7	67
Manchester current smokers	0	1.0	28
	<20	1.9	85
	20-39	3.2	104
	40+	4.0	31
Nagoya current smokers	0	1.0	24
	<20	1.6	47
	20-39	2.1	92
	40+	2.8	33
Hartge et al, 1987	0	1.0	—
	<20	1.8	(1.6-2.0)
	20-39	2.6	(2.3-2.9)
	40+	2.6	(2.2-3.0)
Iscovich et al, 1987	0	1.00	8
	1-14	3.57	12
	15-29	9.55	21
	30+	27.5	21

TABLE 6 continued

Case-Control Studies	Cigarettes per day	RR	95% CI/ No of cases
Augustine et al,1988	0	1.00 (adj OR)	—
	1-10	1.56	(0.92-2.63)
	11-20	2.14	(1.34-3.43)
	21-30	2.59	(1.57-4.27)
	31+	2.43	(1.50-3.92)
Clavel et al, 1989	0	1.00	—
	<20	3.26	(2.10-5.08)
	20-39	4.41	(2.81-6.92)
	40+	6.92	(3.71-12.91)
Anton-Culver et al, 1993	0	1.00	—
	<20	1.04	(0.62-1.71)
	20-39	3.26	(2.29-4.65)
	40+	6.84	(4.67-10.03)
Sorahan et al, 1994	0	1.00	—
	<10	0.98	(0.66-1.46)
	about 10	1.73	(1.26-2.37)
	about 20	1.89	(1.44-2.49)
	about 30	1.42	(0.99-2.04)
	40 or more	1.35	(0.88-2.05)
Siemiatycki et al, 1995	0	1.00	—
	1-500 cig/years	1.6	(1.0-2.6)
	501-1000	2.5	(1.6-3.9)
	1001-1500	3.3	(2.1-5.2)
	1501+	2.5	(1.5-4.2)

TABLE 6 continued

Cohort Studies	Cigarettes per day cpd	RR	95% CI/ No of cases
Hammond and Horn, 1958	0	1.0	38
	<10	2.0	14
	10-20	2.0	42
	>20	3.4	41
Kahn, 1966	0	1.0	52
	<10	1.0	11
	10-20	2.3	71
	21-39	3.1	51
	40+	3.0	9
Doll and Peto, 1976	0	1.0	(total deaths 80)
	1-14	2.2	
	15-25	2.2	
	25+	1.4	
Chyou et al, 1993	0 pack years	1.00	—
	>0-30	2.12	(1.19-3.79)
	>30	2.30	(1.30-4.06)
McLaughlin et al, 1995	0	1.0	—
	1-9	1.1	(0.8-1.5)
	10-20	2.3	(1.9-2.7)
	21-39	2.7	(2.2-3.3)
	40+	2.2	(1.5-3.3)

Table 7.

Example for a hierarchy of tobacco dose

TOBACCO DOSE	CANCER TYPE
ONE HALF PACK YEAR	LUNG
ONE TO TWO PACK YEARS	LARYNX/ORAL CAVITY/ OESOPHAGUS
TWO AND ONE HALF TO FIVE PACK YEARS	BLADDER/ KIDNEY/ PANCREAS
MORE THAN FIVE PACK YEARS	STOMACH/AML

Questions for Group Discussion

Cigarette Smoking Dose

Another issue of relevance to the question of prostate cancer and cigarette smoking is how to assess smoking dose. This is a problem we have faced in most of our smoking/disease relationships. While we are discussing the dose issue in the context of prostate cancer, we would much appreciate the opportunity to discuss the broader issue of how to define and express cigarette smoking dose as it leads to various outcomes.

The questions we would like to discuss include:

1. Should smoking risk be assessed according to:
   - pack/years
   - total number of cigarettes smoked
   - light/moderate/heavy without specifying numbers
   - amount smoked at different time periods
   - any smoking without specifying dose.
2. In view of what we know about biology, is there likely to be a difference in regard to dose/time relationships between cancers and other types of outcome from smoking?

SECOND QUESTION

How should tobacco dose be assessed?

What is a critical exposure?

- What are the most common confounding variables in smoking studies?
- How to use this information to estimate risk, and for compensation cases?

Report back and discussion of group statements on smoking dose.

PROF DONALD: I think the first task for this morning is probably the report back from yesterday afternoon's break out groups. Group 1? Have we got a group 1 representative?

Group 1

PROF KALDOR: I do not think we solved those two problems so we are looking to the other groups to see whether there is inspiration about what constitutes a minimum duration of smoking to make consideration of smoking-related disease risk. Another thought that occurred to me, and this is not something that came from the group but occurred to me, the idea of asking people whether or not they were regular smokers in some sense at any point in their lives and taking it from there, because you do have this perennial problem of the person who smoked a few cigarettes here and there but never consider themselves to be a regular smoker, and I do not know whether that is routinely asked of veterans about whether they are regular smokers. This is a question of terminology, I guess.

Then we talked about the index (Refer Appendix C) that we want to use as, I guess, the indicator of whether a significant risk has occurred and we worked on the basis of this index that was the likelihood that exposure caused the disease given the person's smoking history, and that really comes down to, in formal terms, the relative risk minus one, divided by the relative risk. Now, that sounds a bit technical, but if you look at the example, it is very straightforward. Just for example, if we take a relative risk of 1.3, the relative risk of 1.3 which is the one we talk about which might be the relative risk for prostate cancer if it happened to be caused by smoking, that would give you that index of 0.3 over 1.3. In other words, the extra bit of risk you get from the smoking is the proportion 0.3 to 1.3, or about a little bit less than

25%. So in other words, for that person, if a person smoked and got prostate cancer there is about a 25% chance or 20% chance that their smoking was the cause of the prostate cancer.

Then our group recommended that a mechanism be established for calculating this relative risk under a simple model for a given dose. They were based essentially on smoking intensity and I guess we were following the suggestions made in the discussion yesterday that most things can be captured by smoking intensity. We did also recognise that for certain forms of cancer only, and especially lung cancer, but possibly bladder cancer, you could take into account the number of years stopped. And then we suggested in the spirit of, I guess, conservatism, that in the absence of data on knowing what the effect of stopping was, you could assume the risk was as if smoking had not stopped. In other words, if someone is a regular smoker for a certain number of years, we assume that the risk is the same as if they had been that sort of smoker for their whole lifetime. So that would give you a higher risk than they already had, but it was in the spirit of the principle of generosity, I guess. So that is I guess the end of the overhead.

So then it would be up to the powers-that-be to take this information and make a decision as to what level of this index, this index here, is a compensatable level, and this is of course assuming that there is no sliding scale or, in other words, a scale that gives differing degrees according to the probability that the disease was actually caused by the exposure. If you did not adopt that model, you would have to adopt the model that said at a certain level of probability the compensation comes in 100% and below that level it is zero. Obviously, it is going to be a bit tricky if you are right around that level, but we of course did not propose to set that level. I think that is the level that it has to be set from the political and negotiated arena rather than a scientific arena. All we could offer was the mechanism by which this index could be derived in a fairly simple and imperfect, but I guess negotiated mutually agreed way for the diseases under consideration. Thanks.

PROF DONALD: Thank you, John. Comments, questions? No comments, no questions, right. Richard?

PROF DOLL: I was surprised by the statement, as I understood the statement, that there was not evidence produced on giving up smoking for other types of cancer other than bladder and lung. I thought there was evidence for a great range of cancers and it would be more reasonable to make the proportional reduction for other cancers as for bladder and lung with time since stopped.

PROF KALDOR: This might partly reflect my incomplete reading of the literature. My awareness is of the very big literature in stopping in relation to lung, and of somewhat smaller literature in relation to bladder, and a very limited amount of data in relation to other cancers. I certainly was not suggesting that it did not reduce as a risk. I was concerned that there might be much more controversy about the coefficients of reduction and, therefore, under the principle of conservatism you might choose to adopt a model that either did not reduce or, I guess you could borrow the coefficient from lung and bladder in some way. You certainly would not claim it did not reduce, but you might accept that the data was insufficient to give a good estimation.

DR BORDUJENKO: Would you consider duration of smoking and intensity of smoking prior to cessation in that rubric?

PROF KALDOR: Well, I think the group felt that most of the impact of smoking would probably be captured by intensity and in time since stopping, if those two are built into the model and, as discussed yesterday, duration does get very confounded with age effects. I think one of the principles here was to try to get a measure of simplicity and once again for lung cancer you could probably go some way down this track in the modelling, but for other cancers the data would not really be there.

Group 2

DR HOAR ZAHM: Actually it is very reassuring to see that what we came up with was very similar to what the first group had. We thought also that smoking risks should be assessed according to the attributable risk percent among the exposed, which is the same index that John just described. We did a little bit of excluding. We said first of all, you know, we defined a never smoker as someone who had either smoked less than 100 cigarettes over their lifetime or less than one cigarette per day for a year, and then we said that we would exclude smokers if they had only started within one year of diagnosis which was mentioned yesterday by Sir Richard. And then we excluded if people had quit more than twice the time over which the relative risk was known to return to unity, if such data were available. So, we were just a little more generic than picking two diseases, but realising that it is not available for many cancers. And then the dose triggers would be measured by, as I mentioned, attributable risk among the exposed. We were told that the RMA usually has two different cut-off points for compensation for veterans who have been in combat and those who have not.

So, we thought that that could easily be built into this kind of a system. And as an example (Refer Appendix D), here we have the data for bladder cancer from the study by Tricia Hartge looking at cigarettes per day, and you can see the attributable risk per cent exposed in the far column. We also got the data for lung cancer. And you can see that at a much lower level of smoking, the attributable risk percent exposed is much higher. So, if the RMA were to pick, say, a cut-off point of 50% which is the level for civil workmen's compensation cases, you would have to have smoked at least 20 cigarettes or more to be compensated for bladder cancer. But, basically, if you were ever a smoker, in lung cancer you would be compensated.

We thought that there was no reason to restrict it to cigarettes per day. It would be whatever measure and data were available in the literature. And if someone actually met the criteria using any of those measures, it would be sufficient for compensation. Annette Dobson prepared just a list of the whole range of relative risks and what the attributable per cents would be, and you can see that actually the 50% is probably a higher cut-off point than what the RMA is currently using intuitively. Probably the cut-off point is more in this range, 25% and below. Thank you.

PROF DOBSON: I guess the important point about the methodology that has been suggested by the first two groups is that it is generalisable to any exposure and any disease, so that if this strategy for assessing risk were adopted, it could be across-the-board. And it is very strongly based on as much evidence as is available for that particular disease, whatever it may be, and the particular disease and exposure for which compensation is being claimed.

DR THUN: There is another intermediate step which the RMA would need to do which would be to figure out what data sets you are going to use to establish the relative risk for a particular level of smoking for the particular diseases for all of the inside of the black box. This would have to be worked out.

PROF HELLER: Yes. I think this is a very valuable discussion and I wonder — Shelia, could we see that red one again, yes. I think this is the one that Annette produced, and I think we have tended to look at relative risk rather than this other statistic. And, I mean, as Shelia said, you can see the relationship between them and the sort of relative risks that we have been talking about, 1.1, 1.2, 1.3. That nicely demonstrates what proportion of the cases in those categories are attributable to their smoking.

In fact we can use either column, once we have actually conceptualised what it is we are talking about, and I think that is a very important contribution. I think one of the problems is when I have tried to do some of these calculations before — and you read the books — and there are different sorts of names to all of these things. I mean, as we were talking yesterday, everyone had a different name for these statistics. And I think it would be useful if we came up with a name because I think, particularly, it would be

very useful in terms of the external credibility of this, that we had a name that people would understand.

I think attributable risk is difficult. I mean, they are difficult concepts and the sort of thing that from there is — proportion attributable to exposure — is a sort of understandable concept that I think we might think about using, or some term such as that. But I think it is very useful.

Table 1

Proportion of cases attributable to exposure at this level of exposure

relative risk	P proportion of cases in this category which are attributable to the exposure
1	0
1.1	0.09
1.2	0.16
1.3	0.23
1.4	0.29
1.5	033
1.8	0.44
2.0	0.5
2.5	0.6
3	0.67
5	0.8

At the level of exposure giving a relative risk of 1.3, some 23% of cases can be attributed to the exposure. At higher levels of exposure the proportion will be greater provided there is some evidence for dose response in the epidemiologic literature.

DR HOAR ZAHM: Yes, we found, in epidemiology, that your terminology depends on where you went to school. Graham is writing this up for the final time; so Harvard terminology will probably win out which is just fine by me.

PROF DOBSON: Perhaps just to extend the point that Michael made: if one were to implement such a system, what would be important would be to have a protocol which enabled you to identify the appropriate relative risk for a given person who was applying for compensation. So, you would have to have a protocol that said how you decided which studies were included and that is incredibly important because there's this document that was passed around yesterday which showed the studies that the Department of Health commissioned, projects done by Dallas English and others, who had looked at the health effects of active smoking.

And, in the case of prostate cancer, they only allowed three studies compared to all the ones that we discussed on Monday. And one of their studies seems to be one that we didn't discuss, so it's terribly important that you have rules for those sorts of things and it's terribly important that you have ways of updating the data all the time. But this is very much in the spirit of the Cochrane collaboration and use of essentially online, almost, use of the evidence for medical practice. So, I think it's very much in the sort of mainstream of current thinking, though the actual implementation would require quite a bit of detailed working up.

PROF MATHEWS: I mentioned, I think, in our session, but maybe not to the larger group, that I think in North America attributable risk has been used for veterans' compensation for the radiation veterans. So, there is some legislation that could be looked at, regardless of whether the RMA decides to go in a legislative direction in the short term.

Group 3

DR HICKEY: This was the statement produced by the group:

> *"From a scientific point of view the group endorses attributable risk as a guide for applying information on dose. Further details are required on the characteristics of veterans re their smoking habits, patterns, and the examination of cohort studies to determine when increased mortality returns to negligible levels."*

PROF COUGHLIN: I would suggest changing "negligible" to "baseline" or "underlying levels of risk". They're certainly not negligible.

Group 4

DR BORDUJENKO: We looked at and discussed attributable risk as well, and I suppose we wrote it as relative risk here, but recognised that a relative risk of two was about a 50 % attributable risk, and saw that for the balance of probabilities statement of principles the dose could be made at a relative risk approximating two, described in cigarettes per day for at least 10 years. There was considerable discussion as to the importance of not only intensity but also duration of smoking, and Sir Richard might like to detail more in that regard.

For a reasonable hypothesis, which is a more generous interpretation of risk, it was seen that perhaps a relative risk as a starting point may be about 1.2 after considering other interactive factors. It may be described in pack years or cigarettes per day, but the issue of duration was seen as quite important. We had a broad ranging discussion, but they were some of the specific points. Does that clarify it?

PROF KEARSLEY: Could I just add to that that some of the agony that we've had in the RMA has been to work out the level for balance of probabilities, having devised a level for reasonable hypothesis, and often the numbers have been abstracted according to our collective wisdom, I suppose. This at least, I suspect, gives some formalisation to the levels that we should choose.

PROF DWYER: I think we agreed with the others that the intensity of smoking was possible to use, despite the fact that duration was the strongest predictor of absolute risk, because relative risk at given ages was roughly the same for an amount of cigarettes smoked. So we went along with what was suggested there.

PROF DOLL: I think the point about duration was that smoking should have occurred at least 10 years before the onset of the cancer, so that's really where the 10 years came in. Smoking limited to the previous five years would be very unlikely to be a cause of cancer, whatever the intensity.

PROF COLDITZ: On that issue, it seems that maybe there's more data but it's less important at the low end for increasing risk, and as a sort of — at least in the western world society — the challenge really is on what happens after cessation. Michael Thun yesterday raised the issue of not penalising people for stopping smoking, or their spouse, or someone else, but we end up with — at least for several cancers, if you go back to the 1990 Surgeon-General's report, which probably is one of the most complete compilations of data, including the ACS data that were in large part specially run for that report — there are still cancers where relative risks are bouncing around.

One question I have is whether, given a fairly consistent pattern across lung, and some of the others, if we're uncertain should we be applying the pattern seen for lung, for some of the rare cancers where risk is going down, but there are so few cases in 20 years there's a huge interval but the point estimate's still up at 1.5. Do you ignore that and extrapolate from other cancers, or do you actually leave it as an elevated risk for cancer, exit 20 years, even after stopping? If anyone has any views on that, that, to me, is one of the data holes and some guidance would be useful.

DR THUN: There might be two reasons, though, or several reasons, to develop a simple approach to the issue of cessation. One is that implementing this is a big job, doing it in a way that really seems well thought through, even for current smoking. The second way is that the data for cessation do become skimpier the less common the cancer, and the third is that philosophically it's not in the best interests of servicemen, or anyone, to penalise cessation, because you really want to reward cessation, so it might be that, at least as an interim measure in developing this thing, you might want to choose a very simple approach to dealing with cessation, either saying, "We're not going to count cessation. We're going to compensate,

based on past exposure", or some very boiled-down version of taking it into account.

DR HOAR ZAHM: When we talked about this issue in our group yesterday, we struggled with the topic, but we finally came to the conclusion that this isn't about reward or punishment; that it really is about: "Is it likely that someone's cancer is related to smoking?" and that time since cessation should enter that metric. What we tried to do, to give the greatest benefit of the doubt to the veteran making the claim, was to say, "Double the number of years that are estimated to return to unity", and for many cancers and many people when they quit smoking, that will be far beyond the length of their life-span, so it essentially becomes a moot issue.

But we really tried to say that this isn't punishment and reward for your smoking habits; it's, "Is it the likelihood that your smoking is causing the cancer?" and as long as we're very conservative and realise those confidence intervals are wide and give the benefit of the doubt — and actually that brings to my mind another issue. We were talking about what risk estimates to use to calculate these attributable risks per cent. There's a couple of ways you could do: you pick one study or you do a meta-analysis; the other way is to pick the studies with the highest risk estimates, because they're all equally likely.

And I know in the US, if you picked a lower level, someone would take you to court and say, "This study shows a higher level of risk in driving down the level at which you could be compensated", so I think to give the benefit of the doubt to the veterans in both of these cases: double the cessation period and take risk estimates from three different studies for each level, whatever is the highest level of risk.

DR BLAIR: This issue about not penalising people who quit: it has a nice ring to it, and I understand the philosophy, but there's another group, and then there's a group who didn't start, and it seems to me like they fall into this same bailiwick, so now we penalise people who didn't start. This is choice.

PROF DONALD: Thank you for coming so quickly to the issues that have troubled the RMA in the application of statistics to some of these human matters, but I must say that this morning's discussion, I think, has helped the members of the RMA a great deal in clarifying that interface between statistics and what we do with them in these sort of contexts. I think that's been very helpful to us. Thank you very much for that. Perhaps we should press on with Section III "Emerging smoking related associations, including those with rare/unusual diseases."

Section III

Emerging smoking related associations, including those with rare/unusual diseases.

Some Cancers Weakly Related to Smoking*

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*Adapted from a paper in the British Medical Bulletin

Introduction

In February 1985, when a working group of the International Agency for Research on Cancer (IARC) met in Lyon to consider the carcinogenic effect of tobacco, it concluded that tobacco was carcinogenic to humans. In particular, it concluded that the smoking of cigarettes was an important cause of cancers of the lung, larynx, mouth, oropharynx, hypopharynx, oesophagus, bladder, renal pelvis, and pancreas, and that, for some of these types of cancer, the smoking of tobacco in other forms was also a cause of some of them (IARC, 1986). These conclusions were not difficult to reach, as the risk of developing each of these cancers had been found to be many times greater in heavy smokers than in lifelong non-smokers, the inhalation of tobacco smoke and the application of tobacco smoke condensate had been shown to cause cancer experimentally in animals, and similar conclusions had already been reached by some other expert committees (for example, Medical Research Council, 1957; Surgeon General, 1964). None of these conclusions has subsequently been seriously questioned and they are now generally accepted.

The evidence relating to several other types of cancer was also considered by the Agency. Cigarette smoking, it was concluded, was 'perhaps' an important cause of renal adenocarcinoma and it was noted that the risk of cervix cancer was increased in tobacco smokers and that associations had been found in some studies between smoking and cancers of the stomach and liver. The working group was, however, unable to conclude whether these last associations were causal in character or due to confounding of smoking with some other carcinogenic factor.

In the ten years that have passed since the Agency's review, much more evidence has been obtained about these last four types of cancer and also about several other types that were not specifically considered or mentioned in the group's conclusions and it is now evident that smoking is also a cause of several more cancers, if only a relatively unimportant cause. With weak associations, it is not to be expected that such direct evidence of causality can be obtained, as was obtained for lung cancer, when 95% of cases in men could be attributed to the habit. It should, nevertheless, not be thought surprising that smoking should be a cause of cancer in many different organs, for tobacco smoke contains several thousand chemicals, some 50 of which have been shown to be carcinogenic in animals (IARC, 1986) and inhalation is an effective way of getting a chemical into the systemic circulation and distributed throughout the body. Causation may, consequently, be deduced by analogy, if an association is consistently demonstrated between smoking and the development of a particular type of cancer and the observed association cannot readily be attributed to chance, bias, or confounding.

In this paper, I review the evidence relating to cancers of the lip, nose, nasopharynx, stomach, colon, rectum, and liver.

Four Common Cancers

The mortality from four of these cancers has been consistently associated with cigarette smoking in large cohort studies. This is shown in the Table, which gives the mortality from cancers of the stomach, colon, rectum, and liver observed in four cohorts of men in Japan, the UK, and the USA, separately for lifelong non-smokers, ex-cigarette smokers, and three categories of continuing smokers, smoking relatively small, moderate, or large numbers of cigarettes a day.

In the Japanese study, smoking habits were obtained from some 260,000 residents in six Japanese prefectures in 1966 and the subjects were followed for 16 years (Akiba & Hirayama, 1990). Altogether 3,935 deaths of men were attributed to the four cancers listed. In the published report, mortality rates are given for five categories of regular cigarette smokers, but they are reduced to three here by taking the means of the men smoking 1-4 and 5-14 cigarettes a day and 25-34 and 35 or more cigarettes a day, weighted by the numbers of deaths in each group.

In the UK study, some 34,000 male British doctors were followed for 40 years (Doll *et al.*, 1994a). The men's smoking habits had been determined in 1951 and again on four later occasions (in or shortly after 1957, 1966, 1971, and 1978) and deaths were related to the last known smoking habits. Altogether 550 deaths were attributed to the four types of cancer in the five relevant smoking categories. In one US study, the smoking habits of some 400,000 American men were recorded by the American Cancer Society in 1982 and the subjects were followed for six years. Mortality rates are, however, given only for the last four years to reduce the impact of including initially only self-reported healthy individuals. Altogether 1,844 deaths in men were attributed to the four cancers in the five smoking categories. The findings, which were made available by C Heath Jr. (personal communication) pertain to cancer sites not examined in a detailed analysis published by the American Cancer Society (Thun *et al.*, 1995). In the other US study, some 180,000 US veterans, who held government life insurance policies at the end of 1953 and were found to have been in one or other of the five selected smoking categories in 1954 or, in response to further enquiry to non-responders, in 1957, were followed to 30 September 1980 (McLaughlin *et al.*, 1995). Altogether 4,252 deaths were attributed to the four cancers listed. In the published report, mortality rates are given for four categories of continuing cigarette smokers, but they are reduced to three categories here by substituting the unweighted mean for the separate figures for men smoking 21-39 cigarettes and 40 or more cigarettes a day. Mortality is related to the men's smoking habits at the beginning of the study, which may have been up to 26 years before death occurred, so that the 'current smokers' for whom rates are given must be presumed to include a substantial proportion of men who had been ex-smokers for five or more years.

Cancer of the stomach

In each of the four cohorts the risk of stomach cancer is lowest in non-smokers, and highest (or equal highest) in heavy cigarette smokers, while the risk in ex-cigarette smokers is equal to that in non-smokers or intermediate between the risks in non-smokers and current cigarette smokers in the three cohorts for which the data are given. Similar findings have generally been obtained in the few other cohort studies and the many case-control studies that have now been reported from north and south America, Asia, Australasia, and Europe (see IARC 1986 and Forman 1991 for review and more recently Hansson *et al.*, 1994 and Inoue *et al.*, 1994) although not infrequently, with relatively small numbers of cases, the excess in cigarette smokers has not been statistically significant (for example, Choi & Kahyo, 1991). When all the data are examined, there can be no doubt about the reality of a positive association between cigarette smoking and the risk of the disease. The association is, however, not necessarily causal and could be due to confounding, most obviously with a diet low in vegetables and fruit, and also with socio-economic status. Neither, however, seems to provide an adequate explanation for the results. Adjustment for dietetic factors has sometimes been possible and has not materially reduced the association, most notably in Hirayama's large cohort study in Japan (Hirayama, 1987), and similar relationships are seen in the socially homogeneous British doctors (Doll *et al.*, 1994a) and in the two large American studies of men employed in a wide variety of occupations (see Table).

No help can be obtained from ecological observations as there have been major differences in the prevalence of the principal causes of the disease in different countries and at different times which would have overwhelmed the relatively small effect that, at the most, cigarette smoking could have produced. We have, therefore, to base our conclusion on the consistency of the findings, the dose-response relationship, the presence of chemicals in tobacco smoke that can cause gastric cancer in experimental animals, and the inability to explain the findings by confounding with other aetiological factors. On this basis it is concluded that cigarette smoking is a minor cause of gas-

tric cancer. As, however, tobacco smoke seems to act synergistically with whatever it is in food that causes gastric cancer, the absolute numbers attributable to smoking are large in areas where the risk of gastric cancer is high.

Cancers of the colon and rectum

Cancers of the colon and rectum are not always reliably distinguished on death certification or even in clinical records and, as they certainly have many causes in common and are often considered together in epidemiological studies as cancers of the large bowel, they are, for the most part, considered together here. There is, however, one important difference between them in the relationships shown in the Table, for whereas the mortality from rectal cancer is consistently greater in current cigarette smokers than in ex-smokers, this is not true for colon cancer.

Neither disease is consistently related to smoking in case-control studies (Baron, 1990) and a causal relationship has been postulated only on the basis of a post hoc hypothesis, based on the results of a cohort study (Giovannucci *et al.*, 1994a) in which smoking was related to the presence of large polyps in the large bowel only when it had been continued for more than 20 years and with small polyps when it had been continued for less. Confounding is possible both with a high fat, low fibre diet (Thompson *et al.*, 1992; Margetts & Jackson, 1993) and with the consumption of alcohol (Doll *et al.*, 1994b), both of which have been related to the incidence of the disease (Longnecker *et al.*, 1990; Giovannucci, 1994b) and confounding seems to be as likely an explanation of the associations observed in the cohort studies as causality.

Cancer of the liver

In developed countries, hepatocarcinoma, the principal type of liver cancer, nearly always occurs in association with alcoholic cirrhosis or chronic infection with the hepatitis virus. The disease is consistently related to cigarette smoking, not only in the data shown in the Table, but also in a large number of other cohort and case-control studies. Cigarette smoking, for its part, is closely related to the development of cirrhosis of the liver (Doll *et al.*, 1994a) and to the consumption of alcohol (Doll *et al.*, 1994b). Quantitatively, the relationship between smoking and cirrhosis of the liver in the British study seems capable of being explained by the relationship between smoking and the consumption of alcohol and a simple explanation of the observed association between smoking and liver cancer is that it is due to confounding with the consumption of alcohol.

Cigarette smoking, nevertheless, is likely to contribute to the production of a few cases, for the smoke contains chemicals that are known to cause liver cancer in experimental animals (for example, methylnitrosourea) and both Hirayama (1981) and Trichopoulos *et al.* (1980) found that liver cancer was associated with cigarette smoking after adjusting for the consumption of alcohol. More importantly, smoking has been found to be associated with hepatomas in China in areas where little alcohol is drunk and infection with the hepatitis B virus is rare (Lin Bogi and Richard Peto, personal communication).

Three Rare Cancers

Three rare types of cancer might be expected to be caused by smoking, as the organs in which they arise are exposed directly to tobacco smoke in the act of smoking: namely, cancers of the lip, nose, and nasopharynx. All are rare in developed countries and are more effectively studied by the case-control method than by following up cohorts.

Cancer of the lip

Lip cancer was the first type of cancer to be linked with smoking, when Sömmering (1795) noted in a treatise for a prize offered by the Rhineland-Frankfurt Society, that 'Carcinoma of the lip is most frequent when people indulged in tobacco pipes. For the lower lip is particularly attacked by carcinoma because it is compressed between the pipe and the teeth' (cited by Clemmesen, 1965). In the first half of this cen-

tury, as in the century before, lip cancer was relatively common; in recent years, however, it has become progressively less common, until by 1991-2 the mortality attributed to it in men in the UK was only about one tenth of that 40 years earlier, while that in women (now about 30 % of the mortality in men) had been reduced by about two thirds. Some of the reduction is due to improved treatment, but much is due to reduced incidence. Now, less than 250 cases occur each year in the whole of England and Wales, about half the number that occurred in the early 1970s, when cancer registration was first established on a national basis.

No recent case-control study has been reported, but seven were published between 1920 and 1970. Six showed a clear relationship with pipe smoking. Six provided estimates of relative risk for men who smoked only cigarettes, which were respectively nearly zero, 1.0, 1.4, 1.4, 2.4, and 2.6 (Surgeon General, 1979). The two completely negative studies were published before 1945, whereas the others were published later, and the validity of the negative results may be questioned. There can be no doubt that the disease is caused by pipe smoking, nor that the effect is increased in outdoor workers with prolonged exposure to ultraviolet light (Doll *et al.*, 1996). There may also be some small contribution from cigarette smoking, but it remains to be proved.

Cancer of the nose

Cancers of the nasal cavity and nasal sinuses, commonly grouped together as cancers of the nose, occur only rarely throughout the world, apart from a few special situations in which people are heavily exposed at work to some specific carcinogenic substances. The most important of these have been situations in which men have been heavily exposed to some nickel compounds in the refining of nickel and to fine hardwood dusts in some sections of the furniture industry. Under these conditions the incidence of the disease has, on occasions, been increased several hundred-fold. Apart from these situations, which have, in total, caused only few cases and have had little impact anywhere on the national incidence of the disease, the incidence has been about twice as great in men as in women and has shown little or no change over the last few decades. The disease is, therefore, unlikely to be closely related to smoking.

In view of the known, and several other suspected, occupational hazards, the causes of the disease have been investigated in case-control studies. Six have reported the relationship with cigarette smoking, five of which have found the risk in cigarette smokers to be increased. In the largest study, based on 175 patients with squamous carcinoma of the maxillary sinus in Japan, Fukuda & Shibata (1990) found a significantly increasing trend with the amount smoked in 125 cases in men, with a relative risk of 4.6 in those smoking 40 or more cigarettes a day. In the two other studies based on more than 100 patients with cancer of the nose, only a small and non-significant increase of about 20% was observed for all cases in all cigarette smokers. Brinton *et al.* (1984), however, found a significant increase (of 78%) for the 86 patients with squamous carcinomas and a significantly increasing trend with years of use and Zheng *et al.* (1992) (who were unable to classify cases by histological type) found a significantly increasing trend with amount smoked per day and with duration of smoking and a significantly decreasing trend with years stopped.

Of the three smaller studies, one found relative risks of 1.6 for 92 patients with nasal cancers and 3.0 for the 50 patients with squamous carcinomas, with a significantly increasing trend with amount smoked and a significantly decreasing trend with time stopped in the latter group (Hayes *et al.*, 1987). Another, with 60 patients, found a decreased relative risk for ever use of cigarettes of 0.7 but an increased risk of 1.6 in the 24 patients with squamous carcinomas (Zheng *et al.*, 1993), while the smallest study found a relative risk of 1.75 in 53 patients when those who had smoked 40 or more 'pack-years' were compared with those who had smoked 1 'pack-year' or less, which rose to 3.4 and was statistically significant in the 27 patients with squamous carcinomas (Strader *et al.*, 1983).

For nasal cancer, exceptionally, two studies have found a statistically significant association with exposure to environmental smoke. In a cohort study of 265,000 Japanese, Hirayama (1984) found a relative risk of two in non-smoking women married to smoking men and, in a case-control study, Fukuda & Shibata (1990) found that the risk in non-smoking women increased with the number of smokers in the household.

The consistency of the results, the biological gradients observed with amount smoked and time since smoking stopped, and the experimental findings of nasal tumours in laboratory animals exposed to tobacco-specific nitrosamines (Rivenson *et al.*, 1983) justify the conclusion that cigarette smoking is a cause of some squamous carcinomas of the nasal cavity and nasal sinuses, despite the small numbers studied. All methods of smoking are likely, too, to contribute substantially to the risk of developing the disease through their contribution to environmental pollution. This, for physical reasons, could be relatively more important for the nose than for the lung.

Cancer of the nasopharynx

Nasopharyngeal cancer is common in South China and some other areas in Asia and North Africa, where it has been shown to be dependent on infection with the Epstein-Barr virus and, in Chinese populations, with the consumption, particularly in childhood, of a special type of dried fish. Case-control studies in these areas and among Chinese migrants to the United States have failed to show any consistent relationship with smoking, possibly because a small effect is masked by the much larger effects of viral infection and diet (see Chow *et al.*, 1993 for references).

In developed countries, the disease is rare everywhere. It is about twice as common in men as in women and has shown little or no change in incidence and it is, therefore, unlikely to be closely related to smoking. Only two substantial case-control studies have been carried out (Henderson *et al.*, 1976; Nam *et al.*, 1992). In one, which obtained an odds ratio of 1.0 for cigarette smokers, Chinese constituted 47 % of the population of 156 affected patients and other Orientals 11 % (Henderson *et al.*, 1976). In the other (Nam *et al.*, 1992), information about smoking habits was obtained for 204 white men and women who died from nasopharyngeal cancer in the USA and twice that number of controls, matched for sex and age, but otherwise drawn at random from a 1 % sample of all who died in the country over the same period, excluding all whose deaths were thought to have been due to smoking-related diseases. The results gave odds ratios that increased with the amount smoked to levels of 3.1 for men and 4.9 for women with histories of 60 or more 'pack-years' of smoking. These findings closely resemble those obtained in the only other case-control study of a principally white population (Mabuchi *et al.*, 1985) and in the cohort study of US veterans (Chow *et al.*, 1993). The former, based on 39 cases and 39 matched controls, recorded an odds ratio of 2.8 for men and women whose maximum consumption had been greater than one pack a day. The latter, based on 48 cases, recorded odds ratios of 3.9 for current cigarette smokers, 1.5 for ex-cigarette smokers, and ratios that increased progressively from 1.8 for men smoking less than 10 a day to 6.4 (which was significantly greater than 1.0) for men smoking 40 or more a day.

The only other suspected cause of nasopharyngeal cancer in developed countries is occupational exposure to formaldehyde, which is present in tobacco smoke, and experimental studies have shown that tobacco specific nitrosamines can cause nasal cavity tumours in experimental animals (Rivenson *et al.*, 1983). Despite the small numbers on which the evidence is based, it can be concluded that cigarette smoking is probably a contributory cause of the disease.

Conclusion

None of the seven types of cancer reviewed is now closely related to smoking, but there is good evidence that cigarette smoking contributes to the causation of four of them: namely, cancers of the stomach, liver, nose, and nasopharynx. For cancer of the nose the conclusion is firm only for squamous carcinoma. Pipe

smoking, in contrast, is a cause of cancer of the lip and has been an important cause in the past in conjunction with exposure to ultraviolet light. Whether cigarette smoking accounts for any cases of cancers of the colon and rectum is uncertain; the small excesses that have been observed in some studies may be due to confounding with dietary factors and the consumption of alcohol.

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Table: RELATIVE RISK OF FOUR CANCERS BY SMOKING HABIT IN 4 LARGE COHORT STUDIES

				Risk in Cigarette smokers relative to lifelong non-smokers				
Typer of cancer	Study reference	No. of deaths†		Ex-	Current	Current+ Light	Moderate	Heavy
Stomach	a	168	(32)	1.0	1.7	1.6	1.7	1.7
	b(M)	353	(66)	1.6	2.1	2.0	2.1	2.4
	b(F)	217	(122)	1.4	1.4	1.5	1.0	1.5
	c	1058	—	1.0	1.4	1.3	1.4	1.7
	d	2839	(491)	—	1.5	1.4	1.5	1.5
Colon	a	246	(49)	1.4	1.3	1.3	1.1	1.4
	b(M)	1121	(279)	1.5	1.3	1.3	1.2	1.3
	b(F)	1082	(642)	1.0	1.1	1.3	1.2	0.7
	c	2596	—	1.4	1.2	1.1	1.2	1.5
	d	190	(45)	—	1.1	1.0	1.1	1.4
Rectum	a	85	(13)	1.4	2.3	1.3	1.9	4.4
	b(M)	172	(41)	1.2	1.5	1.1	1.7	1.5
	b(F)	156	(88)	1.0	1.6	1.5	2.1	1.1
	c	735	—	1.3	1.4	1.3	1.3	1.6
	d	254	(50)	—	1.4	1.3	1.4	1.4
Liver	a	51	(10)	1.4	1.6	2.4	0.4	2.2
	b(M)	198	(35)	1.7	2.5	1.8	2.6	3.0
	b(F)	101	(53)	2.1	1.6	1.0	2.0	2.1
	c	363	—	1.5	1.8	1.8	1.4	2.5
	d	652	(106)	—	1.5	1.6	1.4	1.7

a, Doll *et al.*, 1994 a; b, C. Heath Jr (personal communication); c, McLaughlin *et al.*, 1995; d, Akiba *et al.*, 1990; M, males; F, females.

† Number of deaths in non-smokers in parentheses.

+ Light, 1-14 a day, studies a, b, and d; 1-9 a day, study c.Moderate, 15-24 a day, studies a, b, and d; 10-20 a day, study c. Heavy, 25 or more a day, studies a, b, and d; unweighted mean 21-39 and 40 or more a day, study c.

Cigarette Smoking and Death from Selected Cancers in CPS-II

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Abstract

Background: Although some retrospective studies suggest there may be an association between cigarette smoking and non-Hodgkin's lymphoma (NHL) or multiple myeloma (MM), few prospective studies are large enough to assess these hypotheses.

Methods: In an American Cancer Society prospective study of over one million U.S. adults, we identified 438 deaths from NHL, 220 from MM, and 43 from Hodgkin's disease (HD) during six years of follow up (1982-86). Based on smoking histories collated in 1982, we measured sex- and smoking-specific death rates among 227,641 current cigarette smokers and 261,903 ex-smokers, and compared these to rates in 480,427 lifelong non-smokers.

Results: Death rates from NHL and MM were not statistically higher in men or women who currently or formerly smoked cigarettes than among lifelong non-smokers. Although the rates were 7 to 50 percent higher among smokers than never smokers in many strata, the difference was not statistically significant, the risk did not increase consistently with more prolonged smoking or more cigarettes per day. For HD however, death rates were consistently higher in women (10 deaths, RR=5.14, 95% CI=1.98-13.35) and men (9 deaths, RR=2.85, 0.92-8.80) who currently smoked than in lifelong nonsmokers, and the rates increased with the amount and duration of smoking despite the small numbers of deaths.

Conclusion: Cigarette smoking was not adversely associated with fatal NHL or MM in the ACS study during the first six years of followup, but was associated with deaths from Hodgkin's disease.

Tobacco and Non-Hodgkin's Lymphoma

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Abstract

The role of tobacco in the etiology of non-Hodgkin's lymphoma (NHL) was evaluated in a combined analysis of data from three population-based case-control studies conducted in four Midwestern US states, Nebraska, Iowa, Minnesota, and Kansas. Interviews were obtained from 1,177 (993 men, 184 women) cases and 3,625 (2,918 men, 707 women) controls or, if deceased, from their next-of-kin. Overall, there was no association between NHL and tobacco use (odds ratio [OR]=1.0, 95% confidence interval [CI]=0.8,1.1) or cigarette smoking (OR=1.0, CI=0.8,1.1). A slight protective effect evident in analyses by intensity and duration of smoking was not present when interviews from proxy respondents were eliminated. There was a suggestion of a positive association between smoking and NHL among women (OR=1.3, CI=0.9,1.9), although the exposure-response gradients were inconsistent. This large case-control analysis provides no evidence that smoking is linked to the development of NHL among men. The possible role of smoking in the etiology of NHL among women needs further evaluation.

Introduction

Traditionally, non-Hodgkin's lymphoma (NHL) has not been considered a tobacco-related malignancy. Most studies have shown little or no association between NHL and smoking[1-9]. Two recent studies[10,11], however, were more supportive of an association. A population-based case-control study of men in Iowa and Minnesota observed a 40% increased risk of non-Hodgkin's lymphoma among smokers with a two- to three-fold increase for high grade and unclassified non-Hodgkin's lymphoma[10]. Risk increased with duration of smoking, but not intensity. A cohort study of policy holders of the Lutheran Brotherhood Insurance Society reported smokers having a two-fold increase in mortality from NHL, with an almost four-fold increased risk among heavy smokers[11]. No information on cell type or duration of smoking was available. In addition, the growing consensus that cigarette smoking is causally related to leukemia has suggested the need to re-evaluate its role in the etiology of other hematopoietic and lymphatic malignancies, although the evidence is strongest for myeloid, not lymphoid, leukemia[12-16].

To examine the role of tobacco in the etiology of NHL, we combined data from three population-based case-control studies conducted in four Midwestern US states, including the population previously reported by Brown *et al.*[10]. The combined data set provided the large number of subjects required to evaluate the anticipated low level risks and to focus analyses on subgroups of interest suggested by the earlier research.

Methods

The three population-based case-control studies combined for this reanalysis were conducted in Nebraska, Iowa/Minnesota, and Kansas. Detailed descriptions of the methods for each study have been published elsewhere[5,10,17-24]. Each study included several lymphatic and hematopoietic malignancies and, in Kansas only, soft tissue sarcoma. The studies in Iowa/Minnesota and Kansas included white men, while the Nebraska study included both white men and white women. This report will evaluate NHL among white men and women.

Cases

In Nebraska, all cases of NHL among white men and women, age 21 years or older, residing in the 66 counties of eastern Nebraska, and diagnosed between July 1, 1983, and June 30, 1986, were identified through the Nebraska Lymphoma Study Group and area hospitals (N=227 men, 214 women) (Table 1). In the Iowa/Minnesota study, all newly diagnosed cases of NHL among white men, age 30 years or older, were ascertained from Iowa State Health Registry records and a special surveillance of Minnesota hospital and pathology laboratory records (N=780). The diagnosis period for eligibility was March, 1981, through October, 1983, in Iowa and October, 1980, through September, 1982, in Minnesota. In Minnesota, cases who resided in the cities of Minneapolis, St. Paul,

Duluth, or Rochester at the time of diagnosis were excluded because agricultural exposures were the primary focus of the original investigations. In Kansas, all cases of NHL among white men, age 21 years or older, diagnosed from 1979 through 1981, were identified through the University of Kansas Cancer Data Service, a registry covering the state of Kansas. A random sample of 200 men was drawn from the 297 NHL cases diagnosed in Kansas during the eligible time period.

The cases were reviewed by expert pathologists and classified according to the Working Formulation[25-27]. Analyses of follicular (Working Formulation categories B-D), diffuse (Working Formulation categories E-G), small lymphocytic (Working Formulation category A), and other (Working Formulation categories H-J and miscellaneous) NHL are presented. Only histologically confirmed cases were included. The number of confirmed cases was 426 (220 men, 206 women) in Nebraska and 172 in Kansas. In Iowa/Minnesota, the pathology review occurred after the interviews were obtained from cases. Because cases who were not interviewed did not undergo pathology review, the total number of eligible histologically-confirmed cases cannot be determined.

Controls

Controls were randomly selected from the same geographic areas as cases, with frequency matching by race, gender, five-year age group, and vital status at the time of the interview. For living cases under age 65, controls were selected by two-stage random digit dialing[28]. For living cases aged 65 or older, controls were selected from the Health Care Financing Administration (Medicare) records. For deceased cases, controls were selected from state mortality files with additional matching for year of death. Persons with a cause of death from a malignancy under study or, in Kansas and Nebraska, a malignancy of an ill-defined site, homicide, suicide, or legal intervention were excluded. A total of 4,203 controls (Nebraska: 831 men, 824 women; Kansas: 1,005; Iowa/Minnesota: 1,543) were identified.

Interviews

Interviews were conducted with the subjects, or their next-of-kin if the subjects were deceased or incapacitated. The interviews were done by telephone in Nebraska and Kansas and in-person in Iowa/Minnesota. In Nebraska, 385 (201 men, 184 women) cases and 1,432 (725 men, 707 women) controls were interviewed, yielding interview response rates of 91% for male cases, 89% for female cases, 87% for male controls, and 86% for female controls. The overall control response rate, which accounted for the 91% response rate in the household census phase of the random digit dialing procedure, was 85% for men and 84% for women. In Kansas, 170 cases and 948 controls were interviewed, yielding interview response rates of 96% and 94%, respectively. The random digit dialing household census had a 92.3% response rate which made the overall control response rate 90%. In Iowa/Minnesota, 780 presumptive NHL cases were ascertained and 694 (89%) were interviewed. After pathology review of the interviewed cases, 622 were confirmed as NHL. Interviews were also obtained from 1,245 controls (81%) in Iowa/Minnesota. The overall control response rate, accounting for the 87.5% household census response rate, was 78%. Combining the three studies, interviews were obtained from 1,177 (993 men, 184 women) eligible cases and 3,625 (2,918 men, 707 women) controls. Fourteen male controls were excluded from the analyses in this report because of missing data.

In each study, the interviews contained detailed questions on tobacco use including the use of cigarettes, current smoking status, age the person started smoking, number of years of smoking, average number of cigarettes smoked per day, use of cigars or pipes, and use of smokeless tobacco. Because not all of the studies collected detailed information on intensity and duration of use of non-cigarette tobacco products, those data will not be presented. The interviews also included other known and suspected risk factors for non-Hodgkin's lymphoma, such as a family history of cancer, pesticide use, occupational exposures, and medical conditions, with some variation across the three studies.

Risk Measurement

The measure of association was the odds ratio (OR). Combining the subjects from the three studies, risk estimates for tobacco use were adjusted for the effects of age (20-44, 45-64, 65-74, 75+ years), gender, and state (Nebraska, Kansas, Iowa, Minnesota) by stratification. The source of the interview, i.e., study subjects themselves versus proxy respondents, was found to be a negative confounder in these data and was added as a stratification factor. Adjustment for ever having lived or worked on a farm did not change risk estimates and is not presented in this report. Maximum likelihood estimates of the overall risk and 95% confidence intervals (CIs) were computed by Gart's method[29]. For duration and intensity-response relationships, significance was assessed by means of Mantel's one-tailed linear trend test[30].

Results

Table 2 presents the ORs for NHL by characteristics of tobacco use for all subjects combined and by respondent type. Overall, there was no association between NHL and any tobacco use or cigarette smoking. Risk appeared to decrease slightly with increasing intensity and duration of smoking, primarily due to the negative associations among subjects represented by proxy respondents. This pattern was probably due to the inclusion of smoking-related causes of death in the deceased controls matched to the deceased cases. Analyses based on living subjects alone showed an excess of borderline significance among current smokers, but no smoking exposure gradients were observed.

The effect of smoking in the development of NHL appeared to differ by gender (Table 3). While there appeared to be little or no effect in men, particularly among subject respondents, NHL was associated with smoking among women. Among the female subject respondent smokers, NHL was increased about two-fold. However, the exposure gradients, although statistically significant, were inconsistent, with a diminution of risk in the highest category. The ORs were similar for exposure gradients among ex and current smokers (data not shown).

Among men, there was no evidence for a role of tobacco in the development of follicular lymphoma (OR=1.0; CI=0.7,1.3) (Table 4). Smokers had a slightly decreased risk of diffuse lymphoma (OR=0.8; CI=0.6,1.0) and small lymphocytic lymphoma (OR=0.7; CI=0.5,1.1) and an increased risk of the remaining types of NHL (OR=1.4; CI=0.96,2.1). No consistent exposure-response gradients were observed (data not shown). These relationships were not changed when analyses were restricted to interviews supplied directly by subjects.

Among women, tobacco users had nonsignificant increased risks of follicular, diffuse, and small lymphocytic lymphoma (Table 4). Analyses of detailed smoking characteristics were limited by small numbers of exposed female cases, but showed greater risks for these three histologic types of NHL among current smokers than among ex-smokers. Risk for follicular and small lymphocytic lymphoma appeared to increase with years smoked, based on small numbers. Female smokers generally had no greater risk of other histologic types of NHL than nonsmokers.

Other forms of tobacco showed no association with NHL either used alone or in combination with each other. Persons who ever smoked pipes or cigars had an OR of 0.9 (CI=0.7,1.1) for NHL. Smokeless tobacco users had an OR of 1.0 (CI=0.7,1.2). Among persons who used only one type of tobacco, the pipe or cigar smokers had an OR of 1.0 (CI=0.6,1.4) and smokeless tobacco users had an OR of 0.8 (CI=0.4,1.3). Persons who used all forms of tobacco (i.e., cigarettes, pipes or cigars, and smokeless tobacco) at some time during their lives had an OR of 0.9 (CI=0.6,1.3).

There were no consistent modifications of the risk associated with smoking by family history of cancer.

Discussion

This combined analysis of data from three population-based case-control studies was based on approximately 1,200 cases and 3,600 controls. A total of 726 cases and 2,164 controls smoked cigarettes. This study is far larger than any previously published study on NHL and tobacco use. Overall, there was no association with cigarette smoking or use of other forms of tobacco. A slight protective effect evident in the analyses by intensity and duration of smoking was not present when analyses were restricted to information obtained directly from living subjects. Proxy respondents for deceased cases and matched deceased controls showed significantly decreased risks of NHL associated with smoking probably due to the inclusion of controls with smoking-related causes of death[31]. While it would be possible to exclude known smoking-related causes of death from the deceased controls for reanalysis, McLaughlin *et al.*[31] have reported that such exclusion reduces, but does not eliminate the excess of cigarette smokers among deceased controls. For smoking, it would be better to base this study's conclusions on the living subjects only.

There was a suggestion of a positive association between smoking and NHL among women. Elevated ORs from cigarette smoking were evident only among interviews with subjects, not among proxies. The exposure-response gradients were somewhat inconsistent. The association among women may be due to chance. On the other hand, a lack of an exposure-response gradient was also observed in a study of smoking and leukemia[32]. Smoking is known to have effects on the immune system including alterations in T-cell subsets, elevated white blood counts, and lower percentages of natural killer cells[33-37]. Immunodeficiencies and immunosuppression, both genetic and acquired, are strong risk factors for NHL[38-39]. It is difficult to postulate a gender-specific causal association for smoking, however, there is some evidence that women smokers incur a greater risk of lung cancer than men who smoke similar amounts[40-42]. Most previous studies of NHL and smoking have consisted of men onl[1,3-5,9-11] or presented results for men and women combined[6-8]. Williams and Horm[2] reported nonsignificant increases of some types of lymphoma among women in the highest cigarette smoking category based on small numbers of cases. Additional data on smoking and NHL among women are needed.

If smoking were causally related to NHL among women, the increase in smoking among women in recent decades[43] might explain some of the 57% increase among women in the incidence of NHL over the past twenty years[44]. Most other known and postulated causes of NHL, such as human immunodeficiency virus, pesticides, and solvents, are more prevalent among men than women[45-47]. The agents responsible for the rising incidence of NHL might differ among men and women. Cigarette smoking and other factors, such as use of hair coloring products[23,48], may be responsible for the rise in women, but play little or no role among men.

This large case-control study provides strong evidence that smoking has little or no effect on the development of NHL among men. However, the possible role of smoking in the etiology of NHL among women needs further evaluation.

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Table 1. Number of Non-Hodgkin's Lymphoma Cases and Controls, Response Rates, and Study Methods in the Case-Control Studies in Nebraska, Kansas, Iowa, and Minnesota.

	Nebraska		Kansas	Iowa/Minnesota
	Men	Women	Men	Men
Cases identified	227	214	200	780
Histologically confirmed	220	206	172	. .[a]
Interviewed	201	184	170	622
Interview response rate	91%	89%	96%[b]	89%
Controls identified	831	824	1,005	1,543
Interviewed	725	707	948	1,245
Interview response rate	87%	86%	94%	81%
Overall control response rate	85%	84%	90%	78%

a Pathology review occurred after the interviews were conducted. Cases who were not interviewed did not undergo pathology review.

b The 96 % response rate was based on 170 interviews out of 172 confirmed non-Hodgkin's lymphoma cases initially diagnosed as non-Hodgkin's lymphoma and five non-Hodgkin's lymphoma cases initially diagnosed as other cancer types in the study (e.g. Hodgkin's disease).

Table 2. Numbers of Non-Hodgkin's Lymphoma (NHL) Cases and Controls and Odds Ratios (OR) for Tobacco Use by Respondent Type in Eastern Nebraska, Kansas, Iowa, and Minnesota.

	TOTAL				SUBJECT RESPONDENTS				PROXY RESPONDENTS			
	NHL	Controls	OR	(95% CI)[a]	NHL	Controls	OR	(95% CI)[b]	NHL	Controls	OR	(95% CI)[b]
No tobacco	356	1179			221	753			135	426		
Ever tobacco	820	2424	1.0	(0.8,1.1)	516	1330	1.1	(0.9,1.4)	304	1094	0.7	(0.6,0.97)
Unknown	1	8	—	0	3	—	1	5	—			
Cigarettes	726	2164	1.0	(0.8,1.1)	467	1203	1.1	(0.9,1.4)	259	961	0.7	(0.6,0.96)
Ex-smokers	371	1134	0.9	(0.7,1.1)	257	712	1.0	(0.8,1.3)	114	422	0.7	(0.5,0.99)
Current smokers	308	850	1.1	(0.9,1.3)	203	476	1.3	(1.0,1.6)	105	374	0.8	(0.5,1.1)
Unknown[c]	47	180	—	7	15	—	40	165	—			
Cigarettes per day												
1-9	99	253	1.1	(0.8,1.4)	58	157	1.0	(0.7,1.5)	41	96	1.2	(0.7,1.8)
10-19	136	353	1.1	(0.9,1.5)	93	206	1.3	(0.98,1.8)	43	147	0.8	(0.5,1.3)
20	251	753	0.9	(0.8,1.2)	178	451	1.1	(0.9,1.5)	73	302	0.6	(0.4,0.9)
21+	210	693	0.8	(0.6,0.98)	135	377	0.9	(0.7,1.2)	75	316	0.6	(0.4,0.9)
Unknown	30	112	—	3	12	—	27	100	—			
Chi; p-value for trend	-1.787; 0.037				0.333; 0.370				-3.471; <0.0001			
Years smoked												
1-10	79	230	1.2	(0.8,1.6)	56	178	1.1	(0.7,1.6)	23	52	1.4	(0.8,2.5)
11-20	101	294	1.1	(0.8,1.5)	69	211	1.0	(0.7,1.5)	32	83	1.2	(0.7,2.1)
21-30	120	316	1.1	(0.8,1.4)	85	219	1.0	(0.7,1.4)	35	97	1.2	(0.7,2.0)
31-40	136	402	0.8	(0.6,1.1)	97	231	1.1	(0.8,1.5)	39	171	0.5	(0.3,0.8)
41+	244	751	0.9	(0.7,1.1)	153	349	1.1	(0.8,1.5)	91	402	0.6	(0.4,0.8)
Unknown	46	171	—	7	15	—	39	156	—			
Chi; p-value for trend[d]	-1.310; 0.095				1.126; 0.130		-		3.643; <0.0001			
Pack-years												
< 15	159	456	1.1	(0.8,1.4)	108	321	1.1	(0.8,1.4)	51	135	1.1	(0.7,1.7)
15 — < 35	186	511	1.1	(0.8,1.3)	139	343	1.2	(0.9,1.6)	47	168	0.8	(0.5,1.2)
35 — < 55	169	474	0.9	(0.7,1.1)	123	293	1.0	(0.8,1.4)	46	181	0.6	(0.4,1.0)
55 — 155	148	497	0.8	(0.6,0.97)	89	222	0.9	(0.7,1.3)	59	275	0.5	(0.3,0.8)
Chi; p-value for trend	-1.728; 0.042				0.567; 0.285				-3.587; <0.0001			

a Odds ratio (95 % confidence interval) adjusted for age, gender, state, and respondent type.

b Odds ratio (95 % confidence interval) adjusted for age, gender, and state.

c Some smokers could not be classified as ex- or current smokers because of missing values for either age started or years of smoking.

d Trend tests do not include the unknown category.

Table 3. Number of Non-Hodgkin's Lymphoma (NHL) Cases and Controls and Odds Ratios (OR) for Tobacco Use by Gender and Respondent Type in Eastern Nebraska, Kansas, Iowa, and Minnesota.

	MEN						WOMEN					
	TOTAL RESPONDENTS[a]			SUBJECT RESPONDENTS			TOTAL RESPONDENTS[a]			SUBJECT RESPONDENTS		
	NHL	Controls	OR (95% CI)[b]	NHL	Controls	OR (95% CI)	NHL	Controls	OR (95% CI)	NHL	Controls	OR (95% CI)
No tobacco	240	685		154	434		116	494		67	319	
Ever tobacco	752	2216	0.9 (0.7,1.1)	466	1203	1.0 (0.8,1.2)	68	208	1.3 (0.9,1.9)	50	127	1.9 (1.2,3.0)
Unknown	1	3	—	0	0	—	0	5	—	0	3	—
Cigarettes	658	1957	0.9 (0.7,1.1)	417	1076	1.0 (0.8,1.2)	68	207	1.3 (0.9,1.9)	50	127	1.9 (1.2,3.0)
Ex-smokers	350	1054	0.9 (0.7,1.1)	238	660	0.9 (0.7,1.2)	21	80	1.0 (0.6,1.9)	19	52	1.7 (0.9,3.3)
Current smkrs	269	746	1.0 (0.8,1.2)	175	402	1.1 (0.9,1.5)	39	104	1.5 (0.9,2.4)	28	74	1.9 (1.1,3.3)
Unknown[c]	39	157	—	4	14	—	8	23	—	3	1	—
Cigarettes per day												
1-9	86	194	1.1 (0.8,1.5)	48	114	1.0 (0.7,1.6)	13	59	0.9 (0.5,1.9)	10	43	1.1 (0.5,2.5)
10-19	115	318	1.0 (0.7,1.3)	80	182	1.2 (0.8,1.7)	21	35	2.5 (1.3,4.8)	13	24	2.9 (1.3,6.5)
20	229	690	0.9 (0.7,1.1)	157	414	1.0 (0.7,1.3)	22	63	1.3 (0.7,2.3)	21	37	2.7 (1.4,5.3)
21+	203	652	0.8 (0.6,1.0)	130	356	0.9 (0.7,1.2)	7	41	0.5 (0.2,1.3)	5	21	1.1 (0.3,3.4)
Unknown	25	103	—	2	10	—	5	9	—	2	2	—
Chi; p-value for trend[d]		-2.164; 0.015			-0.744; 0.228			0.666; 0.253			2.928; 0.002	
Years smoked												
1-10	73	191	1.2 (0.9,1.8)	53	149	1.2 (0.8,1.7)	6	39	0.8 (0.3,2.0)	3	29	0.6 (0.1,2.4)
11-20	93	270	1.1 (0.8,1.4)	62	192	1.0 (0.7,1.4)	8	24	1.5 (0.5,3.8)	7	19	1.8 (0.6,5.0)
21-30	113	287	1.1 (0.8,1.4)	79	198	1.0 (0.7,1.4)	7	29	1.0 (0.4,2.6)	6	21	1.5 (0.5,4.2)
31-40	118	371	0.7 (0.6,0.99)	80	212	0.9 (0.6,1.2)	18	31	1.9 (0.95,3.9)	17	19	3.7 (1.7,8.4)
41+	223	690	0.8 (0.7,1.0)	139	311	1.0 (0.8,1.4)	21	61	1.2 (0.7,2.1)	14	38	1.7 (0.8,3.4)
Unknown	38	148	—	4	14	—	8	23	—	3	1	—
Chi; p-value for trend[d]		-2.162; 0.015			-0.133; 0.447			1.738; 0.041			3.091; 0.001	
Pack-years												
< 15	144	384	1.1 (0.8,1.4)	96	265	1.0 (0.8,1.4)	15	72	0.9 (0.5,1.8)	12	56	1.1 (0.5,2.4)
15 — < 35	163	460	1.0 (0.7,1.2)	120	305	1.0 (0.8,1.4)	23	51	1.8 (0.99,3.3)	19	38	2.5 (1.3,4.8)
35 — < 55	154	439	0.8 (0.6,1.1)	110	273	0.9 (0.7,1.2)	15	35	1.5 (0.7,3.0)	13	20	2.9 (1.2,6.9)
55 — 155	143	475	0.8 (0.6,0.99)	86	212	0.9 (0.7,1.3)	5	22	0.6 (0.2,1.9)	3	10	1.3 (0.3,5.2)
Chi; p-value for tren[d]		-2.241; 0.013			-0.451; 0.326			1.147; 0.126			2.971; 0.001	

a Total respondents includes subject respondents and proxy respondents. b Odds ratio (95 % confidence interval) adjusted for age, state, and respondent type.

c Some smokers could not be classified as ex- or current smokers because of missing values for either age started or years of smoking. d Trend tests do not include the unknown category.

Table 4. Number of Non-Hodgkin's Lymphoma (NHL) Cases and Controls and Odds Ratios (OR) for Tobacco Use by Histologic Type[a] and Gender in Eastern Nebraska, Kansas, Iowa, and Minnesota.

		FOLLICULAR			DIFFUSE			SMALL LYMPHOCYTIC			OTHER		
	Controls	NHL	OR	(95% CI)[b]	NHL	OR	(95% CI)	NHL	OR	(95% CI)	NHL	OR	(95% CI)
Men													
No tobacco	685	69			100			32			37		
Ever tobacco	2216	216	1.0	(0.7,1.3)	268	0.8	(0.6,0.99)	80	0.7	(0.5,1.1)	188	1.4	(0.96,2.1)
Unknown	3	0	—		1	—		0	—		0	—	
Cigarettes	1957	191	1.0	(0.7,1.3)	237	0.8	(0.6,1.0)	61	0.6	(0.4,1.0)	169	1.4	(0.97,2.1)
Ex-smokers	1054	99	0.9	(0.6,1.2)	134	0.8	(0.6,1.1)	37	0.6	(0.4,1.0)	80	1.2	(0.8,1.9)
Current smkrs	746	88	1.1	(0.8,1.7)	88	0.8	(0.5,1.1)	22	0.7	(0.4,1.3)	71	1.7	(1.1,2.7)
Unknown[c]	157	4	—		15	—		2	—		18	—	
Women													
No tobacco	494	35			40			4			36		
Ever tobacco	208	20	1.3	(0.7,2.5)	27	1.6	(0.9,2.8)	5	3.4	(0.7,16.0)	16	0.9	(0.4,1.8)
Unknown	5	0	—		0	—		0	—		0	—	
Cigarettes	207	20	1.3	(0.7,2.5)	27	1.6	(0.9,2.8)	5	3.4	(0.7,16.0)	16	0.9	(0.4,1.8)
Ex-smokers	80	6	0.9	(0.3,2.3)	7	1.1	(0.4,2.8)	2	3.1	(0.4,21.4)	6	0.9	(0.3,2.4)
Current smkrs	104	12	1.4	(0.6,3.0)	16	1.9	(0.9,3.9)	3	3.8	(0.6,22.3)	8	0.9	(0.3,2.2)
Unknown[c]	23	2	—		4	—		0	—		2	—	
Cigarettes per day													
1-9	59	4	0.9	(0.3,2.9)	5	1.0	(0.3,3.0)	2	3.8	(0.5,25.9)	2	0.4	(0.07,2.0)
10-19	35	6	2.2	(0.7,6.4)	10	3.8	(1.5,9.8)	1	3.8	(0.1,41.6)	4	1.3	(0.3,4.6)
20	63	6	1.0	(0.3,2.8)	9	1.8	(0.7,4.5)	2	6.7	(0.7,53.6)	5	0.8	(0.2,2.4)
21+	41	3	0.8	(0.2,3.0)	2	0.5	(0.1,2.4)	0	—		2	0.4	(0.1,1.9)
Unknown	9	1	—		1	—		0	—		3	—	
Chi; p-value for trend[d]		0.605; 0.273			1.002; 0.158			1.225; 0.110			-0.847; 0.198		
Years smoked													
1-10	39	1	0.4	(0.02,3.1)	1	0.4	(0.02,3.0)	0	—		4	1.4	(0.4,4.7)
11-20	24	3	1.2	(0.3,5.0)	4	3.2	(0.87,12.7)	0	—		1	0.5	(0.02,4.4)
21-30	29	0			4	2.2	(0.6,7.7)	1	4.8	(0.2,73.4)	2	0.9	(0.1,4.2)
31-40	31	4	1.1	(0.3,3.7)	7	3.1	(1.0,9.3)	3	11.4	(1.5,91.6)	4	1.2	(0.3,4.5)
41+	61	10	2.0	(0.9,4.7)	7	1.0	(0.4,2.6)	1	1.9	(0.1,18.7)	3	0.5	(0.1,1.8)
Unknown	23	2	—		4	—		0	—		2	—	
Chi; p-value for trend[d]		1.445; 0.074			1.522; 0.064			2.119; 0.017			-0.563; 0.287		

Table 4 continued

	Controls	FOLLICULAR NHL	OR	(95% CI)[b]	DIFFUSE NHL	OR	(95% CI)	SMALL LYMPHOCYTIC NHL	OR	(95% CI)	OTHER NHL	OR	(95% CI)
Pack-years													
< 15	72	3	0.6	(0.1,1.9)	6	1.2	(0.4,3.3)	2	3.4	(0.4,22.9)	4	0.7	(0.2,2.3)
15 — < 35	51	6	1.4	(0.5,3.8)	13	3.3	(1.5,7.4)	1	2.3	(0.1,24.0)	3	0.7	(0.2,2.7)
35 — < 55	35	8	2.1	(0.8,5.6)	2	0.7	(0.1,3.4)	2	11.5	(1.0,124.4)	3	0.8	(0.2,3.1)
55 — 155	22	1	0.4	(0.02,3.6)	2	0.7	(0.1,3.8)	0	—		2	0.7	(0.1,3.7)
Chi; p-value for trend		1.204; 0.114			0.859; 0.195			1.613; 0.053			-0.545; 0.293		

a Histology: Follicular (Working Formulation B-D), diffuse (Working Formulation E-G), small lymphocytic (Working Formulation A), other (Working Formulation H-J and miscellaneous).

b Odds ratio (95 % confidence interval) adjusted for age, state, and respondent type.

c Some smokers could not be classified as ex- or current smokers because of missing values for either age started or years of smoking.

d Trend tests do not include the unknown category.

Risks of Leukemia and Multiple Myeloma from Cigarette Use in Case-Control Studies Conducted at the National Cancer Institute

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Abstract

Relative risks for leukemia and multiple myeloma from cigarette use were evaluated using pooled data from population-based case-control studies conducted in Iowa, Minnesota, and Nebraska. The pooled studies included 634 cases of leukemia, 245 cases of multiple myeloma, and 2,677 age and state of residence matched controls. Leukemia was significantly associated with cigarette use, but multiple myeloma was not. Odds ratios for leukemia did not increase with amount or duration of smoking. Risks were seen with all histologic types of leukemia, except acute nonlymphocytic, which had too few cases for meaningful analysis.

Introduction

Lymphatic and hematopoietic cancers are not usually thought of as smoking-related. An article by Austin and Cole (1986), however, increased interest in leukemia and smoking. During the 1980s the National Cancer Institute conducted three population-based case-control studies to evaluate the etiology of various lymphatic and hematopoietic cancers. Information on tobacco use was sought in each investigation. This report deals with studies of leukemia and multiple myeloma. Tobacco use has been reported for the study conducted in the states of Iowa and Minnesota (Brown et al., 1992a; 1992b). Results presented here are new analyses of pooled data from these earlier studies.

Methods

Population-based case-control studies were conducted on leukemia and multiple myeloma among men Iowa, leukemia among from men from Minnesota, and on leukemia and multiple myeloma among men and women in Nebraska. Details of the study designs have been presented in earlier papers (Brown et al., 1992a, 1992b; Zahm et al., 1990). All cases in Iowa, Minnesota (except major metropolitan areas), and eastern Nebraska were ascertained through tumor registries or direct review of hospital records in the catchment area. Controls for living cases were selected by random digit dialing for those under age 65 and from Health Care Financing Administration files for those aged 65 or older. Controls for deceased cases were selected from state death certificate files. Interviews with subjects or their proxies sought information on many factors including agricultural practices and exposures, occupations held, medical conditions, family history of cancer, and smoking and alcohol use. Odds ratios from logistic regression presented here are adjusted for age, gender, and state unless noted otherwise.

Results

Leukemia

The risk of leukemia was slightly elevated among persons who ever used cigarettes (OR=1.3) compared to those who never used any tobacco product (Table 1). Odds ratios were 1.2 for current smokers and 1.4 for ex-smoker. Evaluation of risk by cigarettes consumed per day, years of smoking, and pack years showed no obvious exposure-response patterns. Odds ratios were slightly larger among persons starting smoking after age 25 than among those starting earlier.

Analyses by histologic type of leukemia are shown in Table 2. Numbers of acute lymphocytic leukemia (ALL) are generally too small for meaningful interpretation. The odds ratios from ever using cigarettes were larger for chronic nonlymphocytic leukemia and myelodysplasias than for the other histologic types. This also held true for current and ex-smokers. No clear exposure-response gradient was evident for any histologic type. Odds ratios were slightly larger among persons who started smoking after age 21 than those who started earlier for all histologic types except myelodysplasia.

Information on cigarette use in these studies was obtained by interview with the subjects or with their proxies when the subjects were deceased. Odds ratios were consistently larger when based on direct interviews than when based on proxy reports, except possibly for duration of use (Table 3). Ever smokers had an OR of 1.5 based

on direct interviews and 1.0 based on proxies, while current smokers had an OR of 1.6 for subject and 1.1 for proxy interviews. No clear trends were observed with duration or intensity of smoking for either subject or proxy interviews. For both subjects and proxies, odds ratios were larger among persons starting smoking at older rather than younger ages.

Table 4 presents odds ratios for leukemia by smoking characteristics and family history of cancer. Risk of leukemia by smoking habit did not differ according to presence or absence of a family history of cancer.

Multiple Myeloma

Odds ratios for multiple myeloma from cigarette use are shown Table 5. This cancer is not associated with cigarette use in these data. Evaluations by direct and proxy interviews showed no relationship either.

Discussion

Leukemia

Pooled data from these two population-based case-control studies show a slight association between leukemia and cigarette smoking. This is consistent with other reports (Bain, 1995). Odds ratios tended to be larger for chronic nonlymphocytic leukemia and myelodysplasia than for other histologic types. Contrary to other reports, however, we did observe an excess risk of chronic lymphatic leukemia among smokers. It was of a similar magnitude to that associated with acute nonlymphocytic leukemia. As previously reported, there was little evidence of an exposure-response gradient. Separate analyses by source of the interview data, i.e., subject or proxy interviews, underscore this problem. Relative risks were closer to unity when based on proxy respondents than when based on direct interviews with the subjects. Family history of cancer has been shown to accentuate the effects of tobacco for some cancers (Ooi, 1986), but no such effect was observed here for leukemia. Risks associated with tobacco use were similar among persons with and without a family history of cancer. Low relative risks such as these are highly susceptible to exposure misclassification, bias and confounding and these effects cannot be ruled out. Adjustment for many potential confounders, including occupation, pesticide and hair dye use, and medical conditions, however, had no effect on the estimates of relative risk associated with cigarette use. The consistency of the leukemia excess in cohort and case-control studies from many countries suggests that it is most likely a causal association.

Multiple Myeloma

No association between multiple myeloma and cigarette use was found in these data. This is generally consistent with other reports (Brown, 1992b).

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Table 1. Odds ratios and 95% confidence intervals for the association between leukemia and cigarette smoking

Cigarette Use	Odds Ratio*	No. Cases/ Controls	95% Confidence Interval
Never Used	1.0	129/963	
Ever Used	1.3	444/1522	1.0-1.7
Current Smoker	1.2	168/566	1.0-1.6
Ex-Smoker	1.4	246/804	1.0-1.9
Cigarettes per day			
1-9	1.0	40/211	0.6-1.5
10-19	1.8	99/246	1.3-2.5
20	1.2	154/518	0.9-1.8
21 or more	1.2	133/413	0.9-1.7
Years Smoked			
1-10	1.5	45/152	1.0-2.4
11-20	1.5	54/176	1.0-2.2
21-30	1.6	76/213	1.1-2.3
31-40	1.0	73/301	0.7-1.4
41 or more	1.3	166/528	1.0-1.7
Pack years			
< 15	1.3	86/318	0.9-1.8
15-<35	1.5	121/350	1.1-2.1
35-<55	1.0	88/350	0.7-1.4
55-195	1.4	110/315	1.0-1.9
Cigarettes Per Day (Current Smokers Only)			
1-9	1.0	11/72	0.5-2.1
10-19	1.4	26/106	0.8-2.4
20	1.3	75/248	0.9-1.9
21 or more	1.5	76/238	1.0-2.2
Age Started Smoking Cigarettes			
< 18	1.2	252/809	0.9-1.6
19-21	1.3	78/301	0.9-1.8
22-25	1.2	41/145	0.8-1.9
26-30	1.6	20/54	0.8-3.0
31 years or older	1.9	27/74	1.0-3.3

* Odds ratios adjusted for age, gender, and state of residence

Table 2. Odds ratios (OR) and 95% Confidence Intervals the association between Leukemia and Cigarette Smoking, by Histologic Type

	ALL		CLL		ANL		CNL		Myelodysplasia	
Smoking Characteristic	**OR***	**95% CI**	**OR***	**95% CI**	**OR***	**95% CI**	**OR***	**95% CI**	**OR***	**95% CI**
Used cigarettes	0.7	0.2-2.6	1.3	1.0-1.9	1.2	0.8-2.0	1.8	0.8-4.2	1.7	0.8-3.7
Current smoker	1.1	0.3-4.6	1.4	0.9-2.1	1.4	0.8-2.3	1.5	0.5-4.2	1.8	0.7-4.9
Ex-smoker	0.5	0.1-2.4	1.4	1.0-1.9	1.0	0.6-1.8	2.1	0.9-5.3	1.7	0.8-3.8
Number Cigarettes Smoked per Day										
1-9	0.7	0.1-7.2	1.2	0.7-2.0	0.8	0.3-2.0	1.2	0.2-5.4	0.5	0.1-2.7
10-19	-		2.0	1.3-3.2	1.8	1.0-3.3	2.7	0.9-8.5	1.6	0.5-4.5
20	1.6	0.4-6.1	1.1	0.7-1.7	1.2	0.7-2.0	1.5	0.5-4.2	2.4	1.0-5.6
21 or more	0.5	0.1-3.0	1.4	0.9-2.1	1.2	0.6-2.1	2.1	0.8-5.7	1.6	0.6-4.4
Years Smoked										
1-10	-		1.8	1.0-3.2	2.2	1.0-4.6	2.1	0.5-7.8	-	
11-20	1.2	0.2-6.5	1.9	1.1-3.3	1.1	0.5-2.5	1.6	0.4-6.0	1.2	0.2-5.4
21-30	-		1.7	1.0-2.9	1.3	0.7-2.7	1.9	0.6-5.9	2.3	0.7-7.4
31-40	2.3	0.3-17.9	1.0	0.6-1.6	0.9	0.4-1.8	1.7	0.5-6.0	1.4	0.5-4.3
41 or more	1.2	0.2-10.5	1.3	0.9-2.0	1.0	0.6-1.8	1.7	0.6-5.3	2.0	0.9-4.6
Packyears										
<15	-		1.5	1.0-2.4	1.4	0.8-2.6	2.3	0.8-6.7	0.6	0.1-2.7
15-34	1.3	0.3-5.5	1.5	1.0-2.4	1.7	1.0-3.0	1.9	0.7-5.4	1.4	0.5-4.0
35-54	0.4	0.1-3.4	1.0	0.6-1.6	0.6	0.3-1.3	1.0	0.3-3.4	2.8	1.1-7.2
55 or more	1.6	0.3-9.6	1.5	1.0-2.4	1.0	0.5-1.9	2.3	0.8-6.8	1.5	0.6-4.2

Table 2 continued

	ALL		CLL		ANL		CNL		Myelodysplasia	
Smoking Characteristic	**OR***	**95% CI**	**OR***	**95% CI**	**OR***	**95% CI**	**OR***	**95% CI**	**OR***	**95% CI**
Age Started Smoking										
<18	0.8	0.2-2.9	1.3	0.9-1.9	1.1	0.7-1.9	1.7	0.7-4.3	1.5	0.7-3.5
19-21	1.0	0.1-6.2	1.2	0.7-1.9	1.4	0.7-2.6	1.3	0.4-4.4	2.6	0.9-7.2
22-25	1.0	0.1-11.2	1.5	08-2.7	0.6	0.2-1.6	2.4	0.6-9.0	1.5	0.4-5.6
26-30	4.6	0.2-75	1.2	0.4-2.9	1.8	0.5-5.5	1.6	0.1-15	1.8	0.2-10
31 or more	-		2.2	1.1-4.4	2.8	1.0-8.0	6.6	0.6-68	0.6	0.1-5.1

*Odds ratios adjusted for age, gender, and state of residence

ALL, acute lymphocytic leukemia

CLL, chronic lymphocytic leukemia or chronic lymphatic leukemia

ANL, acute nonlymphocytic leukemia

CNL, chronic nonlymphocytic leukemia

Table 3. Odds ratios (OR) and 95% confidence intervals for the association between leukemia and cigarette smoking, by type of respondent.

	Subject			Proxy		
Cigarette Use	**OR***	**95% CI**	**No. ca/co**	**OR**	**95% CI**	**No. ca/co**
Never Used	1.0		73/617	1.0		56/346
Ever Used	1.5	1.1-2.1	273/927	1.0	0.7-1.6	171/602
Current Smoker	1.6	1.1-2.3	105/359	1.1	0.6-1.8	63/201
Ex-smoker	1.4	1.0-2.0	163/547	1.1	0.7-1.7	83/257
Cigarette Per Day						
1-9	1.1	0.6-1.9	23/133	0.9	0.4-1.9	17/78
10-19	2.2	1.4-3.4	65/157	1.3	0.7-2.3	34/89
20	1.3	0.9-2.0	93/334	1.1	0.7-1.8	61/184
21 or more	1.5	1.0-22	87/286	1.0	0.6-1.7	46/177
Years Smoked						
1-10	1.6	0.9-2.7	35/118	1.8	0.6-5.2	10/34
11-20	1.6	1.0-2.6	40/38	1.5	0.6-3.5	14/38
21-30	1.6	1.0-2.6	53/160	1.8	0.8-3.8	23/53
31-40	1.0	0.6-1.6	43/195	1.0	0.5-1.4	30/106
41 or more	1.7	1.1-2.5	97/295	0.9	0.5-1.4	69/233
Pack years						
<15	1.4	0.9-2.1	58/232	1.5	0.8-3.0	28/86
15-34	1.7	1.1-2.5	78/248	1.3	0.7-2.2	43/102
35-54	1.2	0.8-1.8	63/240	0.7	0.4-1.3	25/110
55-195	1.7	1.1-2.6	67/178	1.1	0.4-1.8	43/137
Age Started Smoking						
<18	1.4	1.0-2.0	163/525	1.0	0.6-1.5	89/284
19-21	1.6	1.0-2.4	61/220	0.9	0.4-1.8	17/81
22-25	1.2	0.7-2.2	23/95	1.2	0.6-2.6	18/50
26-30	1.6	0.6-4.0	9/32	1.5	0.6-3.9	11/22
31 or older	2.0	0.9-4.5	12/42	1.7	0.7-4.2	15/32

*Odds ratios adjusted for age, gender and state of residence

Table 4. Risk of leukemia by cigarette use and family history of cancer

	No 1st Degree Relatives with Cancer			1st Degree Relatives with Cancer		
Cigarette Use	**OR***	**95% CI**	**No. ca/co**	**OR***	**95% CI**	**No. ca/co**
Never Used	1.0		55/575	1.0		70/375
Ever Used	1.3	0.9-1.9	207/886	1.3	0.9-1.8	222/606
Current Smoker	1.2	0.8-1.8	74/333	1.5	1.0-2.3	88/226
Ex-smoker	1.3	0.9-2.0	116/464	1.1	0.8-1.7	122/329
Cigarettes per Day						
1-9	1.0	0.5-2.0	17/123	1.0	0.5-1.8	21/84
10-19	1.7	1.0-2.8	49/157	1.9	1.1-3.2	46/84
20	1.1	0.7-1.8	69/309	1.3	0.8-1.9	78/202
21 or more	1.3	0.8-2.2	61/248	1.2	0.8-1.9	71/208
Years Smoked						
1-10	1.6	0.9-3.1	26/109	1.6	0.8-3.4	18/42
11-20	1.4	0.7-2.7	24/100	1.4	0.8-2.6	28/71
21-30	1.4	0.8-2.5	35/123	1.6	0.9-2.8	38/86
31-40	1.0	0.6-2.0	37/181	1.0	0.6-1.7	34/120
41 or more	1.3	0.8-2.0	68/284	1.2	0.8-1.8	92/236
Packyears						
<15	1.4	0.8-2.3	43/204	1.3	0.8-2.2	40/109
15-34	1.4	0.9-2.3	58/209	1.5	0.9-2.4	57/135
35-54	0.9	0.6-1.5	41/205	1.0	0.6-1.7	44/142
55-195	1.4	0.8-2.3	44/157	1.3	0.8-2.0	64/156

*Odds ratios adjusted for age, gender and state of residence.

Table 5. Odds ratios (OR) and 95% confidence intervals for the association between multiple myeloma and cigarette use.

Cigarette Use	OR*	95% CI	No. Ca/CO
Never Used	1.0		76/828
Ever Used	1.0	0.7-1.4	150/1144
Current Smokers	0.8	0.5-1.2	54/476
Ex-smokers	0.8	0.8-1.8	85/534
Number per Day			
1-9	0.9	0.5-1.6	17/164
10-19	1.0	0.6-1.8	27/193
20	1.0	0.7-1.6	60/384
21 or more	0.9	0.5-1.4	39/332
Years Smoked			
1-10	1.4	0.6-3.0	12/114
11-20	1.2	0.6-2.3	19/135
21-30	1.0	0.6-1.9	21/164
31-40	0.7	0.4-1.2	22/212
41 or more	1.0	0.7-1.6	65/385
Packyears			
<15	0.9	0.5-1.6	25/245
15-34	1.2	0.7-1.9	40/262
35-54	1.0	0.6-1.6	38/251
55 or more	0.8	0.5-1.4	32/225

*Odds ratios adjusted for age, gender, and state of residence.

Risk Factors for Adrenal Cancer: An Exploratory Study

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Abstract

Adrenal cancer is a heterogeneous group of neoplasms with unknown etiology. In search of risk factors, we conducted a case-control study based on data from the 1986 National Mortality Followback Survey, which included a questionnaire sent to the next of kin of almost 20,000 deceased adults (age ≥25 years) in the United States. Information was obtained on a large number of items, including use of cigarettes, alcohol, oral contraceptives(OCs), height and weight, and food consumption patterns. A total of 176 subjects who died of adrenal cancer (88 men and 88 women) and 352 controls (176 men and 176 women) who died of causes unrelated to smoking, drinking, or oral contraceptives (for female controls) were included in the study. Although information on histologic type was not available, most cases were estimated from incidence surveys to be adrenocortical carcinoma, with a small percentage being malignant pheochromocytoma or neuroblastoma. An increased risk was associated with heavy smoking (≥25 cigarettes/day) among men (odds ratio (OR)=2.0, 95% confidence interval (CI) 1.0-4.4), but not women. No clear association was seen for alcohol use, height and weight or food consumption patterns in either sex. Among women, increased risks were found for ever users of OCs (OR=1.8, 95% CI 1.0-3.2) and especially those who used them before age 25 (OR=2.5, 95% CI 1.2-5.5). When the analysis was restricted to subjects with spousal respondents, more pronounced risks were seen for ever users of OCs and for those who used OCs before age 25 (OR=2.8, 95% CI 1.0-7.5). Our findings suggest that cigarette smoking and use of OCs may increase the risk of adrenal cancer, but additional studies are needed with more detailed information on risk factors and histologic type of adrenal cancer.

Introduction

Cancers of the adrenal gland arise from either the adrenal cortex or the medulla (Robbins and Kumar, 1987), and they are extremely rare. Based on data from the Surveillance, Epidemiology and End Results (SEER) program in the United States 1975-92, the average annual age-adjusted incidence rates were 0.29 per 100,000 for white males, 0.25 for black males, 0.25 for white females and 0.18 for black females (Hsing et al., 1995). The annual age-adjusted U.S. mortality rates for adrenal cancer 1985-92 were 0.24 per 100,000 for white males, 0.23 for black males, 0.21 for white females and 0.18 for black females (Hsing et al., 1995), which resembles the incidence rates, suggesting that adrenal cancer is usually fatal. Adrenal cancer is a heterogeneous group of neoplasms, with 34% at all ages classified as adrenocortical carcinoma, 28% as neuroblastoma (including ganglioblastoma), 8% as malignant pheochromocytoma and 30% as other malignancies (mostly poorly specified; Hsing et al., 1995). Adrenocortical carcinomas occur mainly in adults (58% of cases were over age 50 years), while 90% of adrenal neuroblastomas arise in children 0-4 years of age (Hsing et al., 1995).

The role of genetic susceptibility in adrenal neoplasms has been suggested by the relation of adrenocortical carcinoma to Li-Fraumeni syndrome (Garber et al., 1991), congenital hemihypertrophy (Fraumeni and Miller, 1967), and Beckwith-Wiedemann syndrome (Henry et al., 1989); pheochromocytoma to multiple endocrine neoplasia type 2 and von Hippel-Lindau syndrome (Neumann et al., 1993); and neuroblastoma to mutations of the gene responsible for neurofibromatosis type 1 (The et al., 1993). Environmental determinants of these tumors are obscure, though geographic variation has been suggested by the elevated risks of adrenocortical cancer in Brazil (Stiller et al., 1994) and the deficit of neuroblastoma in tropical areas of Africa (Miller, 1977).

In search of risk factors, we conducted a case-control study using data from the 1986 National Mortality Followback Survey (NMFS), which included a questionnaire sent to the next of kin of almost 20,000 deceased adults (age ≥25) in the United States. Although information on histologic type was not available, most cases in this study probably were either adreno-

cortical carcinoma or poorly specified adrenal malignancies, since among adult patients (age ≥25 years) with adrenal cancer neuroblastoma and malignant pheochromocytoma account for 12% of the adrenal cancer cases reported in national incidence surveys (Hsing et al., 1995).

Subjects and Methods

NMFS

Study subjects were selected from the 18,733 decedents included in the 1986 NMFS, conducted by the National Center for Health Statistics (NCHS). Details of this study have been reported elsewhere (Seeman et al., 1989; Hsing et al., 1992). Briefly, a 10% systematic sample of 1986 U.S. death certificates, excluding Oregon because of the State's respondent consent requirement, was sent by each of the states to NCHS. From these death certificates, a probability sample comprising approximately 1% of U.S. adult deaths (age 25 years or older) was selected. In addition, among whites aged 25-74 years, all 1985 deaths from several rare cancers, including cancer of the adrenal gland, were ascertained and included in the study.

Questionnaires were sent to next of kin of these selected decedents to obtain information on the subject's demographic characteristics, use of cigarette, alcohol, oral contraceptives (OCs), dietary habits (e.g., frequency of consumption of meat, vegetables, and fruits), height and weight and medical history. The response rate for the informant questionnaire was 89%.

A total of 190 deaths from cancer of the adrenal gland (ICD-9 code 194.0) were included in the NMFS (18 from the 10 % sample of U.S. deaths in 1986 and 172 from all adrenal cancer deaths in 1985). After exclusion of the few subjects who were nonwhites (n=2), and the non-respondents (n=12), 176 (88 men and 88 women) cases were available for analysis.

Controls were selected from white decedents dying of causes other than cancer of the adrenal gland whose next of kin completed a questionnaire. Excluded as potential controls were subjects who died of smoking- or alcohol-related causes or of the other five rare cancers selected for study (nasopharynx, nasal cavity, small intestine, male breast and primary liver cancer in young women). For female controls, deaths related to OC use were also excluded from potential controls.

Among the 792 eligible male and 317 female controls, two controls per case were randomly selected from the matching sex- and age-specific (five-year age groups) stratum. In total, 176 male controls and 176 female controls were included in the analysis. The major causes of death among male controls were accident and injury (16%), diabetes mellitus (13%), lymphoma (7%), brain cancer (6%), and prostate cancer (4%). Among female controls, major causes of death were accident and injury (15%), lymphoma (10%), brain cancer (7%), skin melanoma (7%) and rectal cancer (5%).

Odds ratios (OR) and corresponding 95 % confidence intervals (CI) for adrenal cancer in relation to potential risk factors were estimated using the exact method (Gart, 1971; Thomas, 1975). Tests for linear trends in proportions were also performed (Cochran, 1954; Armitage, 1955). Potential confounding effects of age, income, education, and marital status were examined and adjusted for when necessary, using multiple logistic regression when necessary (Breslow and Day, 1980).

Results

A total of 176 cases (88 men and 88 women) and 352 controls (176 men and 176 women) were included in the analysis. The median age at death for cases was 54 years for men and 52 for women. Selected characteristics for cases dying of adrenal cancer and for their controls are shown in Table I. Compared to controls, cases were more likely to be married and to have a higher income. Cases tended to have a slightly higher educational level than controls. For male subjects, spouses were the main respondents, while spouses and parents were the major surrogate respondents for female subjects.

Table II shows that male heavy smokers (≥25 cigarettes/day) had a 2-fold increased risk of adrenal cancer (95% CI 1.0-4.4). Current smokers had a 1.6-fold risk, which was not statistically significant. No increased risk was associated with smoking among women or with alcohol drinking in either sex. Limiting responses to spousal informants did not affect the results for tobacco or alcohol use.

As shown in Table III, women who ever used OCs (OR=1.8; 95% CI=1.0-3.2) and those who used them before age 25 years (OR=2.5; 95% CI=1.2-5.5) had an increased risk of adrenal cancer. In addition, among subjects with a spousal respondent, risks were significantly elevated for ever users of OCs (OR=2.4; 95% CI 1.0-5.4) and for those who used them before age 25 years (OR=2.8; 95% CI 1.0-7.5). A 5-fold risk was found for those who used OCs before age 25 and for more than 5 years (OR=5.1; 95% CI 1.5-16.7). No information was available on current use (prior to death), type or dosage of OCs, or on time since last use.

No clear association was found with consumption of meat, vegetables, fruits, cured meat or dairy products or with body mass index in either sex, though a statistically significant association was found for fruit consumption among women (Table IV).

Discussion

Our exploratory case-control study of adrenal cancer suggests that cigarette smoking and use of OCs are potential risk factors. No association was seen with alcohol, food consumption patterns, height, weight or body mass index in either sex. Although data were not available to enable an assessment of risk by histologic type, our findings pertain largely to adrenocortical carcinoma since we included only subjects between the ages of 25 and 64 years, and in this age group adrenal neuroblastoma and malignant pheochromocytoma constitute only 12% of adrenal cancer cases in national incidence surveys (Hsing et al., 1995). Furthermore, among SEER patients aged 25 years and over who were diagnosed with adrenal cancer and had adrenal cancer mentioned as an underlying cause of death on their death certificates, only 9 % were reported with pheochromocytoma and less than 1 % with neuroblastoma (data not shown).

Although the next-of-kin informant may have limited knowledge about the deceased subject's exposure history, it has been shown that for broad categories of exposure, such as smoking, drinking, and use of OCs, reliable information can be obtained from surrogate respondents, particularly a spouse (Glass et al., 1974; Thorogood and Vessey, 1989; McLaughlin et al., 1990). Differential recall between surrogate respondents for cases and controls is unlikely, since controls were also deceased, a large percentage of them had other cancers as well and the respondents were probably not sensitized to any potential relationship of smoking and OC use with adrenal cancer. Due to anticipated recall problems with surrogate interviews, the NMFS questionnaire sought only limited information on particular exposures.

Although combination OCs have been reported to increase the risk of breast, cervical, and hepatic cancers (IARC, 1987), an association with adrenal cancer has not been previously investigated, perhaps due to its low incidence and the absence of case-control studies. Experimental studies, however, have indicated a high risk of adrenal tumors in ovariectomized mice (Strickland et al., 1980) and in rats given exogenous estrogens (Noble et al., 1975). Since the observed OC associations we observed were borderline significant and the trend with duration of use was not strong, these findings need to be confirmed in future studies. We had no information on current use of OCs. In future studies it will be of interest to evaluate the risks among current and past users and in relation to cessation of use.

It is also important to clarify the smoking-related risk of adrenal cancer that was seen primarily among men in our study. There are some experimental data consistent with a smoking effect on the adrenal glands. In an inhalation study of cigarette smoke in rats, a low but statistically significant incidence of adrenocortical carcinomas

and adenomas was noted (Dalbey et al., 1980). In hamsters, the intratracheal administration of benzo(a)pyrene also resulted in a significant yield of adrenocortical adenomas (Beems and Beck, 1984; Beems, 1986). To our knowledge, adrenal tumors have not been linked to tobacco-specific nitrosamines (Hoffmann et al., 1984), although other N-nitroso compounds have induced adrenocortical tumors in rats (Moore et al., 1989). In interpreting our findings, it is noteworthy that smoking and drinking are usually overrepresented in dead controls (McLaughlin et al., 1985a; b). Although we excluded persons who died of alcohol- and smoking-related causes of death as potential controls, the prevalence of smoking among the male controls (32%) was still higher than that in the U.S. population (25%) during the time period of this study (US Surgeon General, 1989). This high frequency may have resulted in an underestimate of the real association between smoking and adrenal cancer.

In summary, despite its limitations, this nationwide case-control study represents a systematic attempt to examine risk factors for adrenal cancer. Further investigations with more direct and detailed exposure information and specific histologic types of adrenal cancer are needed to clarify the risks that may be associated with cigarette smoking and use of OCs.

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TABLE 1. PERCENT DISTRIBUTION OF SELECTED CHARACTERISTICS AMONG ADRENAL CANCER CASES AND CONTROLS, BY SEX

	Males				Females			
	Cases		Controls		Cases		Controls	
	N	%	N	%	N	%	N	%
Total	88	100.0	176	100.0	88	100.0	176	100
Age at death (yr)								
25-34	14	15.9	28	15.9	12	13.6	24	13.6
35-44	11	12.5	22	12.5	17	19.3	37	21.0
45-54	21	23.9	42	23.9	22	25.0	43	24.4
55-64	42	47.7	84	47.7	37	42.1	72	40.9
Marital status at death								
Never married	9	10.2	39	22.2	3	3.4	18	10.2
Divorced/separated	10	11.4	30	17.1	16	18.2	32	18.2
Widowed	3	3.4	5	2.8	11	12.5	21	11.9
Married	64	72.7	96	54.6	54	61.4	101	57.4
Unknown	2	2.3	6	3.4	4	4.5	4	2.3
Education (yr)								
< 9	12	13.6	29	16.5	7	8.0	24	13.6
9-11	13	14.8	38	21.6	10	11.4	30	17.0
12	28	31.8	49	27.8	40	45.4	70	39.8
>12	29	33.0	50	28.4	23	26.1	48	27.3
Unknown	6	6.8	10	5.7	8	9.1	4	2.3
Total annual family income								
<$11,000	19	21.6	42	23.9	17	19.3	51	29.0
$11,000-$24,999	21	23.9	36	20.4	24	27.3	39	22.2
≥$25,000	33	37.5	45	25.6	31	35.2	46	26.1
Unknown	15	17.0	53	30.1	16	18.2	40	22.7
Type of respondent								
Spouse	52	59.1	85	48.3	43	48.9	79	44.9
Parent	6	6.8	17	9.7	18	20.4	28	15.9
Child	10	11.4	30	17.0	13	14.8	27	15.3
Sibling	10	11.4	21	11.9	4	4.5	19	10.8
Other	10	11.4	23	13.1	10	11.4	23	13.1

TABLE 2. ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR ADRENAL CANCER IN RELATION TO CIGARETTE SMOKING AND ALCOHOL CONSUMPTION, BY SEX

	Males				Females			
	Cases	Controls	OR[a]	95% CI	Cases	Controls	OR[a]	95% CI
Cigarette use								
Nonsmoker	17	46	1.0	-	35	73	1.0	-
Current smoker	35	62	1.6	0.8-3.3	26	60	1.0	0.6-1.9
Exsmoker	34	56	1.4	0.7-2.9	25	39	1.2	0.6-2.4
Ever smoker	69	121	1.4	0.8-2.8	52	100	1.1	0.6-1.9
1-14 cigarettes/day	13	33	1.0	0.4-2.4	13	24	1.0	0.5-2.4
15-24 cigarettes/day	22	39	1.4	0.6-3.1	20	40	1.1	0.5-2.1
≥25 cigarettes/day	32	41	2.0	1.0-4.4	16	31	1.2	0.6-2.5
Alcohol use								
Nondrinker	10	22	1.0	-	15	42	1.0	-
Drinker	75	145	0.9	0.4-2.1	72	129	1.4	0.7-2.1
<1 time/week	25	54	0.7	0.3-1.9	47	73	1.5	0.7-3.1
1-2 times/week	17	26	1.1	0.4-3.1	7	29	0.6	0.2-1.6
≥3 times/week	27	60	0.8	0.3-2.1	15	26	1.3	0.5-3.3

a Adjusted for marital status and income.

TABLE III. ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR ADRENAL CANCER IN RELATION TO ORAL CONTRACEPTIVE (OC) USE, BY TYPE OF RESPONDENT

	All subjects				Spouse respondents			
	Cases (n=88)	Controls (n=176)	OR[a]	95% CI	Cases (n=43)	Controls (n=79)	OR[b]	95% CI
OC use								
Non-users	52	118	1.0	-	22	57	1.0	-
Ever users	29	37	1.8	1.0-3.2	18	19	2.4	1.0-5.4
Years of use								
< 5	13	17	1.6	0.7-3.6	10	12	2.1	0.8-5.6
> 5	14	17	1.9	0.8-4.2	7	7	2.5	0.8-8.3
Unknown	9	24	1.0	0.4-2.5	4	3	3.6	0.7-17.8
Age at first use (yr)								
<25	18	16	2.5	1.2-5.5	11	10	2.8	1.0-7.5
>25	9	16	1.2	0.5-2.9	6	7	2.2	0.7-7.5
Unknown	9	26	0.9	0.4-2.2	4	5	2.0	0.5-8.6

a Adjusted for marital status and income.

b Adjusted for income.

TABLE IV. ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR ADRENAL CANCER IN RELATION TO CONSUMPTION OF MEAT, VEGETABLES, FRUITS AND CURED MEAT AND TO BODY MASS INDEX, BY SEX

	Males				Females			
	Cases	Controls	OR[a]	95% CI	Cases	Controls	OR[b]	95% CI
Meat								
<3 times/week	10	29	1.0	-	24	40	1.0	-
3-6 times/week	43	72	1.2	0.5-2.9	38	76	0.7	0.4-1.4
≥7 times/week	29	57	1.2	0.5-2.8	24	51	0.8	0.4-1.6
Fruits								
<3 times/week	17	49	1.0	-	12	54	1.0 -	
3-6 times/week	29	41	1.9	0.9-4.1	37	39	4.0	1.8-8.9
≥7 times/week	34	67	1.7	0.8-3.6	35	74	2.2	1.0-4.8
Vegetables								
<3 times/week	2	8	1.0	-	4	15	1.0	-
3-6 times/week	22	30	2.6	0.3-14.1	16	40	1.3	0.4-4.7
≥7 times/week	58	119	1.7	0.3-9.0	66	112	2.2	0.7-7.0
Cured meat								
<1 time/week	21	53	1.0	-	29	56	1.0	-
1-2 times/week	37	48	1.7	0.9-3.5	35	70	0.9	0.5-1.7
≥3 times/week	23	50	1.0	0.5-2.2	20	41	1.0	0.5-2.0
Dairy food								
<3 times/week	3	21	1.0	-	20	29	1.0	-
3-6 times/week	23	49	2.7	0.9-10.4	23	48	0.7	0.3-1.5
≥7 times/week	57	88	4.3	1.2-15.4	42	90	0.7	0.3-1.4

TABLE IV. continued

	Males				Females			
	Cases	Controls	OR[a]	95% CI	Cases	Controls	OR[b]	95% CI
Body Mass Index								
Quartile 1	22	39	1.0	-	25	40	1.0	-
Quartile 2	21	42	1.2	0.6-2.6	25	42	0.9	0.4-1.8
Quartile 3	20	41	0.9	0.4-1.9	18	41	0.7	0 3-1.5
Quartile 4	20	40	0.8	0.4-1.7	17	42	0.6	0.3-1.4

a Adjusted for marital status, income, and smoking.

b Adjusted for marital status, income, and OC use.

Consensus Conference Participants

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Dr Shelia Hoar Zahm
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PROGRAMME

CONSENSUS CONFERENCE 12-14 February 1996

BRISBANE NOVOTEL HOTEL

Monday 12/2/96 DAY 1

8.30 — 9.00 am	Registration — Coffee	
9.00 am	Opening	Mr Keith Lyon (Deputy President, Repatriation Commission)
	Background	Prof. K. Donald
	Legislation & ground rules Questions of a scientific nature List of specific issues	(Chairman, Repatriation Medical Authority)
	Contextual Overview of the Conference Program	Assoc. Prof. G. Colditz (Harvard Medical School)

MORNING TEA

FIRST QUESTION: Does smoking cause Malignant Neoplasm of the Prostate?

Chairman — Professor Graham Colditz

Presentations by the following:

Dr. Hsing	A population-based case-control study of prostate cancer in China
Dr. Thun	Smoking and fatal prostate cancer in a large cohort of adult men
Prof. Coughlin	Cigarette smoking as a predictor of death from prostate cancer

LUNCH

Dr. Lumey	Prostate cancer and smoking: A review Lifetime smoking habits and prostate cancer: An Evaluation of multiple measures of exposure
Dr. Giles	Smoking and prostate cancer: an interim analysis of the Australian Collaborative case-control study of risk factors for prostate cancer
Prof. Doll	Comment on papers by above presenters

Observer Question Time — 15 Minutes

AFTERNOON TEA

Break up into 4 Syndicates for discussion until 6.00 PM

Tuesday 13/2/96 DAY 2

8.30 — 9.00 am	Registration — Coffee
9.00 am	Report back from Syndicates
OUTCOME	By Morning tea have a CONSENSUS Position on Question One.

MORNING TEA

SECOND QUESTION — How should tobacco dose be assessed? What is a critical exposure? (Refer to cigarette smoking dose question attached.)

- What are the most common confounding variables in smoking studies?
- How to use this information to estimate risk, and for compensation cases?

Chairman — Professor Ken Donald

Presentations by the following:

Prof. Hakulinen	Various measures of smoking as predictors of cancer of different types in two Finnish cohorts
Dr. Horsley	Factors that confound smoking
Dr. Bordujenko	Cigarette smoking: Quantity, quality and comparison.

Observer Question Time — 15 Minutes

LUNCH

Comments on above papers by:

Prof. Doll

Dr. Thun

Dr. Hoar Zahm

Dr. Blair

Prof. Dwyer

Break up into 4 Syndicates for discussion.

AFTERNOON TEA

Discussion continues until 6.00 PM

Wednesday 14/2/96 DAY 3

8.30 — 9.00 am Registration — Coffee

Report back and reach agreement on calculation of critical exposure.

MORNING TEA

THIRD QUESTION Emerging smoking related associations including those with rare/unusual diseases.

Chairman — Professor Graham Colditz

Presentations by the following:

Prof. Doll	Some cancers weakly related to smoking
Dr. Thun	Cigarette smoking and death from selected cancer in CPS II
Dr. Hoar Zahm	Tobacco and non-Hodgkin's lymphoma

LUNCH

Presentations by the following:

Dr. Blair	Risks of leukaemia and multiple myeloma from cigarette use
Dr. Hsing	Risk factors for adrenal cancer: An exploratory study

AFTERNOON TEA

SUMMARY DISCUSSION Where to from here?

- Future research objectives
- Future study designs

Chairman — Professor Ken Donald

Observer Question Time — 15 Minutes

CLOSE.

OBSERVERS

EX-SERVICE ORGANISATIONS:

Australian Veterans and Defence Services Council

Legacy

Regular Defence Force Welfare Association

Returned and Services League of Australia Limited

Vietnam Veterans' Association of Australia

Vietnam Veterans' Federation of Australia

War Widows' Guild of Australia

DEPARTMENT OF VETERANS' AFFAIRS REPRESENTATIVES:

Mr Bill Maxwell

Mr John Douglas

Mr Bob Connolly

Dr Mekala Srirajalingam

Dr Ian Smith

Dr Beverley Grehan

Ms Ruth Jowett

Mr Steven Medza

Mr David Goldrick

Section IV

APPENDICES

Syndicate Group II

- present evidence is insufficient to suggest a causal association between smoking and prostate cancer
- there is no adequate evidence that smoking is associated with an increased incidence of prostate cancer
- there is limited evidence that smoking is associated with progression of prostate cancer

Strength of Association

- there is limited evidence of a weak association for progression of prostate cancer based upon cohort studies of mortality
- there is no evidence of an association of prostate cancer incidence and smoking

Biological Plausibility

- indirect evidence only, very weak

Biological Gradient (Dose- Response)

- evidence of dose-response noted only in US Veterans' study of prostate cancer mortality

Future needs to determine causality

- replication of studies addressing incidence and progression of prostate cancer particularly staging of disease
- concern that reliance on prostate cancer deaths (cohort studies) substantially underestimate real prostate cancer incidence
- more adequate determination of ongoing exposure (smoking status)
- more adequate determination of screening status

Figure 1. Summary from Syndicate Group 2.

Syndicate Group I

1. There is inadequate evidence that smoking is causally related to the occurrence of prostate cancer

   (a) There is limited evidence that smoking is associated with increased mortality from prostate cancer

   (b) There is inadequate evidence that smoking is associated with prostate cancer incidence

2. A plausible inference from these statements is that smoking may be associated with poorer survival once prostate cancer has been diagnosed.

Figure 2. Summary from Syndicate Group 1.

Minimum duration of smoking? "Regular" smoke?

Index = Likelihood that exposure caused the disease, given the person's smoking history

= (RR–1)/RR

e.g. RR = 1.3

gives an index of 0.3/1.3

- Calculate RR under simple model for a given dose level, based on smoking intensity.
- For lung cancer and bladder cancer, take into account years stopped

(In the absence of data, assume the risk was as if smoking did not stop).

Group II

1. Smoking risk should be assessed according to attributable risk percentage among the exposed.

   Never smoker: <100 cig./lifetime or <1 cigarette per day for a year

Ever smoker:

- exclude if started smoking within one year of diagnosis
- exclude if quit more than twice the time over which relative risk returns to unity, if such data are available
- dose "triggers" to be measured by attributable risk percentage amount the exposed.

RMA will determine the cut off for compensation for the 2 groups of veterans (i.e. veterans who served in combat/veterans who have not).

Example:

Bladder Cancer (Hartge, 1987)

Cig per day	Odds Ratio	Attributable Risk % In Exposed
0	1.0	—
<20	1.8	44%
20–39	2.6	62%
40+	2.6	62%

Lung Cancer

Cig per day	Odds Ratio	Attributable Risk % In Exposed
0	1.0	—
<10	3.2	69%
10–<20	10.4	90%
20+	18.4	95%

If RMA compensated at AR% exposed >50% (the level of assurance of association needed in civil workman's compensation cases), then smoking at any level would be the "trigger" for lung cancer while smoking 20+ cigarettes per day would be required for bladder cancer. The smoking measure (e.g. cig per day) would depend on what was available in the literature.

Several could be used (e.g. cigarettes per day), duration.

Meeting the AR% exposed criteria for any one measure would be sufficient for compensation.