TABLE IV - IMPACT OF *FGFR2* POLYMORPHISM (RS2420946) STRATIFIED BY REPRODUCTIVE HORMONES-RELATED ENVIRONMENTAL RISK FACTORS ACCORDING TO MENOPAUSAL STATUS

	Premenopausal [No. of cases/controls, ORs (95% CIs)]				Postmenopausal [No. of cases/controls, ORs (95% CIs)]			
	CC	CT	TT	p_{trend}	CC	CT	TT	p_{trend}
BMI								
<25	66/174, 1.00 (ref.)	97/169, 1.49 (1.01–2.19)	22/39, 1.49 (0.81–2.74)	0.061	69/146, 1.00 (ref.)	79/166, 1.01 (0.68–1.5)	26/47, 1.25 (0.71–2.22)	0.534
≥25.0	10/20, 1.00 (ref.)	16/24, 1.48 (0.51–4.3)	4/6, 1.23 (0.24–6.16)	0.635	22/57, 1.00 (ref.)	34/54, 1.82 (0.91–3.63)	8/5, 4.77 (1.27–17.93)	0.012
Age at menarche								
≥15	12/23, 1.00 (ref.)	14/22, 1.47 (0.43–5.02)	0/6, NE	0.569	30/61, 1.00 (ref.)	34/77, 0.96 (0.52–1.78)	12/18, 1.60 (0.66–3.88)	0.452
13–14	39/90, 1.00 (ref.)	47/101, 1.09 (0.63–1.87)	12/22, 1.25 (0.54–2.9)	0.598	48/104, 1.00 (ref.)	55/101, 1.24 (0.76–2.03)	16/25, 1.59 (0.75–3.36)	0.191
≤12	25/81, 1.00 (ref.)	52/71, 2.35 (1.31–4.23)	14/18, 2.90 (1.2–7.02)	0.003	10/31, 1.00 (ref.)	24/32, 2.26 (0.88–5.76)	6/6, 3.23 (0.82–12.68)	0.049
Parity								
≥3	11/41, 1.00 (ref.)	16/38, 1.45 (0.56–3.76)	2/13, 0.53 (0.08–3.34)	0.928	27/55, 1.00 (ref.)	29/63, 0.93 (0.47–1.84)	9/22, 0.91 (0.35–2.37)	0.815
1–2	55/110, 1.00 (ref.)	74/112, 1.32 (0.84–2.09)	18/27, 1.28 (0.63–2.62)	0.296	55/127, 1.00 (ref.)	76/139, 1.29 (0.84–1.97)	20/26, 1.89 (0.95–3.78)	0.062
0	10/43, 1.00 (ref.)	23/41, 3.02 (1.14–7.97)	6/5, 5.54 (1.27–24.11)	0.008	9/20, 1.00 (ref.)	8/19, 0.88 (0.24–3.23)	5/5, 4.89 (0.6–39.98)	0.306
Age at menopause								
≤49					48/91, 1.00 (ref.)	30/56, 1.38 (0.78–2.45)	5/8, 0.86 (0.28–2.65)	0.632
≥50					74/163, 1.00 (ref.)	63/128, 1.06 (0.69–1.64)	18/26, 1.97 (1.09–3.58)	0.056

BMI, body mass index; NE, not estimated.
ORs were matched for age and menopausal status and adjusted for drinking habit, smoking habit, current body mass index, regular exercise, family history of breast cancer, age at menarche, parity, hormone use for contraception, infertility treatment or hormone replacement and referral pattern to our hospital.

the OR for homozygotes of the minor allele (TT) compared with CC was 1.46 (95% CI: 1.01–2.12).

Discussion

This study demonstrated that *FGFR2* intronic polymorphism had significant interactions with age at menarche and parity, which are considered to be reproductive risk factors of breast cancer. On stratified analysis, BMI $\geq$ 25 revealed a significant association with the rs2420946 polymorphism only among postmenopausal subjects. In contrast, BMI < 25 had no significant association with this polymorphism regardless of menopausal status. These findings suggest that *FGFR2* intronic SNPs affect the reproductive hormone-related pathway in the development of female breast cancer in the Japanese population.

High BMI is associated with increased risk of postmenopausal breast cancer.[21] The mechanism of this increased risk is considered to be related to the increase in circulating hormone levels. In postmenopausal women, the major supplier of estrogen is adipose tissue and a linear association between BMI and estrogen level was shown.[22] On the other hand, most epidemiological studies showed an inverse association in premenopausal women, that is, high BMI was associated with reduced risk of premenopausal breast cancer.[23] These features are compatible with our finding that BMI $\geq$ 25 had a significant association with *FGFR2* polymorphism in postmenopausal women, which is in support of the hypothesis that the intronic SNP of interest is associated with the carcinogenic process of breast cancer due to exposure to high levels of reproductive hormones.

Early onset of menarche has been associated with increased risk of both premenopausal and postmenopausal breast cancer, because early onset of menarche leads to early onset of elevated reproductive hormone levels.[24] This is consistent with the finding that late onset of menopause is associated with increased risk of postmenopausal breast cancer.[24] The current study demonstrated that *FGFR2* intronic polymorphisms had a significant interaction with age at menarche (Table III and Supporting Information Tables I–III), and that the rs2420946 intronic polymorphism had a marginal association with age at menopause $\geq$50 years among postmenopausal subjects (Table IV). The relationship between parity and breast cancer risk is complex, although nulliparous women have a higher risk of breast cancer than parous women.[24] A possible explanation according to reproductive hormone levels is that the increased risk due to high hormone levels during pregnancy is overcome by the reduction in risk due to an extended period of lower hormone levels after pregnancy.[25] Thus, the current findings of an interaction between *FGFR2* polymorphism and these reproductive risk factors on the development of breast cancer support the notion that the *FGFR2* intronic polymorphism is associated with the carcinogenic process of breast cancer in individuals who have been exposed to high reproductive hormone levels in Japan.

We did not find any interaction between hormone use and the 5 SNPs of interest. One possible explanation is that the low prevalence of hormone use in this Japanese population missed detection of an association; another explanation is that the SNPs of interest interact with internal hormone production, and not with externally supplemented hormone. Rebbeck *et al.*[9] reported an interaction between combined hormone replacement therapy and *FGFR2* intronic polymorphism in European-American women but not in African-American women. There may be ethnic disparities in this interaction. We also found significant inverse interaction between family history of breast cancer and risk genotypes of *FGFR2* intronic polymorphisms in the analysis of reproductive risk factors for breast cancer. Although this interaction would be difficult to be explained plausibly, the inverse interaction with family history may be a surrogate for the interaction with an unknown genetic susceptibility factor, for example, hormone metabolism-modifying genetic polymorphisms. Further investigation of this point is warranted. We can not deny the possibility of a random effect due to the small number of breast cancer cases with a family

history (n = 32) in the current study, especially the subset of cases who were homozygotes of the risk allele with a family history.

Recently, Meyer *et al.*[26] clarified that 2 *FGFR2* intronic SNPs (rs7895676 and rs2981578) alter the binding affinity of *FGFR2* for transcription factors and increase FGFR2 expression. These 2 SNPs are located in the same linkage disequilibrium block of interest, although these 2 SNPs were not evaluated in this study. The study by Meyer *et al.* was the first evidence regarding mechanisms between particular *FGFR2* intronic SNPs and breast cancer risk by an experimental study. In epidemiological studies, a significant additive interaction of risk genotypes of *FGFR2* intronic polymorphisms with menopausal status was found in Chinese women[8] and with combined hormone replacement therapy use[9] in European-American women. In this study, we could demonstrate clear interactions of *FGFR2* intronic polymorphisms with age at menarche and parity in Japanese women. These recently accumulated evidences from both epidemiological and experimental studies including this study suggest that the risk alleles of *FGFR2* polymorphisms increase FGFR2 expression on breast cancer cells and this effect would depend on the exposed reproductive hormone level. Elevated expression of FGFR2 may induce proliferation of the cells due to establishing an autocrine signaling loop and inhibition of apoptosis.[27] Therefore, individuals with expected high lifetime exposure to reproductive hormones, for example, women with early age at menarche or nulliparous women, would be more susceptible to the effect of risk alleles of *FGFR2* polymorphisms on increasing breast cancer risk. Thus, FGFR2 would be considered to play an important role in the association between reproductive hormone level and increased breast cancer risk. Further epidemiological and experimental studies are warranted to explore and confirm the roles of *FGFR2* polymorphisms in increasing breast cancer risk.

The methodology of this study warrants discussion. First, with regard to the control population, we used noncancer patients at the ACCH on the basis of the fact that our subjects arose within this population, warranting internal validity. To account for the difference in background between the cases and controls, we adjusted for referral pattern to our hospital. In addition, with regard to the external validity of our results, we previously showed that individuals selected randomly from our control population were similar to the general population from which they were drawn in terms of the exposure of interest.[15] Second, as with other case-control studies, this study may have suffered from recall bias. As the questionnaires were completed before diagnosis at our hospital, the HERPACC system is less prone to this type of bias. A further potential source of bias was the medical background of the controls, but this would have had only limited impact[16] as described in the Material and Methods section. However, several of the diagnoses of the controls (benign tumors, mastitis and benign gynecologic disease) could be influenced by hormone exposure. This could possibly explain some oddities in our analyses, namely, that null parity and hormone replacement therapy use seem to protect against breast cancer (Table I). Third, although we tried to perform conditional logistic regression as the primary analysis, we finally applied unconditional logistic regression to avoid dropping of controls, leading to unstable estimation in stratified analysis. Bias from ignoring the matching was possible; however, consistency between conditional and unconditional logistic regression models was confirmed. Lastly, the results in this study may be false-positive due to small sample size, particularly in subgroup analysis; thus, a large-scale study is needed to confirm our results.

In conclusion, our case-control study revealed a significant association between *FGFR2* intronic SNPs and breast cancer risk with a relatively high population-attributable risk (17.7%), as well as a significant interaction between *FGFR2* intronic SNPs and reproductive hormones-related environmental risk factors in the Japanese population. These findings suggest that *FGFR2* intronic SNPs contribute to the development of female breast cancer through a reproductive hormone-related pathway. Furthermore, with the results of genotyping of *FGFR2* intronic polymorphisms, it would be possible to tell the risk of individual Japanese women for breast cancer according to their reproductive lifestyles or reproductive history, and develop individualized plans for preventive actions against the development of breast cancer.

Acknowledgements

The authors are grateful to all the doctors, nurses, technical staff and hospital business staff of Aichi Cancer Center Hospital for daily administration of the HERPACC study. They also thank Dr. Setsuko Kawase for her expert technical assistance.

References

1. IARC. Breast cancer. In: Stewart BW, Kleihues P, eds. World cancer report. Lyon: IARC, 2003:188–193.
2. Bray F, McCarron P, Parkin DM. The changing global patterns of female breast cancer incidence and mortality. Breast Cancer Res 2004;6:229–39.
3. Matsuno RK, Anderson WF, Yamamoto S, Tsukuma H, Pfeiffer RM, Kobayashi K, Devesa SS, Levine PH. Early- and late-onset breast cancer types among women in the United States and Japan. Cancer Epidemiol Biomarkers Prev 2007;16:1437–42.
4. IARC. Cancer incidence in five continents, vol.IX. Lyon: IARC, 2007.
5. Easton DF, Pooley KA, Dunning AM, Pharoah PD, Thompson D, Ballinger DG, Struewing JP, Morrison J, Field H, Luben R, Wareham N, Ahmed S, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 2007;447:1087–93.
6. Hunter DJ, Kraft P, Jacobs KB, Cox DG, Yeager M, Hankinson SE, Wacholder S, Wang Z, Welch R, Hutchinson A, Wang J, Yu K, et al. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. Nat Genet 2007;39:870–4.
7. Raskin L, Pinchev M, Arad C, Lejbkowicz F, Tamir A, Rennert HS, Rennert G, Gruber SB. FGFR2 is a breast cancer susceptibility gene in Jewish and Arab Israeli populations. Cancer Epidemiol Biomarkers Prev 2008;17:1060–5.
8. Liang J, Chen P, Hu Z, Zhou X, Chen L, Li M, Wang Y, Tang J, Wang H, Shen H. Genetic variants in fibroblast growth factor receptor 2 (FGFR2) contribute to susceptibility of breast cancer in Chinese women. Carcinogenesis 2008;29:2341–6.
9. Rebbeck TR, DeMichele A, Tran TV, Panossian S, Bunin GR, Troxel AB, Strom BL. Hormone-dependent effects of FGFR2 and MAP3K1 in breast cancer susceptibility in a population-based sample of postmenopausal African-American and European-American women. Carcinogenesis 2009;30:269–74.
10. Adnane J, Gaudray P, Dionne CA, Crumley G, Jaye M, Schlessinger J, Jeanteur P, Birnbaum D, Theillet C. BEK and FLG, two receptors to members of the FGF family, are amplified in subsets of human breast cancers. Oncogene 1991;6:659–63.
11. Pollock PM, Gartside MG, Dejeza LC, Powell MA, Mallon MA, Davies H, Mohammadi M, Futreal PA, Stratton MR, Trent JM, Goodfellow PJ. Frequent activating FGFR2 mutations in endometrial carcinomas parallel germline mutations associated with craniosynostosis and skeletal dysplasia syndromes. Oncogene 2007;26:7158–62.
12. Davies H, Hunter C, Smith R, Stephens P, Greenman C, Bignell G, Teague J, Butler A, Edkins S, Stevens C, Parker A, O'Meara S, et al. Somatic mutations of the protein kinase gene family in human lung cancer. Cancer Res 2005;65:7591–5.
13. Jang JH, Shin KH, Park JG. Mutations in fibroblast growth factor receptor 2 and fibroblast growth factor receptor 3 genes associated with human gastric and colorectal cancers. Cancer Res 2001;61:3541–3.
14. Suzuki T, Matsuo K, Hirose K, Hiraki A, Kawase T, Watanabe M, Yamashita T, Iwata H, Tajima K. One-carbon metabolism-related gene polymorphisms and risk of breast cancer. Carcinogenesis 2008;29:356–62.
15. Inoue M, Tajima K, Hirose K, Hamajima N, Takezaki T, Kuroishi T, Tominaga S. Epidemiological features of first-visit outpatients in Japan: comparison with general population and variation by sex, age, and season. J Clin Epidemiol 1997;50:69–77.
16. Hamajima N, Hirose K, Takazaki T, Kuroishi T, Tajima K. Age-specific risk factors of breast cancer estimated by a case-control study in Japan. J Epidemiol 1995;5:99–105.
17. Hamajima N, Matsuo K, Saito T, Hirose K, Inoue M, Takezaki T, Kuroishi T, Tajima K. Gene-environment Interactions and

Polymorphism Studies of cancer risk in the Hospital-based Epidemiologic Research Program at Aichi Cancer Center II (HERPACC-II). Asian Pac J Cancer Prev 2001;2:99–107.
18. Tajima K, Hirose K, Inoue M, Takezaki T, Hamajima N, Kuroishi T. A model of practical cancer prevention for out-patients visiting a hospital: the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC). Asian Pac J Cancer Prev 2000;1:35–47.
19. Livak KJ. Allelic discrimination using fluorogenic probes and the 5′ nuclease assay. Genet Anal 1999;14:143–9.
20. Klatsky AL, Siegelaub AB, Landy C, Friedman GD. Racial patterns of alcoholic beverage use. Alcohol Clin Exp Res 1983;7:372–7.
21. Hunter DJ, Willett WC. Diet, body size, and breast cancer. Epidemiol Rev 1993;15:110–32.
22. Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, Longcope C, Stanczyk FZ, Stephenson HE, Jr, Falk RT, Miller R, Schatzkin A, Allen DS, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. J Natl Cancer Inst 2003;95:1218–26.
23. Ursin G, Longnecker MP, Haile RW, Greenland S. A meta-analysis of body mass index and risk of premenopausal breast cancer. Epidemiology 1995;6:137–41.
24. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiol Rev 1993;15:36–47.
25. Bernstein L, Ross RK. Endogenous hormones and breast cancer risk. Epidemiol Rev 1993;15:48–65.
26. Meyer KB, Maia AT, O'Reilly M, Teschendorff AE, Chin SF, Caldas C, Ponder BA. Allele-specific up-regulation of FGFR2 increases susceptibility to breast cancer. PLoS Biol 2008;6:e108.
27. Hishikawa Y, Tamaru N, Ejima K, Hayashi T, Koji T. Expression of keratinocyte growth factor and its receptor in human breast cancer: its inhibitory role in the induction of apoptosis possibly through the overexpression of Bcl-2. Arch Histol Cytol 2004;67:455–64.

Cancer Science
The official journal of the Japanese Cancer Association JCA

Incidence and survival trends for childhood cancer in Osaka, Japan, 1973–2001

Sachiko Baba,[1,2] Akiko Ioka,[3] Hideaki Tsukuma,[3] Hiroyuki Noda,[1,4] Wakiko Ajiki[5] and Hiroyasu Iso[1,6]

[1]Public Health, Department of Social and Environmental Medicine, and [2]Center for International Relations, Graduate School of Medicine, Osaka University, Osaka; [3]Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan; [4]Harvard Center for Population and Development Studies, Boston, Massachusetts, USA; [5]Cancer Information Services and Surveillance Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan

(Received June 26, 2009/Revised October 31, 2009/Accepted November 6, 2009/Online publication February 2, 2010)

Mortality for childhood cancer has declined in Osaka, as well as all over Japan, since the 1970s, but whether this decline can be explained by trends of incidence or survival of childhood cancer has not been examined. A total of 5960 malignant tumors diagnosed between 1973 and 2001 in children <15 years of age were registered at the Osaka Cancer Registry in Japan. The time trends for childhood cancer were analyzed over 29 years for incidence and 20 years for survival. Leukemia was the most common among childhood cancer for both sexes and accounted for one-third of all cases. The age-standardized annual incidence rate of all tumors was highest in 1988–1992: 155.1 per million for males and 135.9 for females. Five-year survival for all tumors improved from 50.1% in 1978–1982 to 73.0% in 1993–1997 for males and from 52.3% to 76.3% for females. Thus, the constant decline in mortality in childhood cancer was primarily due to improved survival between the 1970s and 1980s and reduced incidence after the 1990s. (*Cancer Sci* 2010; 101: 787–792)

Cancer is the second-highest cause of death for children <15 years of age in Japan, following accident as unintentional injury.[1] According to Vital Statistics, mortality rates for childhood cancer all over Japan have declined consistently since the beginning of 1970s for both sexes and it is similar to Osaka.[1,2] However, no studies have systematically examined trends for incidence and survival of childhood cancer to explain this mortality decline in Japan. In the USA, the Surveillance Epidemiology and End Result (SEER) program publishes annual reports on mortality, incidence, and survival.[3] Europe has large-scale registries such as the Automated Childhood Cancer Information System Project (ACCIS) and the EUROCARE study which reports incidence and survival periodically.[4–6] However, mortality data for individual countries is not available. Information on mortality, incidence, and survival has been exceptionally available from Britain.[7] An important question is to what degree the decline in the mortality from childhood cancer reflects incidence and survival trends. Marugame *et al.* have reported on the incidence of childhood cancer from 1993 to 2001, using the data of 15 population-based cancer registries in Japan, but long-term trends have not been examined.[8] In Japan there is no nationwide cancer registry, although a large population is needed to monitor childhood trends of cancer. The Osaka Cancer Registry is one of the few registries in the world that has a long history and covers a large-enough population to monitor trends of childhood cancer. Ajiki *et al.* described incidence trends for childhood cancer based on 12 major cancer classifications from 1971 to 1988 by using data from the Osaka Cancer Registry.[9] They also reported trends for survival from cancer between 1975 and 1994.[10] However, they treated incidence and survival separately, and did not focus on the effects of these two factors on mortality trends. This article reports incidence trends for childhood cancer in Osaka from 1973 to 2001 and survival trends from 1978 to 1997 to clarify whether the continuous decline in cancer mortality between 1973 and 2001 was caused by trends for incidence, survival, or both.

Materials and Methods

The incidence data were obtained from the Osaka Cancer Registry, which covers all communities in Osaka Prefecture. The population in Osaka Prefecture was 8.8 million at the 2000 census, which accounts for 7% of the total Japanese population, and the analysis of incidence included childhood cancer cases diagnosed between 1973 and 2001. The data on survival was collected from patients diagnosed in 1975 for all communities except for Osaka City, which is the biggest city in Osaka Prefecture and includes a quarter of its population, and we completed the 5-year follow-up for the cases diagnosed until 1997. Although the survival data for Osaka City was available from 1993, for the analysis in this study it was not used to examine long-term trends in the defined population of Osaka Prefecture excluding Osaka City. Compared with the data for incidence trends, the analysis of survival covered approximately 3500 childhood cancer cases (82%) diagnosed between 1978 and 1997.

The Osaka Cancer Registry gathers information from reports from (1) medical institutions in Osaka Prefecture; (2) death records of inhabitants of Osaka Prefecture mentioning neoplasms; (3) autopsy records of medical institutions in Osaka Prefecture (originally compiled in the Autopsy Records of the Japanese Society of Pathology); (4) information on cancer cases in Osaka Prefecture extracted from the Nationwide Registry of Childhood Cancer of the Society for Protection of Children with Cancer; (5) records of cancer patients in Osaka Prefecture extracted from the Childhood Cancer Registry of the Committee for Malignant Tumors of the Japanese Society for Pediatric Surgeons; and (6) information from application forms used in the Research Project for Pediatric Chronic Severe Diseases.[11]

For the analysis of incidence, cases were children <15 years of age who were diagnosed with neoplasms defined by the International Classification of Childhood Cancers second revision (ICCC-2) between 1973 and 2001, and for analysis of survival, those diagnosed between 1978 and 1997.[12] Secondary or more neoplasms were included in the analysis of incidence but not in that of survival.

To examine trends for the incidence of all tumors and all tumors excluding neuroblastoma, joinpoint analysis was performed and the annual percent change (APC) was calculated from the joinpoint model by the Joinpoint 3.3 package (US National Cancer Institute, Bethesda, MD, USA)[13,14]. In each diagnostic group, the annual number of the patients was so small that we need to examined the number of cases in six periods (1973–1977, 1978–1982, 1983–1987, 1988–1992, 1993–1997,

[6]To whom correspondence should be addressed.
E-mail: iso@pbhel.med.osaka-u.ac.jp

doi: 10.1111/j.1349-7006.2009.01443.x

and 1998–2001), where the joinpoint analysis was not conducted because of the small number of observations.

The number of cases was expressed in six periods. Incidence rates were calculated with the direct method as the number of cases per million person-years. Age-standardized rates (ASR) were calculated from age-specific incidence rates (for age groups <1, 1–4, 5–9, and 10–14 years) using the world standard population in 1970 and expressed in the six periods. Age-specific rates were expressed for two time periods, the first 15 years (1973–1987) and the following 14 years (1988–2001). The average change in incidence rate over time was modeled using Poisson regression, and expressed as the average annual percentage change (AAPC) for all tumors between 1973–1987 and 1988–2001 in age-specific rates. In order to rule out the effect of the introduction of nationwide mass screening for neuroblastoma from 1985, a calculation excluding neuroblastoma cases was added to each analysis. The *P*-values and 95% confidence intervals (CI) of the trend tests were also calculated.

The distribution of the number of cases used for the analysis of survival was expressed in 5-year periods: 1978–1982, 1983–1987, 1988–1992, and 1993–1997. The data of prognoses was obtained through a magnetic death file of vital statistics and resident cards.[9] Observed survival rates and 95% CIs were calculated with the Kaplan–Meier method. Death Certificate Only (DCO) cases were excluded from the survival analyses. Relative survival was not used since mortality from competing causes of death is low and our analyses indicated that the difference between observed and relative survival was at most 0.3%. Changes in survival among the four periods were tested by log-rank test for trend followed by calculation of the corresponding *P*-values.

The annual number of deaths by cancer, stratified for sex, was derived from reports from the Osaka Cancer Registry.[2] Mortality was calculated and joinpoint analysis was performed by sex. APC was calculated from the joinpoint model.

SAS software for Windows (version 9.1; SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

Results

Analyses for incidence are based on 5960 cases diagnosed between 1973 and 2001. Malignant tumors with a 5th-digit morphology behavior code of 3 according to the International Classification of Diseases for Oncology accounted for 98% of all childhood cancer cases (5822/5960), and the remaining cases were non-malignant tumors occurring in the central nervous system (120 cases; 2.0%), intracranial germ cell tumors (18; 0.3%). DCO cases accounted for 3.5% of the total for 1973–2001, 4.0% for 1973–1987, and 2.7% for 1988–2001. No difference was observed in the distributions of major diagnostic groups between the DCO cases and the other reported cases, except for central nervous system tumors: 34.0% *vs* 31.4% for leukemia, 9.6% *vs* 9.9% for lymphoma, 32.1% *vs* 19.2% for central nervous system tumors, and 3.8% *vs* 9.8% for sympathetic nervous system tumors. The majority (83.9%) of the tumors were microscopically confirmed for the entire study period, and the proportion increased from 80.6% for 1973–1987 to 88.7% for 1988–2001.

Figure 1 shows the trends of incidence, survival, and mortality of all tumors from 1973 to 2001 by sex. The trends of ASR for all tumors increased, and the peak was identified in 1988 for males and 1992 for females. In order to rule out the effect of mass screening for neuroblastomas initiated in 1985, the trends for ASR for all tumors excluding neuroblastomas were also examined. ASRs for all tumors excluding neuroblastoma showed the same trends except for the shift of the peaks from 1988 to 1987 for males and from 1992 to 1986 for females. The trends of mortality steadily decreased for both sexes with an APC of −3.7% since 1977 for males and −3.3 to −5.1% during the time period for females.

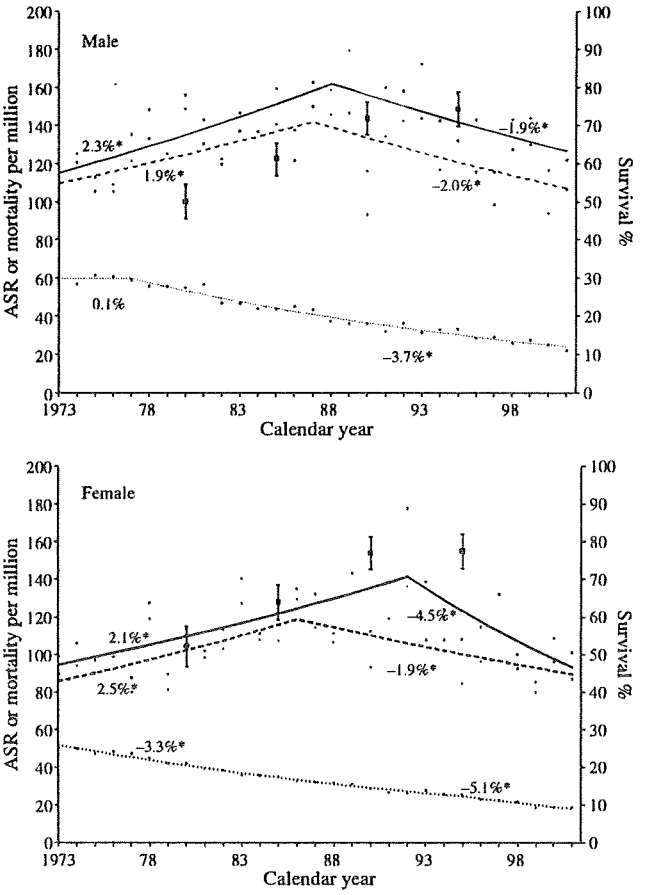

Fig. 1. Trends for incidence, 5-year survival, and mortality of all childhood cancer in Osaka, Japan. Age-standardized rates (ASRs) of all tumors (observation; black point and fitted; black line), ASR of all tumors excluding neuroblastoma (observation; cross mark and fitted; dashed line), mortality (observation; black point and fitted; dotted line) and 5-year survival (black square) and 95% CI. The annual percent changes (APCs) are indicated in the graph. *$P < 0.05$.

Figure 2 and Table S2 presents the sex-specific trends in the age-standardized rate (ASR) of childhood cancer incidence by diagnostic group. Leukemia in males and females showed the highest frequency for the whole period, followed by central nervous system tumors, except for the excess in sympathetic nervous system tumors in 1993–1997 in males and 1988–1997 in females. Childhood cancer was more common among males than females with a male-to-female ratio of 1.27 (Table S1). This ratio was particularly high for lymphomas (1.69) and renal tumors (1.70) and slightly higher for retinoblastomas (1.10), malignant bone tumors (1.05), and epithelial tumors (1.02). The cases in the four major diagnostic groups (leukemia, lymphoma, central nervous system tumors, and sympathetic nervous system tumors) accounted for approximately 70% of all tumors for both sexes.

The incidence rates for sympathetic nervous system tumors increased until 1993–1997 for males and until 1988–1992 for females, and then declined. For males, the incidence rates for leukemias, lymphomas, and malignant bone tumors increased until 1983–1987 and showed no consistent trends. ASRs for germ-cell tumors and hepatic tumors declined from 1988–1992 to 1998–2001. For females, the incidence rates for lymphomas, germ-cell tumors, and soft tissue tumors increased until 1983–1987 and then declined.

doi: 10.1111/j.1349-7006.2009.01443.x

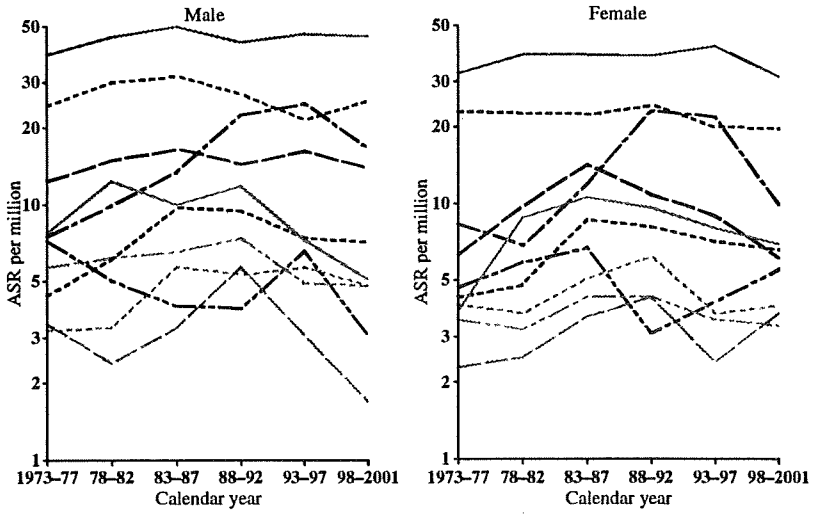

Fig. 2. Trends for age-standardized rates (ASRs) of childhood cancer by diagnostic groups in Osaka, Japan, from 1973 to 2001. Central nervous system (CNS) (---), germ-cell tumor (—), hepatic tumor (--), leukemia (—), lymphoma (—), malignant bone tumor (---), renal tumor (—), retinoblastoma (—), soft tissue tumor (--- in the middle), sympathetic nervous system tumor (—).

Age-specific incidence rates for all tumors were highest in the 0-year age group, followed by the 1–4-year age group for both sexes (Table 1). This trend was similar to the incidence rates for all tumors excluding neuroblastomas for both sexes. For the other diagnostic groups, higher rates in the 0- and 1–4-year age groups and lower rates for the 5–14-year age groups were observed for leukemias, sympathetic nervous system tumors, retinoblastomas, renal tumors, hepatic tumors, and germ-cell tumors in both sexes. Incidence rates for malignant bone tumors increased with age for both sexes. Age-specific rates for all tumors in the 0-year old increased substantially from 1973–1987 to 1988–2001, primarily due to the increased rate of neuroblastoma. AAPCs for all tumors for the various age groups ranged from 2.0% to 3.1% between 1973 and 1989 and from −0.4% to −4.2% between 1988 and 2001 for males, and from 1.2% to 3.7% and −1.8% to −2.9% for females.

The distribution of cases used for survival analysis was expressed by tumor group over 5-year periods (Table S3). A total of 3460 childhood cancer cases diagnosed during 1978–1997 were used for the survival analysis. DCO cases numbered 47 (1.4%) between 1978 and 1987 with 22 cases between 1978 and 1982. Central nervous system tumors, leukemias, and lymphomas accounted for more than half of the DCO cases in every period.

Figure 3 illustrates trends for sex-specific 5-year survival rates in each diagnostic group in 5-year periods. Survival improved significantly over the four survey periods for all tumor groups. Overall survival for all tumors increased from 50% (95% CI: 46–55) to 74% (95% CI: 70–79) for males, and from 52% (95% CI: 47–58) to 77% (95% CI: 73–82) for females. These trends did not change for all tumors excluding neuroblastomas. Survival for all tumors excluding neuroblastomas was slightly higher (at most 2%) during 1978–1982 and 1983–1988 and slightly lower (at most 2%) during 1988–1992 and 1993–1998 than survival for all tumors for both sexes. Improvement in survival was statistically significant for leukemias, lymphomas, sympathetic nervous system tumors, germ cell tumors, all tumors excluding neuroblastomas, and all tumors. Central nervous system tumors and some other minor diagnostic groups showed no significant changes in survival.

Discussion

The data presented here from the large-scale and long-term cancer registry in Osaka showed a unique trend in the incidence of total childhood cancer: an increase until 1988 with an APC of 1.5% for males and until 1992 with an APC of 1.7% for females, and then successive decrease with declining APCs of −2.0% for males and −1.9% for females. These trends did not change when neuroblastomas were excluded from this analysis.

As for survival, we have found an approximately 50–75% increase for the periods 1978–1982 and 1993–1997 for both sexes. The trend for mortality in Osaka was similar to that in all over Japan (Fig. 1).[15] These findings indicate that the continuous decline in mortality from childhood cancer throughout the period 1973–2001 was due to substantial improvement in survival in spite of an increase in incidence between the 1970s and 1980s, and a stable survival but declining incidence after the 1990s. Mortality and survival in our study showed similar trends to those in the USA and European countries, although these countries reported a continuous increase in the incidence of childhood cancer between the 1970s and 1990s.[3,4,7]

The reason why the total childhood incidence in Osaka increased but has declined since 1998 for males and 1992 for females is unknown. That decline is unlikely due to a systematic drift for collecting data. If systematic drift occurs, the trends would be similar regardless of diagnostic grouping. However, the incidence of. leukemia, retinoblastoma, central nervous system in males, and hepatic tumors in females did not decline over time, while other tumors such as sympathetic nervous system tumors and germ-cell tumors declined from the middle of the study period for both sexes, a tendency which is not seen in other areas such as the USA and Europe.[3,4] Moreover, the incidence of sympathetic nervous system tumors declined in spite of continuous and vigorous national screening and accurate detection of neuroblastoma. There is a concern that data came mostly from the Research Project for Pediatric Chronic Severe Diseases, which is originally for subvention of treatment costs. However, this research project has been conducted vigorously and the possibility of the systematic drift of detection may be small.

The proportion of DCO cases in the registry used for this study was 3.5% throughout the study period, higher than the percentages in other registries in the USA and Europe, which according to the SEER and ACCIS project was <1% in almost all European areas.[3,4] The distribution among diagnostic groups between DCO and other cases did not differ substantially except for central nervous system tumors, which consists of various morphological types in the present study.

The screening for neuroblastomas in 6-month-old infants from 1985 to 2003 resulted in an increase of almost six times the incidence of neuroblastomas among infants in 1988–2001 compared to 1973–1987. The ASR for neuroblastomas tripled

Table 1. Sex- and age-specific rate and average annual percent change of childhood cancer in Osaka, Japan, from 1973 to 2001 by period

Classification	Males								Females							
	Age-specific rate								Age-specific rate							
	0 year		1–4 years		5–9 years		10–14 years		0 year		1–4 years		5–9 years		10–14 years	
	73–87	88–2001	73–87	88–2001	73–87	88–2001	73–87	88–2001	73–87	88–2001	73–87	88–2001	73–87	88–2001	73–87	88–2001
I. Leukemia	50.0	56.6	65.6	63.0	38.5	38.3	25.1	30.8	49.3	53.9	51.8	56.4	29.0	27.8	24.6	23.8
II. Lymphoma	13.8	6.5	16.0	13.6	11.8	17.8	15.9	15.7	15.7	8.4	11.3	11.4	8.4	6.9	7.9	8.5
III. Central nervous system tumors	57.4	42.0	28.4	31.3	24.2	21.5	25.1	17.1	35.9	35.3	23.7	23.1	21.9	19.0	17.6	18.8
IV. Sympathetic nervous system tumors	33.0	179.4	18.2	19.2	4.4	4.1	1.4	1.4	37.0	175.1	15.5	13.0	2.6	3.9	1.0	0.3
V. Retinoblastoma	26.6	22.6	10.7	7.6	0.6	1.6	0.2	0.0	31.4	10.1	9.5	9.7	0.8	1.0	0.0	0.0
VI. Renal tumors	33.0	19.4	9.7	10.8	1.3	1.6	0.4	1.7	12.3	8.4	6.8	8.8	0.8	0.3	1.0	0.9
VII. Hepatic tumors	9.6	19.4	5.0	3.2	1.0	1.9	1.8	2.0	12.3	16.8	4.2	5.9	0.8	0.7	0.8	0.6
VIII. Malignant bone tumors	2.1	4.8	1.5	1.6	3.4	2.8	7.8	12.0	1.1	0.0	0.5	1.3	3.4	4.3	9.9	10.3
IX. Soft-tissue sarcomas	22.3	19.4	6.0	9.2	4.6	7.2	4.9	5.0	25.8	15.1	5.0	7.6	3.4	5.2	3.9	7.3
X. Germ-cell tumors	36.2	27.5	12.5	8.8	3.1	5.3	7.8	6.2	13.5	23.6	4.7	5.1	5.4	4.9	11.4	11.5
XI. Epithelial tumors	2.1	0.0	1.2	0.0	1.3	0.9	2.7	5.3	2.2	0.0	1.1	0.4	1.0	1.6	3.7	4.1
XII. Unspecified tumors	7.4	8.1	2.7	3.6	2.5	0.3	1.4	1.4	11.2	3.4	3.2	0.8	1.0	1.0	1.9	2.1
All tumors	**293.5**	**405.6**	**177.5**	**172.0**	**96.7**	**103.2**	**94.4**	**98.4**	**247.7**	**350.1**	**137.2**	**143.5**	**78.7**	**76.6**	**83.7**	**88.1**
All tumors excluding neuroblastoma	**260.5**	**226.2**	**159.3**	**152.8**	**92.3**	**99.1**	**93.0**	**97.0**	**210.7**	**175.1**	**121.7**	**130.5**	**76.0**	**72.6**	**82.7**	**87.8**
AAPC (%) for all tumors	3.1	−4.2	2.0	−0.4	2.0	−2.7	2.6	−1.4	1.2	−1.8	3.7	−2.3	1.8	−2.9	1.9	−2.1
95% confidence interval	(0.3–5.9)*	(−7.1–−1.2)**	(0.3–3.8)*	(−2.7–1.9) *	(−0.1–4.1)	(−5.3–−0.1)*	(0.4–4.8)*	(−3.9–1.2)	(−1.8–4.3)	(−5.1–1.5)	(1.7–5.8)***	(−4.8–0.3)	(−0.6–4.2)	(−6.0–0.2)	(−0.4–4.3)	(−4.8–0.7)

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. AAPC, average annual percentage change.

doi: 10.1111/j.1349-7006.2009.01443.x

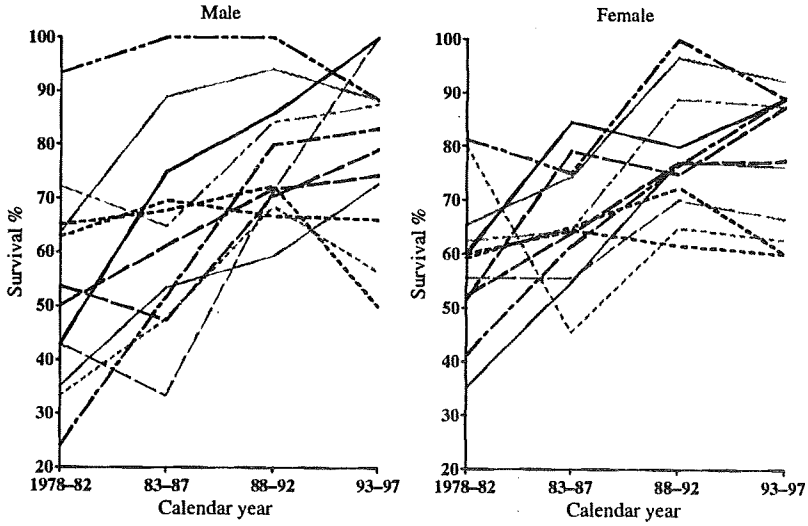

Fig. 3. Trends for age-standardized rates (ASRs) of childhood cancer by diagnostic groups in Osaka, Japan, from 1978 to 1997. Central nervous system (CNS) (---), germ-cell tumor (—), hepatic tumor (—), leukemia (—), lymphoma (—), malignant bone tumor (---), renal tumor (----), retinoblastoma (——), soft tissue tumor (--- in the middle), sympathetic nervous system tumor (—).

but the ASR for all tumors increased by only 10% because 0-year infants accounted for only approximately 5–7% of all incident cases. Although our reports covered the period until 2001, this screening was stopped in 2004 after two reports that screening for neuroblasotomas among infants had no effects on mortality.[16,17]

The survival of childhood cancer patients in the leukemia and other diagnostic groups in Osaka markedly improved between 1978 and 1992, probably due to earlier diagnosis and more effective therapies.[3,18] The introduction of mass screening for neuroblastomas had no effect on the total tumor survival rates, since the rates excluding and including neuroblastomas were similar.

Survival for the major diagnostic groups in 1993–1997 in our study was generally lower than that in the USA and UK.[3,5] The 5-year survival for leukemias, for example, was 73% for males and 76% for females in Osaka, 80% in the USA, and 76% in the UK. The exception is the higher 5-year survival rate for neuroblastomas in our study (86%) compared with that in the USA (69%) and UK (57%), probably due to over-diagnosis resulting from nationwide mass screening.[19,20]

In conclusion, our study has clarified the trends for incidence, survival, and mortality of childhood cancer in Japan. The constant decline in mortality from childhood cancer was primarily due to the improvement in survival during the 1970s and 1980s, and the reduction in incidence after the 1990s.

Acknowledgments

This study was supported in part by a Grant-in Aid for Cancer Research (14-2) from the Ministry of Health, Labour and Welfare of Japan. Authors appreciate Ms Miho Imanaka for her assistance with making graphs.

Disclosure Statement

The authors have no conflict of interest.

References

1 Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare. *Vital Statistics of Japan 2005*. Tokyo: Health and Welfare Statistics Association, 2007. (In Japanese.)
2 Osaka Prefectural Department of Public Health and Welfare, Osaka Medical Association, Osaka Medical Center for Cancer and Cardiovascular Diseases. *Annual Report of Osaka Cancer Registry No.71 – Cancer Incidence and Medical Care in Osaka in 2004 and the Survival in 2000*. OPDPHW, 2008. (In Japanese.)
3 Ries Melbert D, Krapcho M, eds. *SEER Cancer Statistics Review, 1975–2004*. Bethesda, MD: National Cancer Institute. [Cited 22 Dec 2009.] Available from URL: http://seer.cancer.gov/csr/1975_2004/.
4 Kaatsch P, Steliarova-Foucher E, Crocetti E, Magnani C, Spix C, Zambon P. Time trends of cancer incidence in European children (1978–1997): report from the Automated Childhood Cancer Information System project. *Eur J Cancer* 2006; **42**: 1961–71.
5 Magnani C, Pastore P, Coebergh JW, Viscomi S, Spix C, Steliarova-Foucher E. Trends in survival after childhood cancer in Europe, 1978–1997: reports from the Automated Childhood Cancer Information System project (ACCIS). *Eur J Cancer* 2006; **42**: 1981–2005.
6 Gatta G, Gorazziari I, Magnani C *et al.* Childhood cancer survival in Europe. *Ann Oncol* 2003; **14**: 119–27.
7 Cancer Research UK. *Childhood Cancer Statistics Trends*, 2001. [Cited 22 Dec 2009.] Available from URL: http://info.cancerresearchuk.org/cancerstats/childhoodcancer/trends/?a = 5441.
8 Marugame T, Katanoda K, Matsuda T *et al.* The Japan Cancer Surveillance Report: incidence of childhood, bone, penis, and testis cancers. *Jpn J Clin Oncol* 2007; **37**: 319–23.
9 Ajiki W, Hanai A, Tsukuma H, Hiyama T, Fujimoto I. Incidence of childhood cancer in Osaka, Japan, 1971–1988: reclassification of registered cases by Birch's scheme using information on clinical diagnosis, histology and primary site. *Jpn J Cancer Res* 1994; **85**: 139–46.
10 Ajiki W, Tsukuma H, Oshima A. Survival rates of childhood cancer patients in Osaka, Japan. *Jpn J Clin Oncol* 2004; **34**: 50–4.
11 Ajiki W, Tsukuma H, Oshima A. *The Source of Registration of Childhood Cancer in Osaka Cancer Registry* In. JACR Monograph NO.8. Osaka: Japanese Association of Cancer Registries, 2003. (In Japanese.)
12 Kramarova E, Stiller CA. The international classification of childhood cancer. *Int J Cancer* 1996; **68**: 759–65.
13 Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation Tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000; **19**: 335–516.
14 National Cancer Institute. Joinpoint Regression Program ver 3.3 [Cited 22 Dec 2009.] Available from URL: http://srab.cancer.gov/joinpoint/
15 Yang L, Fujimoto J, Qiu D, Saskamoto N. Childhood cancer in Japan: focusing on trend in mortality from 1970 to 2006. *Annals of Oncology* 2009; **20**: 166–74.
16 Woods WG, Gao RN, Shuster JJ *et al.* Screening of infants and mortality due to neuroblastoma. *NEJM* 2002; **346**: 1041–6.
17 Schilling FH, Spix C, Berthold F *et al.* Neuroblastoma screening at one year of age. *NEJM* 2002; **346**: 1047–53.
18 Rubnits JE, Pui CH. Recent advances in the treatment and understanding of childhood acute lymphoblastic leukemia. *Cancer Treat Rev* 2003; **29**: 31–44.
19 Ajiki W, Tsukuma H, Ohshima A, Kawa K. Effects of mass screening for neuroblastoma on incidence, mortality, and survival rates in Osaka, Japan. *Cancer Causes Control* 1998; **9**: 631–6.
20 Honjo S, Doran HE, Stiller CA *et al.* Neuroblastoma trends in Osaka, Japan, and Great Britain 1970–1994, in relation to screening. *Int J Cancer* 2003; **103**: 538–43.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Sex-specific trends in incident cases of childhood cancer in Osaka, Japan, from 1973 to 2001.

Table S2. Sex-specific trends in age-standardized incidence rate and average annual percent changes of childhood cancer in Osaka, Japan, from 1973 to 2001.

Table S3. Sex-specific 5-year survival rates (%) of childhood cancer in Osaka, Japan, from 1978 to 1997.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

doi: 10.1111/j.1349-7006.2009.01443.x

Regional differences in population-based cancer survival between six prefectures in Japan: Application of relative survival models with funnel plots

Yuri Ito,[1,5] Akiko Ioka,[1] Hideaki Tsukuma,[1] Wakiko Ajiki,[2] Tomoyuki Sugimoto,[3] Bernard Rachet[4] and Michel P. Coleman[4]

[1]Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka; [2]Cancer Information Services and Surveillance Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo; [3]Department of Biomedical Statistics, Osaka University Graduate School of Medicine, Osaka, Japan; [4]Non-Communicable Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, London, UK

(Received January 8, 2009/Revised March 3, 2009/Accepted March 15, 2009/Online publication April 21, 2009)

We used new methods to examine differences in population-based cancer survival between six prefectures in Japan, after adjustment for age and stage at diagnosis. We applied regression models for relative survival to data from population-based cancer registries covering each prefecture for patients diagnosed with stomach, lung, or breast cancer during 1993–1996. Funnel plots were used to display the excess hazard ratio (EHR) for each prefecture, defined as the excess hazard of death from each cancer within 5 years of diagnosis relative to the mean excess hazard (in excess of national background mortality by age and sex) in all six prefectures combined. The contribution of age and stage to the EHR in each prefecture was assessed from differences in deviance-based R^2 between the various models. No significant differences were seen between prefectures in 5-year survival from breast cancer. For cancers of the stomach and lung, EHR in Osaka prefecture were above the upper 95% control limits. For stomach cancer, the age- and stage-adjusted EHR in Osaka were 1.29 for men and 1.43 for women, compared with Fukui and Yamagata. Differences in the stage at diagnosis of stomach cancer appeared to explain most of this excess hazard (61.3% for men, 56.8% for women), whereas differences in age at diagnosis explained very little (0.8%, 1.3%). This approach offers the potential to quantify the impact of differences in stage at diagnosis on time trends and regional differences in cancer survival. It underlines the utility of population-based cancer registries for improving cancer control. (*Cancer Sci* 2009; 100: 1306–1311)

The Japanese Government launched the Fundamental Planning of Cancer Control Promotion based on the Fundamental Bill on Cancer Control in June 2007. One of the mainstays of this new strategy was to 'narrow the inequalities of cancer medical services'. Monitoring cancer survival among the prefectures of Japan is important, both to evaluate progress toward this goal and as a contribution to the next Cancer Control Plan or regional cancer control planning. Wide regional differences in cancer survival in Japan have been reported, but the findings were only adjusted by age at diagnosis.[1]

Multivariable models of relative survival have increasingly been used to quantify the impact of various prognostic factors (e.g. country, hospital, calendar period, age).[2–4] Funnel plots, mostly used in meta-analyses, have been used more recently as additional tools for such comparisons.[5–7] In the present study, we combined multivariable relative survival models with the funnel plot approach,[8] to investigate differences in population-based cancer survival between six prefectures in Japan. The role of age and stage at diagnosis was evaluated for cancers of the stomach, lung, and breast (women).

Materials and Methods

Patients. The collaborative study of cancer survival[9] collated data from 11 prefectural cancer registries on some 373 000 cancer patients diagnosed between 1993 and 1996. The national cancer survival figures were estimated on 279 469 records from the seven registries (Yamagata, Miyagi, Niigata, Osaka, Fukui, Tottori, and Nagasaki) that met the quality requirements (death certificate only cases less than 25%; death certificate notification less than 30%; vital status unknown for less than 5% of patients).[9]

These data formed the basis of the analyses reported here, but the data from the Tottori registry (4% of the total) were excluded because tumor stage was missing. Overall, 84 350 cases diagnosed with a first, primary, invasive malignant tumor of the stomach (ICD-10[10] code C16), lung (C33-C34), or breast (C50; only women) between 1993 and 1996 and followed up for at least 5 years were considered as eligible for survival analysis. Of these, we excluded 11 874 patients (14.1% of those eligible) for whom the tumor stage at diagnosis was unknown, and 72 476 patients (85.9%) were included in the survival analyses.

Methods. We first applied relative survival models to examine differences in cancer survival between the six prefectures. The adjusted excess hazard of death for each prefecture was then compared with the grand mean using the funnel plot approach.

In a second step, focussing on the prefecture with the lowest survival, we assessed the influence of age and stage at diagnosis on survival using the R^2 measure to estimate the proportion of variation explained by each variable.

Regional differences in survival up to 5 years since diagnosis: the funnel plots. The excess hazard ratios (EHR) of death from each cancer within 5 years of diagnosis were estimated for each prefecture with a Poisson regression model for relative survival,[11] adjusting first for age, then for age and stage combined. The expected (background) mortality, which is removed from the observed overall mortality, was obtained from complete (single-year-of-age) national life tables.[12] The contrasts used in the model were modified such that the excess hazard of each prefecture was compared to the overall mean hazard of death in excess of the national background mortality. This 'grand mean' across the six prefectures represents the 'target' in the funnel plots,[7,8] that is, the excess hazard of death against which the hazard among cancer patients in each prefecture was compared. Both 95 and 99.8% control limits were estimated according to the 'precision', represented by the inverse variance of the grand mean, and displayed on the x-axis of the funnel plots. An excess hazard outside the 95 (dotted lines) or 99.8% (dashed lines) control limits means that the excess hazard of death from that cancer in that prefecture was considerably higher (if above the limits) or lower (if below) than the risk of death from that cancer in all the prefectures combined.

Evaluation of the role played by prognostic factors on the lowest survival. We then focused on the prefecture with the lowest

[5]To whom correspondence should be addressed. E-mail: itou-yu2@mc.pref.osaka.jp

doi: 10.1111/j.1349-7006.2009.01170.x

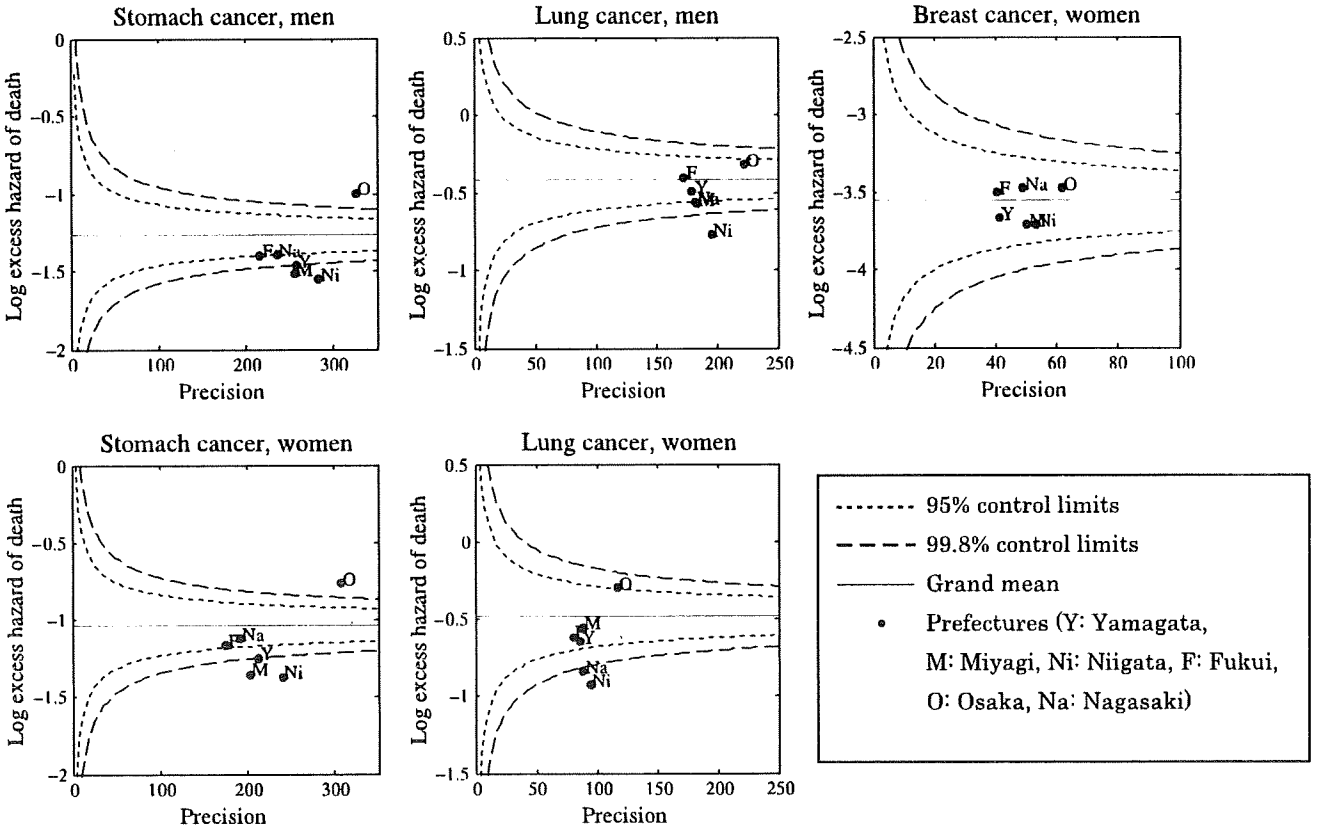

Fig. 1. Funnel plots of the age-adjusted log excess hazard of death within 5 years of diagnosis, by prefecture: cancers of the stomach, lung, and breast. Precision (*x*-axis) is the inverse of the variance of the age-adjusted log excess hazard of death. The target ('grand mean') is the average of the log excess hazard of death across the six prefectures

survival for each cancer and evaluated the role of age and tumor stage at diagnosis using R^2 measures for the Poisson regression model, based on deviance residuals.[13] We used four models to quantify the effect of adjusting the excess hazard for age and stage. Model 1 comprised the follow-up time (0-, 0.25-, 0.5-, 1-, 2-, and 3–5 years since diagnosis) and the region. In model 2, age at diagnosis was added to model 1, whereas model 3 consisted of model 1 plus stage at diagnosis. Model 4 included both age and stage. The effect of age adjustment was defined as the difference in R^2 between model 4 (adjusted for both age and stage) and model 3 (adjusted for stage). The effect of adjusting the excess hazard for stage was represented by the difference in R^2 between model 4 (age and stage) and model 2 (age).

Results

Stomach cancer. Five-year relative survival was lower in Osaka than in the other five prefectures for both sexes (data not shown). After adjustment for age at diagnosis, the excess hazard of death in Osaka was above the upper 99.8% control limit (Fig. 1). Additional adjustment for stage at diagnosis reduced the excess hazard in Osaka slightly, but it was still above the upper 95% control limit for both sexes (Fig. 2). Some realignment of the prefectural excess hazards was also observed. The data from Miyagi and Niigata showed a significantly low excess hazard of death from stomach cancer. In Miyagi, this persisted after adjustment for both age and stage (Figs 1, 2).

We examined further the role of age and stage on the lower survival in Osaka. Cancer patients in Osaka tended to be diagnosed at a younger age and, for stomach cancer, at a more advanced stage (Table 1). We further restricted the analysis to those cancer registries that conducted active follow up of cancer patients, namely Osaka, Yamagata, and Fukui.

In this restricted analysis, the excess hazard of death for both sexes in Osaka was still significantly higher than in the comparison group of Yamagata and Fukui combined (Table 2: model 1). The EHR barely changed after adjustment for age (model 2). The EHR fell after accounting for stage (models 3 and 4), but it was still significantly high. We estimated that differences in age at diagnosis explained as little as 0.8% in men and 1.3% in women of the difference in cancer survival between Osaka and Yamagata and Fukui combined (Table 3). By contrast, differences in tumor stage appeared to explain 61.3 and 56.8% of the survival differences in men and women respectively (Table 3). This mainly reflects a higher proportion of patients with advanced stage (Table 1), particularly for regional disease (data not shown).

Lung cancer. Age-adjusted excess hazards were lower than the 99.8% control limit in both sexes in Niigata and among women in Nagasaki (Fig. 1). These populations had a higher proportion of localized tumors (Table 1) and, after additional adjustment for tumor stage, the excess hazards of death were all within the 95% control limits except for men in Miyagi prefecture (Fig. 2).

Breast cancer. No outlier was found among the six prefectures for 5-year relative survival or the excess hazard of death from breast cancer within 5 years of diagnosis (Figs 1, 2).

Discussion

Analysis of population-based cancer data showed wide differences in 5-year relative survival from stomach cancer between the six prefectures, after adjustment for age and stage. Patients in Osaka

Table 1. Characteristics of cancer patients diagnosed between 1993 and 1996 in six prefectures in Japan: selected cancers

		Prefecture												Total	
		Yamagata		Fukui		Osaka		Niigata		Miyagi		Nagasaki			
Resident population (1995)		1 256 958		826 996		8 797 268		2 488 364		2 328 739		1 544 934		17 243 259	
Stomach															
Men	Incidence (per milion)†	111.8		104.3		74.2		113.5		97.7		82.3		87.1	
	Mortality (per milion)‡	48.5		37.5		47.5		49.3		42.8		37.5		42.1	
	Age (years)	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	15–44	157	4.5	87	4.7	466	4.5	263	4.6	177	5.2	125	5.5	1275	4.7
	45–54	389	11.2	208	11.1	1582	15.4	658	11.5	437	12.9	233	10.2	3507	13.0
	55–64	908	26.0	484	25.9	3212	31.3	1637	28.6	992	29.2	636	27.9	7869	29.1
	65–74	1308	37.5	649	34.7	3170	30.9	2082	36.4	1215	35.8	813	35.6	9237	34.2
	75–99	724	20.8	441	23.6	1830	17.8	1082	18.9	577	17.0	474	20.8	5128	19.0
	Stage														
	Localized	2007	57.6	1040	55.6	4830	47.1	3391	59.3	1914	56.3	1193	52.3	14 375	53.2
	Regional	941	27.0	499	26.7	3442	33.5	1619	28.3	919	27.0	716	31.4	8136	30.1
	Distant	538	15.4	330	17.7	1988	19.4	712	12.4	565	16.6	372	16.3	4505	16.7
	Total	3486	100.0	1869	100.0	10260	100.0	5722	100.0	3398	100.0	2281	100.0	27 016	100.0
Women	Incidence (per milion)†	48.5		44.0		28.2		40.8		35.2		34.4		33.7	
	Mortality (per milion)‡	22.0		17.8		17.9		17.5		14.9		14.4		16.4	
	Age (years)	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	15–44	110	5.9	84	7.9	438	8.7	215	7.5	170	10.4	107	9.1	1124	8.3
	45–54	138	7.4	109	10.3	876	17.4	309	10.8	210	12.8	134	11.4	1776	13.0
	55–64	354	19.1	208	19.6	1118	22.3	610	21.4	330	20.1	243	20.7	2863	21.0
	65–74	690	37.2	312	29.4	1371	27.3	951	33.3	545	33.3	362	30.8	4231	31.1
	75–99	565	30.4	348	32.8	1221	24.3	772	27.0	384	23.4	330	28.1	3620	26.6
	Stage														
	Localized	1018	54.8	526	49.6	2198	43.8	1668	58.4	841	51.3	590	50.2	6841	50.2
	Regional	526	28.3	351	33.1	1761	35.1	841	29.4	495	30.2	371	31.5	4345	31.9
	Distant	313	16.9	184	17.3	1065	21.2	348	12.2	303	18.5	215	18.3	2428	17.8
	Total	1857	100.0	1061	100.0	5024	100.0	2857	100.0	1639	100.0	1176	100.0	13 614	100.0
Lung															
Men	Incidence (per milion)†	51.8		56.8		65.0		63.4		60.3		68.8		55.9	
	Mortality (per milion)‡	45.7		50.8		57.9		47.8		50.8		55.3		47.3	
	Age (years)	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	15–44	22	1.8	21	2.2	179	2.7	41	1.7	35	2.7	36	2.8	334	2.4
	45–54	63	5.1	50	5.3	696	10.4	180	7.3	101	7.8	92	7.2	1182	8.5
	55–64	263	21.3	184	19.5	1636	24.4	509	20.5	275	21.4	256	19.9	3123	22.4
	65–74	517	41.8	386	40.9	2514	37.5	1077	43.5	587	45.6	565	44.0	5646	40.5
	75–99	372	30.1	303	32.1	1680	25.1	671	27.1	290	22.5	335	26.1	3651	26.2
	Stage														
	Localized	236	19.1	240	25.4	1209	18.0	808	32.6	245	19.0	320	24.9	3058	21.9
	Regional	444	35.9	372	39.4	2826	42.1	986	39.8	485	37.7	507	39.5	5620	40.3
	Distant	557	45.0	332	35.2	2670	39.8	684	27.6	558	43.3	457	35.6	5258	37.7
	Total	1237	100.0	944	100.0	6705	100.0	2478	100.0	1288	100.0	1284	100.0	13 936	100.0
Women	Incidence (per milion)†	15.6		14.9		19.0		17.4		16.0		19.2		16.8	
	Mortality (per milion)‡	12.0		9.4		17.1		10.5		10.8		14.1		12.6	
	Age (years)	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	15–44	17	3.7	13	3.8	101	3.9	24	2.9	19	4.4	23	4.4	197	3.8
	45–54	44	9.6	26	7.6	309	12.1	77	9.3	48	11.0	43	8.3	547	10.6
	55–64	97	21.1	61	17.9	526	20.5	177	21.3	104	23.9	117	22.5	1082	21.0
	65–74	156	33.9	119	35.0	814	31.8	310	37.3	156	35.8	195	37.4	1750	34.0
	75–99	146	31.7	121	35.6	813	31.7	242	29.2	109	25.0	143	27.4	1574	30.6
	Stage														
	Localized	133	28.9	110	32.4	514	20.1	344	41.4	109	25.0	178	34.2	1388	27.0
	Regional	112	24.3	114	33.5	1003	39.1	250	30.1	131	30.0	160	30.7	1770	34.4
	Distant	215	46.7	116	34.1	1046	40.8	236	28.4	196	45.0	183	35.1	1992	38.7
	Total	460	100.0	340	100.0	2563	100.0	830	100.0	436	100.0	521	100.0	5150	100.0

doi: 10.1111/j.1349-7006.2009.01170.x

Table 1. *Continued*

		Prefecture												Total	
		Yamagata		Fukui		Osaka		Niigata		Miyagi		Nagasaki			
Breast															
Women	Incidence (per milion)†	43.5		40.3		41.6		38.8		53.5		43.1		43.6	
	Mortality (per milion)‡	9.2		9.6		12.0		8.3		9.8		9.7		10.4	
	Age (years)	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	15–44	189	19.9	152	20.2	1174	19.7	511	23.9	371	21.5	272	22.1	2669	20.9
	45–54	247	25.9	232	30.9	2121	35.6	647	30.2	536	31.0	352	28.6	4135	32.4
	55–64	201	21.1	156	20.7	1330	22.3	424	19.8	389	22.5	240	19.5	2740	21.5
	65–74	210	22.1	135	18.0	840	14.1	389	18.2	305	17.7	254	20.6	2133	16.7
	75–99	105	11.0	77	10.2	489	8.2	171	8.0	127	7.3	114	9.3	1083	8.5
	Stage														
	Localized	563	59.1	439	58.4	3275	55.0	1215	56.7	930	53.8	641	52.0	7063	55.4
	Regional	320	33.6	263	35.0	2324	39.0	827	38.6	686	39.7	521	42.3	4941	38.7
	Distant	69	7.2	50	6.6	355	6.0	100	4.7	112	6.5	70	5.7	756	5.9
	Total	952	100.0	752	100.0	5954	100.0	2142	100.0	1728	100.0	1232	100.0	12 760	100.0

†The age-adjusted incidence rates per 100 000 (Standard Population: Japanese 1985 model population) in 1998 (the estimation of the incidence in each prefecture was based on the collaborative study of cancer incidence in Japan[21] and the total incidence was estimated using data from the 12 population-based cancer registries in Japan[22]).
‡Age-adjusted mortality rate per 100 000 (Std. Pop.: 1985 Japanese model population) in 1998 (data from vital statistics of Japan[23]).

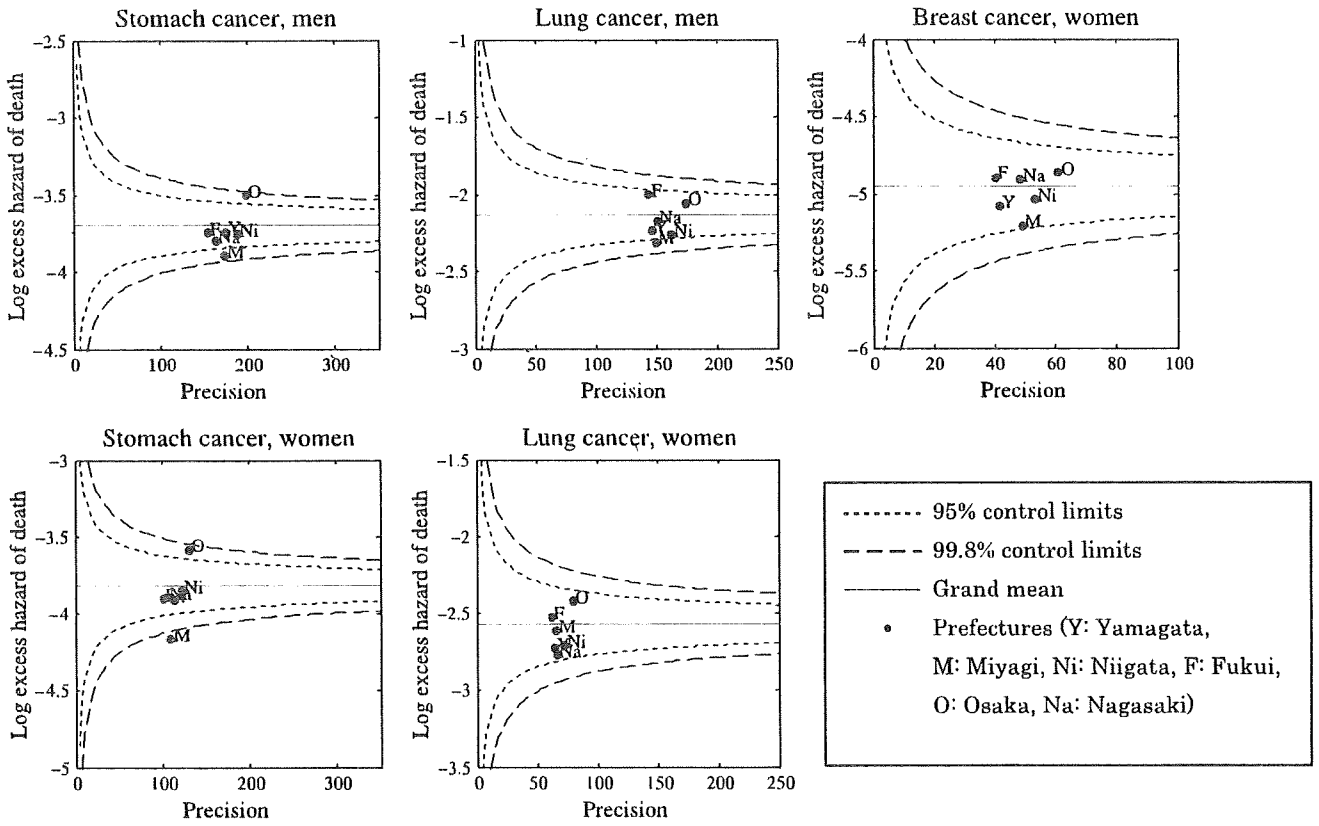

Fig. 2. Funnel plots of the age- and stage-adjusted log excess hazard of death within 5 years of diagnosis, by prefecture: cancers of the stomach, lung, and breast. Precision (*x*-axis) is the inverse of the variance of the age- and stage-adjusted log excess hazard of death. The target ('grand mean') is the average of the log excess hazard of death across the six prefectures

prefecture had higher than average excess mortality attributable to stomach cancer, whereas lower excess mortality was seen in Miyagi prefecture. Additional analyses restricted to three prefectures showed that more advanced stage at stomach cancer diagnosis accounted for approximately 60% of the excess hazard of death in Osaka.

Many cancer screening programmes (stomach, lung, breast, cervix, colorectal, even prostate cancer) have been implemented

Table 2. Stomach cancer: excess hazard ratio (EHR) of death within five years since diagnosis in Osaka relative to Yamagata and Fukui combined· patients diagnosed 1993–1996

	No. patients	Model 1 Follow-up time and region		Model 2 Model 1 + age at diagnosis		Model 3 Model 1 + stage at diagnosis		Model 4 Model 1 + age and stage	
		EHR	95% CI	EHR	95% CI	EHR	95% CI	EHR	95% CI
Men									
Region									
Yamagata + Fukui		5355		1.00		1.00		1.00	
Osaka	10 260	1.53	1.44–1.62	1.59	1.50–1.68	1.26	1.19–1.33	1.29	1.22–1.36
Age group									
15–59	4858			1.00				1.00	
60–69	5508			1.29	1.21–1.37			1.16	1.09–1.24
70–99	5249			1.77	1.66–1.88			1.42	1.33–1.52
Stage									
Localized	7877					1.00		1.00	
Regional	4882					12.43	11.07–13.95	11.54	11.07–13.95
Distant	2856					47.02	41.78–52.90	42.77	41.78–52.90
Women									
Region									
Yamagata + Fukui	2918	1.00		1.00		1.00		1.00	
Osaka	5024	1.55	1.44–1.68	1.65	1.53–1.78	1.34	1.25–1.45	1.43	1.32–1.54
Age group									
15–59	2522			1.00				1.00	
60–69	2057			1.09	0.99–1.20			1.12	1.02–1.24
70–99	3363			1.70	1.57–1.85			1.52	1.40–1.65
Stage									
Localized	3742					1.00		1.00	
Regional	2638					12.90	10.96–15.17	11.69	10.03–13.63
Distant	1562					49.43	41.85–58.38	44.19	37.75–51.73

CI, confidence interval.

Table 3. Summary of the excess hazard of death for stomach cancer patients in Osaka compared with Fukui + Yamagata

Model	Variables included in model	Men		Women	
		EHR	R^2	EHR	R^2
1	Follow up, region	1.53	0.344	1.55	0.380
2	+ Age	1.59	0.364	1.65	0.403
3	+ Stage	1.26	0.970	1.34	0.958
4	+ Age and stage	1.29	0.978	1.43	0.971

The effect of age (difference in R^2 between model 4 and model 3: see text) was 0.8 and 1.3% in men and women respectively. The effect of stage (difference in R^2 between model 4 and model 2) was 61.3 and 56.8% in men and women respectively. EHR, excess hazard ratio.

in Japan with public resources, but they have often not been well organized, with deficient management, poor definition of the target population, low participation (e.g. stomach cancer screening uptake 43.2% in Yamagata, 28.8% in Fukui, 17.9% in Osaka),[14] and poor quality control. Although such issues have not yet been fully documented, the uptake or quality of screening may have been worse in Osaka, by far the most populous prefecture examined here (Table 1).

The proportion of records excluded from analysis because of missing data on stage varied widely by prefecture. The inclusion of cases with missing stage in unadjusted analyses did not, however, eliminate regional differences in stomach cancer survival. Stage distribution is an indication of early detection of cancer, but it does not explain the lower overall survival in Osaka: stage-specific survival was also lower. Patients with regional disease and, to a lesser degree, those with localized cancer, had much lower survival in Osaka prefecture than in Yamagata and Fukui.

Regional disparities in health care management could play a major role in the remaining differences in stomach cancer survival. First, differential cancer screening coverage between Osaka and Yamagata-Fukui was likely to produce lead-time bias and/or length bias and might explain some of the differences in survival. Second, only 25% of cancer patients in Osaka were treated in the designated cancer care hospitals, whereas this proportion reached 70–80% in Fukui and Yamagata.[15] Third, lower 5-year survival has been reported for cancer patients treated in low-volume hospitals:[16–19] in Osaka, a higher proportion of cases was treated in such hospitals.

Significant differences between prefectures in the age-adjusted EHR for lung cancer disappeared after adjustment for stage. We infer that the differences in lung cancer survival arose mainly from differences in stage at diagnosis. In particular, cancer patients in Niigata and Nagasaki were on average diagnosed at an earlier stage than those in other prefectures. The high proportion of localized cases in Niigata could be explained by the high participation in screening. In Miyagi, the survival of localized cases was much higher than in other prefectures (data not shown), which could be due to lead-time bias and/or length bias among screen-detected cases. Niigata and Miyagi are two of the prefectures that have promoted cancer screening the most.

By contrast, no large disparities in survival were observed for breast cancer while all six prefectures achieved high survival on an international scale.[5] Such observations show that regional differences in survival are not inevitable and that the overall organization of health care (from early diagnosis and screening through to treatment) can reach a uniformly high standard. It also demonstrates that the differences in survival observed

doi: 10.1111/j.1349-7006.2009.01170.x

for the other cancers were not simply the result of a complex data artefact.

This is to our knowledge the first report of differences in population-based cancer survival in Japan using multivariable relative survival models, whereas crude survival (e.g. estimated with Cox proportional hazard models) does not account for the differences in background mortality. We did not control for background mortality by prefecture because it was shown to vary very little.[20]

The contrast used here for the funnel plots enabled us to examine the distribution of the excess hazard of death from each cancer in each prefecture in relation to an overall mean excess hazard, after adjustment for age and stage at diagnosis. This approach also enabled us to take into account the differences in precision of the estimates arising from the wide differences in the population of each prefecture.

This cancer survival study was limited to six prefectures. Population-based cancer registration is present in 35 of the 47 prefectures and one city in Japan, but the quality of registration and follow up is often too poor and the proportion of records with missing information on stage too high for systematic survival analysis. Even in the six prefectures that met the predetermined quality criteria, there were some unresolved data management issues. Furthermore, we limited the additional analysis on three prefectures with similar follow-up procedure in order to make the results more comparable.

Analysis of secular trends in these regional disparities in survival, using more recent data, will enable us to improve these investigations. Comparable approaches could also be applied to examine differences in cancer survival between smaller administrative geographies within a given prefecture, such as second-level medical care districts.

High-quality cancer registries with individual follow-up information are a key requirement for effective cancer control. The infrastructure of cancer registration in Japan has lagged behind that in European countries, Canada, and the USA. Systematic analysis of the data from a network of cancer registries is indispensable for monitoring improvements in cancer survival, for assessing equity in the outcome of cancer care, and for implementing and evaluating cancer control policies.

We showed that the use of the multivariable relative survival model combined with funnel plot approach was useful for assessing the regional disparities in cancer survival. It enabled us to quantify the impact of differential age and stage distributions on these regional inequalities. Our study illustrates the value of population-based cancer registries for improving cancer control.

Acknowledgments

In 2005, the Research Group conducted a collaborative study on population-based cancer survival with contribution from 11 cancer registries: Miyagi (D Shibuya), Yamagata (T Matsuda), Chiba (H Mikami), Kanagawa (N Okamoto), Niigata (KOgoshi), Fukui (M Fujita), Aichi (H Ito), Osaka (HT), Tottori (T Kishimoto), Hiroshima City (N Nishi), and Nagasaki (M Soda). The study was supported by a Grant-in-Aid for Cancer Research from the Japanese Ministry of Health, Labour, and Welfare (14-2 and 20-2).

References

1 Ajiki W, Matsuda T, Sato Y *et al.* A standard method of calculating survival rates in population-based cancer registries. *Jpn J Cancer Clin* 1998; **44**: 981–93.
2 Allemani C, Sant M, De Angelis R *et al.* Hodgkin disease survival in Europe and the US prognostic significance of morphologic groups. *Cancer* 2006; **107**: 352–60.
3 Eaker S, Dickman PW, Hellstrom V *et al.* Regional differences in breast cancer survival despite common guidelines. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 2914–18.
4 Yu XQ, O'Connell DL, Forman D. Comparison of cancer survival in UK and Australia: rates are higher in Australia for three major sites. *Br J Cancer* 2004; **91**: 1663–5.
5 Coleman MP, Quaresma M, Berrino F *et al.* Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008; **9**: 730–56.
6 Spiegelhalter D. Funnel plots for institutional comparison. *Qual Saf Health Care* 2002; **11**: 390–1.
7 Spiegelhalter DJ. Funnel plots for comparing institutional performance. *Stat Med* 2005; **24**: 1185–202.
8 Rachet B, Quaresma M, Coleman MP. Population-based audit of the clinical management of breast cancer. In Proceeding of the UICC World Cancer Congress; 8–12 July 2006, Washington, DC, USA: UICC, 2006; 168–18.
9 Tsukuma H, Ajiki W, Ioka A *et al.* Survival of cancer patients diagnosed between 1993 and 1996: a collaborative study of population-based cancer registries in Japan. *Jpn J Clin Oncol* 2006; **36**: 602–7.
10 World Health Organization. International Statistical Classification of Diseases and Health Related Problems (The) ICD-10 Second Edition, Geneva: World Health Organization, 2004.
11 Dickman PW, Sloggett A, Hills M *et al.* Regression models for relative survival. *Stat Med* 2004; **23**: 51–64.
12 Ministry of Health, Labour and Welfare. Abridged life tables in Japan for 1962–2006. (Website on the internet), Tokyo: Center for Cancer Control and Information Services, National Cancer Center, 2008. [Cited 15 Nov 2008] Available from URL: http://ganjoho.ncc.go.jp/professional/statistics/cohort01.html (in Japanese).
13 Mittlböck M, Waldhör T. Adjustments for R2-measures for Poisson regression models. *Comp Statist Data Anal* 2000; **34**: 461–72.
14 Ministry of Health, Labour and Welfare. Comprehensive Survey of Living Conditions of the People on Health and Welfare (H.16), Tokyo: Health and Welfare Statistics Association, 2004. (in Japanese)
15 Tsukuma H, Ioka A, Matsuda T *et al.* Proportion and survival of cancer patients treated in the designated regional cancer hospitals: 3 prefectures comparison. In Proceeding of 66th Annual Meeting of the Japanese Cancer Association; 3–5 Oct. 2007, Yokohama, Japan. Tokyo: The Japan Cancer Association, 2007; **514** (P-1198).
16 Ioka A, Tsukuma H, Ajiki W *et al.* Influence of hospital procedure volume on ovarian cancer survival in Japan, a country with low incidence of ovarian cancer. *Cancer Sci* 2004; **95**: 233–7.
17 Ioka A, Tsukuma H, Ajiki W *et al.* Influence of hospital procedure volume on uterine cancer survival in Osaka, Japan. *Cancer Sci* 2005; **96**: 689–94.
18 Ioka A, Tsukuma H, Ajiki W *et al.* Hospital procedure volume and survival of cancer patients in Osaka, Japan: a population-based study with latest cases. *Jpn J Clin Oncol* 2007; **37**: 544–53.
19 Nomura E, Tsukuma H, Ajiki W *et al.* Population-based study of relationship between hospital surgical volume and 5-year survival of stomach cancer patients in Osaka, Japan. *Cancer Sci* 2003; **94**: 998–1002.
20 Okamoto N, Ito Y, Tsukuma H. Difference in relative survival using regional versus national life tables in Japan. In: Tsukuma H, ed. *Report for Grant-in-Aid for Cancer Research (14-2) from the Ministry of Health, Labour and Welfare*, Osaka: Department of Cancer Control and Statistics, Osaka Medical Centre for Cancer and Cardiovascular Diseases, 2008: 38–40. (in Japanese)
21 Ajiki W, Tsukuma H, Oshima A *et al.* The 28th collaborative study of population-based cancer incidence and survey of medical treatment for cancer patients and the 8th collaborative study of the distribution of stage at diagnosis of cancer patients in Japan. In: Oshima A, ed. *Report for Grant-in-Aid for Cancer Research (8-2) from the Ministry of Health, Labour and Welfare*, Osaka: Department of Cancer Control and Statistics, 2002: 17–40. (in Japanese)
22 Research Group for Population-based Cancer Registration in Japan. Cancer incidence and incidence rates in Japan in 1998: estimates based on data from 12 population-based cancer registries. *Jpn J Clin Oncol* 2003; **33**: 241–5.
23 Ministry of Health. Labour and Welfare. Vital Statistics of Japan (Website on the internet), Tokyo: Center for Cancer Control and Information Services, National Cancer Center. 2009. [Cited 20 Feb. 2009] Available from URL: http://ganjoho.ncc.go.jp/professional/statistics/odjrh3000000hwsa-att/cancer_mortality(1958–2006).xls (in Japanese).

Cancer Science
The official journal of the Japanese Cancer Association JCA

Fresh and pickled vegetable consumption and gastric cancer in Japanese and Korean populations: A meta-analysis of observational studies

Hyun Ja Kim,[1] Sun Young Lim,[2] Jung-Sug Lee,[2] Sohee Park,[3] Aesun Shin,[2] Bo Youl Choi,[1] Taichi Shimazu,[4,5] Manami Inoue,[4,5] Shoichiro Tsugane[4,5] and Jeongseon Kim[2,6]

[1]Department of Preventive Medicine, Hanyang University College of Medicine, Seoul; [2]Cancer Epidemiology Branch, Research Institute, National Cancer Center, Goyang; [3]Cancer Registration and Statistics Branch, National Cancer Control Research Institute, National Cancer Center, Goyang, Korea; [4]Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan; [5]Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan, Tokyo, Japan

(Received May 21, 2009/Revised September 17, 2009/Accepted September 23, 2009/Online publication October 27, 2009)

It is widely known that vegetable consumption contributes to reducing the risk of gastric cancer (GC). However, the incidence rates of GC remain high in both Japanese and Korean populations, even though they have a high consumption of total vegetables. This may be due to the fact that Japanese and Koreans mainly consume processed vegetables, such as cooked, salted, or pickled vegetables, rather than fresh vegetables. To determine whether the intakes of fresh and pickled vegetables have different effects on the risk of GC in Japanese and Korean populations, we carried out a meta-analysis of published epidemiological reports. Eight studies on the consumption of fresh vegetables and 14 studies on the consumption of pickled vegetables related to GC risk were included in this meta-analysis. Four studies exploring differences in GC risk in men and women were considered separately. We observed that a high intake of fresh vegetables was significantly associated with a decreased risk of GC (overall summary OR = 0.62, 95% CI = 0.46–0.85) but that a high intake of pickled vegetables was significantly associated with an increased risk of GC (overall summary OR = 1.28, 95% CI = 1.06–1.53). The results of this meta-analysis provide evidence that a high intake of pickled vegetables may increase GC risk and suggest that a high consumption of fresh vegetables, rather than a large total amount of vegetables including pickled vegetables, is important to reduce GC risk. (*Cancer Sci* 2010; 101: 508–516)

Vegetable consumption is known to contribute to a reduction of gastric cancer (GC) risk.[1–6] The mean daily intake of vegetables in Korea (327.0 g/day)[7] and Japan (253.9 g/day)[8] is higher than that of the USA (189 g/day)[9] and northern Europe (104.6–119.1 g/day in men and 119.4–131.0 g/day in women),[10] all regions characterized by low rates of GC incidence (<15/100 000).[11] However, the age-standardized incidence rate of GC remained high in Korea (67–73/100 000 men and 20–30/100 000 women) and Japan (60–92/100 000 men and 24–39/100 000 women) during the 1990s.[12] Moreover, the seroprevalence of *Helicobacter pylori* infection, considered as a major risk factor for GC, is also high in Japan (60.0%) and Korea (59.6%).[13,14]

This paradox might be explained by the fact that Japanese and Korean people consume more pickled vegetables than fresh vegetables. Vegetables are the main source of various antioxidants (such as carotenoids, vitamin C, folate, and selenium), fiber, and phytochemicals that play an important role in the etiology of cancer.[15–17] However, vegetables have varying effects on GC risk, depending on how they are prepared and preserved. Fresh vegetables contain greater amounts of these nutrients because there is no nutrient loss due to preparation, so fresh vegetable consumption appears to be a stronger protective factor against GC than total vegetable consumption.[16] Unfortunately, Japanese and Korean people often consume processed vegetables, such as cooked, salted, or pickled vegetables, rather than fresh vegetables.[7] Pickling, also known as brining or corning, is the process of preserving food by soaking and storing it in vinegar or brine.[18] Although pickled vegetables may offer health benefits due to the fermentation process,[19] they may have adverse effects on GC risk due to the addition of large amounts of salt and the loss of key nutrients contained in vegetables under acidic and oxygenic conditions.[15,20,21] In addition, pickled vegetables are a possible source of nitroso compounds that may contribute to gastric carcinogenesis.[22,23]

Although the evidence from case–control studies supporting the protective effects of vegetables against GC risk remains strong, evidence about the effects of vegetable consumption on GC risk from cohort studies is equivocal,[16,24–26] and meta-analyses of the relationships between pickled vegetable intake and GC risk have not been carried out. Therefore, we examined the relationships between the consumption of fresh vegetables and pickled vegetables and GC risk through a meta-analysis of studies carried out in Japanese and Korean populations that indicated a high risk of GC but also a high intake of vegetables.

Materials and Methods

Selection of studies for meta-analysis. Case–control studies and cohort studies evaluating the relationships between vegetable intake and GC risk published before November 2008 were identified using databases including PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), KoreaMed (http://www.koreamed.org/SearchBasic.php), and Ichushi (Japana Centra Revuo Medicina, http://www.jamas.or.jp). The keywords used in these searches were (''gastric cancer'' or ''stomach cancer''), (''vegetable'' or ''pickled vegetable''), and (''Japan'' or ''Korea''). We also reviewed the references cited in the articles to identify additional studies for inclusion. We included published works written in Japanese, Korean, and English.

Inclusion/exclusion criteria. Inclusion/exclusion criteria for this meta-analysis were as follows.

1 To examine the relationships between overall fresh or pickled vegetables intake and GC risk, we included only the results that specified the food item to be ''fresh vegetables,'' ''raw vegetables,'' ''pickled vegetables,'' ''pickles,'' or ''pickled food'' in each study, and the results obtained from single food item questions have been excluded.

[6]To whom correspondence should be addressed. E-mail: jskim@ncc.re.kr

doi: 10.1111/j.1349-7006.2009.01374.x

2 Subjects were of Japanese or Korean ethnicities. Migrant studies were also included.
3 Cohort or case–control studies were included. Review or meta-analysis articles were excluded.
4 The studies that presented adjusted 95% confidence intervals (CI) as well as relative risks (RR) or odds ratios (OR) were included for meta-analysis in order to use adjusted values. Studies that did not report adjusted 95% CI or that presented regression coefficient values were excluded even if the number of cases and controls were presented.
5 In cases of multiple publications drawn from studies of the same population, only the most recent study was included.
6 Case–control studies that evaluated mortality instead of GC incidence were excluded.

Data abstraction. The studies were reviewed independently by two reviewers using the same inclusion/exclusion criteria, with disagreements between the reviewers resolved by consensus. The following information was collected from each study: the study design; author; publication year; nation; study period; study subjects (type and sources, definition, and numbers of subjects); measure unit of food intake (consumption frequency or quantitative intake amount); category of food intake; RR/OR and 95% CI; *P* for trend; and confounding variables.

Statistical analysis. To consider the values adjusted for the confounding factors and to include the studies that did not present each cell number (cross-tabulation) in the tables,[6,27] we used the values of RR or OR with its 95% CI. Statistical heterogeneity across the studies was assessed by calculating the between-study variation (τ^2) from the Q statistic.[28] In addition to Q, the I^2 statistic describing the percentage of variation attributable to heterogeneity across the studies was also calculated from Q values because it is easily interpretable. It has been suggested that I^2 values of 25%, 50%, and 75% is assigned to low, moderate, and high heterogeneity, respectively.[29] Depending on these results for heterogeneity, we decided whether a fixed-effect or random-effect model would be used to calculate the summary OR and its 95% CI. Additionally, we discovered sources of heterogeneity between studies through a meta-regression analysis including nationality (Japanese *vs* Korean), study design (cohort *vs* case–control study), sex (total, men, *vs* women), and the year the study started. To assess the degree of publication bias, we tested asymmetry in the funnel plot using Begg's test.[30] *P*-values less than 0.05 were considered statistically significant. All analyses were carried out using STATA 10 software (STATA, College Station, TX, USA).

Results

We identified a total of 75 articles through an initial computerized search of published work. By screening the articles according to title and abstract, 54 articles (11 review papers, 1 meta-analysis study, 9 experiment studies or clinical trials, 9 studies of populations from other countries, 23 studies on other foods or vegetables or non-dietary factors, and 1 study on atrophic gastritis) were excluded. We added 11 articles through citation searches, and then 32 original articles related to the relationships between the consumption of fresh and/or pickled vegetables and GC risk were included. Among these articles, the number of studies on the relationships between fresh vegetable intake and GC risk was 14 (2 cohort studies[31,32] and 12 case–control studies[6,27,33–42]), and the number of studies on the relationships between pickled vegetable intake and GC risk was 25 (15 cohort studies[23,31,32,43–54] and 10 case–control studies[27,33,34,36,41,55–59]). Based on the exclusion criteria, three case–control studies that did not report adjusted 95% CI values,[33,55,56] one cohort study that presented the regression coefficient values,[43] one cohort study that compared the mean intake times per week,[44] nine publications presenting multiple studies of the same population,[31,35,37–39,45,47,48,54] and one case–control study using death cases[57] were excluded. Finally, a total of eight articles (one cohort study[32] and seven case–control studies[6,27,34,36,40–42]) on the effects of consuming fresh vegetables and 14 articles (eight cohort studies[23,32,46,49–53] and six case–control studies[27,34,36,41,58,59]) on the effects of consuming pickled vegetables were included in this meta-analysis. Four articles[34,50,51,53] that presented results separately for men and women were considered in the separate articles for meta-analysis.

The details of the eligible studies are presented in Tables 1 and 2 by vegetable type (fresh or pickled). Confounding factors, including typical confounders such as age and sex, were adjusted for in most studies. We obtained statistically significant results in tests of heterogeneity between studies of fresh vegetables (Q = 28.369 on 8 degrees of freedom, $P < 0.001$; $I^2 = 71.8\%$) and pickled vegetables (Q = 45.292 on 16 degrees of freedom, $P < 0.001$; $I^2 = 64.7\%$). Therefore, we selected a random-effect model to present the summary statistics. The results of the meta-analysis of the relationships between fresh and pickled vegetable intake and GC risk are presented in Figures 1 and 2, respectively. A high intake of fresh vegetables was significantly associated with a decreased risk of GC (overall summary OR = 0.62, 95% CI = 0.46–0.85), whereas a high intake of pickled vegetables was significantly associated with an increased risk of GC (overall summary OR = 1.28, 95% CI = 1.06–1.53). The adjusted RR/OR for the highest category of fresh vegetable intake were skewed in the negative direction (RR/OR range, 0.20–0.92) except for one study (OR = 1.20),[36] whereas the adjusted RR/OR for the highest category of pickled vegetable intake varied (RR/OR range, 0.60–3.80). After excluding two studies by Lee JK *et al.*[36] and Lee SA *et al.*,[40] which reported excessive right- or left-sided skew in their associations between fresh vegetable intake and GC risk, the level of heterogeneity became low (Q = 13.074 on 6 degrees of freedom, $P = 0.042$; $I^2 = 54.1\%$; data not shown). However, the significance levels of the overall summary estimate of the effect of the consumption of fresh vegetables on GC risk did not change (overall summary OR = 0.64, 95% CI = 0.49–0.83; data not shown).

To explore the possible variables that explain why the results varied from study to study, a meta-regression analysis was carried out that included nationality (Japanese *vs* Korean), study design (cohort *vs* case–control study), sex (total, men *vs* women), and the year the study started. Of these variables, nationality ($P = 0.043$ for fresh vegetables and $P < 0.001$ for pickled vegetables) was observed as a source of heterogeneity. However, study design ($P = 0.690$ for fresh vegetables and $P = 0.126$ for pickled vegetables), sex ($P = 0.449$ for fresh vegetables and $P = 0.567$ for pickled vegetables), and the year the study started ($P = 0.081$ for fresh vegetables and $P = 0.512$ for pickled vegetables) were not significant sources of heterogeneity between studies. Therefore, we carried out a subgroup analysis according to nationality. The protective effects of fresh vegetables on GC risk from Japanese studies (OR = 0.56, 95% CI = 0.45–0.69) was stronger than that of the overall analysis, and the heterogeneity between studies disappeared (Q = 3.609 on four degrees of freedom, $P = 0.461$, $I^2 = 0\%$). However, the heterogeneities between Korean studies on fresh vegetables as well as Japanese studies on pickled vegetables remained after the subgroup analysis according to nationality (data not shown).

Begg's funnel plots for assessment of publication bias are presented in Figure 3. Begg's test and funnel plots did not detect publication bias in the meta-analyses of the effect of fresh ($Z = 0.94$, $P = 0.348$) or pickled vegetables ($Z = 0.78$, $P = 0.434$) on GC risk.

Table 1. Intake of fresh vegetables and gastric cancer (GC) risk: cohort and case–control studies among Japanese and Korean populations

Author (year), country[Ref.]	Study period	Study subjects: Source of subjects	Study subjects: No. of subjects	Study subjects: Event followed	Study subjects: No. of incident cases or deaths	Measure unit of food intake	Category	RR/OR (95% CI)	*P* for trend	Confounding variables considered
Cohort studies										
Inoue *et al.* (1996), Japan[32]	1985–1995	Patients who received gastroscopy (Aichi Cancer Center)	5373	Incidence	69 (51 men, 18 women)	Frequency	Rarely Occasionally Daily	1.0 0.73 (0.34–1.55) 0.67 (0.29–1.57)†	NA	Adjusted for sex and age
Case–control studies										
Kato *et al.* (1990), Japan[34]	1985–1989	Cases: histologically confirmed cases/Controls: patients with normal gastric mucosa (Aichi Cancer Center)	Cases: 289 men/ Controls: 1247 men			Frequency	≤1–2/month 2–3/week Daily	1.0 0.77 (0.51–1.15) 0.59 (0.37–0.93)	NA	Adjusted for age and residence
			Cases: 138 women/ Controls: 1767 women				≤1–2/month 2–3/week Daily	1.0 1.04 (0.62–1.74) 0.84 (0.47–1.51)	NA	
Hoshiyama *et al.* (1992), Japan[27]	1984–1990	Cases: newly histologically confirmed cases/Controls: residents in the study area (Saitama Cancer Center)	Cases: 294 (206 men, 88 women)/ Controls: 294 (206 men, 88 women)			Frequency	≤1/week 2–5/week ≥6/week	1.0 0.5 (0.3–0.8) 0.4 (0.2–0.7)‡	<0.0100	Matched for sex, age, administrative division, and smoking status
Lee *et al.* (1995), Korea[36]	1990–1991	Cases: histologically confirmed cases/Controls: hospitalized patients (Hanyang University Hospital and Asan Medical Center)	Cases: 213 (132 men, 81 women)/ Controls: 213 (132 men, 81 women)			Quantitative amount	Tertile 1 Tertile 2 Tertile 3	1.0 1.1 (0.7–1.9) 1.2 (0.8–1.9)	0.6400	Matched for sex and age (±2 years)/Adjusted for age, sex, education, economic status and residence
Kim *et al.* (2002), Korea[6]	1997–1998	Cases: newly histologically confirmed cases/Controls: patients without GC of the same hospital (Hanyang University Hospital and Hallim University Hospital)	Cases: 136 (93 men. 43 women)/ Controls: 136 (93 men, 43 women)			Quantitative amount	Quartile 1 Quartile 2–3 Quartile 4	1.0 0.61 (0.34–1.09) 0.55 (0.28–1.09)	0.1579	Matched for sex, age (±2 years), and hospital/ Adjusted for age, sex, socioeconomic status, family history of GC, and refrigerator use
Ito *et al.* (2003), Japan[41]	1988–1998	Cases: histologically confirmed cases/Controls: cancer-free first visit outpatients at the center (Aichi Cancer Center)	Cases: 508 women/ Controls: 36 490 women			Frequency	Almost never Occasionally 3–4 times/week Everyday	1.00 0.68 (0.48–0.97) 0.74 (0.52–1.05) 0.50 (0.36–0.71)	<0.0010	Adjusted for age, year and season of first hospital visit, smoking, and family history of GC
Lee *et al.* (2003), Korea[40]	2000	Cases: newly histologically confirmed cases/Controls: outpatients without GC (Asan Medical Center)	Cases: 69 (50 men, 19 women)/ Controls: 199 (116 men, 83 women)			Frequency	<4/week 4–6/week >6/week	1.0 0.2 (0.1–0.5) 0.2 (0.1–0.5)	<0.0100	Adjusted for age, sex, and *Helicobacter pylori* infection
Nan *et al.* (2005), Korea[42]	1997–2003	Cases: histologically confirmed cases/Controls: patients of the same hospital (Chungbuk National University Hospital and Eulji University Hospital)	Cases: 421 (276 men, 145 women)/ Controls: 632 (414 men, 218 women)			Quantitative amount	Low High	1.0 0.92 (0.72–1.17)	NA	Matched for sex, age (±3 years), and hospital

†Compared with subjects without atrophic gastritis. ‡Compared with general population controls. CI, confidence interval; NA, not available; OR, odds ratio; RR, relative risk.

doi: 10.1111/j.1349-7006.2009.01374.x

Table 2. Intake of pickled vegetables and gastric cancer (GC) risk: cohort and case–control studies among Japanese or Korean populations

Author (year), country[Ref.]	Study period	Study subjects: Source of subjects	Study subjects: No. of subjects	Study subjects: Event followed	Study subjects: No. of incident cases or deaths	Measure unit of food intake	Category	RR/OR (95% CI)	*P* for trend	Confounding variables considered
Cohort studies										
Kato *et al.* (1992), Japan[23]	1985–1991	Population-based subjects (Aichi prefectures)	9753	Death	57 (35 men, 22 women)	Frequency	≤1–2/week 3–4/week Daily	1.0 0.51 (0.18–1.48) 0.75 (0.38–1.49)	0.593	Adjusted for age and sex
Inoue *et al.* (1996), Japan[32]	1985–1995	Patients who received gastroscopy at Aichi Cancer Center	5373	Incidence	69 (51 men, 18 women)	Frequency	Rarely Occasionally Daily	1.0 2.40 (0.91–6.34) 2.31 (0.87–6.10)†	NA	Adjusted for sex and age
Galanis *et al.* (1998), Japan[46]	1975–1994	Japanese-American residents of Hawaii	11 907 (5610 men, 6297 women)	Incidence	108 (64 men, 44 women)	Frequency	None 1–6/week ≥7/week	1.0 1.3 (0.8–2.2) 1.1 (0.7–1.8)	0.750	Adjusted for sex, age, years of education, and Japanese place of birth
Ngoan *et al.* (2002), Japan[49]	1986–1999	Population-based subjects (Fukuoka prefectures)	13 250 (5917 men, 7333 women)	Death	116 (77 men, 39 women)	Frequency	≤2–4/week Once/day ≥2/day	1.0 1.3 (0.7–2.5) 1.5 (0.7–3.2)	≥0.050	Adjusted for age, sex, smoking, processed meat, liver, cooking or salad oil, suimono soup
Khan *et al.* (2004), Japan[50]	1984–2002	Population-based subjects (Hokkaido prefectures)	1524 men	Death	36 men	Frequency	≤Several/month ≥Several/week	1.0 0.9 (0.3–3.1)‡	NA	Adjusted for age and smoking
Tsugane *et al.* (2004), Japan[51]	1990–2001	Participants in JPHC cohort I (four prefectures; Iwate, Akita, Nagano, Okinawa)	18 684 men	Incidence	358 men	Frequency	Almost none 1–2 days/week 3–4 days/week Almost every day	1.0 1.54 (0.97–2.46) 2.71 (1.76–4.19) 2.35 (1.57–3.54)	<0.001	Adjusted for age, smoking, fruit and non green-yellow vegetable intake
			20 381 women	Incidence	128 women		Almost none 1–2 days/week 3–4 days/week Almost every day	1.0 1.01 (0.44–2.31) 2.20 (1.05–4.58) 1.74 (0.89–3.41)	0.050	
Sauvaget *et al.* (2005), Japan[52]	1980–1999	Participants in LSS cohort§ (two prefectures; Hiroshima and Nagasaki)	38 576 (14 885 men, 23 691 women)	Incidence	1270 (719 men, 551 women)	Frequency	<2/week 2–4/week ≥5/week	1.0 0.91 (0.77–1.07) 1.11 (0.98–1.26)	0.025	Adjusted for age, sex, city, radiation dose, sex-specific smoking habit, and education
Tokui *et al.* (2005), Japan[53]	1988–1999	Participants in JACC study (45 areas)	110 792	Death	574 men	Frequency	≤1–2/month 1–2/week 3–4/week ≥1/day	1.0 1.04 (0.72–1.51) 1.00 (0.70–1.42) 1.09 (0.82–1.47)	0.480	Adjusted for age
					285 women		≤1–2/month 1–2/week 3–4/week ≥1/day	1.0 1.56 (0.87–2.81) 1.32 (0.74–2.36) 1.47 (0.90–2.39)	0.260	
Case–control studies										
Kato *et al.* (1990), Japan[34]	1985–1989	Cases: histologically confirmed cases/Controls: patients with normal gastric mucosa (Aichi Cancer Center)	Cases: 289 men/ Controls: 1247 men Cases: 138 women/ Controls: 1767 women			Frequency	≤1–2/month 2–3/week Daily ≤1–2/month 2–3/week Daily	1.0 1.54 (1.00–2.39) 1.37 (0.88–2.13) 1.0 1.16 (0.71–1.90) 0.75 (0.45–1.27)	NA NA	Adjusted for age and residence

Table 2. (continued)

Author (year), country[Ref.]	Study period	Study subjects: Source of subjects	Study subjects: No. of subjects	Study subjects: Event followed	Study subjects: No. of incident cases or deaths	Measure unit of food intake	Category	RR/OR (95% CI)	*P* for trend	Confounding variables considered
Hoshiyama *et al.* (1992), Japan[27]	1984–1990	Cases: newly histologically confirmed cases/Population controls: residents in the study area (Saitama Cancer Center)	Cases: 294 (206 men, 88 women)/ Controls: 294 (206 men, 88 women)			Frequency	≤1/week 2–9/week ≥10/week	1.0 0.8 (0.4–1.5) 1.3 (0.7–2.6)¶	0.030	Matched for sex, age, administrative division, and smoking status
Lee *et al.* (1995), Korea[36]	1990–1991	Cases: histologically confirmed cases/Controls: hospitalized patients (Hanyang University Hospital and Asan Medical Center)	Cases: 213 (132 men, 81 women)/ Controls: 213 (132 men, 81 women)			Quantitative amount	Tertile 1 Tertile 2 Tertile 3	1.0 2.9 (1.6–5.2) 3.8 (2.3–6.5)	<0.001	Matched for sex and age (±2 years)/Adjusted for age, sex, education, economic status and residence
Watabe *et al.* (1998), Japan[58]	1996–1997	Cases: histologically confirmed cases/Controls: randomly selected from the telephone book (Sapporo Medical University Hospital)	Cases: 242 (180 men, 62 women)/ Controls: 484 (360 men, 124 women)			Frequency	≤3–6/week Daily	1.0 1.10 (0.78–1.55)	NA	Matched for sex, age (±3 years), and registered residence
Ito *et al.* (2003), Japan[41]	1988–1998	Cases: histologically confirmed cases/Controls: cancer- free first visit outpatients (Aichi Cancer Center)	Cases: 508 women/ Controls: 36 490 women			Frequency	<1/week 1–2/week 3–4/week ≥5/week	1.00 0.92 (0.72–1.18) 1.36 (1.02–1.81) 1.04 (0.74–1.47)	NS	Adjusted for age, year and season of first hospital visit, smoking, and family history of GC
Machida-Montani *et al.* (2004), Japan[59]	1998–2002		Cases: 122 (82 men, 40 women)/ Controls: 235 (159 men, 76 women)			Quantitative amount	Tertile 1 Tertile 2 Tertile 3	1.0 0.6 (0.3–1.2) 0.6 (0.3–1.3)	0.17	

†Compared with subjects without atrophic gastritis. ‡Only for men (relative risk [RR] in women was not estimated due to zero cases in both intake groups). §Life Span Study (LSS) cohort includes atomic bomb survivors and unexposed subjects in Hiroshima and Nagasaki. ¶Compared with general population control. CI, confidence interval; JACC, Japan Collaborative Cohort Study for Evaluation of Cancer Risk; JPHC cohort, Japan Public Health Center-based prospective study; NA, not available; NS, not significant; OR, odds ratio.

doi: 10.1111/j.1349-7006.2009.01374.x