IDENTIFICATION OF RISK FACTORS ASSOCIATED WITH CERVICAL INTRA-EPITHELIAL NEOPLASIA AMONG WOMEN IN BRITISH COLUMBIA

By

DANIELLE SIEW YEE CHEW

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Department of Statistics

The University of British Columbia
Vancouver, Canada

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Abstract

Multiple etiologic factors have been described for invasive cervical cancer. The most important ones being *sexual activity and smoking.* Less is known regarding the factors predisposing to risk of Cervical Intraepithelial Neoplasia (CIN). The increasing incidence among women prompted a study of this disease in British Columbia in carrying out a case control study to identify the risk factors associated with the disease. Incidentally, that is the main focus of this paper.

A case-control design was used with cases and controls identified from the Cytology database of the British Columbia Cancer Agency which contains a complete record of all cervical cytology done in British Columbia. Cases were women with diagnosis of cervical dysplasia or carcinoma in-situ whereas controls were women with no history of cervical abnormality. Estimates of the relative risk together with its 95% confidence interval are obtained from the maximum likelihood estimates of the binary logistic regression models.

The important risks factors associated with CIN that have been identified in this study are current cigarette smoking, sexual frequency, number of different lifetime sexual partners, combine usage of both condom and diaphragm and dietary intake of vitaminA.

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Chapter 1

INTRODUCTION

Cervical dysplasia is generally regarded as a precursor lesion for cervical cancer. Along with carcinoma in-situ, it forms the entity known as cervical intra-epithelial neoplasia (CIN). Its identification and successful treatment has formed the basis of screening programmes which have reduced the incidence and mortality from invasive cervical cancer in women, including those in British Columbia over the past decades.

The natural history of cervical-cancer is believed to involve stepwise progression of sequential epithelial changes from dysplasia to carcinoma in-situ which eventually results in an invasive lesion. It is not known whether all lesions progress through each stage of the disease. Diagnosis is usually made in two steps: First, women have a pap smear whereby a sample of cells is scraped form the cervix and transferred to microscope slide. Here it is read by a technician and examined for the presence of cells suspicious of dysplasia or malignancy. If such cells are recognised, then the subject is referred for a biopsy, usually colposcopically directed, in which the cervix is directly examined

and suspicious areas excised for definitive diagnosis. Areas of disease are then treated by cryotherapy (freezing), laser therapy , cone biopsy (excision of a large part of the cervix) or hysterectomy depending on the extent of the disease. The pap-smear screening method, together biopsy has lead to characterising the dysplasia as mild, moderate , severe or carcinoma in-situ. Analysis of histories of women who were not treated for the disease has shown that spontaneous reversion is common. However, it is generally recognised that all invasive cancer develops from CIN so that some form of treatment for the more serious forms of CIN is always indicated.

In British Columbia, the incidence rate of invasive cervical cancer has fallen from *19.7* per *100,000* in 1960's to a value of *6.6* per *100,000* in 1980's. During this time, the number and incidence of histologically confirmed cervical dysplasia and carcinoma in-situ has risen steadily in BC. The success of the screening program, in combination with changes in sexual activity, have resulted in CIN becoming a major health cost to the province.

Multiple etiologic factors have been described for cervical cancer. The most important ones being *sexual activity and smoking.* Less is known regarding the factors predisposing to risk of CIN. The division of Epidemiology, Biometry and Occupational Oncology of The British Columbia Cancer Agency (BCCA), was interested in identifying the risk factors associated with the development of cervical dysplasia and cervical cancer among women in British Columbia. The study of this disease is of great interest both practically and scientifically since the identification of factors which may influence its development may increase our ability to control this disease. Moreover, a greater

understanding of its etiology may also allow a better appreciation of factors common to a number of pre-malignant conditions.

Chapter 2

EPIDEMIOLOGY OF CERVICAL CANCER

The Epidemiology of cervical cancer has been studied for many years. It was first remarked in the 17th century that the disease was rare among nuns but common in prostitutes leading to early speculation on its relationship with sexual activity. This has led to a large number of epidemiological studies which examine *sexual frequency, age at 1st intercourse and number of sexual partners* as possible risk factors[1,3–4]. Because cervical dysplasia is considered a precursor lesion of cervical cancer, they should be expected to share important epidemiological features. More recently, studies of the effect of sexual activity have been undertaken for cervical dysplasia; although the data is not as extensive, a similar relationship is seen to that for cervical cancer[2]. The findings of all studies are not unanimous; however, the majority show that *Multiple sexual partners* has the strongest relationship to cervical dysplasia and cancer of all

factors reflecting sexual behavior.

The relationship of the disease to sexual behavior suggests a sexually transmitted infectious agent may be responsible for the initiation or promotion of cervical neoplasia. This inference is further strengthened by the finding that cervical cancer is higher in wives of males with penile cancer[5] and that a direct relationship with sexual activity of the subject's usual partner[4] has been seen. *Herpes simplex virus type 2 (HSV-2)* has been considered as an etiologic agent[4,6–7] and recent evidence suggests *Human papilloma virus(HPV) or wart virus* may play an important role in causing cervical cancer[8–10]. A large number of sero-epidemiological studies have found a higher frequency of *HSV-2* antibodies among cases with CIN than normal controls[4,6]. Similar evidence exists for *HPV*[10]. However final evidence that any of these viruses is a primary cause of CIN is not yet available since their common sexually transmitted epidemiology implies they would be closely associated with cervical cancer risk.

Since cervical cancer behaves like a sexually transmitted disease, certain methods of contraception may afford some degree of protection against the disease. The role of contraceptive use in the epidemiology of cervical neoplasia has been an area of intensive epidemiologic research and conflicting findings have been presented. Among the common contraceptive methods (*oral contraceptive, intrauterine device, diaphragm, chemical spermicide, condoms*), the method most frequently studied has been *oral contraceptives.* Several epidemiological studies find a positive relationship between *oral contraceptive* usage and cervical dysplasia as well as cervical cancer[11–14]; a similar number find no relationship[1–2,4]. One study shows women with multiple sex partners have greater

protection using barrier methods of contraception[4]. The role of other contraceptive methods has not been thoroughly explored. One impediment has been that the association of various contraceptive methods to cervical cancer is confounded by pap-smear utilization, smoking status and sexual behavior[15]. In summary, it seems reasonable to assume that contraceptive usage is a potential risk factor for CIN and should be included in the studies of this disease.

Cigarette smoking has been implicated as a risk factor for CIN and cervical cancer in numerous studies in past years[16,18–23]. It was originally supposed that the relationship seen with cigarette consumption reflected confounding beween this factor and others such as social-economic status and sexual habits known to be associated with CIN. However, control for these variables does not remove the effect of smoking. Similar results are also reported for cervical dysplasia[2,16]. In both studies, no dose-response relationship is seen between smoking and CIN risk whereas one is found for cervical cancer[20,23].

Diet has been associated with many malignancies and with CIN in particular. A number of epidemiological studies have suggested that *carotenoids, vitamin A, vitamin C and folic acid* may reduce the risk of cervical cancer[19,26–32]. Low levels of *vitamin A*, or its precursor β-carotene could result in alterations of the cervical tissue that cause the area to be more vulnerable to carcinogenesis. Several case-control studies have found significantly decreased intake of β-carotene among cases of cervical dysplasis and for invasive cervical cancer[26–27,29,33–34], when compared to controls. However, the relationship with preformed *vitamin A* is not consistent[19,27,35]. This may be due to

the anti-oxidant effect of β-carotene with its ability to trap free radicals, and possibly prevent malignant transformation[24]. *Vitamin C* is an essential nutrient in the synthesis of collagen, the major component of the extracellular matrix which is the first barrier of the body against tumor cell invasion. Levels of *vitamin C* have been found to be inversely associated with CIN with a relative risk of 6.8 seen in those consuming less than 50% of the recommended daily allowance (30 mg)[26].

Another nutrient which has attracted much attention with a role in CIN has been *Folic acid.* Folic acid deficiency has been shown to produce megaloblastic changes in the cervical epithelium[37] which have a similar appearance to dysplasia. Megaloblastic changes have also been seen in 19% of women using oral contraceptives[38]. These observations lead to a clinical trial of folic acid supplementation in the treatment of mild or moderate cervical dysplasia, which found a statistically significant reduction in disease present at biopsy compared to those not receiving folic acid[25]. Although no relationship has been seen between the development of CIN and dietary folic acid where it has been examined[26], these studies have been small, and the possibility exists that there is an effect among users of oral contraceptives.

Total fat consumption has also been found to be related to invasive cervical cancer[19] although this effect has not been seen for CIN[26]. This discrepancy may be due to the supposed tumor promotional effects of fat. The previously mentioned (small) studies indicate possible nutritional influence in the genesis of CIN and these relationships need further exploration. In the next Chapter, a detailed description of the British Columbia study is presented.

Chapter 3

STUDY DESCRIPTION

3.1 Study Objectives

The aims of this case control study were: 1. to identify using a case-control methology, risk factors which influence the development of cervical dysplasia and carcinoma in-situ in BC; 2. to compare and contrast the risk factors for mild dysplasia, moderate dysplasia, severe dysplasia and carcinoma in-situ; 3. to identify factors which may influence the progression of the disease.

There is increasing evidence that *Diet* is a major contributor to cancer incidence and mortality. By retrospective examination of the use of vitamin and mineral supplements and usual diet, we hope to identify dietary components which prevent the development of the disease.

3.2 Study design

A case control study was conducted to investigate the etiology of cervical cancer. Potential study participants were identified from the Central Cytology database maintained within the British Columbia Cancer Agency (BCCA) which keeps records on all women receiving pap-smears in BC. An introductory letter together with a self-administered postal questionnaire (*see Appendix 1*). was mailed to identified cases and controls upon consent of their physicians. Detailed information on demographic characteristics, lifetime cigarette smoking history, alcohol intake, sexual behaviour, reproductive history, contraceptive usage and diet was obtained. The smoking information included the currency of smoking, the average number of cigarettes smoked per day, the age at which smoking started and the age at which smoking stopped. For the sexual history, women were asked the age at which they first had sexual intercourse, the average frequency of sexual intercourse, the number of different sexual partners in the last year and in their lifetime. Contraceptive information included the use of oral contraceptives, intrauterine device, diaphragm , chemical spermicide and condoms. Women were asked which contraceptive devices they had ever used, the age when they first used them, the age when they last used them as well as the duration for which they had used. Information on venereal diseases and genital infection was self reported by the study participants.

Diet was assessed by asking the prospective subjects about their usual consumption of 122 food items as given in the questionnaire in the *Appendix 1.* The dietary component of this questionnaire was developed using the National Health and Nutrition

Examination Survey(NHANES II) and included foods which represented major sources of total calories, vitamin A, carotenoids, vitamin C, total fat and total folate of U.S. population intake. Subjects were asked to respond in terms of serving size and food frequencies. Supplementary vitamin intake was assessed by obtaining the duration of years used, the number of tablets taken per day, brand names and dosages and whether they were currently taking it. Specifically supplements included vitamin A, vitamin B complex, folate, vitamin C, vitamin E, carotene, cod liver oil and some minerals. Indices of the relative intake of various nutrients (including total fat, total vitamin A, carotene, total folate and vitamin C) were estimated from the amount consumed of the foods included in the questionnaire.

3.3 Study population

Cases eligible for this case-control study were selected from English-speaking Caucasian women aged 16 to 65 years, residing in the Greater Vancouver region who had an abnormal smear leading to a histologically confirmed diagnosis of cervical dysplasia (mild, moderate or severe) or carcinoma in-situ in the last 12 months prior to the study. Age and race matched "controls" were selected from women in the same community and who had no history of abnormality. A random sample of 1 in 23 women among controls was selected giving a total of 275 controls. A random sample of 1 in 12 women was drawn from women with mild dysplasia, 1 in 11 from those with moderate dysplasia and 1 in 9 from those with either severe or carcinoma in-situ. Thus, the resulting sample sizes of

mild, moderate, severe and carcinoma in-situ were 145, 137, 104 and 104 respectively. The criteria used in classifying the four different stages of cervical dysplasia and normals were:

Stage I: normal : at least one previous negative cervical cytologic smear within the three years prior to commencement of the study but no history of abnormal cytology or abnormal gynecologic pathology;

Stage II: mild : pathologically proven mild cervical dysplasia in the last 12 months with no previous history of pathologically proven moderate or severe dysplasia or cervical cancer;

Stage III: moderate : pathologically proven moderate cervical dysplasia in the last 12 months with no previous history of pathologically proven severe dysplasia or cervical cancer;

Stage IV: severe : pathologically proven severe cervical dysplasia in the last 12 months with no previous history of pathologically proven cervical cancer;

Stage V: carcinoma in-situ : pathologically proven CIN in the last 12 months with no previous history of pathologically proven invasive cervical cancer.

Women who were pregnant at the diagnosis of abnormality or pregnant at the time of smears were excluded to improve comparability of subjects.

3.4 Data collected

The data set contains information on 765 patients with 490 patients identified as having CIN (cases) and 275 normal patients (controls). Among those with CIN (stage 2 or higher), the distribution by stage was as follows: stage II 145 (30%); stage III 137 (28%); stage IV 104 (21%) and stage V 104 (21%). There are 180 variables recording patient information on social status, details of smoking and sexual habits, contraceptive practices, diet and disease level. Our response variable is the polytomous variable known as disease level. It refers to the five stages of the disease: *normal, mild, moderate, severe, carcinoma in-situ.* A sample coding sheet together with the questionnaire are included in the *Appendix 2.*

A certain amount of data cleaning and correction was necessary before any attempts were made to examine the variables. Variables which were thought to be irrelevant to the development of the disease (eg. weights, birthdates, exercises) were identified by Dr. A. Coldman of the BCCA and were eliminated from the data files, leaving 60 variables to be examined.

Due to ambiguities in the coding values, a careful examination of each of the remaining variables was necessary. For example, a "blank" was not always a missing values; it sometimes meant that the "event is still ongoing" or that it was a code dependent on previous variable. Examples: for non-smokers, the variable "*the number of cigarettes smoked per day*" had to be blank; for current-smokers, the variable "*age at which smoking was terminated*" had to be blank also to mean "currently still smoking". The use

of several missing value codes ($blank, 9, 99$) was misleading; they were all recoded as "99" for uniformity. Examples: for the variable "*number of lifetime sexual partners*", "9" meant nine partners in the subjects's lifetime; for the variable "*contraceptive ever used* ", "9" meant a missing value code. Values not listed as coding options ("0" for "*number of lifetime sexual partners*") were checked and recoded appropriately. Some variables, whose proportion of "Yes" responses relative to "No" was low (for example, the variable *syphillis*, where *percent of Yes = 0.13*) were eliminated. New variables were created from existing variables when appropriate and redundant variables were deleted. Examples: "*duration of smoking*"; "*age at which smoking was terminated*". Thus the final number of variables included in the preliminary analysis was 44 and these are listed in *Table 3.1.* For the purpose of our analysis, the data were divided into five hierachical groups: the first group consisted of *age and smoking* variables; the second of *age, smoking and sexual* variables; the third of *age, smoking, sexual behaviour and contraceptive usage*; the fourth of *age, smoking, sexual behaviour and sexually transmitted disease* variables; and the fifth of *age, smoking, sexual behaviour and diet.* Due to the substantial number of missing values present for some of the variables, deletions of missing values were done sequentially from groups 1 to 5 to avoid unnecessary loss of information. This resulted in 7 missing values deleted from Group 1 and 52 from Group 2. For Group 3, there were 47, 108, 62, 70, 66 and 122 missing values eliminated from *contraceptive ever used , oral contraceptive, intrauterine device, diaphragm, chemical spermicide, condoms* respectively. For Group 4, 48, 49, 50, 51 missing values were deleted from gonorrhoea, oralherpes, genital warts, genital herpes respectively. For the final group, 138 missing

Table 3.1: Variable names and descriptions

dlevel	disease levels (normal, mild, moderate, severe, carcinoma in-situ)
age	age of patients at time of questionnaire
smkcur	currently smoking (no/yes)
smkage	age at which the patient began smoking
smkstop	age at which the patient stopped smoking
sexage	age at first intercourse
sexmonth	intercourse: number of times per month
sexpart	number of sex partners in a year
sexlife	number of sex partners in lifetime
contracpt	ever used contraceptive (no/yes)
oralcpt	duration of oral contraceptive used (years)
iud	duration of intrauterine device used (years)
diaphram	duration of diaphragm used (years)
spcide	duration of chemical spermicide used (years)
gonor	ever have Gonorrhoea (no/yes)
oralherp	ever have Oral Herpes (cold sores) (no/yes)
genwarts	ever have Genital Herpes (no/yes)
genherp	ever have Condylomata (HPV) (no/yes)
carotdly	estimated daily intake of carotene in mgs
retequiv	estimated daily intake of retinol equivalents
fatpc	% of total calories from fat
totcal	estimated total daily calory intake

Table 3.1(cont'd)

est_vitA	estimated daily vitamin A intake in I.U.s'
est_vitC	estimated daily vitamin C intake in mgs
alpha_car	estimated daily *alpha*-carotene intake in mgs
beta_car	estimated daily *beta*-carotene intake in mgs
lycopene	estimated daily lycopene intake in mgs
totfol	estimated daily total folate intake in mgs
est_fib	estimated daily dietary fiber in grams
citfr_wk	estimated weekly consumption of citrus fruit
veg_wk	estimated average weekly consumption of vegetables
nonlycar	estimated daily nonlycopene carotenoids intake in mgs
vitamin	do you regularly take multivitamins or megavitamins (no/yes)
vitbcur	currently taking vitamin B supplement (no/yes)
vitccur	currently taking vitamin C supplement (no/yes)
alc	do you usually consume alcoholic beverages (no/yes)
winecur	currently still taking wine (no/yes)
winenum	average number of bottles of wine taken per week
beercur	currently still taking beer (no/yes)
beernum	average number of bottles of beer taken per week

Below are some of the additional variables created for each patient:

smkstat	smoking status (non, ex-smokers, current smokers)
smklong	duration of (years) smoking for current smokers
smkquit	years since quitting
barrier	either condom and/or diaphragm used
condiaph	combined usage of both condom and diaphragm

values were removed. Descriptive statistics for the five groups (*normal, mild, moderate, severe or carcinoma in-situ*) of patients appear in *Table 3.2* and the percent distribution in *Table 3.3.*

Table 3.2: Study group characteristics among 484 cases and 274 controls

Variable		**Stage I**	**Stage II**	**Stage III**	**Stage IV**	**Stage V**
total number N		274	141	136	104	103
age		38(13)	36(11)	33†(11)	32†(9)	34†(8)
smkstat	%non	50	49	34	32	22
	%ex	27	18	25	16	26
	%current	23	33	41	52	52
smknum	current	15(7)	18(9)	17(8)	19†(7)	18(8)
	ex	15(7)	16(7)	14(12)	20(11)	15(4)
smklong	current	18(10)	15(9)	16(9)	15(8)	16(8)
	ex	14(13)	15(7)	13(10)	16(10)	15(4)
sexage		19(3)	18(4)	18†(3)	17†(3)	17†(2)
sexmonth		7(6)	8(7)	8(7)	10†(10)	11†(14)
	median	5	5	5	7	8
sexpart		1(1)	1†(1)	2†(2)	1(1)	2†(9)
	median	1	1	1	1	1
sexlife		6(10)	8†(11)	12†(16)	13†(16)	13†(20)
	median	3	5	7	8	7
	% report> 6	28	49	57	59	62
contracpt	% used	85	86	92	97	96
barrier	% used	34	27	27	27	22

Table 3.2(cont'd)

Variable	Stage I	Stage II	Stage III	Stage IV	Stage V
Vit C	154(97)	171(112)	150(93)	133(90)	140(99)
Vit A	11300(7075)	10800(6322)	10451(7456)	9600(6049)†	9200(4849)†
α_carotene	756(790)	655(4660)	661(695)	580(503)†	534(425)†
β_carotene	3098(2695)	2841(2050)	2842(2967)	2495(2085)	2338(1931)†
lycopene	412(370)	377(387)	369(315)	365(286)	306(217)†
nonlycar	4392(3662)	3979(2632)	3972(3636)	2654(3459)†	2431(3322)†
totfol	303(180)	323(193)	286(146)	303(228)	253(131)†
citfr_wk	6(7)	6(5)	6(6)	5(5)	5(5)
est_fib	15(8)	16(9)	13(7)†	14(9)	13(6)†
veg_wk	23(13)	23(14)	23(15)	22(10)	20(10)

**All values tabulated are means with standard deviation given in parenthesis except otherwise stated.*

†*t_test:significantly different between the means of stages I and that of the corresponding stage* ($p < 0.05$).

Table 3.3: Percent distribution of cases and controls according to selected risk factors

Variable	Stage I	Stage II	Stage III	Stage IV	Stage V
Age,yr					
< 25	9	11	16	12	10
25-29	19	23	31	37	25
30-34	22	21	17	25	24
35-39	14	14	15	10	20
40-49	17	21	10	12	16
> 49	19	11	10	6	5
Smkstat					
non	66	57	45	38	38
ex	10	8	11	6	7
current	24	35	44	56	55
smknum					
1-10	32	26	22	26	21
11-20	58	54	58	50	63
> 20	11	20	20	24	16
smklong,yrs					
1-10	24	32	28	21	26
11-15	26	30	27	41	37
> 15	50	38	45	38	37
Sexage					
< 17	26	35	35	47	37
17-20	44	39	50	39	52
> 20	30	26	15	15	11

Table 3.3(cont'd)

Variable	Normal	Stage II	Stage III	Stage IV	Stage V
Sexmonth					
<= 1	23	16	17	11	20
2-3	14	17	15	12	8
4-6	21	23	27	27	16
7-11	25	23	14	22	21
> 11	16	21	27	29	36
Sexpart					
<= 1	92	83	78	86	74
2-3	6	10	15	9	23
> 3	2	8	7	5	3
Sexlife					
<= 1	35	23	13	11	5
2-3	22	19	10	16	16
4-5	15	10	20	14	17
6-10	17	28	25	24	36
> 10	11	21	32	36	25
est_vitC, mg's					
< 87	24	20	27	28	31
87-131	23	23	26	31	23
131-186	27	23	18	28	27
> 186	26	34	29	14	19

Table3.3(cont'd)

Variable	Stage I	Stage II	Stage III	Stage IV	Stage V
α-carotene, mg's					
< 262	21	22	33	28	24
262-487	20	26	27	30	29
487-913	30	24	14	20	34
> 913	29	28	27	22	13
β-carotene, mg's					
< 1236	22	22	33	28	23
1236-2138	20	25	26	22	38
2138-3592	29	23	17	29	24
> 3592	29	29	25	21	14
total folate, mg's					
< 189	24	21	25	24	33
189-263	21	20	27	34	30
263-352	28	27	27	17	21
> 352	27	32	22	24	16
est_vitA in I.U.s'					
< 6103	20	25	29	28	30
6103-9080	24	24	28	22	28
9080-13355	28	24	17	31	22
> 13355	28	27	26	19	20

Table 3.2 reveals we see that the total number of women in the control group was about twice that for each of the cases at four stages of the disease (*mild, moderate, severe, carcinoma in-situ*). Cases from stage III to stage V of the disease were significantly younger (*mean age = 34*) than controls (*mean age = 38*). Differences between the cases and controls with respect to indices of smoking and sexual behaviour were marked. We had defined the non-smokers to include those who had never smoked and those who had quit for more than 5 years at the time of questionnaire. Ex-smokers were those who had quit for 2 to 5 years. Current smokers included those still smoking and those who had quit for 1 year or less. In general, cases (stages II to V) had a greater proportion of current smokers than controls (stage I), with the highest proportion in the severe and carcinoma in-situ (approximately *52%* in each case, 23% in controls). Among current smokers, cases smoked more heavily than controls (*mean smknum = 18 versus 15 in controls*). But the duration of smoking was shorter for them than for controls because they were younger. The number of cigarettes smoked per day and the duration of smoking for ex-smokers varied only slightly among the five groups. Controls had a significantly higher mean age at first intercourse "*sexage*" (19) than cases (18). Cases reported a higher frequency of sexual intercourse per month, a greater number of partners in previous year and a higher number of different sexual partners in their lifetime. Among all cases, women who had carcinoma in-situ had the highest frequency of sexual intercourse and most sexual partners in the last year and in their lifetime, the means being 11; 2 and 13 respectively. Women in the severe and carcinoma in-situ groups both had a mean number of 13 sexual partners in their lifetime, with the

median being 8 for severe dysplasia, 7 for carcinoma in-situ and 3 for controls. More than *85%* of all women in this data set had previously used some form of contraceptives regularly, the proportion being higher in cases than controls; *97%* in severe dysplasia vs *85%* in control. A greater proportion of controls (*34%*) than cases (*26%*) used either a condom or a diaphragm or both methods of contraception. The proportion decreased with increasing severity of the disease.

The remainder of *Table 3.2* presents the mean values of the nutrient indices for cases at various stages of the disease compared with controls. In general, cases in stage V consumed significantly less vitamin A, α-carotene, β-carotene, lycopene, nonlycopene carotenoids, total folate and daily dietary fiber than controls. Cases in stage IV also consumed significantly less vitamin A, α-carotene and nonlycopene carotenoids than controls. Ingestion of the other nutrients (vitamin C, citrus fruit, vegetables per week) was similar among all cases and controls.

3.5 Statistical Methods

In this study, we seek to find the risk factors associated with the development of cervical cancer. A basic epidemiological approach to this problem involves the notion of *Relative Risk* as the natural measure of association of cervical cancer and exposure to potential risk factors.

In general, relative risk relates the presence or absence of a specific disease to exposure levels for some possible risk factors[37]. The exposure levels can be dichotomous

(exposed vs non-exposed) or polychotomous with more than 2 exposure levels. A relatively high risk of disease among an exposed subgroup points to that factor as a possible cause of disease.

Let X be a random variable denoting the levels of exposure to a particular risk factor. For expository simplicity, X is assumed to take only 2 levels: X = 1 for exposed, X = 0 for unexposed.

Definition 3.1: *Relative risk* is defined as:

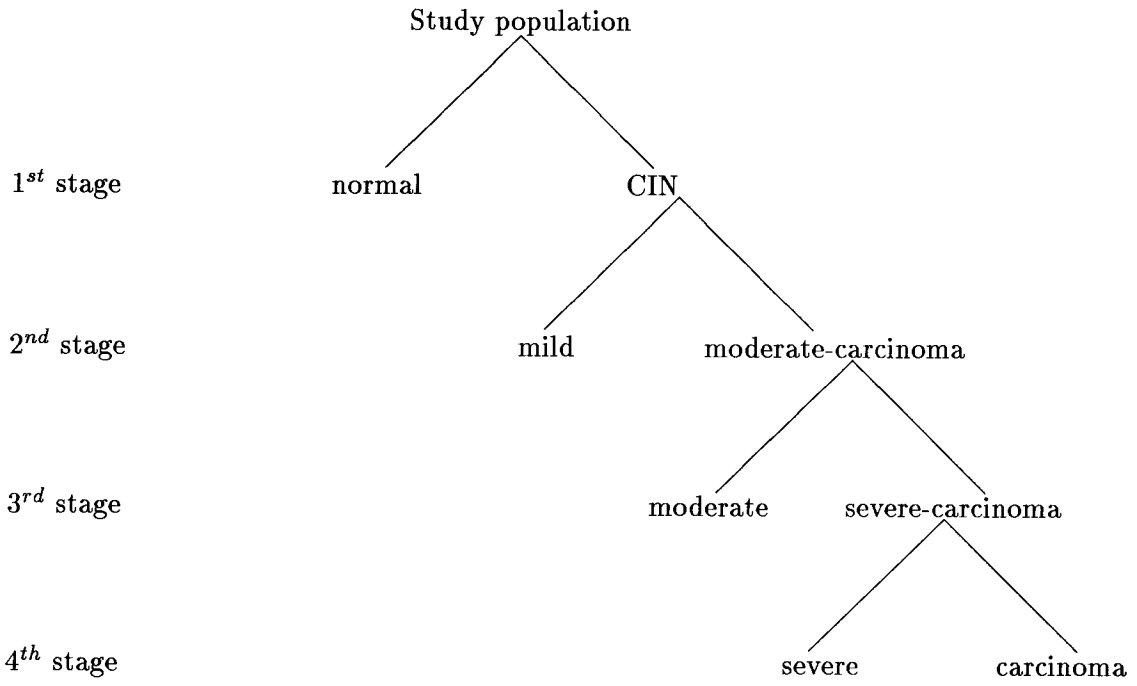
$$RR = \frac{P(disease \mid X = 1)}{P(disease \mid X = 0)}$$

RR > 1 implies that the probability of disease in the exposed subgroup is greater than the probability of disease in the unexposed subgroup. The reverse is true for RR < 1.

Using case control study design, it is possible to estimate the odds ratio so that when the disease is rare, it approximates the RR well. The *odds ratio* of the disease probabilities is defined as the *ratio of the 'odds' of disease occurrence in the exposed and non-exposed subgroups.*

Cervical cancer is thought to arise by a stepwise progression from dysplasia to carcinoma in-situ to cervical cancer; however we do not know whether all lesions progress through each stage of the disease. In other words, the disease could progress from a normal stage to any one of the dysplasia or from any one stage of the dysplasia to carcinoma in-situ without going through all stages. Moreover given their biological differences we may reasonably assume the response categories (ie the five stages of disease level) are arranged in the hierarchical format illustrated in *Fig 3.1.*

Figure 3.1: Stages in the Development of carcinoma in-situ



The response at stage 1 represents the dichotomy between diseased and normal, that at stage 2 the dichotomy between the mild and moderate forms of the disease, that at stage 3 between the moderate and more severe forms and finally that at stage 4 is between the severe form and carcinoma in-situ.

The special structure of the hierachical representation of the response variables enables us to subdivide each multinomial observation into 4 binomial components. The 1st component specifies the number of disease cases as a proportion of the total number of patients at risk (1 vs 2-5), the 2nd, the number of moderate or more severe disease cases as a proportion of those with the disease (2 vs 3-5), the 3rd, the number of cases with severe or more severe disease forms as a proportion of those with an above moderate form of the disease (3 vs 4-5) and finally the number of carcinoma in-situ cases as a proportion of those with severe disease comprises the 4th component (4 vs 5). Since each stage of the hierarchy corresponds to a simple dichotomy, it is natural to adopt a binary logistic regression model[38]:

Let Y_{ij} be a binary random variable which for $i = 1,\ldots,N;\ j = 1,\ldots,5$ is given by:

$$Y_{ij} = \begin{cases} 1, & \text{if patient } i \text{ has disease } j \\ 0, & \text{otherwise.} \end{cases}$$

with $\sum_{i=1}^{N}\sum_{j=1}^{5} y_{ij} = N$ and $P\{\sum_{j=1}^{5} y_{ij} = 1\} = 1; \quad i = 1,\ldots,N.$

Let $p_{ij} = P\{\textit{patient } i \textit{ will be in disease state } j\}$ and let $\pi_{ij} = P\{Y_{ij} = 1 | \sum_{j'=j}^{5} Y_{ij'} = 1\}$ for j = 1,2,3,4,5.

The likelihood function for the N independent multinomial observations

$M(1, p_{i1}, p_{i2}, p_{i3}, p_{i4}, p_{i5})$ is:

$$L(\vec{p}; \vec{y}) = \prod_{i=1}^{N} \frac{p_{i1}^{y_{i1}} p_{i2}^{y_{i2}} p_{i3}^{y_{i3}} p_{i4}^{y_{i4}} p_{i5}^{y_{i5}}}{y_{i1}! y_{i2}! y_{i3}! y_{i4}! y_{i5}!} \qquad where \sum_{j=1}^{5} p_{ij} = 1. \tag{3.1}$$

Then

$$\pi_{ij} = \frac{p_{ij}}{\sum_{j'=j}^{5} p_{ij'}} \tag{3.2}$$

Substituting (3.2) into (3.1) yields

$$L(\vec{\pi}; \vec{y}) = f(\vec{y}) \prod_{i=1}^{N} \pi_{i1}^{y_{i1}} (1 - \pi_{i1})^{\sum_{j=2}^{5} y_{ij}} \prod_{i=1}^{N} \pi_{i2}^{y_{i2}} (1 - \pi_{i2})^{\sum_{j=3}^{5} y_{ij}}$$
$$\prod_{i=1}^{N} \pi_{i3}^{y_{i3}} (1 - \pi_{i3})^{\sum_{j=4}^{5} y_{ij}} \prod_{i=1}^{N} \pi_{i4}^{y_{i4}} (1 - \pi_{i4})^{y_{i5}} \tag{3.3}$$

From equation (3.3), we see that the product of the N independent multinomial distributions can be reduced to the product of N independent binomial distributions. By the Factorization theorem, we see that $(y_{i1}, \sum_{j=2}^{5} y_{ij})$ is a sufficient statistic for π_{i1}; $(y_{i2}, \sum_{j=3}^{5} y_{ij})$ for π_{i2}; $(y_{i3}, \sum_{j=4}^{5} y_{ij})$ for π_{i3} and (y_{i4}, y_{i5}) for π_{i4}.

We will fit the following binary logistic regression model:

$$ln(\frac{\pi_{ij}}{1 - \pi_{ij}}) = \alpha_j + \sum_{k=1}^{K} \beta_{jk} x_{ik}, \qquad j = 1, \ldots, 4, i = 1, \ldots, N, k = 1, \ldots, K. \tag{3.4}$$

here the $\{\alpha_j\}$ and $\{\beta_{jk}\}$ are unknown parameters to be estimated while the $\{x_{ik}\}$ are the observed covariates for each i. To estimate the parameters, $\{\beta_{jk}\}$, we write the log likelihood function for the N independent binomial observations (equation 3.3) as follows:

$$l(\vec{\pi}; \vec{y}) = \sum_{i=1}^{N} \sum_{j=1}^{4} \sum_{j'>=j}^{5} y_{ij'} \left[y_{ij} \ln \left(\frac{\pi_{ij}}{1 - \pi_{ij}} \right) + \ln(1 - \pi_{ij}) \right] \tag{3.5}$$

Substituting (3.4) into (3.5) yields

$$l(\vec{\pi}, \vec{\alpha}; \vec{y}) = \sum_{i=1}^{N} \sum_{j=1}^{4} \sum_{j'>=j}^{5} y_{ij'} \left[y_{ij} \sum_{k=1}^{K} x_{ik}\beta_{jk} + y_{ij}\alpha_j - \ln(1 + \exp(\alpha_j + \sum_{k=1}^{K} \beta_{jk}x_{ik}) \right] \quad (3.6)$$

The maximum likelihood estimates of the log odds ratio as denoted by the vector $\vec{\beta}$ can be obtained by using the Newton-Raphson procedure. The result is a consistent estimate of the log odds ratio along with asymptotic estimates of the 95% confidence interval. Based on the sufficient statistics obtained above, we obtain the following four logit functions i.e. (1 vs 2-5, 2 vs 3-5, 3 vs 4-5, 4 vs 5). They derive from the assumption that the disease progresses through each transition stage from mild to carcinoma in-situ in the following manner: stage 1 $\rightarrow$ stage 2 $\rightarrow$ stage 3 $\rightarrow$ stage 4 $\rightarrow$ stage 5. Denote the relative risks of developing the next stage of the disease by Φ_1, Φ_2, Φ_3, Φ_4 respectively. Assume $\Phi_i > 1$ for all i. Denote the relative risks of the first 4 comparison groups (1 vs 2-5, 2 vs 3-5, 3 vs 4-5, 4 vs 5) by Ψ_1, Ψ_2, Ψ_3 and Ψ_4. If the Φ's are all equal, it can be shown that (see *Appendix*3)

$$\Psi_1 > \Psi_2 > \Psi_3 > \Psi_4 > 1.$$

Potential confounders were controlled by incorporating them into the logistic model (3.1). The risk estimates of the 'age' variable are of no particular interest to us. But due to its epidemiological importance, it was included in all logistic regressions in our analyses to adjust for the difference in ages between cases and controls. In this study, we divided the 'age' variable into 6 categories based on the combined distributions of cases and controls. They are less than or equal to 24 years, 25-29, 30-34, 35-39, 40-49 and greater or equal to 50 years. Discrete variables like smoking status are grouped into

categories. Continuous variables are assessed by grouping them into quartiles based on the combined frequency distribution of the cases and controls. Tests for significance of individual regression coefficients were single degree of freedom tests for trend; they were achieved by entering quartiles of a giving continuous variable into the logistic model as different values of a single ordinal values. Interactions between variables were analysed by constructing the appropriate variables in the continuous scale and including them in the model.

Because of the large number of initial variables, it is impossible to carry out the stepwise selection of variables using all the main factors and interactions at the same time. Hence, to make the problem manageable, we identify the important variables in a sequential manner as shown below:

$$\text{Smoking variables} \rightarrow \text{Sexual variables} \rightarrow \text{Diet variables.}$$

We begin the selection procedure with univariate analysis of each of the initial variables while controlling for the 'age' variable. A stepwise selection procedure was used in each of the 3 blocks of variables (smoking, sexual, diet). Smoking variables identified as significant after adjustment for age are included in the next block. Sex variables found significant in the univariate analyses are added to the multiple logistic regression one at a time while controlling for age and smoking. Sex found to be most significant are then included in the model to see if other sex variables were still significant after controlling for those variables already found to be significant. Finally, significant variables identified in blocks 1 and 2 are further incorporated in the regression model together with each

diet variable to help identify the significant diet variables. Let $\hat{l}_{H_i}$ denote the likelihood function under any given model H_i.

Definition 3.2: The deviance function is defined as

$$D = 2log\hat{l}_{H_0} - 2log\hat{l}_{H_1}; \tag{3.7}$$

where H_0 designates the saturated model, H_1 the logistic model to be fitted. The deviance function is twice the difference between the maximum achievable log likelihood and that attained under the fitted model.

At each step of the selection process, the adjacent models which are nested with respect to the terms in the linear predictor are compared with respect to the difference in deviances between successive nested model to see if the addition of a further covariate significantly improved the fit.

Definition 3.3: The difference in deviance is defined as

$$\triangle D = 2\log \hat{l}_{H_2} - 2\log \hat{l}_{H_0} \tag{3.8}$$

where H_2 designates the extended model with additional covariates and H_0 the model under test. The difference in deviance $\triangle$D has an asymptotic χ^2 distribution whose degrees of freedom is the difference between the number of parameters in H_2 and H_0. Covariates significant for some but not all logit functions, are forced into all logit functions for uniformity of comparisons among different comparison groups. Analyses were also carried out for the following comparison groups: 1 vs 2, 1 vs 3, 1 vs 4, 1 vs 5 due to their epidemiological significance. In the next chapter, results obtained from our analyses are presented.

Chapter 4

ANALYSIS

Women in the case groups were significantly younger than controls (mean of 34 vs 38 years of age). We begin the analyses with current smokers referred to smokers who were currently smoking and those who quit for less than 1 year. Ex-smokers are referred to those who had quit for 1 year or more. Relative risks adjusted for age are estimated in terms of *smoking status, number of cigarettes smoked per day, how long since quit and duration of smoking.* Looking at the adjusted relative risk estimates we get for *how long since quitting* using non-smokers as the baseline, we notice those who quit smoking for more than 5 years had adjusted relative risks close to 1, ie they behaved like non-smokers. Those who quit for 1 year had adjusted relative risks close to those for current smokers. Based on out results, it seems reasonable to pool those who quit for 1 year into the smoking category and those who quit for more than 5 years into non-smokers category. Based on the pooled data, we see a significantly greater proportion of the cases (43%) than controls (23%) stating that they were current smokers and the proportion seemed

to increase with the severity of the disease. It ranged from 33% in the mild dysplasia to 52% in carcinoma in-situ. Among current smokers, cases smoked significantly more heavily than controls (18 vs 15 cigarettes a day). Age adjusted relative risk estimates for the association of different comparison groups (1 vs 2-5, 2 vs 3-5, 3 vs 4-5, 4 vs 5, 1 vs 2, 1 vs 3, 1 vs 4, 1 vs 5) with cigarette smoking are shown in *Table 4.1* and *4.2*. Relative risks tend to be higher for current smokers than ex-smokers in all comparison groups. Among current smokers, women with more severe lesions had a higher risk than women with milder dysplasia (3.91 vs 1.64) compared to ex-smokers (those who quit between 2 to 5 years). Across the first four comparison groups (1 vs 2-5, 2 vs 3-5, 3 vs 4-5, 4 vs 5), there seems to be a linear decrease in risks among current smokers compared to nonsmokers (2.50, 1.80, 1.53, 1.24). However, ex-smokers do not show elevated risk compared to non-smokers. In fact, they behave rather like non-smokers. Current smokers among cases smoke significantly more cigarettes a day compared to current smokers among normals. Nevertheless current smokers who smoked more than 20 cigarettes a day in the first four comparison groups do not show an increase in risk compared to those in the same group who smoked less that 10 cigarettes a day (*Table 4.1*). Except in 1 vs 2-5, a barely significant increase in risk at the 5% level ($p = 0.056$) was observed. For the second group of comparison groups in *Table 4.2*, current smokers show an elevated risk with an increased number of cigarettes smoked a day except that none of them were significant at the 5% significant level. Also, current smokers who smoked more than 20 cigarettes a day showed a linear decrease in relative risks compared to those who smoked less than 10 cigarettes a day as we moved across the 1st four comparison

groups (2.61, 1.14, 0.95, 0.77). This is consistent with the findings for current smokers versus non-smokers. In terms of duration of smoking among current smokers, there is no significant difference between cases and controls though controls seemed to smoke for a longer period than cases. From *Tables 4.1* and 4.2, current smokers who smoked for a longer period of years (say more than 15 years) did not have higher risk compared to those who smoked for a shorter period of time (say less than 10 years).

The next group of variables that we examined relate to sexual behavior . Consistent with the literature reviewed, sexual activity turned out to be one of the major risk factors to the disease. Fifty percent or more of each of the cases and 28% of the controls reported having 6 or more sexual partners during their lifetime. The average number of lifetime sexual partners was significantly different among cases and controls (13 for carcinoma in-situ vs 6 for normals). In general, cases also had more frequent sexual intercourse and had their first sexual intercourse at an earlier compared to normals ($\approx$ 17 vs 19 age years of age). The relative risks adjusted for age and the confounding effect of smoking associated with sexual activity are tabulated in *Table 4.3* and *4.4*. Five categories relating to smoking are created for the smoking variable and used in all future analyses. They were: 0 for nonsmokers; 1 for ex-smokers; 2 for current and smoked < 10; 3 for current and smoked between 11-20; 4 for current and smoked > 20 cigarettes a day. When compared to women who had one or less lifetime sexual partners, women with 10 or more sexual partners had a significant 5 fold increase in risk in the comparison group (1 vs 2-5), RR = 4.93 and a significant 3 fold increase in risk in the comparison group (2 vs 3-5), RR = 2.64. Similarly, a significant 3 fold increase in

adjusted risk was observed in mild dysplasia (RR = 2.72), 6 fold increase in moderate dysplasia (RR = 5.95), 7 fold increase in severe dysplasia (RR = 6.40) and 11 fold increase in carcinoma in-situ (RR = 10.53) compared to normals. In fact, an increasing linear pattern in adjusted relative risks among women with 10 or more lifetime sexual partners is seen from mild to carcinoma in-situ (RR = 2.72, 5.95, 6.40, 10.53) compared to those with 1 or less sexual partners in their lifetime. On the other hand, an inverse pattern is seen in the first 4 comparison groups (RR = 4.93 ,2.64, 1.21, 0.56) which suggests that a large number of lifetime sexual partners seems to promote the onset of the disease. A significant 3 fold increase in adjusted risk is observed among women with 3 or more sexual partners in the last year compared to those with 1 or less sexual partners in the following comparison groups (1 vs 2-5, 1 vs 3). A significant 4 fold increase in risk is observed in 1 vs 2. Other interesting variables relating to sexual behavior are examined (sexmonth and sexage). We see that women with 11 or more episodes of sexual intercourse have an adjusted relative risk of 3.41 of developing severe dysplasia compared to women with 1 or less episodes. Compared to women who had 1 or less episodes, women with 11 or more episodes have an adjusted relative risk of 2.22 of developing carcinoma in-situ. Sexmonth and sexpartners seem to be confounded by lifetime number of sexual partners. After simultaneous adjustment for age, smoking and sexlife, sexpartners are found to be insignificant while the adjusted relative risks associated with sexmonth remain significant in some comparison groups (1 vs 4 and 1 vs 5). For uniformity of comparison among various groups, we control for both sexlife and sexmonth in subsequent analyses. Contrary to findings in some previous studies,

no increase in risk is observed in women who had had 1st intercourse at an early age after adjustment for age and smoking.

Because sexual activity is such a strong risk factor for cervical cancer, it is possible that certain contraceptive methods may offer some protective barrier against the disease. As *Tables 4.5* and *4.6* show, women who use any form of contraceptives seem to decrease their risks of developing the disease compared to those who never used any, though none of the results was significant at the 5% level except in 1 vs 5 (RR = 0.31). Among the various methods of contraceptives, the greatest protective effect is seen in women who used a diaphragm and who reported that their partners were using condoms (after adjustment for age, smoking, sexmonth and sexlife). The adjusted relative risks are 0.47 in the 1st comparison group 1 vs 2-5, 0.39 in 1 vs 2, 0.34 in 1 vs 3, 0.49 in 1 vs 4 and 0.49 in 1 vs 5.

Table 4.7 presents information on cervical cancer risks associated with certain types or venereal disease. In general, few women reported ever having any of the diseases. Six percent of women reported genital herpes or gonorrhoea. This low proportion results in unstable estimates of relative risks. Similary, 12% of the women reported condylomata (genital warts). Women who had genital wart infections increased their risk of developing the disease compared to those who did not have them in the comparison groups (1 vs 2, 1 vs 3, 1 vs 4 and 1 vs 2-5). The corresponding relative risks and confidence intervals are 2.28(1.02,5.09), 2.03(0.90,4.55), 1.51(0.60,3.77), 1.80(0.94,3.44) respectively. Twenty nine percent of the women reported oral herpes, however, no significant increase in risk is observed.

The major risk factors identified so far have been smoking, sexlife, sexmonth and both condom and diaphragm usage. The role of diet as a risk factor for invasive cervical cancer in other research raises the question whether it may play a role in CIN. Using the Health Habits and History Questionnaire Personal Computer System Package, estimates of various dietary components are obtained from the dietary questionnaire. The mean values of the nutrients by stage of disease are shown in Table 3.2. Cases with a higher stage (stage V) of the disease have a significantly lower intake of vitamin A, α-carotene, β-carotene, lycopene, nonlycopene carotenoids, total folate and fiber than normals. However, cases in general did not consume less vitamin C, citrus fruit and vegetable per week than normals. Across the different stages of disease (stage II to stage V), we notice that the nutrient level of selected nutrients (vitamin C, vitamin A, β-carotene, lycopene, nonlycopene carotenoids, total folate, estimated fiber, vegetable per week) decrease with an increase in severity of the disease. *Tables 4.8* and *4.9* shows the relative risks associated with increasing levels of dietary nutrients for the 8 comparison groups after adjustment for age, smoking, sexmonth, sexlife , both condom and diaphragm usage. Dietary components are categorised into quartiles based on the combined frequency of cases and controls.

No clear reduction in risk among the 8 comparison groups is noted with an increase in intake of carotene, retinol, fat percent, total calories, citrus fruit per week and vegetable per week. A significant reduction in adjusted relative risk is observed with an increase in intake of vitamin A in the moderate dysplasia and carcinoma in-situ compared to normals, with risk decreasing to 0.53 for the highest versus lowest quartile (p-value for

trend = 0.038) among moderate dysplasia and 0.31 among carcinoma in-situ (p-value for trend = 0.008), respectively. Increasing levels of vitamin C intake only seem to have a significant reduction in risk among those women with moderate or more advanced stages of the disease compared to those with mild dysplasia (2 vs 3-5), the RR being 0.45 in the highest quartile compared to the lowest quartile (p-value = 0.013). Higher levels of fiber intake also seem to decrease the risk in the comparison groups 2 vs 3-5, 1 vs 3, 1 vs 4 and 1 vs 5. Significant trends of decreasing risk are evident for α-carotene with risk decreasing to 0.33 for the highest vs lowest quartile of intake (p-value of trend = 0.027), β-carotene (RR = 0.38, p = 0.010), nonlycopene carotenoids (RR = 0.34, p = 0.005), total folate (RR = 0.36, p = 0.010) among the comparison groups 1 vs 5. An increasing level of total folate and lycopene also seem to decrease the risk among those in group 2 vs 3-5 (p-value for trend = 0.038) and 1 vs 2 (p-value = 0.036) respectively. *Table 4.19* shows the correlation of nutrient indices among controls. The correlation between β-carotene and vitamin A was 0.900, it was therefore impossible to reliably determine their independent effects. For β-carotene and vitamin C, the correlation coefficient is 0.359. Likewise for vitamin A and folate, the correlation is 0.354. *Table 4.10* and *Table 4.11* shows the results of the analyses when carotenoids, vitamin C, folate are each included with vitamin A in the multiple regression model. The association observed with α-carotene, β-carotene, nonlycopene carotenoids and total folate is weakened and the trend test becomes insignificant in all the comparison groups. But the association with vitamin C remains virtually unchanged in the 2nd comparison groups (2 vs 3-5), p-value = 0.014.

Results for repeated analyses controlled additionally for folate and β-carotene respectively, are tabulated in *Tables 4.12, 4.13, 4.14, 4.15.* The reduced risks associated with vitamin A and folate are evident among cases in 1 vs 2-5, 1 vs 2 and 1 vs 3 comparison groups with the adjusted relative risks in the highest quartile compared to the lowest quartile being 0.50, 0.40, 0.33, respectively. Controlling for β-carotene reduce the adjusted risks for nonlycopene carotenoids and lycopene in the 1 vs 2-5 and 1 vs 2 comparison groups, respectively. No significant trends are observed in other carotene, vitamin C and vitamin A.

Few women took any vitamins supplements (78% of no vs 22% yes). Eighty one percent of women did not take multivitamin while less than 1% of the women took megavitamins. After adjusting for age, smoking, sexmonth and sexlife, the log odds ratios of the variable *multivitamin* fails to converge to some value due to collinearlities present among the various variables in the model. Hence, we cannot obtain any estimates of the log odds ratios for the multivitamins. Among the normals in this study, 10% were currently taking vitamin B supplement and 15% were taking vitamin C supplement currently. A reduction in risk is observed with current users of vitamin B and vitamin C supplements compared to non vitamin B and non vitamin C users, respectively. Nevertheless, none of the reduction is significant in all 8 comparison groups at the 5% level (*Table 4.16*).

The effect of alcohol intake on cervical cancer risk is shown in *Tables 4.17* and *4.18.* Adjusted relative risk of cervical cancer (adjusted for age, smoking, sexmonth, sexlife, both diaphragm and condom usage) by wine intake showed that women in the compar-

ison groups 1 vs 2-5, 1 vs 2 have a significant increase in risk if they are current wine drinkers compared to non drinkers. However, no significant increase in risk is observed with increasing number of bottles of wine consumed per week. Current beerdrinkers also exhibited significantly elevated risk compared to non drinkers in the comparison groups 1 vs 2-5, 4 vs 5 and 1 vs 3, the RR being 1.53, 2.38 and 1.82 respectively. No dose response relationship was seen with the amount of beer consumed.

Later in chapter 5, a summary of the results and conclusions will be discussed. Before that we present our detailed findings in a series of tables.

Table 4.1: Adjusted Relative Risks of various comparison groups of cervical dysplasia by Smoking variables*

	Comparison groups			
	1 vs 2-5	2 vs 3-5	3 vs 4-5	4 vs 5
smoking status §				
Ex smokers	1.04(0.61,1.78)	1.37(0.65,2.93)	0.66(0.30,1.53)	1.13(0.33,3.88)
Current smokers	2.50(1.76,3.55)	1.80(1.17,2.77)	1.53(0.94,2.34)	1.24(0.67,2.30)
No. of cig smoked per day †				
11-20	1.25(0.66,2.36)	1.16(0.54,2.50)	0.88(0.40,1.96)	1.64(0.64,4.20)
> 20	2.61(1.02,6.72)	1.14(0.44,2.97)	0.95(0.36,2.52)	0.77(0.24,2.48)
P_{trend}	0.056	0.769	0.905	0.738
No. of years of smoking ‡				
11-15	1.60(0.63,4.06)	1.15(0.41,3.20)	1.71(0.58,5.01)	0.85(0.24,3.01)
> 15	1.64(0.56,4.81)	1.37(0.40,4.64)	1.21(0.32,4.54)	0.46(0.10,2.19)
P_{trend}	0.390	0.617	0.770	0.312

* *relative risks (95% CI) adjusted for age.*

§*non-smokers was used as reference category.*

ex refers to those who quitted between 2 to 5 years. current refers to those currently smoking and those who quitted for less than or equal to 1 year. non refers to non smokers and those who quitted for more than 5 years.

† *current smokers who smoked less than or equal to 10 cigarettes per day was used as reference.*

‡*current smokers who smoked less than or equal to 10 years was used as reference.*

Table 4.2: Adjusted Relative Risks of various comparison groups of cervical dysplasia by Smoking variables*

	Comparison groups			
	1 vs 2	1 vs 3	1 vs 4	1 vs 5
smoking status §				
Ex smokers	0.82(0.38,1.77)	1.28(0.62,2.63)	0.75(0.28,1.99)	1.15(0.45,2.89)
Current smokers	1.64(1.03,2.63)	2.41(1.51,3.85)	3.28(1.97,5.45)	3.91(2.32,6.60)
No. of cig smoked per day †				
11-20	1.07(0.44,2.59)	1.51(0.65,3.52)	0.82(0.34,1.99)	1.67(0.70,3.94)
> 20	2.57(0.75,8.85)	2.85(0.86,9.41)	2.93(0.90,9.57)	2.41(0.68,8.48)
P_{trend}	0.188	0.085	0.137	0.137
No. of years of smoking ‡				
11-15	1.29(0.40,4.17)	1.34(0.37,4.86)	2.65(0.71,9.91)	1.84(0.55,6.13)
> 15	1.17(0.31,4.42)	1.77(0.37,8.42)	3.51(0.73,16.96)	1.20(0.30,4.74)
P_{trend}	0.829	0.471	0.126	0.840

* *relative risks (95% CI) adjusted for age.*

§*non-smokers was used as reference category.*

ex refers to those who quitted between 2 to 5 years. current refers to those currently smoking and those who quitted for less than or equal to 1 year. non refers to non smokers and those who quitted for more than 5 years.

† *current smokers who smoked less than or equal to 10 cigarettes per day was used as reference.*

‡*current smokers who smoked less than or equal to 10 years was used as reference.*

Table 4.3: Adjusted Relative Risks of various comparison groups of cervical dysplasia by indicators of sexual activity*

	Comparison groups			
	1 vs 2-5	2 vs 3-5	3 vs 4-5	4 vs 5
Sexage §				
17-20	0.90(0.60,1.34)	1.20(0.73,1.96)	0.77(0.46,1.31)	1.46(0.75,2.83)
> 20	0.70(0.42,1.16)	0.64(0.33,1.24)	0.82(0.36,1.86)	0.71(0.25,2.07)
P_{trend}	0.176	0.317	0.465	0.996
Sexmonth §				
2-3	1.24(0.70,2.19)	0.67(0.32,1.42)	0.76(0.32,1.85)	0.30(0.08,1.14)
4-6	1.59(0.96,2.63)	1.01(0.51,1.98)	0.90(0.43,1.90)	0.32(0.11,0.93)
7-11	0.92(0.55,1.54)	0.70(0.34,1.41)	1.67(0.73,3.85)	0.48(0.16,1.38)
> 11	1.93(1.12,3.30)	1.27(0.63,2.54)	1.45(0.68,3.09)	0.71(0.26,1.93)
P_{trend}	0.106	0.430	0.084	0.812
Sexpart §				
2-3	1.88(1.03,3.42)	1.40(0.71,2.74)	1.05(0.54,2.02)	3.66(1.48,9.03)
> 3	2.94(1.10,7.86)	0.60(0.26,1.40)	0.55(0.19,1.56)	0.69(0.14,3.28)
P_{trend}	0.002	0.648	0.443	0.128
Sexlife §				
2-3	1.63(1.00,2.66)	1.41(0.69,2.91)	2.33(0.87,6.25)	2.03(0.55,7.54)
4-5	2.09(1.23,3.57)	3.25(1.43,7.41)	1.05(0.40,2.76)	2.51(0.63,9.98)
6-10	3.25(1.96,5.37)	1.74(0.86,3.54)	1.41(0.56,3.53)	3.31(0.92,11.85)
> 10	4.93(2.81,8.65)	2.64(1.25,5.56)	1.21(0.48,3.07)	0.56(0.42,5.74)
P_{trend}	0.000	0.020	0.753	0.795

* *relative risks (95% CI) adjusted for age, smoking status (non, ex, current & smoke 1-10, current & smoke 11-20, current & smoke(> 20) cigarettes per day).*

§ *All values are compared with the lowest level. For sexage (<= 16)years was used. For sexmonth, sexpart and sexlife, their respective lowest level (<= 1) were used as the reference category.*

Table 4.4: Adjusted Relative Risks of various comparison groups of cervical dysplasia by indicators of sexual activity*

	Comparison groups			
	1 vs 2	1 vs 3	1 vs 4	1 vs 5
Sexage §				
17-20	0.78(0.45,1.35)	1.18(0.68,2.04)	0.66(0.37,1.19)	1.08(0.58,2.01)
> 20	0.90(0.47,1.76)	0.68(0.32,1.45)	0.61(0.27,1.37)	0.48(0.19,1.21)
P_{trend}	0.753	0.418	0.171	0.192
Sexmonth §				
2-3	1.69(0.79,3.62)	1.13(0.51,2.49)	1.59(0.58,4.41)	0.36(0.12,1.05)
4-6	1.64(0.81,3.34)	1.75(0.86,3.55)	2.65(1.08,6.50)	0.86(0.35,2.13)
7-11	1.17(0.57,2.38)	0.69(0.32,1.51)	1.71(0.68,4.30)	0.71(0.30,1.67)
> 11	1.71(0.81,3.62)	1.70(0.80,3.59)	3.41(1.34,8.63)	2.22(0.95,5.18)
P_{trend}	0.463	0.512	0.020	0.024
Sexpart §				
2-3	1.41(0.63,3.14)	2.18(1.02,4.64)	1.13(0.45,2.87)	3.78(1.71,8.36)
> 3	4.23(1.37,13.08)	3.25(1.00,10.61)	2.680.64,11.21)	1.16(0.22,6.11)
P_{trend}	0.011	0.007	0.232	0.014
Sexlife §				
2-3	1.33(0.70,2.52)	1.08(0.48,2.42)	2.48(1.04,5.94)	5.10(1.73,15.02)
4-5	0.98(0.46,2.13)	2.78(1.32,5.86)	2.41(0.96,6.03)	6.39(2.13,19.00)
6-10	2.35(1.24,4.46)	3.29(1.60,6.76)	3.56(1.54,8.24)	11.09(3.96,31.04)
> 10	2.72(1.33,5.56)	5.95(2.80,12.64)	6.40(2.69,15.20)	10.53(3.56,31.13)
P_{trend}	0.002	0.000	0.000	0.000

* *relative risks (95% CI) adjusted for age, smoking status (non, ex, current & smoke 1-10, current & smoke 11-20, current & smoke(> 20) cigarettes per day).*

§ *All values are compared with the lowest level. For sexage (<= 16)years was used. For sexmonth, sexpart and sexlife, their respective lowest level (<= 1) were used as the reference category.*

Table 4.5: Adjusted Relative Risks of various comparison groups of cervical dysplasia according to methods of Contraception*

	Comparison groups			
	1 vs 2-5	2 vs 3-5	3 vs 4-5	4 vs 5
Contracpt §				
ever	0.74(0.40,1.37)	1.03(0.45,2.32)	0.68(0.25,1.81)	0.53(0.16,1.79)
Condoms §				
ever	0.66(0.43,1.01)	1.19(0.66,2.15)	1.12(0.60,2.10)	0.91(0.40,2.06)
Diaphram(only) §				
ever	1.03(0.49,2.16)	0.56(0.23,1.37)	0.59(0.21,1.64)	0.47(0.08,2.88)
Spcide §				
ever	0.87(0.50,1.51)	0.88(0.45,1.74)	1.16(0.52,2.58)	0.84(0.32,2.20)
Oralcpt §				
ever	0.78(0.47,1.28)	1.37(0.72,2.59)	0.72(0.32,1.60)	1.08(0.41,2.86)
Iud §				
ever	0.89(0.58,1.37)	0.74(0.45,1.24)	0.85(0.47,1.53)	0.84(0.39,1.80)
Condiap §				
ever	0.47(0.22,0.97)	1.01(0.33,3.11)	1.28(0.35,4.73)	1.14(0.22,5.98)

* *relative risks (95% CI) adjusted for age, smoking status (non, ex, current & smoke 1-10, current & smoke 11-20, current & smoke*(>20) *cigarettes per day), sexmonth and sexlife.*
§ *women who had never used the respective contraceptive were used as reference category.*

Table 4.6: Adjusted Relative Risks of various comparison groups of cervical dysplasia according to methods of Contraception*

	Comparison groups			
	1 vs 2	1 vs 3	1 vs 4	1 vs 5
Contracpt §				
ever	0.71(0.31,1.65)	0.83(0.32,2.18)	0.65(0.21,2.04)	0.31(0.10,0.96)
Condoms §				
ever	0.54(0.29,0.99)	0.65(0.36,1.20)	0.63(0.32,1.24)	0.75(0.37,1.51)
Diaphram(only) §				
ever	1.33(0.53,3.34)	0.87(0.34,2.26)	1.10(0.34,3.50)	0.21(0.03,1.46)
Spcide §				
ever	0.93(0.46,1.90)	0.58(0.25,1.38)	0.78(0.33,1.86)	0.68(0.28,1.66)
Oralcpt §				
ever	0.62(0.32,1.18)	1.22(0.57,2.62)	0.91(0.40,2.04)	0.61(0.25,1.48)
Iud §				
ever	1.00(0.56,1.77)	0.86(0.46,1.59)	0.83(0.41,1.68)	0.61(0.30,1.24)
Condiap §				
ever	0.39(0.13,1.14)	0.34(0.10,1.09)	0.49(0.14,1.68)	0.49(0.14,1.70)

* *relative risks (95% CI) adjusted for age, smoking status (non, ex, current & smoke 1-10, current & smoke 11-20, current & smoke(> 20) cigarettes per day), sexmonth and sexlife.*
§ *women who had never used the respective contraceptive were used as reference category.*

Table 4.7: Adjusted Relative Risks of various stages of cervical dysplasia according to Venereal Disease*

	Comparison groups			
	1 vs 2-5	2 vs 3-5	3 vs 4-5	4 vs 5
Genherps §				
ever	1.08(0.53,2.33)	1.99(0.78,5.10)	0.69(0.30,1.61)	2.01(0.61,6.64)
Genwarts §				
ever	1.80(0.94,3.44)	0.72(0.39,1.34)	0.83(0.42,1.63)	0.83(0.33,2.07)
Gonor §				
ever	1.07(0.48,2.39)	1.62(0.59,4.49)	1.69(0.65,4.38)	0.53(0.18,1.53)
Oralherps §				
ever	1.13(0.78,1.64)	0.72(0.46,1.14)	1.27(0.76,2.14)	0.38(0.19,0.77)
	1 vs 2	1 vs 3	1 vs 4	1 vs 5
Genherps §				
ever	0.69(0.23,2.08)	1.29(0.49,3.43)	0.63(0.19,2.04)	1.35(0.45,4.00)
P_{trend}	0.504	0.605	0.43 2	0.594
Genwarts §				
ever	2.28(1.02,5.09)	2.03(0.90,4.55)	1.51(0.60,3.77)	1.04(0.40,2.69)
Gonor §				
ever	0.63(0.19,2.07)	0.72(0.24,2.19)	1.89(0.69,5.17)	1.23(0.39,3.90)
Oralherps §				
ever	1.48(0.90,2.43)	0.94(0.55,1.61)	1.62(0.92,2.85)	0.59(0.30,1.15)
P_{trend}	0.122	0.819	0.097	0.118

* *relative risks (95% CI) adjusted for age, smoking status (non, ex, current & smoke 1-10, current & smoke 11-20, current & smoke(> 20) cigarettes per day), sexmonth and sexlife.*
§ *Women who never had the disease were used as reference category.*

Table 4.8: Adjusted Relative Risks of various comparison groups of cervical dysplasia by nutrient intake*

	Comparison groups			
	1 vs 2-5	2 vs 3-5	3 vs 4-5	4 vs 5
carotdly (mg's)				
< 1901	1.00	1.00	1.00	1.00
1901-3101	1.53(0.88,2.65)	1.00(0.52,1.92)	1.50(0.79,2.88)	1.85(0.75,4.54)
3101-5150	1.19(0.53,2.71)	0.34(0.07,1.60)	2.08(0.76,5.70)	1.75(0.75,4.54)
> 5150	1.73(0.76,3.95)	0.20(0.04,0.93)	0.94(0.34,2.56)	1.10(0.25,4.85)
P_{trend}	0.076	0.031	0.975	0.647
retequiv (unit)				
< 932	1.00	1.00	1.00	1.00
932-1348	1.39(0.79,2.42)	0.53(0.27,1.05)	0.88(0.45,1.73)	0.56(0.21,1.46)
1348-1910	1.29(0.71,2.35)	0.47(0.22,0.98)	1.51(0.71,3.21)	0.84(0.31,2.31)
> 1910	1.35(0.72,2.53)	0.70(0.31,1.58)	0.87(0.40,1.91)	0.79(0.28,2.24)
P_{trend}	0.465	0.410	0.900	0.816
fatpc (percent)				
< 33	1.00	1.00	1.00	1.00
33-38	1.33(0.80,2.19)	1.51(0.79,2.87)	1.14(0.56,2.35)	2.25(0.82,6.14)
38-42	1.44(0.86,2.39)	1.37(0.73,2.59)	1.36(0.66,2.83)	1.85(0.68,5.01)
> 42	1.12(0.66,1.88)	1.95(0.98,3.90)	0.98(0.47,2.01)	1.53(0.55,4.28)
P_{trend}	0.564	0.091	0.984	0.619

Table 4.8(cont'd)

	Comparison groups			
	1 vs 2-5	2 vs 3-5	3 vs 4-5	4 vs 5
tot_cal (cal)				
< 1393	1.00	1.00	1.00	1.00
1393-1783	0.76(0.45,1.29)	0.82(0.42,1.60)	1.15(0.59,2.27)	0.79(0.31,2.02)
1783-2223	0.84(0.51,1.41)	0.61(0.32,1.16)	0.96(0.48,1.92)	0.23(0.08,0.67)
> 2223	0.76(0.45,1.28)	0.81(0.41,1.58)	1.26(0.64,2.47)	0.67(0.27,1.66)
P_{trend}	0.390	0.368	0.635	0.203
est_vitA (I.U.s)				
< 6103	1.00	1.00	1.00	1.00
6103-9080	0.78(0.46,1.32)	1.00(0.53,1.91)	0.81(0.42,1.56)	0.85(0.34,2.11)
9080-13355	0.64(0.38,1.08)	0.87(0.46,1.67)	1.80(0.88,3.69)	0.57(0.23,1.44)
> 13355	0.67(0.40,1.14)	0.81(0.42,1.55)	0.78(0.38,1.56)	0.82(0.31,2.15)
P_{trend}	0.102	0.468	0.925	0.471
est_vitC (mg's)				
< 87	1.00	1.00	1.00	1.00
87-131	1.17(0.70,1.97)	0.87(0.44,1.70)	0.97(0.50,1.89)	0.61(0.24,1.55)
131-186	0.92(0.54,1.55)	0.73(0.37,1.45)	1.27(0.62,2.59)	0.54(0.21,1.37)
> 186	1.12(0.67,1.88)	0.45(0.23,0.87)	0.49(0.24,1.00)	1.14(0.40,3.30)
P_{trend}	0.913	0.013	0.119	0.901

Table 4.8(cont'd)

	Comparison groups			
	1 vs 2-5	2 vs 3-5	3 vs 4-5	4 vs 5
est_fib (g's)				
< 10	1.00	1.00	1.00	1.00
10-13	0.73(0.43,1.23)	0.62(0.31,1.23)	2.41(1.21,4.79)	0.61(0.26,1.44)
13-17	0.94(0.55,1.60)	0.41(0.21,0.81)	0.95(0.49,1.88)	1.05(0.40,2.78)
> 17	0.54(0.32,0.91)	0.41(0.21,0.82)	0.84(0.41,1.70)	1.03(0.37,2.85)
P_{trend}	0.056	0.004	0.390	0.756
citfr_wk				
< 2	1.00	1.00	1.00	1.00
2-5	1.41(0.84,2.36)	0.81(0.45,1.75)	1.16(0.58,2.31)	1.66(0.63,4.39)
5-8	1.27(0.75,2.14)	0.55(0.28,1.06)	0.75(0.37,1.52)	0.69(0.25,1.88)
> 8	1.30(0.77,2.18)	0.80(0.41,1.57)	0.98(0.48,1.98)	1.78(0.65,4.86)
P_{trend}	0.448	0.289	0.633	0.649
veg_wk				
< 14	1.00	1.00	1.00	1.00
14-20	0.82(0.49,1.37)	0.79(0.41,1.52)	0.92(0.45,1.88)	0.58(0.23,1.47)
20-27	0.92(0.55,1.54)	0.94(0.49,1.80)	0.61(0.30,1.21)	0.71(0.27,1.89)
> 27	0.83(0.53,1.50)	0.96(0.50,1.85)	0.81(0.40,1.63)	0.35(0.13,0.95)
P_{trend}	0.784	0.970	0.346	0.061

Table 4.8(cont'd)

	Comparison groups			
	1 vs 2-5	2 vs 3-5	3 vs 4-5	4 vs 5
α-carotene (mg's)				
< 262	1.00	1.00	1.00	1.00
262-487	1.13(0.66,1.91)	0.84(0.44,1.60)	1.46(0.76,2.81)	0.94(0.39,2.29)
487-913	0.62(0.37,1.03)	0.77(0.39,1.51)	2.47(1.19,5.13)	1.95(0.77,4.93)
> 913	0.79(0.47,1.33)	0.60(0.31,1.17)	0.87(0.43,1.76)	0.51(0.17,1.50)
P_{trend}	0.118	0.136	0.793	0.724
β-carotene (mg's)				
< 1236	1.00	1.00	1.00	1.00
1236-2138	1.15(0.68,1.95)	0.86(0.45,1.65)	1.57(0.82,3.00)	1.99(0.81,4.87)
2138-3592	0.77(0.46,1.30)	0.89(0.45,1.76)	2.32(1.12,4.80)	1.02(0.41,2.57)
> 3592	0.81(0.48,1.37)	0.57(0.29,1.10)	0.99(0.48,2.00)	0.67(0.24,1.89)
P_{trend}	0.230	0.119	0.628	0.309
lycopene (mg's)				
< 170	1.00	1.00	1.00	1.00
170-312	0.80(0.48,1.35)	1.49(0.78,2.84)	1.45(0.74,2.84)	0.59(0.24,1.49)
312-484	0.75(0.34,1.69)	1.12(0.60,2.11)	1.49(0.74,2.99)	0.91(0.36,2.26)
> 484	0.62(0.36,1.05)	1.05(0.55,2.00)	0.74(0.37,1.47)	0.46(0.17,1.26)
P_{trend}	0.075	0.946	0.465	0.295

Table4.8(cont'd)

	Comparison groups			
	1 vs 2	1 vs 3	1 vs 4	1 vs 5
nonlycar (mg's)				
< 1895	1.00	1.00	1.00	1.00
1895-3096	1.42(0.83,2.45)	1.00(0.53,1.89)	1.41(0.74,2.67)	1.76(0.74,4.19)
3096-5149	0.57(0.34,0.95)	1.00(0.51,1.99)	1.78(0.87,3.66)	1.18(0.47,2.96)
> 5149	0.81(0.48,1.37)	0.59(0.31,1.14)	0.79(0.39,1.63)	0.64(0.22,1.87)
P_{trend}	0.072	0.135	0.847	0.433
totfol (mg's)				
< 189	1.00	1.00	1.00	1.00
189-263	1.58(0.93,2.69)	1.43(0.72,2.85)	1.11(0.57,2.18)	0.55(0.23,1.34)
263-352	1.04(0.62,1.75)	0.75(0.39,1.48)	0.60(0.30,1.23)	0.71(0.26,1.98)
> 352	1.15(0.68,1.94)	0.61(0.32,1.18)	0.88(0.43,1.80)	0.37(0.14,1.00)
P_{trend}	0.949	0.038	0.355	0.088

* *relative risks (95% CI) adjusted for age, smoking status, sexmonth, sexlife, both condom and diaphragm usage.*

Table 4.9: Adjusted Relative Risks of various comparison groups of cervical dysplasia by nutrient intake*

	Comparison groups			
	1 vs 2	1 vs 3	1 vs 4	1 vs 5
carotdly (mg's)				
< 1901	1.00	1.00	1.00	1.00
1901-3101	1.51(0.70,3.27)	1.31(0.63,2.75)	1.55(0.67,3.55)	2.35(0.96,5.80)
3101-5150	3.50(0.70,17.50)	0.57(0.19,1.69)	0.96(0.30,3.00)	1.93(0.51,7.39)
> 5150	6.55(1.31,32.70)	1.17(0.41,3.36)	1.16(0.36,3.70)	1.24(0.30,5.15)
P_{trend}	0.005	0.458	0.590	0.584
retequiv (unit)				
< 932	1.00	1.00	1.00	1.00
932-1348	2.35(1.05,5.24)	0.99(0.47,2.08)	1.29(0.55,3.03)	0.66(0.26,1.68)
1348-1910	2.54(1.03,6.22)	0.81(0.34,1.92)	0.93(0.38,2.29)	1.04(0.39,2.77)
> 1910	1.85(0.70,4.86)	1.15(0.48,2.73)	1.09(0.43,2.78)	0.80(0.30,2.15)
P_{trend}	0.356	0.811	0.980	0.845
fatpc (percent)				
< 33	1.00	1.00	1.00	1.00
33-38	1.10(0.57,2.14)	1.12(0.56,2.24)	1.05(0.47,2.32)	2.24(0.91,5.55)
38-42	1.22(0.62,2.38)	1.08(0.52,2.25)	1.12(0.50,2.53)	3.00(1.20,7.50)
> 42	0.70(0.34,1.46)	1.26(0.62,2.54)	1.23(0.55,2.78)	1.60(0.61,4.16)
P_{trend}	0.505	0.557	0.603	0.279

Table 4.9(cont'd)

	Comparison groups			
	1 vs 2	1 vs 3	1 vs 4	1 vs 5
tot_cal (cal)				
< 1393	1.00	1.00	1.00	1.00
1393-1783	0.72(0.35,1.50)	0.53(0.25,1.10)	0.72(0.31,1.67)	0.57(0.24,1.33)
1783-2223	0.92(0.46,1.86)	0.62(0.31,1.26)	1.14(0.52,2.50)	0.33(0.13,0.84)
> 2223	0.79(0.38,1.66)	0.58(0.28,1.19)	0.89(0.39,2.02)	0.63(0.27,1.46)
P_{trend}	0.751	0.189	0.904	0.185
est_vitA (I.U.s)				
< 6103	1.00	1.00	1.00	1.00
6103-9080	0.74(0.37,1.50)	0.64(0.28,1.47)	0.64(0.28,1.47)	0.65(0.28,1.53)
9080-13355	0.39(0.18,0.86)	0.98(0.45,2.12)	0.98(0.45,2.12)	0.48(0.20,1.14)
> 13355	0.53(0.25,1.10)	0.63(0.27,1.48)	0.63(0.27,1.48)	0.31(0.12,0.76)
P_{trend}	0.309	0.038	0.508	0.008
est_vitC (mg's)				
< 87	1.00	1.00	1.00	1.00
87-131	1.21(0.58,2.56)	1.04(0.51,2.14)	1.32(0.59,2.93)	0.67(0.28,1.58)
131-186	0.96(0.45,2.04)	0.65(0.30,1.42)	1.17(0.51,2.67)	0.90(0.37,2.16)
> 186	1.80(0.89,3.64)	1.16(0.57,2.36)	0.51(0.20,1.29)	0.42(0.16,1.06)
P_{trend}	0.146	0.914	0.167	0.119

Table 4.9(cont'd)

	Comparison groups			
	1 vs 2	1 vs 3	1 vs 4	1 vs 5
est_fib (g's)				
< 10	1.00	1.00	1.00	1.00
10-13	0.78(0.36,1.69)	0.28(0.13,0.61)	1.14(0.53,2.45)	0.59(0.25,1.38)
13-17	1.46(0.69,3.07)	0.64(0.32,1.31)	0.64(0.27,1.50)	0.79(0.33,1.90)
> 17	0.88(0.42,1.85)	0.34(0.16,0.70)	0.95(0.14,0.85)	0.30(0.12,0.75)
P_{trend}	0.898	0.023	0.008	0.021
citfr_wk				
< 2	1.00	1.00	1.00	1.00
2-5	1.22(0.59,2.54)	1.27(0.62,2.60)	1.77(0.79,3.98)	2.32(1.00,5.34)
5-8	1.78(0.87,3.62)	1.22(0.28,2.59)	1.17(0.52,2.64)	1.13(0.44,2.87)
> 8	1.36(0.66,2.80)	1.26(0.60,2.63)	1.12(0.49,2.56)	1.34(0.56,3.21)
P_{trend}	0.279	0.590	0.965	0.863
veg_wk				
< 14	1.00	1.00	1.00	1.00
14-20	0.90(0.45,1.80)	0.73(0.35,1.52)	0.80(0.36,1.76)	0.77(0.33,1.78)
20-27	0.92(0.46,1.84)	1.06(0.51,2.19)	0.82(0.35,1.91)	0.80(0.34,1.88)
> 27	0.83(0.40,1.69)	0.78(0.37,1.64)	1.39(0.62,3.12)	0.52(0.21,1.27)
P_{trend}	0.642	0.763	0.427	0.178

Table 4.9(cont'd)

	Comparison groups			
	1 vs 2-5	2 vs 3-5	3 vs 4-5	4 vs 5
α-carotene (mg's)				
< 262	1.00	1.00	1.00	1.00
262-487	1.24(0.60,2.58)	0.83(0.41,1.70)	1.45(0.66,3.21)	1.05(0.44,2.52)
487-913	0.68(0.33,1.40)	0.25(0.11,0.55)	0.63(0.28,1.43)	0.78(0.34,1.77)
> 913	0.98(0.48,2.00)	0.66(0.32,1.34)	0.90(0.40,2.05)	0.33(0.12,0.90)
P_{trend}	0.590	0.048	0.373	0.027
β-carotene (mg's)				
< 1236	1.00	1.00	1.00	1.00
1236-2138	1.12(0.54,2.33)	0.96(0.47,1.96)	0.95(0.41,2.21)	2.06(0.87,4.90)
2138-3592	0.85(0.41,1.76)	0.40(0.18,0.85)	0.97(0.44,2.12)	0.77(0.32,1.85)
> 3592	1.10(0.54,2.24)	0.66(0.32,1.35)	0.90(0.39,2.04)	0.38(0.14,1.04)
P_{trend}	0.980	0.078	0.819	0.010
lycopene (mg's)				
< 170	1.00	1.00	1.00	1.00
170-312	0.55(0.27,1.13)	0.56(0.27,1.15)	1.28(0.57,2.89)	0.62(0.26,1.47)
312-484	0.57(0.28,1.16)	0.57(0.27,1.19)	0.96(0.40,2.30)	0.71(0.30,1.70)
> 484	0.44(0.21,0.90)	0.72(0.35,1.45)	0.96(0.41,2.28)	0.33(0.13,0.86)
P_{trend}	0.036	0.407	0.722	0.041

Table4.9(cont'd)

	Comparison groups			
	1 vs 2	1 vs 3	1 vs 4	1 vs 5
nonlycar (mg's)				
< 1895	1.00	1.00	1.00	1.00
1895-3096	1.33(0.63,2.80)	1.31(0.64,2.68)	1.51(0.66,3.45)	2.32(0.96,5.60)
3096-5149	0.57(0.51,2.08)	0.36(0.17,0.77)	0.74(0.34,1.61)	0.69(0.30,1.61)
> 5149	1.03(0.51,2.08)	0.73(0.36,1.51)	0.91(0.39,2.09)	0.34(0.12,0.94)
P_{trend}	0.584	0.075	0.454	0.005
totfol (mg's)				
< 189	1.00	1.00	1.00	1.00
189-263	1.01(0.47,2.16)	1.65(0.80,3.39)	2.02(0.91,4.46)	1.26(0.55,2.90)
263-352	1.16(0.56,2.37)	1.11(0.54,2.30)	0.78(0.33,1.86)	0.53(0.22,1.26)
> 352	1.41(0.70,2.84)	1.03(0.49,2.18)	1.18(0.51,2.74)	0.36(0.14,0.92)
P_{trend}	0.292	0.807	0.702	0.010

* *relative risks (95% CI) adjusted for age, smoking status, sexmonth, sexlife, both condom and diaphragm usage.*

Table 4.10: Adjusted Relative Risks of various comparison groups of cervical dysplasia associated with selected nutrients and vitamin A†

	Comparison groups			
	1 vs 2-5	2 vs 3-5	3 vs 4-5	4 vs 5
α-carotene				
< 262	1.00	1.00	1.00	1.00
262-487	1.24(0.69,2.22)	0.78(0.38,1.57)	1.61(0.80,3.27)	1.13(0.44,2.91)
487-913	0.73(0.37,1.44)	0.64(0.27,1.54)	2.33(0.92,5.86)	3.36(0.98,11.57)
> 913.0	0.94(0.42,2.11)	0.42(0.14,1.25)	0.74(0.23,2.40)	0.64(0.13,3.26)
P_{trend}	0.634	0.130	0.719	0.782
β-carotene				
< 1236	1.00	1.00	1.00	1.00
1236-2138	1.47(0.78,2.75)	0.75(0.34,1.66)	2.12(0.95,4.72)	2.78(0.90,8.63)
2138-3592	1.14(0.53,2.43)	0.69(0.26,1.84)	2.42(0.85,6.87)	1.51(0.39,5.90)
> 3592	1.20(0.47,3.05)	0.26(0.07,0.94)	1.17(0.29,4.70)	0.35(0.05,2.31)
P_{trend}	0.794	0.077	0.370	0.430
nonlycar				
< 1895	1.00	1.00	1.00	1.00
1895-3096	1.61(0.84,3.07)	0.94(0.43,2.04)	1.59(0.73,3.46)	2.44(0.85,7.02)
3096-5149)	0.61(0.27,1.35)	0.82(0.29,2.33)	1.29(0.44,3.79)	2.13(0.49,9.27)
> 5149	0.83(0.31,2.25)	0.23(0.06,0.89)	0.49(0.11,2.15)	0.34(0.05,2.39)
P_{trend}	0.423	0.084	0.711	0.696

Table4.10(cont'd)

	Comparison groups			
	1 vs 2-5	2 vs 3-5	3 vs 4-5	4 vs 5
lycopene				
< 170	1.00	1.00	1.00	1.00
170-312	0.86(0.50,1.45)	1.55(0.80,3.01)	1.34(0.67,2.70)	0.63(0.25,1.61)
312-484	0.84(0.48,1.46)	1.22(0.62,2.37)	1.33(0.64,2.76)	0.98(0.38,2.52)
> 484	0.70(0.40,1.24)	1.16(0.58,2.30)	0.67(0.32,1.41)	0.51(0.18,1.48)
P_{trend}	0.239	0.850	0.320	0.435
totfol				
< 189	1.00	1.00	1.00	1.00
189-263	0.52(0.20,1.35)	1.35(0.64,2.84)	0.98(0.47,2.01)	2.50(1.04,6.03)
263-352	0.62(0.19,2.03)	0.67(0.31,1.45)	0.48(0.20,1.12)	1.01(0.36,2.83)
> 352	0.32(0.09,1.11)	0.51(0.22,1.18)	0.63(0.25,1.63)	1.48(0.51,4.24)
P_{trend}	0.212	0.036	0.185	0.111
est_vitC				
< 87	1.00	1.00	1.00	1.00
87-131	1.35(0.78,2.31)	0.84(0.42,1.67)	0.80(0.40,1.63)	0.69(0.26,1.87)
131-186	1.17(0.66,2.07)	0.68(0.33,1.42)	1.06(0.49,2.30)	0.61(0.23,1.66)
> 186	1.50(0.83,2.72)	0.41(0.20,0.86)	0.41(0.18,0.93)	1.31(0.40,4.29)
P_{trend}	0.276	0.014	0.072	0.867

†*relative risks (95% CI) adjusted for age, smoking status, sexmonth, sexlife, both condom and diaphragm usage and vitamin A.*

Table 4.11: Adjusted Relative Risks of various comparison groups of cervical dysplasia associated with selected nutrients and vitamin A†

	Comparison groups			
	1 vs 2	1 vs 3	1 vs 4	1 vs 5
α-carotene				
< 262	1.00	1.00	1.00	1.00
262-487	1.52(0.67,3.45)	0.87(0.40,1.91)	1.60(0.65,3.92)	1.31(0.51,3.34)
487-913)	0.98(0.37,2.56)	0.33(0.12,0.88)	0.54(0.18,1.62)	1.33(0.45,3.97)
> 913.0	1.46(0.47,4.49)	1.11(0.35,3.54)	0.85(0.25,2.91)	0.66(0.16,2.69)
P_{trend}	0.648	0.929	0.496	0.736
β-carotene				
< 1236	1.00	1.00	1.00	1.00
1236-2138	1.64(0.69,3.85)	1.14(0.51,2.54)	1.26(0.46,3.49)	2.95(1.08,8.05)
2138-3592	1.84(0.63,5.40)	0.63(0.21,1.90)	1.10(0.32,3.81)	1.21(0.34,4.29)
> 3592	2.99(0.83,10.75)	1.15(0.28,4.69)	1.59(0.35,7.28)	0.55(0.11,2.81)
P_{trend}	0.105	0.929	0.611	0.469
nonlycar				
< 1895	1.00	1.00	1.00	1.00
1895-3096	1.69(0.69,4.14)	1.61(0.69,3.75)	1.71(0.61,4.80)	3.10(1.11,8.62)
3096-5149	0.85(0.27,2.67)	0.56(0.18,1.73)	0.53(0.14,2.02)	0.94(0.28,4.00)
> 5149	1.92(0.49,7.53)	1.48(0.33,6.66)	0.89(0.17,4.58)	0.32(0.05,1.99)
P_{trend}	0.493	0.995	0.643	0.290

Table 4.11(cont'd)

	Comparison groups			
	1 vs 2	1 vs 3	1 vs 4	1 vs 5
lycopene				
< 170	1.00	1.00	1.00	1.00
170-312	0.56(0.27,1.15)	0.62(0.29,1.29)	1.36(0.60,3.12)	0.66(0.28,1.60)
312-484	0.62(0.30,1.30)	0.76(0.34,1.68)	1.01(0.41,2.48)	0.85(0.34,2.14)
> 484	0.46(0.21,1.01)	0.99(0.46,2.17)	1.10(0.44,2.73)	0.48(0.17,1.34)
P_{trend}	0.078	0.859	0.930	0.256
totfol				
< 189	1.00	1.00	1.00	1.00
189-263	1.62(0.66,3.97)	2.22(1.02,4.86)	1.35(0.59,3.10)	1.62(0.66,3.97)
263-352	0.79(0.29,2.19)	2.05(0.85,4.94)	1.79(0.78,4.11)	0.79(0.29,2.19)
> 352	0.60(0.19,1.90)	2.20(0.84,5.77)	2.56(1.05,6.27)	0.60(0.84,5.77)
P_{trend}	0.032	0.137	0.965	0.245
est_vitC				
< 87	1.00	1.00	1.00	1.00
87-131	1.46(0.68,3.13)	1.35(0.64,2.83)	1.30(0.55,3.04)	0.87(0.35,2.15)
131-186	1.37(0.60,3.12)	1.00(0.42,2.36)	1.17(0.48,2.88)	1.25(0.49,3.21)
> 186	2.90(1.25,6.72)	2.05(0.89,4.76)	0.49(0.17,1.42)	0.68(0.24,1.92)
P_{trend}	0.017	0.140	0.188	0.689

†*relative risks (95% CI) adjusted for age, smoking status, sexmonth, sexlife, both condom and diaphragm usage and vitamin A.*

Table 4.12: Adjusted Relative Risks of various comparison groups of cervical dysplasia associated with selected nutrients and folate‡

	Comparison groups			
	1 vs 2-5	2 vs 3-5	3 vs 4-5	4 vs 5
est_vitA				
< 6103	1.00	1.00	1.00	1.00
6103-9080	0.63(0.35,1.12)	1.10(0.54,2.24)	0.97(0.47,1.20)	1.12(0.42,2.98)
9080-13355	0.49(0.26,0.89)	1.19(0.55,2.59)	2.45(1.05,5.73)	0.90(0.31,2.60)
> 13355	0.50(0.25,0.96)	1.35(0.58,3.14)	1.20(0.48,3.01)	1.50(0.44,5.16)
P_{trend}	0.036	0.474	0.322	0.655
α-carotene				
< 262	1.00	1.00	1.00	1.00
262-487	1.08(0.63,1.88)	0.87(0.45,1.69)	1.68(0.86,3.28)	1.08(0.43,2.72)
487-913)	0.56(0.32,0.97)	0.85(0.42,1.71)	2.93(1.36,6.33)	2.65(0.95,7.45)
> 913.0	0.72(0.40,1.28)	0.76(0.36,1.59)	1.02(0.46,2.27)	0.70(0.22,2.29)
P_{trend}	0.077	0.484	0.436	0.820
β-carotene				
< 1236	1.00	1.00	1.00	1.00
1236-2138	1.08(0.62,1.86)	0.89(0.45,1.74)	1.74(0.89,3.41)	2.51(0.96,6.53)
2138-3592	0.69(0.39,1.22)	0.99(0.48,2.07)	2.96(1.34,6.51)	1.39(0.49,3.91)
> 3592	0.74(0.41,1.35)	0.75(0.35,1.60)	1.27(0.56,2.91)	0.96(0.29,3.22)
P_{trend}	0.169	0.535	0.248	0.771

Table 4.12(cont'd)

	Comparison groups			
	1 vs 2-5	2 vs 3-5	3 vs 4-5	4 vs 5
nonlycar				
< 1895	1.00	1.00	1.00	1.00
1895-3096	1.26(0.71,2.22)	1.03(0.53,2.02)	1.60(0.82,3.15)	2.39(0.93,6.11)
3096-5149	0.48(0.27,0.85)	1.16(0.55,2.46)	2.31(1.04,5.12)	1.71(0.60,4.90)
> 5149	0.68(0.36,1.25)	0.80(0.37,1.72)	1.01(0.43,2.37)	0.99(0.28,3.53)
P_{trend}	0.035	0.632	0.637	0.974
lycopene				
< 170	1.00	1.00	1.00	1.00
170-312	0.78(0.46,1.33)	1.70(0.88,3.31)	1.60(0.80,3.20)	0.61(0.24,1.54)
312-484	0.70(0.41,1.21)	1.30(0.67,2.53)	1.57(0.77,3.20)	1.01(0.39,2.56)
> 484	0.57(0.33,0.99)	1.28(0.64,2.53)	0.80(0.39,1.66)	0.56(0.20,1.59)
P_{trend}	0.046	0.671	0.606	0.532
est_vitC				
< 87	1.00	1.00	1.00	1.00
87-131	0.67(0.36,1.24)	1.20(0.55,2.64)	0.51(0.23,1.15)	0.48(0.15,1.52)
131-186	0.58(0.27,1.25)	1.30(0.50,3.39)	1.04(0.37,2.91)	0.48(0.12,1.86)
> 186	0.61(0.24,1.56)	2.49(0.70,8.87)	0.72(0.18,2.83)	1.91(0.32,11.32)
P_{trend}	0.257	0.222	0.748	0.806

†*relative risks (95% CI) adjusted for age, smoking status, sexmonth, sexlife, both condom and diaphragm usage and total folate.*

Table 4.13: Adjusted Relative Risks of various comparison groups of cervical dysplasia associated with selected nutrients and folate‡

	Comparison groups			
	1 vs 2	1 vs 3	1 vs 4	1 vs 5
est_vitA				
< 6103	1.00	1.00	1.00	1.00
6103-9080	0.61(0.28,1.34)	0.54(0.24,1.20)	0.51(0.20,1.31)	0.66(0.26,1.65)
9080-13355	0.41(0.18,0.93)	0.27(0.11,0.67)	0.86(0.34,2.17)	0.56(0.20,1.55)
> 13355	0.40(0.16,0.98)	0.33(0.13,0.88)	0.57(0.20,1.67)	0.41(0.13,1.29)
P_{trend}	0.037	0.015	0.554	0.135
α-carotene				
< 262	1.00	1.00	1.00	1.00
262-487	1.14(0.54,2.41)	0.80(0.38,1.69)	1.57(0.67,3.65)	1.25(0.50,3.10)
487-913)	0.57(0.26,1.23)	0.22(0.09,0.52)	0.64(0.26,1.56)	1.08(0.44,2.64)
> 913.0	0.77(0.35,1.69)	0.60(0.27,1.35)	0.98(0.39,2.49)	0.50(0.17,1.46)
P_{trend}	0.268	0.044	0.480	0.223
β-carotene				
< 1236	1.00	1.00	1.00	1.00
1236-2138	1.04(0.49,2.20)	0.91(0.44,1.90)	0.92(0.38,2.24)	2.42(0.97,6.00)
2138-3592	0.73(0.33,1.60)	0.36(0.16,0.81)	0.96(0.41,2.27)	1.00(0.38,2.63)
> 3592	0.86(0.38,1.95)	0.60(0.26,1.37)	0.98(0.38,2.56)	0.60(0.20,1.82)
P_{trend}	0.561	0.072	0.981	0.157

Table 4.13(cont'd)

	Comparison groups			
	1 vs 2	1 vs 3	1 vs 4	1 vs 5
nonlycar				
< 1895	1.00	1.00	1.00	1.00
1895-3096	1.17(0.53,2.54)	1.18(0.55,2.51)	1.39(0.58,3.36)	2.64(1.05,6.63)
3096-5149	0.45(0.20,1.02)	0.31(0.13,0.71)	0.71(0.29,1.73)	0.88(0.34,2.26)
> 5149	0.72(0.31,1.67)	0.64(0.27,1.52)	0.92(0.34,2.48)	0.52(0.16,1.66)
P_{trend}	0.184	0.060	0.542	0.103
lycopene				
< 170	1.00	1.00	1.00	1.00
170-312	0.50(0.24,1.03)	0.54(0.26,1.14)	1.39(0.61,3.17)	0.72(0.29,1.75)
312-484	0.47(0.22,0.99)	0.53(0.25,1.16)	0.93(0.38,2.25)	0.86(0.34,2.15)
> 484	0.35(0.16,0.75)	0.68(0.47,1.46)	0.93(0.38,2.29)	0.45(0.16,1.24)
P_{trend}	0.009	0.382	0.618	0.194
est_vitC				
< 87	1.00	1.00	1.00	1.00
87-131	0.55(0.23,1.29)	0.76(0.34,2.90)	0.57(0.21,1.57)	0.44(0.16,1.21)
131-186	0.36(0.12,1.06)	0.54(0.18,1.63)	0.87(0.25,3.00)	0.51(0.15,1.79)
> 186	0.30(0.08,1.06)	0.50(0.12,2.09)	0.44(0.09,2.05)	0.56(0.12,2.57)
P_{trend}	0.054	0.280	0.377	0.418

** relative risks (95% CI) adjusted for age, smoking status, sexmonth, sexlife, both condom and diaphragm usage and total folate.*

Table 4.14: Adjusted Relative Risks of various comparison groups of cervical dysplasia associated with selected nutrients and β-carotene‡

	Comparison groups			
	1 vs 2-5	2 vs 3-5	3 vs 4-5	4 vs 5
est_vitA				
< 6103	1.00	1.00	1.00	1.00
6103-9080	1.08(0.62,1.90)	0.79(0.38,1.67)	1.01(0.47,2.19)	0.87(0.31,2.47)
9080-13355	0.86(0.46,1.61)	0.71(0.31,1.60)	1.35(0.56,3.26)	0.89(0.30,2.66)
> 13355	1.17(0.58,2.37)	0.51(0.21,1.26)	0.47(0.17,1.28)	3.26(0.76,14.00)
P_{trend}	0.850	0.146	0.249	0.217
α-carotene				
< 262	1.00	1.00	1.00	1.00
262-487	0.94(0.49,1.79)	0.87(0.40,1.90)	1.24(0.58,2.68)	0.77(0.27,2.22)
487-913)	0.52(0.25,1.11)	0.78(0.30,2.05)	1.53(0.55,4.32)	3.14(0.78,12.63)
> 913.0	0.74(0.28,1.97)	0.96(0.26,3.47)	0.50(0.12,2.12)	1.09(0.15,7.62)
P_{trend}	0.240	0.803	0.869	0.403
nonlycar				
< 1895	1.00	1.00	1.00	1.00
1895-3096	1.06(0.42,2.66)	1.45(0.47,4.44)	0.63(0.19,2.13)	1.91(0.22,16.42)
3096-5149	0.24(0.07,0.78)	1.44(0.30,6.89)	0.24(0.04,1.48)	3.60(0.22,58.73)
> 5149	0.37(0.08,1.85)	0.65(0.06,6.55)	0.05(0.00,0.98)	2.34(0.06,95.57)
P_{trend}	0.040	0.968	0.047	0.523

Table 4.14(cont'd)

	Comparison groups			
	1 vs 2-5	2 vs 3-5	3 vs 4-5	4 vs 5
lycopene				
< 170	1.00	1.00	1.00	1.00
170-312	0.80(0.47,1.35)	1.55(0.80,2.97)	1.35(0.68,2.67)	0.59(0.23,1.50)
312-484	0.76(0.44,1.31)	1.25(0.65,2.40)	1.38(0.67,2.83)	0.94(0.36,2.43)
> 484	0.64(0.37,1.10)	1.21(0.62,2.36)	0.72(0.35,1.47)	0.44(0.16,1.26)
P_{trend}	0.116	0.712	0.427	0.295
est_vitC				
< 87	1.00	1.00	1.00	1.00
87-131	1.24(0.73,2.12)	0.87(0.44,1.73)	0.78(0.39,1.58)	0.63(0.23,1.71)
131-186	1.03(0.58,1.80)	0.77(0.37,1.58)	1.14(0.54,2.43)	0.61(0.23,1.66)
> 186	1.32(0.74,2.36)	0.49(0.24,1.01)	0.42(0.19,0.90)	1.58(0.47,5.34)
P_{trend}	0.487	0.047	0.086	0.670
total folate				
< 189	1.00	1.00	1.00	1.00
189-263	1.73(1.00,3.00)	1.33(0.56,3.16)	0.90(0.45,1.81)	0.47(0.18,1.20)
263-352	1.21(0.69,2.12)	0.62(0.24,1.60)	0.45(0.21,0.98)	0.68(0.22,2.13)
> 352	1.40(0.77,2.55)	0.51(0.18,1.49)	0.75(0.32,1.72)	0.36(0.11,1.14)
P_{trend}	0.545	0.135	0.224	0.141

** relative risks (95% CI) adjusted for age, smoking status, sexmonth, sexlife, both condom and diaphragm usage and β-carotene.*

Table 4.15: Adjusted Relative Risks of various comparison groups of cervical dysplasia associated with selected nutrients and β-carotene‡

	Comparison groups			
	1 vs 2	1 vs 3	1 vs 4	1 vs 5
est_vitA				
< 6103	1.00	1.00	1.00	1.00
6103-9080	1.23(0.56,2.69)	0.91(0.41, 2.03)	1.18(0.49,2.82)	0.77(0.30,1.98)
9080-13355	0.98(0.41,2.34)	0.59(0.22, 1.55)	0.97(0.37,2.56)	1.29(0.45,3.66)
> 13355	1.84(0.70,4.82)	1.37(0.48, 3.90)	0.31(0.09,1.06)	0.93(0.26,3.33)
P_{trend}	0.310	0.695	0.089	0.795
α-carotene				
< 262	1.00	1.00	1.00	1.00
262-487	1.01(0.41,2.50)	0.66(0.28,1.55)	1.35(0.53,3.44)	0.73(0.27,2.00)
487-913)	0.51(0.18,1.44)	0.24(0.08, 0.74)	0.42(0.13,1.32)	0.78(0.24,2.47)
> 913.0	0.61(0.17,2.21)	0.90(0.21,3.83)	0.55(0.13,2.34)	0.71(0.13,3.90)
P_{trend}	0.255	0.241	0.207	0.674
nonlycar				
< 1895	1.00	1.00	1.00	1.00
1895-3096	0.82(0.24,2.83)	1.41(0.48, 4.18)	1.45(0.47,4.44)	1.28(0.22,7.44)
3096-5149	0.19(0.04,0.92)	0.40(0.09, 1.80)	1.44(0.30,6.87)	0.36(0.04,3.06)
> 5149	0.33(0.04,2.70)	1.21(0.12,12.56)	0.65(0.06,6.55)	0.16(0.01,3.77)
P_{trend}	0.082	0.632	0.102	0.130

Table 4.15(cont'd)

	Comparison groups			
	1 vs 2	1 vs 3	1 vs 4	1 vs 5
lycopene				
< 170	1.00	1.00	1.00	1.00
170-312	0.52(0.25,1.08)	0.54(0.26,1.14)	1.29(0.57,2.93)	0.63(0.26,1.54)
312-484	0.54(0.26,1.13)	0.64(0.30,1.39)	0.97(0.40,2.36)	0.68(0.27,1.74)
> 484	0.40(0.19,0.87)	0.84(0.40,1.76)	0.98(0.41,2.36)	0.38(0.13,1.05)
P_{trend}	0.029	0.766	0.753	0.091
est_vitC				
< 87	1.00	1.00	1.00	1.00
87-131	1.27(0.59,2.73)	1.22(0.58,2.55)	1.29(0.55,3.00)	0.73(0.29,1.82)
131-186	1.07(0.47,2.45)	0.83(0.36,1.93)	1.13(0.46,2.78)	1.09(0.43,2.76)
> 186	2.10(0.93,4.73)	1.62(0.73,3.60)	0.47(0.17,1.34)	0.64(0.23,1.80)
P_{trend}	0.089	0.336	0.149	0.641
total folate				
< 189	1.00	1.00	1.00	1.00
189-263	1.07(0.49,2.35)	1.86(0.89,3.91)	2.04(0.90,4.63)	1.33(0.56,3.16)
263-352	1.25(0.58,2.69)	1.43(0.66,3.11)	0.79(0.31,2.03)	0.62(0.24,1.60)
> 352	1.59(0.71,3.56)	1.43(0.61,3.38)	1.19(0.45,3.10)	0.51(0.18,1.49)
P_{trend}	0.231	0.501	0.762	0.132

** relative risks (95% CI) adjusted for age, smoking status, sexmonth, sexlife, both condom and diaphragm usage and β-carotene.*

Table 4.16: Adjusted Relative Risks of various comparison groups of cervical dysplasia by supplement intakes*

	Comparison groups			
	1 vs 2-5	2 vs 3-5	3 vs 4-5	4 vs 5
vitB current †	0.76(0.38,1.52)	0.50(0.20,1.23)	0.55(0.19,1.57)	0.88(0.18,4.40)
P_{trend}	0.442	0.137	0.265	0.876
vitC current ‡	0.66(0.38,1.15)	0.44(0.21.0.91)	1.08(0.43,2.67)	0.90(0.27,3.00)
P_{trend}	0.145	0.030	0.873	0.869
	1 vs 2	1 vs 3	1 vs 4	1 vs 5
vitB current †	1.23(0.50,3.00)	0.81(0.31,2.12)	0.98(0.28,3.43)	0.66(0.18,2.42)
P_{trend}	0.659	0.665	0.967	0.530
vitC current ‡	1.17(0.57,2.43)	0.44(0.19,1.06)	0.73(0.28,1.86)	0.48(0.17,1.36)
P_{trend}	0.667	0.057	0.500	0.154

** relative risks (95% CI) adjusted for age, smoking status,sexmonth, sexlife, both condom and diaphragm usage.*

† *Non vitB user was used as reference category.*

‡ *Non vitC user was used as reference category.*

Table 4.17: Adjusted Relative Risks of various comparison groups of cervical dysplasia by alcohol intake*

	Comparison groups			
	1 vs 2-5	2 vs 3-5	3 vs 4-5	4 vs 5
wine current†	1.59(1.09,2.32)	0.88(0.54,1.42)	0.91(0.54,1.53)	0.91(0.45,1.84)
P_{trend}	0.014	0.592	0.721	0.780
winenum ‡				
2-4	1.07(0.54,2.13)	1.25(0.55,2.81))	0.80(0.54,1.53)	0.62(0.15,2.56)
> 4	0.81(0.38,1.73)	2.13(0.78,5.78)	1.21(0.43,3.42)	0.15(0.03,0.83)
P_{trend}	0.609	0.143	0.825	0.022
beer current §	1.53(1.01,2.31)	0.82(0.50,1.35)	0.74(0.43,1.27)	2.38(1.12,5.07)
P_{trend}	0.045	0.438	0.278	0.022
beernum ‡				
2-4	0.66(0.29,1.50)	2.57(0.90,7.34))	0.32(0.10,0.98)	1.14(0.15,8.44)
> 4	1.29(0.46,3.62)	1.03(0.35,2.99)	0.70(0.20,2.39)	1.14(0.21,6.06)
P_{trend}	0.778	0.143	0.471	0.858

* *relative risks (95% CI) adjusted for age, smoking status, sexmonth, sexlife, both condom and diaphragm usage.*

† *Non wine drinkers were used as reference category.*

§ *Non beer drinkers were used as reference category.*

‡ *The lowest level ($<= 1$) bottles was used as reference category.*

Table 4.18: Adjusted Relative Risks of various comparison groups of cervical dysplasia by alcohol intake*

	Comparison groups			
	1 vs 2	1 vs 3	1 vs 4	1 vs 5
wine current†	1.88(1.12,3.13)	1.59(0.95,2.67)	1.29(0.72,2.31)	1.19(0.65,2.18)
P_{trend}	0.016	0.080	0.385	0.582
winenum ‡				
2-4	1.09(1.12,3.13)	0.65(0.24,1.79)	1.11(0.34,3.57)	0.49(0.15,1.62)
> 4	0.54(0.19,1.57)	0.64(0.20,2.04)	2.29(0.66,7.99)	0.34(0.08,1.42)
P_{trend}	0.311	0.420	0.205	0.126
beer current §	1.67(0.96,2.92)	1.82(1.03,3.23)	0.93(0.49,1.77)	1.77(0.89,3.50)
P_{trend}	0.072	0.041	0.816	0.101
beernum ‡				
2-4	0.41(0.12,1.35)	1.09(0.33,3.59)	0.49(0.09,2.59)	1.19(0.26,5.52)
> 4	1.08(0.28,4.16)	1.67(0.35,8.02)	3.19(0.56,18.10)	3.09(0.44,21.71)
P_{trend}	0.756	0.542	0.243	0.286

** relative risks (95% CI) adjusted for age, smoking status, sexmonth, sexlife, both condom and diaphragm usage.*

† *Non wine drinkers were used as reference category.*

§ *Non beer drinkers were used as reference category.*

† *The lowest level (<= 1) of bottles per week was used as reference .*

Table 4.19: Pearson correlation coefficients for selected nutrients among controls

	vitA	*vitC*	α-carotene	β-carotene	*nonlycar*	*folate*
vitA	1.000	0.438	0.867	0.900	0.911	0.354
vitC	0.438	1.000	0.287	0.359	0.364	0.504
α-carotene	0.867	0.287	1.000	0.935	0.968	0.290
β-carotene	0.900	0.359	0.935	1.000	0.987	0.374
nonlycar	0.911	0.364	0.968	0.987	1.000	0.385
folate	0.354	0.504	0.290	0.374	0.385	1.000

Chapter 5

Discussion and Conclusions

The important risk factors found to be associated with CIN in this case-control study are: *current smoking, sexual frequency, number of different lifetime sexual partners, combined usage of both condom and diaphragm and dietary vitamin A intake.* Because cervical dysplasia is often considered to be a precursor lesion for invasive cervical cancer, it is not surprising that risk factors similar to those for cervical cancer are found.

Our finding of an association between cigarette smoking and CIN is similar to that of several other studies which analysed women with cervical dysplasia[2,16] and carcinoma in-situ[18]. Our study indicates that current cigarette smoking affects disease progression. The decreasing pattern of relative risk adjusted for age across the first four comparison groups in *Table 4.1* suggests that current smoking has a greater effect on earlier stages of the disease. Cigarette smoking may initiate or promote CIN and current smokers have a higher risk of developing into the more advanced stages of the disease than non smokers. Likewise, dysplasia is more likely to progress to carcinoma in-situ among current smokers

than non smokers (see *Table 4.2*). However, no dose response relationship with current cigarette smoking is found in out study unlike that found for invasive cervical cancer and carcinoma in-situ in other studies[18,20,23]. Contrary to several case control studies[2,18,21] which find ex-smokers at increased risk of cervical cancer compared to non smokers, our study has not established this effect. The accumulation of tobacco products in cervical epithelial cells and a local immunologic deficiency of smoking may explain how cigarette smoking contributes to the development of CIN.

The findings of an increased risk of CIN associated with an increased number of lifetime sexual partners after controlling for the confounding effect of age and smoking are consistent with those for invasive cervical cancer[1,3–4]. Our study, is the first to report a relationship between episodes of sexual intercourse (denoted by *sexmonth* in this study) and CIN. Sexmonth is found significant even after controlling for age, smoking and sexlife. These findings (*i.e. both sexmonth and sexlife*) support the hypothesis that cervical cancer and it's percursors behave as a sexually transmitted disease.

If cervical cancer is a sexually transmitted disease, would barrier forms of contraception reduce risk for the disease? In this study, we find in answer to this natural question that women who use diaphragms concurrently with their current sexual partners using condoms had the greatest protective effect against the disease. As shown in *Tables 4.5* and *4.6*, both condom and diaphragm usage had the greatest effect in protecting women against developing the disease, the RR was 0.47 in 1 vs 2-5. For those who already had dysplasia, the adjusted relative risks of condom and diaphragm usage are close to unity, suggesting that both condom and diaphragm usage does not offer any protection against

further development into the latter stage of dysplasia. The reasons for this pattern are unclear. Also, women who used a diaphragm alone reduced their risk of developing carcinoma in-situ compared to non users (RR = 0.21). One of the limitations of this study is that information obtained on condom use is limited to the womans' current partners. No information was elicited about condom usage by former partners whereas for diaphragm usage, information was obtained on the history of lifetime usage. Hence, results obtained about the effects of condom usage might not be comparable with those for diaphragms. Like most studies on oral contraceptive usage, our study finds no relationship between *oral contraception* and CIN[1,2–4]. The study of contraceptive usage and cervical cancer risk in one which has entails considerable methodological difficulty. The choice of a contraceptive is considered to be related to sexual practice, lifestyle etc. so determining the underlying reasons for any altered risks is complex. Also, none of the several venereal diseases are significantly associated with the risk of CIN. Self reporting of venereal disease is potentially open to bias. In particular the main disease of interest, HPV infection, can frequently be symptomless so that disease status cannot be truly detected without tissue sampling and typing. Thus all results on venereal infection must be considered inconclusive. Moreover, it should be noted that the results presented here are generally in agreement with those found elsewhere.

Vitamin A plays an important role in cell differentiation. Deficiency in vitamin A or carotene may allow more rapid proliferation of malignant cells. The results of previous studies on vitamin A and the risk of invasive cervical cancer are controversial with protective effects being detected in some studies[27] but not in others[33,35].

Our study finds lower levels of dietary vitamin A associated with an elevated risk. The association appears stronger than carotene, vitamin C and folate. The correlations between vitamin A and carotene and other carotenoids were relatively high, particularly for β-carotene and vitamin A where the correlation is 0.90 and between nonlycopene carotenoids and vitamin A, they are 0.91. A high correlation between the nutrients hampered interpretation of their independent associations with risk, but nevertheless vitamin A appears to be the strongest determinant. This can also be seen when we control for folate when vitamin A still appeared significant. No evidence of protection by high dietary intake of vitamin C is revealed in this study. Moreover, no reduction in risk is observed with women taking vitamin B and vitamin C supplements. However, alcohol drinkers seem to increase their risk of developing the disease although the results are not conclusive.

As with most cancers, it appears cervical cancer is the result of several interrelated factors working together to cause the disease. The findings in this study further strengthened the importance of smoking, sexual activity, barrier form of contraceptive usage and vitamin A as significant etiologic factors in CIN.

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Study of Cervical Intra-Epithelial Neoplasia

This form asks a variety of questions on your diet, your habits and your life-style. Information on this questionnaire will be used to help us understand more about the causes of diseases of the female cervix.

We ask you to be as careful as possible in answering these questions. If you are presently pregnant, please indicate your usual diet prior to pregnancy. If you are uncertain of the meaning of the question, or if your answers do not fit into the space provided, write any comments you may have alongside the question. If you need any assistance in completing the questionnaire please telephone 877-6010 LOCAL 3057 OR 3065

Your answers on this questionnaire will be kept completely confidential and will be used for the purposes of this study only.

OFFICE USE

1 _ _ _ _ _ _ _ _ _ _

1. When were you born? _____/_____/_____ (Day / Mo. / Yr.) 11 _ _ _ _ _ _
2. How old are you? _____ years 17 _ _
3. How many years have you been a resident of B.C.? _____ 19 _ _
4. Please indicate the highest grade you completed in school _____ 21 _ _
5. Please check any post-secondary education:

   Trade School_____ College_____ University_____ 23 _

6. What is your marital status? Single_____ Married_____ 24 _

   Widowed_____ Divorced/Separated_____

7. How many times have you moved or changed residence in the last 10 years? ____ times 25 _ _
8. Have you ever smoked cigarettes daily for more than 3 months? No____ Yes____ 27 _

   If no: Continue with question 9.

   If yes: How many cigarettes did you smoke on average?____number/day 28 _ _

   At what age did you start smoking cigarettes?_____years 30 _ _

   Do you currently smoke cigarettes? No____ Yes____ 32 _

   If you have stopped smoking, how old were you when you stopped? _____years 33 _ _

Appendix 1 (cont'd)

9. Do you usually consume alcoholic beverages? No ___ Yes ___ 35 ___

If yes: Please complete the following table.

	Average number per week	Total years you consumed alcoholic beverages	At what age did you begin to consume alcoholic beverages	If stopped at what age did you permanently stop?	Are you currently consuming alcoholic beverages?
Beer *(bottles)*					
Wine *(glasses)*					
Spirits *(shots)*					

36 ___ ___
38 ___ ___
40 ___ ___
42 ___ ___ ___
45 ___ ___
47 ___ ___
49 ___ ___
51 ___ ___ ___
54 ___ ___
56 ___ ___
58 ___ ___
60 ___ ___ ___

10. Do you regularly take multivitamins or megavitamins? No ___ Yes ___ 63 ___

If yes: Please complete the following table

	# of Tablets per day	BRAND NAMES ÷ Dosage mg/IU	Total Time Used years / months	Presently Using	
Multivitamins	_____	_____	___yrs/___mths	___no___yes	11 ___ ___ ___ ___ ___ ___ ___ ___
Megavitamins	_____	_____	___yrs/___mths	___no___yes	19 ___ ___ ___ ___ ___ ___ ___ ___

Do you regularly take other supplements? No ___ Yes ___ 27 ___

If yes: Please complete the following table

Vitamin A	_____	_____	___yrs/___mths	___no___yes	28 ___ ___ ___ ___ ___ ___ ___ ___
Vitamin B complex	_____	_____	___yrs/___mths	___no___yes	36 ___ ___ ___ ___ ___ ___ ___ ___
Folate	_____	_____	___yrs/___mths	___no___yes	44 ___ ___ ___ ___ ___ ___ ___ ___
Vitamin C	_____	_____	___yrs/___mths	___no___yes	52 ___ ___ ___ ___ ___ ___ ___ ___
Vitamin E	_____	_____	___yrs/___mths	___no___yes	60 ___ ___ ___ ___ ___ ___ ___ ___
Iron	_____	_____	___yrs/___mths	___no___yes	68 ___ ___ ___ ___ ___ ___ ___ ___
Betacarotene	_____	_____	___yrs/___mths	___no___yes	11 ___ ___ ___ ___ ___ ___ ___ ___
Cod Liver Oil	_____	_____	___yrs/___mths	___no___yes	19 ___ ___ ___ ___ ___ ___ ___ ___
Zinc	_____	_____	___yrs/___mths	___no___yes	27 ___ ___ ___ ___ ___ ___ ___ ___
Calcium	_____	_____	___yrs/___mths	___no___yes	35 ___ ___ ___ ___ ___ ___ ___ ___
Magnesium	_____	_____	___yrs/___mths	___no___yes	43 ___ ___ ___ ___ ___ ___ ___ ___
Selenium	_____	_____	___yrs/___mths	___no___yes	51 ___ ___ ___ ___ ___ ___ ___ ___
Other	_____	_____	___yrs/___mths	___no___yes	59 ___ ___ ___ ___ ___ ___ ___ ___

OFFICE USE

70 ___ ___

11. Are you on a special diet?

1 ___ No 2 ___ Weight loss 3 ___ For medical condition 4 ___ Vegetarian 5 ___ Low salt
6 ___ Low cholesterol 7 ___ Weight gain

12. How often do you eat foods from the following *restaurants?*

TYPE OF RESTAURANT	1 Almost every day	2 2-4 times a week	3 Once a week	4 1-3 times a month	5 5-10 times a year	6 1-4 times a year	7 Never, or less than once a year
Fried chicken							
Burgers							
Pizza							
Chinese food							
Mexican food							
Fried Fish							
Other restaurants							

72 ___ ___
73 ___ ___
74 ___ ___
75 ___ ___
76 ___ ___
77 ___ ___
78 ___ ___

C 79 80

13. This section is about your *usual* eating habits. Thinking back over the past year, how often do you usually eat the foods listed on the next page?

First, check (✓) whether your usual serving size is small, medium or large. (A small portion is about one-half the medium serving size shown, or less; a large portion is about one-and-a-half times as much, or more.) Don't check any serving size if you eat the food less than once a year. Some items mention several foods (for example, "bread, rolls, crackers.") *Check the serving size for the one you eat most often.*

Then, put a *NUMBER* in the most appropriate column to indicate *HOW OFTEN*, on the average, you eat the food. You may eat bananas *twice a week* (put a *2 in the "week"* column) and sweet potatoes or yams *three times a month* (put a *3 in the "month"* column). If you never eat the food, check "Rarely/Never".

Some items say "in season". Indicate how often you eat these just in the 3-4 month time when that food is in season. For example, you may eat cantaloupe once a week when it is in season, but only once a month during the rest of the year. (See example)

Please look at the *example* below. This person

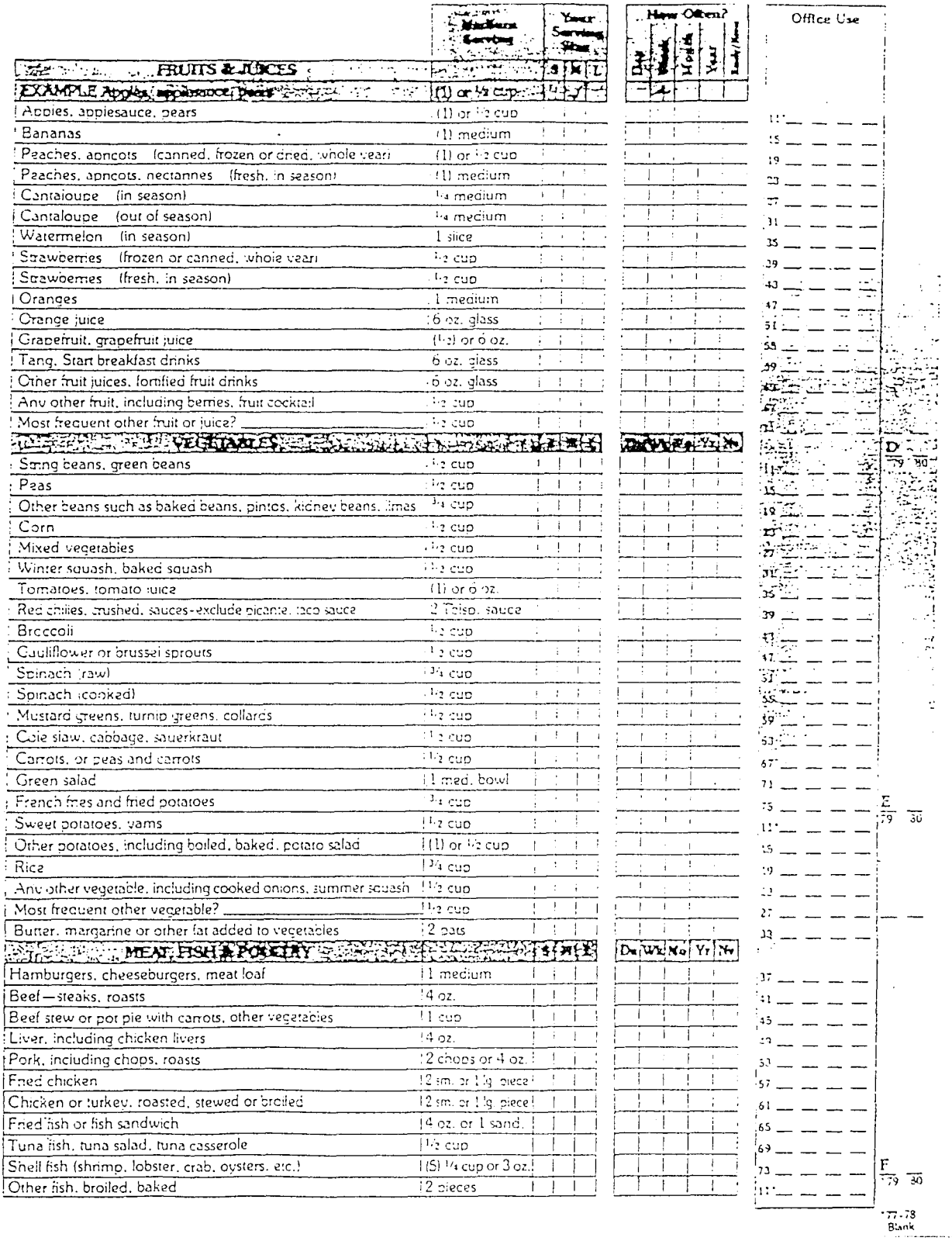
1) eats a medium serving of cantaloupe once a week, in season
2) eats a medium serving of cantaloupe once a month, the rest of the year
3) has ½ grapefruit about once a week, and grapefruit juice about once a month. That is about 5 times a month for that item.
4) has a small serving of sweet potatoes about 3 times a year.
5) has a large hamburger or cheeseburger or meat loaf about 4 times a week.

EXAMPLE:

	Medium Serving	Your Serving Size S	M	L	How Often? Day	Week	Month	Year	Rarely/ Never
Cantaloupe (in season)	¼ medium		✓			1			
Cantaloupe (out of season)	¼ medium		✓				1		
Grapefruit, grapefruit juice	(½) or 6 oz.		✓				5		
Sweet potatoes, yams	½ cup	✓						3	
Hamburger, cheeseburger, meat loaf	1 medium			✓		4			

PLEASE GO TO NEXT PAGE

Appendix 1 (cont'd)



	Medium Serving	Your Serving Size	How Often? Day	Week	Month	Year	Never/Almost Never	Office Use
FRUITS & JUICES		S M L						
EXAMPLE Apples, applesauce, pears	(1) or ½ cup	L		✓				
Apples, applesauce, pears	(1) or ½ cup							11 15 19 23 27 31 35 39 43 47 51 55 59
Bananas	(1) medium							
Peaches, apricots (canned, frozen or dried, whole year)	(1) or ½ cup							
Peaches, apricots, nectarines (fresh, in season)	(1) medium							
Cantaloupe (in season)	¼ medium							
Cantaloupe (out of season)	¼ medium							
Watermelon (in season)	1 slice							
Strawberries (frozen or canned, whole year)	½ cup							
Strawberries (fresh, in season)	½ cup							
Oranges	1 medium							
Orange juice	6 oz. glass							
Grapefruit, grapefruit juice	(½) or 6 oz.							
Tang, Start breakfast drinks	6 oz. glass							
Other fruit juices, fortified fruit drinks	6 oz. glass							
Any other fruit, including berries, fruit cocktail	½ cup							
Most frequent other fruit or juice? _____	½ cup							
VEGETABLES		S M L	Day	Week	Month	Year	Never/Almost Never	63 67 71 75 79 83 87 91 95 99 103 107 111
String beans, green beans	½ cup							
Peas	½ cup							
Other beans such as baked beans, pintos, kidney beans, limas	¾ cup							
Corn	½ cup							
Mixed vegetables	½ cup							
Winter squash, baked squash	½ cup							
Tomatoes, tomato juice	(1) or 6 oz.							
Red chilies, crushed, sauces-exclude picante, taco sauce	2 Tbsp. sauce							
Broccoli	½ cup							
Cauliflower or brussel sprouts	½ cup							
Spinach (raw)	¾ cup							
Spinach (cooked)	½ cup							
Mustard greens, turnip greens, collards	½ cup							
Cole slaw, cabbage, sauerkraut	½ cup							
Carrots, or peas and carrots	½ cup							
Green salad	1 med. bowl							
French fries and fried potatoes	¾ cup							
Sweet potatoes, yams	½ cup							
Other potatoes, including boiled, baked, potato salad	(1) or ½ cup							
Rice	¾ cup							
Any other vegetable, including cooked onions, summer squash	½ cup							
Most frequent other vegetable? _____	½ cup							
Butter, margarine or other fat added to vegetables	2 pats							
MEAT, FISH & POULTRY		S M L	Day	Week	Month	Year	Never/Almost Never	37 41 45 49 53 57 61 65 69 73 111
Hamburgers, cheeseburgers, meat loaf	1 medium							
Beef—steaks, roasts	4 oz.							
Beef stew or pot pie with carrots, other vegetables	1 cup							
Liver, including chicken livers	4 oz.							
Pork, including chops, roasts	2 chops or 4 oz.							
Fried chicken	2 sm. or 1 lg. piece							
Chicken or turkey, roasted, stewed or broiled	2 sm. or 1 lg. piece							
Fried fish or fish sandwich	4 oz. or 1 sand.							
Tuna fish, tuna salad, tuna casserole	½ cup							
Shell fish (shrimp, lobster, crab, oysters, etc.)	(S) ¼ cup or 3 oz.							
Other fish, broiled, baked	2 pieces							

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	Medium Serving	Your Serving Size			How Often?					Office Use
MIXED DISHES/LUNCH ITEMS		S	M	L	Day	Week	Month	Year	Rarely/Never	
Spaghetti, lasagna, other pasta with tomato sauce	1 cup									15
Pizza	2 slices									19
Mixed dishes with cheese (such as macaroni and cheese)	1 cup									23
Liverwurst	2 slices									27
Hot dogs	2 dogs									31
Ham, lunch meats	2 slices									35
Vegetable soup, vegetable beef, minestrone, tomato soup	1 medium bowl									39
Other soups	1 medium bowl									43
BREADS/SALTY SNACKS/SPREADS		S	M	L	Da	Wk	Mo	Yr	Nv	
White bread, rolls, crackers, (including sandwiches)	2 slices, 3 crack									47
Dark bread, incl. whole wheat, rye, pumpernickel	2 slices									51
Corn bread, corn muffins, corn tortillas	1 medium piece									55
Salty snacks (such as chips, popcorn)	1 handful									59
Peanuts, peanut butter	2 Tblsp.									63
Butter on bread or rolls	2 pats									67
Margarine on bread or rolls	2 pats									71
Salad dressing, mayonnaise (including on sandwiches)	2 Tblsp.									75 G 79 80
Gravies made with meat drippings, or white sauce	2 Tblsp.									11
BREAKFAST FOODS		S	M	L	Da	Wk	Mo	Yr	Nv	
High fiber, bran or granola cereals, shredded wheat	1 med. bowl									15
Highly fortified cereals, such as Special K, Total	1 med. bowl									19
Other cold cereals, such as Corn Flakes, Rice Krispies	1 med. bowl									23
Cooked cereals	1 med. bowl									27
Sugar added to cereal	2 teaspn.									31
Eggs	2 eggs									35
Bacon	2 slices									39
Sausage	2 patties or links									43
SWEETS		S	M	L	Da	Wk	Mo	Yr	Nv	
Ice cream	1 scoop									47
Doughnuts, cookies, cake, pastry	1 pce or 3 cook									51
Pumpkin pie, sweet potato pie	1 med. slice									55
Other pies	1 med. slice									59
Chocolate candy	small bar, 1 oz									63
Other candy, jelly, honey, brown sugar	3 pce, or 1 Tblsp.									67
DAIRY PRODUCTS		S	M	L	Da	Wk	Mo	Yr	Nv	
Cottage cheese	½ cup									71
Other cheeses and cheese spreads	2 slice or 2 oz.									75 H 79 80
Flavored yogurt	1 cup									11
Whole milk and beverages with whole milk	8 oz. glass									15
2% milk and beverages with 2% milk	8 oz. glass									19
Skim milk, 1% milk or buttermilk	8 oz. glass									23
BEVERAGES		S	M	L	Da	Wk	Mo	Yr	Nv	
Regular soft drinks	12 oz.can or bottle									27
Diet soft drinks	12 oz.can or bottle									31
Beer	12 oz.can or bottle									35
Wine	1 med. glass									39
Liquor	1 shot									43
Decaffeinated coffee	1 med. cup									47
Coffee, not decaffeinated	1 med. cup									51
Tea (hot or iced)	1 med. cup									55
Non-dairy creamer in coffee or tea	1 Tblsp.									59
Milk in coffee or tea	1 Tblsp.									63
Cream (real) in coffee or tea	1 Tblsp.									67
Sugar in coffee or tea	2 teaspn.									71
Artificial sweetener in coffee or tea	1 packet									75 I 79 80

14. Think about your diet over the last year and the responses you have just made on this questionnaire. Are there any foods not mentioned which you eat *at least once a week*, even in small quantities, or eat frequently in a particular season? Consider other meats, breakfast foods, catsup, green chilies or jalapenos, salsa picante or taco sauce, avocado (guacamole), Mexican dishes, Chinese or other ethnic foods, other fruits or vegetables, as well as nutritional supplements (bran, etc.). *Please take a look at the list of foods at the bottom of the page.*

FOOD	Your Serving Size S	M	L	How Often? Day	Week	OFFICE USE Code	Amts
						11	
						17	
						23	
						29	
						35	
						41	

	1 Seldom/Never	2 Sometimes	3 Often/Always	
15. How often do you eat the skin on chicken?	_____	_____	_____	47
How often do you eat the fat on meat?	_____	_____	_____	48
How often do you add salt to your food?	_____	_____	_____	49
How often do you add pepper to your food?	_____	_____	_____	50

16. How often do you eat raw vegetables (carrots, cauliflower, etc.) as a snack or in salad?

1 Almost every day	2 2-4 times a week	3 Once a week	4 1-3 times a month	5 5-10 times a year	6 1-4 times a year	7 Never, or less than once a year	
							51

17. How often do you use fat or oil in cooking?
For example, in frying eggs, meat or vegetables? _____ times per _____ (day, wk., month) 52

18. What do you *usually* cook with? 1 ___ Don't know or don't cook 2 ___ Soft margarine
3 ___ Stick margarine 4 ___ Butter 5 ___ Oil 6 ___ Lard, fatback, bacon fat 7 ___ Pam or no oil 55

19. What kind of fat do you *usually* add to vegetables, potatoes, etc.?
1 ___ Don't add fat 2 ___ Soft margarine 3 ___ Stick margarine 4 ___ Butter
5 ___ Half butter, half margarine 6 ___ Lard, fatback, bacon fat 57

20. If you eat cold cereal, what kind do you eat most often? _____ 59

21. Are you now losing or gaining weight?
1 ___ No 2 ___ Yes, losing 3 ___ Yes, gaining 68

Have you gained or lost more than five pounds in the past year?
1 ___ No 2 ___ Lost 5-15 lbs. 3 ___ Lost 16-25 lbs. 4 ___ Lost more than 25 lbs.
5 ___ Gained 5-15 lbs. 6 ___ Gained 16-25 lbs. 7 ___ Gained more than 25 lbs. 69

PLEASE GO TO NEXT PAGE

OFFICE USE

22. How did your weight compare with others of your height and age at the following times during your life? 70 _ _ _ _ _ _ _ _ _ _

	Lighter than average	About average	Heavier than average	79	80
As a child	_____	_____	_____		11 ___
As a teenager	_____	_____	_____		12 ___
As a young adult	_____	_____	_____		13 ___

Now we would like you to answer some questions about your lifestyle.

23. How many hours of sleep do you usually get at night?

6 hours or less _____ 7 hours _____ 8 hours _____ 9 hours or more _____ 14 ___

24. Here is a list of active things that people do in their free time. How often do you do any of these things?

	More than once a week	About once a week	A few times a month	A few times a year	Rarely or never	
Active sports	_____	_____	_____	_____	_____	15 ___
Doing physical exercise	_____	_____	_____	_____	_____	16 ___
Jogging or running	_____	_____	_____	_____	_____	17 ___
Swimming or taking long walks	_____	_____	_____	_____	_____	18 ___
Gardening, fishing, hunting	_____	_____	_____	_____	_____	19 ___
Something else _____	_____	_____	_____	_____	_____	20 ___

25. How many close friends do you have? (People that you feel at ease with, can talk to about private matters and can call on for help).

_____none _____1 or 2 _____3 or 5 _____6 to 9 _____10 or more 21 ___

How many relatives do you have that you feel close to?

_____none _____1 or 2 _____3 or 5 _____6 to 9 _____10 or more 22 ___

How many of these friends or relatives do you see or talk to at least once a month?

_____none _____1 or 2 _____3 or 5 _____6 to 9 _____10 or more 23 ___

OFFICE USE

26. How often do you feel under stress which makes you tense or worried, or causes physical problems such as stomach or back trouble or headaches?

Every day	____	Several times a week	____	24 ___
Several times a month	____	Several times a year	____	
Rarely or never	____			

27. Do you regularly have any of the following complaints? If so, please indicate how many days on average you have them per month.

	Yes	No	No. of Days	
Sore or chapped lips	____	____	_____	25 ___ ___ ___
Headaches	____	____	_____	28 ___ ___ ___
Dizziness	____	____	_____	31 ___ ___ ___
Loss of appetite	____	____	_____	34 ___ ___ ___
Nausea	____	____	_____	37 ___ ___ ___
Breast pain	____	____	_____	40 ___ ___ ___
Depression	____	____	_____	43 ___ ___ ___
Sleeplessness	____	____	_____	46 ___ ___ ___
Sore eyes or conjunctivitis	____	____	_____	49 ___ ___ ___
Dry skin	____	____	_____	52 ___ ___ ___
Other	____	____	_____	55 ___ ___ ___

28. Please check if you have or have ever had any of the following diseases:

	Yes	No		Yes	No	
Asthma	____	____	Syphilis	____	____	58 ___ ___
Diabetes	____	____	Gonorrhoea	____	____	60 ___ ___
Hepatitis	____	____	Oral Herpes (cold sores)	____	____	62 ___ ___
Condylomata (Human papilloma virus)	____	____	Genital Herpes	____	____	64 ___ ___

OFFICE USE

29. No we would like you to answer some questions about your reproductive life.

How many pregnancies have you had? ____ number 66 __

If you have been pregnant, how old were you when you had your first pregnancy?

_____ age _____ not applicable 67 __ __

Are you currently pregnant? No ____ Yes ____ 69 __

30. Have you previously regularly used any contraceptives? No ____ Yes ____
(i.e. the pill, I.U.D., diaphragm etc.) 70 __

Has your usual sexual partner regularly used contraceptives? No ____ Yes ____ 71 __

If you have used contraceptives, please complete the following table.

If you are continuing to use any of these methods, please leave the "age when last used" column blank. K (79) ____ (80)

	Age when first used	Age when last used	Total time used (yrs.)	Presently using		
Oral Contraceptives (the pill)	_____	_____	_____	____ Yes	____ No	11 __ __ __ __ __ __
I.U.D. (loop, coil, etc.)	_____	_____	_____	____ Yes	____ No	18 __ __ __ __ __ __
Diaphragm	_____	_____	_____	____ Yes	____ No	25 __ __ __ __ __ __
Chemical spermicide	_____	_____	_____	____ Yes	____ No	32 __ __ __ __ __ __
Condom (partner)	_____	_____	_____	____ Yes	____ No	39 __ __ __ __ __ __
Other (specify)	_____	_____	_____	____ Yes	____ No	46 __ __ __ __ __ __

The following questions asks for information of a personal nature.
Sexual activity has previously been found to be related to disease of the cervix and we request that you make every effort to give a complete response to this question.

31. How old were you when you first had sexual intercourse? _____ years 53 __ __

Over the last year approximately how many times per month (on average)
have you had sexual intercourse?_____number/month 55 __ __

How many different sexual partners have you had in the last year? _____ 57 __ __

and how many have you had in your lifetime_____ 59 __ __

L (79) ____ (80)

Thank you very much for taking the time to complete the questionnaire.
Your co-operation is sincerely appreciated.

APPENDIX 2: SAMPLE CODING SHEET

Item	Card	Column	Variable	Code Contents
	A	1-4	Study ID	0001-1066 = Study numbers
	A	5-6		CP = = Chemoprevention
				CN = = Cervical Neoplasia
	A	7-10	Cytology ID	0001-9998 = Cytology ID #
1	A	11-12	Birth Day	01-31 = Day 99 = Unknown, or no response
1	A	13-14	Birth Month	01-12 = Month 99 = Unknown, or no response
1	A	15-16	Birth Year	1911-1969 = Year 999 = Unknown, or no response
2	A	17-18	Age	17-65 = Years 99 = Unknown, or no response
3	A	19-20	Residents in B.C.	01-65 = Years 99 = Unknown, or no response
4	A	21-22	Education	1-13 = Grades 99 = Unknown, or no response
5	A	23	Post-Secondary	1 = Trade school 2 = College 3 = University 9 = Unknown, or no response if more than one tick code to highest
6	A	24	Marital Status	1 = Single 2 = Married 3 = Widowed 4 = Divorced/separated 9 = Unknown, or no response
7	A	25-26	Moves	00-20 = times 99 = Unknown, or no response
8	A	27	Smoking	1 = No 2 = Yes 9 = Unknown, or no response

APPENDIX 3:

Let n_1 denotes the number of individuals in the exposed subgroup; n_2 denotes the number of individuals in the nonexposed subgroup. Let p_{1j} denotes the probability of developing disease j in the exposed subgroup; Let p_{2j} denotes the probability of developing disease j in the non-expposed subgroup, j= 1,2,3,4,5. Let r_j denotes the sampling proportions for disease stage j.

Denoting the relative risks of developing the subsequent stage of the disease by Φ_i and the relative risks of the 1st 4 comparison groups by Ψ_i for i=1,2,3,4. Assuming the $\Phi_i > 1$ for all i,

We show that if the Φ's are all equal, then $\Psi_3 > \Psi_4 > 1$

The relative risks of developing the disease from stage 3 to 4, i.e. Φ_3

$$\Phi_3 = \frac{r_4 n_1 p_{13}(1-p_{14}) r_3 n_2 (1-p_{23})}{r_3 n_1 (1-p_{13}) r_4 n_2 p_{23}(1-p_{24})} = \frac{p_{13}(1-p_{23})(1-p_{14})}{(1-p_{13})p_{23}(1-p_{24})}$$

$$\Psi_3 = \frac{(r_4 n_1 p_{13}(1-p_{14}) + r_5 n_1 p_{13} p_{14})(r_3 n_2 (1-p_{23})}{(r_4 n_2 p_{23}(1-p_{24}) + r_5 n_2 p_{23} p_{24})(r_3 n_1 (1-p_{13})}$$

If $r_4 = r_3$,

Then $\Psi_3 = \Phi_3[1 + (\Phi_4 - 1)p_{24}] = \Phi_3[(1 - p_{24}) + \Phi_4 p_{24}]$

Hence we see that $\Psi_3 > \Phi_4 = \Psi_4 > 1$