School of Public Health

A Case Control study of Lifestyle Factors in the Aetiology of Ovarian Cancer

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Doctor of Philosophy
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Declaration

To the best of my knowledge and belief this thesis contains no materials previously published by any other person except where due acknowledgement has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Signature:

Date:
Acknowledgements

I would never have been able to finish my thesis without the help and support of the kind people around me.

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Abstract

The objective of this study was to investigate associations between ovarian cancer and lifestyle factors among Southern Chinese women. The investigation mainly focused on the effects of tea consumption, physical activity, breastfeeding and body size on the risk of ovarian cancer. A case-control study was undertaken in Guangzhou, the capital city of Guangdong Province in Southern China, between August 2006 and July 2008. Subjects were recruited from four public hospitals, i.e., The Overseas Hospital (affiliated with Jinan University), Zhujiang Hospital, General Hospital of Guangzhou Military Command, and Second Affiliated Hospital of Zhongshan University. Eligible cases were those diagnosed with an incident, histopathologically confirmed epithelial ovarian tumour within the past 12 months. Controls were recruited from inpatient wards of the Departments of Gastroenterology, Ophthalmology, Respiratory Disease, Orthopedics and Physiotherapy. Inclusion criteria for all subjects were women under 75 years of age, who had been residents of the metropolitan Guangzhou area for at least the past ten years. Of the total 504 cases consecutively recruited from the four hospitals, 500 ovarian cancer patients consented to participate and were capable of being interviewed. Of the total 512 eligible controls, 500 controls were available for interview. A validated and reliable questionnaire was used to obtain demographic characteristics, information on frequency, quantity and duration of tea drinking, amount of dried tea leaves brewed, together with habitual diet, habitual physical activity, reproductive factors and other lifestyle characteristics by face-to-face interviews. Logistic regression analyses were performed to assess the association between lifestyle factors and the ovarian cancer risk. Ethics approval for the study was obtained from the Curtin University Human Ethics Review Committee and the local health authorities and hospitals in Guangzhou. In this study, the control subjects reported higher tea consumption levels and prevalence (78.8%) than the ovarian cancer patients (51.4%). Regular drinking of green tea, black tea and/or oolong tea was associated with a lower risk of ovarian cancer, the adjusted odds ratio being 0.29 (95% confidence interval 0.22 to 0.39) after accounting for confounding factors. When compared with non-drinkers, apparent inverse dose-response relationships were observed for years of drinking, number of cups and quantity of tea consumed, as well as amount of dried tea leaves brewed (p < 0.01).
This study also found the control subjects had significantly longer duration of strenuous sports and moderate activity in daily life than the ovarian cancer patients. Increased engagements in such leisure time activities were associated with reduced cancer risks after adjustment for confounding factors. A significant inverse dose-response relationship was also found for total physical activity exposure, with adjusted odds ratio 0.49 (95% confidence interval 0.35-0.68) for women engaged in 23 or more metabolic equivalent tasks (MET)-hours per week relative to those less than 12 MET-hours per week.

Significant inverse dose-response relationships were found for both duration of lactation and number of children breastfed. The adjusted odds ratios were 0.09 (95% confidence interval (CI) 0.04 to 0.19) for women with at least 31 months of total lactation compared to those with 10 months or less lactation; and 0.38 (95% CI 0.27 to 0.55) for women with three or more children breastfed compared to those with one child breastfed.

In this study, compared with women having body weight ≤ 50 kg and body mass index (BMI) < 18.5 kg/m², the adjusted odds ratios (ORs) of ovarian cancer were 1.84 (95% confidence interval (CI) 1.34-2.54) and 1.77 (95% CI 1.04-3.02) in those women who had body weight > 55 kg and BMI ≥ 23 kg/m², respectively. Significant dose-response relationships were also observed for both weight and BMI (p < 0.01). Body height was not significantly associated with ovarian cancer risk.

The findings of the study suggest that regular tea consumption, habitual physical activity and prolonged lactation are associated with reduced risk of ovarian cancer. Higher body weight (overweight or obese) and higher BMI levels were associated with increased risk of ovarian cancer in Southern Chinese women.
Abbreviations

ACS  American Cancer society
BMI  Body Mass Index
BRCA1 Breast Cancer Gene One
BRCA2 Breast Cancer Gene Two
CASH Cancer and Steroid Hormone
CCC  Clear Cell Carcinoma
CI   Confidence Interval
COX  cycloxygenase
DNA Deoxyribonucleic Acid
FFQ  Food Frequency Questionnaire
EGCG Epicatechin-3-Gallate
FIGO International Federation of Gynecology and Obstetrics
GDP  Gross Domestic Product
GI   Glycemic Index
GL   Glycemic Load
GZ   Guangzhou
HNPCC Hereditary Nonpolyposis Colorectal Cancer
HR   Hazard Ratio
IARC International Agency for Research on Cancer
MET  Metabolic Equivalent Tasks
N    Number
NSAIDs Non-Steroidal Anti-Inflammatory Drugs
OR   Odds Ratio
P    Probability
RR   Relative Risk
SAC  Serous Adenocarcinoma
SD   Standard Deviation
SEER Surveillance, Epidemiology, and End Results
UICC International Union against Cancer
UK   United Kingdom
U.S. United States
USD  United States Dollars
USFDA United States Food and drug Administration
<table>
<thead>
<tr>
<th>WDR</th>
<th>Two weekdays and one weekend day</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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CHAPTER 1

INTRODUCTION

1.1 Significance of the study

Ovarian cancer is the eighth most common cancer in women and the second most common gynaecological cancer, accounting for about 140,000 deaths annually worldwide (Ferlay et al., 2010). There is geographic variation in the incidence of ovarian cancer. The age-standardised rate (per 100,000 females) of ovarian cancer is higher in Europe (10.1), the United States (8.8) and Malaysia (7.5) (Ferlay et al., 2010). In China the incidence of ovarian cancer is relatively lower, at 3.8 per 100,000 females (Ferlay et al., 2010). However, ovarian cancer incidence has increased during the period 1978-2002 among women in Qidong, China, from 24 to 67 per 100,000 females (Chen et al., 2006). The variation in incidence suggests that risk and progression of the disease may be related to both genetic and environmental factors, especially dietary factors. The populations of most Western nations are ageing, increasing the importance of evaluating methods of prevention of ovarian cancer.

Ovarian cancer ranks as the 7th cause of death from cancer in females, accounting for approximately 140,000 deaths each year (Ferlay et al., 2010). Ovarian cancer is the second most common gynaecological malignancy (Sankaranarayanan & Ferlay, 2006) and has the highest case-fatality rate of all gynaecological cancers (Holschneider & Berek, 2000). Currently, there is no effective screening method available for the detection of ovarian cancer (Freedman, 2009). Symptoms are often vague, non-specific, and generally appear only in the advanced stages of the disease, contributing to the high case-fatality ratio (Buys et al., 2011). The five-year survival rate of ovarian cancer is about 45% overall (Siegel, Naishadham & Jemal, 2012).
Ovarian cancer tends to recur, even in the patients who achieve a complete response to primary treatment of surgery and chemotherapy (ACS, 2001). Ovarian cancer is, therefore, an important public health issue.

1.2 Location of Study—Guangzhou, Guangdong, China

Guangzhou is the capital city of Guangdong, and the center of its political, economic, scientific, educational and cultural life. It is located in the middle south of Guangdong Province, north of the Pearl River Delta and lies close to the South China Sea, Hong Kong, and Macau (Figure 1.1) (Asia Times, 2012). The Pearl River, the third largest river of China, runs through Guangzhou and is navigable to the South China Sea. Situated in such a good geographical region, Guangzhou is called China's South Gate.

Covering an area of 7,435 square kilometers (2,870 square miles), Guangzhou is home to more than 11 million people, including a 3.7 million transitory population and a 3.95 million urban population. With the opening of China to the outside world, a large number of people from other regions of China swarmed into Guangzhou (Tang & Li, 2010). The average life expectancy of women in Guangzhou is 80.94 years, 5.69 years more than that of men, according to the Guangzhou Statistics Bureau (Guangzhou Statistics Bureau, 2010). The birth rate is 9.30‰ and the mortality rate is 5.55‰. The natural growth rate of the population is 7.02‰ (Guangzhou Statistics Bureau, 2010).
The gross domestic product (GDP) of Guangzhou in 2011 reached 1,260.4 (192.43 billion USD) billion Yuan, 11% up than 2010, and ranked the 3rd largest among all cities in China. GDP per capita in Guangzhou in 2010 amounted to 87, 458 Yuan (12,911 USD, based on registered citizen population), 12.3% more than 2009 (Li, 2012).

Guangdong is known as the food paradise in China. The famous saying "Eating in Guangzhou" and Cantonese cuisine are well known to all Chinese. Because Guangzhou was a major trading port, its access to trade from all over the planet brought a wide variety of foods to the city, creating a huge amount of diversity within the cuisine. The usual breakfast in Guangdong is tea with fried pastries and/or porridge, which is eaten with peanuts, salt vegetables, soy sauce, or similar strong-flavored foods mixed in. Special occasions call for a long, lingering breakfast over tea and *tim sam*. This ritual, known as *yam ch'a* "drinking tea," has recently migrated to brunch or even lunch hour, and become a weekend fixture.

1.3 Statement of the Problems

Ovarian cancer is a significant problem in the health of women, however little is known of its aetiological factors (Kristensen & Trope, 1997); (World Cancer...
Research Fund, 1997); (Holschneider & Berek, 2000); (La Vecchia, 2001). Despite much effort has been put into attempts to correlate differences in incidence rates of ovarian cancer with environmental, endocrinologic, and genetic factors, our present level of knowledge is limited. The fivefold international variation between countries and relatively high incidence of ovarian cancer in industrialized countries, suggest that the etiology of ovarian cancer may be related to environmental factors such as diet or lifestyle (Baker & Piver, 1994). Few risk factors have been studied adequately and only three suggestive risk factors have been established (World Cancer Research Fund, 2007). The limited data available suggest that protective factors for ovarian cancer include non-starchy vegetables intake and lactation, while adult attained height is a probable risk factor for increased rates of fatal disease (World Cancer Research Fund, 2007). The interactions of these various factors and other factors are still poorly understood. In particular, the role of dietary and lifestyle factors on ovarian cancer risk have not been thoroughly investigated, particularly in a variety of different cultures.

1.4 Objectives of the study

Research question: Are there any foods, nutrients and lifestyle and reproductive factors in the Guangzhou population that are associated with, or prevent ovarian cancer?

Specific objectives of the study

1. To identify dietary risk factors associated with ovarian cancer. The following nutrients will be examined in detail – fat, saturated fat, animal and vegetable protein, carotenoids including β-carotene and lycopene, soy products and carbohydrates.

2. To assess whether a higher intake of green tea and other varieties of tea reduce the risk ovarian cancer.

3. To investigate whether fermented soybean products and vitamins A, C and E are protective against ovarian cancer.

4. To identify lifestyle factors, including exercise levels, reproductive history and occupational history that are related to ovarian cancer.
1.5 Benefits of the study

Ovarian cancer is a significant problem in the health of women, with an estimated 224,747 new cases reported in 2008 (Ferlay et al., 2010). The risk and protective factors for ovarian cancer identified from this study will be of value in the further study of aetiologic factors of ovarian cancer. Data obtained from this study will assist in developing health promotion programs targeting the prevention of ovarian cancer in China and elsewhere.

1.6 Outline of the thesis

In this thesis I will describe a case-control study undertaken to answer the research objectives listed above. The thesis follows a traditional structure with a literature review of relevant studies of ovarian cancer and case control methodology. The methodology used in the study will then be described in detail followed by the results. Following the concluding chapters the Appendix will contain further details of the study, including the questionnaires used and papers that have already been published or are under review.
CHAPTER 2

LITERATURE REVIEW

2.1 Diet and cancer

The theory that diet is a factor in the causation of cancer goes back to ancient times. Yong-He Yan, living in the Song Dynasty (960-1279 AD), believed that poor nutrition was a cause of esophageal cancer (Neal & Barnard, 2002). Wiseman (1676) thought that cancer might arise from ‘an error in diet’ and advised abstention from ‘salt, sharp and gross meats’ (Wiseman, cited in World Cancer Research Fund, 1997). Bennet (1849) suggested that ‘the circumstances which diminish obesity, and a tendency to the formation of fat, would seem, a priori, to be opposed to the cancerous tendency’ (Bennett, cited in World Cancer Research Fund, 1997).

Throughout the twentieth century, the effects of diet upon cancer were increasingly recognized in both experimental systems and epidemiological studies. Shaw (1907) advocated more foods of vegetable origin, less foods of animal origin, less alcohol, tea, and tobacco to reduce the risk of cancer (Shaw, cited in World Cancer Research Fund, 1997). Stocks (1933) identified that a higher intake of plant foods were capable of reducing the risk of cancer (Stocks, 1933). By 1940s and 1950s, the considerable influence of diet on the process of cancer causation and development in experimental animals were recognized (Tannenbaum, 1942); (Tannenbaum, 1942); (Tannenbaum & Silverstone, 1953). In the 1980s, Doll and Peto attempted the first relative quantification of environmental contributions of a variety of factors such as diet, tobacco, alcohol, occupation and radiation (Doll & Peto, 1981).

The results of experimental and epidemiological studies have led to hypotheses concerning factors involved in cancer causation. Two influential hypotheses on the environmental causes of cancer were developed in early half of the twentieth century.
Hueper has found the occupational causes of cancer, notably exposure of workers to carcinogens (Hueper, 1942). Hoffman developed that excessive nutrition if not the chief cause is at least a contributory factor of the first importance (Hoffman, 1937). Among the earliest epidemiological studies of diet and cancer, Orr, who conducted an ecological study of oral cancer in India, concluded that oral cancer in India related to low consumption of fruits and vegetables (Orr, 1933). A case-control study of cancer taken in England and Wales also identified distortions of dietary patterns as risk factors (Stocks, 1933).

In the second half of the twentieth century, theories of dietary origins of cancer received less emphasis in favor of random genetic error and exposures to viruses and carcinogens because of the advances in molecular biology (Hardman, 2004). Laboratory research began to concentrate on the investigation of cellular and ultimately, molecular carcinogenesis, as well as on the effectiveness of surgery, radiotherapy and chemotherapy, as cancer treatments (World Cancer Research Fund, 1997).

However, as cancer rates continued to rise in industrialized countries, studies of variation between countries in incidence and migrant studies indicated that the causes of cancer were largely environmental (Hardman, 2004). A new body of experimental and epidemiological work (Tannenbaum & Silverstone, 1957); (Armstrong & Doll, 1975), began to indicate that diet was indeed a major environmental factor affecting the incidence of cancers of a number of sites. The first reliable data for cancer incidence worldwide were collected by cancer registries set up for the purpose of epidemiological investigation. The data were published initially by the International Union against Cancer (UICC, 1965); (UICC, 1970). Higginson and Muir analyzed these data and noted that the incidence of many cancers varied greatly between different countries and regions, and concluded that 80 to 90% of cancers were due to external factors and were thus theoretically preventable (Higginson & Muir, 1973). Observational studies had also been conducted with migrants from countries with lower incidence rates to countries with higher incidence rates. A rapid increase from the lower to the higher incidence in those migrants supported the suggestion that environmental causes, and especially prevailing dietary habits, may influence the development of a number of neoplasms (Dunn, 1975).
A wide range of specific hypotheses about diet and cancer have emerged since the 1970s. By the mid-1970s, descriptive, ecological and analytical epidemiological studies were providing a growing body of evidence on links between diet and cancer. Wynder and Gori proposed that the preventive potential for all cancers was 80 to 90% and that diet accounted for 40% of all male cancers and 60% of all female cancers (Wynder & Gori, 1977). Doll and Peto suggested that it is plausible that US cancer death rates may be reduced by practicable dietary means as much as 35% with a range of 10% to 90% for specific cancers (Doll & Peto, 1981). The interpretation of such multidisciplinary investigations has provided an understanding of the role of specific dietary risk factors.

Compared with previous studies in the 1970s, there were several developments in epidemiological studies on the relationship of diet, nutrition and lifestyle with cancers during the 1980s and 1990s. Firstly the number of epidemiological studies on diet and cancer increased substantially. Another change was that case-control and cohort studies increased and became the most commonly used designs for observational epidemiological studies. The third feature was that these studies focused on a specific cancer rather than all possible sites of cancers when they investigated the links between diet and lifestyle and cancer. The protective effect of regular physical activity was increasingly mentioned during the 1980s and 1990s. During the past decade interest in gene-nutrient interactions has grown considerable, and this emerging research area shows great promise as a means to further progress in the overall reduction of cancer risk (Greenwald, Clifford & Milner, 2001); (Peto, 2001).

Although data from epidemiological, pre-clinical and clinical intervention studies have contributed to the extensive body of evidence linking diet and cancer, current knowledge of the underlying basis of diet-cancer relationship is minuscule (Greenwald et al., 2001); (Peto, 2001). Not surprisingly, the diet and cancer story is complex. The new findings and evidence uncovered are awaited by the efforts of epidemiologists in this field and researchers in other disciplines.
2.2 Epidemiology of ovarian cancer

Ovarian cancer is the eighth most common cancer in the women. In Caucasian women it is the 5th most common cancer and it causes more deaths than any other form of reproductive cancer. On a worldwide basis, around 200,000 cases were recorded in 2002, 224,747 new cases were reported in 2008 (Ferlay et al., 2010), representing 4% of all new incident cancer cases in women in most developed countries (World Cancer Research Fund, 2007).

Ovarian cancer is the seventh most common cause of cancer mortality among women, accounting for approximately 140,000 deaths each year (Ferlay et al., 2010). Ovarian cancer is the second most common gynaecological malignancy (Sankaranarayanan & Ferlay, 2006) and has the highest case-fatality rate of all gynaecological cancers (Holschneider & Berek, 2000). Currently, there is no effective screening method available for the detection of ovarian cancer (Freedman, 2009). Symptoms are vague, non-specific, and generally appear in the advanced stages of the disease, contributing to the high case-fatality ratio (Buys et al., 2011).

Although the survival of patients with ovarian cancer has increased steadily during the past 20-30 years, it remains low. The five-year survival rate of ovarian cancer is about 45% overall (Siegel et al., 2012). Ovarian cancer tends to recur, even in the patients who achieve a complete response to primary treatment of surgery and chemotherapy (ACS, 2001). Ovarian cancer prevention and studying risk factors is, therefore, an important public health issue.

Incidence

The annual incidence of ovarian cancer, worldwide, regardless of age, is 42 cases per 100,000 (WHO, 2008). There are considerable variations in the incidence of ovarian cancer in different countries (Greenlee et al., 2000). The incidence is nearly three times higher in high than in middle- to low-income countries. Age-adjusted incidence rates range from more than 10 per 100,000 women in Europe and North America, to less than 5 per 100,000 in parts of Africa and Asia (World Cancer Research Fund, 2007). The incidence of ovarian cancer is highest in the U.S., Europe (especially Nordic countries and the United Kingdom), and Israel, and lowest in
Japan and in developing countries (Levi et al., 1999); (Parkin, Pisani & Ferlay, 1999); (Holschneider & Berek, 2000). Figure 2.1 presents the estimated ovarian cancer incidence by sex and area. In Europe the incidence is 13.92 per 100,000 females (WHO, 2001). In the U.S., the incidence of ovarian cancer is higher for Caucasian women than for African-American or Asian-American women (Coleman et al., 1993) although there is some evidence that these differences may be narrowing. For women who migrate from low-risk countries of origin, such as Asia, to high-risk areas, such as North America, there is a gradual increase observed in the incidence of ovarian cancer to rates expected for native-born women (Kliwer & Smith, 1995). Compared with other countries, China has a relatively low incidence (5 per 100,000 women), which is about one quarter of the incidence in northern European countries (World Cancer Research Fund, 1997). However, over half the global incidence of ovarian cancer is now in developing world (100,000 cases in 1996) (World Cancer Research Fund, 1997).

Over the last three decades, a decline in ovarian cancer incidence has been reported in those countries that previously had high rates such as U.S., Canada, Scandinavia and UK (Dos Santos Silva & Swerdlow, 1995); (La Vecchia et al., 1998); (Gnagy et al., 2000); (Tarone & Chu, 2000); (Goodman & Howe, 2003); (Howe et al., 2006). However, an increasing trend has been observed in previous low-risk countries such as Japan, India and Singapore (La Vecchia et al., 1993). In Japan, there was a fourfold increase in the age adjusted mortality rate (from 0.9 to 3.6 per 100,000 women between 1950 and 1997) (World Cancer Research Fund, 2007).
Figure 2.1 Estimated incidence of ovarian cancer by sex and area
(World Cancer Research Fund, 1997)
**Mortality**

Ovarian cancer is often described as a “silent killer” because it typically causes no symptoms until it has spread quite extensively and has a high fatality rate. Between 70 and 75% of ovarian carcinomas are not discovered until they have reached an advanced stage III or later (Argento, Hoffman & Gauchez, 2008). There has been little improvement in the survival rates for over three decades. About 65% of women with epithelial ovarian cancer will die within five years of their diagnosis (Levi et al., 2004). It is the fifth most deadly cancer. In 1996, mortality attributable to cancer of the ovary was estimated at 124,000 women, 1.7% of all cancer death (WHO, 1997) and an estimated 15,460 deaths in 2011 (ACS, 2011). The age-adjusted mortality rates are 1.69, 3.02, 7.04, and 11.02 per 100,000 for Japan, Italy, the United States, and Denmark, respectively (National Cancer Institute, 1992).

**Pathology and pathogenesis**

The malignancies of the ovary have been classified in the World Health Organization Histological Classification according to the most probable tissue of origin. The malignancies of the ovaries arise ultimately from one of three ovarian components: (1) the surface coelomic epithelium; (2) the germ cells; and (3) the stroma of the ovary. As the ovaries are common sites of metastases from a variety of other cancers, there are secondary or metastatic tumors on ovaries. Using this simplified classification version of ovarian cancer, the relative frequency and age distribution of each category of ovarian cancer in U.S. are displayed in Table 2.1 (Cotran, 1999).

Table 2.1 Frequency and age distribution of ovarian cancer

<table>
<thead>
<tr>
<th>Origin of ovarian cancer</th>
<th>Epithelial cells</th>
<th>Germ cell</th>
<th>Sex cord-stroma</th>
<th>Metastasis to ovaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of ovarian cancers (%)</td>
<td>90</td>
<td>3–5</td>
<td>2–3</td>
<td>5</td>
</tr>
<tr>
<td>Age group (in years) affected</td>
<td>20 +</td>
<td>0-25 +</td>
<td>All ages</td>
<td>Variable</td>
</tr>
</tbody>
</table>

(Cotran, 1999).
Approximately 90% of all ovarian cancers are epithelial in origin. They have been divided into benign, borderline or malignant. About 10% to 20% of epithelial ovarian neoplasms are borderline or low malignant potential tumors, which are characterized by a high degree of cellular proliferation in the absence of stromal invasion. Of the invasive epithelial ovarian cancers, about 75% to 80% are serous, 10% are mucinous, and 10% are endometrioid. Less common types include clear cell, Brenner, small cell, and undifferentiated carcinoma (Holschneider & Berek, 2000). Table 2.2 shows the histological typing of epithelial ovarian cancer recommended by FIGO based on the version of WHO publication no. 9, 1973 (Heintz et al., 2006).

In spite of the simple biologic features of the epithelium, epithelial ovarian cancer is probably among the most histopathologically complex of human malignancies. One unique characteristic of this cancer is the müllerian differentiation accompanied by neoplastic progression (Auersperg et al., cited in (Tung et al., 2003). This aberrant differentiation changes the original stromal characteristics to müllerian duct-derived epithelia, including oviduct, endometrium, and uterine cervix. Serous, endometrioid/clear cell, and mucinous tumors resemble the phenotypes of the fallopian tube, endometrium, and endocervix/gastrointestinal tract, respectively (Scully, cited in (Tung et al., 2003). Compared with nonmucinous types, mucinous tumors exhibit unique histologic characteristics, including more common occurrences of benign and borderline tumors than invasive tumors, and a greater likelihood of K-ras than p53 mutations (Garrett et al., cited in (Tung et al., 2003). It is biologically plausible that the unique morphologic and immunohistochemical features of the ovary may reflect diverse histopathogenesis pathways in the development of ovarian cancer.

Table 2.2 Histological typing of ovarian cancer

<table>
<thead>
<tr>
<th>Serous tumors</th>
<th>Benign serous cystadenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Of borderline malignancy: serous cystadenomas with proliferating activity of the epithelial cells and nuclear abnormalities, but with no infiltrative destructive growth (carcinomas of low potentialmalignancy)</td>
<td>Serous cystadenocarcinomas</td>
</tr>
</tbody>
</table>


Mucinous tumors

- Benign mucinous cystadenomas
  Of borderline malignancy: mucinous cystadenomas with proliferating activity of the epithelial cells and nuclear abnormalities, but with no infiltrative destructive growth (carcinomas of low potential malignancy)

Mucinous cystadenocarcinomas

Endometrioid tumors

- Benign endometrioid cystadenomas
  Endometrioid tumors with proliferating activity of the epithelial cells and nuclear abnormalities, but with no infiltrative destructive growth (carcinomas of low potential malignancy)

Endometrioid adenocarcinomas

Clear cell tumors

- Benign clear cell tumors
  Clear cell tumors with proliferating activity of the epithelial cells and nuclear abnormalities, but with no infiltrative destructive growth (low potential malignancy)

Clear cell cystadenocarcinomas

Brenner

- Benign Brenner
  Borderline malignancy
  Malignant
  Transitional cell

Undifferentiated carcinomas

A malignant tumor of epithelial structure that is too poorly differentiated to be placed in any other group

Mixed epithelial tumors

These tumors are composed of two or more of the five major cell types of common epithelial tumors (types should be specified).

Extra-ovarian peritoneal carcinoma

Cases with intraperitoneal carcinoma in which the ovaries appear to be incidentally involved and not the primary origin

(Heintz et al., 2006)
Research has shown that repeated passage of rat ovarian surface epithelial cells in culture results in spontaneous transformation to a malignant phenotype in the absence of carcinogens (Godwin et al., 1992). The majority of ovarian cancer begins in a single layer of epithelial cells lining the surface of the ovary, and proliferation of cells in epithelial cell surface occurs following every ovulation in order to repair damage produced by the rupture of mature follicles (World Cancer Research Fund, 1997). After ovulation, the mitotic activity required to repair the ovarian epithelium increases the likelihood of multiple genetic changes, such as mutations of the p53 gene, loss or mutation of tumour-suppressor genes, which lead to malignant transformation (Kristensen & Trope, 1997).

Little is known regarding etiological factors and the natural history of ovarian cancer. Most of the known risk factors are related to hormonal and reproductive factors, with higher parity and oral contraceptive use significantly decreasing the risk of ovarian cancer (Milne et al., 2010). Table 2.3 shows the factors influencing the risk for ovarian cancer. There are two main mechanisms proposed for ovarian carcinogenesis that are relevant to the effects of hormonal factors: excessive levels of circulating gonadotrophins, associated with less childbirth, could cause neoplastic changes in the ovary, or the decreased number of ovulatory cycles experienced during pregnancy and breastfeeding, and with oral contraceptive use, could reduce mitotic events in the ovary, thereby reducing potential opportunities for mutation to be fixed (World Cancer Research Fund, 1997).

Additionally, a family history of ovarian cancer increases the risk for ovarian cancer. The risk of ovarian cancer depends on the number of affected first- and second-degree relatives, as well as their age at diagnosis with ovarian cancer. This holds true for relatives on both the maternal and paternal side (Holschneider & Berek, 2000). Risk of ovarian cancer is more than four times greater among women with a family history of the disease (Kerber & Slattery, 1995). The majority of hereditary ovarian cancer appear to be due to mutations in the BRCA genes, with at least two-thirds of those cases linked to BRCA1 gene mutations on chromosome 17q, and up to one-third associated with BRCA2 mutations, located on chromosome 13q (Frank et al., 1998). Several families with BRCA1 and BRCA2 mutations have members who have ovarian cancer (World Cancer Research Fund, 1997). Furthermore recent
research has linked ovarian cancer to Lynch syndrome which is a genetic cancer predisposition syndrome caused by an inherited defect in 1 of 4 DNA mismatch repair genes (mutL homolog 1, mutS homolog 2, mutS homolog 6, and postmeiotic segregation 2) (Oman, Ballinger & Cerilli, 2009).

Table 2.3 Factors Influencing the Risk for Ovarian Cancer

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Estimated Risk (%)</th>
<th>Estimated Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline lifetime risk</td>
<td>1.4 to 1.8</td>
<td>1</td>
</tr>
<tr>
<td>Family history</td>
<td>9.4</td>
<td>5–7</td>
</tr>
<tr>
<td>BRCA1 mutation</td>
<td>30–40</td>
<td>18–29</td>
</tr>
<tr>
<td>BRCA2 mutation</td>
<td>27</td>
<td>16–19</td>
</tr>
<tr>
<td>Lynch II/HNPCC*</td>
<td>10</td>
<td>6–7</td>
</tr>
<tr>
<td>Infertility</td>
<td>2–5</td>
<td></td>
</tr>
<tr>
<td>Nulliparity</td>
<td>2–3</td>
<td></td>
</tr>
<tr>
<td>Late menopause</td>
<td>1.5–2</td>
<td></td>
</tr>
<tr>
<td>Early menarche</td>
<td>1–1.5</td>
<td></td>
</tr>
<tr>
<td>Protective Factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiparity</td>
<td></td>
<td>0.4–0.6</td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 years</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>8 years</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>12 years</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Hysterectomy or tubal ligation</td>
<td></td>
<td>0.4–0.6</td>
</tr>
</tbody>
</table>

*HNPCC, hereditary nonpolyposis colorectal cancer.
(World Cancer Research Fund, 1997)

**Diagnosis and staging**

Ovarian cancer is often asymptomatic at the early stages, and the recognized signs and symptoms, even of last-stage disease, are vague, so the disease is generally advanced when it is diagnosed. The 5-year survival rate ranges from approximately 30 to 50 per cent (World Cancer Research Fund, 2007). However, the progress in reducing mortality in women diagnosed with ovarian cancer has still been limited due to the fact that there are no effective biomarkers that can identify early-stage...
disease and no reliable prognostic markers for predicting clinical response and guiding treatment regimes (Lawrenson & Gayther, 2009). Huntsman and colleagues tackled the issue of clino-pathological heterogeneity in epithelial ovarian cancer (Kobel et al., 2008). The study gave a message that biomarker expression is more strongly associated with histological sub-type than it is with disease stage. In another new study, Crijns and colleagues took a very different approach of gene expression microarrays to the analysis of ovarian cancers (Crijns et al., 2009).

The stage is the single most important determinant of prognosis. Table 2.4 provides the current FIGO staging classifications published in the Twenty-sixth Volume of the FIGO Annual Report (Cited in (Odicino et al., 2008). A recent study was performed between 1990 to 2000 among 448 patients with ovarian cancer International Federation of Gynecology and Obstetrics stages I to IIa, which compared survival of patients with clear cell carcinoma (CCC) to patients with serous adenocarcinoma (SAC) in early ovarian cancer. It has been found no worse prognosis in patients with CCC as compared with patients with serous carcinoma in early ovarian cancer (Timmers et al., 2009).
<table>
<thead>
<tr>
<th>Stage</th>
<th>Growth limited to the ovaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Growth limited to one ovary: no ascites present containing malignant cells. No tumor on the external surface; capsule intact</td>
</tr>
<tr>
<td>Ib</td>
<td>Growth limited to both ovaries: no ascites present containing malignant cells. No tumor on the external surfaces; capsules intact</td>
</tr>
<tr>
<td>Ica</td>
<td>Tumor either Stage Ia or Ib, but with tumor on surface of one or both ovaries, or with capsule ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings</td>
</tr>
<tr>
<td>Stage II</td>
<td>Growth involving one or both ovaries with pelvic extension</td>
</tr>
<tr>
<td>IIa</td>
<td>Extension and/or metastases to the uterus and/or tubes</td>
</tr>
<tr>
<td>IIb</td>
<td>Extension to other pelvic tissues</td>
</tr>
<tr>
<td>IIca</td>
<td>Tumor either Stage Ia or IIb, but with tumor on surface of one or both ovaries, or with capsule(s) ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings</td>
</tr>
<tr>
<td>Stage III</td>
<td>Tumor involving one or both ovaries with histologically-confirmed peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastases equals Stage III. Tumor is limited to the true pelvis, but with histologically-proven malignant extension to small bowel or omentum</td>
</tr>
<tr>
<td>IIIa</td>
<td>Tumor grossly limited to the true pelvis, with negative nodes, but with histologically-confirmed microscopic seeding of abdominal peritoneal surfaces, or histologic proven extension to small bowel or mesentery</td>
</tr>
<tr>
<td>IIIb</td>
<td>Tumor of one or both ovaries with histologically-confirmed implants, peritoneal. metastasis of abdominal peritoneal surfaces, none exceeding 2 cm in diameter: nodes are negative</td>
</tr>
<tr>
<td>IIIc</td>
<td>Peritoneal metastasis beyond the pelvis &gt;2 cm in diameter and/or positive retroperitoneal or inguinal nodes</td>
</tr>
</tbody>
</table>
Stage IV  Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to Stage LV. Parenchymal liver metastasis equals Stage LV.

a In order to evaluate the impact on prognosis of the different criteria for allotting cases to Stage Ic or hic, it would be of value to know if rupture of the capsule was spontaneous, or caused by the surgeon; and if the source of malignant cells detected peritoneal washings, or ascites. (Odicino et al., 2008)

**Aetiologic factors**

Ovarian cancer is a significant problem in the health of women, but little is known of its aetiologic factors (Kristensen & Trope, 1997); (World Cancer Research Fund, 1997); (Holschneider & Berek, 2000); (La Vecchia, 2001). Histologic differences in ovarian cancer contribute further to difficulties in understanding its aetiologic factors. Despite much effort has been put into attempts to correlate differences in incidence rates of ovarian cancer with environmental, endocrinologic, and genetic factors, our present level of knowledge is limited. The fivefold international variation and relatively high incidence of ovarian cancer in industrialized countries, suggest that the aetiologic factors of ovarian cancer may be related to environmental factors such as diet or life style (Baker & Piver, 1994). Few risk factors have been studied adequately and only three suggestive risk factors have been established (World Cancer Research Fund, 2007). The available evidence for factors that decrease the risk of ovarian cancer include non-starchy vegetables intake and lactation, while a probable risk factor increased in fatal disease is adult attained height (World Cancer Research Fund, 2007). The interactions of these various factors and other factors are still poorly understood. In particular, the role of dietary and lifestyle factors on ovarian cancer risk have not been thoroughly investigated.

2.3 Risk factors for ovarian cancer

2.3.1 Non-dietary factors

**Age**

The risk of ovarian cancer increases with age, although the rate of increase slows after the menopause, and most ovarian cancers occur after menopause. Only 10–15
per cent of cases occur before the menopause (World Cancer Research Fund, 2007). 80% to 90% of epithelial ovarian cancers occur after the age of 40, less than 1% of epithelial ovarian cancers occur before the age of 20, and two-thirds of ovarian malignancies in these young patients are germ-cell tumors. Ovarian cancers peak in women aged at 60 (Yancik, 1993). Hereditary ovarian cancers generally occur about 10 years earlier (Boyd & Rubin, 1997). The annual incidence of ovarian cancer in women between the ages of 75 and 79 years in the United States is 61.3 per 100,000, higher than any other age group, when age is considered independent of all other risk factors (Ries et al., 2007). When all other risk factors are considered, incidence is highest in women between the ages of 60 and 64 years (WHO, 2008).

Considering all stages of ovarian cancer, women younger than 35 years at diagnosis have a three-year survival as high as 50%, compared to 13% for patients older than 75 years (O'Malley et al., 2012). This may be explained in part by the fact that younger women tend to have earlier stage disease. As reported in a SEER study of more than 21,000 patients with ovarian cancer, the incidence of Stage I and II disease in women younger than 45 years of age is 51% vs. 24% for those older than 55 years. Conversely, Stage III and IV disease was reported for 49% of women younger than 45 and for 76% of women older than 55 (Yancik, 1993). However, based on the Gynecologic Oncology Group data, age continues to exhibit a significant prognostic effect, even after correction for stage, residual disease, and performance status (Thigpen et al., 1993).

**Geography**

There is geographic variation in the incidence of ovarian cancer. The incidence of ovarian cancer is highest in the U.S., Europe (especially Nordic countries and the United Kingdom), and Israel, and lowest in Japan and in developing countries. In mortality there is a fourfold ratio between the highest and the lowest incidence countries and more than threefold difference between the corresponding mortality figures (Levi et al., 1999); (Holschneider & Berek, 2000); (La Vecchia, 2001); (Parkin et al., 2001). The age-standardised rate (per 100,000 females) of ovarian cancer is 10.1 in Europe and 8.8 in the United States (Ferlay et al., 2010). Within Europe a 2.5-fold difference was observed in the late 1990s between the highest overall mortality rate of 9.3/100,000 in Denmark, and the lowest of 3.6 in Portugal.
(Bray et al., 2005). For women who immigrate from low-risk countries of origin, such as Asia, to high-risk areas, such as North America, there is a gradual increase observed in the incidence of ovarian cancer to rates expected for native-born women (Kliewer & Smith, 1995). Compared with other countries, the incidence of ovarian cancer in China is relatively lower at 3.8 per 100,000 females (Ferlay et al., 2010), however this rate has increased slightly in recent years (Kim et al., 2009).

A declining trend in ovarian cancer incidence has been reported in some countries that previously had high rates such as U.S., Canada, Scandinavia and UK between 1980 and 1995 (La Vecchia et al., 1998); (Tarone & Chu, 2000); (Levi et al., 2004); (Bray et al., 2005). However, an increasing trend has been observed in previous low-risk countries such as Japan, India and Singapore, and in southern and Eastern Europe (La Vecchia et al., 1993); (Levi et al., 2004); (Bray et al., 2005).

**Ethnicity and religion**

Limited studies have reported differences in the incidence of ovarian cancer among ethnic groups, primarily because of their small sample size. In the U.S., rates of ovarian cancer are higher among white women than in those from other ethnic groups (Walter, 1976); (Whittemore, 1982); (Jemal et al., 2004). The incidence of ovarian carcinoma for African-American women is 10.9 compared with 15.6 per 100,000 among white women (Parham et al., 1997). It has been reported 46 percent higher in whites than in blacks (National Cancer Institute, 1992). Wynder and other colleagues found that there was particularly frequent in postmenopausal New York Jewish women (Wynder, Dodo & Barber, 1969). The rates are also higher in Jewish women of Ashkenazi descent (Chaitchik et al., 1985), as women of Ashkenazi Jewish descent are at greater risk for BRCA1/2 mutations, which gives them an overrepresentation in the numbers of hereditary ovarian cancer cases (John et al., 1993).

It has been reported that there is an increased risk of epithelial ovarian cancer in Caucasian women. In the U.S., the incidence of ovarian cancer is higher for Caucasian women than for African-American or Asian-American women, although there is some evidence that these differences may be narrowing (Coleman et al., 1993).
**Height**

Relatively few studies have examined the relationship between height and ovarian cancer risk. Whereas these studies suggest an increased ovarian cancer risk overall with odds ratios (OR) between 1.2 and 2.8 for the tallest women (variously ≥168-177 cm) versus the shortest women (152-167 cm) (Rodriguez et al., 2002); (Engeland, Tretli & Bjorge, 2003); (Schouten, Goldbohm & van den Brandt, 2003). Larger effects have been reported for serous borderline malignancy (OR, 3.10 for women ≥168 cm versus those <168 cm) (Kuper, Cramer & Titus-Ernstoff, 2002).

Results from studies investigating the relationship between ovarian cancer and height are inconclusive. Several case-control studies have reported no statistically significant associations between height and risk (Chen et al., 1992); (Polychronopoulou et al., 1993); (Mori et al., 1998); (Jordan, Webb & Green, 2005); (Rossing et al., 2006); (Greer et al., 2006); (Peterson et al., 2006). In contrast, one case-control study (Zhang, Xie & Holman, 2005) observed a statistically significant elevated risk. A Norwegian cohort (Engeland et al., 2003) of 1.1 million women with 7,882 cases of ovarian cancer reported a positive association between height and ovarian cancer: women taller than 175 cm had a RR of 1.29 (95% CI, 1.11, 1.51) compared with women between 160 and 164 cm. A recent cohort study of 788,789 Koreans (339,575 women) also showed a positive association between height and risk of cancer of breast and ovary (Sung et al., 2009). Two further studies also have found positive associations for ovarian cancer with height (Lukanova et al., 2002); (Baer, Hankinson & Tworoger, 2008).

It has been reported that height was positively associated with ovarian cancer mortality in the Cancer Prevention Study-II, a prospective mortality study of 1.2 million women and men begun by the American Cancer Society in 1982. Ovarian cancer death rates were lowest among the shortest women (<152 cm tall; RR, 0.72; 95% CI, 0.47, 1.10), stable at heights between 152 and 171 cm, and increased with increasing height among women 172 cm tall or higher. Compared with women 152–156 cm tall, ovarian cancer mortality rates were 41% higher among women ≥177 cm (RR, 1.41; 95% CI, 0.95, 2.09) (Rodriguez et al., 2002).
The relationship between the factors that lead to greater adult attained height and ovarian cancer has also been explored. Seven cohort studies, nine case-control studies, and two ecological studies have investigated adult attained height. All seven cohort studies showed increased risk with greater adult attained height. Meta-analysis of cohort data showed an 8 per cent increased risk per 5 cm of height and a summary effect estimate of 1.15 (95% CI, 1.08,1.21) per 10 cm. Seven case-control studies found non-significant increased risk with greater adult attained height with a summary effect estimates of 0.96 (95% CI,0.87,1.05) per 10cm (3.9 inches). Figure 2.2 shows these cohort studies and case-control studies conducted to investigate adult attained height and ovarian cancer (World Cancer Research Fund, 2007).

Figure 2.2 Height and ovarian cancer; cohort and case-control studies
(World Cancer Research Fund, 2007)

Body weight and body mass index
Body mass index is defined as weight in kilograms divided by height in meters squared. Current guidelines from the National Heart, Lung, and Blood Institute define a normal BMI to be 18.5 to 24.9 kg/m²; overweight, 25 to 29.9 kg/m²; obesity class 1, 30 to 34.9 kg/m²; obesity class 2, 35 to 39.9 kg/m²; and extreme obesity as greater than 40 kg/m² (National Heart Lung and Blood Institute, 2000). Excess body weight and higher body mass index (BMI) are independent and well-established prognostic factors for mortality from several hormone-related cancers, such as breast and endometrial cancer (Ballard-Barbash & Swanson, 1996); (Weiderpass et al., 2000); (Daling et al., 2001); (Key et al., 2003); (Rapp et al., 2005); (Montazeri et al., 2008). The evidence for a consistent association with obesity is strongest for breast, colorectal, endometrial, gallbladder, kidney, and prostate cancer (Bergstrom et al., 2001); (Bianchini, Kaaks & Vainio, 2002).

Endogenous hormones have been hypothesized to be involved in the aetiologic factors of ovarian cancer (Risch, 1998). Obese women have higher concentrations of estrone and estradiol, which were regarded as tumor-promoting hormones (McTiernan et al., 2003). An American Cancer Society study linked obesity to increased risk of ovarian cancer (Lew & Garfinkel, 1979); (Garfinkel, 1985). However, the results of other epidemiologic studies evaluating the relation between obesity and ovarian cancer have been inconsistent. Joly et al. suggested that obesity in women over 50 years of age has been associated with increased risk of epithelial ovarian cancer (Joly et al., 1974). Numerous studies have also found positive associations for ovarian cancer with body mass index (BMI) (Farrow et al., 1989); (Purdie et al., 2001); (Riman et al., 2001); (Schouten et al., 2003); (Riman et al., 2004); (Hoyo et al., 2005); (Niwa et al., 2005); (Zhang et al., 2005); (Reeves et al., 2007); (Chionh et al., 2010); (Lahmann et al., 2010). A nested case-control study within a multicenter cohort study observed an inverse association (Lukanova et al., 2002).

However in a recent pooled analysis of 12 cohort studies, no association was observed between BMI at baseline and risk of ovarian cancer in all women (Schouten et al., 2008). This finding is not in agreement with a systematic review from Olsen et al. who concluded that overweight and obesity were associated with a small to moderately increased risk of ovarian cancer in population-based case-control studies.
and prospective cohort studies (pooled effect estimate for adult obesity versus normal BMI=1.3; 95% CI, 1.1, 1.5) (Olsen et al., 2007). The association was weaker and not statistically significant in prospective cohort studies in the systematic review (RR,1.12; 95% CI, 0.95, 1.32), and results between cohort studies were heterogeneous (Olsen et al., 2007).

**Menstrual and menopausal status**

There is substantial evidence that early menarche and late menopause increases the risk of, and may be seen as causes of, ovarian cancer (World Cancer Research Fund, 2007). The association between menstrual history and the risk of epithelial ovarian cancer has been studied frequently. A weak risk increase with menarche at a young age has been found in a number of studies, with odds ratios in these studies ranging from 1.1 to 1.5 when comparing menarche before 12 years with more than 14 years of age, and often are not statistically significant (Wu et al., 1988); (Parazzini et al., 1989); (Tavani et al., 1993); (Hankinson et al., 1995); (Purdie et al., 1995); (Riman et al., 2004). No association was found when menarche begins after age 16 years (Cramer & Welch, 1983); (Pike et al., 2004). The possibility that very late menarche may exert a protective effect deserves further attention, concentrating on data from developing countries, where a wider age range at menarche is observed (La Vecchia, 2001). Another study showed a slight increased risk with late age at menarche (Tzonou et al., 1984). A recent case-control study in Japan found that older age at menarche was associated with a decreased risk of ovarian cancers (Fujita et al., 2008). Several recent epidemiological studies found that age at menarche was not associated with ovarian cancer (Braem et al., 2010); (Tsilidis et al., 2011).

The effect of menopause on ovarian cancer risk has also been investigated in several studies. Figure 2.3 shows the age-specific incidence curve for epithelial ovarian cancer in women in the Birmingham region of the UK, 1968–1972 (Waterhouse et al., cited in (Pike et al., 2004). The rate of increase of ovarian cancer decreases around the age of 50 years. This change in the slope of the age-specific incidence curves at this age strongly suggests an effect of menopause. By reducing mitosis, menopause slows the rates of both spontaneous and environmentally induced mutations in the relevant stem cells. Therefore, early menopause will have a protective effect on ovarian cancer (Pike et al., 2004).
Figure 2.3 Age-specific incidence rates for ovarian cancer in the Birmingham region of the UK, 1968-1972
(Waterhouse et al., cited in (Pike et al., 2004).

A direct relationship between age at natural menopause and ovarian cancer risk was found in several case-control studies, with relative risk estimates varying from 1.4 to 4.6 for the oldest menopause category (Wu et al., 1988); (Parazzini et al., 1989); (Shu et al., 1989); (Franceschi et al., 1991); (Polychronopoulou et al., 1993). The increased risk from late menopause persisted also among older women (Parazzini et al., 1989). In some recent studies, positive associations were also found with late age of natural menopause and risk for ovarian cancer (Ho, 2003); (Pike et al., 2004); (Riman et al., 2004); (Tsilidis et al., 2011); (Le et al., 2012). Odds ratios for late natural menopause were reported as low as 1.19 and as high as 1.25 (95% CI, 0.95, 1.49). The ratios did not achieve statistical significance, but late natural menopause was associated with increased risk for ovarian cancer (Pike et al., 2004); (Ries et al., 2007). However, no association between age at menopause and ovarian cancer risk has also been reported in two cohort studies (Hankinson et al., 1995).
Studies so far show divergent results for the risk factor of menstrual and menopausal status, and indicate that these factors are likely to be weak predictors of ovarian cancer. The definition of menarche and menopause in epidemiological studies can be subject to recall and misclassification problems, which may explain some of the conflicting results.

**Parity and pregnancy**

Numerous epidemiologic studies have found parity to be protective against ovarian cancer. Overall, parous women have a lower risk for ovarian cancer than nulliparous women (Pike et al., 2004); (Braem et al., 2010); (Tsilidis et al., 2011); (Le et al., 2012). It is estimated that each delivery confers a 16% to 22% risk reduction, independent of the age at first pregnancy (Risch, Marrett & Howe, 1994); (Hankinson et al., 1995). A significant risk decline with increasing parity, with a relative risk estimate of 0.36 for five or more births, was noticed in a prospective study (Kvale et al., 1988). Parous women compared to nulliparous have relative risk estimates in the range of 0.3-0.7 (Negri et al., 1991); (Whittemore et al., 1992); (Polychronopoulou et al., 1993). Protection of increasing parity was also found in a large case-control study taken in a nationwide cohort of Swedish women, with a trend of 0.81 per pregnancy (Adami et al., 1994). A recent case-control study conducted in Japan also detected a decreased risk with increasing parity number (p = 0.0002) (Fujita et al., 2008). A few previous studies noted a greater reduction in risk with first birth than with subsequent births. There is an approximately 40% reduction in risk with first birth compared to approximately 10% with each subsequent birth (Whittemore et al., 1992); (Risch et al., 1994); (Ness et al., 2000); (Titus-Ernstoff et al., 2001); (Riman et al., 2002); (Tung et al., 2003).

The effect of age at first birth has been investigated in a number of studies. Several case-control studies with hospital controls indicate that a later age at first birth reduces epithelial ovarian cancer risk (Whittemore et al., 1992); (Polychronopoulou et al., 1993); (Tavani et al., 1993). A reduced risk with late age at first birth also has been indicated in some case-control studies with population controls (Whittemore et al., 1992); (Polychronopoulou et al., 1993); (Purdie et al., 1995). However, many research papers showed no association between age at first birth and epithelial ovarian cancer risk (Shu et al., 1989); (Chen et al., 1992); (Lund, 1992); (Risch et al.,
A population based case-control study found a major effect of age at last birth: the later the age at last birth the lower the risk of ovarian cancer. Compared to a nulliparous woman, the overall risk of ovarian cancer in a woman with a last birth after the age of 35 years was reduced by 58%, with a reduction of 51% solely due to the last birth. A last birth before the age of 25 years was associated with only a 16% reduced risk of ovarian cancer (Pike et al., 2004). Titus-Ernstoff et al. also observed a trend of increased protective effect with late age at last birth (Titus-Ernstoff et al., 2001). However, this effect was not seen in other two population based case control studies (Risch et al., 1994); (Riman et al., 2002).

Nulliparity is consistently associated with an increased risk of ovarian cancer (Negri et al., 1991), including among BRCA1/BRCA2 mutation carriers (Modan et al., 2001). After correcting for the effect of voluntary nulliparity, studies have found infertility to be a significant risk factor for ovarian cancer (Venn et al., 1995); (Bristow & Karlan, 1996); (Ness et al., 2002). Another study compared nulliparous women with women who had late first-time live births (Pike et al., 2004). The findings from the study suggest that regardless of age at first birth, pregnancy still confers a significant risk reduction for the development of ovarian cancer. In this study, maternal age at last birth was also implicated in decreasing the risk for ovarian cancer if the last birth was at age 35 years or older (Pike et al., 2004).

One of the most consistent findings in ovarian cancer epidemiology is the protective effect of full-term pregnancies on epithelial ovarian cancer risk (Shu et al., 1989); (Negri et al., 1991); (Whittemore et al., 1992); (Polychronopoulou et al., 1993); (Baker & Piver, 1994); (Albrektsen, Heuch & Kvale, 1996). However, the influence of incomplete pregnancies on epithelial ovarian cancer risk is unclear. Incomplete pregnancies have been found to have either a slight protective effect (Mori et al., 1988); (Whittemore et al., 1992) or no association (Shu et al., 1989); (Tsilidis et al., 2011). Under-reporting and definition of incomplete pregnancies is a concern for the conflicting results.

The difference in fertility rates between developed and developing nations has been well documented for many years (Population Reference Bureau, 2012). The higher average parity in developing nations is likely an important reason for the lower
incidence of epithelial ovarian cancer in these populations. However, ovarian cancer incidence has increased during the period 1978-2002 among women in Qidong, China, from 24 to 67 per 100,000 females. The rising trend in ovarian cancer may be related to the delay in age at first childbirth and the decline in the number of births. These demographic changes are reflected in the number of children aged 0–14, which accounted for 28.1% of the population of Qidong in 1978, and 17.2% in 2002, for instance (Chen et al., 2006).

**Fertility drug use**

Concern about the risk of ovarian cancer and the use of fertility agents has been raised during the past decade. Some studies suggested the risk of ovarian cancer may be increased among those women who took fertility drugs, yet did not become pregnant, as well as those with longer durations of fertility drug exposure (Whittemore et al., 1992); (Rossing et al., 1994); (Brinton et al., 2004). An increased risk for the development of borderline tumours has been reported for nulliparous women who received treatments with fertility drugs (Zreik et al., 2008). The risk for epithelial ovarian cancer associated with the use of fertility drugs was as high as 27-fold for nulliparous women (95% CI, 2.3, 315.6) (Rossing et al., 1994). A subsequent, larger, and more rigorous study found that the use of clomiphene resulted in a 2.3 increased risk for ovarian cancer in nulliparous women (95% CI, 0.5, 11.4) (Shushan et al., 1996). A large Danish study that enrolled 684 cases and 1,721 controls found an increased incidence of cancer in women with a history of infertility. The overall OR in all women in the study with known fertility status for ovarian cancer was 1.54 (95% CI, 1.22, 1.95). The unadjusted OR for ovarian cancer in infertile nulliparous women who were not treated for infertility was 3.13 (95% CI, 1.60, 6.08). This 3-fold increase was observed even after adjustment for infertility treatment, drug type, and pregnancy outcome (ie, miscarriage, induced abortion, ectopic pregnancy), where the adjusted OR was 2.71 (95% CI, 1.33, 5.52) (Mosgaard et al., 1997). However, findings from the literature on fertility drug use are somewhat inconsistent. Some recent studies provided evidence that fertility drug use does not significantly contribute to ovarian cancer risk (Jensen et al., 2009); (Vlahos, Economopoulos & Creatsas, 2010); (Kurta et al., 2012). These observations suggest that the relationship between fertility drugs and cancer is likely not a causal one. The
use of fertility drugs is likely a marker of an underlying pathology that gives rise to both ovarian cancer and refractory infertility.

**Lactation**

Breastfeeding is thought to delay ovulation and inhibits the release of reproductive hormones implicated in ovarian cancer development (McNeilly, 2001). While there is a plausible biological mechanism for a protective effect of prolonged lactation on ovarian cancer, findings from the literature are somewhat inconsistent. There is evidence for a reduced risk among women who have ever breastfed (Gwinn et al., 1990; Whittemore et al., 1992; Titus-Ernstoff et al., 2001; Zhang et al., 2004; McLaughlin et al., 2007; World Cancer Research Fund, 2007; Titus-Ernstoff et al., 2009; Jordan et al., 2012). In terms of duration of breastfeeding, an inverse association with ovarian cancer risk has been reported in some case-control studies (Risch et al., 1983; Gwinn et al., 1990; Greggi et al., 2000; Mills, Riordan & Cress, 2004; Zhang et al., 2004; Huusom et al., 2006; Jordan et al., 2010; Jordan et al., 2012). A meta-analysis of case-control data conducted by World Cancer Research Fund showed statistically significant decreased risk with increased accumulated lifetime duration of breastfeeding, with a clear dose-response relationship. The magnitude of the risk reduction is usually weak with odds ratios 0.6-0.9, and trends with increasing duration of lactation often are inconsistent (World Cancer Research Fund, 2007). Figure 2.4 showed seven case-control studies with a summary effect estimate of 0.96 (95% CI, 0.93, 0.99) per six months of breastfeeding with high heterogeneity (World Cancer Research Fund, 2007). While others have found no association (Cramer & Welch, 1983; Booth, Beral & Smith, 1989; Chen et al., 1992; Hirose et al., 1999; Chiaffarino et al., 2005), or borderline significance (Yen et al., 2003). Data pooled from two prospective studies revealed a significant decrease in ovarian cancer risk among parous women who breastfed for 18 months or more, compared to those who never breastfed (Danforth et al., 2007). Few studies have investigated risk in relation to number of children breastfed, however, findings are suggestive of an inverse association (Mink et al., 1996; Zhang et al., 2004; Chiaffarino et al., 2005; Titus-Ernstoff et al., 2009).
Oral contraceptive and other hormone use

There is a strong protective association between oral contraceptive use and ovarian cancer (Royer, Becher & Chang-Claude, 2001); (Riman et al., 2002); (Pike et al., 2004); (Lurie et al., 2008); (Tsiliidis et al., 2011); (Veljkovic & Veljkovic, 2011). A large majority of studies have found the protection from ever use of oral contraceptive. The oral combined contraceptive pill (containing both oestrogen and progesterone) has been estimated to halve the risk of ovarian cancer, if taken for 5 years or more (Bosetti, cited in (World Cancer Research Fund, 2007). The overall estimated protection is approximately 40% in ever oral contraceptives users (Tavani et al., 1993); (Risch et al., 1994); (Hankinson et al., 1995); (Purdie et al., 1995). A meta-analysis including 20 studies from the 1970s and the 1990s calculated a summary relative risk of 0.64 (95 CI, 0.57, 0.73) for ever use of oral contraceptive (Hankinson et al., 1992). In a large review of 12 case-control studies in the United States, oral contraceptive use and ovarian cancer risk had an overall OR of 0.67 (95% CI, 0.37, 1.2), an OR of 0.62 (95% CI, 0.24, 1.6) in African-American women, and an OR of 0.70 (95% CI, 0.52, 0.94) in white women (John et al., 1993). The only
outlier is a Chinese case-control study, where an odds ratio of 1.8 (95% CI, 1.0.8, 4.1) was found (Shu et al., 1989).

Longer duration of oral contraceptive use appears to increase the protection against epithelial ovarian cancer (Franceschi et al., 1991); (Whittemore et al., 1992); (Risch et al., 1994); (Rosenberg et al., 1994); (Vessey & Painter, 1995); (La Vecchia & Franceschi, 1999); (Whittemore et al., 2004); (Lurie et al., 2008); (Tsilidis et al., 2011). Women reduce their risk of ovarian cancer by 40%, 53%, and 60% with oral contraceptive use for four, eight, and 12 years, respectively (Schlesselman, 1995). In an European prospective study, women who used oral contraceptives for 10 or more years had a significant 45% (HR, 0.55; 95% CI, 0.41, 0.75) lower risk compared with users of 1 year or less (Tsilidis et al., 2011). Lurie and his colleagues found that epithelial ovarian cancer risk was reduced 5 or more years after initiation of oral contraceptive use (OR = 0.18; 95% CI, 0.08, 0.39). Each year of use provided a 5% reduction (95% CI, 0.02, 0.08) in risk (Lurie et al., 2008). Some studies also suggest that short term oral contraceptive use (<1 year) may lead to a decreased risk (Whittemore et al., 1992); (Greer et al., 2005); (Lurie et al., 2008). The protective effect of oral contraceptives appears to persist for a long time after discontinued use (Veljkovic & Veljkovic, 2011). A 40-70% risk reduction persisted when at least 10 years had elapsed since last use (Rosenberg et al., 1994). Five years of oral contraceptive use confers a 50% decrease in the risk for ovarian cancer with a protective effect that remains for up to 10 years after oral contraceptive use is discontinued (Cramer & Welch, 1983); (Whittemore et al., 1992); (Modugno, 2003). In a population based case control study, women who used oral contraceptive for a year or more were protected for at least 3 decades after they stopped use (Lurie et al., 2008). Some studies have also found that the favorable effect of oral contraceptives on ovarian cancer risk seems to persist for at least 15-20 years after oral contraceptive use has ceased, and it is not confined to any particular type of oral contraceptive formulation (Beral et al., 1999); (La Vecchia & Franceschi, 1999); (World Cancer Research Fund, 2007).

Oral contraceptive use appears to protect against epithelial ovarian cancer across various strata of parity. Results of the Cancer and Steroid Hormone (CASH) study suggest that nulliparous women who use oral contraceptives for five years or more
can reduce their ovarian cancer risk to that of parous women who never used oral contraceptives (Gross & Schlesselman, 1994). There is an additive effect between parity and oral contraceptive use reflected in the observation that women who have two children and have used oral contraceptives for at least five years have a 70% risk reduction for ovarian cancer (Franceschi et al., 1991). A meta-analysis including 20 studies from the 1970s and the 1990s calculated a summary relative risk of 0.55 for both nulliparous and parous women (Hankinson et al., 1992). For women in the U.S., the overall lifetime risk of developing ovarian cancer varies from 0.6% for women with no family history, at least three term pregnancies, and four or more years of oral contraceptive use, to 3.4% for nulliparous women with no oral contraceptive use (Hartge et al., 1994).

Some studies have examined the protective association of oral contraceptive use and ovarian cancer by major histologic subtypes. Oral contraceptive use seems to protect against all histological subtypes of epithelial ovarian tumours (Westhoff et al., 2000), with the possible exception of mucinous tumours (Risch et al., 1996). Riman et al. and Adami et al. reported that the use of oral contraceptives was not associated with the risk of borderline tumors (Adami et al., 1994); (Riman et al., 2001). In a pooled collaborative analysis of 12 U.S. case-control studies, the association of oral contraceptive use was weaker and less consistent for borderline tumors than for malignant tumors (Whittemore et al., 1992). More recently, in a large population-based case-control study, use of oral contraceptives was found to reduce the risk of borderline tumor, the effect being most pronounced for serous tumors (Huusom et al., 2006).

It has been found that ten years of oral contraceptive use by women with a family history appeared to reduce their risk to levels below the general population baseline (Gross & Schlesselman, 1994). In a population based case-control study, risk reduction from long-term use of oral contraceptives (>48 months) was found greater in women with a positive family history of ovarian cancer (OR, 0.12) than in women with a negative family history of ovarian cancer (Walker, Schlesselman & Ness, 2002). The association between oral contraceptive use and ovarian cancer risk in women who are BRCA carriers has also been studied. In a family-based study, a compatible 60% risk reduction with six or more years of oral contraceptive use has
been observed in high-risk patients with BRCA1 and BRCA2 mutations (Narod et al., 1998). In a study of 451 BRCA1/2 mutation carriers, the odds ratio for ovarian cancer associated with the use of oral contraceptives for six or more years was 0.62 (95% CI, 0.35, 1.09) after adjusting for parity (Whittemore et al., 2004). A recent meta-analysis showed that use of oral contraceptive was associated with a significant reduced risk of ovarian cancer for BRCA1/2 carriers (summary relative risk=0.50; 95% CI, 0.33, 0.75). A significant 36% risk reduction for each additional 10 years of oral contraceptive use was also observed (Iodice et al., 2010).

Several studies have examined associations between hormone replacement therapy and ovarian cancer (Gompel & Plu-Bureau, 2007); (Riman, 2007); (Zhou et al., 2008). Some studies suggested hormone replacement therapy has a protective effect (Smith, Sowers & Burns, 1984); (Hartge et al., 1988); (Kotsopoulos et al., 2006), while others found no association (Hildreth et al., 1981); (Harlow et al., 1988); (Wu et al., 1988); (Hopkins et al., 2004), or an increased relationship between hormone replacement therapy and ovarian cancer (Weiss et al., 1982); (Cramer & Welch, 1983); (Booth et al., 1989); (Kaufman et al., 1989); (Polychronopoulou et al., 1993); (Zhou et al., 2008). However, most recent studies suggest that hormone replacement therapy in menopause is not protective, and some studies have reported that hormone replacement therapy is related to increased ovarian cancer risk (Rodriguez et al., 1995); (Negri et al., 1999); (Beral et al., 2007). In the UK Million Study, current users of hormone replacement therapy were significantly more likely to develop and die from ovarian cancer than never users (relative risk 1.20 [95% CI, 1.09, 1.32; p=0.0002] for incident disease and 1.23 [95% CI, 1.09, 1.38; p=0.0006] for death). In this study, it has also been found that incidence of ovarian cancer increased with increasing duration of use for current users of hormone replacement therapy (Beral et al., 2007). A meta-analysis of eight cohort and 19 case-control studies reported a summary relative risk of 1.24 (95% CI, 1.15, 1.34) from cohort studies and a summary odds ratio of 1.19 (95%CI, 1.02, 1.40) from case-control studies for ever hormone replacement therapy use (Zhou et al., 2008).

The current epidemiologic studies of epithelial ovarian cancer suggest a moderate increase in risk among women with a long duration of use of unopposed menopausal estrogen therapy (Weiss et al., 1982); (Cramer & Welch, 1983); (Risch, 1996);
(Purdie et al., 1999); (Rodriguez et al., 2001); (Lacey et al., 2002); (Riman et al., 2002); (Sit et al., 2002). The risk of ovarian cancer among women taking estrogen-only hormone replacement therapy rises by 25 per cent after 5 years of use (Genazzani, 2002); (Pike et al., 2004). However, use of hormone replacement therapy that combines estrogen and progesterone does not increase ovarian cancer risk (Genazzani, 2002); (Lacey et al., 2002); (Pike et al., 2004). A Swedish case-control study found elevated ovarian cancer risk in users of estrogen replacement therapy and hormone replacement therapy with sequentially added progestins but not with continuously added progestins (Riman et al., 2002).

**Family history of ovarian cancer**

Although reproductive, demographic, and lifestyle factors affect risk of ovarian cancer, the single greatest ovarian cancer risk factor is a family history of the disease. The incidence of ovarian cancer attributable to genetic factors is estimated to be in the range of 5 to 10% (Risch et al., 2001). According to the National Cancer Institute, a woman without a family history of ovarian cancer has a 1 in 55 lifetime chance of developing ovarian cancer (Ries et al., 2007). This risk increases 10-fold when known familial/hereditary conditions exist (Elit et al., 2001); (Ries et al., 2007). For women in the U.S., the overall lifetime risk of developing ovarian cancer is 1.4% to 1.8%. For women with a family history, the lifetime risk for ovarian cancer is estimated at 9.4% (Hartge et al., 1994). Women with one first-degree relative with ovarian cancer have a 5% lifetime risk and women with two or more first-degree relatives have a 7% risk. The risk is greater for the sisters and daughters than for the mother (Cook, 2002). According to the nationwide Swedish Family Cancer Database, when a mother had ovarian cancer, the standardized incidence ratios for incident ovarian cancer in daughters was 2.69, and when a sister had ovarian cancer it was 3.49 (Hemminki, Sundquist & Brandt, 2011).

Most case-control studies that have included data on family history have confirmed that a family history of ovarian cancer increases the risk for ovarian cancer (Negri et al., 2003). A large meta-analysis of 15 published studies estimated an odds ratio (OR) of 3.1 for the risk of ovarian cancer associated with at least one first-degree relative with ovarian cancer (Stratton et al., 1998). Furthermore, the risks related to belonging to families prone to ovarian cancer were quantitatively evaluated.
Inheritance of mutation in some specific genes is now established (WHO, 1997). Three autosomal dominant inherited syndromes have been identified (Ford & Easton, 1995).

Ovarian cancer is a component of several autosomal dominant cancer syndromes. The syndromes most strongly associated with ovarian cancer are the BRCA1 or BRCA2 mutation syndromes. Ovarian cancer has also been associated with Lynch syndrome, basal cell nevus (Gorlin) syndrome, and multiple endocrine neoplasia type 1 (Lindor et al., 2008). Mutations of the breast cancer 1 gene, BRCA1, increase susceptibility to breast and ovarian cancers. The cumulative risk for women who carry this gene is 63% for ovarian cancer and 85% for breast cancer by age 70 (Ford & Easton, 1995). Mutations of the BRCA2 gene may also predispose to ovarian cancer, but the cumulative risk by age 70 appears to be less than 10% (Ford & Easton, 1995).

The risk of ovarian cancer depends on the number of affected first- and second-degree relatives, as well as their age at diagnosis with ovarian or breast cancer. This holds true for relatives on both the maternal and paternal side. There are at least two distinct groups of individuals with a hereditary predisposition to ovarian cancer for which pedigree analyses suggest autosomal dominant transmission with variable penetrance. Families with BRCA1 and BRCA2 mutations represent the formerly separate syndromes of site-specific familial ovarian cancer and hereditary breast/ovarian cancer (Boyd & Rubin, 1997); (Russo et al., 2009). On the other hand, there are those individuals who have ovarian cancer as part of the hereditary nonpolyposis colorectal cancer (HNPCC) syndrome (Lynch II syndrome) due to mutations in DNA mismatch repair genes (Lynch & Smyrk, 1996); (Russo et al., 2009).

**Tubal Ligation and Hysterectomy**

Several studies have examined the association between ovarian cancer and tubal ligation and hysterectomy (Chi, 1996); (Lu, 2008). In several cohort and case-control study, tubal ligation and hysterectomy have been associated on average with a 67% risk reduction for ovarian cancer. This protective effect appears to last for at least 20 to 25 years after surgery (Hankinson et al., 1993); (Rosenblatt & Thomas, 1996);
(Miracle-McMahill et al., 1997). After 12 years of follow-up in the Nurses’ Health Study (Hankinson et al., 1993), a strong inverse relation between tubal ligation and ovarian cancer was seen (OR = 0.33; 95% CI, 0.16, 0.64). In a meta-analysis of case-control studies of tubal ligation and ovarian cancer, the relative risk was estimated to be 0.59 or 0.87, dependent on whether hospital-based or community-based controls were used (Whittemore et al., 1992). A matched case-control study has been conducted to assess the potential of tubal ligation in reducing the risk of ovarian cancer in women who carry predisposing mutations in the BRCA1 or BRCA2 genes. The result suggested that tubal ligation is a feasible option to reduce the risk of ovarian cancer in women with BRCA1 mutations who have completed childbearing (Narod et al., 2001). In a large case-control study, risk for ovarian cancer was decreased by 36% (RR, 0.64; 95% CI, 0.48, 0.85), and tubal ligation decreased risk by 39% (RR, 0.61; 95% CI, 0.46, 0.85) (Gambacciani et al., 2003). A meta-analysis of 13 strictly selected studies showed a reduced risk of epithelial ovarian cancer by 34%. The protective effect of tubal ligation was confirmed even in a subgroup of women 10-14 years after the procedure (Cibula et al., 2010). In a recent meta-analysis, the summary relative risk for women with vs. without tubal ligation was 0.70 (95%CI, 0.64, 0.75). Similarly, the summary RR for women with vs. without hysterectomy was 0.74 (95%CI, 0.65, 0.84) (Rice, Murphy & Tworoger, 2012).

History of breast cancer

Rose et al. noticed that carcinoma of the ovary has a number of epidemiological features in common with breast cancer. They found that there was a strong positive correlation (r = 0.77) between the international death rates for cancers of the breast and ovary in 1978 and 1979 (Rose, Boyar & Wynder, 1986). It supports the hypothesis that there are common aetiological factors for both breast and ovarian diseases (National Research Council, 1982). In the United States, 10 to 20 percent of patients with breast cancer and patients with ovarian cancer have a first- or second-degree relative with one of these diseases (Madigan et al., 1995). Two major genes associated with susceptibility to breast and ovarian cancer—breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2) have been identified (Miki et al., 1994); (Wooster et al., 1995). Mutations in either of these genes confer a lifetime risk of breast cancer of between 60 and 85 percent and a
lifetime risk of ovarian cancer of between 15 and 40 percent (Brose et al., 2002). In a recent prospective study, breast cancer in a first- or second-degree relative was found associated with increased risk of ovarian cancer (RR = 1.4; 95% CI, 1.1, 1.7). Having 2 or more affected first-degree relatives was associated with increased risk (RR = 1.8; 95% CI, 1.1, 2.8), especially for women diagnosed with ovarian cancer before age 60 (RR = 4.2; 95% CI, 1.9, 9.2) or with a personal history of breast cancer (RR = 3.7; 95% CI, 1.8, 7.7) (Kazerouni et al., 2006). In a large case-control study conducted in Japan, women with a family history of breast cancer had odds ratio of ovarian cancer of 2.2 (95% CI, 1.3, 3.8) (Komata et al., 2009).

**Talcum powder**

Talcum powder (talc) use was implicated in ovarian cancer risk in the early 1960s when it was found to be a carcinogen (Graham & Graham, 1967). It has been suggested that talcum powder applied directly to the genital area may be carcinogenic to the ovaries. It has been postulated that an aetiologic agent could enter the peritoneal cavity through the lower genital tract. The hypothesis was supported by the finding that a high proportion of ovarian tumors contained talc particles within them (Henderson et al., 1971).

Epidemiologic studies have suggested an increased risk for ovarian cancer associated with the use of talcum powder in genital hygiene. Cramer and his colleagues firstly examined the association between the use of talc in genital hygiene and ovarian cancer by an epidemiologic study in 1982 (Cramer et al., 1982). An elevated odds for genital talc exposure was observed in this study. Several subsequent epidemiological studies also concluded that there is a significant association between the use of talc in genital hygiene and risk of epithelial ovarian cancer (Whittemore et al., 1988); (Booth et al., 1989); (Harlow et al., 1992); (Chen et al., 1992); (Tzonou et al., 1993); (Purdie et al., 1995); (Shushan et al., 1996); (Cook, Kamb & Weiss, 1997); (Mills et al., 2004); (Merritt et al., 2008). A meta-analysis of 16 studies that included 11,933 patients examined the effect of talc use and increased risk for ovarian cancer. The use of talc conferred a 33% increased risk for ovarian cancer (RR, 1.33; 95% CI, 1.16, 1.45) (Huncharek, Geschwind & Kupelnick, 2003). Only 3 smaller studies reported a null association (Hartge et al., 1983); (Rosenblatt, Szklo & Rosenshein, 1992); (Tzonou et al., 1993).
**Aspirin**

Aspirin has been associated with a reduced risk of colorectal cancer and to cancers of the oesophagus, stomach, breast, ovary and lung. A possible target of the cancer chemopreventive effect of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) is the inhibition of cyclooxygenase (COX). COX (in particular the isoform COX-2) has been reported to be abnormally expressed in many cancer cell lines, and has been implicated in the process of carcinogenesis, tumour growth, apoptosis and angiogenesis (Bosetti, Gallus & La Vecchia, 2009). Epidemiological studies have suggested that aspirin use might have a favourable effect on ovarian cancer: the overall RR estimate was 0.82 (95% CI, 0.69, 0.99), although the evidence is too limited to permit firm conclusions (Bosetti, Gallus & La Vecchia, 2002). A population-based, case-control study gave the support that use of any nonsteroidal anti-inflammatory drugs, including aspirin, within 5 years of diagnosis/interview was associated with a reduction in the risk of ovarian cancer (adjusted OR = 0.72; 95% CI, 0.56, 0.92) (Schildkraut et al., 2006). However, the epidemiological research results stayed inconsistent. Another population-based, case-control study found that aspirin were associated with weakly increased risks of ovarian cancer. And the association was stronger after more than 10 years of use (OR = 1.6, 95% CI, 1.1, 2.2) (Hannibal et al., 2008).

**Smoking**

Although early reports suggested that smoking was not associated with ovarian cancer risk (Byers et al., 1983); (Tzonou et al., 1984); (Franks et al., 1987); (Hartge et al., 1989); (Polychronopoulou et al., 1993); (Kuper et al., 2000), recent studies have reported positive associations for cancers of the mucinous subtype (Marchbanks et al., 2000); (Modugno, Ness & Cottreau, 2002); (Rossing et al., 2008); (Tworoger et al., 2008). These studies found there was a significant doubling of risk of mucinous ovarian cancer in current smokers compared to never smokers. The risk of mucinous cancer increased with increasing amount smoked but returned to that of never smokers within 20-30 years of stopping smoking (Marchbanks et al., 2000); (Modugno et al., 2002). A study by Gram et al. also demonstrated that current smokers had a significantly increased risk for mucinous tumors (HR = 1.85, 95% CI, 1.08, 3.16) compared with never smokers and those smoking more than 10 cigarettes
per day had a doubling in risk (HR = 2.25, 95% CI, 1.26, 4.03) as did those who had smoked less than 15 pack-years of cigarettes (HR = 2.18, 95% CI, 1.07, 4.43) (Gram et al., 2011). A recently published pooled analysis of ten case–control studies identified borderline significant decreases in risk of endometrioid and clear cell tumors but no association between smoking and serous or mucinous tumors (Kurian et al., 2005). A systematic literature review and meta-analysis of eight population-based case-control studies, one pooled analysis of case-control studies, and one cohort study confirmed that there was a significant doubling of risk of mucinous ovarian cancer in current smokers compared to never smokers (summary RR=2.1, 95% CI, 1.7, 2.7) (Jordan et al., 2006). Only one study differentiated between nonsmokers with and without exposure to childhood environmental tobacco smoke and found a decreased risk of ovarian cancer among current smokers (OR=0.65, 95% CI, 0.41, 1.00) and long-term former smokers (OR= 0.63, 95% CI, 0.40, 0.99) (Goodman & Tung, 2003).

**Physical activity**

Although a number of studies have examined the relationship between physical activity and ovarian cancer, their findings are inconsistent (Olsen et al., 2007). Three recent case-control studies found recreational/ aerobic physical activity to be protective against the disease (Carnide, Kreiger & Cotterchio, 2009; Moorman et al., 2011; Rossing et al., 2010). However, one of these studies reported that strenuous recreational activity performed early in life may increase the risk of cancer of the ovary (Carnide et al., 2009). Four prospective cohort studies have reported an increased ovarian cancer risk in relation to vigorous or high level physical activity (Mink et al., 1996; Bertone et al., 2001; Anderson, Ross & Folsom, 2004; Chionh et al., 2010). Conversely, a highly significant inverse association was observed between leisure-time vigorous activity and ovarian cancer risk in a combined analysis of three Danish cohort studies (Schnohr et al., 2005). This finding is in accordance with three earlier case-control studies, which found that women reporting higher levels of either leisure-time or occupational physical activity had a significantly lower risk of ovarian cancer, compared with women with the lowest activity level (Cottreau, Ness & Kriska, 2000; Tavani et al., 2001; Riman et al., 2004). Other studies have suggested a modest decrease in risk or have found no association (Bertone et al.,
2002; Hannan et al., 2004; Biesma et al., 2006; Patel et al., 2006; Weiderpass et al., 2006; Olsen et al., 2007; Lahmann et al., 2009; Leitzmann et al., 2009; Weiderpass et al., 2012). Furthermore, there is growing evidence that sedentary behaviours such as sitting increase risk of ovarian cancer (Zhang et al., 2004; Patel et al., 2006). The inconsistent findings may be due, in part, to the use of different definitions of physical activity, different parameters of activity (type, frequency, duration, intensity), and different methods of measurement.

Although evidence is emerging that the different histologic subtypes of ovarian cancer have different risk factor profiles (Purdie et al., 2003); (Kurian et al., 2005) only a small number of studies have examined the effects of physical activity separately for the subtypes (Bertone et al., 2001); (Tavani et al., 2001); (Riman et al., 2004); (Pan, Ugnat & Mao, 2005); (Patel et al., 2005) which requires further investigation.

Research in this area is very limited with respect to Chinese women (Zhang, Lee & Binns, 2003; Zhang et al., 2004). Further investigation among this population is valuable, given the difference in incidence rates, the pathogenesis of ovarian cancer and the potential for physical activity as a modifiable risk factor.

2.3.2 Dietary factors

Carbohydrate

In some early studies, no association between total carbohydrates and risk of ovarian cancer has been found (Shu et al., 1989); (Tzonou et al., 1993). However, Kushi et al. reported that greater intake of carbohydrates was associated with an increased risk of ovarian cancer (RR for highest vs. lowest quartile of intake 1.83, 95% CI, 1.07, 3.13, P = 0.04) (Kushi et al., 1999). In a case-control study carbohydrates have also been shown to increase the risk of epithelial ovarian cancer (Bidoli et al., 2002).

However, different carbohydrates may affect blood glucose and insulin levels to varying degrees depending on the nature of the carbohydrate and the type and extent of food processing, which, in turn, influence levels of sex hormones and insulin-like growth factors (Jenkins et al., 1981). On this basis they have been ranked using the
glycemic index (GI) and glycemic load (GL). A large case-control study has been taken in Italy to analyze the effect of type and amount of carbohydrates on ovarian cancer risk, using the glycemic index (GI) and the glycemic load (GL) measurement. This study reported that ovarian cancer was directly associated with dietary GI (OR for highest versus lowest quartile = 1.7, 95% CI, 1.3, 2.1) and GL (OR = 1.7, 95% CI, 1.3, 2.1) among pre- and postmenopausal women (Augustin et al., 2003). In a population-based case-control study by Nagle et al. suggested that glycemic load (GL) was positively associated with ovarian cancer. The adjusted odds ratio (OR) for the highest versus the lowest quartile of intake was 1.24 (95% CI, 1.00, 1.55) (Nagle et al., 2010).

**Milk and dairy products**

Dairy foods, such as milk, vary in consumption across the world, where highest consumption is found in developed countries compared with developing countries (Delgado, 2003). Dairy foods and some of their constituents, such as lactose and calcium, have been hypothesized to promote the development of ovarian cancer. Higher levels of lactose may affect the ovary and ovarian-pituitary axis through its metabolites (Cramer & Welch, 1983); (Swartz & Mattison, 1988); (Cramer et al., 2000). The strong correlation between national per capita milk consumption in the United States and the national incidence and mortality rates of ovarian cancer raised the hypothesis that consumption of milk and other dairy products may increase the risk of this malignancy (Rose et al., 1986); (Cramer, 1989).

However, analytic epidemiologic studies investigating this hypothesis have showed conflicting results. Several case-control studies of milk intake have reported no association with ovarian cancer risk (Engle, Muscat & Harris, 1991); (Risch et al., 1994); (Bosetti et al., 2001); (Zhang et al., 2002); (Mommers et al., 2006). While a positive association between skim milk and lactose intake and the risk of ovarian cancer was observed in the prospective Iowa Women's Health Study (Kushi et al., 1999), Nurses' Health Study (Fairfield et al., 2004) and Swedish Mammography Cohort study (Larsson, Bergkvist & Wolk, 2004).

In the Iowa Women's Health Study, women who reported a high consumption of total dairy products, skim milk, and cheese had a higher risk of ovarian cancer than did
those who rarely consumed these foods (Kushi et al., 1999). The Nurses’ Health Study and Swedish Mammography Cohort found a stronger positive association between higher lactose intake and specifically risk of serous ovarian cancer (Fairfield et al., 2004); (Larsson et al., 2004).

Although some investigators have reported the association between increased risk of ovarian cancer and frequent intakes of specific types or components of dairy food, such as whole milk (Cramer et al., 1984); (Mettlin & Piver, 1990); (Webb et al., 1998); (Qin et al., 2005), yogurt (Cramer, 1989), and cheese (Cramer, 1989), inverse association with higher consumption of skim or low-fat milk has also been found (Cramer et al., 1984); (Mettlin & Piver, 1990); (Webb et al., 1998); (Bertone et al., 2001); (Goodman et al., 2002).

Many case-control studies have also examined lactose intake and ovarian cancer risk. Some have found no association (Engle et al., 1991); (Risch et al., 1994); (Meloni et al., 1999); (Cramer et al., 2000); (Salazar-Martinez et al., 2002) or an inverse association (Harlow et al., 1991); (Goodman et al., 2002); (Yen et al., 2003). However, a case-control study has found higher risk of ovarian cancer with lactose absorption (Meloni et al., 1999).

A pooled analysis of 12 cohort studies has been done to prospectively assess the association between diet and ovarian cancer risk. In this analysis, no statistically significant associations were observed for milk or calcium intake. A weak, marginally significant positive association was observed for lactose and ovarian cancer risk, although lactose was highly correlated with milk and calcium intake within this pooled analysis (median r across studies >0.83 and 0.90, respectively) (Genkinger et al., 2006). A recent meta-analysis showed that prospective cohort studies, but not case-control studies, support the hypothesis that high intakes of dairy foods and lactose may increase the risk of ovarian cancer (Larsson, Orsini & Wolk, 2006).

**Saturated or animal fat**

Several mechanisms exist to explain how the frequent consumption of fats and animal products may be associated with ovarian cancer. The repeated rupture of the
follicle associated with ovulation is believed to expose the ovarian epithelium to hormones in the surrounding fluid; high estrogen concentrations may increase the likelihood of tumor development (Cramer & Welch, 1983). High consumption of fats may increase circulating estrogen levels, thus increasing the possibility of cell damage and proliferation (Hill, Goddard & Williams, 1971). Studies (Armstrong et al., 1981); (Shultz & Leklem, 1983) have demonstrated significantly higher circulating-estrogen levels among nonvegetarian women than among vegetarian women.

Several epidemiologic studies have reported the positive association of saturated or animal fat intake with risk of ovarian cancer. In a large, population-based case-control study, the investigators have reported significant increases in ovarian cancer with high intake of saturated fat and (Risch et al., 1994). Another two large case-control studies have also found increases in risk of ovarian cancer associated with high intake of saturated fat, animal fat, and/or cholesterol (Cramer et al., 1984); (Shu et al., 1989), which reported a 70–80 percent increase in risk with high intake. A meta-analysis of 6,689 subjects from 8 observational studies was performed to evaluate this association. The study has found that a high vs. low animal fat diet was associated with a raised relative risk (1.7) for ovarian cancer after separately analyzing total fat, saturated and unsaturated fat, and animal fat (Huncharek & Kupelnick, 2001). Recently, a pooled analysis of 12 cohort studies of dietary fat and ovarian cancer reported a positive association for animal fat at the highest level of intake (with relative risk in fourth quartile 1.15; 95% CI, 0.99, 1.33) and ovarian cancer risk (Genkinger et al., 2006).

However other studies have found little or no association of fat intake with ovarian cancer (Slattery et al., 1989); (Engle et al., 1991); (Cramer et al., 2000); (Pan et al., 2004); (Gilsing et al., 2010). There was also no evidence of a positive relation between intake of total, animal, vegetable, saturated, monounsaturated, or polyunsaturated fat and ovarian cancer in the prospective Iowa Women’s Health Study (Kushi et al., 1999).
Carotenoids and Vitamin A

Several studies have examined the association between carotenoid intake and ovarian cancer, but results have been inconsistent. Byers et al. found significant protective effects were observed with carotenoid intake but was limited to pre-menopausal women (30-49 years) (Byers et al., 1983). Some studies also reported a decrease in risk associated with high carotenoid intake (Slattery et al., 1989); (Engle et al., 1991); (Helzlsouer et al., 1996); (Bertone et al., 2001). But in other studies, the protective effect on ovarian cancer was not observed with higher intake of carotenoid (La Vecchia et al., 1987); (Shu et al., 1989); (Tzonou et al., 1993); (Kushi et al., 1999).

Oxidative stress during successive ovulation increases DNA damage resulting in the malignant transformations of ovarian cells (Murdoch & Martinchick, 2004), which in turn gives sound support to the "incessant ovulation" hypothesis. High consumption of antioxidants may, therefore, decrease ovarian cancer risk by counteracting oxidative stress and the resultant DNA damage (Frei, 1994); (Stanczyk, Gromadzinska & Wasowicz, 2005).

Epidemiologic studies have examined the relation between antioxidant intake and ovarian cancer risk, and the results are inconsistent. Byers et al. reported an inverse association of vitamin A intake from vegetables and fruits with ovarian cancer in younger but not older (>50 years) (Byers et al., 1983). Several other case-control investigations have also reported a significant inverse association between dietary intake of vitamin A and/or β-carotene and ovarian cancer risk (Engle et al., 1991); (Cramer et al., 2001); (McCann, Moysich & Mettlin, 2001); (Tung et al., 2005). In addition, an experimental trial to assess whether the vitamin A analogue, fenretinide, might prevent a second breast cancer yielded the surprising finding of a decreased risk for ovarian cancer (De Palo et al., 1995). A meta-analysis of five observational studies reported that a high intake of β-carotene was significantly associated with a reduced risk of ovarian cancer (relative risk=0.84; 95% CI, 0.75, 0.94) (Huncharek, Klassen & Kupelnick, 2001).

In contrast, some other case-control studies of ovarian cancer reported no association with estimated vitamin A consumption; (Fleischauer et al., 2001); (Pan et al., 2004).
Two prospective studies found no association (Kushi et al., 1999); (Fairfield et al., 2001). In addition, Fairfield et al. found no association with any of the other four major carotenoids (α-carotene, β-cryptoxanthin, lycopene, and lutein) or vitamins A or C. However, they did observe a statistically significant increased risk of ovarian cancer associated with relatively high intake of vitamin E from food sources (Fairfield et al., 2001). In a recent prospective cohort study, Silvera and his colleagues also found no association between ovarian cancer risk and dietary intake of carotenoids or vitamins A, C, or E (Silvera et al., 2006).

**Eggs**

Early ecologic and migration studies have showed positive relations between egg consumption and rates of ovarian cancer (Armstrong & Doll, 1975); (Dunn, 1975). Increases in risk associated with high intake of cholesterol from eggs have been reported in some cohort studies. In the Seventh Day Adventist cohort study (Snowdon, 1988), consumption of at least 3 eggs per week was associated with a threefold increased risk of ovarian cancer mortality comparing with less than 1 egg per week, and in the Iowa Women’s Health Study (Kushi et al., 1999), eating eggs several time per week was linked to a twofold excess risk of ovarian cancer. An increase in risk with frequent intake of eggs was also observed in a cohort study in U.S. women (Bertone et al., 2002). Similarly, several case-control studies have found positive associations between ovarian cancer and intake of eggs (Pirozzo et al., 2002); (Pan et al., 2004). In the population-based case-control study in Canada, women in the second, third, and fourth quartiles of cholesterol intake had a multivariate adjusted odds ratio [OR; 95% CI) of 1.12 (0.81, 1.56), 1.20 (0.85, 1.68), and 1.42 (1.03, 1.97), respectively (P = 0.031), compared with women in the lowest quartile of cholesterol intake (Pan et al., 2004). In contrast, some cohort and case-control studies found no relation between egg consumption and risk of ovarian cancer (La Vecchia et al., 1987); (Bosetti et al., 2001); (Zhang et al., 2002). A pooled analysis of 12 cohort studies reported that no association was observed for egg intakes with ovarian cancer risk (Genkinger et al., 2006).
Vegetables and fruits

Fruits and vegetables comprise a diverse food group characterized mostly by low energy density and specific potentially anticarcinogenic and antioxidant compounds. Thus, their consumption may be protective for several cancers, including ovarian cancer (World Cancer Research Fund, 1997). A collaborative evaluation by the IARC of eight previously published case-control and cohort studies through early 2003 concluded that vegetable intake possibly reduces the risk of ovarian cancer (IARC, 2003). On the other hand, IARC precluded a conclusion due to the inconsistent findings among the six studies of fruit intake and ovarian cancer (IARC, 2003). Case-control studies globally suggest a significant decrease in ovarian cancer risk for high vegetable intake, but the results on fruits are inconsistent (Shu et al., 1989); (Bosetti et al., 2001); (Zhang et al., 2002); (McCann et al., 2003); (Yen et al., 2003); (Pan et al., 2004).

There have been few prospective studies that reported on fruit and vegetables intake and ovarian cancer risk (Kushi et al., 1999); (Fairfield et al., 2001); (Larsson, Holmberg & Wolk, 2004); (Mommers et al., 2005); (Schulz et al., 2005). The inverse associations observed in the prospective studies were not as strong as those seen in the case-control studies and only one was statistically significant (Larsson et al., 2004). The cohort study among more than 325,000 European women did not provide evidence for an inverse association between overall fruit and vegetable consumption and risk of ovarian cancer (Schulz et al., 2005). However, analyses of specific botanical groups and green leafy vegetables have been limited and their results have been inconsistent (Shu et al., 1989); (Bosetti et al., 2001); (Bertone et al., 2002); (Zhang et al., 2002); (Salazar-Martinez et al., 2002); (Pan et al., 2004). A pooled analysis of 12 cohort studies showed no association between total fruit and vegetable intake and ovarian cancer (Koushik et al., 2005). However, according to the study by World Cancer Research Fund, non-starchy vegetables intake has been identified as a suggestive decreased risk factor for ovarian cancer (World Cancer Research Fund, 2007).
Meat

Meat consumption in relation to ovarian cancer incidence has been examined in several epidemiological studies. Two cohort studies reported no significant association between meat consumption and ovarian cancer risk (Kushi et al., 1999); (Bertone et al., 2002). In a large population-based prospective cohort study, Larsson and his colleagues have observed no significant association between consumption of red meat, fish, or egg and risk of ovarian cancer (Larsson & Wolk, 2005). Their finding for red meat is broadly consistent with those from two previous cohort studies showing no significant association of red meat (Bertone et al., 2002) or total meat (Kushi et al., 1999) consumption with ovarian cancer risk. In the Netherlands Cohort Study, there were no clear associations between intakes of fresh meat, processed meat and ovarian cancer risk (Gilsing et al., 2010). However, results from 2 Australian population-based case-control studies, a systematic review and meta-analysis showed that women with the highest intake of processed meat had a significantly increased risk of ovarian cancer in the 2 case-control studies (combined OR=1.18; 95% CI, 1.15, 1.21) and the meta-analysis [7 studies; pooled relative risk (RR)=1.20; 95% CI, 1.07, 1.34]. A recent meta-analysis of eight cohort studies confirmed that red and processed meat consumption is not associated with risk of ovarian cancer (Wallin, Orsini & Wolk, 2011).

Alcohol

Alcohol has been hypothesized to prevent ovarian carcinogenesis by decreasing follicle stimulating hormone, luteinizing hormone (Gavaler & Van Thiel, 1992) cited in (Genkinger et al., 2006) and gonadotropins (Verkasalo et al., 2001) levels, all of which have been hypothesized to increase ovarian cancer risk (Cramer & Welch, 1983) cited in (Genkinger et al., 2006).

Previous case-control and cohort studies have reported conflicting results relating alcohol intake to ovarian cancer risk. Webb and his colleagues found that alcohol consumption may reduce risk of ovarian cancer based on a meta-analysis of five previous population-based case-control and two cohort studies (Webb et al., 2004). In contrast, a pooled analysis of ten prospective cohort studies conducted among 529,638 women has observed that no associations for intakes of total alcohol (pooled
multivariate RR=1.12, 95% CI, 0.86, 1.44 comparing ≥30 to 0 g day⁻¹ of alcohol) or alcohol from wine, beer or spirits and ovarian cancer risk (Genkinger et al., 2006). Some other studies also reported null association between alcohol consumption and risk of ovarian cancer (Mori et al., 1988); (Whittemore et al., 1988); (Kuper et al., 2000); (McCann et al., 2003); (Modugno, Ness & Allen, 2003); (Peterson et al., 2006); (Chang et al., 2007); (Tworoger et al., 2008); (Harris et al., 2011). A positive relation between alcohol consumption and ovarian cancer risk has been observed in several studies (Tzonou et al., 1984); (La Vecchia et al., 1992). Alcohol consumption was also found inversely related to postmenopausal ovarian cancer (Kelemen et al., 2004).

To date, few studies have evaluated either the association between alcohol and different histological subtypes of ovarian cancer or the effects of different types of alcohol. Two case-control studies have examined association between alcohol consumption and serous, mucinous, and endometrioid ovarian cancers risk separately (Kuper et al., 2000); (Modugno et al., 2003). Modugno and his colleagues observed a higher risk of mucinous ovarian cancer with higher alcohol intake (Modugno et al., 2003). In the pooled analysis of ten prospective cohort studies, no association between alcohol consumption and ovarian cancer risk by histology was observed (Genkinger et al., 2006). In a population-based case-control study, the elevated risk of ovarian cancer for early adult regular drinking was found for serous invasive tumors (OR=1.52, 95% CI, 1.01, 2.30) (Peterson et al., 2006). A recent systematic review and meta-analysis revealed a modest protective effect of alcohol on endometrioid epithelial ovarian tumors (RR=0.82, 95% CI, 0.70, 0.96), while no association was found for serous (RR=1.00, 95% CI, 0.84, 1.19), mucinous (RR=0.91, 95% CI, 0.78, 1.08) and clear cell (RR=0.93, 95% CI, 0.76, 1.14) cancers. This comprehensive meta-analysis included 27 observational studies, of which 23 were case-control studies, 3 cohort studies and one pooled analysis of prospective cohort studies, including a total of 16,554 epithelial ovarian cancer cases (Rota et al., 2012).

**Tea**

Tea is one of the most popular beverages and on a worldwide basis consumption is second only to water. Of the total tea produced and consumed, 78% is black, 20%
green and less than 2% oolong. Black tea is primarily consumed in America, Europe, and Middle East, while green tea is mainly consumed in China, Japan, India and a few countries in North Africa. Oolong tea is the main tea beverage in Southern China and Taiwan (Yuan, 2011). Tea contains a number of potentially cancer preventive compounds including polyphenols. Catechins are a category of polyphenols including (-)-epicatechin, (-)-epicatechin-3-gallate, (-) epigallocatechin and (-) epigallocatechin-3-gallate and the majority of research has focused on these (Siddiqui et al., 2006). Epicatechin-3-gallate (EGCG) is the major component accounting for 30-40% of the total polyphenol content of green tea extract and is considered to be the most abundant and active constituent (Mukhtar & Ahmad, 2000). In contrast to green tea, by dry weight, a cup of black tea contains only 3–10% catechins, 2–6% theaflavins, and >20% thearubigins (Balentine, Wiseman & Bouwens, 1997). All types of tea are originally derived from the same plant, *Camellia sinensis*, however they undergo different manufacturing processes, changing the profile of compounds (Graham, 1992). Green tea leaves are steamed when harvested to prevent fermentation, oolong tea is partially fermented, whereas black tea leaves are allowed to wither and are rolled and crushed, initiating fermentation of the polyphenols present (Graham, 1992). This process results in oxidation of simple polyphenols to complex compounds such as theaflavins and thearubigins, and reduces the catechin content of black tea to approximately a third of that in green tea (Graham, 1992). This means consumption of different types of tea may have varying effects on cancer prevention.

There has been considerable interest in the protective role played by tea and its components, both in vitro and in vivo (Boehm et al., 2009); (Yang & Wang, 2010); (Yuan, Sun & Butler, 2011). Recent experimental studies have demonstrated the chemo-preventive properties of tea polyphenols. Such compounds are known to offer protection against all stages of carcinogenesis by suppressing tumor promotion and inflammation, due to their antioxidant properties against free radicals, blocking signal transduction and nuclear oncogene expression, trapping of ultimate carcinogens, and inducing apoptosis and cell cycle arrest (Yang, Prabhu & Landau, 2001); (Kumar, Pillare & Maru, 2010).
A study conducted in China by the Curtin School of Public Health and Zhejiang University reported a significant dose response relationship for green tea consumption and ovarian cancer risk (Zhang, Binns & Lee, 2002). A total of 254 cases with histologically confirmed epithelial ovarian cancer and 652 controls comprised hospital visitors, non-neoplasm hospital outpatients and women recruited from the community completed a food frequency questionnaire that included information on the type, duration and frequency of tea consumption. Those who reported drinking tea had a significantly reduced risk of ovarian cancer compared to those who did not drink green tea:

- Overall tea drinking daily OR: 0.39 (95% CI: 0.27, 0.57),
- Green tea drinking daily OR: 0.43 (95% CI: 0.30, 0.63), and
- Tea drinking longer than 30 years OR: 0.23 (95% CI: 0.13, 0.41).

To evaluate whether tea consumption can enhance ovarian cancer survival, the same researchers conducted a prospective cohort study on the patients originally participated in the previous case-control study. The cohort was followed up by measuring the frequency, quantity and type of tea they consumed after diagnosis of cancer. A new finding was reported that increasing the consumption of green tea post-diagnosis may enhance epithelial ovarian cancer survival (Zhang et al., 2004).

A literature search located 12 human observational studies investigating tea consumption and the ovarian cancer risk (Zheng et al., 1996); (Zhang et al., 2002); (Goodman et al., 2003); (Yen et al., 2003); (Jordan et al., 2004); (Larsson & Wolk, 2005); (Baker et al., 2007); (Gates et al., 2007); (Silvera et al., 2007); (Steevens et al., 2007); (Song et al., 2008); (Nagle et al., 2010), but their results have been inconsistent. Furthermore, long-term tea consumption was seldom assessed. The onset of cancer typically requires many years to develop, information on long-term tea exposure is thus important. Despite the advances in laboratory experiments and animal studies and the available epidemiological evidence, the role of tea in the aetiologic factors of ovarian cancer still has some uncertainty, mainly due to different tea consumption patterns between populations, and in particular a lack of accurate measurements on tea exposure in most studies (Yuan, 2011).
Lycopene and tomato products

The antioxidant properties of lycopene, a carotenoid consumed largely from tomatoes, have raised interest in the tomato as a food with potential anticancer properties (Di Mascio, Kaiser & Sies, 1989). Although apparent anticancer properties of tomatoes result from lycopene remains unproven. Lycopene has several notable characteristics that may confer potentially beneficial properties. Because lycopene is not converted to vitamin A, it may be entirely available for other properties (e.g., antioxidation). The lack of the ß-ionone ring structure for lycopene may increase its antioxidant activity (Stahl & Sies, 1996). The stereochemical properties of lycopene are quite different from those of other commonly consumed carotenoids (Britton, 1995), making it uniquely present in specific subcellular environments.

Oxidative stress during successive ovulation increases DNA damage resulting in the malignant transformations of ovarian cells, which in turn gives sound support to the "incessant ovulation" hypothesis (Tung et al., 2005). High consumption of antioxidants such as lycopene may reduce the risk of ovarian cancer based on this hypothesis (Tung et al., 2005). Epidemiologic studies have examined the relation between lycopene intake and ovarian cancer risk, and lycopene has been inversely related to the risk of ovarian cancer in studies conducted in America (Tung et al., 2005); (Kiani et al., 2006), as well as in a number of studies from China, and Japan (Giovannucci, 1999); (Zhang et al., 2004). However, the relationships between ovarian cancer and lycopene and tomato products remain inconclusive and the limited results available have been inconsistent (Story et al., 2010).

There are no previously reported studies of ovarian cancer and oolong tea. Because of the small numbers of previous studies and the potential importance of lycopene and tea (green, oolong and black) in the prevention of ovarian cancer, it is important to repeat the Hangzhou study in a different location to further test this hypothesis. This is the approach recommended by the USFDA (USFDA, 2005).

Soy and isoflavone intake

Soy food products are widely consumed in Asian countries, and soy is a primary source of isoflavones. Earlier research has suggested soy consumption may prevent
the development of ovarian cancer. An Italian multicentre case-control study reported a 41% risk reduction for women with the highest intake of specific seed oils, such as soya (Bosetti et al., 2002). Another case-control study undertaken in Hangzhou, China, found significant inverse associations between the ovarian cancer risk and intake of soy foods and specific isoflavones (Zhang et al., 2004). Similarly, a large prospective cohort study in the USA observed a relative risk of 0.56 for daily intake of total isoflavones above 3 mg, when compared to below 1 mg per day (Chang et al., 2007). A meta-analysis also concurred the protective effect of soy, with odds ratio (OR) 0.52 (95% confidence interval (CI) 0.42 to 0.66) for the highest versus the lowest level of intake (Myung et al., 2009). However, two population-based cohort studies conducted in the USA and Sweden found little association between the intake of phytoestrogens or phytoestrogen/flavonoid-rich foods and the ovarian cancer incidence (Wang et al., 2009); (Hedelin et al., 2011), which could be attributed to the low consumption of soy products among adults in these countries.

2.4 Nutrition in China

Nutrition transition in China

The economy in China has experienced exponential growth in the past two decades, with more than 8% of the annual growth rate of the gross domestic product (GDP), the highest rate for a large nation in recent world history. A rapid evolution of the Chinese diet has accompanied the high rising economic productivity and related social changes.

The classic Chinese diet includes cereals and vegetables with few animal foods. It is a diet that many scholars consider most healthful when adequate levels of intake are achieved (Du et al., 2004). A few studies have shown rapid changes in the diet and body composition of Chinese adults during the 1980-91 periods (Popkin et al., 1993); (Popkin et al., 1995). Adult intake of cereals, starchy roots and many low-fat, mixed dishes declined, consumption of animal food, especially meat and eggs, are becoming popular, and the consumption of edible oils is increasing quickly (Caballero, 2006); (Zhai et al., 2009) (Figure 2.5 and Figure 2.6). The increase in
intake of animal-source foods and edible oils, along with declines in cereal intake and minimal changes in vegetable intake, has led to large increases in the energy density of the diet and equally large increases in fat intake. In 2006, less than 1 percent of all Chinese adults consumed a diet with less than 10 percent of energy derived from fat. In contrast, in 2006, slightly more than 44 percent of adults consumed a higher-fat diet, with more than 30 percent of energy derived from fat, and close to two-thirds of adults consumed a diet with more than 10 percent of energy derived from animal-source food fats—primarily saturated fats (Popkin, 2008).

The China Economic, Population, Nutrition and Health Surveys were conducted in nine provinces that have different geography, economic development, public resources, and health indicators. The surveys from 1989 and 2004 revealed that energy and protein intake had decreased over time, but the quantity of protein had increased as a percentage of total calories (Figure 2.6) (Zhai et al., 2009).

Popkin has described five periods of dietary pattern change in China that fit together to mark shifts in the stages of the nutrition transition in China (Popkin et al., 1993). The first period was between 1949 and 1957, when food production was inadequate and low cereal consumption patterns existed. The second period was a sharp decrease in food consumption from 1957 to 1962 during the famine linked with The Great Leap Forward. The third period, between 1962 and 1979, was one of a strong recovery. The fourth, or reform period, from 1979 to 1985, came after the liberalisation of food production, when the annual economic growth rate was over 10%. After this rapid growth, further economic improvement led to a shift in energy requirements and the structure of the Chinese diet shifted (Du et al., 2002).
This shift in dietary patterns and corresponding body composition has been accompanied by many positive and some negative changes. Malnutrition and nutrition deficiency diseases are declining rapidly, while the burden is shifting to diet-related, noncommunicable disease with a rapid increase in the prevalence of overweight and obesity among both adults and children. Overweight status among
adult males tripled and among adult females, doubled, between 1989 and 2000. By 2004, nearly a quarter of all Chinese adults were overweight. Moreover, the rate of change of Chinese overweight status, in particular among adults, is one of the most rapid in the world (Popkin & Du, 2003). The prevalence of other diet-related chronic diseases such as hypertension, and diabetes has also been going up very fast. 18% of adults were hypertensive in 2002 and about 30% were overweight or obese. 20% of children aged 7-17 in big cities were overweight or obese (Chen, 2008) (Figure 2.7 and Figure 2.8). Fertility and mortality, particularly infant and child mortality, are declining; respiratory diseases are rapidly receding in importance; and life expectancy has reached high levels. Under nutrition is still a problem, particularly in remote areas with extreme poor conditions despite the emergence of a Western-style diet. Heart diseases, cerebrovascular diseases and cancer are now the major sources of mortality (Du et al., 2002)

Figure 2.7  Trends in obesity in Chinese population with BMI > 25
(Du et al., 2004)
Over the past 20 years, the status of diet and nutrition in China has undergone significant improvement, and the prevalence of malnutrition and nutrition deficiencies has been decreasing continuously. However, China is also undergoing a dramatically fast shift towards a stage of nutrition transition characterized by an intake of high fat, high energy density and low dietary fiber, as well as a high prevalence of diet-related non-communicable diseases such as obesity, diabetes mellitus, cardiovascular disease, and cancer. In recent years China has also experienced a slight increase in the incidence of ovarian cancer, which may be of concern due to the ageing population (Kim et al., 2009) and lifestyle factors including dietary patterns (Zhai et al., 2009). Given this recent increase, further insight into the lifestyle factors among Chinese women is warranted.
CHAPTER 3

METHODOLOGY

3.1 Overview

This chapter presents the methodology used in this case-control study. Section 3.2 describes the study design. The study location is described in section 3.3. Section 3.4 discusses the sample size determination, and the sample included in the data analysis. In section 3.5, questionnaire and measurements of exposure used in this study is described. Data collection is presented in section 3.6. Statistical analyses are presented in section 3.7, followed by the discussion of ethical considerations in section 3.8.

Materials presented in this chapter have been published or accepted for publication in the following journal articles:


Copies of these papers are included in Chapter 3, 4 and 5.

### 3.2 Study design

A hospital-based one to one case-control study was conducted in the Guangdong Province of southern China, between August 2006 and July 2008. This type of study is suitable to test the research objectives that lifestyle factors have an etiological association with ovarian cancer. Firstly, a case-control study can be undertaken within a reasonable time and with limited expense. Secondly, considering the multifactorial nature of the aetiology of ovarian cancer, this study design allowed for multiple aetiologic factors in diet and lifestyle characters to be examined. Finally hospital-based case-control studies are often chosen because subjects are readily accessible and relatively easy to recruit, an important factor in studies in China. The main limitations of case-control studies are that they can be subject to bias, especially in case selection and recall bias. Although a cohort study can sometimes minimize these types of bias, it is not feasible for the study of ovarian cancer in China due to time and budget limitations. Bias in a case-control study can be most effectively dealt with through careful design and meticulous conduct of the study.

A structured questionnaire was administered to collect demographic and personal characteristics including age, weight (kg), height (cm), education level, smoking status and alcohol consumption. Information on reproductive history, hormonal status and heredity was also obtained. Information on habitual food and beverage consumption was obtained using a 125-item semi-quantitative food frequency questionnaire developed for the southern Chinese population (Ke et al., 2005; Song et al., 2005). This validated instrument covered most of the food and beverage items commonly consumed in southern China. Information on habitual physical activity, including occupation, household, commuting and recreational activities, was
solicited (Jian et al., 2005). A reference recall period was set at 5 years before interview. Self-reported anthropometric data were systematically cross-checked with corresponding entries in medical records and any discrepancy found was subsequently rectified.

Subjects were recruited from four public hospitals within Guangzhou, the capital city of Guangdong: The Overseas Hospital (affiliated with Jinan University), Zhujiang Hospital, General Hospital of Guangzhou Military Command, and Second Affiliated Hospital of Zhongshan University. Five hundred patients with epithelial carcinoma of the ovary consented to participate and were capable of being interviewed after consecutively recruited 504 cases from the four hospitals. During the same period, 512 controls were recruited from inpatient wards of the Departments of ophthalmology, orthopedic, respiratory disease, gastroenterology and physiotherapy. These women were frequency matched to cases within 5 years of age. The same age limit and residency requirement also applied. The written consent from participants was obtained before each interview.

3.3  Study location

The study was conducted in Guangzhou, Guangdong province located in the south of China (Figure 3.1) (Asia Times, 2012). Guangzhou is the capital city of Guangdong, and the center of its political, economic, scientific, educational and cultural life. Covering an area of 7435 square kilometers (2,870 square miles), Guangzhou has a population of more than 11 million including a 3.7 million transitory population and a 3.95 million urban population (Tang & Li, 2010).
3.4 Sample size determination

The following formula was used for comparing proportions from two samples (Zhang, Lee & Binns, 2002).

\[
N = \left[ \frac{P_1(1 - P_1) + \frac{P_2(1 - P_2)}{k}Z_{Pow} + \sqrt{\frac{\bar{P}(1 - \bar{P})(1 + \frac{1}{k})Z_{1-\alpha/2}}{P_2 - P_1}}} {P_2 - P_1} \right]^2
\]

Applying the two-sample adjustment for a continuity correction produces the final

\[
N_1 = N_1 + \frac{k + 1}{k|P_2 - P_1|}
\]

\[
N_2 = kN_1
\]

results

Where \(P_1\) = proportion with outcome in control

\(P_2\) = proportion with outcome in case
\[ \alpha = \text{risk of false positive} \]

\[ \beta = \text{risk of false negative} \]

\[ f(\alpha, \beta) = (Z_{\alpha/2} + Z_{\beta}) \_ \]

Since one of the key factors involved is fat, it is used to estimate the sample size. Shu, et al. (Shu et al., 1989) cited that the mean intake of fat was 65.5 g per day from a representative Shanghai population (5-day weighed food records from 2,000 people, 1981). Also Rose et al. (Rose et al., 1986) cited that the animal fat per capita in Hong Kong was 65 g/day.

Assume: \( P_1 = 20\% \) in controls who consume 65 gram of fat per day

\[ P_2 = 32\% \text{ in cases who consume 65 gram of fat per day} \]

\[ \alpha = 0.05 \]

\[ \beta = 0.1, \text{ statistics power } 1-\beta = 0.9 \]

\[ N_1 = 296 \text{ (case group)} \]

\[ N_2 = 296 \text{ (control group)} \]

Thus, it would be necessary to sample at least 290 subjects in each group to find a clinically significant difference. However, in the Hangzhou study 55\% of the cases drank tea regularly, compared to 75\% of the controls (Zhang et al., 2002). In Guangdong a different variety of tea (such as black and oolong teas) is consumed. It is possible that the chemopreventive effect of these teas will not be as strong as green tea. In calculating the sample size, it was assumed that the preventive effect is only half the strength, i.e. 65\% in the cases and 75\% in the controls. A sample size of 460 controls and 460 cases would allow the detection of a 10\% difference in tea drinking rates with an alpha level of 0.05 and a power of 80\%. To further account for refusal and withdrawal, 504 eligible cases and 512 age-matched controls were approached and invited to participate in the study. Of the total 504 cases consecutively recruited from the four hospitals, 500 patients with cancer of the ovary consented to participate.
and were capable of being interviewed. Twelve women who declined the interview or not satisfying the eligibility conditions were later excluded, resulting in a final sample of 500 controls available for analysis. There were no significant differences in age and major demographics between the excluded subjects and the consented participants.

3.5 Study instrument

**Questionnaire**

The instrument for the study was a structured, interview-administered questionnaire to collect information on demographic and lifestyle characteristics, usual diet, regular physical activity, and factors relevant to hormone status that this research interested.

The questionnaire consists of five components: (a) General information: date of birth, weight, height, body mass index (BMI = weight/height²), marital status, address and place of birth; (b) Frequencies of habitual food intake and the amount of foods consumed each time as well as the methods of cooking; (c) Lifestyle characteristics of subjects: family structure, physical activity, alcohol and tobacco use, and socioeconomic factors; (d) Factors relevant to occupation: main occupation prior to retirement, years in workforce, chance of exposure to hazards and adverse reaction; (e) Factors relevant to reproductive history, hormonal status and heredity: history of marriage and reproduction, breastfeeding experience, medical history of benign ovarian diseases, medication intake, first degree relative family history of ovarian or other cancers. The Curtin School of Public Health is a member of the International Consortium for the Study of Ovarian Cancer based at Oxford University. The questions on reproductive health were consistent with their protocol. The same questionnaires were used in both case and control groups. A copy of the English version of the questionnaire is given in Appendix B.

Food Frequency Questionnaire (FFQ) was used to collect the food consumption variables in this research. The FFQ is the most commonly used tool to measure habitual food intake in epidemiological studies of different ethnic, age, and target populations. This questionnaire was modified from the one previously used in Hangzhou (Zhang et al., 2002) and the semi-quantitative food questionnaire.
developed by Song et al. (Ke et al., 2005; Song et al., 2005). The semi-quantitative food frequency questionnaire was developed and tested for the southern Chinese population. The questionnaire was translated into Mandarin and pre-tested on a sample of 30 Chinese women resident in Guangzhou was conducted to ensure cultural relevance to this specific area of China.

**Measurement of food items**

The food items in this FFQ were modified from the one previously used in Hangzhou due to the fact that Guangzhou has different cultures and dietary habits with Hangzhou (Zhang et al., 2002). The selection of food items was obtained through the food frequency questionnaire developed in the Chaoshan research based on the specific dietary habit in Guangdong province, China (Ke et al., 2005; Li et al., 2006; Song et al., 2005). According to the category of the China Food Composition 2002, 125 food items listed in the FFQ comprised: cereals (10 items), legumes (6), fresh legumes (3), vegetables (13), melons and nightshade (5), cauliflower (1), roots (8), fruits (12), meats (11), poultry (5), milk (2), eggs (3), pickles (4), marine products (15), mushrooms (5), nuts (2), cakes (3), condiments (8), oils (3) and beverages (6) (Yang, Wang & Pan, 2002). This validated instrument covered most of the food and beverage items commonly consumed in southern China. All the items were listed in the questionnaire in detail given in the Appendix B.

This FFQ recorded both frequency and amount of intake in detail. The food intake frequencies were classified into seven categories: 1-3 times per month; 1-2 times per week; 3-4 times per week; 5-6 times per week; 1 time per day; 2 time per day and 3 time per day. The quantitative variables were described as standard portion size and portion size. The standard portion size of each food item per meal was determined using the mean amount, typical/standard value or the natural unit. Portion size was divided into six categories: 0.5, 0.7, 1.0, 1.5, >=2.0 (0.5 is the first portion size of the upper limit of portion size). As estimation of condiment and oil consumption per meal was difficult, four categories were employed: none, less than normal, normal and more than normal. The normal intake was determined as the mean amount in the 3-day WDR (two weekdays and one weekend day), and allocation to less or more than normal was estimated with reference to the standard deviation (Ke et al., 2005; Li et al., 2006; Song et al., 2005). Since Chinese women are typically responsible for
buying raw foods and cooking for the household, the quantity of most food items were estimated based on raw weight. The quantity of some foods such as rice, bread, cake and pastry were estimated on their cooked weight. The reference recall period for dietary variables was set at five years before diagnosis for cases and five years before interview for controls. The energy content of each food or beverage item was obtained from the Chinese food composition tables (Yang, Wang & Pan, 2002). We then estimated participant’s total energy intake (kcal) by summing the energy intake across individual items consumed.

**Measurement of tea consumption**

Specific questions on tea drinking were appended to the food frequency questionnaire. The reliability and reproducibility of these questions have been established for southern China (Liang et al., 2009). Subjects were first classified as tea drinkers or non-drinkers (less than once per month). The tea drinkers were asked to report their frequency of habitual intake (number of cups per month, week or day), duration of regular tea drinking (in years), types of tea drank (green, black and oolong), and average amount of dried tea leaves used for brewing tea in “jin” (500 g) and “liang” (50 g) per year. Quantity of liquid tea consumed was measured in terms of the standard cup size of 180 ml. The common method of tea preparation in southern China is to brew dried tea leaves in a tea pot or tea cup using hot water without adding milk or sugar.

**Measurement of habitual physical activity**

Information on habitual physical activity, including occupational, household, commuting and recreational activities, was solicited using a validated questionnaire for cancer studies in China (Jian et al., 2005). Participants were asked to report the number of hours on average engaging in different levels of physical activity per week: (i) strenuous sports including jogging, cycling on hills, tennis, racquet ball, swimming laps, aerobics; (ii) vigorous work including moving heavy furniture, shovelling, weight lifting, loading/unloading trucks, or equivalent manual labour; (iii) moderate activity including housework, brisk walking, golfing, bowling, cycling on level ground, gardening, walking and taichi. The intensity classification was based on the amount of energy or effort a person expends in performing the activity (Jian et
al., 2005). A reference recall period was set at the year that was 5 years before interview. The habitual physical activity recorded thus should reflect the period when the subjects were generally healthy and their activities were not restricted by any disease.

Physical activity exposure at each intensity level was then quantified in terms of metabolic equivalent tasks (MET)-hours per week. The MET is the ratio of metabolic rate during the activity compared with the metabolic rate during rest. Following the standard scoring mechanism for older Chinese women (Zhang, Lee & Binns, 2003), intensity codes 7.5, 6.0 and 4.5 MET were assigned for strenuous sports, vigorous work and moderate activity, respectively, regardless of the actual age. For each individual, total physical activity exposure was calculated by summing the product of MET score and activity duration over the three intensity levels.

Sitting duration in both occupational- and leisure-time was assessed by asking the participants how many hours on average in a day they spent sitting (1) at work, (2) while watching television, (3) in car or bus, (4) at meals, and (5) in other activities (such as reading, playing cards, and sewing). This validated and reliable question was used to investigate the effect of sedentary behaviours on the risk of epithelial ovarian cancer for Chinese women in Hangzhou (Zhang et al., 2004). An overall measure of sedentary exposure, total sitting duration, was obtained for each individual by summing the hours spent in all sitting activities.

**Measurement of breastfeeding**

Information on reproductive history, including lactation history, was obtained. Participants were asked about each of their pregnancies in detail, including the outcome of the pregnancy. Women with at least one live birth were asked to report the number of children breastfed and average duration of lactation per child (months).

**Measurement of body size**

Information on body height and weight was collected. The participants were asked to report body weight (in kg) 5 years before diagnosis and interview for cases and controls, respectively, along with adult height (in cm).
3.6 Data collection

*Identification of cases*

1. *Inclusion criteria:* Cases were defined to be incident patients who had been histopathologically diagnosed with cancer of the ovary within the past 12 months. Eligible cases were required to be under 75 years of age and have resided in the metropolitan Guangzhou area for at least the past ten years.

2. *Exclusion criteria:* Patients were excluded when ovarian cancer was histopathologically confirmed to be not the primary diagnosis, if they confessed to have memory problems affecting their recall of past events, if their ages are above 75 years, if they have other malignant diseases, or if they are non-residents.

The study was restricted to women under the age of 75 years to reduce the limitations from memory in women over 75 years old. Duration of residence was defined as who had been living in Guangdong province for at least 10 years in order to limit cultural variations in diet and lifestyle.

*Recruitment of cases*

Potential cases were identified by searching the daily census of the hospitals. All hospital medical records and laboratory pathology reports were reviewed during the recruitment period to ensure complete ascertainment of cases. Five hundred and four patients with cancer of ovary were recruited from four hospitals in Guangzhou, namely: The Overseas Hospital (Affiliated with Jinan University), Zhujiang Hospital, General Hospital of Guangzhou Military Command, Second Affiliated Hospital of Zhongshan University between August 2006 and July 2008. All the cases included were incident, histologically confirmed epithelial ovarian cancer patients diagnosed within 1 year prior to interview and with no previous diagnosis of cancer. Pathological diagnoses were based on the International Histological Classification of Ovarian Tumors recommended by the International Federation of Gynecology and Obstetrics (Heintz et al., 2006). Of the total 504 cases consecutively recruited from
the four hospitals, 500 ovarian cancer patients consented to participate and were capable of being interviewed.

The sampling from different hospitals helped to minimize recruitment bias. To minimize recall error bias, face-to-face interviews were conducted entirely by the investigators. The advantages of face-to-face interviews include high response rate, immediate and accurate answers, and easy administration.

Identification of controls

1. Inclusion criteria: Women recruited into the control group were frequency matched to cases by age (± 5 years).

2. Exclusion criteria: (i) previous diagnosis of ovarian cancer or other malignant diseases; (ii) a history of bilateral oophorectomy; (iii) memory problems; (iv) on long-term physical activity restriction; in addition to non-residency and advanced age (i.e. exceeding 75 years).

Recruitment of controls

Potential controls were initially screened using the hospital daily census records. On days when more control subjects appeared to be available than could be interviewed, a selection of ward and patient identification was made using random numbers. Five hundred and twelve controls were recruited from inpatient wards of the Departments of ophthalmology, orthopedic, respiratory disease, gastroenterology and physiotherapy. All eligible inpatients had their diagnosis subsequently confirmed by histopathological reports to avoid misclassification of the case-control status. This systematic selection process was adopted throughout the recruitment period. Twelve women who declined the interview or who did not satisfy the eligibility conditions were later excluded, resulting in a sample of 500 controls available for interview. No statistically significant differences were found between the included and excluded women in terms of age and main demographic variables.

Interviews
An appointment for face-to-face interview was then arranged with each participant in conjunction with nursing staff to avoid interference with treatment at the ward and before being discharged from hospital. Subjects were interviewed in the presence of their next-of-kin whenever possible, to minimize recall error. All participants provided formal consent before the interview. They were also assured of confidentiality and their right to withdraw without prejudice. The interviews usually took about 45 minutes to complete and were conducted by research assistants in either Mandarin or the Cantonese dialect. All research assistants were fluent in both dialects, and were trained by researcher for the interviews following a standardised protocol. All participants were blinded to the study hypothesis. The project protocol was approved by the participating hospitals, the doctors-in-charge of the relevant wards, and the Human Research Ethics Committee of Curtin University (approval number HR 78/2006). Access to medical records and pathology reports was granted by the participating hospitals.

3.7 Analysis of data

All statistical analyses were undertaken using SPSS for Windows package version 20. To identify any coding and data entry errors, some analyses of the data distributions were conducted. Plausibility checks were undertaken to identify out of range responses and inconsistent data compared with the original questionnaire and data were cleaned appropriately. Inter observer variation was avoided by coding all the data.

Descriptive statistics

Univariate descriptive statistics were carried out to compare the participants’ demographic characteristics, distribution of outcome variables on tea drinking, physical activity levels, breastfeeding and BMI. Those comparisons between cases and controls were made by using t test for continuous variables and chi-square test for categorical variables. Besides descriptive statistics, univariate logistic regression was used in most cases to screen potentially significant variables for subsequent incorporation into the multivariable model.
Tea consumption

Descriptive statistics were first applied to summarise participant characteristics and their tea consumption pattern. Comparisons between case and control groups were made using chi-square and t tests. To investigate the effects of tea exposure on the ovarian cancer risk, separate unconditional logistic regression analyses were performed for tea drinking (yes or no), duration of drinking, frequency of intake, quantity consumed, and amount of dried tea leaves brewed. The continuous consumption variables were classified into four increasing levels of exposure, with non-drinkers taken as the reference category. Both crude and adjusted odds ratios (OR) and associated 95% confidence intervals (CI) were reported, and tests for linear trend were conducted to assess the dose-response relationship. Analysis by tea type was not undertaken because most of the tea drinkers regularly drank a combination of green, black and oolong teas.

Besides tea consumption, independent variables included in the logistic regression models were age at interview (years), parity, oral contraceptive use (never, ever), body mass index (5 years ago), menopausal status (pre, post), education level (none or primary, secondary, tertiary), smoking status (never, ever), alcohol drinking (no, yes), total energy intake (kcal) and family history of ovarian or breast cancer (no, yes). These variables were considered plausible risk factors according to the literature.

Habitual physical activity

Descriptive statistics were first used to compare the sample characteristics between case and control groups. Unconditional logistic regression analyses were then performed to ascertain the association between habitual physical activity and the ovarian cancer risk. Each physical activity variable was classified into three increasing levels of exposure, with zero (no engagement) taken as the reference category for strenuous sports, vigorous work and moderate activity. The effect of sedentary exposure was also investigated in a separate model. Total sitting duration was categorized as low (≤ 4 hours/day), moderate (4.5 to 8 hours/day), and high (≥ 8.5 hours/day) levels based on the distribution of controls.
In addition to reporting crude and adjusted odds ratios (OR) and associated 95% confidence intervals (CI), tests for linear trend were conducted to assess the dose-response relationship between habitual physical activity and the ovarian cancer risk. Other independent variables included in the logistic regression models were age at interview (years), parity, oral contraceptive use (never, ever), body mass index (5 years ago), menopausal status (pre, post), education level (none/primary, secondary, tertiary), smoking status (never, ever), and family history of ovarian or breast cancer (no, yes). These variables were considered established or plausible risk factors from the literature.

**Breastfeeding**

Only women who had at least one live birth were included in the analysis. The sample of controls with at least one live birth but no breastfed children were excluded from the analysis, as there was no comparison group from the cases. This resulted in a final sample of 493 cases and 472 controls. Total duration of breastfeeding (months) was calculated by multiplying the variables ‘number of children breastfed’ and ‘average duration of lactation per child (months)’.

Descriptive statistics were first used to compare the sample characteristics between case and control groups. Unconditional logistic regression analyses were then performed to ascertain the association between breastfeeding and the ovarian cancer risk. The ‘number of children breastfed’ variable was classified into three levels, with women who had breastfed one child used as the reference group. The breastfeeding duration variables were divided into approximate quartiles based on the distribution of controls, with the lowest quartile used as the reference category.

In addition to reporting crude and adjusted odds ratios (OR) and associated 95% confidence intervals (CI), tests for linear trend were conducted to assess the dose-response relationship between breastfeeding and risk of ovarian cancer. Other independent variables included in the logistic regression models were age at interview (continuous: years), parity (1, ≥2), oral contraceptive use (never, ever), ovarian and/or breast cancer in a first degree relative (no, yes), education level (none/primary, secondary, vocational/tertiary), menopausal status (pre, post), alcohol
drinking (no, yes), and smoking status (never, ever). These variables were either established or plausible risk factors from the literature.

**Body size**

BMI was calculated from self-reported height and weight using the standard formula and expressed in kg/m². The anthropometric variables were divided into approximate tertiles based on the distribution of controls, to facilitate analysis. The lowest tertile was used as the reference category. BMI was further categorised based on the Asian population cut points (< 18.5, 18.5-22.9 and ≥ 23) suggested by the WHO expert consultation (WHO Expert Consultation, 2004). A very small number of participants (2%) fell into the highest category of risk (BMI > 27.5) therefore women with a BMI ≥ 23 remained as one group. Weight and BMI at 5 years prior to diagnosis/ interview was used instead of current weight in order to minimise bias due to reverse causation. To investigate the risk of ovarian cancer by specific histologic type, we compared each case subtype to the entire control group. Six major categories of epithelial ovarian cancer were considered: mucinous tumours, serous tumours, endometrioid tumours, clear cell tumours, mixed tumours and “other” tumours (i.e. undifferentiated carcinoma, borderline malignancy, transitional cell carcinoma and malignant brenner’s tumour).

Descriptive statistics were first used to compare the sample characteristics between case and control groups. Unconditional logistic regression analyses were then performed to ascertain the association between anthropometric variables and the risk of ovarian cancer. Tests for linear trend were also conducted to assess the dose-response relationship between body size and ovarian cancer risk. Multivariate analysis included terms for age (continuous: years), oral contraceptive use (never, ever), parity (≤ 1, ≥ 2), menopausal status (pre, post), ovarian and/or breast cancer in a first degree relative (no, yes), age at menarche (continuous: years), smoking status (never, ever), and alcohol drinking (no, yes). Analyses in relation to height were also adjusted by weight, and analyses in relation to weight were also adjusted by height. These variables were either established or plausible risk factors from the literature.
3.8 Ethical considerations

Confidentiality

The confidentiality of all information obtained was ensured. Questionnaire and individual data were identified only by a confidential code. Only data aggregated for statistical purpose were being published. Records are and will be kept in locked cupboards for 5 years. Clearance has been sought from Curtin University's Human Research Ethics Committee, and the reference number of the approval letter is HR 78/2006. Data collection agreements from the four hospitals have been obtained. Throughout the study period, the privacy of the participants was protected at all times.

Consent

Subjects were informed about the aims and the confidentiality of the study. An information sheet and consent form was provided to each subject; see Appendix A. Written agreement to participate was obtained from each participant. After participants were in the study, they were able to withdraw at any time or terminate the interview without any negative consequences. An appointment for hospital-based interview was made after approval from each subject. Participation or non-participation of the ovarian cancer patients had no influence on their treatment in hospital.
CHAPTER 4

RESULTS

4.1 Overview

This chapter presents the results of the study. In section 4.2, univariate analyses are described, including comparisons of demographic characteristics, anthropometric factors, reproductive factors, lifestyle factors, dietary factors between cases and controls. Histologic subtypes of cases are also displayed. The results of multivariate analyses of tea consumption, habitual physical activity, breastfeeding and body size and risk of ovarian cancer are presented in section 4.3.

Materials presented in this chapter have been published or accepted for publication in the following journal articles:


Copies of these papers are included in Chapter 3, 4 and 5.

### 4.2 Univariate analysis

#### 4.2.1 Demographic characteristics

From the 1016 study subjects recruited, a total of 1000 eligible participants (500 cases and 500 controls) were available for analysis, the non-response rate being 1.6%. The relationship between the various risk factors and ovarian cancer risk was first examined in univariate models to identify risk factors that will qualify for the multivariate model. The general demographic characteristics of cases and controls were compared.

Table 4.1 shows the age distribution of study participants. As expected from the matched case-control study design, there were no significant differences between case and control groups with respect to age. The average age of cases and controls was 59 years. The highest incidence of ovarian cancer was in the 50–59 and 60-69 age groups and the majority of the patients were older than 50 years. Only 27 of total 500 ovarian cancer patients were younger than 40 years.

<table>
<thead>
<tr>
<th>Age group N (%)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>27 (5.4)</td>
<td>29 (5.8)</td>
</tr>
<tr>
<td>50-59</td>
<td>243 (48.6)</td>
<td>206 (41.2)</td>
</tr>
<tr>
<td>60-69</td>
<td>212 (42.4)</td>
<td>240 (48)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of participants</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>Age in years (mean ± S.D.)</td>
<td>59.1 ± 5.7</td>
<td>59.7± 6.5</td>
</tr>
<tr>
<td>Range</td>
<td>36</td>
<td>32</td>
</tr>
<tr>
<td>Min</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>Max</td>
<td>77</td>
<td>74</td>
</tr>
</tbody>
</table>

Table 4.1 Age (years): cases and controls
Table 4.2 gives the distribution of case and control groups according to employment status. No difference was observed between ovarian cancer patients and control subjects.

Table 4.2 Employment status: cases and controls

<table>
<thead>
<tr>
<th>Employment status</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unemployed/housewife</td>
<td>163 (32.6%)</td>
<td>169 (33.8%)</td>
</tr>
<tr>
<td>Working</td>
<td>337 (67.4%)</td>
<td>331 (66.2%)</td>
</tr>
</tbody>
</table>

$\chi^2 = 0.16, df = 1, p = 0.69$

Table 4.3 shows the location of residence for case and control groups. The two groups were similar with respect to the location of residence. Almost one third of the interviewed cases and controls were living in Guangzhou urban area. Both case and control groups were similar in minimum years of being resident in Guangdong province, which was or above 10 years (Table 4.4).

Table 4.3 Location of Residence: cases and controls

<table>
<thead>
<tr>
<th>Location of residence</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urban</td>
<td>362 (72.4%)</td>
<td>375 (75%)</td>
</tr>
<tr>
<td>Rural</td>
<td>138 (27.6%)</td>
<td>124 (24.8%)</td>
</tr>
</tbody>
</table>

$\chi^2 = 0.98, df = 1, p = 0.32$

Table 4.4 Years resident in Guangdong Province: cases and controls

<table>
<thead>
<tr>
<th>Years in GZ (mean ± S.D.)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years in GZ (mean ± S.D.)</td>
<td>51.0 ± 15.1</td>
<td>50.9 ± 15.7</td>
</tr>
<tr>
<td>Range</td>
<td>66</td>
<td>64</td>
</tr>
<tr>
<td>Min</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Max</td>
<td>77</td>
<td>74</td>
</tr>
</tbody>
</table>

$p = 0.90$

Table 4.5 displays the education distribution of cases and controls. The catalogue “Secondary” included junior and senior high school. Tertiary included vocational
school and college or university. Both case and control groups had similar level of education. The family history of various types of cancer was similar between ovarian cancer patients and control subjects. Table 4.6 and Table 4.7.

Table 4.5  Education: cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/ primary</td>
<td>204(40.8)</td>
<td>197(39.4)</td>
</tr>
<tr>
<td>Secondary</td>
<td>171(34.2)</td>
<td>175(35)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>125(25)</td>
<td>128(25.6)</td>
</tr>
</tbody>
</table>

χ²=0.20, df = 2, p=0.90

Table 4.6  History of ovarian cancer: cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of ovarian cancer N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian cancer in first degree relatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>486(92.7)</td>
<td>491(98.2)</td>
</tr>
<tr>
<td>Yes</td>
<td>14(2.8)</td>
<td>9(1.8)</td>
</tr>
</tbody>
</table>

χ²=1.11, df = 1, p=0.29

Table 4.7  History of breast cancer: cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of breast cancer N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer in first degree relatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>494(98.8)</td>
<td>494(98.8)</td>
</tr>
<tr>
<td>Yes</td>
<td>6(1.2)</td>
<td>6(1.2)</td>
</tr>
</tbody>
</table>

χ²=0.00, df = 1, p=1.00
4.2.2  Histologic subtypes

The distribution of histologic subtypes of ovarian tumours is shown in Table 4.8. Half of all case tumours were classified as serous, and mucinous tumours comprised 16% of the cases.

Table 4.8 Distribution of histologic subtypes of ovarian tumours

<table>
<thead>
<tr>
<th>Pathological diagnosis of epithelial ovarian cancer</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous cystadenocarcinoma</td>
<td>250 (50.0)</td>
</tr>
<tr>
<td>Mucinous cystadenocarcinoma</td>
<td>80 (16.0)</td>
</tr>
<tr>
<td>Endometrioid cystadenocarcinoma</td>
<td>19 (3.8)</td>
</tr>
<tr>
<td>Mixed epithelial cystadenocarcinoma</td>
<td>13 (2.6)</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>59 (11.8)</td>
</tr>
<tr>
<td>Borderline malignancy</td>
<td>65 (13.0)</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>Transitional cell carcinoma</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Malignant Brenner’s tumour</td>
<td>3 (0.6)</td>
</tr>
</tbody>
</table>

4.2.3  Anthropometric factors

Table 4.9 compares BMI, height and weight variables by case-control status. BMI and weight were both significantly higher among the cases, while the two groups were similar with respect to mean height.

Table 4.9 Comparison of body size variables between case and control groups

<table>
<thead>
<tr>
<th>Body size variable</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All mean (SD)</td>
<td>Serous mean (SD)</td>
</tr>
<tr>
<td>BMI (5 years ago, kg/m²)</td>
<td>21.70* (2.54)</td>
<td>21.82* (2.59)</td>
</tr>
<tr>
<td>Height (centimetres)</td>
<td>158.21 (4.43)</td>
<td>158.30 (4.57)</td>
</tr>
</tbody>
</table>
Weight (kilograms) | 54.26* (6.00) | 54.60* (6.24) | 53.46 (5.71) | 52.74 (5.82)

* p < 0.001 (t-test for difference between cases and controls)

4.2.4 Reproductive factors

Table 4.10 compares the marital status between case and control groups, which shows that the two groups were not significantly different in marital status. Both ovarian cancer patients and control subjects reported getting married at the same age as shown in Table 4.11.

Table 4.10 Marital status: cases and controls

<table>
<thead>
<tr>
<th>Marital status N (%)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never married</td>
<td>7(1.4)</td>
<td>8(1.6)</td>
</tr>
<tr>
<td>Married</td>
<td>449(89.8)</td>
<td>443(88.6)</td>
</tr>
<tr>
<td>Widowed/divorced/separated</td>
<td>44(8.8)</td>
<td>49(9.8)</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 0.38, \, df = 2, \, p=0.83 \]

Table 4.11 Age of marriage (Years): cases and controls

<table>
<thead>
<tr>
<th>Marriage age (years) (mean ± S.D.)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>Min</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Max</td>
<td>35</td>
<td>39</td>
</tr>
</tbody>
</table>

\[ p = 0.14 \]

Table 4.12 and Table 4.13 show the age at menarche and at regular menarche. Age at menarche in case participants (range 10–20 years and mean 14.68 years) did not differ significantly from that of the controls (range 10–22 years, mean 14.70 years). As shown in Table 4.14 and Table 4.15 both case and control groups were similar in their duration of menstruation and menstruation cycle.
Table 4.12  Age at menarche (Years): cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of menarche (years) (mean ± S.D.)</td>
<td>14.7 ± 1.6</td>
<td>14.7 ± 1.8</td>
</tr>
<tr>
<td>Range</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Min</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Max</td>
<td>20</td>
<td>22</td>
</tr>
</tbody>
</table>

p=0.88

Table 4.13  Age at menarche becoming regular (Years): cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of regular menarche (years) (mean ± S.D.)</td>
<td>15.8 ± 1.7</td>
<td>15.7 ± 2.1</td>
</tr>
<tr>
<td>Range</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Min</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Max</td>
<td>21</td>
<td>22</td>
</tr>
</tbody>
</table>

p=0.47

Table 4.14  Duration of menstruation (Days): cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of menstruation (days) (mean ± S.D.)</td>
<td>5.2 ± 1.1</td>
<td>5.2 ± 1.2</td>
</tr>
<tr>
<td>Range</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Min</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Max</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

p=0.58
Table 4.15  Menstruation cycle (Days): cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstruation cycle (mean ± S.D.)</td>
<td>29.0 ± 1.8</td>
<td>29.1 ± 2.1</td>
</tr>
<tr>
<td>Range</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Min</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Max</td>
<td>40</td>
<td>43</td>
</tr>
</tbody>
</table>

p=0.35

As shown in Table 4.16, no significant differences between cases and controls with respect to age at menopause have been found. Both cases and controls were predominantly post-menopausal. See Table 4.17.

Table 4.16  Age of menopause (Years): cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopause age (mean ± S.D.)</td>
<td>50 ± 2.8</td>
<td>49.7 ± 3.9</td>
</tr>
<tr>
<td>Range</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td>Min</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>Max</td>
<td>57</td>
<td>58</td>
</tr>
</tbody>
</table>

p=0.22

Table 4.17  Menopausal status: cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopausal status N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>28(5.6)</td>
<td>20(4.0)</td>
</tr>
<tr>
<td>Post</td>
<td>472(94.4)</td>
<td>480(96.0)</td>
</tr>
</tbody>
</table>

χ²=1.40, df = 1, p=0.24

The age at first full term pregnancy ranged from 17 to 38 years (mean 24.19 years) for the ovarian cancer patients and 17 to 41 years (mean 24.26 years) for the control participants. The two groups appeared to be similar with respect to the age at first full term pregnancy. See ).

Table 4.18. Women with epithelial ovarian cancer tended to have lower parities than their counterparts without the disease (p< 0.001) (Table 4.19).
Table 4.18  Age at first full term pregnancy (Years): cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first full term</td>
<td>24.6 ± 3.1</td>
<td>24.9 ± 3.4</td>
</tr>
<tr>
<td>pregnancy (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mean ± S.D.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>Min</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Max</td>
<td>38</td>
<td>41</td>
</tr>
</tbody>
</table>

p=0.19

Table 4.19  Parity: cases and controls

<table>
<thead>
<tr>
<th>Parity N (%)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8(1.6)</td>
<td>14(2.8)</td>
</tr>
<tr>
<td>1</td>
<td>172(34.4)</td>
<td>143(28.6)</td>
</tr>
<tr>
<td>2</td>
<td>219(43.8)</td>
<td>176(35.2)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>101(20.2)</td>
<td>167(33.4)</td>
</tr>
</tbody>
</table>

χ²=25.24, df = 3, p<0.001

Table 4.20 compares the breastfeeding patterns between cases and controls. Both duration of breastfeeding per child and total duration of breastfeeding were significantly greater among the controls. The number of children breastfed also differed significantly between groups, with fewer cases breastfeeding three or more children.
Table 4.20  Comparison of breastfeeding variables between case and control groups

<table>
<thead>
<tr>
<th>Breastfeeding outcome</th>
<th>Cases</th>
<th>Controls¹</th>
<th>Both</th>
<th>p²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children breastfed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>190</td>
<td>144</td>
<td>334</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(38.5%)</td>
<td>(30.5%)</td>
<td>(34.6%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>205</td>
<td>167</td>
<td>372</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(41.6%)</td>
<td>(35.4%)</td>
<td>(38.5%)</td>
<td></td>
</tr>
<tr>
<td>≥ 3</td>
<td>98</td>
<td>161</td>
<td>259</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(19.9%)</td>
<td>(34.1%)</td>
<td>(26.8%)</td>
<td></td>
</tr>
<tr>
<td>Mean duration of breastfeeding per child (SD): months</td>
<td>8.46</td>
<td>10.06</td>
<td>9.24</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(2.42)</td>
<td>(3.41)</td>
<td>(3.05)</td>
<td></td>
</tr>
<tr>
<td>Mean total duration of breastfeeding (SD): months</td>
<td>16.33</td>
<td>23.65</td>
<td>19.91</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(10.96)</td>
<td>(17.12)</td>
<td>(14.76)</td>
<td></td>
</tr>
</tbody>
</table>

¹6 controls with parity ≥ 1 but no breastfed children excluded from analysis

² chi-square or t-test for difference between cases and controls

There was a significant difference between patients with ovarian cancer and control group with respect to oral contraceptive use. Ovarian cancer patients tended to have less oral contraceptive use than women without the disease. See Table 4.21.

Table 4.21  Oral contraceptive use: cases and controls

<table>
<thead>
<tr>
<th>Oral contraceptive use N (%)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>417(83.4)</td>
<td>380(76)</td>
</tr>
<tr>
<td>Ever</td>
<td>83(16.6)</td>
<td>120(24)</td>
</tr>
</tbody>
</table>

χ² = 8.46 , df = 1, p = 0.004

As shown in Table 4.22 and Table 4.23, no significant differences between cases and controls with respect to hormone replacement therapy and hysterectomy have been found.
Table 4.22  Hormone replacement therapy: cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone replacement therapy N (%)</td>
<td>493(98.6)</td>
<td>493(98.6)</td>
</tr>
<tr>
<td>No</td>
<td>7(1.4)</td>
<td>7(1.4)</td>
</tr>
</tbody>
</table>

\(\chi^2 = 0.00\), df = 1, p=1.00

Table 4.23 Hysterectomy: cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterectomy N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>478(95.6)</td>
<td>477(95.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>22(4.4)</td>
<td>23(4.6)</td>
</tr>
</tbody>
</table>

\(\chi^2 = 0.02\), df = 1, p=0.88

4.2.5 Lifestyle factors

*Physical activity*

The effect of physical activity on ovarian cancer was assessed by two main indicators: sedentary activity and physical activity. Three-level (low, medium, and high) indexes, which were used in previous studies, were adopted to represent the intensity of sitting both at work and outside work respectively (Dosemeci et al., 1993). Table 4.24 provides total time of spending on sedentary activities presented in hours per day. There was no significant difference in total sitting duration between the two groups. The information of time spent in sedentary activities (sitting at work and outwork) in cases and controls is presented in Table 4.25, Table 4.26, Table 4.27, Table 4.28 and Table 4.29 separately. Compared with controls, more cases tended to spend less time in sitting in a car or bus and eating (p=0.05, p=0.02 respectively).
Table 4.24  Total sitting duration per day (hours) (Mean ± S.D): cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sitting duration per day (hours) (mean ± S.D.)</td>
<td>7.2 ± 4.2</td>
<td>6.9± 4.3</td>
</tr>
<tr>
<td>Range</td>
<td>20.5</td>
<td>25</td>
</tr>
<tr>
<td>Min</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>Max</td>
<td>21</td>
<td>25.5</td>
</tr>
</tbody>
</table>

p=0.35

Table 4.25  Time spent in sitting in a car or bus per day (hours): cases and controls

<table>
<thead>
<tr>
<th>Sitting in a car or bus (hours)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>215(43)</td>
<td>246(49.2)</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>273(54.6)</td>
<td>241(48.2)</td>
</tr>
<tr>
<td>2-6</td>
<td>12(2.4)</td>
<td>11(2.2)</td>
</tr>
<tr>
<td>&gt;6</td>
<td>0(0)</td>
<td>2(.4)</td>
</tr>
</tbody>
</table>

χ²=11.22, df = 5, p=0.05

Table 4.26  Time spent in sitting at work per day (hours): cases and controls

<table>
<thead>
<tr>
<th>Sitting at work (hours)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>165(33)</td>
<td>202(40.4)</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>129(25.8)</td>
<td>90(18.0)</td>
</tr>
<tr>
<td>2-6</td>
<td>140(28.0)</td>
<td>142(28.4)</td>
</tr>
<tr>
<td>&gt;6</td>
<td>66(12.9)</td>
<td>66(12.9)</td>
</tr>
</tbody>
</table>

χ²=11.34, df = 6, p=0.08

Table 4.27  Time spent in sitting in watching television per day (hours) : cases and controls

<table>
<thead>
<tr>
<th>Sitting in watching television or movie (hours)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>13(2.6)</td>
<td>15(3.0)</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>306(61.2)</td>
<td>315(63.0)</td>
</tr>
<tr>
<td>2-6</td>
<td>171(34.2)</td>
<td>159(31.8)</td>
</tr>
<tr>
<td>&gt;6</td>
<td>10(2.0)</td>
<td>11(2.2)</td>
</tr>
</tbody>
</table>
Table 4.28  Time spent in sitting in eating per day (hours): cases and controls

<table>
<thead>
<tr>
<th>Sitting in eating (hours)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>2(4%)</td>
<td>11(2.2)</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>480(96.0)</td>
<td>469(93.8)</td>
</tr>
<tr>
<td>2-6</td>
<td>18(3.6)</td>
<td>20(4.0)</td>
</tr>
<tr>
<td>&gt;6</td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 2.57, df = 5, p=0.77 \]

Table 4.29  Time spent in sitting at other activities per day: cases and controls

<table>
<thead>
<tr>
<th>Other sitting activities (hours)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>169(33.8)</td>
<td>204(40.8)</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>273(54.6)</td>
<td>232(46.4)</td>
</tr>
<tr>
<td>2-6</td>
<td>52(10.4)</td>
<td>61(12.2)</td>
</tr>
<tr>
<td>&gt;6</td>
<td>6(1.0)</td>
<td>3(.5)</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 9.41, df = 3, p=0.02 \]

Total physical activity among case and control groups is presented in MET-hours per week. Total physical activity was defined in chapter 3, as the total time spent on strenuous sports, vigorous work and moderate activity. Table 4.30, Table 4.31, Table 4.32 and Table 4.33 shows the propensity and intensity of habitual physical activity engagement by the cases and controls. The low prevalence of strenuous sports was expected for these older women. Fewer cases participated in strenuous sports and vigorous work and generally they had lower levels of physical activity exposure when compared with the control subjects.
Table 4.30  Total physical activity per week (MET-hours): cases and controls

<table>
<thead>
<tr>
<th>Activity</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total physical activity per week (MET-hours) (mean ± S.D.)</td>
<td>16.2 ± 14.1</td>
<td>18.8 ± 13.0</td>
</tr>
<tr>
<td>Range</td>
<td>114.75</td>
<td>84.75</td>
</tr>
<tr>
<td>Min</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Max</td>
<td>114.75</td>
<td>84.75</td>
</tr>
</tbody>
</table>

p<0.001

Table 4.31 Strenuous sports per week (MET-hours): cases and controls

<table>
<thead>
<tr>
<th>Activity</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>mean (SD)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Strenuous sports</td>
<td>47 (9.4)</td>
<td>0.6 (2.3)</td>
</tr>
</tbody>
</table>

p=0.03

Table 4.32  Vigorous work per week (MET-hours): cases and controls

<table>
<thead>
<tr>
<th>Activity</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>mean (SD)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Vigorous work</td>
<td>133 (26.6)</td>
<td>2.6 (7.0)</td>
</tr>
</tbody>
</table>

p=0.35

Table 4.33  Moderate activity per week (MET-hours): cases and controls

<table>
<thead>
<tr>
<th>Activity</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>mean (SD)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Moderate activity</td>
<td>497 (99.4)</td>
<td>12.93 (12.2)</td>
</tr>
</tbody>
</table>

p=0.01

_Tobacco smoking and alcohol drinking_

Table 4.34, Table 4.35 and Table 4.36 provide information on several aspects of tobacco smoking. The two groups appeared to be similar in terms of tobacco smoking. Cigarette smoking was not a common practice among study participants as
only 3.8% cases and 3.0% controls reported having smoked cigarettes ever and few current smokers were reported. Among the ever smokers, the majority of them smoked occasionally 1-2 cigarettes daily. As shown in Table 4.37, the two groups appeared to be similar with respect to alcohol drinking.

Table 4.34 Tobacco smoking: cases and controls

<table>
<thead>
<tr>
<th>Tobacco smoking N (%)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>481(96.2)</td>
<td>485(97.0)</td>
</tr>
<tr>
<td>Ever</td>
<td>19(3.8)</td>
<td>15(3.0)</td>
</tr>
</tbody>
</table>

$\chi^2=0.49, df = 1, p=0.49$

Table 4.35 Current smoking status: cases and controls

<table>
<thead>
<tr>
<th>Smoking now N (%)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>495(99.0)</td>
<td>493(98.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>5(1.0)</td>
<td>7(1.4)</td>
</tr>
</tbody>
</table>

$\chi^2=0.34, df = 1, p=0.56$

Table 4.36 Number of cigarettes smoked per day: cases and controls

<table>
<thead>
<tr>
<th>Cigarettes no. per day N (%)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occasional 1-2</td>
<td>11(2.2)</td>
<td>10(2.0)</td>
</tr>
<tr>
<td>1-4</td>
<td>1(.2)</td>
<td>3(.6)</td>
</tr>
<tr>
<td>5-9</td>
<td>0(0)</td>
<td>2(.4)</td>
</tr>
</tbody>
</table>

$\chi^2=3.06, df = 3, p=0.38$
Table 4.37 Alcohol drinking: cases and controls

<table>
<thead>
<tr>
<th>Alcohol drinking N (%)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>352(70.4)</td>
<td>372(74.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>148(29.6)</td>
<td>128(25.6)</td>
</tr>
</tbody>
</table>

$\chi^2 = 2.00, df = 1, p=0.16$

4.2.6 Dietary factors

Tea drinking

Table 4.38 compares the habitual tea consumption pattern between cases and controls. Among the tea drinkers, about 60% regularly drank green tea in combination with oolong tea and/or black tea. This mixed tea drinking habit appeared to be consistent for women in both groups, but the overall prevalence of tea drinking (irrespective of tea type) was apparently higher among the controls (78.8%) than the cases (51.4%). Moreover, the tea consumption levels of controls were about 35% greater than those of ovarian cancer patients, whose average cumulative exposure to tea drinking was 22.7 years and 18.3 years, respectively.

Table 4.38 Comparison of tea consumption variables between case and control groups

<table>
<thead>
<tr>
<th>Tea consumption</th>
<th>Cases</th>
<th>Controls</th>
<th>Total</th>
<th>p^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tea drinking: n</td>
<td>257 (51.4%)</td>
<td>394 (78.8%)</td>
<td>651 (65.1%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Green tea drinking: nb</td>
<td>156</td>
<td>233</td>
<td>389</td>
<td></td>
</tr>
<tr>
<td>Oolong tea drinking: nb</td>
<td>134</td>
<td>216</td>
<td>350</td>
<td></td>
</tr>
<tr>
<td>Black tea drinking: nb</td>
<td>53</td>
<td>93</td>
<td>146</td>
<td></td>
</tr>
<tr>
<td>Tea drinkers only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean duration of drinking (SD): years</td>
<td>18.3 (9.4)</td>
<td>22.7 (11.3)</td>
<td>21.0 (10.8)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Mean tea leaves used (SD): grams/year</td>
<td>710.6 (790.8)</td>
<td>974.5 (1052.8)</td>
<td>870.3 (966.0)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>
Mean quantity consumed (SD): ml/week

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>2189</td>
<td>2922</td>
<td>2633</td>
</tr>
<tr>
<td>(1846)</td>
<td>(2110)</td>
<td>(2040)</td>
</tr>
</tbody>
</table>

< 0.01

Frequency of intake: cups/day

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>79 (30.7%)</td>
<td>92 (23.4%)</td>
</tr>
<tr>
<td>1-3</td>
<td>122 (47.5%)</td>
<td>148 (37.6%)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>56 (21.8%)</td>
<td>154 (39.1%)</td>
</tr>
</tbody>
</table>

< 0.01

\(^a\) Chi-square or t-test for difference between cases and controls

\(^b\) not mutually exclusive

As shown in Table 4.39 and Table 4.40, more control subjects appeared to use a larger size of teacup and teapot compared with patients with ovarian cancer (p<0.001).

Table 4.39 Size of tea pot: cases and controls

<table>
<thead>
<tr>
<th>Size of tea pot N (%)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not applicable</td>
<td>236(47.2)</td>
<td>106(21.2)</td>
</tr>
<tr>
<td>Small</td>
<td>74(14.8)</td>
<td>91(18.2)</td>
</tr>
<tr>
<td>Middle</td>
<td>164(32.8)</td>
<td>255(51.0)</td>
</tr>
<tr>
<td>Big</td>
<td>26(5.2)</td>
<td>48(9.6)</td>
</tr>
</tbody>
</table>

\(\chi^2=77.47, \text{ df } = 3, \text{ p}<0.001\)

Table 4.40 Size of tea cup: cases and controls

<table>
<thead>
<tr>
<th>Size of tea cup N (%)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not applicable</td>
<td>235(47)</td>
<td>106(21.2)</td>
</tr>
<tr>
<td>Small</td>
<td>86(17.2)</td>
<td>102(20.4)</td>
</tr>
<tr>
<td>Middle</td>
<td>141(28.2)</td>
<td>229(45.8)</td>
</tr>
<tr>
<td>Big</td>
<td>37(7.4)</td>
<td>62(12.4)</td>
</tr>
</tbody>
</table>

\(\chi^2=77.41, \text{ df } = 4, \text{ p}<0.001\)

Size of tea cups
Small = 100mls
Medium = 180 ml
Large = 250mls
*Soy bean products intake*

Table 4.41, Table 4.42, Table 4.43 and Table 4.44 display data for daily intake of soybean products including soybean, soy milk, tofu and dried tofu among cases and controls. The consumption of those four main types of soy foods, namely soybean ((p=0.001), soy milk (p<0.001), tofu (p=0.003) and dried tofu (p=0.001) were significant lower among ovarian cancer patients than control subjects.

Table 4.41 Mean quantity of soybean consumed per day (grams): cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soy bean consumed per day (grams) (mean ± S.D.)</td>
<td>6.3 ± 9.3</td>
<td>9.5 ± 18.4</td>
</tr>
<tr>
<td>Range</td>
<td>95.14</td>
<td>184.88</td>
</tr>
<tr>
<td>Min</td>
<td>2.63</td>
<td>2.63</td>
</tr>
<tr>
<td>Max</td>
<td>97.76</td>
<td>187.5</td>
</tr>
</tbody>
</table>

p=0.001

Table 4.42 Mean quantity of soy milk (mls) consumed per day: cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soy milk consumed per day (mls) (mean ± S.D.)</td>
<td>24.5 ± 36.4</td>
<td>38.1 ± 48.0</td>
</tr>
<tr>
<td>Range</td>
<td>311.85</td>
<td>293.85</td>
</tr>
<tr>
<td>Min</td>
<td>3.15</td>
<td>3.15</td>
</tr>
<tr>
<td>Max</td>
<td>315</td>
<td>297</td>
</tr>
</tbody>
</table>

p <0.001

Table 4.43 Mean quantity of tofu consumed per day (grams): cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofu consumed per day (grams) (mean ± S.D.)</td>
<td>7.2 ± 9.8</td>
<td>12.9 ± 21.0</td>
</tr>
<tr>
<td>Range</td>
<td>50.74</td>
<td>198.60</td>
</tr>
<tr>
<td>Min</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Max</td>
<td>52.14</td>
<td>200</td>
</tr>
</tbody>
</table>

p =0.003
Table 4.44 Mean quantity of dried tofu consumed (grams) per day: cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dried tofu consumed per day (grams) (mean ± S.D.)</td>
<td>7.2 ± 7.9</td>
<td>12.2 ± 22.2</td>
</tr>
<tr>
<td>Range</td>
<td>45.00</td>
<td>119.06</td>
</tr>
<tr>
<td>Min</td>
<td>4.38</td>
<td>4.38</td>
</tr>
<tr>
<td>Max</td>
<td>49.38</td>
<td>123.44</td>
</tr>
</tbody>
</table>

p=0.001

4.3 Multivariate analysis

*Tea drinking and risk of ovarian cancer*

Table 4.45 summarises the results of logistic regression analyses in relation to tea consumption. Overall, regular tea drinking was associated with a lower risk of ovarian cancer, the adjusted OR being 0.29 (95% CI 0.22 to 0.39) after accounting for plausible confounding factors. When compared with non-drinkers, apparent inverse dose-response relationships were observed for all aspects of tea exposure, namely, duration of drinking (years), frequency (number of cups) and quantity (ml) of tea consumed, and the amount of dried tea leaves brewed. In particular, the greatest reduction in ovarian cancer risk could be achieved by long term tea drinking over 30 years. Among the confounding factors, both parity and oral contraceptive use were associated with the ovarian cancer risk (p < 0.01).
Table 4.45 Crude and adjusted odds ratios (95% confidence intervals) of ovarian cancer risk for tea consumption in southern Chinese women

<table>
<thead>
<tr>
<th>Tea consumption</th>
<th>Cases n (%)</th>
<th>Controls n (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR\textsuperscript{a} (95% CI)</th>
<th>Test for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tea drinking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>243 (48.6)</td>
<td>106 (21.2)</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>257 (51.4)</td>
<td>394 (78.8)</td>
<td>0.29 (0.22, 0.38)</td>
<td>0.29 (0.22, 0.39)</td>
<td>67.73\textsuperscript{b}</td>
</tr>
<tr>
<td>Duration of drinking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>243 (48.6)</td>
<td>106 (21.2)</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>\leq 20</td>
<td>172 (34.4)</td>
<td>202 (40.4)</td>
<td>0.37 (0.27, 0.50)</td>
<td>0.38 (0.27, 0.52)</td>
<td>80.06\textsuperscript{b}</td>
</tr>
<tr>
<td>21-30</td>
<td>76 (15.2)</td>
<td>118 (23.6)</td>
<td>0.28 (0.20, 0.41)</td>
<td>0.29 (0.20, 0.43)</td>
<td></td>
</tr>
<tr>
<td>\geq 31</td>
<td>9 (1.8)</td>
<td>74 (14.8)</td>
<td>0.05 (0.03, 0.11)</td>
<td>0.06 (0.03, 0.13)</td>
<td></td>
</tr>
<tr>
<td>Frequency of intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cups/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>79.12\textsuperscript{b}</td>
</tr>
<tr>
<td>0</td>
<td>243 (48.6)</td>
<td>106 (21.2)</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>79 (15.8)</td>
<td>92 (18.4)</td>
<td>0.38 (0.26, 0.55)</td>
<td>0.37 (0.25, 0.54)</td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>122 (24.4)</td>
<td>148 (29.6)</td>
<td>0.36 (0.26, 0.50)</td>
<td>0.36 (0.25, 0.51)</td>
<td></td>
</tr>
<tr>
<td>\geq 4</td>
<td>56 (11.2)</td>
<td>154 (30.8)</td>
<td>0.16 (0.11, 0.23)</td>
<td>0.18 (0.12, 0.27)</td>
<td></td>
</tr>
<tr>
<td>Quantity consumed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50.05\textsuperscript{b}</td>
</tr>
<tr>
<td>(ml/week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4.46 presents the logistic regression results. Significant inverse association with the ovarian cancer incidence was evident for strenuous sports and moderate activity but not vigorous work. For total physical activity exposure, the ovarian cancer risk reduced to half for engaging in 23 or more MET-hours relative to less than 12 MET-hours per week. The corresponding dose-response relationship was also significant. However, the slight increase in cancer risk for a longer sitting duration did not attain statistical significance.
Table 4.46 Crude and adjusted odds ratios (OR, 95% confidence intervals) of ovarian cancer risk for physical activity in southern Chinese women, 2006-2008

<table>
<thead>
<tr>
<th>Activity</th>
<th>Cases n (%)</th>
<th>Controls n (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR&lt;sup&gt;a&lt;/sup&gt; (95% CI)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strenuous sports (MET-hours/week)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>0</td>
<td>453 (90.6)</td>
<td>428 (85.6)</td>
<td>1.00 (1.00)</td>
<td>1.00 (1.00)</td>
<td></td>
</tr>
<tr>
<td>&lt; 6</td>
<td>43 (8.6)</td>
<td>65 (13.0)</td>
<td>0.63 (0.42-0.94)</td>
<td>0.58 (0.38-0.88)</td>
<td></td>
</tr>
<tr>
<td>≥ 6</td>
<td>4 (0.8)</td>
<td>7 (1.4)</td>
<td>0.54 (0.16-1.86)</td>
<td>0.40 (0.11-1.44)</td>
<td></td>
</tr>
<tr>
<td><strong>Vigorous work (MET-hours/week)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>0</td>
<td>367 (73.4)</td>
<td>333 (66.6)</td>
<td>1.00 (1.00)</td>
<td>1.00 (1.00)</td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>85 (17.0)</td>
<td>98 (19.6)</td>
<td>0.79 (0.57-1.09)</td>
<td>0.89 (0.63-1.25)</td>
<td></td>
</tr>
<tr>
<td>≥ 5</td>
<td>48 (9.6)</td>
<td>69 (13.8)</td>
<td>0.63 (0.42-0.94)</td>
<td>0.81 (0.53-1.25)</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate activity (MET-hours/week)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>0</td>
<td>3 (0.6)</td>
<td>1 (0.2)</td>
<td>1.00 (1.00)</td>
<td>1.00 (1.00)</td>
<td></td>
</tr>
<tr>
<td>&lt; 11.5</td>
<td>370 (74.0)</td>
<td>333 (66.6)</td>
<td>0.37 (0.04-3.58)</td>
<td>0.14 (0.01-1.53)</td>
<td></td>
</tr>
<tr>
<td>≥ 11.5</td>
<td>127 (25.4)</td>
<td>166 (33.2)</td>
<td>0.57 (0.03-2.48)</td>
<td>0.10 (0.01-1.06)</td>
<td></td>
</tr>
<tr>
<td><strong>Total physical activity (MET-hours/week)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>&lt; 12</td>
<td>287 (57.4)</td>
<td>226 (45.2)</td>
<td>1.00 (1.00)</td>
<td>1.00 (1.00)</td>
<td></td>
</tr>
</tbody>
</table>
Breastfeeding and risk of ovarian cancer

The logistic regression results in relation to breastfeeding are presented in Table 4.47. There was a strong inverse association between lactation and ovarian cancer, with a four-fold protective effect observed for duration of breastfeeding. The adjusted OR was 0.37 (95% CI 0.22 to 0.62) for women whose average lactation per child was 13 months or more, compared with those with 7 months or less lactation per child. The estimated OR for women with at least 31 months of total lactation, compared to those with 10 months or less lactation was 0.09 (95% CI 0.04 to 0.19). A reduced risk was evident for women breastfeeding three or more children, compared to those with only one child breastfed (adjusted OR 0.38, 95% CI 0.27 to 0.55). The corresponding dose-response relationships were also significant (p < 0.01).

Table 4.47 Crude and adjusted odds ratios (95% confidence intervals) of ovarian cancer risk for lactation in southern Chinese women with at least one live birth

<table>
<thead>
<tr>
<th>Breastfeeding outcome</th>
<th>Cases</th>
<th>Controls</th>
<th>Crude OR</th>
<th>Adjusted OR</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-22</td>
<td>133</td>
<td>133</td>
<td>0.79</td>
<td>0.82</td>
<td>(0.59-1.06)</td>
</tr>
<tr>
<td>≥ 23</td>
<td>80</td>
<td>141</td>
<td>0.45</td>
<td>0.49</td>
<td>(0.32-0.62)</td>
</tr>
<tr>
<td>Sitting (hours/day)</td>
<td>0.94</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 4</td>
<td>159</td>
<td>175</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>(31.8)</td>
<td>(35.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.5-8</td>
<td>152</td>
<td>156</td>
<td>1.07</td>
<td>1.01</td>
<td>(0.79-1.46)</td>
</tr>
<tr>
<td>(30.4)</td>
<td>(31.2)</td>
<td></td>
<td></td>
<td></td>
<td>(0.73-1.41)</td>
</tr>
<tr>
<td>≥ 8.5</td>
<td>189</td>
<td>169</td>
<td>1.23</td>
<td>1.07</td>
<td>(0.91-1.66)</td>
</tr>
<tr>
<td>(37.8)</td>
<td>(33.8)</td>
<td></td>
<td></td>
<td></td>
<td>(0.77-1.48)</td>
</tr>
</tbody>
</table>

* Estimates from separate logistic regression models adjusting for age (years), parity, oral contraceptive use (never, ever), body mass index (5 years ago), menopausal status (pre, post), education level (none/primary, secondary, tertiary), smoking status (never, ever), family history of ovarian or breast cancer (no, yes).
<table>
<thead>
<tr>
<th>Number of children breastfed&lt;sup&gt;3&lt;/sup&gt;</th>
<th>n (%)</th>
<th>n (%)</th>
<th>(95% CI)</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>190</td>
<td>144</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>(38.5)</td>
<td>(30.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>205</td>
<td>167</td>
<td>0.93</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>(41.6)</td>
<td>(35.4)</td>
<td>(0.69, 1.25)</td>
<td>(0.62, 1.15)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>98</td>
<td>161</td>
<td>0.46</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>(19.9)</td>
<td>(34.1)</td>
<td>(0.33, 0.64)</td>
<td>(0.27, 0.55)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Average duration of breastfeeding per child (months)</th>
<th>&lt; 0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 7</td>
<td>178</td>
</tr>
<tr>
<td></td>
<td>(36.1)</td>
</tr>
<tr>
<td>8-10</td>
<td>240</td>
</tr>
<tr>
<td></td>
<td>(48.7)</td>
</tr>
<tr>
<td>11-12</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>(9.1)</td>
</tr>
<tr>
<td>≥ 13</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>(6.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total duration of breastfeeding (months)</th>
<th>&lt; 0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10</td>
<td>182</td>
</tr>
<tr>
<td></td>
<td>(36.9)</td>
</tr>
<tr>
<td>11-20</td>
<td>203</td>
</tr>
<tr>
<td></td>
<td>(41.2)</td>
</tr>
<tr>
<td>21-30</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>(15.8)</td>
</tr>
<tr>
<td>≥ 31</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>(6.1)</td>
</tr>
</tbody>
</table>
16 controls with parity ≥ 1 but no breastfed children excluded from analysis

Estimates from separate logistic regression models include terms for age at interview (continuous: years), parity, oral contraceptive use (never, ever), ovarian and/or breast cancer in a first degree relative (no, yes), education (none/primary, secondary, vocational/tertiary), menopausal status (pre, post), alcohol drinking (no, yes), smoking status (never, ever).

Adjustment made for all variables listed above, except parity.

Body size and risk of ovarian cancer

Table 4.48 presents the logistic regression results for each anthropometric variable. Analyses were not performed for endometrioid, mixed and clear cell subtypes due to the low number of cases available. Ovarian cancer risk increased with greater body weight and BMI. The adjusted odds ratios (ORs) were 1.84 (95% confidence interval (CI) 1.34-2.54) for body weight > 55 kg versus ≤ 50 kg and 1.77 (95% CI 1.04-3.02) for BMI ≥ 23 kg/m² versus < 18.5 kg/m² at 5 years before diagnosis. Significant dose-response relationships were also observed for weight and BMI (p < 0.01). Higher BMI was associated with a significantly increased risk for serous tumours (OR 1.98, 95% CI 1.33-2.95), mucinous tumours (OR 1.84, 95% CI 1.00-3.38) and tumours of other histologic subtypes (OR 1.64, 95% CI 1.01-2.66). Height was associated with a non-significant decreased risk of ovarian cancer overall, with similar results observed for serous tumours and other histologic subtypes. When analysis was restricted to post-menopausal women only, similar results were obtained; adjusted ORs of 1.90 (95% CI 1.37-2.64) and 1.84 (95% CI 1.07-3.17) in those women who had body weight > 55 kg and BMI ≥ 23 kg/m² compared with women having body weight ≤ 50 kg and BMI < 18.5 kg/m².

Table 4.48 Adjusted odds ratios (95% confidence intervals) of ovarian cancer risk for body size in southern Chinese women

<table>
<thead>
<tr>
<th>Body size variable</th>
<th>Cases All (n = 500)</th>
<th>Serous (n = 250)</th>
<th>Mucinous (n = 80)</th>
<th>Controls n (%)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (5 years ago, kg/m2): Asian population cut-off</td>
<td>Adjusted ORa (95% CI)</td>
<td>Adjusted ORa (95% CI)</td>
<td>Adjusted ORa (95% CI)</td>
<td>n (%)</td>
<td>Adjusted ORa (95% CI)</td>
</tr>
<tr>
<td>≤ 18.49</td>
<td>36</td>
<td>1.00</td>
<td>15</td>
<td>1.00</td>
<td>8</td>
</tr>
<tr>
<td>&gt; 18.49</td>
<td>164</td>
<td>2.00</td>
<td>75</td>
<td>2.28</td>
<td>22</td>
</tr>
</tbody>
</table>

0.27)
In summary, regular drinking of green tea, black tea and/or oolong tea was associated with a lower risk of ovarian cancer. Apparent inverse dose-response relationships were observed for years of drinking, number of cups and quantity of tea consumed, as well as amount of dried tea leaves brewed (p < 0.01). Increased engagement in leisure time activities was associated with reduced cancer risks after adjustment for confounding factors. Significant inverse dose-response relationships were found for both duration of lactation and number of children breastfed. A significant increase in

\[ \text{BMI (5 years ago, kg/m}^2\text{): tertiles} \]

\[ \leq 20.00 \]

\[ 121 \quad (24.2) \]

\[ 1.00 \]

\[ 55 \quad (22.0) \]

\[ 1.00 \]

\[ 19 \quad (23.8) \]

\[ 1.00 \]

\[ 168 \quad (33.6) \]

\[ 20.01-21.88 \]

\[ 158 \quad (31.6) \]

\[ 1.24 \]

\[ (0.89, 1.72) \]

\[ 83 \quad (33.2) \]

\[ 1.47 \]

\[ (0.97, 2.22) \]

\[ 26 \quad (32.5) \]

\[ 1.31 \]

\[ (0.69, 2.49) \]

\[ 163 \quad (32.6) \]

\[ \geq 21.89 \]

\[ 221 \quad (44.2) \]

\[ 1.75 \]

\[ (1.28, 2.40) \]

\[ 112 \quad (44.8) \]

\[ 1.98 \]

\[ (1.33, 2.95) \]

\[ 35 \quad (43.8) \]

\[ 1.84 \]

\[ (1.00, 3.38) \]

\[ 169 \quad (33.8) \]

\[ \text{Height (cm): tertiles} \]

\[ \leq 156 \]

\[ 165 \quad (33.0) \]

\[ 1.00 \]

\[ 82 \quad (32.8) \]

\[ 1.00 \]

\[ 24 \quad (30.0) \]

\[ 1.00 \]

\[ 164 \quad (32.8) \]

\[ 157-160 \]

\[ 216 \quad (43.2) \]

\[ 0.86 \]

\[ (0.63, 1.17) \]

\[ 110 \quad (44.0) \]

\[ 0.83 \]

\[ (0.57, 1.21) \]

\[ 34 \quad (42.5) \]

\[ 0.94 \]

\[ (0.52, 1.71) \]

\[ 213 \quad (42.6) \]

\[ \geq 161 \]

\[ 119 \quad (23.8) \]

\[ 0.76 \]

\[ (0.53, 1.08) \]

\[ 58 \quad (23.2) \]

\[ 0.66 \]

\[ (0.42, 1.03) \]

\[ 22 \quad (27.5) \]

\[ 1.04 \]

\[ (0.54, 2.02) \]

\[ 123 \quad (24.6) \]

\[ \text{Weight (kg): tertiles} \]

\[ \leq 50 \]

\[ 162 \quad (32.4) \]

\[ 1.00 \]

\[ 74 \quad (29.6) \]

\[ 1.00 \]

\[ 27 \quad (33.8) \]

\[ 1.00 \]

\[ 208 \quad (41.6) \]

\[ 50.1-55 \]

\[ 151 \quad (30.2) \]

\[ 1.14 \]

\[ (0.83, 1.56) \]

\[ 76 \quad (30.4) \]

\[ 1.50 \]

\[ (0.88, 1.95) \]

\[ 26 \quad (32.5) \]

\[ 1.21 \]

\[ (0.66, 2.20) \]

\[ 164 \quad (32.8) \]

\[ \geq 55.1 \]

\[ 187 \quad (37.4) \]

\[ 1.84 \]

\[ (1.34, 2.54) \]

\[ 100 \quad (40.0) \]

\[ 2.23 \]

\[ (1.50, 3.33) \]

\[ 27 \quad (33.8) \]

\[ 1.67 \]

\[ (0.91, 3.06) \]

\[ 128 \quad (25.6) \]

\[ a \text{ Estimates from logistic regression models include terms for age, oral contraceptive use, parity, menopausal status, ovarian and/or breast cancer in a first degree relative, age at menarche, smoking status, alcohol drinking.} \]

\[ b \text{ Additional adjustment for weight} \]

\[ c \text{ Additional adjustment for height} \]
ovarian cancer risk was observed for higher body weight and body mass index (BMI).
CHAPTER 5

DISCUSSION

5.1 Overview

The aims of this study were to evaluate the role of dietary, lifestyle and reproductive risk factors in the aetiology of ovarian cancer among the Guangdong population in China. In this chapter, the study findings are discussed and limitations and conclusions of the study are presented. In section 5.2, the observed association between tea consumption and the risk of ovarian cancer is discussed. In section 5.3, the observed association between habitual physical activity and the risk of ovarian cancer is discussed. In section 5.4, the observed association between breastfeeding and the risk of ovarian cancer is discussed. In section 5.5, the observed association between body size and the risk of ovarian cancer is discussed. Limitations, potential bias are given in section 5.6. The conclusions in section 5.7 summarize the significance of the findings.

Materials presented in this chapter have been published or accepted for publication in the following journal articles:


Copies of these papers are included in Chapter 3, 4 and 5.

### 5.2 Tea consumption and ovarian cancer risk

This is the first reported study to document in detail the association between tea consumption and the ovarian cancer risk in southern Chinese women. All cases included in the study were histologically confirmed incident ovarian cancer patients, and all controls had been carefully screened and subsequently confirmed with pathology to avoid misclassification of the case-control status. Another strength of the study was that accurate measurements on long term tea exposure were made using a validated and reliable questionnaire specifically developed for the southern Chinese population. In addition to recording the frequency of intake, information was also obtained on duration of drinking and average amount of dried tea leaves brewed. These exposure measures are important to determine and ascertain the effect of habitual tea consumption.

It is possible that some ovarian cancer patients may restrict their tea intake since the onset of the disease. To avoid reverse causation, the reference period for habitual tea consumption was set at five years before diagnosis for cases and five years before interview for controls. Indeed, the average duration of tea drinking was about 21 years among the 651 tea drinkers in our sample, and none of them reported any change in drinking habits within the past five years. However, the separate effects of green tea, black tea and oolong tea could not be determined due to the mixed tea drinking behaviours of the southern Chinese women.
Our results have indicated an inverse association between regular tea consumption and the risk of ovarian cancer. Moreover, apparent inverse dose-response relationships were found for all aspects of tea exposure including years of drinking, number of cups and quantity consumed, and the amount of tea leaves brewed. The protective effect of tea and its components is supported by a growing body of literature from experimental studies. Previous animal and in vitro studies and clinical trials have demonstrated that polyphenols and other antioxidant compounds contained in tea can inhibit carcinogenesis in a variety of organs (Patel, Ingle & Maru, 2008; Patel et al., 2008; Manna et al., 2009). As summarised by recent reviews, tea polyphenols, particularly epigallocatechin-3-gallate (EGCG), suppress enzyme activities and signal transduction pathways, limiting cell proliferation and inducing apoptosis. Tea polyphenols have been shown to inhibit cell invasion, proteasome activity, angiogenesis and metastasis (Yang et al., 2006; Chen & Zhang, 2007; Yang et al., 2009).

This study suggests that tea consumption is associated with a lower risk of ovarian cancer, and the risk can be further reduced by a longer term or higher dose of tea exposure. The findings are consistent with those from our previous case-control study undertaken in Hangzhou, China (Zhang et al., 2002), where the adjusted OR was 0.39 (95% CI 0.27 to 0.57) for daily tea drinkers and 0.23 (95% CI 0.14 to 0.31) for those drinking over 30 years, when compared to non-tea drinkers. Among the different types of tea considered, green tea appeared to have the strongest protective effect (Zhang et al., 2002). However, a small case-control study in Taiwan reported little association between tea drinking (assessed as yes or no) and the risk of developing ovarian cancer; the adjusted OR being 0.79 (95% CI 0.47 to 1.32)(Yen et al., 2003).

The present findings are contrary to results from European/Western countries (Zheng et al., 1996; Goodman et al., 2003; Jordan et al., 2004; Silvera et al., 2007) where a consistent inverse association could not be established. A case-control study from the USA found no relation between either black tea or green tea consumption and the ovarian cancer risk (Goodman et al., 2003). Compared to non-drinkers, the adjusted OR was 1.1 (95% CI 0.6 to 2.0) for drinking at least 2.5 cups of black tea weekly and 0.9 (95% CI 0.5 to 1.6) for drinking over 1 cup of green tea weekly. However,
frequent (i.e. daily) tea intake was not assessed (Goodman et al., 2003). A large Australian case-control study reported an OR of 1.1 (95% CI 0.76 to 1.61) for drinking more than 4 cups of tea daily versus none, but concluded “no strong evidence” for the need to modify tea drinking habits (Jordan et al., 2004). An early prospective cohort study conducted in the USA observed only weak association, with relative risks of 0.53 for weekly tea intake and 0.98 for at least 2 cups of tea per day (p for trend = 0.64) (Zheng et al., 1996), whereas another large cohort study involving almost 50,000 Canadian women concluded no association between tea intake and ovarian cancer (Silvera et al., 2007). Women who drank 2 to 3 cups of tea daily had a non-significant decreased risk (hazard ratio 0.81, 95% CI 0.53 to 1.23), but the risk increased for those who consumed over 4 cups daily (hazard ratio 1.07, 95% CI 0.64 to 1.79), when compared to non-tea drinkers (Silvera et al., 2007). The contradictory evidence may be attributed to the differences in tea consumption pattern and drinking habit among the various populations. In particular, the type of tea consumed and the method of preparation vary across countries and geographical regions. Unlike women in Western countries who typically drink black tea, our study population commonly drinks green tea (60% of tea drinkers) in combination with oolong and/or black teas. Furthermore, milk and sugar are not added after brewing the dried tea leaves with hot water. Scientific evidence has shown that the addition of milk to liquid tea will inhibit the antioxidant activity of tea (Ryan & Petit, 2010). In particular, the milk protein casein binds to the tea catechins (Lorenz et al., 2007), most notably EGCG, consequently decreasing the concentration of free polyphenols (Kartsova & Alekseeva, 2008). These differences may partially explain the discrepancies with previous reports.

5.3 Habitual physical activity and ovarian cancer risk

The present epidemiological study has found an inverse association between habitual physical activity and the risk of epithelial ovarian cancer in southern Chinese women. Both occupational and leisure time activity levels were measured using a validated and reliable instrument specifically developed for the Chinese population (Jian et al., 2005).
Total physical activity in daily life was found to be associated with a lower risk of ovarian cancer in this southern China population. The risk also reduced significantly for higher exposure to leisure time (strenuous sport and moderate) activities but to a lesser extent vigorous work. The majority of Chinese women were involved in occupations requiring intensive labour before the 1980s. Most of our participants would have been exposed to a high level of vigorous work when they were young. The results are consistent with our previous study in Hangzhou (Zhang et al., 2003) and provide further epidemiological evidence to support the positive findings from other countries (Cottreau et al., 2000; Tavani et al., 2001; Riman et al., 2004; Pan, Ugnat & Mao, 2005; Schnohr et al., 2005; Carnide et al., 2009; Rossing et al., 2010; Moorman et al., 2011). Reick and Fiander conducted a review of the effect lifestyle factors on gynaecological malignancies and reported that physical activity protects against ovarian cancer, independently of BMI (Rieck & Fiander, 2006). A recent meta-analysis of 12 studies examining recreational physical activity and ovarian cancer risk has also documented a protective association, with a pooled estimate of an approximate 20% decline in overall risk when comparing the highest to the lowest levels of physical activity (Olsen et al., 2007).

The protective effect of regular physical activity is biologically plausible. Experimental studies have shown that physical exercise can affect energy balance and prevent weight gain (Erlichman, Kerbey & James, 2002); enhance the immune system by improving the capacity and numbers of natural killer cells (Pedersen & Ullum, 1994); induce the activities of key free radical scavenger enzymes and levels of antioxidants, which in turn reduce the ovarian cancer risk.

A positive association between total sitting duration and ovarian cancer incidence was also observed though the relation was not statistically significant. The finding is consistent with the marginal increase in risk among women in Hangzhou, adjusted OR 1.77 (95% CI 1.0 to 3.1, p = 0.08), for sitting over 10 hours relative to sitting less than 4 hours per day (Zhang et al., 2004). There are several plausible mechanisms to explain the adverse effect of prolonged sitting on ovarian cancer, which include the reduction of insulin sensitivity and its contribution to obesity (Hamburg et al., 2007; Venables & Jeukendrup, 2009). Reduced insulin sensitivity leads to higher blood levels of insulin and elevated levels of the hormone insulin-like growth factor one.
(Cordain, 2012), which has been associated with ovarian cancer (Lukanova et al., 2002) and other hormone-related cancers including breast and prostate cancer (Roddam et al., 2008; Rowlands et al., 2009; Key et al., 2010). Studies linking sedentary behaviours with obesity and metabolic disorders suggest that cell proliferation may be promoted by the elevated levels of insulin, oestrogen and other hormones in circulation.

### 5.4 Breastfeeding and ovarian cancer risk

In this case-control study of Chinese parous women, number of children breastfed and duration of breastfeeding were inversely associated with the ovarian cancer risk. These findings are consistent with our previous study in Hangzhou (Zhang et al., 2004) and support the positive results from other countries (Gwinn et al., 1990; Greggi et al., 2000; Mills, Riordan & Cress, 2004; Huusom et al., 2006; Jordan et al., 2010; Jordan et al., 2012). The 2007 World Cancer Research Fund report stated that there is only limited evidence for a protective effect of lactation on ovarian cancer (World Cancer Research Fund / American Institute for Cancer Research, 2007). More recently this position has been altered to some degree, as evidenced by a current review which listed breastfeeding as a factor that may lower the risk of ovarian cancer (Cramer, 2012) and a meta-analysis of nine case-control studies reporting a 30% decrease in risk of women who had ever breastfed (Ip et al., 2009). A combined analysis of two prospective cohorts found a significant 2% decrease in ovarian cancer risk with each month of breastfeeding (Danforth et al., 2007). Similar results were reported in an early collaborative analysis of five population-based case-control studies (relative risk (RR) = 0.99 per month, p < 0.01) (Whittemore, 1993). A review of reproductive factors and risk of ovarian cancer found the evidence for an association between breastfeeding duration and ovarian cancer risk to be inconsistent, but stated that most studies indicate an inverse association (Riman, Nilsson & Persson, 2004). Reduced risk of ovarian cancer appeared to be dependent upon menopausal status in two case-control studies from Australia and the US, with inverse relationships found among pre-menopausal women only (Siskind et al., 1997; Tung et al., 2005).
Breastfeeding is associated with delayed ovulation and a prolonged period of amenorrhea (Malkani & Mirchandani, 1960; Cronin, 1968; Chao, 1987; Cui et al., 1999). Lactation suppresses ovulation via elevated levels of prolactin which inhibits the secretion of gonadotropins (follicle-stimulating hormone and luteinising hormone) (McNeilly, 1980; McNeilly, Tay & Glasier, 1994). The process of ovulation involves recurrent repair of ovarian epithelium and exposure to oestrogen-rich follicular fluid (Fathalla, 1971). This proliferation of epithelial cells forms the basis of the theory of incessant ovulation, which suggests that a higher number of ovulations increases the probability of spontaneous mutations and hence increases the risk of ovarian cancer (Fathalla, 1971; World Cancer Research Fund / American Institute for Cancer Research, 2007). Lactation may influence ovarian cancer development in this way, by reducing the number of ovulatory cycles. The gonadotropin hypothesis suggests that high levels of gonadotropins cause ovarian epithelial cells to become trapped within the surrounding connective tissue, which may lead to the formation of inclusion cysts (Cramer & Welch, 1983; Hanna & Adams, 2006; Zheng et al., 2007). These hormones have been shown to be elevated in postmenopausal women (Brodowska et al., 2012) and it is during the postmenopausal stage when diagnoses of ovarian cancer are more common (Lutz et al., 2011). Furthermore, many studies have reported increased expression of gonadotropin receptors among women with ovarian cancer (Parrott et al., 2001; Chu et al., 2002; Chudecka-Glaz, Rzepka-Gorska & Kosmowska, 2004; Choi et al., 2007). Two other theories which propose a reduced ovarian cancer risk from breastfeeding involve retrograde transportation of endogenous carcinogens through the fallopian tubes (Cramer & Xu, 1995) and progesterone deficiency (Risch, 1998).

5.5 Body size and ovarian cancer risk

This case-control study investigated the association between ovarian cancer risk and body height, weight and BMI in Southern Chinese women. We found a significant, positive association between ovarian cancer risk and higher body weight and BMI. These results are consistent with the findings from countries that have a high prevalence of obesity (Farrow et al., 1989; Purdie et al., 2001; Hoyo et al., 2005; Chionh et al., 2010) and a previous case-control study conducted in China (Zhang, Xie & Holman, 2005). Research conducted in other low BMI populations such as
Japan, Sweden and the Netherlands have reported mixed results in relation to the effect of BMI on the risk of ovarian cancer. Some studies have found higher BMI to confer an increase in ovarian cancer risk of between 37 and 124% (Schouten et al., 2003); (Riman et al., 2004); (Niwa et al., 2005), whereas two recent prospective cohort studies observed no association (Brandstedt et al., 2011); (Weiderpass et al., 2012). In our study, the increased risk remained when analysis was restricted to serous and mucinous tumours. Women in the upper tertile for BMI had an increased risk of mucinous tumours and a two-fold greater risk for serous tumours, findings of which are supported by earlier research (Farrow et al., 1989); (Riman et al., 2001); (Riman et al., 2004). There was no statistically significant association between height and ovarian cancer risk, a finding which corresponds well to results from previous studies conducted in Asian populations (Hirose et al., 1999; Zhang et al., 2005; Weiderpass et al., 2012). Studies which have found an association between height and ovarian cancer risk had a variation in height of 15cm, based on the difference between upper and lower categories for height (Schouten, Goldbohm & van den Brandt, 2003; Baer, Hankinson & Tworoger, 2008). The range for height observed in our study (5cm) as well as the aforementioned Japanese and Chinese studies (7 and 10cm, respectively) indicate less variation in height among Asian populations, which may explain the lack of association. Other measures of adiposity (i.e., waist and hip circumferences) were not obtained from our sample; however, hip circumference has been shown to increase the risk of premenopausal ovarian cancer (Kotsopoulos, Baer & Tworoger, 2010) and associations between waist-to-hip ratio and greater risk of mucinous tumours have been reported (Lahmann et al., 2010).

A recent meta-analysis of 47 epidemiological studies from 14 countries found ovarian cancer risk increased significantly with increasing weight and BMI among women who had never used menopausal hormone therapy (Beral et al., 2012). A systematic review of 29 studies which examined the relationship between body weight or BMI and risk of ovarian cancer reported a positive but weak association for higher BMI and ovarian cancer risk (Purdie et al., 2001). Conversely, two analyses of prospective cohort studies revealed no overall association between BMI and risk of ovarian cancer (Renehan et al., 2008; Schouten et al., 2008).
Endogenous hormones are thought to play a role in ovarian cancer development. Excess body weight, particularly among postmenopausal women, is associated with higher circulating levels of oestrogen and androgens (Lukanova et al., 2004; Delort et al., 2009). In postmenopausal women, adipose tissue is the main site for oestrogen production (Key et al., 2001) and hence increased adiposity results in higher concentrations of oestrogen (Lukanova et al., 2004). Increased levels of these sex hormones have been shown to stimulate cell proliferation in ovarian surface epithelial cell lines (Syed et al., 2001). Studies have also observed a positive correlation between androgens and insulin-like growth factors (IGFs) (Helle et al., 2002; Lukanova et al., 2004). A prospective study found that elevated circulating IGFs are directly associated with a greater risk of ovarian cancer (Lukanova et al., 2002). High levels of IGFs inhibit apoptosis and stimulate cellular proliferation (Fürstenberger & Senn, 2002; Gallagher & LeRoith, 2010). Body height has been positively associated with circulating IGF-I concentrations during adulthood (Juul et al., 1994); (Key et al., 2010). Higher body weight also lowers levels of progesterone; a hormone which is considered a protective factor for ovarian cancer (Risch, 1998; Lukanova & Kaaks, 2005). Overweight and obesity is associated raised levels of circulating adipokines, an indicator for a subclinical form of chronic inflammation (Greenberg & Obin, 2006; Thorand et al., 2006). Leptin, another hormone related to adipose tissue, is involved in ovarian folliculogenesis and the regulation of body weight (Pralong & Gaillard, 2001; Moschos, Chan & Mantzoros, 2002). Unlike weight, height is an anthropometric factor which cannot be modified, and most likely does not interact with endogenous hormones during adulthood (Brändstedt et al., 2011).

5.6 Limitations

Several limitations should be taken into consideration when interpreting the results of the present case-control study. A major limitation concerns the inherent limitations of retrospective cross-sectional designs so that a direct cause-effect relationship could not be established. The use of incident cases of ovarian cancer and the high response rates of cases and controls are important factors in reducing bias. Our results could also be affected by several sources of bias. Information bias was unlikely because all participants were blind to the study hypothesis, while the
potential protective effects of tea drinking and physical activity against ovarian cancer have not been established in China at the time of interview.

Assessment of habitual physical activity was based on self-report, with a reference period set at five years before interview to avoid reverse causation. A single reference time point was also adopted because assessment of lifetime physical activity/sedentary exposure appeared impractical. However, responses from the subjects might incur some recall error. Therefore, face-to-face interviews were conducted in the presence of their next-of-kin to help recall and to improve the accuracy of their answers. All interviews were conducted by the researcher and her assistants who followed the same procedure for both case and control groups to avoid intra- and inter-interviewer biases, while recruitment bias was minimized by sampling from different hospitals.

Of the women with at least one live birth, 16 controls had not breastfed while all of cases reported having breastfed. This may reflect some recall bias in self reports of breastfeeding, however rates of ever breastfeeding are typically high in this region of China. Analysis of average duration of breastfeeding per child was undertaken using quartiles (≤ 7, 8-10, 11-12 and ≥ 13 months). A recent study examined the relationship between average duration of breastfeeding and ovarian cancer risk using categories which capture prolonged lactation i.e. ≥ 18 months vs. no breastfeeding (Jordan et al., 2012). Comparisons of larger and more distinct differences in average duration of breastfeeding were not possible in this study given the inadequate sample size. Average duration of breastfeeding was less than 10 months, and only 3.4% of the sample had an average duration of breastfeeding exceeding 15 months.

The habitual tea consumption pattern should not be affected by the case-control status. Dietary assessment was based on self-report using a validated and reliable questionnaire specifically developed for the southern Chinese population. While the participants could recall tea consumption without any difficulty, their responses to dietary questions would inevitably incur some recall error. There is also no evidence from the literature supporting habitual tea consumption as a marker of healthy lifestyle among southern Chinese women. Nevertheless, further replications of the study and cohort studies are recommended before generalizing the findings to other populations.
Participants were not weighed or measured, i.e. height and weight data was self-reported. However, self-reported height and weight has demonstrated sufficient validity in Asian populations with low levels of obesity (Lee et al., 2011; Nakamura et al., 1999; Wada et al., 2005). Furthermore, we analysed participants’ weight at 5 years prior interview to minimise bias due to reverse causation.

Despite the low refusal rate, selection bias was unavoidable because all participants were voluntary and the hospital-based controls were not randomly selected from the community. Nevertheless, the four participating hospitals serve the entire catchment region so that our subjects were still representative of the target population.

Finally, residual confounding might still exist even though established risk factors have been controlled for in the multivariable logistic regression analyses. Nevertheless, further replications of the study are recommended before generalizing the findings to other populations.

5.7 Conclusions

5.7.1 Tea drinking and risk of ovarian cancer

Tea consumption was assessed in this southern Chinese population. An inverse association was found between tea consumption and the risk of ovarian cancer, with apparent dose-response relationships for higher tea exposure especially long term drinking. The results of this study support the hypothesis that tea consumption is associated with the lower risk of ovarian cancer. Nevertheless, further replications of the study are recommended before generalizing the findings to other populations. Tea is a safe and inexpensive beverage. Its consumption should be encouraged in the mean time because of the potential benefit in preventing this common and deadly disease for women.

5.7.2 Habitual Physical activity and risk of ovarian cancer

Physical activity levels and ovarian cancer risk was assessed in this case-control study. An inverse association was found between habitual physical activity and the risk of epithelial ovarian cancer among southern Chinese women, with significant
dose-response relationships observed for engaging in strenuous sports and moderate activity. The results of our study support the hypothesis that habitual physical activity may reduce the risk of ovarian cancer. Unlike other risk factors of ovarian cancer, physical activity is a modifiable lifestyle factor. Leisure time exercise activities should be further promoted and encouraged among women because of the potential benefit in ovarian cancer prevention.

5.7.3 Breastfeeding and risk of ovarian cancer

The relationship between breastfeeding and risk of ovarian cancer was assessed in this case-control study. Prolonged lactation was found to be protective against ovarian cancer in this population of Chinese parous women. Our results are in agreement with current national guidelines which promote the maternal benefits of breastfeeding. This study adds further knowledge to the relatively limited amount of research from countries with low incidence of this disease and provides more detail of the breastfeeding parameters associated with a reduced risk of ovarian cancer. Breastfeeding, especially long-duration breastfeeding should be promoted to women of reproductive age. Women should be educated this long-term maternal benefit of prolonged breastfeeding.

5.7.4 Body size and risk of ovarian cancer

In this study, body weight and BMI were found to be associated with increased risk of ovarian cancer in Southern Chinese women. Lifestyle changes leading to excess body weight among the Chinese population poses potential health problems, one of which is an increased risk of ovarian cancer. This study provides further evidence that higher weight and BMI are positively associated with ovarian cancer risk, in a population with a comparatively low but rising incidence of both obesity and ovarian cancer.
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Appendix A  Information sheet and consent form

Research title: A case control study of lifestyle factors in the aetiology of ovarian cancer

The School of Public Health at Curtin University is investigating the relationship between dietary factors and ovarian cancer. The research will make a significant contribution towards improving women’s health in terms of ovarian cancer prevention and health promotion by guiding women with healthy food intake. As part of this project subjects are being asked about lifestyle characteristics, food consumption and factors relevant to hormonal status by personal interview using a structured questionnaire. If you are able to help us with our research, please sign the consent form below and provide us with your name and telephone number.

Questionnaire will be identified only by a confidential code. All information from the questionnaire is to be treated as confidential and only data aggregates for statistical purpose will be published. The information gained from this study will be stored in a locked cupboard for seven years following the completion of this study and then they will be destroyed. The ethics committee of Curtin University of Technology has approved this study. If you have any questions or require any further information concerning this study, please do not hesitate to contact us below.

Thank you in anticipation of your assistance.

Yours sincerely

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Fax: 9266-2958

Dada Su
PhD candidacy
Curtin University of Technology
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Tel: 0433325686
Fax: 9266-2958

September 2006

Consent Form

I agree to participate in the study of lifestyle factors in the aetiology of ovarian cancer. I understand that my participation is completely voluntary and I am able to withdraw from the study at any time without any negative consequences. I understand that my participation will be limited to completing a questionnaire by personal interview. I understand that all researchers working on the study are qualified health professionals and that all individual data will be kept strictly confidential.

____________________________     _____________________
Signature                              Date

____________________________     _____________________
Name (please print)                  Telephone number
Appendix B

Study Questionnaire

Name: ______________________________
Tel: ______________________________
Add: ______________________________

Next of kin at present during the interview

Yes 1 No 2

Medical history record No.: ______________________________

Diagnosis Date: ___________ / ___________ / ___________.

Diagnosis Hospital:

Province Hospitals 1
City Hospitals 2
County Hospitals 3

ICD code: ______________________________

Evidences of Diagnosis:

Pelvic examination 1
Tumor marker (CA125, AFP, Chorionic gonadotropin) 2
Radiology (Type-B ultrasonic, CT MRI) 3
Biopsy 4
Cytology (Ascites, posterior fornix puncture fluid) 5

Pathology:

Serous cystadnocarcinoma 1
Endometrioid cystadnocarcinoma 3
Undifferentiated carcinoma 5
Clear cell carcinoma 7
Malignant Brenner’s tumor 9
Mucinous cystadnocarcinoma 2
Mixed epithelial cystadnocarcinoma 4
Borderline malignancy 6
Transitional cell carcinoma 8

(A) GENERAL INFORMATION

Q1. Data of Birth (month/day/year): ___________ / ___________ / ___________

Q2. Birth place: _______________________________________________________

Page 171
Q3. Years in Guangzhou, Guangdong province: ________________________________

Q4. Weight (Kg) 
   a. now 
   b. usual weight before the disease 

Q5. Height (CM, putting off shoes) 

Q6. Marital status 

   Married/remarried  1  Divorced  3  Never married  5  
   Widowed  2  Separated  4  De facto  6  

Q7. Education 

   No formal education  0  Junior high school  2  Vocational school  4  
   primary school  1  Senior high school  3  College or university  5  

Q8. Occupation 

   Laborer or farm worker  1  Factory worker or machine operator  2  
   Clerical or office  3  Sales  4  
   Manager or administrator  5  Craftsperson  6  
   Small business owner  7  Professional/technical  8  
   Unemployed  9  Housewife  10  
   Other  11  

Q9. Residence belonging: 

   City  1  Suburb  2  
   Town  3  Country  4  

Q10. Do you shopping foods?  Never  0  sometime  1  usual  2  

Q11. Do you cooking foods?  Never  0  sometime  1  usual  2  

(B) DIETARY HISTORY

Your usual dietary habits as an adult (before the disease or about 5 years ago). If there is any change in your dietary habits or for any reason that you are on a special diet recently, please tell me what you ate before you changes your diet.

Q1. Were you on a special diet listed below now or 5 years ago?

   Now  □  5 years ago  □  
   No  0  low fat  2  
   Vegetarian  1  low salt  3  List other  .  

Q2. Do you have meals regularly (having 3 main meals per day (A) and eating at the suitable time (B))? 

   Regularly  1  
   Occasionally irregular  2  
   Sometimes irregular  3  
   Often irregular  4  

Page 172
Q3. Your eating habit (5 years ago / before the disease):

<table>
<thead>
<tr>
<th></th>
<th>Everyday</th>
<th>frequently</th>
<th>Sometimes</th>
<th>Occasionally</th>
<th>never</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Eating breakfast</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>b. Eating take-away food or eating out</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>c. Eating snacks (biscuits, melon seeds)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>d. Eating sweet food (candy, congee, ice cream)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Q4. Whether you ate the following specially processed food Five years ago / before the disease?

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>1 time/m</th>
<th>1 time/w</th>
<th>Every day</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Fried food</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>b. Smoked food</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>c. Cured food</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>d. Grilled food</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

Q5. Five years ago / before the disease, the meat you ate was usually

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Well done (not burnt)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under done</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never eat meat</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclear</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Q6. When you ate meat, did you trim off all of the fat?

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>0</td>
<td>some times</td>
<td>1</td>
<td>usual</td>
</tr>
</tbody>
</table>

Q7. When you ate chicken, did you eat the skin?

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>0</td>
<td>some times</td>
<td>1</td>
<td>usual</td>
</tr>
</tbody>
</table>

Q8. Did you eat animal brain

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>0</td>
<td>some times</td>
<td>1</td>
<td>usual</td>
</tr>
</tbody>
</table>

or yolk?

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>0</td>
<td>some times</td>
<td>1</td>
<td>usual</td>
</tr>
</tbody>
</table>

or roe(spawn)?

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>0</td>
<td>some times</td>
<td>1</td>
<td>usual</td>
</tr>
</tbody>
</table>
Q9. Five years ago / before the disease, how much of oil did you consume on average in a month?

1. Lard liang each month
2. Rapeseed oil liang each month
3. Soybean oil liang each month
4. Peanut oil liang each month
5. Salad oil liang each month

Q10.a. Have you ever drunk tea in your lifetime? (if the answer is 0, turn to Q13)

Never or hardly never 0 2-4 cups/week 2
1-4 cups / month 1 ____Cups / day

b. What kind of tea did you drink? Green tea 1 Black tea 2
Both 3 Ratio ( )

c. What is the total number of years you drank tea?

d. How many new batches of tea per day?

e. How much tea leaves per brew?

Little 1 Medium 2 Much 3

f. How much tea leaves was consumed per year?

g. What size of tea pot do you use?

Small size, 1 Medium size 2 Large size 3

h. What size of tea cup do you use?

Small size 1 Medium size 2 Large size 3

Q11. Five to ten years ago / before the disease, how many times and quantities per meal did you usually eat the following food? Some of the food would be on market only in certain seasons, please estimate how frequently and how much you ate average in this season (Please answer as exact as possible. If you cannot remember exactly, give the closest answer).

**Cereals**

<table>
<thead>
<tr>
<th>Food items</th>
<th>1/3/ M</th>
<th>1-2/W</th>
<th>3-4/W</th>
<th>5-6/W</th>
<th>1/2 D</th>
<th>2/3 D</th>
<th>Standard Portion Size</th>
<th>Portion size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice</td>
<td>a b c d e f g</td>
<td>125g / bowl</td>
<td>a b c d e f</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porridge</td>
<td>a b c d e f g</td>
<td>50g / bowl</td>
<td>a b c d e f</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thin rice noodle</td>
<td>a b c d e f g</td>
<td>250g / plate</td>
<td>a b c d e f</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fried sticks</td>
<td>a b c d e f g</td>
<td>100g / two</td>
<td>a b c d e f</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noodle</td>
<td>a b c d e f g</td>
<td>50g / bowl</td>
<td>a b c d e f</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rice noodle</td>
<td>a b c d e f g</td>
<td>250g / plate</td>
<td>a b c d e f</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Instant noodle</td>
<td>a b c d e f g</td>
<td>100g/package</td>
<td>a b c d e f</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Legumes

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Soybean milk</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>180ml/bowl</td>
<td>a</td>
</tr>
<tr>
<td>Tofu</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>80g/block</td>
<td>a</td>
</tr>
<tr>
<td>Soybean</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>150g/plate</td>
<td>a</td>
</tr>
<tr>
<td>Dried tofu</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>250g/plate</td>
<td>a</td>
</tr>
<tr>
<td>Mung bean</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>20g/bowl</td>
<td>a</td>
</tr>
<tr>
<td>Black soybean</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>150g/plate</td>
<td>a</td>
</tr>
</tbody>
</table>

### Fresh legumes

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Green bean</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>250g/plate</td>
<td>a</td>
</tr>
<tr>
<td>Kidney bean</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>250g/plate</td>
<td>a</td>
</tr>
<tr>
<td>Bean sprout</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>250g/plate</td>
<td>a</td>
</tr>
</tbody>
</table>

### Leafy vegetables

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese cabbage</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>250g/plate</td>
</tr>
<tr>
<td>Lettuce</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>250g/plate</td>
</tr>
<tr>
<td>Flowering stalk</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>250g/plate</td>
</tr>
<tr>
<td>Cole</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>250g/plate</td>
</tr>
<tr>
<td>Spinach</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>250g/plate</td>
</tr>
<tr>
<td>Water Spinach</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>250g/plate</td>
</tr>
<tr>
<td>Cabbage</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>250g/plate</td>
</tr>
<tr>
<td>Celery</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>250g/plate</td>
</tr>
<tr>
<td>Mustard Leaf</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>250g/plate</td>
</tr>
<tr>
<td>Leek</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>250g/plate</td>
</tr>
<tr>
<td>Caraway</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>5g/one</td>
</tr>
</tbody>
</table>
### Green Onion

<table>
<thead>
<tr>
<th>Food items</th>
<th>1-3/M</th>
<th>1-2/W</th>
<th>3-4/W</th>
<th>5-6/W</th>
<th>1/3</th>
<th>2/3</th>
<th>3/3</th>
<th>Portion size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>0.5</td>
<td>0.75</td>
<td>1.0</td>
<td>1.5</td>
<td>≥2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balsam pear</td>
<td>a b</td>
<td>c d e</td>
<td>f g</td>
<td>250g</td>
<td>plate</td>
<td>a</td>
<td>b</td>
<td>c</td>
</tr>
<tr>
<td>White gourd</td>
<td>a b</td>
<td>c d e</td>
<td>f g</td>
<td>200g</td>
<td>/4 piece</td>
<td>a e</td>
<td>b</td>
<td>c</td>
</tr>
<tr>
<td>Tomato</td>
<td>a b</td>
<td>c d e</td>
<td>f g</td>
<td>250g</td>
<td>plate</td>
<td>a</td>
<td>b</td>
<td>c</td>
</tr>
<tr>
<td>Cucumber</td>
<td>a b</td>
<td>c d e</td>
<td>f g</td>
<td>250g</td>
<td>plate</td>
<td>a</td>
<td>b</td>
<td>c</td>
</tr>
<tr>
<td>Pinxiente</td>
<td>a b</td>
<td>c d e</td>
<td>f g</td>
<td>250g</td>
<td>plate</td>
<td>a</td>
<td>b</td>
<td>c</td>
</tr>
</tbody>
</table>

### Melon and Nightshade

<table>
<thead>
<tr>
<th>Food items</th>
<th>1-3/M</th>
<th>1-2/W</th>
<th>3-4/W</th>
<th>5-6/W</th>
<th>1/3</th>
<th>2/3</th>
<th>3/3</th>
<th>Standard Portion Size</th>
<th>Portion size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>0.5</td>
<td>0.75</td>
<td>1.0</td>
<td>1.5</td>
<td>≥2.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balsam pear</td>
<td>a b</td>
<td>c d e</td>
<td>f g</td>
<td>250g</td>
<td>plate</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
</tr>
<tr>
<td>White gourd</td>
<td>a b</td>
<td>c d e</td>
<td>f g</td>
<td>200g</td>
<td>/4 piece</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
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### Cauliflower

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### Meats

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<td>c</td>
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<td>f</td>
<td>g</td>
<td>100g / one</td>
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<td>c</td>
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### Milk

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<td>e</td>
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<td>f</td>
<td>g</td>
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<td>g</td>
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**Pickles**

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**Marine products**

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<td>g</td>
<td>250g / one</td>
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<td>c</td>
<td>d</td>
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<td>c</td>
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<td>e</td>
<td>f</td>
<td>g</td>
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<td>c</td>
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<td>e</td>
<td>f</td>
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<td>g</td>
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<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>250g / plate</td>
<td>a b c d e f</td>
</tr>
<tr>
<td>Dried squid</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>150g / plate</td>
<td>a b c d e f</td>
</tr>
<tr>
<td>Fish-pellet</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>100g / four</td>
<td>a b c d e f</td>
</tr>
</tbody>
</table>

**Mushrooms**
### Food items

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mushrooms</td>
<td>a b c d e f g</td>
<td>30g / six</td>
<td>a b c d e f</td>
<td>0.5</td>
<td>0.75</td>
<td>1.0</td>
<td>1.5</td>
<td>2.0</td>
<td>≥2.0</td>
</tr>
<tr>
<td>Straw mushroom</td>
<td>a b c d e f g</td>
<td>60g / six</td>
<td>a b c d e f</td>
<td>0.5</td>
<td>0.75</td>
<td>1.0</td>
<td>1.5</td>
<td>2.0</td>
<td>≥2.0</td>
</tr>
<tr>
<td>Winter mushroom</td>
<td>a b c d e f g</td>
<td>250g / plate</td>
<td>a b c d e f</td>
<td>0.5</td>
<td>0.75</td>
<td>1.0</td>
<td>1.5</td>
<td>2.0</td>
<td>≥2.0</td>
</tr>
<tr>
<td>Long thread moss</td>
<td>a b c d e f g</td>
<td>5g / bowl soup</td>
<td>a b c d e f</td>
<td>0.5</td>
<td>0.75</td>
<td>1.0</td>
<td>1.5</td>
<td>2.0</td>
<td>≥2.0</td>
</tr>
<tr>
<td>Fungus</td>
<td>a b c d e f g</td>
<td>250g / plate</td>
<td>a b c d e f</td>
<td>0.5</td>
<td>0.75</td>
<td>1.0</td>
<td>1.5</td>
<td>2.0</td>
<td>≥2.0</td>
</tr>
</tbody>
</table>

### Nuts

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>a b c d e f g</td>
<td>50g / dish</td>
<td>a b c d e f</td>
<td>0.5</td>
<td>0.75</td>
<td>1.0</td>
<td>1.5</td>
<td>2.0</td>
<td>≥2.0</td>
</tr>
<tr>
<td>Sunflower seed</td>
<td>a b c d e f g</td>
<td>50g / dish</td>
<td>a b c d e f</td>
<td>0.5</td>
<td>0.75</td>
<td>1.0</td>
<td>1.5</td>
<td>2.0</td>
<td>≥2.0</td>
</tr>
</tbody>
</table>

### Cakes

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bread</td>
<td>a b c d e f g</td>
<td>100g / one</td>
<td>a b c d e f</td>
<td>0.5</td>
<td>0.75</td>
<td>1.0</td>
<td>1.5</td>
<td>2.0</td>
<td>≥2.0</td>
</tr>
<tr>
<td>Biscuit</td>
<td>a b c d e f g</td>
<td>50g / 10 pieces</td>
<td>a b c d e f</td>
<td>0.5</td>
<td>0.75</td>
<td>1.0</td>
<td>1.5</td>
<td>2.0</td>
<td>≥2.0</td>
</tr>
<tr>
<td>Cake</td>
<td>a b c d e f g</td>
<td>35g / one</td>
<td>a b c d e f</td>
<td>0.5</td>
<td>0.75</td>
<td>1.0</td>
<td>1.5</td>
<td>2.0</td>
<td>≥2.0</td>
</tr>
</tbody>
</table>

### Condiments

<table>
<thead>
<tr>
<th>Food items</th>
<th>1/-3/M</th>
<th>1/-2/W</th>
<th>3/-4/W</th>
<th>5/-6/W</th>
<th>1/ D</th>
<th>2/ D</th>
<th>3/ D</th>
<th>Normal</th>
<th>Answer types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salt</td>
<td>a b c d e f g</td>
<td>4g</td>
<td>a b c d</td>
<td>No</td>
<td>Less</td>
<td>Normal</td>
<td>More</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monosodium glutamate</td>
<td>a b c d e f g</td>
<td>1g</td>
<td>a b c d</td>
<td>No</td>
<td>Less</td>
<td>Normal</td>
<td>More</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soy sauce</td>
<td>a b c d e f g</td>
<td>10g</td>
<td>a b c d</td>
<td>No</td>
<td>Less</td>
<td>Normal</td>
<td>More</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinegar</td>
<td>a b c d e f g</td>
<td>3ml</td>
<td>a b c d</td>
<td>No</td>
<td>Less</td>
<td>Normal</td>
<td>More</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fermented fish sauce</td>
<td>a b c d e f g</td>
<td>2ml</td>
<td>a b c d</td>
<td>No</td>
<td>Less</td>
<td>Normal</td>
<td>More</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White sugar</td>
<td>a b c d e f g</td>
<td>0.8ml</td>
<td>a b c d</td>
<td>No</td>
<td>Less</td>
<td>Normal</td>
<td>More</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tomato sauce</td>
<td>a b c d e f g</td>
<td>10g</td>
<td>a b c d</td>
<td>No</td>
<td>Less</td>
<td>Normal</td>
<td>More</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garlic oil</td>
<td>a b c d e f g</td>
<td>5ml</td>
<td>a b c d</td>
<td>No</td>
<td>Less</td>
<td>Normal</td>
<td>More</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Attention: “values of the normal” came from the averages consumed by one subject per meal in 3-day WDR.

### Oils

<table>
<thead>
<tr>
<th>Food items</th>
<th>1/-3/M</th>
<th>1/-2/W</th>
<th>3/-4/W</th>
<th>5/-6/W</th>
<th>1/ D</th>
<th>2/ D</th>
<th>3/ D</th>
<th>Normal</th>
<th>Answer types</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Less</td>
<td>Normal</td>
<td>More</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Page 179
| Peanut oil | a | b | c | d | e | f | g | 10ml a | b | c | d |
| Mixed oil | a | b | c | d | e | f | g | 7ml a | b | c | d |
| Animal oil | a | b | c | d | e | f | g | 5ml a | b | c | d |

**Beverages (alcohol and tea)**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Red wine</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>15ml/small cup a</td>
</tr>
<tr>
<td>Beer</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>200ml/cup a</td>
</tr>
<tr>
<td>Iron kwan-yin tea</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>12.5g/1pota</td>
</tr>
<tr>
<td>Oolong</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>12.5g/pota a</td>
</tr>
<tr>
<td>Longjing tea</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>12.5g/pota a</td>
</tr>
<tr>
<td>Black tea</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>d</td>
<td>e</td>
<td>f</td>
<td>g</td>
<td>12.5g/pota a</td>
</tr>
</tbody>
</table>
(C) LIFESTYLE

Q1. Household
   a. Numbers in your family (now/5-10 years ago)
   b. Nuclear type 1 traditional type 2

Q2. On the average, five to ten years ago / before the disease how many hours in a day did you sleep (including naps)? Fall asleep easy 1 difficult 2

Q3. On the average, five to ten years ago / before the disease how many hours in a day (/week) did you spend in the following sitting activities? If you have retired, please indicate the time separately (before/after retired)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Never</th>
<th>&lt;1 h</th>
<th>1-2 h</th>
<th>3-4 h</th>
<th>5-6 h</th>
<th>7-10 h</th>
<th>&gt;10 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting in car or bus</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Sitting at work</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Watching TV/ movie</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Other sitting activities</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

Q4. On the average, five to ten years ago / before the disease how many hours in a day/week did you spend in the following activities? If you have retired, please indicate the time separately (before/after retired)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Never</th>
<th>½ to 1 h</th>
<th>2-3 h</th>
<th>4-6 h</th>
<th>7-10 h</th>
<th>11-20 h</th>
<th>21-30 h</th>
<th>&gt;30 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strenuous sports (i.e. jogging, bicycling on hills, tennis, racquet ball, swimming, aerobics)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Vigorous work (i.e. moving heavy furniture, shoveling, weight lifting, loading/ unloading trucks, or equivalent manual labor)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Moderate activity (i.e. housework, brisk walking, golfing, bowling, bicycling on level ground, gardening, walking, Taichi)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

Q5.a. Have you ever smoked? (If No, turn to Q5-g) No 0 Yes 1

b. Are you smoking now? No 0 Yes 1

c. What is the average number of cigarettes that you smoked per day?
   Occasionally 1 to 2 1 5 to 9 3 15 to 19 5 ≥30 7
   Often 1 to 4 2 10 to 14 4 ≥20 6 ≥40 8

d. What is the total number of years you smoked?
e. If you quit smoking, how many years ago did you quit?
f. Have you ever smoked a total of 20 or more packs of cigarettes in your lifetime? No 0 Yes 1
g. Are your relatives living with you smoking at home? (If No, turn to Q6) No 1 Not in the same room 2
   Having smog in room 3 Heavy smog in room 4
h. What is the total number of cigarettes that your relatives smoked at home per day?
i. How many years have you been living with them in such smog room?
Q6. Type of cooking fuel now:
Gas 1  Coal 2  Firewood 3  Others 4

Q7. Type of cooking fuel 10 years ago
Gas 1  Coal 2  Firewood 3  Others 4

Q8. Drinking water now:
Tap-water 1  Well-water 2  Rivulet 3  Others 4

Q9. Drinking water 10 years ago:
Tap-water 1  Well-water 2  Rivulet 3  Others 4

Q10. What is the total number of years you used oil-remover in your kitchen?

Q11. Are there any industrial sources listed below around your home (within 500 m)?
If “YES”, then, how many years have you been living in this environment?
Smelting 1  Coking 2  Electroplating 3
Printing & dyeing 4  Chemical industry 5  Rubber 6
Tanning 7  Plastics 8
Pesticides 9  Others 10

Q12. Per capita (person) income / month in 2001 (mean Yuan RMB)
<500 0  501 – 1000 1  1001 – 2000 2
2001 – 3000 3  3001 – 5000 4  5001 – 8000 5
≥8001 6

Q13. In recent 10 years or before you get the disease, have you had any mental strike or depression?
No 0  Yes 1
### (D) FACTORS RELEVANT TO HORMONE & HEREDITY

**Q1. History of menstruation**

<table>
<thead>
<tr>
<th>a. Age of menarche</th>
<th>b. How old were you when your periods became regular?</th>
<th>c. Duration of menstruation</th>
<th>d. Menstruation cycle</th>
<th>e. Age of menopause</th>
<th>f. Reason of menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>natural 1 surgery 2 radiation 3 medication 4</td>
</tr>
</tbody>
</table>

**Q2. History of marriage and reproduction**

<table>
<thead>
<tr>
<th>a. Age of marriage</th>
<th>b. The number of delivery of full-term pregnant</th>
<th>c. Age of first full-term pregnant</th>
<th>d. The number of premature delivery</th>
<th>e. The number of abortions</th>
<th>f. The number of exist children</th>
<th>g. The outcome of your first pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abortion 1 Premature 2 Full-term 3</td>
</tr>
</tbody>
</table>

**Q3. History of lactation**

<table>
<thead>
<tr>
<th>a. The number of children breast fed</th>
<th>b. On the average, the number of months you lactated each time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Q4. History of contraception**

<table>
<thead>
<tr>
<th>OC</th>
<th>1</th>
<th>IUD</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth control injections</td>
<td>2</td>
<td>Vasoligation</td>
<td>7</td>
</tr>
<tr>
<td>Condom</td>
<td>3</td>
<td>Tubes tied</td>
<td>8</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>4</td>
<td>Withdrawal</td>
<td>9</td>
</tr>
<tr>
<td>Spermatocide</td>
<td>5</td>
<td>None of the above</td>
<td>0</td>
</tr>
</tbody>
</table>

**Q5. Oral contraceptive pills**

<table>
<thead>
<tr>
<th>The age of started taking OC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of OC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Short-term pill</th>
<th>1</th>
<th>Long-term Pill</th>
<th>2</th>
<th>Emergent pill</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of OC (the number of tablets/time)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The number of years taken OC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Q6. History of medication**

<table>
<thead>
<tr>
<th>Biopsy-confirmed benign proliferation breast disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>No 0</td>
</tr>
</tbody>
</table>

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Biopsy-confirmed benign ovarian cysts  No 0  Yes 1

Have you ever had a hysterectomy?  No 0  Yes 1

Did you ever take estrogen (pill, injection, or patch) for menopause or other reasons?
No 0  Yes 1

How old were you when you started taking estrogen?

How many years did you take estrogen?

Did you ever take progesterone along with estrogen for menopause or other reasons?
Never 0  some times 1  usual 2

How many years did you take progesterone in total?

Have you ever had any cervical smear?  No 0  Yes 1

How many years it has been since you last had cervical smear?

Age of menopause

Has menopause been natural or caused?
Not provided 0  natural 1
hysterectomy 2  Both-side ovariectomy 3
Hysterectomy & ovariectomy 4  others 5

Q7. Family medical history

How many full sisters do you have?

How many full brothers do you have?

First degree relative with ovarian cancer  No 0  Yes 1
First degree relative with breast cancer  No 0  Yes 1
First degree relative with other cancer  No 0  Yes 1

If yes, what kind of cancer

<table>
<thead>
<tr>
<th>who</th>
<th>cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Five years ago / before the disease, how many times and quantities per meal did you usually drank alcohol?

<table>
<thead>
<tr>
<th>Beverages (alcohol)</th>
<th>0-2 times a year</th>
<th>3-10 times a year</th>
<th>Once a month</th>
<th>2-3 times a month</th>
<th>Once a week</th>
<th>2-3 times a week</th>
<th>4-6 times a week</th>
<th>Once a day</th>
<th>Twice a day</th>
<th>3=3 times/day</th>
<th>Quantity ml/time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Beer (regular or light beer)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>200ml/cup/meal</td>
</tr>
<tr>
<td>2. Red Wine</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>15ml/small cup</td>
</tr>
<tr>
<td>3. Rice wine</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>15ml/small cup</td>
</tr>
<tr>
<td>4. White wine, Maotai, spirits</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>115ml/small cup</td>
</tr>
</tbody>
</table>

5 years ago / before the disease, do you usually eat the following foods?

Vitamins, Ginseng, Ganoderma lucidum, Cubilose, Snow frog, Aweto, Medicated wine, Sea horse, Turtle, Hawthorn, radix-polygoni multiflori, old arable soil, milk veteh, Traditional Chinese anticancerogen.

If you ate the previous foods 5 years ago/ before the disease, please describe the frequency and quantity per time you usually ate.

Have you changed your eating habit of previous foods after your disease has been diagnosed?

No 0  Yes 1