www.AUSTRALIANACADEMICPRESS.com.au

ARTICLE AVAILABLE ONLINE
Twin Research and Human Genetics
Volume 15 ▮ Number 1 ▮ pp. 79–86

The Roles of Genetic and Environmental Factors on Risk of Cervical Cancer: A Review of Classical Twin Studies

Elya E. Moore [1, 2], John D. Wark [3], John L. Hopper [4], Bircan Erbas [4, 5], Suzanne M. Garland, [1, 2, 6], for the CeCaGeEn Study Group

[1] *Microbiology and Infectious Diseases Department, Royal Women's Hospital, Melbourne, Australia*
[2] *Murdoch Childrens Research Institute, Melbourne, Australia*
[3] *University of Melbourne Department of Medicine, and Bone and Mineral Service, Royal Melbourne Hospital, Australia*
[4] *School of Population Health, University of Melbourne, Australia*
[5] *School of Public Health, La Trobe University, Melbourne, Australia*
[6] *Department of Obstetrics and Gynaecology, University of Melbourne, Australia*

Cervical cancer is the third most common cancer in women worldwide. Persistent infection with an oncogenic human papillomavirus (HPV) is necessary, but not sufficient, for its development. Over many years, only a small proportion of women with chronic HPV infection progress to develop disease. The role of host genes and environmental factors in the pathogenesis of, or predisposition to, cervical cancer is still unclear. We conducted a systematic review of published literature in MEDLINE–PubMed to identify studies of cervical cancer susceptibility that used a twin study design. We used standard MeSH terms (controlled vocabulary) as well as specific free-text terms and combinations of terms related to cervical cancer, with no restriction on publication date. We performed a full text review to ensure the identified articles met our inclusion criteria and, if so, extracted information on demographics, sample size, study definitions, and key statistical findings. Of the 285 articles identified, three utilized a classical twin design and reported results specific to cervical cancer. The studies were based on cancer registry data from Scandinavia, with sample sizes ranging from 312 to 710 twin pairs. The findings from one study were consistent with a genetic mechanism for the causation of *carcinoma in situ*. Future research studies using the strength of the classic twin design, together with incorporation of HPV DNA status, are indicated to determine whether there is a potential role for genetic factors in the development of cervical cancer or high-grade cervical dysplasia from chronic oncogenic HPV infection.

■ **Keywords:** cervical cancer, classical twin studies, human papillomavirus

In their 2008 Global Burden of Cancer (GLOBOCAN) report, the International Agency for Cancer Research estimated that each year approximately 530,000 women develop cervical cancer and 270,000 die because of this disease, making cervical cancer the third most common cancer and fourth leading cause of cancer death for women worldwide (Jemal et al., 2011). Over 85% of new cases and deaths occur in developing countries, where cervical screening programs and treatment are not accessible (Jemal et al., 2011). As is the case for many common cancers, cervical cancer is a familial disease, in that close relatives of affected women are at increased risk (Zelmanowicz & Hildesheim, 2004).

One of the most important findings in the field of cancer and molecular epidemiology is that an oncogenic human papillomavirus (HPV) is detectable in nearly all cervical cancers (Bosch, Lorincz, Munoz, Meijer, & Shah, 2002; Munoz et al., 2003; Schiffman & Castle, 2003; Walboomers et al., 1999). HPV–16 and 18 are particularly virulent as they are the consistent causative agents of

RECEIVED 11 April, 2011; ACCEPTED 03 November, 2011.

ADDRESS FOR CORRESPONDENCE: Elya Moore, Microbiology and Infectious Diseases Department, Royal Women's Hospital, Parkville VIC 3052, Australia. Email: elya.moore@gmail.com

approximately 70% of cervical cancers worldwide (de SanJose et al., 2010). It is now understood that persistent infection with an oncogenic HPV is necessary for the precursor lesions of cervical cancer, cervical intraepithelial neoplasia Grade 3 (CIN3), to develop. A proportion of these precursor lesions will become neoplastic if untreated (Bosch et al., 2002; Munoz et al., 2003; Schiffman & Castle, 2003; Walboomers et al., 1999). Of the many HPV genotypes that are sexually transmitted, 12 have been classified as oncogenic or 'high-risk' (HR) types that are capable of causing cancer. Of these, eight are frequently found in cervical cancer (HPV-16, 18, 31, 33, 35, 45, 52 and 58), and four are less commonly found (HPV-39, 51, 56 and 59). An additional eight genotypes (HPV-68, 26, 53, 66, 67, 70, 73 and 82) have been classified as having limited evidence for causing cervical cancer, with HPV-68 classified as 'probably carcinogenic to humans', and the others, 'possibly carcinogenic' (Bouvard et al., 2009).

It is important to highlight that, although the presence of HPV might be necessary, it is not sufficient for carcinogenesis; only a proportion of women with chronic oncogenic HPV infection will progress over years to develop the precursor lesion to cervical cancer, high-grade dysplasia, or, for that matter, invasive cervical cancer (Winer et al., 2005). In Denmark, in a prospective study of approximately 11,000 women aged 20 to 29 years, 39% of women with HR HPV at enrolment developed high-grade lesions (81 incident cases in 208 women). The proportion was higher, 45%, in women with persistent HR HPV infection (58 incident cases in 128 women) (Kjaer et al., 2002). For women with HR HPV infection, several cofactors have been associated with progression to CIN3 or cancer, such as cigarette smoking, high parity, early age at first term pregnancy, long-term oral contraception use, and coinfection with human immunodeficiency virus (HIV). However, the results across studies are not consistent, and odds ratios are of the order of ≤ 2, which could reflect residual confounding (Almonte et al., 2008; Castellsague & Munoz, 2003; Vaccarella et al., 2006).

Based on retrospective data from New Zealand for women diagnosed with CIN3 between 1955 and 1976, and managed only by the diagnostic punch or wedge biopsy, the 30-year cumulative incidence of invasive cervical cancer was 31%, 95% CI [23, 42] (McCredie et al., 2008). It is possible that those developing cancer have a predisposition to mutagenic events within the host cell regulatory pathway. Identifying causal factors for progression from precancerous lesions (e.g., CIN3) to cancer would involve observing progression without intervening. Clearly, such a design would be unethical, given that highly effective treatments exist for cervical dysplasia (Soutter et al., 1997).

Classical Twin Studies

Genetic epidemiologists often utilize a family study design to better understand how a particular disease might be caused by genetics and/or environmental factors. A special case of a family study is the classical twin study, a powerful design for investigating the possible role of genetic factors in risk of disease. This design takes advantage of the fact that monozygotic (MZ) twin pairs share 100% of their germline DNA, while dizygotic (DZ) twin pairs, on average, share 50% (as do siblings). Twin pairs also share many environmental exposures, from conception and into childhood, when most twins cohabit.

The classic twin model assumes that, for the disease of interest, the environmental factors relevant to the trait of interest are shared to the same extent within MZ pairs as they are within DZ pairs. For twin studies, the definition of a trait is a characteristic, condition, or disease that is genetically determined. Under the assumption above, if the disease concordance is statistically greater for MZ pairs than it is for DZ pairs, then the data are consistent with there being causal genetic factors. Note that this does not imply genetic causes exist, because that assumption could be untrue, or there could be other causal models that give the same prediction. Observational data cannot prove causation — one can, at best, consider evidence consistent or otherwise with causation (Hill, 1965). In particular, if the disease concordance for MZ pairs is not statistically different from that for DZ pairs, then the data are consistent with genetic factors not being involved (within the limits of statistical power to detect an association). If, in addition, the concordances are statistically different than expected by chance, the data are consistent with the existence of disease-associated environmental factors that are shared within twin pairs (Boomsma, Busjan, & Peltonen, 2002; Hopper, Bishop, & Easton, 2005).

The main assumptions of the classical twin study are: 1) the effects of environmental (i.e. nongenetic) factors shared within twin pairs are the same for MZ and DZ pairs, 2) random mating, 3) no interaction between the effects of genes and the environment, and 4) genetic variants having an additive effect (within and across loci) on the trait of interest (Kendler, Neale, Kessler, Heath, & Eaves, 1993; Martin, Boomsma, & Machin, 1997). A violation of the first assumption can occur when, for example, parents treat one twin differently from the other twin, a phenomenon that more commonly occurs among DZ pairs than MZ pairs (Kendler, Neale, Kessler, Heath, & Eaves, 1994), or when MZ pairs are more similar for the lifestyle and environmental factors that determine the trait. Nevertheless, the twin design has the potential to help disentangle the etiological components of cervical carcinogenesis. Subject to good methodology and adequate sample size, by studying twin pairs we can make inferences about the likely roles played by inherited genetic factors (heritability), environmental factors shared by both twins, and environmental factors specific to one member of a twin pair.

https://doi.org/10.1375/twin.15.1.79 Published online by Cambridge University Press

TABLE 1

Twin Design Search Strategy: MEDLINE–PubMed[a]

Search	Search parameters	Results	Meet inclusion criteria[b]	Articles (Lead author, Journal, Year)
#1	cervical [TI] AND cancer [TI] AND twin [TI]	2	0	
#2	cervi* [TI] AND genetic* [TI] AND twin* [TI]	1	0	
#3	cancer* [TI] AND twinning [TI]	1	0	
#4	cervi* [TI] AND twin [TI]	87	1	1. Thomsen, *Gynecologic Oncology*, 2006
#5	cervi* [TI] AND genetic* [TI]	164	1	2. Magnusson, *Nature*, 1999
#6	cervi* [TI] AND heritability [TI]	1	1	3. Magnusson, *International Journal of Cancer*, 2000
#7	cancer* [TI] AND twin* [TI]	163	5	4. Neale, *Cancer Epidemiology Biomarkers and Prevention*, 2005
				5. Hemminki, *International Journal of Cancer*, 2002
				6. Lichtenstein, *New England Journal of Medicine*, 2000
				7. Ahlbom, *Journal of the National Cancer Institute*, 1997
				8. Neale, *Cancer Causes and Control*, 2004
#8	cervi* [TI] AND twin* [TI]	121	1	9. Vink, *European Journal of Human Genetics*, 2011
#9	Relevant citations selected from the bibliographies of the nine articles selected from PubMed	5	3	10. Verkasalo, *International Journal of Cancer*, 1999
				11. Iverson, *British Journal of Cancer*, 2001
				12. Braun, *Cancer Epidemiology Biomarkers and Prevention*, 1995

Note:TI = words included in the title of a citation.

[a] Search performed February 7, 2011;[b] Restricted to papers written in English, published in a peer-reviewed journal, and using a classical twin study design.

The aim of this paper is to identify, review, and analyze published studies of MZ and DZ twin pairs in order to better understand roles of genetic and environmental factors in cervical carcinogenesis.

Methods

We conducted a systematic search of the published literature (MEDLINE–PubMed) to identify studies that used a classical twin design to evaluate the possible influence of genetic factors on the risk of cervical cancer or its precursor diseases. Searches were conducted using standard MeSH terms (controlled vocabulary), as well as specific free-text terms and combinations of terms related to cervical cancer. In addition, bibliographies of all retrieved articles were reviewed. A complete description of databases searched, search strategies, and listing of search terms used is presented in Table 1.

Criteria for inclusion and exclusion of relevant articles were determined a priori and assessed by a single reviewer. Articles were included if they utilized a classical twin design and examined the risk of cervical cancer or its precursor lesions. A range of cervical diseases related to cancer was considered, including invasive cervical cancer, carcinoma in situ, cervical tumors, and CIN3. Original reports, editorials, letters to the editor, and commentaries were included if they were published in a peer-reviewed journal and written in English, with no restriction on publication date. We excluded unpublished papers and meeting abstracts that had not resulted in peer-reviewed publication. Given that this review only included a single study design, there was no assessment of quality of evidence (e.g., level of evidence rating).

From each identified study, we extracted the lead author, publication year, demographics and sample size, definitions of cervical disease and, when appropriate, the statistical estimates (e.g., probandwise estimate of casewise concordance, defined as the probability that one twin is affected, given that the other is affected [Witte, Carlin, & Hopper, 1999]; relative risk [RR], defined as the probability of being affected for persons whose twins had cervical cancer, as compared with those whose twins did not; and coincidence ratio, a measure of the extent to which the number of concordant pairs is more than expected if there was no familial clustering effect). A Fisher's exact test was used to compare the casewise concordance in MZ compared with DZ pairs. Relative risks were compared using statistical methodology developed by Altman and Bland (2003). Data for MZ and DZ pairs were pooled across all studies, and the casewise concordance was calculated, along with 95% confidence intervals.

Results

We identified 545 articles on PubMed using our MeSH and related articles searches. Of these, 12 appeared to have utilized a classical twin design and examined the risk of cervical cancer and its precursor lesions, and thus were selected to undergo a full-text review. After a full-text review, 9 of the 12 articles were excluded; two did not include twin pairs (Magnussen, Lichtenstein, & Gyllensten, et al., 1999; Magnussen, Sparen, & Gyllensten, 2000), five did not utilize a classical twin design but evaluated twinning itself as a risk factor (Braun, Ahlbom, Floderus, Brinton, & Hoover 1995; Hemminki & Li, 2002; Iversen, Tretli, & Kringlen, 2001; Neale, Mineau, Whiteman, Brownbill, & Murphy, 2005; Neale et al., 2004),

https://doi.org/10.1375/twin.15.1.79 Published online by Cambridge University Press

one reported results aggregated for all cancers, not specifically cervical cancer (Verkasalo, Kaprio, Koskenvuo, & Pukkala, 1999), and one did not report data on dizygotic pairs separately from other first-degree relatives (Vink et al., 2011). Therefore, three articles met our inclusion criteria (Ahlbom et al., 1997; Lichtenstein et al., 2000; Thomsen, Jochumsen, & Mogensen, 2006).

Ahlbom and colleagues linked data from the Swedish Twin Registry to the Swedish Cancer Registry to study several common cancers, including cervical cancer in situ (CIS) as defined by the seventh edition of the International Classification of Diseases (ICD-7) (Ahlbom et al., 1997). Two cohorts of twins were analyzed. The older cohort consisted of twins born between 1886 and 1925 and alive when the registry was established in 1959–1961. In this cohort, there were 95 pairs available for analysis in which one or both twins had a diagnosis of CIS (39 MZ pairs and 56 DZ pairs).

Using these data, we computed casewise concordance and relative risk estimates. For MZ pairs, the casewise concordance was .14, meaning that for MZ pairs the probability was 14% that the twin of a woman with CIS will have that same lesion. The RR for CIS for one twin whose twin had been diagnosed, compared with one twin whose twin had not been diagnosed was 18.2. There were no concordant DZ pairs, and therefore the casewise concordance and the RR could not be estimated. There was marginally significant evidence that the casewise concordance was greater for MZ pairs than for DZ pairs (Fisher's exact test, p value = .07) (Ahlbom et al., 1997) (Table 2).

For the younger and larger cohort, there were 658 twin pairs (263 MZ and 395 DZ) available for analysis, in which one or both twins had a diagnosis of CIS. These women were born between 1926 and 1958, and alive in 1970. For MZ pairs, the casewise concordance was .19, and there was a five-fold risk for CIS for women whose twin also had CIS. For DZ pairs, the casewise concordance was .11 and the RR was 2.4. Therefore, the concordance and RR were greater in MZ pairs compared with DZ pairs (p = .02 and p = .04, respectively). On pooling data from both cohorts, the casewise concordance was greater for MZ pairs than for DZ pairs (p = .007) (Ahlbom et al., 1997) (Table 2).

Lichtenstein and colleagues linked and pooled data from the cancer and twin registries of Sweden, Denmark, and Finland to study a variety of cancers in both men and women (Lichenstein et al., 2000). For cervical cancer, the analysis was restricted to 108 MZ twin pairs and 204 DZ twin pairs, in which at least one twin from each pair had a diagnosis of cervical cancer. The relative risk for cervical cancer was similar for MZ and DZ pairs, 2.9 and 4.5 respectively (p = .70). The casewise concordance for MZ and DZ pairs was also similar, .02 compared to .03, respectively (p = .99).

Thomsen and colleagues linked data from the Danish Twin Register to the Danish Cancer Register for twin pairs born between 1870 and 1982 (Thomsen et al., 2006). Similar to the study by Ahlbom and colleagues, ICD-7 diagnosis of CIS was used. There were 710 twin pairs in which at least one twin had a diagnosis of CIS (275 MZ pairs and 435 DZ pairs). The casewise concordances for MZ and DZ pairs were similar, .11 and .10 respectively (p = .87). The coincidence ratio was 3.96 for MZ pairs and 3.78 for DZ pairs (Thomsen et al., 2006) (Table 2).

When data from all three studies were pooled, the casewise concordance was slightly higher for MZ pairs compared with DZ pairs, .12 and .08, respectively (p = .03).

Discussion

In spite of the global health significance of cervical cancer, we identified only three studies, all from the same region, that used a classical twin design to investigate the pathogenesis of cervical cancer. None of the studies had information on HPV DNA or HPV antibody status, environmental factors, or behavioral information from participants. Furthermore, it is possible that the twin pair data from each study were not distinct; each study drew from either the Swedish or Danish twin registries. These observations draw attention to the need and opportunity to further address the genetic and environmental etiology of cervical cancer through twin studies.

The results of these studies were mixed, with two consistent with no genetic effect. When the data from all three studies were pooled, there was marginally significant evidence, under the assumptions of the classic twin model, to support a genetic influence on the development of cervical cancer. Of note, none of the studies identified for this review incorporated HPV DNA detection as a marker of infection, and a necessary cause of cervical cancer, into their designs.

While the role of genetics in the etiology of cervical cancer remains unclear, there is evidence to suggest that cervical cancer aggregates within families. A review by Zelmanowicz and Hildesheim (2004) presented data from 15 studies published between 1980 and 2003 that estimated the risk of in situ cervical cancer or invasive cervical cancer associated with a family history of cervical cancer. The authors concluded that the majority of these studies, irrespective of study design, found a one to two-fold increase in risk of cervical cancer associated with having an affected first-degree relative. These studies were limited in their capacity to account for the possibility that shared cervical cancer screening practices or similar behavior patterns within families may have accounted for some or all of the observed association. The studies were further limited by not assessing previous or current HPV infection. Nonetheless, the strongest epidemiological evidence for a genetic etiology of cervical cancer came from two studies that reported a greater increased risk for biological mothers and full sisters than for half-sisters of affected women, and no increased risk for nonbiological relatives (Magnussen et al., 1999; Magnussen et al., 2000).

https://doi.org/10.1375/twin.15.1.79 Published online by Cambridge University Press

TABLE 2

Demographics, Definitions, Statistics, and Conclusions of Selected Studies

Author (Year)	Demographics	Outcome definition	Statistics [95% CI] Casewise concordance (MZ)	Casewise concordance (DZ)	Relative Risk (MZ)	Relative Risk (DZ)	Authors' Conclusion
Ahlbohm (1997)	Population: Swedish twins. Older cohort (born 1886 to 1925): MZ: 39 (3 concordant, 36 discordant), DZ: 56 (0 concordant, 56 discordant). Younger cohort (born 1926 to 1958): MZ: 263 (27 concordant, 236 discordant), DZ: 395 (22 concordant, 373 discordant)	Carcinoma in situ: ICD-7 diagnosis from Swedish Cancer Register	Older cohort: .14 [.00, .30] Younger cohort: .19 [.13, .25] Combined: .18 [.12, .24]	Older cohort: could not be calculated Younger cohort: .11 [.07, .15] Combined: .09 [.05, .13]	Older cohort: 18.2 [4.9, 67.4] Younger cohort: 4.8 [3.0, 7.6] Combined: Not provided	Older cohort: could not be calculated Younger cohort: 2.4 [1.5, 3.8] Combined: Not provided	Evidence of a heritable component for in situ cervical cancer.
Lichtenstein (2000)	Population: Swedish, Danish, and Finnish female twins. MZ: 108 (1 concordant, 107 discordant), DZ: 204 (3 concordant, 201 discordant)	Cervix uteri: Site of cancer according to Swedish, Danish, and Finnish cancer registry	.02 [.00, .06]	.03 [.00, .07]	2.9 [0.4, 21.4]	4.5 [1.4, 14.4]	No evidence that genetic actors influence development of cervical cancer. The overwhelming contributor of all cancer in twins was the environ ment.
Thomsen (2006)	Population: Danish female twins. MZ: 275 (16 concordant, 259 discordant), DZ: 435 (24 concordant, 411 discordant)	Carcinoma in situ: ICD-7 diagnosis from Danish Cancer Register	.11 [.06, .16]	.10 [.06, .14]	Not provided	Not provided	No evidence that genetic factors influence develop ment of CIS, but shared environment is important.
Pooled data	Population: MZ: 685 (47 concordance, 638 discordant), DZ: 1090 (49 concordant, 1041 discordant)	Carcinoma in situ or cervix uteri	.12 [.10, .14]	.08 [.06, .10]	Could not be calculated	Could not be calculated	Not Applicable

Note: CI = confidence interval

There is also evidence from genetic studies that genetic factors contribute to the persistence of HPV infection and the progression to cervical cancer via several pathways. Single nucleotide polymorphisms (SNPs) have been associated with an increased risk of CIN3 or cancer, and with HPV persistence. These SNPs interfere with a variety of important gene functions such as DNA repair, immune function, viral infection, and cell entry (Wang et al., 2010; Wang et al., 2009). The presence of certain human leukocyte antigen (HLA) alleles and haplotypes has been associated in some studies with an increased risk of developing cervical cancer (Hildesheim & Wang, 2002; Lin et al., 2001) or CIN3 (Tabrizi et al., 1999). However, haplotypes have not been consistent across studies, and some did not use population controls.

Like all epidemiological studies, twin studies of cervical cancer would be enhanced if they were able to take into account the natural history of the disease. In the current context, given the integrative role HPV infection plays in the development of cervical cancer, this would mean incorporating HPV status into the study design. The global prevalence of HPV infection, as determined by DNA testing, in women with normal cervical cytology is 10.4%, 95% CI [10.2%, 10.7%], and is higher in younger women (de SanJose et al., 2007). Only a small fraction of infected women will continue to have persistent infection, and an even smaller fraction will develop the precursor lesion, CIN3, and, finally, invasive cervical cancer if not treated (Khan et al., 2005; Schiffman & Kjaer, 2003). Given that HPV infection is a necessary cause of cervical cancer, epidemiologic studies designed to identify risk factors for progression to cervical cancer should be limited to those women who are positive for oncogenic HPVs, and thus at risk of developing cancer (Schiffman & Castle, 2003; Wacholder, 2003). The relevant question is: Why do some women become chronically infected while the majority is able to clear the infection with their host immune response, and hence have only a transient infection. Moreover, of those with persistent infection, why do some develop high-grade dysplasia while others do not? More importantly, of those with high-grade dysplasia, why do only some develop cervical cancer while others do not? These questions have implications for the design of epidemiologic studies in this field, in that the comparison group must represent the population at risk of cervical cancer (Schiffman & Castle, 2003; Wacholder, 2003). The same implications apply to family studies, including classical twin studies.

In summary, few classical twin studies have assessed the evidence for a possible genetic component in cervical cancer pathogenesis. More work in this area is needed. Future research studies in this area should incorporate HPV DNA status into the study design, so that lesions can be specifically defined as associated with HPV.

Author Contribution

All authors provided input for this manuscript. EM completed the literature review and data analysis. JH and BE provided statistical oversight. JD and SM provided scientific oversight. All authors read, revised and approved the final manuscript. We are grateful to the Australian Twin Registry for their partnership in this study.

Acknowledgments

The CeCaGeEn Study Group stands for Cervical, Cancer, Genes, and Environment, and is lead by Professor Suzanne Garland, in partnership with professors Marian Pitts, John Wark, John Hopper, and Ian Frazer; associate professors Dorota Gertig, Sepehr Tabrizi, and Michael McCullough; doctors Elya Moore and Bircan Erbas; Research Assistant Ms Nicole Taylor; and project managers Ms Amanda Richardson, Nichole Lister, and Juliana Tasevska. Funding for this study was provided by National Health and Medical Research Council project grant (509002) and Cancer Australia grant (1008811).

References

Ahlbom, A., Lichtenstein, P., Malmstrom, H., Feychting, M., Hemminki, K., & Pedersen, N.L. (1997). Cancer in twins: Genetic and nongenetic familial risk factors. *Journal of the National Cancer Institute, 89*, 287–293.

Almonte, M., Albero, G., Molano, M., Carcamo, C., Garcia, P. J., & Perez, G. (2008). Risk factors for human papillomavirus exposure and co-factors for cervical cancer in Latin America and the Caribbean. *Vaccine, 26*, L16–36.

Altman, D. G., & Bland, J. M. (2003). Interaction revisited: The difference between two estimates. *British Medical Journal, 326*, 219.

Boomsma, D., Busjahn, A., & Peltonen, L. (2002). Classical twin studies and beyond. *Nature Reviews Genetics, 3*, 872–882.

Bosch, F. X., Lorincz, A., Munoz, N., Meijer, C. J., & Shah, K. V. (2002). The causal relation between human papillomavirus and cervical cancer. *Journal of Clinical Pathology, 55*, 244–265.

Bouvard, V., Baan, R., Straif, K., Grosse, Y., Secretan, B., El Ghissassi, F., Benbrahim-Tallaa, L., Guha, N., Freeman, C., Galichet, L., & Cogliano, V. (2009). A review of human carcinogens-Part B: Biological agents. *Lancet Oncology, 10*, 321–322.

Braun, M. M., Ahlbom, A., Floderus, B., Brinton, L. A., & Hoover, R. N. (1995). Effect of twinship on incidence of cancer of the testis, breast, and other sites (Sweden). *Cancer Causes and Control, 6*, 519–524.

Castellsague, X., & Munoz, N. (2003). Chapter 3: Cofactors in human papillomavirus carcinogenesis—role of parity, oral contraceptives, and tobacco smoking. *Journal of the National Cancer Institute Monograph, 31*, 20–28.

de Sanjose, S., Diaz, M., Castellsague, X., Clifford, G., Bruni, L., Munoz, N., & Bosch, F. X. (2007). Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: A meta-analysis. *Lancet Infectious D*iseases, *7*, 453–459.

de Sanjose, S., Quint W. G. V., Alemany, L., Geraets, D. T., Klaustermeier, J. E., Lloveras, B., Tous, S., Felix, A., Bravo, L. E., Shin, H., Vallejos, C. S., de Ruiz, P. A., Lima, M. A., Guimera, N., Clavero, O., Alejo, M., Llombart-Bosch, A., Cheng-Yang, C., Tatti, S. A., Kasamatsu, E., Iljazovic, E., Odida, M., Prado, R., Seoud, M., Grace, M., Usubutun, A., Jain, A., Suarez, G. A. H., Lombardi, L. E., Banjo, A., Menéndez, C., Domingo, E. J., Velasco, J., Nessa, A., Chichareon, S. C. B., Qiao, Y. L., Lerma, E., Garland, S. G., Sasagawa, T., Ferrera, A., Hammouda, D., Mariani, L., Pelayo, A., Steiner, I., Oliva, E., Meijer, C. J. L. M., Al-Jassar, W. F., Cruz, E., Wright, T. C., Puras, A., Llave, C. L., Tzardi, M., Agorastos, T., Garcia-Barriola, V., Clavel, C., Ordi, J., Andújar, M., Castellsagué, X., Sánchez, G. I., Nowakowski, A. M., Bornstein, J., Muñoz, N., & Bosch, X., on behalf of the Retrospective International Survey and HPV Time Trends Study Group. (2010). Human papillomavirus genotype attribution in invasive cervical cancer: A retrospective cross-sectional worldwide study. *Lancet, 11*, 1048–1056.

Hemminki, K., & Li, X. (2002). Cancer risks in twins: Results from the Swedish family-cancer database. *International Journal of Cancer, 99*, 873-878.

Hildesheim, A., & Wang, S. S. (2002). Host and viral genetics and risk of cervical cancer: A review. *Virus Research, 89*, 229–240.

Hill, A. (1965). The environment and disease: Association or causation? *Proceedings of the Royal Society of Medicine, 58*, 295–300.

Hopper, J. L., Bishop, D. T., & Easton, D. F. (2005). Population-based family studies in genetic epidemiology. *Lancet, 366*, 1397–1406.

Iversen, T., Tretli, S., & Kringlen, E. (2001). An epidemiological study of cancer in adult twins born in Norway 1905–1945. *British Journal of Cancer, 84*, 1463–1465.

Jemal, A., Bray, F., Center, M. M., Ferlay, J., Ward, E., Forman, D. (2011). Global cancer statistics. *CA: A Cancer Journal for Clinicians, 61*, 69–90.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1993). A test of the equal-environment assumption in twin studies of psychiatric illness. *Behavior Genetics, 23*, 21–27.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1994). Parental treatment and the equal environment assumption in twin studies of psychiatric illness. *Psychological Medicine, 24*, 579–590.

Khan, M. J., Castle, P. E., Lorincz, A. T., Wacholder, S., Sherman, M., Scott, D. R., Rush, B. B., Glass, A. G., & Schiffman, M. (2005). The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. *Journal of the National Cancer Institute, 97*, 1072–1079.

Kjaer, S. K., van den Brule, A. J., Paull, G., Svare, E. I., Sherman, M. E., Thomsen, B. L., Suntum, M., Bock, J. E., Poll, P. A., & Meijer, C. J. (2002). Type specific persistence of high risk human papillomavirus (HPV) as indicator of high-grade cervical squamous intraepithelial lesions in young women: Population based prospective follow up study. *British Medical Journal, 325*, 572.

Lichtenstein, P., Holm, N. V., Verkasalo, P. K., Iliadou, A., Kaprio, J., Koskenvuo, M., Pukkala, E., Skytthe, A., & Hemminki, K. (2000). Environmental and heritable factors in the causation of cancer—-analyses of cohorts of twins from Sweden, Denmark, and Finland. *New England Journal of Medicine, 343*, 78–85.

Lin, P., Koutsky, L. A., Critchlow, C. W., Apple, R. J., Hawes, S. E., Hughes, J. P., Touré, P., Dembele, A., & Kiviat, N. B. (2001). HLA class II DR-DQ and increased risk of cervical cancer among Senegalese women. *Cancer, Epidemiology, Biomarkers, and Prevention, 10*, 1037–1045.

Magnusson, P. K., Lichtenstein, P., & Gyllensten, U.B. (2000). Heritability of cervical tumors. *International Journal of Cancer, 88*, 698–701.

Magnusson, P. K., Sparen, P., & Gyllensten, U.B. (1999). Genetic link to cervical tumors. *Nature, 400*, 29–30.

Martin, N., Boomsma, D., & Machin, G. (1997). A twin-pronged attack on complex traits. *Nature Genetics, 17*, 387–392.

McCredie, M. R., Sharples, K. J., Paul, C., Baranyai, J., Medley, G., Jones, R. W., & Skegg, D. C. (2008). Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: A retrospective cohort study. *Lancet Oncology, 9*, 425–434.

Munoz, N., Bosch, F. X., de Sanjose, S., Herrero, R., Castellsague, X., Shah, K. V., Snijders, P. J. F., Meijer, C. J. L. M. (2003). Epidemiologic classification of human papillomavirus types associated with cervical cancer. *New England Journal of Medicine, 348*, 518–527.

Neale, R. E., Mineau, G., Whiteman, D. C., Brownbill, P. A., & Murphy, M. F. (2005). Childhood and adult cancer in twins: Evidence from the Utah genealogy. *Cancer Epidemiology, Biomarkers and Prevention, 14*, 1236–1240.

Neale, R. E., Purdie, D. M., Murphy, M. F., Mineau, G. P., Bishop, T., & Whiteman, D. C. (2004). Twinning and the incidence of breast and gynecological cancers (United States). *Cancer Causes and Control, 15*, 829–835.

Schiffman, M., & Kjaer, S. K. (2003). Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia. *Journal of the National Cancer Institute Monographs, 31*, 14–19.

Schiffman, M. H., & Castle, P. (2003). Epidemiologic studies of a necessary causal risk factor: Human papillomavirus infection and cervical neoplasia. *Journal of the National Cancer Institute, 95*, E2.

Soutter, W. P., de Barros Lopes, A., Fletcher, A., Monaghan, J. M., Duncan, I. D., Paraskevaidis, E., & Kitchener, H. C. (1997). Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. *Lancet, 349*, 978–980.

Tabrizi, S. N., Fairley, C. K., Chen, S., Borg, A. J., Baghurst, P., Quinn, M. A., & Garland, S. M. (1999). Epidemiological characteristics of women with high-grade CIN who do and do not have human papillomavirus. *British Journal of Obstetrics and Gynaecology, 106*, 252–257.

https://doi.org/10.1375/twin.15.1.79 Published online by Cambridge University Press

Thomsen, L. S., Jochumsen, K. M., & Mogensen, O. (2006). Carcinoma in situ cervicis uteri and inheritance: A Danish twin study. *Gynecologic Oncology, 103*, 688–691.

Vaccarella, S., Herrero, R., Dai, M., Snijders, P. J., Meijer, C. J., Thomas, J. O., Hoang Anh, P. T., Ferreccio, C., Matos, E., Posso, H., de Sanjosé, S., Shin, H. R., Sukvirach, S., Lazcano-Ponce, E., Ronco, G., Rajkumar, R., Qiao, Y. L., Muñoz, N., & Franceschi, S. (2006). Reproductive factors, oral contraceptive use, and human papillomavirus infection: Pooled analysis of the IARC HPV prevalence surveys. *Cancer, Epidemiology, Biomarkers, and Prevention, 15*, 2148–2153.

Verkasalo, P. K., Kaprio, J., Koskenvuo, M., & Pukkala, E.(1999). Genetic predisposition, environment and cancer incidence: A nationwide twin study in Finland, 1976–1995. *International Journal of Cancer, 83*, 743–749.

Vink, J. S., Folkert, J. V. K., Meijer, C .J. L. M., Casparie, M. K., Meijer, G. A., & Boomsma, D. I. (2011). Cervix smear abnormalities: Linking pathology data in female twins, their mothers and sisters. *European Journal of Human Genetics, 19*, 108–111.

Wacholder, S. (2003). Chapter 18: Statistical issues in the design and analysis of studies of human papillomavirus and cervical neoplasia. *Journal of the National Cancer Institute Monographs, 31*, 125–30.

Walboomers, J. M., Jacobs, M. V., Manos, M. M., Bosch, F. X., Kummer, J. A., Shah, K. V., Snijders, P. J., Peto, J., Meijer, C. J., & Munoz, N. (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *Journal of Pathology*, *189*, 12–19.

Wang, S. S., Bratti, M. C., Rodriguez, A. C., Herrero, R., Burk, R. D., Porras, C., Gonzalez, P., Sherman, M. E., Wacholder, S., Lan, Z. E., Schiffman, M., Chanock, S. J., & Hildesheim, A. (2009). Common variants in immune and DNA repair genes for human papillomavirus persistence and progression to cervical cancer. *Journal of Infectious Diseases, 199*, 20–30.

Wang, S. S., Gonzalez, P., Yu, K., Porras, C., Li, Q., Safeeian, M., Rodriguez, A. C., Sherman, M. E., Bratti, C., Schiffman, M., Wacholder, S., Burk, R. D., Herrero, R., Chanock, S. J., & Hildesheim, A. (2010). Common genetic variants and risk for HPV persistence and progression to cervical cancer. *PLos ONE, 5*, e86667.

Winer, R. L., Kiviat, N. B., Hughes, J. P., Adam, D. E., Lee, S. K., Kuypers, J. M., & Koutsky, L. A. (2005). Development and duration of human papillomavirus lesions, after initial infection. *Journal of Infectious Diseases, 191*, 731–738.

Witte, J. S., Carlin, J. B., & Hopper, J. L. (1999) Likelihood-based approach to estimating twin concordance for dichotomous traits. *Genetic Epidemiology, 16*, 290–304.

Zelmanowicz, A., & Hildesheim, A. (2004). Family history of cancer as a risk factor for cervical carcinoma: A review of the literature. *Pap Report, 15*, 113–120.

https://doi.org/10.1375/twin.15.1.79 Published online by Cambridge University Press