THE FINANCIAL IMPACT OF GENETIC INFORMATION ON THE INSURANCE INDUSTRY

By

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I hereby declare that the work presented in this thesis was carried out by myself at Heriot-Watt University, Edinburgh, except where due acknowledgement is made, and has not been submitted for any other degree.

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Appendix A

Intensity of Contracting Other Critical Illness and Adjusted Intensity of Death

The estimation of the intensities μ_x^{02} and μ_x^{03} has been provided by Gutiérrez & Macdonald (2003). These intensities are used in Chapters 2, 3 and 4.

- Estimation of μ_x^{02}

  From (1), μ_x^{02} is the sum of four intensities, μ_x^{02h}, μ_x^{02c}, μ_x^{02s} and μ_x^{02o} (Gutiérrez & Macdonald, 2003).

  1. For males:

$$\begin{aligned} \mu_x^{02c} &= \exp(-11.25 + 0.105x)(x < 51), \\ \mu_x^{02c} &= 0.2591585 - 0.01247354x + 0.0001916916x^2 \\ &\quad -8.952933 \times 10^{-7} x^3 (x \geqslant 60), \end{aligned}$$

     with a blending by linear interpolation between ages 51 and 60.

     By linear interpolation, we mean interpolation between both functions at each

age, for example

$$\mu_{55}^{02c} = \frac{[(60-55)\mu_{55}^{1} + (55-51)\mu_{55}^{2}]}{60-51}.$$

For females:

$$\begin{aligned} \mu_x^{02c} &= \exp(-10.78 + 0.123x - 0.00033x^2)(x < 53), \\ \mu_x^{02c} &= \exp(-0.01545632 + 0.0003805097x)(x \geqslant 53). \end{aligned}$$

2. For males:

$$\begin{aligned} \mu_x^{02h} &= \exp(-13.2238 + 0.152568x)(x < 44), \\ \mu_x^{02h} &= \exp(-0.01245109 + 0.000315605x)(x > 49), \end{aligned}$$

with a blending by linear interpolation between ages 44 and 49.

For females:

$$\mu_x^{02h} = \frac{0.598694}{\Gamma(15.6412)} \times 0.15317^{15.6412} \exp(-0.15317)x^{14.6412}.$$

In practice, the onset of a heart attack will not result in an instant CI benefit payment. The patient has to survive for another 28 days after onset to get the payment. Let p_x^h be the 28-day survival probability after the first-ever heart attack. We take 28-day mortality rates following a heart attack ($q_x^h = 1 - p_x^h$) from Dinani *et al.* (2000). For females $q_x^h = 0.21$ at ages 20 – 80. The rates for males are given in Table 1.

3. For males:

$$\mu_x^{02s} = \exp(-16.9524 + 0.294973x - 0.001904x^3 + 0.00000159449x^3).$$

Table A.1: 28-day mortality rates ($q_x^h = 1 - p_x^h$) for males following heart attack.

Age	q_x^h	Age	q_x^h	Age	q_x^h	Age	q_x^h
20–39	0.15	47–52	0.18	58–59	0.21	65–74	0.24
40–42	0.16	53–56	0.19	60–61	0.22	75–79	0.25
43–46	0.17	57	0.20	62–64	0.23	80+	0.26

For females:

$$\mu_x^{02s} = \exp(-11.1477 + 0.08107x).$$

Following a stroke, the 28-day survival probabilities p_x^s, are taken from Dinani *et al.* (2000). For males and females $p_x^s = (0.9 - 0.002x)/0.9$.

4. Following Macdonald, Waters & Wekwete (2003b) and Dinani *et al.* (2000), we suppose that other minor causes of CI insurance claims amount to 15% of those arising from cancer, heart attack, and stroke. Therefore:

$$\mu_x^{02o} = 0.15(\mu_x^{02c} + p_x^h \times \mu_x^{02h} + p_x^s \times \mu_x^{02s}).$$

By summing all four intensities, we have:

$$\mu_x^{02} = 1.15(\mu_x^{02c} + p_x^h \times \mu_x^{02h} + p_x^s \times \mu_x^{02s}).$$

- Estimation of μ_x^{03}

  Mortality μ_x^{03} is based on the English Life Tables No.15 (μ_x^{ELT15}) with mortality from causes leading to CI claims removed. We added back the 28-days mortality following heart attack and strokes as follows:

$$\mu_x^{03} = (1 - \theta_x)\mu_x^{ELT15} + (1 - p_x^h)\mu_x^{02h} + (1 - p_x^s)\mu_x^{02s},$$

where for males:

$$\begin{aligned}\theta_x &= 0.0185408 + 0.0655723x - 0.00667150x^2 \\ &\quad +0.000223974x^3 - 0.00000228356x^4 (x < 30), \\ \theta_x &= -2.80056 + 0.149759x \\ &\quad -0.00203616x^2 + 0.00000881081x^3 (x > 44),\end{aligned}$$

with a linear blending between ages 30 and 44,

For females:

$$\begin{aligned}\theta_x &= -0.0261291 + 0.104641x - 0.0118145x^2 \\ &\quad +0.000467135x^3 - 0.00000579010x^4 (x < 30), \\ \theta_x &= -1.34514 + 0.0897216x - 0.00119978x^2 \\ &\quad 0.00000486785x^3 (x > 35),\end{aligned}$$

with a linear blending between ages 30 and 35.

Appendix B

An Expanded CI Insurance Market Model of MD

Figure **??** shows the C.I. insurance market model adopted from Gutiérrez & Macdonald (2004). This model is deceptively simple in the case of MD. A more detailed expanded model for computation is shown in Figure B.1:

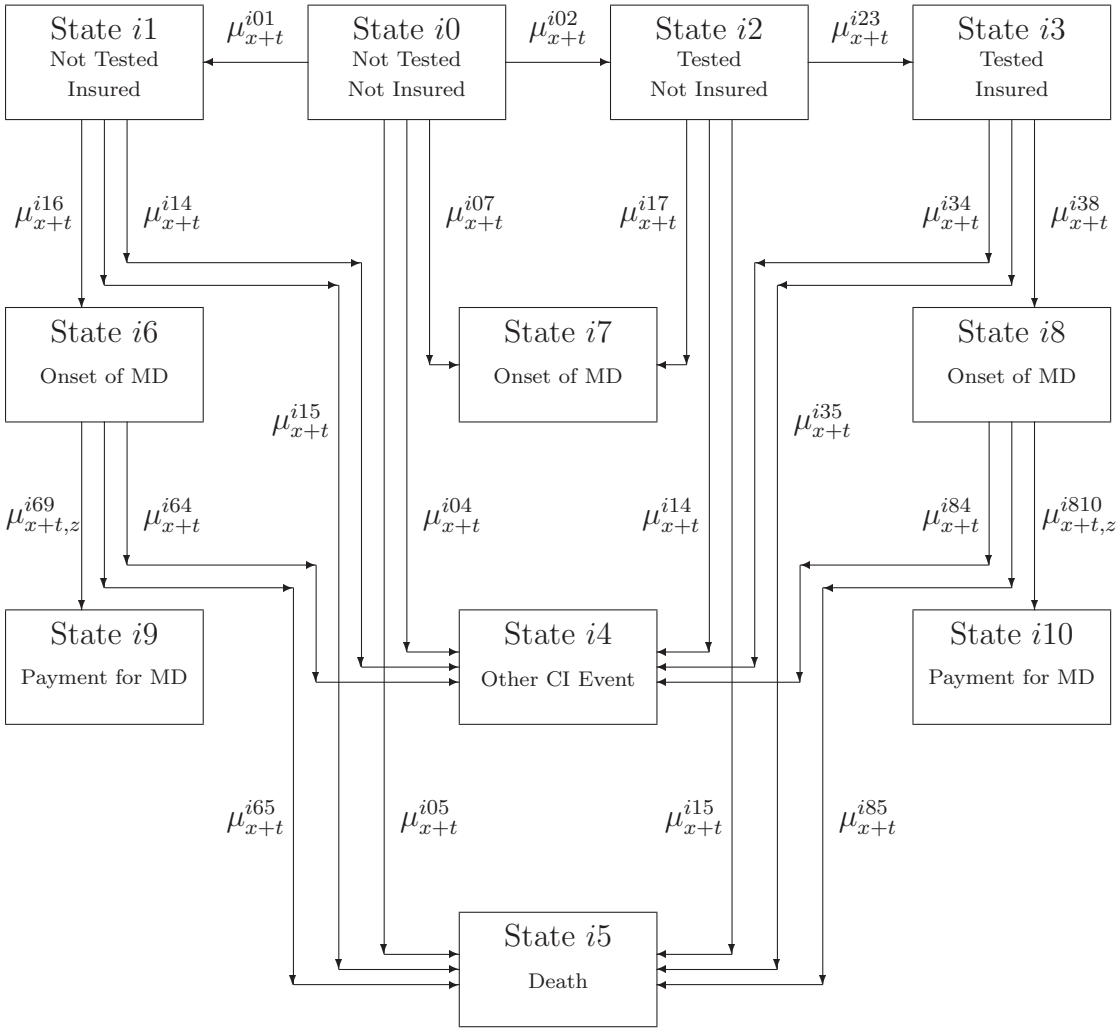

Figure B.1: An expanded semi-Markov model of insurance purchase and critical illness insurance events for a person in sub-population i.

Appendix C

Technical Details of Epidemiologies of Genetic Disorders

The Appendix C presents the technical details of genetic disorders we reviewed in Chapter **??**.

C.1 Adult Polycystic Kidney Disease (APKD)

The Section C.1 correspondents with Section **??** in Chapter **??**.

C.1.1 Onset Rates of ESRD for APKD1 and APKD2 Mutation Carriers

We use $q(x)$ to denote the penetrance at age x. As mentioned before, three studies have published penetrance estimates of APKD1 and APKD2 mutations: Johnson & Gabow (1997), Hateboer *et al.* (1999) and Ravine *et al.* (1992). These papers gave graphs of Kaplan-Meier estimates of the 'survival' probability $1 - q(x)$. In these cases, the event of interest was the first time to occur of ESRD, or death by any cause. That is, death

was not treated as a type of censoring. The approach we adopt is to fit suitable curves to each Kaplan-Meier estimate, which we take to be estimates of:

$$S(x) = \exp(-\int_0^x (\mu_t^{ESRD} + \mu_t^{DEAD})dt),$$

where μ_x^{ESRD} is the onset rate of ESRD and μ_x^{DEAD} is the force of mortality. Then μ_x^{ESRD} on its own can be found using a suitable population mortality table. In Gutiérrez & Macdonald (2007), English Life Table No. 15 is used to adjust. The fitted survival functions based on time to ESRD or death in Hateboer *et al.* (1999) is:

For APKD1:

$$S(x) = 1 - \exp(-9.08371 + 0.231087x - 0.00138536x^2)(x < 40)$$

$$S(x) = 23.0056 \left(\frac{0.345615^{15.1344} \exp(-0.345615x)x^{14.1344}}{\Gamma(15.1344)} \right) (x > 55),$$

with blending by sine curve between ages 40 and 55, and for APKD2:

$$S(x) = 1 - \exp(-11.8117 + 0.25559x - 0.00136435x^2)(x < 58)$$

$$S(x) = 24.7781 \left(\frac{0.364067^{21.278} \exp(-0.364067x)x^{20.278}}{\Gamma(21.278)} \right) (x > 70),$$

with blending by sine curve between ages 58 and 70. The numerical results are plotted in Figure **??**.

C.1.2 Post-ESRD Mortality

The following are mathematical expressions of the Gamma functions fitted to Kaplan-Meier estimates of survival probability functions for ESRD patients receiving treatment, either dialysis or transplantation, based on which the intensity $\mu_{x,z}^{APKD,Mortality}$ is derived.

The fitted cumulative survival probability is

$$1 - S(z) = \frac{a^b}{\Gamma(b)} \int_0^z t^{b-1} e^{-at} dt,$$

with different choices of the parameters based on different age ranges. Variable z denotes the length of time patients have been in ESRD. The numerical results are plotted in Figures **??** and **??**.

Table C.1: Parameterizations of Gamma function fitted to cumulative probability of duration of death following onset of dialysis or kidney transplant.

Ages at Onset	State	a	b
20-44	Dialysis	0.0442787	1.36159
20-44	Transplant	0.0746419	2.54771
45-59	Dialysis	0.0902674	1.61700
45-59	Transplant	0.0249060	1.26870

C.2 Early-onset Alzheimer's Disease (EOAD)

The Section C.2 correspondents with Section **??** in Chapter **??**.

C.2.1 Onset Rates of EOAD for PSEN-1 Mutation Carriers

Espinosa-Castañeda (2006) produced empirical results for the onset rate of EOAD, which does not have a mathematical expression. Please refer to Espinosa-Castañeda (2006) for more details.

C.2.2 Post-onset Mortality Rate for PSEN-1 Mutation Carriers

The mathematical expression of post-onset mortality rate $\mu_z^{EOAD,Mortality}$ for PSEN-1 mutation carriers is:

$$\mu(z) = \left[0.012250264 z^{1.37601} \exp\left(-0.00168128 z^{2.37601}\right)\right],$$

where variable z denotes the length of time people have been in the EOAD state. The numerical results are plotted in Figure **??**.

C.3 Huntington's Disease (HD)

The Section C.3 correspondents with Section **??** in Chapter **??**.

C.3.1 Onset Rates of HD

Since we assume the age of onset, X to have a $N(\mu, \sigma)$ distribution, its density function is:

$$f_X(x) = \frac{1}{\sigma\sqrt{2\pi}} \exp\left\{-\frac{1}{2}\left(\frac{x-\mu}{\sigma}\right)^2\right\}.$$

Denote its cumulative distribution function $F_X(x)$. So the onset rate is:

$$\begin{aligned} \mu_x(\mu, \sigma) &= \frac{f_X(x)}{1 - F_X(x)} \\ &= \frac{\frac{1}{\sigma\sqrt{2\pi}} \exp\{-\frac{1}{2}(\frac{x-\mu}{\sigma})^2\}}{1 - \Phi(\frac{x-\mu}{\sigma})}, \end{aligned}$$

where $\Phi(x)$ is the C.D.F of the unit normal distribution. In our case the estimated parameters are $\mu = 45.038543$ and $\sigma = 14.516176$ (MacCalman, 2009). We are mainly interested in ages between 20 and 60. The numerical results are plotted in Figure **??**.

C.3.2 Post-Onset Mortality of HD Mutation Carriers

In Gutiérrez & Macdonald (2004), the probability of surviving for z years since onset of HD, $S(z)$, is defined as follows.

For age at onset 20–34:

$$1 - S(z) = \frac{0.174219^{4.11789}}{\Gamma(4.11789)} \int_0^z t^{3.11789} e^{-0.174219t} dt.$$

For age at onset 35–49:

$$1 - S(z) = \frac{0.177225^{4.35064}}{\Gamma(4.35064)} \int_0^z t^{3.35046} e^{-0.177225t} dt.$$

For age at onset 50 and over:

$$1 - S(z) = \frac{0.183372^{4.1465}}{\Gamma(4.1465)} \int_0^z t^{3.1465} e^{-0.183372t} dt.$$

The numerical results are plotted in Figure **??**.

C.4 HNPCC

The Section C.4 correspondents with Section ?? in Chapter ??.

C.4.1 Estimation of Onset Rates in HNPCC

The following are the fitted cumulative onset probabilities of contracting CRC for mutation MLH1 and MSH2 carriers, males and females (Lu *et al.*, 2007).

$$F(x)^{CRC}_{MLH1.m} = 0.3406 - 0.039040x + 0.001294x^2 - 0.000009611x^3 (22 \leq x \leq 70),$$

in which we assume $F(x)^{CRC}_{MLH1.m} = 0$ below age 22.

$$F(x)^{CRC}_{MLH1.f} = 0.2193 - 0.02570x + 0.0008584x^2 - 0.000006075x^3 (23 \leq x \leq 70),$$

in which we assume $F(x)^{CRC}_{MLH1.f} = 0$ below age 23.

$$F(x)^{CRC}_{MSH2.m} = \frac{\exp\left(-10.92 + 0.3512x - 0.002579x^2\right)}{1 + \exp\left(-10.92 + 0.3512x - 0.002579x^2\right)} (20 \leq x \leq 68).$$

$$F(x)^{CRC}_{MSH2.f} = \frac{\exp\left(-12.36 + 0.3498x - 0.002421x^2\right)}{1 + \exp\left(-12.36 + 0.3498x - 0.002421x^2\right)} (20 \leq x \leq 70).$$

The following are the fitted cumulative onset probabilities of contracting EC for mutation MLH1 and MSH2 carriers, females only (Lu *et al.*, 2007).

$$F(x)^{EC}_{MLH1} = \frac{\exp(-17.78 + 0.4975x^1 - 0.003655x^2)}{1 + \exp(-17.78 + 0.4975x^1 - 0.003655x^2)} (20 \leq x \leq 65).$$

$$F(x)^{EC}_{MSH2} = \frac{\exp(-4.307 - 0.1973x + 0.008763x^2 - 7.432 \times 10^{-5}x^3)}{1 + \exp(-4.307 - 0.1973x + 0.008763x^2 - 7.432 \times 10^{-5}x^3)} (20 \leq x \leq 65).$$

The following are the fitted cumulative onset probabilities of contracting OECC for mutation MLH1 and MSH2 carriers, males and females. OECC stands for extracolonic cancers, including the cancers of stomach, urinary tract, small bowel, ovary (female only) and brain (Lu *et al.*, 2007).

$$F(x)^{OECC}_{MLH1.m} = \frac{\exp\left(-30.6539 + 0.8128x^1 - 0.0058x^2\right)}{1 + \exp\left(-30.6539 + 0.8128x^1 - 0.0058x^2\right)}(20 \leq x \leq 70).$$

$$F(x)^{OECC}_{MLH1.f} = \frac{\exp\left(-18.76 + 0.4747x - 0.003334x^2\right)}{1 + \exp\left(-18.76 + 0.4747x - 0.003334x^2\right)}(20 \leq x \leq 70).$$

$$F(x)^{OECC}_{MSH2.m} = \frac{\exp\left(-7.1635 + 0.10027x - 2.3206 \times 10^{-4}x^2\right)}{1 + \exp\left(-7.1635 + 0.10027x - 2.3206 \times 10^{-4}x^2\right)}(42 \leq x \leq 65),$$

in which below age 42, the intensity corresponding to $F(x)^{OECC}_{MSH2.m}$ is extrapolated linearly to the origin.

$$F(x)^{OECC}_{MSH2.f} = \frac{\exp\left(-10.45 + 0.2501x - 0.001618x^2\right)}{1 + \exp\left(-10.45 + 0.2501x - 0.001618x^2\right)}(20 \leq x \leq 70).$$

The following are the fitted onset rates of CRC for populations, both males and females (Lu *et al.*, 2007).

$$\mu^{CRC}_{pop.m}(x) = 0.001401\frac{\Gamma(10.196)}{\Gamma(8.196)\Gamma(x)}\left(\frac{80x}{89^2}\right)^{7.196}\left(1 - \frac{80x}{89^2}\right)$$

$$\mu^{CRC}_{pop.f}(x) = 0.001092\frac{\Gamma(8.207)}{\Gamma(6.742)\Gamma(1.465)}\left(\frac{80x}{89^2}\right)^{5.742}\left(1 - \frac{80x}{89^2}\right)^{0.465}$$

The following are the fitted onset rates of EC for populations, females only (Lu *et al.*, 2007).

$$\mu_{pop}^{EC}(x) = \begin{cases} \exp(-17.32 - 0.09261x + 0.004273x^2 - 5.200 \times 10^{-5}x^3) & (20 \leq x \leq 54) \\ -4.665 \times 10^{-4} + 2.446 \times 10^{-5}x - 1.555 \times 10^{-7}x^2 & (57 \leq x \leq 89), \end{cases}$$

blended linearly between age 54 and 57.

C.4.2 Estimation of Post-onset Mortality in HNPCC

We surveyed the following papers, in order to estimate the post-onset mortality associated with CRC.

1. Watson *et al.* (1998)

   In this case-control study, the study group was the sampled HNPCC patients and the control group was the sporadic CRC patients. In the study group, CRC cases were selected from 98 HNPCC families in the registries at Roswell Park Cancer Institute and Creighton University. Amsterdam criteria is used to ascertain the HNPCC patients. In the control group, the sporadic CRC patients were selected from the tumor registry (TR) of a single hospital affiliated with Creighton University. Every patient was staged at the time of diagnosis based on TNM system. The diagnosis of CRC was treated as the start of survival analysis. The observation ends either by censoring because of death, or development of CRC, or 10 years after the analysis. The Kaplan-Meier methods were used in the survival analysis. We obtained the original data from Dr. Patrice Watson, the principal author of Watson *et al.* (1998).

2. Sankila *et al.* (1996)

   Sankila *et al.* (1996) is a case-control study, where the sampled HNPCC patients represent the study group and sampled sporadic CRC patients represent the study group. In the study group, 175 HNPCC patients from 39 families were ascertained

by using Amsterdam Criteria. Genetic testing was carried out in these families. One similar germline mutation of MLH1 has been found in 17 of these families, another mutation has been found in 4 families. Of the 175 patients, 120 were from the families with germline mutation in MLH1 gene. From 1953 to 1993, 14,261 sporadic CRC patients were reported to Finnish Cancer Registry. Of These people, 14,086 patients younger than 65 year old represent the control group. The follow-up will stop either at the date of death or emigration or on the closing day of December 31, 1993, whichever occurred first. No patient was lost from the follow-up. Cumulative relative survival rates (RSRs) were calculated by dividing the observed with the expected survival rates. The expected survival rates were derived from the sex, age and calendar period-specific life tables of the general Finnish population. The main conclusion drawn from this paper is that survival rate of HNPCC patients is better than sporadic CRC patients.

3. Lin *et al.* (1998)

   Lin *et al.* (1998) is a case-control study. The study group was composed of members from seven MLH1 germline mutation families and five MSH2 germline mutation families diagnosed with colorectal cancer from 1945 to 1991 and registered at the Hereditary Cancer Institute (Creighton University). Colorectal cancer patients from 1965 to 1996, totalling 1,189, registered with the Creighton University tumor registry, served as the general population cohort. Ten-year survival was calculated using Kaplan-Meier methodology. The result is that combined MLH1 and MSH2 ten-year survival was 68.7% compared with 47.8% for the general population. Therefore HNPCC patients indeed have a better survival probability than the sporadic CRC patients.

4. Tomoda, Baba & Akazawa (1999)

The authors compared the survival between 46 HNPCC patients (study group) and 1185 sporadic CRC patients registered at the National Kyushu Cancer Center between 1972 and 1995 (control group). Five-year survival probabilities were 78.1% and 62.2% for study group and control group respectively. The survival probabilities were calculated using Kaplan-Meier methods. The main conclusion is that the prognosis of HNPCC patients is better than that of sporadic CRC patients, and it agreed with the conclusion drawn in Sankila *et al.* (1996).

5. Bertario *et al.* (1999)

   The authors examined 2,340 colorectal-cancer patients: 144 HNPCC patients (Amsterdam Criteria), 161 FAP patients and 2,035 patients with sporadic cancer. Data on hereditary-cancer patients treated between 1980 and 1995 was collected in a registry. The 2,035 sporadic colorectal-cancer patients (controls) included all new cases treated in the Department of Gastrointestinal-Tract Surgery during the same period. Observed survival was estimated using the Kaplan-Meier method. Cumulative survival probability was estimated at 5 years within each group. All patients were staged using the Dukes system. In the sporadic group, 51% were early-stage cancers (Dukes A or B) vs. 48.4% and 52.1% in the FAP and HNPCC groups respectively. In the HNPCC, FAP and sporadic-cancer groups, the 5-year cumulative survival rates was 56.9%, 54.4% and 50.6% respectively. The survival rates were calculated using the Kaplan-Meier methods. The conclusion is that FAP patients, especially HNPCC patients appear to have a better prognosis than sporadic CRC patients.

6. Elsakov & Kurtinaitis (2006)

   The authors aimed to evaluate survival rates in Lithuanian HNPCC patients and compare them with survival rates of sporadic cases arising from the general population. This is a case-control study. The study group consisted of 8 patients from

6 HNPCC families, diagnosed between 1995 and 1999. HNPCC patients characteristic (age and stage) were used to trace the records of the Cancer Registry at the same period to identify the control cases corresponding the required criteria. 263 sporadic CRC patients were found - 106 at stage II and 157 at stage III. The result is that the 10-year survival was 87.5% in the HNPCC study group compared with only 44.8% in the control group. The 10-year survival probabilities were calculated using Kaplan-Meier methodology. The conclusion is that HNPCC patients with confirmed MSH2 or MLH1 mutations diagnosed with stages II and III CRC have a good 10-year survival prognoses compared with those from the general population.

7. Percesepe *et al.* (1997)

   This study evaluated the clinical outcome of HNPCC patients with respect to that of patients with colorectal cancer recorded in a population-based cancer registry. The authors assessed survival of 85 colorectal cancer patients from 24 unrelated families defined as having HNPCC according to the criteria of the International Collaborative Group and a 5-year follow-up (cancer diagnosis from 1980-1989) were available. 377 sporadic CRC patients, registered from 1984-1986, with a 5-year follow-up, were used for comparison. Overall, Colorectal cancer-specific 5-year survival rates were 55.2% and 42.5% for HNPCC patients and sporadic CRC patients, respectively. The patients were stage-stratified and compared in terms of 5-year survival probabilities. Stage II HNPCC patients exhibited a better prognosis than the corresponding cases in the sporadic CRC patients. Other stages were incomparable due to the small number of HNPCC patients. The survival rates were calculated using Kaplan-Meier methods. The conclusion is both overall and stage II HNPCC patients showed a survival advantage in comparison with sporadic CRC patients.

We surveyed a series of papers, in order to estimate the post-onset mortality associated with OECC, including cancer of stomach, urinary tract, small bowel, ovarian (female

only) and brain. However, only three papers were located, which related to stomach cancer, small bowel cancer and ovarian cancer. As to HNPCC-associated urinary tract cancer and brain cancer, we can not locate any paper.

1. Ovarian Cancer: Crijnen *et al.* (2005)

   The aim of this study was to compare the survival after contracting OC between HNPCC patients (study group) and sporadic OC patients (control group). A total of 26 HNPCC patients with OC, as study group, were identified from the Dutch HNPCC Registry. A control group (52 cases) matched for age, stage and year of diagnosis was derived from the population-based Eindhoven Cancer Registry. Kaplan-Meier methods were used to calculate the survival probabilities. The authors found the cumulative 5-year-survival rates were 64.2 and 58.1% respectively, and concluded that the survival rates was not significantly different between HNPCC patients with OC and the sporadic OC patients.

2. Gastric Cancer: Aarnio *et al.* (1997)

   The authors gathered clinical data relating to patients recorded in the Finnish HNPCC registry, in order to identify characteristics of HNPCC-associated gastric cancer. This study is not a case-control study. The data included 51 families with a characterized mutation and/or that met the Amsterdam criteria. Of 570 members affected by malignancy, gastric cancer occurred in 62. The overall 5-year survival rate was 15%. The 5-year survival rate was 48% in cases in whom radical surgery had been undertaken. Kaplan-Meier methods were used to calculate the survival rates. However, this paper did not include the information about the 5-year survival rate for the sporadic gastric cancer.

3. Small bowel cancer: Schulmann *et al.* (2005)

The authors aimed to study the risk of HNPCC-associate small bowel cancer (HNPCC-SBC). In the study, the information of 32 HNPCC-SBC patients were retrieved from the databased of the German HNPCC Consortium based on the Amsterdam and Bethesda criteria. The overall 10-year survival rate was 87%. Kaplan-Meier methods were used to calculate the survival rate. However, this paper did not include the information about the 5-year survival rate for the sporadic small bowel cancer.

C.5 BC & OC

The Section C.5 correspondents with Section **??** in Chapter **??**.

C.5.1 Onset Rates of Breast Cancer and Ovarian Cancer

The following are the fitted onset rates of breast cancer and ovarian cancer for mutation BRCA1 and BRCA2 carriers (Gui *et al.*, 2006).

$$\mu_x^{BC,BRCA1} = 1.1874 \times 10^{-16} e^{-0.21x} x^1 1.2,$$

$$\mu_x^{BC,BRCA2} = 8.3108 \times 10^{-13} e^{-0.1x} x^7 .37,$$

$$\mu_x^{OC,BRCA1} = 1.3318 \times 10^{-9} e^{-0.03x} x^4 .48,$$

$$\mu_x^{OC,BRCA2} = 3.5915 \times 10^{-79} e^{1.00x} x^5 6.95.$$

The following are the fitted onset rates of breast cancer and ovarian cancer for non-mutation carriers (Gui *et al.*, 2006).

$$\mu_x^{BC,POP} = \begin{cases} 6.0425 \times 10^{-15} e^{-0.0742} x^{7.7305} & (0 \le x \le 53) \\ 0.00012 + 0.00018(x-35) - 0.00005(x-35)^2 + 0.0000000529(x-35)^3 & (x \ge 53), \end{cases}$$

$$\mu_x^{OC,POP} = \begin{cases} 1.3567 \times 10^{-13} e^{-0.035x} x^5 .92 & (0 \le x \le 45) \\ 0.0001554 + 0.000029(x-45) - 0.00000048(x-45)^2 & (x \ge 55). \end{cases} \tag{C.1}$$

C.5.2 Post-onset Mortality Associated with Breast Cancer and Ovarian Cancer

The following are the graduated post-onset mortality associated with breast cancer and ovarian cancer for each duration separately up to 6 years, and then to 6 years and over (Gui *et al.*, 2006).

$0 \le Duration \le 1$

$$\begin{aligned} \mu_{x,d}^{BC} &= 2.00266 - 0.1507811x + 0.004264272x^2 - 5.27552 \times 10^{-5} x^3 + 2.456224 \times 10^{-7} x^4, \\ \mu_{x,d}^{OC} &= \exp(-2.71394 + 0.023657x + 0.1960156 \times 10^{-3} x^2). \end{aligned}$$

$1 \le Duration \le 2$

$$\begin{aligned} \mu_{x,d}^{BC} &= \exp(0.6037712037 - 0.01500175x + 0.1111315 \times 10^{-3} x^2) \\ &\quad \times (0.0474102 + 0.307835 \times 10^{-3} x + \exp(3.06993 - 0.284105x + 0.00266558x^2)), \\ \mu_{x,d}^{OC} &= \exp(-9.6097147 + 0.3634146x - 0.005149204x^2 + 0.2471276 \times 10^{-4} x^3). \end{aligned}$$

$2 \le Duration \le 3$

$$\begin{aligned} \mu_{x,d}^{BC} &= \exp(0.4971436820 - 0.01500175x + 0.1111315 \times 10^{-3} x^2) \\ &\quad \times (0.0474102 + 0.307835 \times 10^{-3} x + \exp(3.06993 - 0.284105x + 0.00266558x^2)), \\ \mu_{x,d}^{OC} &= \exp(-10.1965014 + 0.3634146x - 0.005149204x^2 + 0.2471276 \times 10^{-4} x^3). \end{aligned}$$

$3 \leq Duration \leq 4$

$$\begin{aligned}
\mu_{x,d}^{BC} &= \exp(0.3905161603 - 0.01500175x + 0.1111315 \times 10^{-3}x^2) \\
&\quad \times (0.0474102 + 0.307835 \times 10^{-3}x + \exp(3.06993 - 0.284105x + 0.00266558x^2)), \\
\mu_{x,d}^{OC} &= \exp(-13.4719011 + 0.52647732x - 0.008227498x^2 + 0.4354431 \times 10^{-4}x^3).
\end{aligned}$$

$4 \leq Duration \leq 5$

$$\begin{aligned}
\mu_{x,d}^{BC} &= \exp(0.352482834 - 0.003144911x) \\
&\quad \times (0.02902753 + \exp(-0.1624326x + 0.00164027x^2)), \\
\mu_{x,d}^{OC} &= \exp(-14.1632748 + 0.52647732x - 0.008227498x^2 + 0.4354431 \times 10^{-4}x^3).
\end{aligned}$$

$5 \leq Duration \leq 6$

$$\begin{aligned}
\mu_{x,d}^{BC} &= \exp(0.082950962 - 0.000880887x) \\
&\quad \times (0.02902753 + \exp(-0.1624326x + 0.00164027x^2)), \\
\mu_{x,d}^{OC} &= \exp(-14.8546485 + 0.5384382x - 0.008227498x^2 + 0.4354431 \times 10^{-4}x^3).
\end{aligned}$$

$6 \leq Duration$

$$\begin{aligned}
\mu_{x,d}^{BC} &= \exp(0.082950962 - 0.000880887x) \\
&\quad \times (0.02902753 + \exp(-0.1624326x + 0.00164027x^2)), \\
\mu_{x,d}^{OC} &= \exp(-14.8546485 + 0.5384382x - 0.008227498x^2 + 0.4354431 \times 10^{-4}x^3).
\end{aligned}$$

C.5.3 Mortality Rates Excluding the Death Caused by BC and OC

For females, the fitted function for r_x^{BCOC} is

$$r_x^{BCOC} = \begin{cases} 2.0785 \times 10^{-17} e^{-0.28} x^{13.05} & (0 \leq x \leq 54) \\ 1.30144 - 0.02850194x + 0.0001588314x^2 & (x \geq 65), \end{cases}$$

with linear blending of the two functions between ages 54 and 65 (Gui *et al.*, 2006).

Appendix D

Fourth Order Runge-Kutta Method

Fourth Order Runge-Kutta methods are one of the most commonly used methods to solve ODE. We give a short summary here. See Press *et al.* (1988) for details.

Let $y' = f(x, y)$ and the initial value is that $y(x_0) = y_0$. Suppose h is the stepsize, we have the following recursive equations:

$$\begin{aligned} y_{n+1} &= y_n + \frac{1}{6}h(k_1 + 2k_2 + 2k_3 + k_4) \\ x_{n+1} &= x_n + h, \end{aligned}$$

where y_{n+1} is the approximation of $y(x_{n+1})$, and

$$\begin{aligned} k_1 &= f(x_n, y_n) \\ k_2 &= f(x_n + \frac{1}{2}h, y_n + \frac{1}{2}hk_1) \\ k_3 &= f(x_n + \frac{1}{2}h, y_n + \frac{1}{2}hk_2) \\ k_4 &= f(x_n + h, y_n + hk_3) \end{aligned}$$

The analogy is that the next value y_{n+1} is determined by the previous value y_n plus

the increment between x_n and x_{n+1}, which is the product of stepsize h and an estimated slope $\frac{1}{6}(k_1 + 2k_2 + 2k_3 + k_4)$.